Infectious Diseases

PART XV

Section 1

General Considerations

Chapter 214

Public Health Approach to Pandemics

Kevin P. O'Callaghan

INTRODUCTION

Public health as a field aims to promote healthy lifestyles and communities and to protect the public at large from health threats from known and emerging diseases, chronic noncommunicable diseases, and environmental risks and vulnerabilities. In this context, public health authorities have a core role in prevention, preparedness, and response to epidemic and pandemic infectious diseases. The field of public health has a long and storied history in investigating and ending outbreaks of infectious diseases, extending back to one of the founders of modern epidemiology, John Snow, and the Broad Street pump cholera outbreak. Modern epidemiology and public health practices have an integral role in the management of outbreaks, epidemics, and pandemics, using both traditional methodologies that look like the "shoe leather epidemiology" of John Snow's time, meshed with modern best practices that leverage genomic sequencing, data analytics, and medical innovations in therapeutics and vaccination.

DEFINITIONS

Infectious disease outbreak response hinges on an understanding of current and ongoing incidence and prevalence of the disease in the affected community. The transmission dynamics of a disease will look different in a population that is entirely **susceptible** (e.g., a novel or emerging disease) than in a population in which some members are **recovered/immune** (e.g., a disease has been present for some time).

Sporadic diseases occur infrequently and irregularly in a population. **Endemic** diseases are continually circulating, often at low levels, maintaining a constant presence among members of the community. **Epidemic** disease occurs when there is a substantial increase above the baseline amount of a disease. This may occur as an increase in a disease that is already endemic at low levels or by the introduction of a novel disease that has not been seen in the affected population. A **pandemic** refers to an epidemic that has spread over several countries and continents, affecting large numbers of people. This is frequently defined and declared by international public health authorities, for example, the World Health Organization.

Public Health Authorities and Partners

Although describing "public health" as a specialty may sound somewhat monolithic, the majority of public health work is done collaboratively across a variety of partners, including local, city, state, and national public health authorities, city and state governments, healthcare systems, individual clinical providers, and members of the affected communities. The most important aspect of public health work is often community involvement, whether as part of outbreak investigations, public-facing communications, or education around prevention and response measures.

At an international level, the World Health Organization operates as an international collaborative agency set up in 1948 under the auspices of the United Nations. One of its core responsibilities is to direct and coordinate the world's response to health emergencies, working with national governments, international organizations, researchers, and health systems. At a national level, responsibility for public health management typically devolves to national and federal government departments (e.g., the Department of Health and Human Services in the United States) and their constituent agencies, such as the Centers for Disease Control and Prevention (CDC). The CDC coordinates national surveillance systems for a variety of health conditions, including endemic and newly emergent diseases.

The bulk of regional and local public health surveillance, preparedness, and response work falls under the purview of city, county, and state public health departments. These agencies liaise closely with healthcare systems, specialty and primary care practices, and individual clinicians within their region to help facilitate their public health goals, as well as with nonmedical partners, including school districts, other government agencies, and community groups.

Aims of Public Health Response to Infectious Diseases

Broadly, the aims of a public health response are to prevent the emergence of novel diseases in human hosts, prevent the spread of new diseases or the increase in prevalence of a known endemic disease, and mitigate the health effects of any spread that may occur. Based on these goals, the arms of public health response for epidemic and pandemic infectious diseases fall into four groupings: mitigation/prevention, preparedness, response, and recovery. These areas stem from a common approach to emergency management in general but have specific meanings and impact in the context of pandemic response. Some active public health measures, such as education and public-facing communication, occur across all four arms.

Arms of Intervention

Mitigation/Prevention

A primary approach to pandemic management includes proactive activities to prevent new human infections with target diseases, both to prevent endemic diseases from becoming epidemic and to arrest emergence of novel diseases. Some recent epidemics and pandemics likely represent "spillover" events from animal populations, with these zoonoses then becoming prevalent in human populations through human-to-human transmission (e.g., Zika, SARS-CoV-2). There is a complex interplay between human and animal populations related to farming, deforestation, changes in land use, water management, and climate change that makes the emergence of new zoonotic diseases intermittently more likely and unfortunately somewhat unpredictable. Prevention of emergence of these diseases is best approached through a One Health approach, which is an international project using a "collaborative, multisectoral, and transdisciplinary approach" at local, national, and international levels to optimize health outcomes, recognizing the interconnectedness of people, animals, plants, and their environment. Individual approaches to prevent disease outbreaks of this type may require the involvement of agricultural regulators and inspectors, veterinarians, and environmental health specialists, among others.

A more concrete example of a salient mitigation effort involving human healthcare providers is antimicrobial stewardship. The emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) organisms in response to the selection pressure of antimicrobial usage is a critical vulnerability in epidemic and pandemic preparedness. Stewardship efforts at a grassroots, individual patient level provide a necessary bulwark against the proliferation of further MDR and XDR strains of currently endemic diseases.

Preparedness

Separate from mitigation and prevention, a preparedness stance plans for the potentially inevitable outcome of the emergence of a novel epidemic or pandemic disease. Preparedness efforts can be targeted against specific disease threats (e.g., seasonal and pandemic influenza, which has predictable seasonality) or against previously unknown or less predictable threats (e.g., SARS-CoV-2, Ebola virus disease). Given the broad range of potential pathogens that may pose a threat over time, much preparedness planning takes place in an "all hazards" stance, where the preparation is necessarily agnostic as to the specific pathogen, with surveillance and resources that can be quickly pivoted to cover a broad variety of potential risks.

A core element of preparedness involves case-based surveillance or the active observation and documentation of incidence and prevalence of a specific disease or syndrome at local, regional, and national levels. Robust surveillance infrastructure requires both regulatory and material support, including both voluntary and mandatory reporting requirements, as well as a reporting infrastructure that includes clear and consistent case definitions that are reproducible across venues of care. In the United States, the National Notifiable Diseases Surveillance System (NNDSS) coordinates case definitions and reporting requirements for approximately 120 nationally notifiable diseases. A coherent and centralized reporting infrastructure such as that provided by NNDSS allows for a more global understanding of burden of disease and disease trends over time. However, case surveillance as described here remains dependent on close partnership with healthcare systems, clinical laboratories, and individual providers at a local level to ensure that these systems are both sensitive and specific. Case-based surveillance is also predicated on a good understanding of both the pathophysiology and available diagnostics for a specific disease. For newly emergent diseases, where a coherent case definition is less readily available, early warning systems seek to detect syndromic clusters that elude identification on routine diagnostics. Expansion of such programs in the wake of the 2019 SARS-CoV-2 pandemic have received governmental support and may use novel approaches such as wastewater screening and genomic sequencing within syndromic clusters.

In terms of tangible supplies that may be required for an acute response, personal protective equipment (PPE) and medical countermeasures (MCMs, e.g., vaccines, therapeutics) may be needed in high volume on short notice, at which point a "just in time" supply chain approach may prove lacking. Stockpiling of critical supply needs is a necessary part of pandemic preparedness, particularly with regard to high-risk, low-frequency, unpredictable events such as international travel of a patient with undiagnosed Ebola virus disease. For a longer-term outbreak or epidemic, such as that seen with the 2020 response to COVID-19, even the most aggressive stockpiling cannot support a protracted pandemic response, and close collaboration with manufacturers of durable medical supplies, therapeutics, and vaccines may be necessary to ensure sustained availability and a flexible supply chain.

Lastly, healthcare capacity is a separate but critically important resource with concrete limits (e.g., total bed spaces, provider person-days, and critical care and ventilator availability). In responding to the exponential growth of a rapidly reproducing pathogen, hospital capacity may be rapidly overwhelmed, as seen in some early surges of COVID-19 in 2020. Infrastructure planning for healthcare systems can help alleviate some of these pressures through rapidly accessible, flexible patient care space normally kept in reserve and through thoughtful capacity management, such as plans that allow for restriction of elective or nonemergent care for short periods. Ultimately, such efforts need to be matched with public-facing interventions described later, which can "flatten the curve" of epidemic transmission.

Response

Pandemic response begins with identification of the emergence of a specific risk (through surveillance systems described previously), followed by activation of applicable plans developed during the preparedness phase. Early pandemic response may be, by necessity, nonspecific to a known disease, particularly if the identification of risk is predicated on a syndromic cluster or a novel, not-yet-identified pathogen.

For novel pathogens, short-term goals will include rapid identification of the pathogen at a genus and species level, sequencing of its genome, development of accurate and readily available diagnostic tests, and development of targeted therapeutics and vaccines. As these individual targets may take weeks to months to come to fruition, early response will focus on mitigation of disease transmission through the application of standard public health measures, including social distancing, transmission-based precautions, isolation of cases, contact tracing, and quarantine of known contacts. All of these approaches occur simultaneously and require extensive public communication and education to ensure their effectiveness. **Social distancing** involves the temporary application of new social norms and social constructs designed to keep individuals, particularly those from separate households, physically distanced so that the likelihood of disease transmission between individuals is substantially reduced or eliminated. This may include infrastructural changes that promote contactless payment options at stores, physical barriers in offices and at public-facing service desks, and others. This distancing is assisted by application of **transmission-based precautions**, which are PPE recommendations based on the transmission modality of a specific pathogen. In non-healthcare settings, the most common application of PPE is facial masking designed to protect oral and nasal mucosa from diseases spread by droplets (e.g., influenza). **Isolation of cases** is a public health measure that strongly encourages or, depending on regulatory support, legally requires diagnosed cases of a specific disease to isolate for the duration of their period of infectivity, usually at home, in a healthcare setting, or at a designated isolation facility. After identification of a case, **contact tracing** should occur, during which identification of potential contacts of the known case (during the period of infectivity) is made. Completion of contact tracing involves notification of the affected contacts and a recommendation that they quarantine, typically for the duration of the upper bound of the incubation period for the disease. All of these responses require a large commitment in terms of time, personnel, and resources, and in a rapidly accelerating epidemic, these resources may ultimately be overwhelmed.

While these core public health responses are ongoing, rapid development of diagnostics, therapeutics, and vaccine candidates will continue. Of these, the earliest steps involve genomic sequencing and targeted diagnostics, the latter of which ultimately will greatly assist with consistent case definitions and subsequent contact tracing, isolation, and quarantine. The timeline for development of suitable vaccine candidates has greatly decreased in recent decades, with development of messenger RNA (mRNA) vaccine candidates during the COVID-19 pandemic being a hallmark example. Regulatory changes in timelines for vaccine assessment and approval for emergency use have assisted in these efforts, while not altering safety and efficacy oversight.

Recovery

Termination of pandemic response is rarely clear-cut, as elimination or eradication of specific pathogens from human population is rare. Most epidemic or pandemic responses end with a slow decrease in case counts and ultimate quiescence for a period (e.g., Ebola virus disease outbreaks) or the attainment of endemicity—the low-level constant circulation of a pathogen within remaining susceptible human hosts. Ultimately, transition from response to recovery is predicated on ongoing case counts, pressure on healthcare infrastructure, and an amalgamation of other metrics that may include test positivity, case severity, vaccine uptake, and hospitalization rates.

A core aspect of the recovery phase is an analysis of pandemic response measures as a whole, including their relative success, their tolerability, and their tangible and intangible costs. Future pandemic response, for the same and other pathogens, can be informed and improved by this analysis, typically developed in an after-action report or similar post hoc analytic framework.

Communication and Education

A core element of public health response to epidemic and pandemic disease, which spans across all four stances, is public communication and education. At each stage of pandemic preparedness and response, public engagement is key. This is particularly true in a response phase, where data become available rapidly and contradictory findings in early reports can cause confusion and mistrust. Clear, concise messaging

that focuses on core concepts of preparedness and response is key. A large portion of public health response may be spent in developing and promulgating this messaging, but it can be extremely worthwhile insofar as it can lead to dramatic increases in tolerability and uptake of other public health interventions, including social distancing, isolation and quarantine, and vaccines.

Viruses, bacteria, fungi, and other microbes are a fact of life on this earth and are an integral part of the biodiversity upon which we as humans depend. Although infectious diseases may also be a dependable fact of life, their broader societal impact can be shifted, reduced, and controlled in the ways described here. Pandemic preparedness and response can be difficult and time-consuming, but done well, with engaged partners at all levels, can be lifesaving on a societal level.

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Section 2

Preventive Measures

Chapter 215

Immunization Practices

Alexandra Kilinsky, Henry H. Bernstein, and Walter A. Orenstein

Immunization is one of the most beneficial and cost-effective disease prevention measures available. As a result of effective and safe vaccines, smallpox has been eradicated, polio is close to worldwide eradication, and measles and rubella are no longer endemic in the United States. However, cases of vaccine-preventable diseases, including measles, mumps, and pertussis, continue to occur in the United States. Incidence of most vaccine-preventable diseases of childhood has been reduced by ≥99% from representative 20th-century annual morbidity, usually before development of the corresponding vaccines (Table 215.1), with most of the newer vaccines not achieving quite the same percentage decrease (Table 215.2). An analysis of effective prevention measures recommended for widespread use by the U.S. Preventive Services Task Force (USPSTF) reported that childhood immunization received a perfect score based on clinically preventable disease burden and cost-effectiveness.

Immunization is the process of inducing immunity against a specific disease. Immunity can be induced either passively or actively. **Passive immunity** is generated through administration of an antibody-containing preparation. **Active immunity** is achieved by administering a vaccine or toxoid to stimulate the immune system to produce a prolonged humoral and/or cellular immune response. As of 2023, infants, children, and adolescents in the United States are recommended to be routinely immunized against **19 pathogens**: *Corynebacterium diphtheriae, Clostridium tetani, Bordetella pertussis,* polio virus, *Haemophilus influenzae* type b **(Hib)**, hepatitis A, hepatitis B, measles virus, mumps virus, rubella virus, rotavirus, varicella-zoster virus, SARS-CoV-2, pneumococcus, meningococcus, influenza virus, human papillomavirus **(HPV)**, and respiratory syncytial virus **(RSV)**.

PASSIVE IMMUNITY

Rather than producing antibodies through the body's own immune system, passive immunity is achieved by administration of preformed antibodies. Protection is immediate, yet transient, lasting weeks to months. Products used include:

- Immunoglobulin administered intramuscularly **(IMIG)**, intravenously **(IVIG)**, or subcutaneously **(SCIG)**
- Specific or hyperimmune immunoglobulin preparations administered IM or IV

Table 215.1 Comparison of 20th-Century Annual Morbidity and Current Morbidity: Vaccine-Preventable Diseases

DISEASE	20TH-CENTURY ANNUAL MORBIDITY*	2019 REPORTED CASES†	PERCENT DECREASE
Smallpox	29,005	0	100
Diphtheria	21,053	2	>99
Measles	530,217	1275	>99
Mumps	162,344	3780	98
Pertussis	200,752	18,617	91
Polio (paralytic)	16,316	0	100
Rubella	47,745	6	>99
Congenital rubella syndrome	152	1	>99
Tetanus	580	26	95
Haemophilus influenzae type b (Hib)	20,000	18‡	>99

*Data from Roush SW, Murphy TV; Vaccine-Preventable Disease Table Working Group. Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States. *JAMA*. 2007;298(18):2155–2163.

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‡Hib <5 yr of age. An additional 667 cases of *Haemophilus influenzae* invasive disease (<5 yr of age)—non-b serotype (213 cases), nontypeable (200 cases), and unknown serotype (254 cases)—are estimated to have occurred.

Table 215.2 Comparison of Pre–Vaccine Era Estimated Annual Morbidity with Current Estimate: Vaccine-Preventable Diseases

DISEASE	PRE–VACCINE ERA ANNUAL ESTIMATE*	2019 ESTIMATE (UNLESS OTHERWISE SPECIFIED)	PERCENT DECREASE
Hepatitis A	117,333*	18,846†	86
Hepatitis B (acute)	66,232*	3544†	95
Pneumococcus (invasive)			
All ages	63,067*	19,689†	69
<5yr of age	16,069*	1091†	93
Rotavirus (hospitalizations, <3yr of age)	62,500‡	30,625‖	51
Varicella	4,085,120*	8297†	>99

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- Antibodies of animal origin
- Monoclonal antibodies

Passive immunity also can be induced naturally through transplacental transfer of maternal antibodies (IgG) during gestation. This transfer can provide protection during an infant's first few months of life; other antibodies (IgA) are transferred to the infant during breastfeeding. Protection for some diseases can persist for as long as 1 year after birth, depending on the quantity of antibody transferred and the time until levels fall below those considered protective.

The major indications for inducing passive immunity are immunodeficiencies in children with B-lymphocyte defects who have difficulty making antibodies (e.g., hypogammaglobulinemia, secondary immunodeficiencies), who have exposure to infectious diseases or to imminent risk of exposure when there is inadequate time for them to develop an active immune response to a vaccine (e.g., newborn exposed to maternal hepatitis B), and who have infectious diseases that require antibody administration as part of the specific therapy (Table 215.3).

Intramuscular Immunoglobulin

Immunoglobulin is a sterile antibody-containing solution, usually derived through cold ethanol fractionation of large pools of human plasma from adults. Antibody concentrations reflect the infectious disease exposure and immunization experience of plasma donors. IMIG contains 15–18% protein and is predominantly IgG. Intravenous use of human IMIG is contraindicated. Immunoglobulin is not known to transmit infectious agents, including viral hepatitis and HIV. The major indications for immunoglobulin are:

- Replacement therapy for children with antibody deficiency disorders
- Measles prophylaxis
- Hepatitis A prophylaxis

For **replacement therapy**, the usual dose of IMIG is 100 mg/kg (equivalent to 0.66 mL/kg) monthly. The usual interval between doses is 2-4 weeks depending on trough IgG serum concentrations and clinical response. In practice, IVIG has replaced IMIG for replacement therapy.

IMIG can be used to prevent or modify **measles** if administered to susceptible children within 6 days of exposure (usual dose: 0.5 mL/kg body weight; maximum dose: 15 mL). The recommended dose of IVIG is 400 mL/kg. Data suggest that measles vaccine, if given within 72 hours of measles exposure, will provide protection in some cases to infants ≥6 months of age. Measles vaccine and immunoglobulin should not be administered at the same time.

Two methods are available for **postexposure prophylaxis** against **hepatitis A** depending on the patient's age: Children 6-11 months old should receive a dose of hepatitis A vaccine before international travel. However, the dose of hepatitis A vaccine received before 12 months should not be counted in determining compliance with the recommended two-dose schedule. In those 12 months to 40 years of age, hepatitis A immunization is preferred over immunoglobulin for postexposure prophylaxis and for protection of people traveling to areas where hepatitis A is endemic. Persons age >40 years, persons with immunocompromising conditions, and persons with chronic liver disease planning on traveling to an area with high or intermediate hepatitis A virus (HAV) endemicity should receive a single dose of hepatitis A vaccine as soon as travel is considered. Persons traveling in <2 weeks should receive the initial dose of hepatitis A vaccine and simultaneously may be administered immunoglobulin in a different anatomic injection site (e.g., separate limbs). A second dose of hepatitis A vaccine is not required for postexposure prophylaxis; however, for long-term immunity, the vaccination series should be completed with a second dose at least 6 months after the first dose.

The most common adverse reactions to immunoglobulin are pain and discomfort at the injection site and, less commonly, flushing, headache, chills, and nausea. Serious adverse events are rare and include chest pain, dyspnea, anaphylaxis, and systemic collapse. Immunoglobulin should *not* be administered to people with selective IgA deficiency who can produce antibodies against the trace amounts of IgA in immunoglobulin preparations and can develop reactions after repeat doses. These reactions can include fever, chills, and a shocklike syndrome. Because these reactions are rare, testing for selective IgA deficiencies is not recommended.

Intravenous Immunoglobulin

IVIG is a highly purified preparation of immunoglobulin antibodies prepared from adult plasma donors using alcohol fractionation and is

Table 215.3 Immunoglobulin and Animal Antisera Preparations

PRODUCT	MAJOR INDICATIONS
Intramuscular immunoglobulin (IMIG)	Replacement therapy in antibody-deficiency disorders Hepatitis A prophylaxis Measles prophylaxis Rubella prophylaxis (pregnant women)
Intravenous immunoglobulin (IVIG)	Replacement therapy in antibody-deficiency disorders Kawasaki disease Pediatric HIV infection Hypogammaglobulinemia in chronic B-lymphocyte lymphocytic leukemia Varicella postexposure prophylaxis Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy Toxic shock syndrome Postexposure measles prophylaxis for immunocompromised contacts May be useful in a variety of other conditions
Subcutaneous immunoglobulin (SCIG)	Treatment of patients with primary immunodeficiencies
Hepatitis B immunoglobulin (IM)	Postexposure prophylaxis Prevention of perinatal infection in infants born to hepatitis B surface antigen–positive mothers
Rabies immunoglobulin (IM)	Postexposure prophylaxis
Tetanus immunoglobulin (IM)	Wound prophylaxis Treatment of tetanus
Varicella-zoster immunoglobulin (VariZIG, IM)	Postexposure prophylaxis of susceptible people at high risk for complications from varicella
Cytomegalovirus (IV)	Prophylaxis of disease in seronegative transplant recipients
Vaccinia immunoglobulin (IV)	Reserved for certain complications of smallpox immunization and has no role in treatment of smallpox
Human botulism (IV), BabyBIG	Treatment of infant botulism
Diphtheria antitoxin, equine	Treatment of diphtheria
Heptavalent botulinum antitoxin against all seven (A-G) botulinum toxin types (BAT)	Treatment of noninfant food and wound botulism
Palivizumab (monoclonal antibody), humanized mouse (IM)	Prophylaxis for infants against respiratory syncytial virus (see Chapter 307)
Nirsevimab (monoclonal antibody) produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. (IM)	Passive immunization to prevent RSV-associated lower respiratory tract infection among infants and younger children (see Chapter 307)
Crotalidae immune F(ab')2 (equine)	Effective for viper and pit viper bites, including rattlesnakes, copperheads, moccasins

Data from Passive Immunization. In Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. Red Book: 2021–2024 Report of the Committee on Infectious Diseases, 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021. (Recommendations for use of specific immunoglobulins are located in the sections for specific diseases in Section 3 of *Red Book*.)

modified to allow IV use. IVIG is more than 95% IgG and is tested to ensure minimum antibody titers to *C. diphtheriae,* hepatitis B virus, measles virus, and poliovirus. Antibody concentrations against other pathogens vary widely among products and even among lots from the same manufacturer. Liquid and lyophilized powder preparations are available. IVIG does not contain thimerosal.

Not all IVIG products are approved by the U.S. Food and Drug Administration (FDA) for all indications. The major recommended FDA-approved indications for IVIG are:

- Replacement therapy for primary immunodeficiency disorders
- Kawasaki disease to prevent coronary artery abnormalities and shorten the clinical course
- Replacement therapy for prevention of serious bacterial infections in children infected with HIV
- Prevention of serious bacterial infections in people with hypogammaglobulinemia in chronic B-lymphocyte leukemia
- Immune-mediated thrombocytopenia to increase platelet count

IVIG may be helpful for patients with severe toxic shock syndrome, Guillain-Barré syndrome, and anemia caused by parvovirus B19. IVIG is also used for many other conditions based on clinical experience, such as multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19. IVIG may be used for varicella after exposure when varicella-zoster immunoglobulin is not available.

Reactions to IVIG may occur in up to 25% of patients. Some of these reactions appear to be related to the rate of infusion and can be mitigated by decreasing the rate. Such reactions include fever, headache, myalgia, chills, nausea, and vomiting. More serious reactions, including anaphylactoid events, thromboembolic disorders, aseptic meningitis, hemolytic anemia, and renal insufficiency, have rarely been reported. Renal failure occurs mainly in patients with preexisting renal dysfunction.

Specific or hyperimmune immunoglobulin preparations are derived from donors with high titers of antibodies to specific agents and are designed to provide protection against those agents (see Table 215.3).

Subcutaneous Immunoglobulin

(SCIG) is safe and effective in children and adults with primary immune deficiency disorders. Smaller doses administered weekly result in less fluctuation of serum IgG concentrations over time. Systemic reactions are less frequent than with IVIG, and the most common adverse effects of SCIG are injection site reactions. There are no data on administration of IMIG by the subcutaneous route.

Hyperimmune Animal Antisera Preparations

Animal antisera preparations are derived from horses. The immunoglobulin fraction is concentrated using ammonium sulfate, and some products are further treated with enzymes to decrease reactions to foreign proteins. The following two equine antisera preparations are available for humans (as of 2018):

- **Diphtheria antitoxin**, which can be obtained from the U.S. Centers for Disease Control and Prevention (CDC) (http://www.cdc.gov/diphtheria/dat.html) and is used to treat diphtheria.
- **Heptavalent botulinum antitoxin**, available from the CDC for use in adults with botulism. To request it, one can call the CDC's 24-hour line at 770-488-7100. This product contains antitoxin against all seven (A-G) botulinum toxin types.

Great care must be exercised before administering animal-derived antisera because of the potential for severe allergic reactions. Due caution includes testing for sensitivity before administration, desensitization if necessary, and treating potential reactions, including febrile events, serum sickness, and anaphylaxis. For infant botulism, IVIG (BabyBIG), a human-derived antitoxin, is licensed and should be used.

Monoclonal Antibodies

Monoclonal antibodies (mAbs) are antibody preparations produced against a single antigen. They are mass-produced from a hybridoma, a hybrid cell used as the basis for production of large amounts of antibodies. A hybridoma is created by fusing an antibody-producing B lymphocyte with a fast-growing immortal cell such as a cancer cell. There are two injectable monoclonal antibody products that help protect infants and young children from lower respiratory tract infection caused by RSV: nirsevimab and palivizumab. **Palivizumab** is used for prevention of severe disease from respiratory syncytial virus (RSV) among children ≤24 months old with bronchopulmonary dysplasia (BPD, a form of chronic lung disease), a history of premature birth, or congenital heart lesions or neuromuscular diseases. The American Academy of Pediatrics (AAP) has developed specific recommendations for the use of palivizumab. **Nirsevimab** is recommended for infants younger than 8 months of age who were born shortly before or are entering their first RSV season if the mother did not receive RSV vaccine (Abrysvo) during pregnancy, if the mother's RSV vaccination status is unknown, or the infant was born within 14 days of maternal RSV vaccination. Additionally, a dose of nirsevimab is recommended for some children 8 to 19 months of age who are at increased risk for severe RSV disease and entering their second RSV season. Given the atypical interseasonal change in RSV epidemiology in 2021-2023, the AAP strongly supports the use of palivizumab and nirsevimab in patients who would be candidates per the current eligibility recommendations. See https://publications.aap.org/redbook/resources/25379/ for details (see Chapter 307).

mAbs also are used to prevent transplant rejection and to treat some types of cancer, autoimmune diseases, and asthma. Use of mAbs against interleukin (IL)-2 and tumor necrosis factor (TNF)-α are being used as part of the therapeutic approach to patients with a variety of malignant and autoimmune diseases.

Serious adverse events associated with palivizumab are rare, primarily including cases of anaphylaxis and hypersensitivity reactions. Adverse reactions to nirsevimab are rare and mild to moderate in severity, including rash and injection site reactions. Adverse reactions to mAbs directed at modifying the immune response, such as antibodies against IL-2 or TNF-α, can be more serious and include cytokine release syndrome, fever, chills, tremors, chest pain, immunosuppression, and infection with various organisms, including mycobacteria.

ACTIVE IMMUNIZATION

Vaccines are defined as whole or parts of microorganisms administered to prevent an infectious disease. Vaccines can consist of whole inactivated microorganisms (e.g., polio, hepatitis A), parts of the organism (e.g., acellular pertussis, HPV, hepatitis B), polysaccharide capsules (e.g., pneumococcal and meningococcal polysaccharide vaccines), polysaccharide capsules conjugated to protein carriers (e.g., Hib, pneumococcal, and meningococcal conjugate vaccines), live-attenuated microorganisms (e.g., measles, mumps, rubella, varicella, rotavirus, and live-attenuated influenza vaccines), and toxoids (e.g., tetanus, diphtheria) (Table 215.4). In addition, vaccines against SARS-CoV-2 are messenger RNA (mRNA) vaccines, viral vector vaccines, or protein subunit vaccines. A **toxoid** is a bacterial toxin modified to be nontoxic but still capable of inducing an active immune response against the toxin.

Vaccines can contain a variety of other constituents besides the immunizing antigen. *Suspending* fluids may be sterile water or saline but can be a complex fluid containing small amounts of proteins or other constituents used to grow the immunobiologic culture. Preservatives, stabilizers, and antimicrobial agents are used to inhibit bacterial growth and prevent degradation of the antigen. Such components can include gelatin, 2-phenoxyethanol, and specific antimicrobial agents. Preservatives are added to multidose vials of vaccines, primarily to prevent bacterial contamination on repeated entry of the vial. In the past, many vaccines for children contained thimerosal, a preservative containing ethyl mercury. Removal of thimerosal as a preservative from vaccines for children began as a precautionary measure in 1999 in the absence of any data on harm from the preservative. This objective was accomplished by switching to single-dose packaging. Of the vaccines recommended for young children, only some preparations of influenza vaccine contain thimerosal as a preservative.*

Adjuvants are used in some vaccines to enhance the immune response. In the United States, the only adjuvants currently licensed by the FDA to be part of vaccines are **aluminum salts**: AsO_4, composed of 3-O-desacyl-4′-monophosphoryl 301 lipid A (MPL) adsorbed on to aluminum (as hydroxide salt) and MF59 and 1018 adjuvant. **AsO_4** is

*The thimerosal content in U.S.-licensed vaccines currently being manufactured is listed at http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/ucm096228.htm#pres.

Table 215.4 Currently Available* Vaccines and Immunizing Agents in the United States by Type

PRODUCT	TYPE
Adenovirus	Live, oral vaccine indicated for active immunization for the prevention of febrile acute respiratory disease caused by adenovirus types 4 and 7 for use in military populations 17-50 yr of age
Anthrax vaccine adsorbed	Cell-free filtrate of components including protective antigen
Bacille Calmette-Guérin (BCG) vaccine	Live-attenuated mycobacterial strain used to prevent tuberculosis in very limited circumstances
Cholera vaccine	Oral vaccine containing live-attenuated *Vibrio cholerae* CVD 103-HgR strain for protection against serogroup O1 in adults age 18-64 traveling to cholera-affected areas
COVID-19 vaccines	Two messenger mRNA-based: Comirnaty (Pfizer-BioNTech) and Spikevax (Moderna). A single adjuvanted, protein subunit-based vaccine, is a Novavax product.
Dengue vaccine	Tetravalent live-attenuated dengue virus (DENV) manufactured by Sanofi Pasteur Use in children age 9-16 yr, with laboratory-confirmed previous dengue virus infection and living in an area where dengue is endemic
Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine	Toxoids of diphtheria and tetanus and purified and detoxified components from *Bordetella pertussis*
DTaP–hepatitis B–inactivated polio vaccine (DTaP-HepB-IPV)	DTaP with hepatitis B surface antigen (HBsAg) produced through recombinant techniques in yeast with inactivated whole polioviruses
DTaP with IPV and *Haemophilus influenzae* type b (Hib) (DTaP-IPV/Hib)	DTaP with inactivated whole polioviruses and Hib polysaccharide conjugated to tetanus toxoid
DTaP with inactivated polio vaccine, *Haemophilus influenzae* type b, and hepatitis B (DTaP-IPV-Hib-HepB)	DTaP with inactivated whole polioviruses, Hib conjugate, and hepatitis B vaccine
DTaP and inactivated polio vaccine (DTaP-IPV)	DTaP with inactivated whole polioviruses
Ebola	Live, recombinant viral vector vaccine: backbone: vesicular stomatitis virus (VSV), with gene encoding for envelope glycoprotein of *Zaire ebolavirus*. Approved for individuals 18 yr of age and older as a single-dose administration.
Hib conjugate vaccine (Hib)	Polysaccharide conjugated to either tetanus toxoid or meningococcal group B outer membrane protein
Hepatitis A vaccine (HepA)	Inactivated whole virus
Hepatitis A–hepatitis B vaccine (HepA-HepB)	Combined hepatitis A and B vaccine
Hepatitis B vaccine (HepB)	HBsAg produced through recombinant techniques in yeast
Human papillomavirus vaccine 9-valent (9vHPV)	The L1 capsid proteins of HPV types 6 and 11 to prevent genital warts and types 16 18, 31, 33, 45, 52, and 58 to prevent cervical cancer (9vHPV)
Influenza virus vaccine inactivated (IIV†)	Available as quadrivalent inactivated formulations that contain hemagglutinin-derived influenza A(H1N1)pdm09 and influenza A(H3N2) components, along with two influenza B viruses (one from each Victoria and Yamagata lineage) Flucelvax is a cell-based inactivated quadrivalent vaccine
Influenza virus vaccine live-attenuated, intranasal (LAIV4)	Live-attenuated, temperature-sensitive, cold-adapted quadrivalent intranasal vaccine containing the hemagglutinin and neuraminidase genes from the wild strains reassorted to have the six other genes from the cold-adapted parent; recommended for 2-49 yr of age
Recombinant influenza vaccine (RIV4)	A quadrivalent formulation of influenza vaccine approved for persons 18 yr old and older
Japanese encephalitis vaccine	Purified, inactivated whole virus
Measles, mumps, rubella (MMR) vaccine	Live-attenuated viruses
Measles, mumps, rubella, varicella (MMRV) vaccine	Live-attenuated viruses
Meningococcal conjugate vaccine against serogroups A, C, W135, and Y (MenACWY)	Polysaccharide from each serogroup conjugated to diphtheria toxoid CRM_{197} protein
Meningococcal polysaccharide vaccine against serogroups A, C, W135, and Y (MPSV4)	Polysaccharides from each of the serogroups conjugated to diphtheria toxoid protein. No longer available in the United States.
Meningococcal B (MenB)	Recombinant proteins from serogroup B developed in *Escherichia coli*
Mpox vaccine	Live replication-deficient modified vaccinia Ankara vaccine
Pneumococcal conjugate vaccine (15, 20 valent PCV15, PCV20)	Pneumococcal polysaccharides conjugated to diphtheria toxin CRM_{197}, containing 15 and 20 pneumococcal serotypes, respectively. These serotypes accounted for >80% of invasive disease in young children before vaccine licensure
Pneumococcal polysaccharide vaccine (23 valent) (PPSV23)	Pneumococcal polysaccharides of 23 serotypes responsible for 85–90% of bacteremic disease in the United States
Poliomyelitis (inactivated, enhanced potency) (IPV)	Inactivated whole virus highly purified from monkey kidney cells, trivalent types 1, 2, and 3
Rabies vaccines (human diploid and purified chicken fibroblasts)	Inactivated whole virus
Respiratory syncytial virus vaccines	RSVPreF3 (Arexvy) and RSVpreF (Abrysvo). Both vaccines are recombinant protein vaccines and are currently approved as a single dose in adults ages 60 and older. Arexvy is adjuvanted. For pregnant women during RSV season, one dose of Abrysvo is recommended
RSV immunization	Human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

Table 215.4 Currently Available* Vaccines and Immunizing Agents in the United States by Type—cont'd

PRODUCT	TYPE
Rotavirus vaccines (RV5 and RV1)	Bovine rotavirus pentavalent vaccine (RV5), live reassortment attenuated virus, and human live-attenuated virus (RV1)
Smallpox vaccine	Vaccinia virus, an attenuated poxvirus that provides cross-protection against smallpox (variola)
Tetanus and diphtheria toxoids, adsorbed (Td, adult use)	Tetanus toxoid plus a reduced quantity of diphtheria toxoid compared with diphtheria toxoid used for children <7 yr of age
Tetanus and diphtheria toxoids adsorbed plus acellular pertussis (Tdap) vaccine	Tetanus toxoid plus a reduced quantity of diphtheria toxoid plus acellular pertussis vaccine to be used in adolescents and adults and in children 7-10 yr of age who have not been appropriately immunized with DTaP
Tickborne encephalitis vaccine	Whole tickborne-encephalitis virus (TBE) inactivated vaccine. Currently no ACIP/CDC recommendations available for this vaccine
Typhoid vaccine (polysaccharide)	Vi capsular polysaccharide of *Salmonella* Typhi Ty2 strain
Typhoid vaccine (oral)	Live-attenuated Ty21a strain of *S. typhi*
Varicella vaccine	Live-attenuated Oka/Merck strain
Yellow fever vaccine	Live-attenuated 17D-204 strain
Herpes zoster (shingles) vaccine	Zoster vaccine recombinant, adjuvanted (Shingrix) for use in adults ≥50 yr and in adults age 18 yr and older who are or will be at increased risk of herpes zoster because of immunodeficiency or immunosuppression caused by known disease or therapy

*As of November 2023.
†There are various types of inactivated flu vaccines—IIV4, ccIIV4, and aIIV4.
Data from U.S. Food and Drug Administration. Vaccines licensed for use in the United States. http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093833.tm.

found in one type of HPV vaccine, no longer available in the United States but still used in Europe. **MF59** is an oil-in-water emulsion found in one type of influenza vaccine approved for people ≥65 years old; it is also being studied in children. 1018 is an immunostimulatory sequence adjuvant used in HepB-CpG, a hepatitis B vaccine approved for persons >18 years. HepB-CpG contains yeast-derived recombinant hepatitis B surface antigen (HBsAg) and is prepared by combining purified HBsAg with small synthetic immunostimulatory cytidine-phosphate-guanosine oligodeoxynucleotide motifs. The 1018 adjuvant binds to toll-like receptor 9 to simulate a directed immune response to HBsAg. Vaccines with adjuvants should be injected deeply into muscle masses to avoid local irritation, granuloma formation, and necrosis associated with SC or intracutaneous administration.

Vaccines can induce immunity by stimulating antibody formation, cellular immunity, or both. Protection induced by most vaccines is thought to be mediated primarily by B lymphocytes, which produce antibodies. Such antibodies can inactivate toxins, neutralize viruses, and prevent their attachment to cellular receptors, facilitate phagocytosis and killing of bacteria, interact with complement to lyse bacteria, and prevent adhesion to mucosal surfaces by interacting with the bacterial cell surface.

Most B-lymphocyte responses require the assistance of CD4 helper T lymphocytes. These T-lymphocyte–dependent responses tend to induce high levels of functional antibody with high avidity. The T-dependent responses mature over time from primarily an IgM response to a persistent, long-term IgG response and induce immunologic memory that leads to enhanced responses on boosting. **T-lymphocyte–dependent vaccines**, which include protein moieties, induce good immune responses even in young infants. In contrast, polysaccharide antigens induce B-lymphocyte responses in the absence of T-lymphocyte help. These **T-lymphocyte–independent vaccines** are associated with poor immune responses in children <2 years old and with short-term immunity and absence of an enhanced or booster response on repeat exposure to the antigen. With some polysaccharide vaccines, repeat doses actually are associated with reduced responses, as measured by antibody concentrations, compared with first doses (i.e., *hyporesponsive*). To overcome problems with plain polysaccharide vaccines, polysaccharides have been **conjugated**, or covalently linked, to protein carriers, converting the vaccine to a T-lymphocyte–dependent vaccine. In contrast to plain polysaccharide vaccines, conjugate vaccines induce higher-avidity antibody, immunologic memory leading to booster responses on repeat exposure to the antigen, long-term immunity, and community protection by decreasing carriage of the organism (Table 215.5). As of 2023 in the United States, licensed conjugate vaccines are available to prevent Hib, pneumococcal, and meningococcal diseases.

Table 215.5 Characteristics of Polysaccharide and Conjugate Vaccines

CHARACTERISTIC	CONJUGATE	POLYSACCHARIDE
T-lymphocyte–dependent immune response	Yes	No
Immune memory	Yes	No
Persistence of protection	Yes	No
Booster effect	Yes	No
Reduction of carriage	Yes	No
Community protection	Yes	No
Lack of hyporesponsiveness	Yes	No

Serum antibodies may be detected as soon as 7-10 days after initial injection of antigen. Early antibodies are usually of the IgM class that can fix complement. IgM antibodies tend to decline as IgG antibodies increase. The IgG antibodies tend to peak approximately 1 month after vaccination and with most vaccines persist for some time after a primary vaccine course. Secondary or booster responses occur more rapidly and result from rapid proliferation of memory B and T lymphocytes.

Assessment of the immune response to most vaccines is performed by measuring serum antibodies. Although detection of serum antibody at levels considered protective after vaccination can indicate immunity, loss of detectable antibody over time does not necessarily mean susceptibility to disease. Some vaccines induce immunologic memory, leading to a booster or anamnestic response on exposure to the microorganism, with resultant protection from disease. In some cases, cellular immune response is used to evaluate the status of the immune system. Certain vaccines (e.g., acellular pertussis) do not have an accepted serologic correlate of protection.

Live-attenuated vaccines routinely recommended for children and adolescents include measles, mumps, and rubella **(MMR)**; MMR and varicella **(MMRV)**; rotavirus; and varicella. In addition, a cold-adapted, live-attenuated quadrivalent influenza vaccine **(LAIV4)** is available for influenza.

Live-attenuated vaccines tend to induce long-term immune responses. They replicate, often similarly to natural infections, until an immune response inhibits reproduction. Most live vaccines are administered in one-dose or two-dose schedules. The purpose of

repeat doses, such as a second dose of the MMR or MMRV vaccine, is to induce an initial immune response in those who failed to respond to the first dose. Because influenza viruses tend to mutate to evade preexisting immunity to prior strains, at least one of the strains in influenza vaccines each year is often different than in the previous year. Thus influenza vaccines are recommended to be administered yearly.

The remaining vaccines in the recommended schedule for children and adolescents are inactivated vaccines. **Inactivated vaccines** tend to require multiple doses to induce an adequate immune response and are more likely than live-attenuated vaccines to need booster doses to maintain that immunity. However, some inactivated vaccines appear to induce long-term or perhaps lifelong immunity after a primary series, including hepatitis B vaccine and inactivated polio vaccine.

VACCINATION SYSTEM IN THE UNITED STATES

Vaccine Production

Vaccine production is primarily a responsibility of private industry. Many of the vaccines recommended routinely for children are produced by only one vaccine manufacturer. Vaccines with multiple manufacturers include Hib, hepatitis B, rotavirus, MCV4 (meningococcal conjugate vaccine against serogroups A, C, W135, and Y), COVID-19 vaccine, diphtheria and tetanus toxoids and acellular pertussis (DTaP), and tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccines for adolescents and adults. Inactivated polio vaccine (IPV) as an IPV-only vaccine has only one manufacturer, but IPV is also available in combination products (DTaP–hepatitis B–IPV, DTaP–IPV/Hib, and DTaP–IPV) from different manufacturers. Influenza vaccine for children 6-35 months of age is produced by fewer manufacturers. MMR, MMRV, varicella, pneumococcal conjugate vaccines, and tetanus and diphtheria (Td) vaccines also are produced by single manufacturers. The FDA has authorized for emergency use the Pfizer-BioNTech and Moderna COVID-19 vaccines for the prevention of COVID-19 disease in individuals 6 months of age and older. The FDA has also authorized the Novavax COVID-19 vaccine for individuals 12 years of age and older.

Vaccine Policy

Two major committees make vaccine policy recommendations for children: the Committee on Infectious Diseases (COID) of the AAP (the *Red Book* Committee) and the Advisory Committee on Immunization Practices (ACIP) of the CDC. Annually, the AAP, ACIP, American Academy of Family Physicians (AAFP), American College of Obstetricians and Gynecologists (ACOG), American College of Nurse-Midwives (www.midwife.org), American Academy of Physician Assistants (www.aapa.org), and National Association of Pediatric Nurse Practitioners (www.napnap.org) issue a harmonized childhood and adolescent immunization schedule. (http://www.cdc.gov/vaccines/schedules/index.html). The ACIP recommendations (http://www.cdc.gov/vaccines/acip/recs/index.html) are official only after adoption by the CDC director, which leads to publication in the *Morbidity and Mortality Weekly Report (MMWR Morb Mortal Wkly Rep)*. The AAP recommendations are published in *Pediatrics* and the *Red Book*, which includes its continuously updated online version (aapredbook.org).

Vaccine Financing

Approximately 50% of vaccines routinely administered to children and adolescents <19 years of age are purchased through a contract negotiated by the federal government with licensed vaccine manufacturers. Three major sources of funds are available to purchase vaccines through this contract. The greatest portion comes from the **Vaccines for Children (VFC)** program (http://www.cdc.gov/vaccines/programs/vfc/index.html), a federal entitlement program established in 1993. The VFC program covers children receiving Medicaid, children without insurance (uninsured), and Native Americans and Alaska Natives. In addition, underinsured children whose insurance does not cover immunization can be covered through VFC, but only if they go to a federally qualified health center (http://www.cms.gov/center/fqhc.asp). In contrast to other public funding sources that require approval of discretionary funding by legislative bodies, VFC funds are immediately available for new recommendations. These funds are only available if the ACIP votes the vaccine and the recommendation for its use into the VFC program, the federal government negotiates a contract, and the Office of Management and Budget (OMB) apportions funds. The VFC program can provide free vaccines to participating private providers for administration to children eligible for coverage under the program. The second major federal funding source is the Section 317 **Discretionary Federal Grant Program** to states and selected localities. These funds must be appropriated annually by Congress, and in contrast to VFC, they do not have eligibility requirements for use. The third major public source of funds is **state appropriations**.

The VFC program itself does not cover vaccine administration costs. Medicaid covers the administration fees for children enrolled in the program. Parents of other children eligible for VFC must pay administration fees out of pocket, although the law stipulates that no one eligible for the program can be denied vaccines because of inability to pay the administration fee. The Affordable Care Act (ACA) states that all vaccines recommended by ACIP and those included in the harmonized annual immunization schedules must be provided by qualified insurance programs with no copay and no deductible. For eligible children and adults, the COVID-19 vaccine is free of charge. (https://www.cdc.gov/vaccines/programs-/bridge/index.html).

Vaccine Safety Monitoring

Monitoring vaccine safety is the responsibility of the FDA, CDC, and vaccine manufacturers. A critical part of that monitoring depends on reports provided to the **Vaccine Adverse Event Reporting System (VAERS)**, the country's early warning system for vaccine safety comanaged by the CDC and the FDA. Adverse events after immunization can be reported by completing a VAERS form, which can be obtained from http://www.vaers.hhs.gov, or by calling 800-822-7967. VAERS can rapidly detect safety signals and rare adverse events but is not designed to assess causality. Individual VAERS case reports may be helpful in identifying potential vaccine safety concerns that can generate hypotheses about whether vaccines are causing certain clinical syndromes. In general, however, the reports are not helpful in evaluating the causal role of vaccines in the adverse event, because most clinical syndromes that follow vaccination are similar to syndromes that occur in the absence of vaccination, which constitute background rates. For causality assessment, epidemiologic studies are often necessary, comparing the incidence rate of the adverse event after vaccination with the rate in unvaccinated individuals. A statistically significant higher rate in vaccinated individuals would be consistent with causation. **V-safe** is a smartphone-based tool that uses text messaging and web surveys to provide personalized health check-ins for up to a year after someone receives a COVID-19 vaccine. Through v-safe, COVID-19 vaccine recipients are able to communicate with the CDC regarding possible side effects (https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/pdfs/v-safe-information-sheet-508c.pdf).

The **Vaccine Safety Datalink** gathers data from nine participating integrated healthcare organizations on over 12 million people per year. It consists of inpatient and outpatient records of some of the largest managed-care organizations in the United States and facilitates causality evaluation. In addition, the **Clinical Immunization Safety Assessment (CISA)** network has been established to advise primary care physicians on evaluation and management of adverse events (http://www.cdc.gov/vaccinesafety/Activities/CISA.html). CISA facilitates the CDC's collaboration with a network of vaccine safety experts at seven leading academic medical centers and strengthens national capacity for vaccine safety monitoring and clinical research.

The Health and Medicine Division (HMD) of the National Academies of Sciences, Engineering and Medicine, previously the Institute of Medicine (IOM), has independently reviewed a variety of vaccine safety concerns and published reports summarizing its findings.* From 2001 through 2004, the IOM released eight reports, concluding that the body of epidemiologic evidence did not show an association between vaccines and autism. In 2012 the IOM (HMD) report *Adverse Effects of Vaccines: Evidence and Causality*** reviewed a list of reported adverse effects associated with eight vaccines to evaluate the scientific evidence, if any, of an event-vaccine relationship. The IOM committee had developed 158 causality conclusions and assigned each relationship between a vaccine and

* http://nationalacademies.org/hmd/Reports.aspx?filters=inmeta:activity=Immunization+Safety+Review.
** https://www.nap.edu/catalog/13164/adverse-effects-of-vaccines-evidence-and-causality

an adverse health problem to one of four causation categories. The committee concluded that available evidence convincingly supported a causal relationship between **anaphylaxis** and MMR, varicella-zoster, influenza, hepatitis B, meningococcal, and tetanus-containing vaccines. Additionally, the evidence *favored rejection* of five vaccine–adverse event relationships, including MMR vaccine and autism, inactivated influenza vaccines and asthma episodes and Bell palsy, and MMR and DTaP and type 1 diabetes mellitus. For the majority of cases (135 vaccine–adverse event pairs), the evidence was inadequate to accept or reject a causal relationship because of the rarity of the events. Overall, the committee concluded that few health problems are caused by or clearly associated with vaccines.

In 2013, the HMD released the report *Childhood Immunization Schedule and Safety: Stakeholder Concerns, Scientific Evidence, and Future Studies.*[†] The HMD uncovered no evidence of major safety concerns associated with adherence to the recommended childhood immunization schedule. The HMD specifically found no links between the immunization schedule and autoimmune diseases, asthma, hypersensitivity, seizures, child developmental disorders, learning or developmental disorders, or attention-deficit or disruptive disorders. Additionally, use of nonstandard schedules is harmful, because it increases the period of risk of acquiring vaccine-preventable diseases and increases the risk of incomplete immunization.[‡] In addition, the Agency for Healthcare Research and Quality (AHRQ) contracted with the Rand Corporation for an independent systematic review of the immunization schedule. That review concluded that although some vaccines are associated with serious adverse events, these events are extremely rare and must be weighed against the protective benefits that vaccines provide. The AAP has summarized the information on a variety of safety issues and different vaccines.[§]

The **National Vaccine Injury Compensation Program (VICP)** is designed to compensate people injured by vaccines in the childhood and adolescent immunization schedule. The program is funded through an excise tax of $0.75 on vaccines recommended by the CDC per disease prevented per dose (e.g., the quadrivalent influenza vaccine is taxed $0.75 because it prevents one disease; the MMR vaccine is taxed $2.25 because it prevents three diseases). As of 2023, this program covers all the routinely recommended vaccines that protect children against 16 diseases. The VICP was established to provide a no-fault system, with a table of related injuries and time frames. In April 2018 the table was modified to reflect changes in the 21st Century Cures Act, requiring that the VICP cover vaccines recommended for routine administration in pregnant women. All people alleging injury from covered vaccines must first file with the program. If the injury meets the requirements of the table, compensation is automatic. If not, the claimant has the responsibility to prove causality. If compensation is accepted, the claimant cannot sue the manufacturer or physician administering the vaccine. If the claimant rejects the judgment of the compensation system, the claimant can enter the tort system, which is uncommon. Information on the VICP is available at http://www.hrsa.gov/vaccinecompensation or by calling 800-338-2382. All vaccines included in the child and adolescent vaccine schedule are covered by VICP except dengue, PPSV23, and COVID-19 vaccines. COVID-19 vaccines that are authorized or approved by the FDA are covered by the Countermeasures Injury Compensation Program (CICP). For more information, see www.hrsa.gov/ vaccinecompensation or www.hrsa.gov/cicp. All physicians administering a vaccine covered by the program are required by law to give the approved **Vaccine Information Statement (VIS)** to the child's parent or guardian at each visit before administering vaccines. Information on the VIS can be obtained from http://www.cdc.gov/vaccines/hcp/vis/index.html. There is no VIS for COVID-19 vaccines authorized under an emergency use authorization (EUA). For each COVID-19 vaccine approved by the FDA, a Vaccine Information Fact Sheet for recipients and caregivers is available. The FDA also requires that recipients or their caregivers be provided with certain vaccine-specific information for any COVID vaccine authorized under an EUA to help make an informed decision about vaccination. This is accomplished by providing an EUA Fact Sheet for Recipients and Caregivers. The fact sheet is similar in purpose and content to VISs for licensed vaccines but differs in that the EUA fact sheet is specific to each authorized COVID-19 vaccine, is developed by the manufacturer of the vaccine, and is authorized by the FDA. EUA fact sheets are available at https://www.cdc.gov/vaccines/covid-19/eua/index.html.

[†] https://www.nap.edu/catalog/13563/the-childhood-immunization-schedule-and-safety-stakeholder-concerns-scientific-evidence.

[‡] For more information on the reports, see http://nationalacademies.org/hmd/Reports.aspx.

[§] https://www.healthychildren.org/English/safety-prevention/immunizations/Pages/Vaccine-Studies-Examine-the-Evidence.aspx.

Vaccine Delivery

To ensure potency, vaccines should be stored at recommended temperatures before and after reconstitution. A comprehensive resource for providers on vaccine storage and handling recommendations and best practice strategies is available (https://www.cdc.gov/vaccines/hcp/admin/storage/index.html). Expiration dates should be noted and expired vaccines discarded. Lyophilized vaccines often have long shelf lives. However, the shelf life of reconstituted vaccines generally is short, ranging from 30 minutes for varicella vaccine to 8 hours for MMR vaccine.

All vaccines have a preferred route of administration, which is specified in package inserts and in AAP and ACIP recommendations. Most inactivated vaccines, including DTaP, hepatitis A, hepatitis B, Hib, inactivated influenza vaccine (IIV), HPV, PCV, COVID-19 vaccines, MCV4, and Tdap, are administered IM. In contrast, the more commonly used live-attenuated vaccines (MMR, MMRV, and varicella) should be dispensed by the SC route. Rotavirus vaccine is administered orally. IPV and PPS23 (pneumococcal polysaccharide vaccine) can be given IM or SC. One influenza vaccine, LAIV4, when recommended, is administered intranasally. For IM injections, the anterolateral thigh muscle is the preferred site for infants and young children. The recommended needle length varies depending on age and size: ⅝ inch for newborn infants, 1 inch for infants 2-12 months old, and ⅝ to 1 inch for children 3-10 years of age. For adolescents and adults, the deltoid muscle of the arm is the preferred site for IM administration with needle lengths of 1-1¼ inches depending on patient size. Most IM injections can be made with 23- to 25-gauge needles. For SC injections, needle lengths generally range from ⅝ to ¾ inch with 23- to 25-gauge needles.

Additional aspects of immunization important for pediatricians and other healthcare providers are detailed on the websites listed in Table 215.6.

RECOMMENDED IMMUNIZATION SCHEDULE

All children in the United States should be immunized against 19 diseases (Fig. 215.1 and Table 215.7) (annually updated schedule available at http://www.cdc.gov/vaccines/schedules/index.html).

Hepatitis B vaccine (HepB) is recommended in a three-dose schedule starting at birth. The birth dose, as well as hepatitis B immunoglobulin, is critical for infants born to mothers who are HBsAg-positive or whose hepatitis B immune status is unknown. The recommendation is to administer the first hepatitis B vaccine to all newborns within 24 hours of birth, the second dose at 1-2 months, with a minimal interval between the first and second dose of 4 weeks, and the third dose from 6 to 18 months of age, ensuring that 8 weeks has passed between the second and third dose. If either the DTaP-HepB-IPV combination vaccine or the DTaP-IPV-Hib-HepB combination vaccine is used, a four-dose schedule is permissible, which includes the stand-alone hepatitis B vaccine at birth and the combination vaccine for the next three doses. There are multiple alternatives for catch-up vaccination with HepB vaccine depending on the child's age. See the immunization schedule notes for clarification.

The **DTaP** series consists of five doses administered at 2, 4, 6, and 15 through 18 months of age and 4 through 6 years of age. The fourth dose of DTaP may be administered as early as 12 months of age, provided at least 6 months have elapsed since the third dose. The fifth (booster) dose of DTaP vaccine is not necessary if the fourth dose was administered at 4 years or older. One dose of an adult preparation of Tdap is recommended for all adolescents 11 through 12 years of age, even if a dose of Tdap or DTaP was administered inadvertently or as part of the catch-up series at 7-9 years of age. If Tdap is administered at 10 years of age, an additional booster at 11-12 years of age is not recommended. Adolescents 13 through 18 years who missed the 11 through 12 year Tdap booster dose should receive a single dose of Tdap if they have completed the diphtheria, tetanus, and pertussis (DTP)/DTaP series. Tdap may be given at any interval after the last Td. Table 215.8 lists preparations in which DTaP is

Table 215.6 Vaccine Websites and Resources

ORGANIZATION	WEBSITE
HEALTH PROFESSIONAL ASSOCIATIONS	
American Academy of Family Physicians (AAFP)	http://www.familydoctor.org/online/famdocen/home.html
American Academy of Pediatrics (AAP)	http://www.aap.org/
American Academy of Physician Assistants (AAPA)	https://www.aapa.org
AAP Childhood Immunization Support Program	http://www.aap.org/immunization/
American Association of Occupational Health Nurses (AAOHN)	http://www.aaohn.org/
American Association of Nurse Practitioners (AANP)	https://www.aanp.org
American College Health Association (ACHA)	http://www.acha.org/
American College of Nurse-Midwives (ACNM)	https://www.midwife.org
American College of Obstetricians and Gynecologists (ACOG)–Immunization for Women	http://www.immunizationforwomen.org/
American Medical Association (AMA)	http://www.ama-assn.org/
American Nurses Association (ANA)	http://www.nursingworld.org/
American Pharmacists Association (APhA)	http://www.pharmacist.com/
American School Health Association (ASHA)	http://www.ashaweb.org/
American Travel Health Nurses Association (ATHNA)	http://www.athna.org/
Association for Professionals in Infection Control and Epidemiology (APIC)	http://www.apic.org/
Association of State and Territorial Health Officials (ASTHO)	http://www.astho.org/
Association of Teachers of Preventive Medicine (ATPM)	http://www.atpm.org/
National Medical Association (NMA)	http://www.nmanet.org/
Society of Teachers of Family Medicine—Group on Immunization Education	http://www.immunizationed.org/
NONPROFIT GROUPS AND UNIVERSITIES	
Albert B. Sabin Vaccine Institute	http://www.sabin.org/
Brighton Collaboration	https://brightoncollaboration.org/public
Center for Vaccine Awareness and Research—Texas Children's Center	http://www.texaschildrens.org/departments/immunization-project
Children's Vaccine Program	http://www.path.org/vaccineresources/
Every Child by Two (ECBT)	http://www.ecbt.org/
Families Fighting Flu	http://www.familiesfightingflu.org/
GAVI, the Vaccine Alliance	http://www.gavialliance.org/
Health on the Net Foundation (HON)	http://www.hon.ch/
Immunization Action Coalition (IAC)	http://www.immunize.org/
Infectious Diseases Society of America (IDSA)	http://www.idsociety.org/Index.aspx
Institute for Vaccine Safety (IVS), Johns Hopkins Bloomberg School of Public Health	http://www.vaccinesafety.edu/
National Academies: Health and Medicine Division	http://www.nationalacademies.org/hmd/
National Alliance for Hispanic Health	http://www.hispanichealth.org/
National Association of Certified Professional Midwives	https://nacpm.org
National Foundation for Infectious Diseases (NFID)	http://www.nfid.org
National Foundation for Infectious Diseases (NFID)—Childhood Influenza Immunization Coalition (CIIC)	http://www.preventchildhoodinfluenza.com/
National Network for Immunization Information (NNii)	http://www.immunizationinfo.net/
Parents of Kids with Infectious Diseases (PKIDS)	http://www.pkids.org/
PATH Vaccine Resource Library	http://www.path.org/resources/vaccine-resource-library-website
Vaccine Education Center at the Children's Hospital of Philadelphia	http://www.chop.edu/service/vaccine-education-center/home.html
Vaccinate Your Baby	http://www.vaccinateyourbaby.org/
GOVERNMENT ORGANIZATIONS	
Centers for Disease Control and Prevention (CDC)	
Advisory Committee on Immunization Practices (ACIP)	http://www.cdc.gov/vaccines/acip/index.html
ACIP Vaccine Recommendations	http://www.cdc.gov/vaccines/hcp/acip-recs/index.html
Current Vaccine Delays and Shortages	http://www.cdc.gov/vaccines/vac-gen/shortages/
Epidemiology and Prevention of Vaccine-Preventable Diseases (also known as the Pink Book)	https://www.cdc.gov/vaccines/pubs/pinkbook/index.html
Manual for the Surveillance of Vaccine-Preventable Diseases	www.cdc.gov/vaccines/pubs/surv-manual/index.html
Public Health Image Library	https://phil.cdc.gov/phil/home.asp
Travelers' Health	http://www.cdc.gov/travel/
CDC Health Information for International Travel (also known as the Yellow Book)	https://wwwnc.cdc.gov/travel/yellowbook/2016/table-of-contents
Vaccine Adverse Events Reporting System (VAERS)	http://www.cdc.gov/vaccinesafety/Activities/vaers.html
Vaccine Administration: Recommendations and Guidelines	http://www.cdc.gov/vaccines/recs/vac-admin/default.htm
Vaccines and Immunizations	http://www.cdc.gov/vaccines/
Vaccines for Children Program	http://www.cdc.gov/vaccines/programs/vfc/index.html
Vaccines for Children—Vaccine Price List	http://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/index.html
Vaccine Information Statements	www.cdc.gov/vaccines/hcp/vis/index.html

Table 215.6 Vaccine Websites and Resources—cont'd

ORGANIZATION	WEBSITE
Vaccine Safety	http://www.cdc.gov/vaccinesafety/index.html
Vaccine Storage and Handling	http://www.cdc.gov/vaccines/recs/storage/default.htm
Department of Health and Human Services (HHS)	
National Vaccine Program Office (NVPO)	http://www.hhs.gov/nvpo/
Health Resources and Services Administration	
National Vaccine Injury Compensation Program	http://www.hrsa.gov/vaccinecompensation/
National Institute of Allergy and Infectious Diseases (NIAID)	
Vaccines	https://www.niaid.nih.gov/about/vrc
World Health Organization (WHO)	
Immunization, Vaccines, and Biologicals	http://www.who.int/immunization/en/

Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger, United States, 2024

These recommendations must be read with the notes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars. To determine minimum intervals between doses, see the catch-up schedule (Table 215.7).

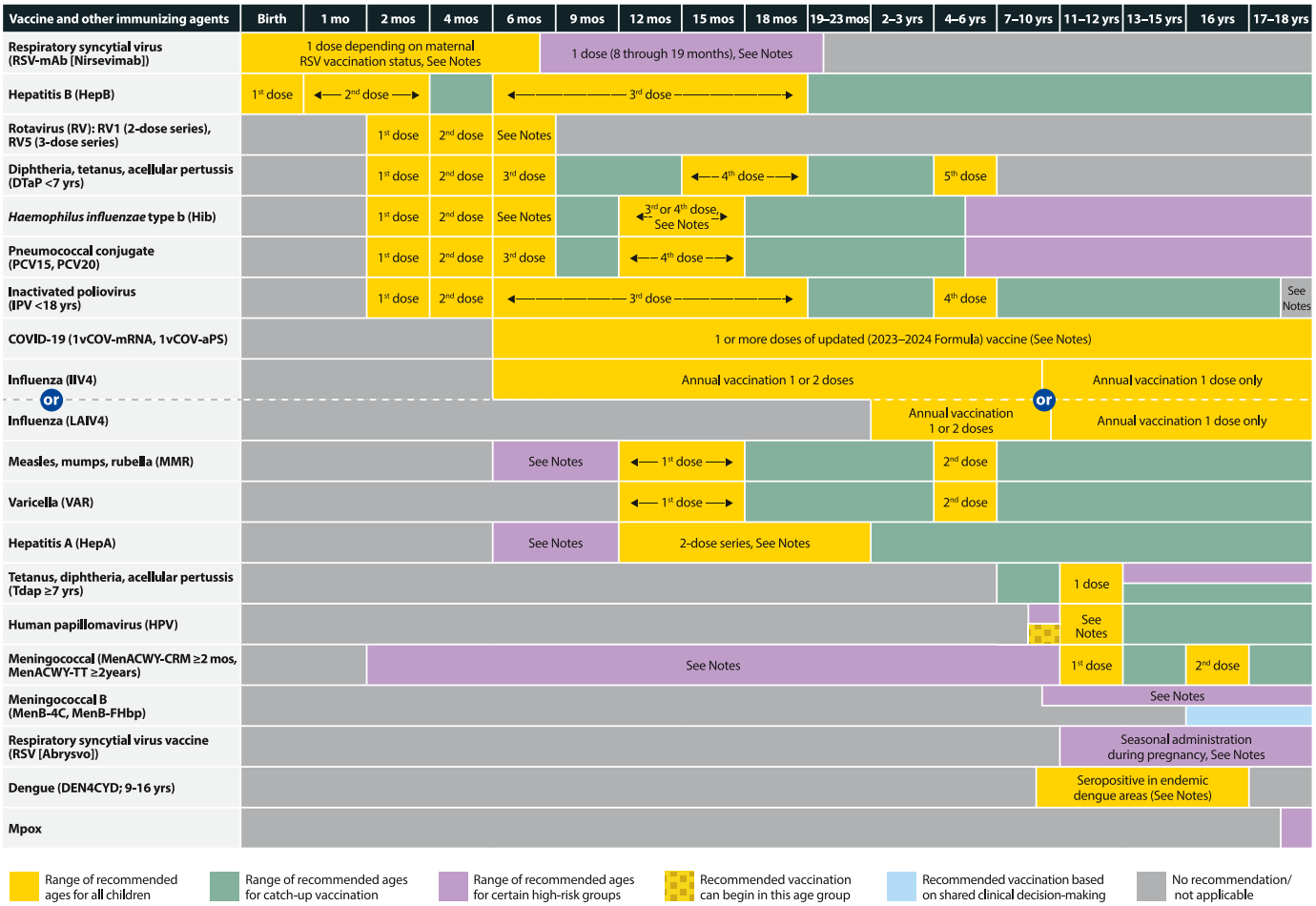

Fig. 215.1 Recommended immunization schedule for children and adolescents age 18 yr or younger—United States, 2024, including an appendix detailing contraindications and precautions for commonly used vaccines. *These recommendations must be read with the notes that follow.* For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the *green bars.* A new addendum section has been added to list any ACIP recommendations that occur by majority vote and are approved by CDC Director after the 2024 immunization schedules are approved and published. To determine minimum intervals between doses, see the Catch-Up Schedule (see Table 215.7). *(Courtesy U.S. Centers for Disease Control and Prevention, Atlanta, 2023. https://www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf; Appendix is adapted from the Advisory Committee on Immunization Practices [ACIP] General Best Practice Guidelines for Immunization: Contraindication and Precautions, Table 4-1, available at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html and from the ACIP's Recommendations for the Prevention and Control of 2023-24 seasonal influenza with vaccines available at www.cdc.gov/mmwr/volumes/71/rr/rr7101a1.htm.)*

Notes

For vaccination recommendations for persons ages 19 years or older, see the Recommended Adult Immunization Schedule, 2024.

Additional information

- For calculating intervals between doses, 4 weeks = 28 days. Intervals of ≥4 months are determined by calendar months.
- Within a number range (e.g., 12–18), a dash (–) should be read as "through."
- Vaccine doses administered ≤4 days before the minimum age or interval are considered valid. Doses of any vaccine administered ≥5 days earlier than the minimum age or minimum interval should not be counted as valid and should be repeated as age appropriate. **The repeat dose should be spaced after the invalid dose by the recommended minimum interval.** For further details, see Table 3-2, Recommended and minimum ages and intervals between vaccine doses, in *General Best Practice Guidelines for Immunization* at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/timing.html.
- Information on travel vaccination requirements and recommendations is available at www.cdc.gov/travel/.
- For vaccination of persons with immunodeficiencies, see Table 8-1, Vaccination of persons with primary and secondary immunodeficiencies, in *General Best Practice Guidelines for Immunization* at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html, and Immunization in Special Clinical Circumstances (In: Kimberlin DW, Barnett ED, Lynfield Ruth, Sawyer MH, eds. *Red Book: 2021–2024 Report of the Committee on Infectious Diseases*. 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021:72–86).
- For information about vaccination in the setting of a vaccine-preventable disease outbreak, contact your state or local health department.
- The National Vaccine Injury Compensation Program (VICP) is a no-fault alternative to the traditional legal system for resolving vaccine injury claims. All vaccines included in the child and adolescent vaccine schedule are covered by VICP except dengue, PPSV23, RSV, Mpox and COVID-19 vaccines. Mpox and COVID-19 vaccines are covered by the Countermeasures Injury Compensation Program (CICP). For more information, see www.hrsa.gov/vaccinecompensation or www.hrsa.gov/cicp.

COVID-19 vaccination (minimum age: 6 months [Moderna and Pfizer-BioNTech COVID-19 vaccines], 12 years [Novavax COVID-19 Vaccine])

Routine vaccination

Age 6 months–4 years

- **Unvaccinated:**
  - 2-dose series of updated (2023–2024 Formula) Moderna at 0, 4-8 weeks
  - 3-dose series of updated (2023–2024 Formula) Pfizer-BioNTech at 0, 3-8, 11-16 weeks
- **Previously vaccinated* with 1 dose of any Moderna:** 1 dose of updated (2023–2024 Formula) Moderna 4-8 weeks after the most recent dose.
- **Previously vaccinated* with 2 or more doses of any Moderna:** 1 dose of updated (2023–2024 Formula) Moderna at least 8 weeks after the most recent dose.
- **Previously vaccinated* with 1 dose of any Pfizer-BioNTech:** 2-dose series of updated (2023–2024 Formula) Pfizer-BioNTech at 0, 8 weeks (minimum interval between previous Pfizer-BioNTech and dose 1: 3-8 weeks).
- **Previously vaccinated* with 2 or more doses of any Pfizer-BioNTech:** 1 dose of updated (2023–2024 Formula) Pfizer-BioNTech at least 8 weeks after the most recent dose.

Age 5–11 years

- **Unvaccinated:** 1 dose of updated (2023–2024 Formula) Moderna or Pfizer-BioNTech vaccine.
- **Previously vaccinated* with 1 or more doses of Moderna or Pfizer-BioNTech:** 1 dose of updated (2023–2024 Formula) Moderna or Pfizer-BioNTech at least 8 weeks after the most recent dose.

Age 12–18 years

- **Unvaccinated:**
  - 1 dose of updated (2023–2024 Formula) Moderna or Pfizer-BioNTech vaccine
  - 2-dose series of updated (2023–2024 Formula) Novavax at 0, 3-8 weeks
- **Previously vaccinated* with any COVID-19 vaccine(s):** 1 dose of any updated (2023–2024 Formula) COVID-19 vaccine at least 8 weeks after the most recent dose.

Special situations

Persons who are moderately or severely immunocompromised**

Age 6 months–4 years

- **Unvaccinated:**
  - 3-dose series of updated (2023–2024 Formula) Moderna at 0, 4, 8 weeks
  - 3-dose series of updated (2023–2024 Formula) Pfizer-BioNTech at 0, 3, 11 weeks.
- **Previously vaccinated* with 1 dose of any Moderna:** 2-dose series of updated (2023–2024 Formula) Moderna at 0, 4 weeks (minimum interval between previous Moderna and dose 1: 4 weeks).
- **Previously vaccinated* with 2 doses of any Moderna:** 1 dose of updated (2023–2024 Formula) Moderna at least 4 weeks after the most recent dose.
- **Previously vaccinated* with 3 or more doses of any Moderna:** 1 dose of updated (2023–2024 Formula) Moderna at least 8 weeks after the most recent dose.
- **Previously vaccinated* with 1 dose of any Pfizer-BioNTech:** 2-dose series of updated (2023–2024 Formula) Pfizer-BioNTech at 0, 8 weeks (minimum interval between previous Pfizer-BioNTech and dose 1: 3 weeks).
- **Previously vaccinated* with 2 or more doses of any Pfizer-BioNTech:** 1 dose of updated (2023–2024 Formula) Pfizer-BioNTech at least 8 weeks after the most recent dose.

Age 5–11 years

- **Unvaccinated:**
  - 3-dose series of updated (2023–2024 Formula) Moderna at 0, 4, 8 weeks
  - 3-dose series updated (2023–2024 Formula) Pfizer-BioNTech at 0, 3, 7 weeks.
- **Previously vaccinated* with 1 dose of any Moderna:** 2-dose series of updated (2023–2024 Formula) Moderna at 0, 4 weeks (minimum interval between previous Moderna and dose 1: 4 weeks).
- **Previously vaccinated* with 2 doses of any Moderna:** 1 dose of updated (2023–2024 Formula) Moderna at least 4 weeks after the most recent dose.
- **Previously vaccinated* with 1 dose of any Pfizer-BioNTech:** 2-dose series of updated (2023–2024 Formula) Pfizer-BioNTech at 0, 4 weeks (minimum interval between previous Pfizer-BioNTech and dose 1: 3 weeks)
- **Previously vaccinated* with 2 doses of any Pfizer-BioNTech:** 1 dose of 2023–2024 Pfizer-BioNTech at least 4 weeks after the most recent dose.
  - **Prospectively:** Dose 4 may be administered as early as age 12 months if at least 6 months have elapsed since dose 3.
  - **Retrospectively:** A 4th dose that was inadvertently administered as early as age 12 months may be counted if at least 4 months have elapsed since dose 3.

Catch-up vaccination

- Dose 5 is not necessary if dose 4 was administered at age 4 years or older and at least 6 months after dose 3.
- For other catch-up guidance, see Table 2.

Special situations

- **Wound management** in children less than age 7 years with history of 3 or more doses of tetanus-toxoid-containing vaccine: For all wounds except clean and minor wounds, administer DTaP if more than 5 years since last dose of tetanus-toxoid-containing vaccine. For detailed information, see www.cdc.gov/mmwr/volumes/67/rr/rr6702a1.htm.

Haemophilus influenzae type b vaccination (minimum age: 6 weeks)

Routine vaccination

- **ActHIB®, Hiberix®, Pentacel®, or Vaxelis®:** 4-dose series (3-dose primary series at age 2, 4, and 6 months, followed by a booster dose* at age 12–15 months)
  - *Vaxelis® is not recommended for use as a booster dose. A different Hib-containing vaccine should be used for the booster dose.
- **PedvaxHIB®:** 3-dose series (2-dose primary series at age 2 and 4 months, followed by a booster dose at age 12–15 months)

Catch-up vaccination

- **Dose 1 at age 7–11 months:** Administer dose 2 at least 4 weeks later and dose 3 (final dose) at age12–15 months or 8 weeks after dose 2 (whichever is later).
- **Dose 1 at age 12–14 months:** Administer dose 2 (final dose) at least 8 weeks after dose 1.
- **Dose 1 before age 12 months and dose 2 before age 15 months:** Administer dose 3 (final dose) at least 8 weeks after dose 2.
- **2 doses of PedvaxHIB® before age 12 months:** Administer dose 3 (final dose) at age12–59 months and at least 8 weeks after dose 2.
- **1 dose administered at age 15 months or older:** No further doses needed
- **Unvaccinated at age 15–59 months:** Administer 1 dose.

- **Previously vaccinated* with 3 or more doses of any Moderna or Pfizer-BioNTech:** 1 dose of updated (2023–2024 Formula) Moderna or Pfizer-BioNTech at least 8 weeks after the most recent dose.

Age 12–18 years

- **Unvaccinated:**
  - 3-dose series of updated (2023–2024 Formula) Moderna at 0, 4, 8 weeks
  - 3-dose series of updated (2023–2024 Formula) Pfizer-BioNTech at 0, 3, 7 weeks
  - 2-dose series of updated (2023–2024 Formula) Novavax at 0, 3 weeks
- **Previously vaccinated* with 1 dose of any Moderna:** 2-dose series of updated (2023–2024 Formula) Moderna at 0, 4 weeks (minimum interval between previous Moderna dose and dose 1: 4 weeks).
- **Previously vaccinated* with 2 doses of any Moderna:** 1 dose of updated (2023–2024 Formula) Moderna at least 4 weeks after the most recent dose.
- **Previously vaccinated* with 1 dose of any Pfizer-BioNTech:** 2-dose series of updated (2023–2024 Formula) Pfizer-BioNTech at 0, 4 weeks (minimum interval between previous Pfizer-BioNTech dose and dose 1: 3 weeks).
- **Previously vaccinated* with 2 doses of any Pfizer-BioNTech:** 1 dose of updated (2023–2024 Formula) Pfizer-BioNTech at least 4 weeks after the most recent dose.
- **Previously vaccinated* with 3 or more doses of any Moderna or Pfizer-BioNTech:** 1 dose of any updated (2023–2024 Formula) COVID-19 vaccine at least 8 weeks after the most recent dose.
- **Previously vaccinated* with 1 or more doses of Janssen or Novavax or with or without dose(s) of any Original monovalent or bivalent COVID-19 vaccine:** 1 dose of any updated (2023–2024 Formula) COVID-19 vaccine at least 8 weeks after the most recent dose.

There is no preferential recommendation for the use of one COVID-19 vaccine over another when more than one recommended age-appropriate vaccine is available.

Administer an age-appropriate COVID-19 vaccine product for each dose. For information about transition from age 4 years to age 5 years or age 11 years to age 12 years during COVID-19 vaccination series, see Tables 1 and 2 at www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html#covid-vaccines.

Current COVID-19 schedule and dosage formulation available at www.cdc.gov/covidschedule. For more information on Emergency Use Authorization (EUA) indications for COVID-19 vaccines, see www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines

***Note:** Previously vaccinated is defined as having received any Original monovalent or bivalent COVID-19 vaccine (Janssen, Moderna, Novavax, Pfizer-BioNTech) prior to the updated 2023–2024 formulation.

****Note:** Persons who are moderately or severely immunocompromised have the option to receive one additional dose of updated (2023–2024 Formula) COVID-19 vaccine at least 2 months following the last recommended updated (2023–2024 Formula) COVID-19 vaccine dose. Further additional updated (2023–2024 Formula) COVID-19 vaccine dose(s) may be administered, informed by the clinical judgement of a healthcare provider and personal preference and circumstances. Any further additional doses should be administered at least 2 months after the last updated (2023–2024 Formula) COVID-19 vaccine dose. Moderately or severely immunocompromised children 6 months–4 years of age should receive homologous updated (2023–2024 Formula) mRNA vaccine dose(s) if they receive additional doses.

Dengue vaccination (minimum age: 9 years)

Routine vaccination

- Age 9–16 years living in areas with endemic dengue **AND** have laboratory confirmation of previous dengue infection
  - 3-dose series administered at 0, 6, and 12 months
- Endemic areas include Puerto Rico, American Samoa, US Virgin Islands, Federated States of Micronesia, Republic of Marshall Islands, and the Republic of Palau. For updated guidance on dengue endemic areas and pre-vaccination laboratory testing see www.cdc.gov/mmwr/volumes/70/rr/rr7006a1.htm?s_cid=rr7006a1_w and www.cdc.gov/dengue/vaccine/hcp/index.html
- Dengue vaccine should not be administered to children traveling to or visiting endemic dengue areas.

Diphtheria, tetanus, and pertussis (DTaP) vaccination (minimum age: 6 weeks [4 years for Kinrix® or Quadracel®])

Routine vaccination

- 5-dose series (3-dose primary series at age 2, 4, and 6 months, followed by a booster doses at ages 15–18 months and 4–6 years

Fig. 215.1, cont'd

- **Previously unvaccinated children age 60 months or older who are not considered high risk:** Do not require catch-up vaccination

For other catch-up guidance, see Table 2. Vaxelis® can be used for catch-up vaccination in children less than age 5 years. Follow the catch-up schedule even if Vaxelis® is used for one or more doses. For detailed information on use of Vaxelis® see www.cdc.gov/mmwr/volumes/69/wr/mm6905a5.htm.

Special situations

- **Chemotherapy or radiation treatment:**
  Age 12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

  Doses administered within 14 days of starting therapy or during therapy should be repeated at least 3 months after therapy completion.
- **Hematopoietic stem cell transplant (HSCT):**
  - 3-dose series 4 weeks apart starting 6 to 12 months after successful transplant, regardless of Hib vaccination history
- **Anatomic or functional asplenia (including sickle cell disease):**
  Age 12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

  Unvaccinated* persons age 5 years or older
  - 1 dose
- **Elective splenectomy:**
  Unvaccinated* persons age 15 months or older
  - 1 dose (preferably at least 14 days before procedure)
- **HIV infection:**
  Age 12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

  Unvaccinated* persons age 5–18 years
  - 1 dose
- **Immunoglobulin deficiency, early component complement deficiency:**
  Age 12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart

Special situations

- Revaccination is not generally recommended for persons with a normal immune status who were vaccinated as infants, children, adolescents, or adults.
- **Post-vaccination serology testing and revaccination** (if anti-HBs <10mIU/mL) is recommended for certain populations, including:
  - Infants born to HBsAg-positive mothers
  - Persons who are predialysis or on maintenance dialysis
  - Other immunocompromised persons
  - For detailed revaccination recommendations, see www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hepb.html.

Note: Heplisav-B and PreHevbrio are not recommended in pregnancy due to lack of safety data in pregnant persons

Human papillomavirus vaccination
(minimum age: 9 years)

Routine and catch-up vaccination

- HPV vaccination routinely recommended at **age 11–12 years (can start at age 9 years)** and catch-up HPV vaccination recommended for all persons through age 18 years if not adequately vaccinated
- 2- or 3-dose series depending on age at initial vaccination:
  - **Age 9–14 years at initial vaccination**: 2-dose series at 0, 6–12 months (minimum interval: 5 months; repeat dose if administered too soon)
  - **Age 15 years or older at initial vaccination**: 3-dose series at 0, 1–2 months, 6 months (minimum intervals: dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 12 weeks / dose 1 to dose 3: 5 months; repeat dose if administered too soon)
- No additional dose recommended when any HPV vaccine series **of any valency** has been completed using recommended dosing intervals.

Special situations

- **Immunocompromising conditions, including HIV infection:** 3-dose series, even for those who initiate vaccination at age 9 through 14 years.
- **History of sexual abuse or assault:** Start at age 9 years
- **Pregnancy:** Pregnancy testing not needed before vaccination; HPV vaccination not recommended until after pregnancy; no intervention needed if vaccinated while pregnant
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

Unvaccinated* = Less than routine series (through age 14 months) **OR no doses (age 15 months or older)

Hepatitis A vaccination
(minimum age: 12 months for routine vaccination)

Routine vaccination

- 2-dose series (minimum interval: 6 months) at age 12–23 months

Catch-up vaccination

- Unvaccinated persons through age 18 years should complete a 2-dose series (minimum interval: 6 months).
- Persons who previously received 1 dose at age 12 months or older should receive dose 2 at least 6 months after dose 1.
- Adolescents age 18 years or older may receive the combined HepA and HepB vaccine, **Twinrix®**, as a 3-dose series (0, 1, and 6 months) or 4-dose series (3 doses at 0, 7, and 21–30 days, followed by a booster dose at 12 months).

International travel

- Persons traveling to or working in countries with high or intermediate endemic hepatitis A (www.cdc.gov/travel/):
  - **Infants age 6–11 months**: 1 dose before departure; revaccinate with 2 doses (separated by at least 6 months) between age 12–23 months.
  - **Unvaccinated age 12 months or older**: Administer dose 1 as soon as travel is considered.

Hepatitis B vaccination
(minimum age: birth)

Routine vaccination

- 3-dose series at age 0, 1–2, 6–18 months **(use monovalent HepB vaccine for doses administered before age 6 weeks)**
  - Birth weight ≥2,000 grams: 1 dose within 24 hours of birth if medically stable
  - Birth weight <2,000 grams: 1 dose at chronological age 1 month or hospital discharge (whichever is earlier and even if weight is still <2,000 grams).
- Infants who did not receive a birth dose should begin the series as soon as possible (see Table 2 for minimum intervals).
- Administration of 4 doses is permitted when a combination vaccine containing HepB is used after the birth dose.
- **Minimum intervals (see Table 2):** when 4 doses are administered, substitute "dose 4" for "dose 3" in these calculations
- **Final (3rd or 4th) dose:** age 6–18 months **(minimum age 24 weeks)**
- **Mother is HBsAg-positive**
  - **Birth dose (monovalent HepB vaccine only):** administer **HepB vaccine** and **hepatitis B immune globulin (HBIG)** (in separate limbs) within 12 hours of birth, regardless of birth weight.
  - **Birth weight <2000 grams:** administer 3 additional doses of HepB vaccine beginning at age 1 month (total of 4 doses)
  - **Final (3rd or 4th) dose:** administer at age 6 months **(minimum age 24 weeks)**
  - Test for HBsAg and anti-HBs at age 9–12 months. If HepB series is delayed, test 1–2 months after final dose. Do not test before age 9 months.
- **Mother is HBsAg-unknown**

  If other evidence suggestive of maternal hepatitis B infection exists (e.g., presence of HBV DNA, HBeAg-positive, or mother known to have chronic hepatitis B infection), manage infant as if mother is HBsAg-positive
  - **Birth dose (monovalent HepB vaccine only):**
    - Birth weight ≥2,000 grams: administer **HepB vaccine** within 12 hours of birth. Determine mother's HBsAg status as soon as possible. If mother is determined to be HBsAg-positive, administer **HBIG** as soon as possible (in separate limb), but no later than 7 days of age.
    - Birth weight <2,000 grams: administer **HepB vaccine** and **HBIG** (in separate limbs) within 12 hours of birth. Administer 3 additional doses of **HepB vaccine** beginning at age 1 month (total of 4 doses)
  - **Final (3rd or 4th) dose:** administer at age 6 months **(minimum age 24 weeks)**
  - If mother is determined to be HBsAg-positive or if status remains unknown, test for HBsAg and anti-HBs at age 9–12 months. If HepB series is delayed, test 1–2 months after final dose. Do not test before age 9 months.

Catch-up vaccination

- Unvaccinated persons should complete a 3-dose series at 0, 1–2, 6 months. See Table 2 for minimum intervals
- Adolescents age 11–15 years may use an alternative 2-dose schedule with at least 4 months between doses (adult formulation **Recombivax HB®** only).
- Adolescents age 18 years may receive:
  - **Heplisav-B®:** 2-dose series at least 4 weeks apart
  - **PreHevbrio®:** 3-dose series at 0, 1, and 6 months
  - Combined HepA and HepB vaccine, **Twinrix®:** 3-dose series (0, 1, and 6 months) or 4-dose series (3 doses at 0, 7, and 21–30 days, followed by a booster dose at 12 months).

Influenza vaccination
(minimum age: 6 months [IIV], 2 years [LAIV4], 18 years [recombinant influenza vaccine, RIV4])

Routine vaccination

- Use any influenza vaccine appropriate for age and health status annually:
  - **Age 6 months–8 years** who have received **fewer** than 2 influenza vaccine doses before July 1, 2023, or whose influenza vaccination history is unknown: 2 doses, separated by at least 4 weeks. Administer dose 2 even if the child turns 9 years between receipt of dose 1 and dose 2.
  - **Age 6 months–8 years** who have received **at least** 2 influenza vaccine doses before July 1, 2023: 1 dose
  - **Age 9 years or older:** 1 dose
- For the 2023-2024 season, see www.cdc.gov/mmwr/volumes/72/rr/rr7202a1.htm.
- For the 2024–25 season, see the 2024–25 ACIP influenza vaccine recommendations.

Special situations

- **Close contacts (e.g., household contacts) of severely immunosuppressed persons who require a protected environment:** should not receive LAIV4. If LAIV4 is given, they should avoid contact with for such immunosuppressed persons for 7 days after vaccination.

Note: Persons with an egg allergy can receive any influenza vaccine (egg-based and non-egg-based) appropriate for age and health status.

Measles, mumps, and rubella vaccination
(minimum age: 12 months for routine vaccination)

Routine vaccination

- 2-dose series at age 12–15 months, age 4–6 years
- MMR or MMRV* may be administered

Note: For dose 1 in children age 12–47 months, it is recommended to administer MMR and varicella vaccines separately. MMRV* may be used if parents or caregivers express a preference.

Catch-up vaccination

- Unvaccinated children and adolescents: 2-dose series at least 4 weeks apart*
- The maximum age for use of MMRV* is 12 years.

Special situations

- **International travel**
  - **Infants age 6–11 months:** 1 dose before departure; revaccinate with 2-dose series at age 12–15 months (12 months for children in high-risk areas) and dose 2 as early as 4 weeks later.*
  - **Unvaccinated children age 12 months or older:** 2-dose series at least 4 weeks apart before departure*
- In mumps outbreak settings, for information about additional doses of MMR (including 3rd dose of MMR), see www.cdc.gov/mmwr/volumes/67/wr/mm6701a7.htm

***Note:** If MMRV is used, the minimum interval between MMRV doses is 3 months

Meningococcal serogroup A,C,W,Y vaccination
(minimum age: 2 months [MenACWY-CRM, Menveo], 2 years [MenACWY-TT, MenQuadfi]), 10 years [MenACWY-TT/MenB-FHbp, Penbraya])

Routine vaccination

- 2-dose series at age 11–12 years; 16 years

Catch-up vaccination

- Age 13–15 years: 1 dose now and booster at age 16–18 years (minimum interval: 8 weeks)
- Age 16–18 years: 1 dose

Special situations

Anatomic or functional asplenia (including sickle cell disease), HIV infection, persistent complement component deficiency, complement inhibitor (e.g., eculizumab, ravulizumab) use:

- **Menveo®***
  - Dose 1 at age 2 months: 4-dose series (additional 3 doses at age 4, 6, and 12 months)
  - Dose 1 at age 3–6 months: 3- or 4-dose series (dose 2 [and dose 3 if applicable] at least 8 weeks after previous dose until a dose is received at age 7 months or older, followed by an additional dose at least 12 weeks later and after age 12 months)
  - Dose 1 at age 7–23 months: 2-dose series (dose 2 at least 12 weeks after dose 1 and after age 12 months)
  - Dose 1 at age 24 months or older: 2-dose series at least 8 weeks apart
- **MenQuadfi®**
  - Dose 1 at age 24 months or older: 2-dose series at least 8 weeks apart

Fig. 215.1, cont'd

Travel to countries with hyperendemic or epidemic meningococcal disease, including countries in the African meningitis belt or during the Hajj (www.cdc.gov/travel/):

- Children less than age 24 months:
  - **Menveo®* (age 2–23 months)**
    - Dose 1 at age 2 months: 4-dose series (additional 3 doses at age 4, 6, and 12 months)
    - Dose 1 at age 3–6 months: 3- or 4-dose series (dose 2 [and dose 3 if applicable] at least 8 weeks after previous dose until a dose is received at age 7 months or older, followed by an additional dose at least 12 weeks later and after age 12 months)
    - Dose 1 at age 7–23 months: 2-dose series (dose 2 at least 12 weeks after dose 1 and after age 12 months)
- Children age 2 years or older: 1 dose Menveo®* or MenQuadfi®

First-year college students who live in residential housing (if not previously vaccinated at age 16 years or older) or military recruits:

- 1 dose **Menveo®*** or **MenQuadfi®**

Adolescent vaccination of children who received MenACWY prior to age 10 years:

- **Children for whom boosters are recommended** because of an ongoing increased risk of meningococcal disease (e.g., those with complement component deficiency, HIV, or asplenia): Follow the booster schedule for persons at increased risk.
- **Children for whom boosters are not recommended** (e.g., a healthy child who received a single dose for travel to a country where meningococcal disease is endemic): Administer MenACWY according to the recommended adolescent schedule with dose 1 at age 11–12 years and dose 2 at age 16 years.

**Menveo has two formulations: lyophilized and liquid. The liquid formulation should not be used before age 10 years. See www.cdc.gov/vaccines/vpd/mening/downloads/menveo-single-vial-presentation.pdf.*

Note: For MenACWY **booster dose recommendations** for groups listed under "Special situations" and in an outbreak setting and additional meningococcal vaccination information, see www.cdc.gov/mmwr/volumes/69/rr/rr6909a1.htm.

Children age 10 years or older may receive a single dose of Penbraya™ as an alternative to separate administration of MenACWY and MenB when both vaccines would be given on the same clinic day (see "Meningococcal serogroup B vaccination" section below for more information).

Meningococcal serogroup B vaccination
(minimum age: 10 years [MenB-4C, Bexsero®; MenB-FHbp, Trumenba®; MenACWY-TT/MenB-FHbp, Penbraya™])

Shared clinical decision-making

- **Adolescents not at increased risk** age 16–23 years (preferred age 16–18 years) based on shared clinical decision-making:
  - **Bexsero®:** 2-dose series at least 1 month apart
  - **Trumenba®:** 2-dose series at least 6 months apart (if dose 2 is administered earlier than 6 months, administer a 3rd dose at least 4 months after dose 2)

For additional information on shared clinical decision-making for MenB, see www.cdc.gov/vaccines/hcp/admin/downloads/isd-job-aid-scdm-mening-b-shared-clinical-decision-making.pdf

Special situations

Anatomic or functional asplenia (including sickle cell disease), persistent complement component deficiency, complement inhibitor (e.g., eculizumab, ravulizumab) use:

- **Bexsero®:** 2-dose series at least 1 month apart
- **Trumenba®:** 3-dose series at 0, 1–2, 6 months (if dose 2 was administered at least 6 months after dose 1, dose 3 not needed; if dose 3 is administered earlier than 4 months after dose 2, a 4th dose should be administered at least 4 months after dose 3)

Note: Bexsero® and **Trumenba®** are not interchangeable; the same product should be used for all doses in a series.

For MenB **booster dose recommendations** for groups listed under "Special situations" and in an outbreak setting and additional meningococcal vaccination information, see www.cdc.gov/mmwr/volumes/69/rr/rr6909a1.htm.

Children age 10 years or older may receive a dose of Penbraya™ as an alternative to separate administration of MenACWY and MenB when both vaccines would be given on the same clinic day. For age-eligible children not at increased risk, if Penbraya™ is used for dose 1 MenB, MenB-FHbp (Trumenba) should be administered for dose 2 MenB. For age-eligible children at increased risk of meningococcal disease, Penbraya™ may be used for additional MenACWY and MenB doses (including booster doses) if both would be given on the same clinic day **and** at least 6 months have elapsed since most recent Penbraya™ dose.

Mpox vaccination
(minimum age: 18 years [Jynneos®])

Special situations

- **Age 18 years and at risk for Mpox infection:** 2-dose series, 28 days apart.

  Risk factors for Mpox infection include:
  - Persons who are gay, bisexual, and other MSM, transgender or nonbinary people who in the past 6 months have had:
    - A new diagnosis of at least 1 sexually transmitted disease
    - More than 1 sex partner
    - Sex at a commercial sex venue
    - Sex in association with a large public event in a geographic area where Mpox transmission is occurring
  - Persons who are sexual partners of the persons described above
  - Persons who anticipate experiencing any of the situations described above
- **Pregnancy:** There is currently no ACIP recommendation for Jynneos use in pregnancy due to lack of safety data in pregnant persons. Pregnant persons with any risk factor described above may receive Jynneos.

For detailed information, see: www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-10-25-26/04-MPOX-Rao-508.pdf

Pneumococcal vaccination
(minimum age: 6 weeks [PCV15], [PCV 20]; 2 years [PPSV23])

Routine vaccination with PCV

- 4-dose series at 2, 4, 6, 12–15 months

Catch-up vaccination with PCV

- Healthy children ages 2–4 years with any incomplete* PCV series: 1 dose PCV
- For other catch-up guidance, see Table 2.

Note: For children **without** risk conditions, PCV20 is not indicated if they have received 4 doses of PCV13 or PCV15 or another age appropriate complete PCV series.

Special situations

Children and adolescents with cerebrospinal fluid leak; chronic heart disease; chronic kidney disease (excluding maintenance dialysis and nephrotic syndrome); chronic liver disease; chronic lung disease (including moderate persistent or severe persistent asthma); cochlear implant; or diabetes mellitus:

Age 2–5 years

- Any incomplete* PCV series with:
  - 3 PCV doses: 1 dose PCV (at least 8 weeks after the most recent PCV dose)
  - Less than 3 PCV doses: 2 doses PCV (at least 8 weeks after the most recent dose and administered at least 8 weeks apart)
- Completed recommended PCV series but have not received PPSV23
  - Previously received at least 1 dose of PCV20: no further PCV or PPSV23 doses needed
  - Not previously received PCV20: administer 1 dose PCV20 OR 1 dose PPSV23 administer at least 8 weeks after the most recent PCV dose.

Age 6–18 years

- Not previously received any dose of PCV13, PCV15, or PCV20: administer 1 dose of PCV15 or PCV20. If PCV15 is used and no previous receipt of PPSV23, administer 1 dose of PPSV23 at least 8 weeks after the PCV15 dose.**
- Received PCV before age 6 years but have not received PPSV23
  - Previously received at least 1 dose of PCV20: no further PCV or PPSV23 doses needed
  - Not previously received PCV20: 1 dose PCV20 OR 1 dose PPSV23 administer at least 8 weeks after the most recent PCV dose.
- Received PCV13 only at or after age 6 years: administer 1 dose PCV20 OR 1 dose PPSV23 at least 8 weeks after the most recent PCV13 dose.
- Received 1 dose PCV13 and 1 dose PPSV23 at or after age 6 years: no further doses of any PCV or PPSV23 indicated.

Children and adolescents on maintenance dialysis, or with immunocompromising conditions such as nephrotic syndrome; congenital or acquired asplenia or splenic dysfunction; congenital or acquired immunodeficiencies; diseases and conditions treated with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, Hodgkin disease, and solid organ transplant; HIV infection; or sickle cell disease or other hemoglobinopathies:

Age 2–5 years

- Any incomplete* PCV series:
  - 3 PCV doses: 1 dose PCV (at least 8 weeks after the most recent PCV dose)
  - Less than 3 PCV doses: 2 doses PCV (at least 8 weeks after the most recent dose and administered at least 8 weeks apart)
- Completed recommended PCV series but have not received PPSV23
  - Previously received at least 1 dose of PCV20: no further PCV or PPSV23 doses needed
  - Not previously received PCV20: administer 1 dose PCV20 OR 1 dose PPSV23 at least 8 weeks after the most recent PCV dose. If PPSV23 is used, administer 1 dose of PCV20 or dose 2 PPSV23 at least 5 years after dose 1 PPSV23.

Age 6–18 years

- Not previously received any dose of PCV13, PCV15, or PCV20: administer 1 dose of PCV15 or 1 dose of PCV20. If PCV15 is used and no previous receipt of PPSV23, administer 1 dose of PPSV23 at least 8 weeks after the PCV15 dose.**
- Received PCV before age 6 years but have not received PPSV23
  - Previously received at least 1 dose of PCV20: no additional dose of PCV or PPSV23
  - Not previously received PCV20: administer 1 dose PCV20 OR 1 dose PPSV23 at least 8 weeks after the most recent PCV dose. If PPSV23 is used, administer either PCV20 or dose 2 PPSV23 at least 5 years after dose 1 PPSV23.
- Received PCV13 only at or after age 6 years: administer 1 dose PCV20 OR 1 dose PPSV23 at least 8 weeks after the most recent PCV13 dose. If PPSV23 is used, administer 1 dose of PCV20 or dose 2 PPSV23 at least 5 years after dose 1 PPSV23.
- Received 1 dose PCV13 and 1 dose PPSV23 at or after age 6 years: administer 1 dose PCV20 OR 1 dose PPSV23 at least 8 weeks after the most recent PCV13 dose and at least 5 years after dose 1 PPSV23.

**Incomplete series* = Not having received all doses in either the recommended series or an age-appropriate catch-up series. See Table 2 in ACIP pneumococcal recommendations at stacks.cdc.gov/view/cdc/133252

***When both PCV15 and PPSV23 are indicated, administer all doses of PCV15 first. PCV15 and PPSV23 should not be administered during the same visit.*

For guidance on determining which pneumococcal vaccines a patient needs and when, please refer to the mobile app, which can be downloaded here: www.cdc.gov/vaccines/vpd/pneumo/hcp/pneumoapp.html

Poliovirus vaccination
(minimum age: 6 weeks)

Routine vaccination

- 4-dose series at ages 2, 4, 6–18 months, 4–6 years; administer the final dose on or after age 4 years and at least 6 months after the previous dose.
- 4 or more doses of IPV can be administered before age 4 years when a combination vaccine containing IPV is used. However, a dose is still recommended on or after age 4 years and at least 6 months after the previous dose.

Catch-up vaccination

- In the first 6 months of life, use minimum ages and intervals only for travel to a polio-endemic region or during an outbreak.
- **Adolescents age 18 years known or suspected to be unvaccinated or incompletely vaccinated:** administer remaining doses (1, 2, or 3 IPV doses) to complete a 3-dose primary series.* Unless there are specific reasons to believe they were not vaccinated, most persons aged 18 years or older born and raised in the United States can assume they were vaccinated against polio as children.

Series containing oral poliovirus vaccine (OPV), either mixed OPV-IPV or OPV-only series:

- Total number of doses needed to complete the series is the same as that recommended for the U.S. IPV schedule. See www.cdc.gov/mmwr/volumes/66/wr/mm6601a6.htm?s_%20cid=mm6601a6_w.
- Only trivalent OPV (tOPV) counts toward the U.S. vaccination requirements.
  - Doses of OPV administered before April 1, 2016, should be counted (unless specifically noted as administered during a campaign).
  - Doses of OPV administered on or after April 1, 2016, should not be counted.
  - For guidance to assess doses documented as "OPV," see www.cdc.gov/mmwr/volumes/66/wr/mm6606a7.htm?s_cid=mm6606a7_w.
- For other catch-up guidance, see Table 2.

Fig. 215.1, cont'd

Special situations

- **Adolescents aged 18 years at increased risk of exposure to poliovirus and completed primary series*:** may administer one lifetime IPV booster

***Note:** Complete primary series consist of at least 3 doses of IPV or trivalent oral poliovirus vaccine (tOPV) in any combination.

For detailed information, see: www.cdc.gov/vaccines/vpd/polio/hcp/recommendations.html

Respiratory syncytial virus immunization (minimum age: birth [Nirsevimab, RSV-mAb (Beyfortus™)]

Routine immunization

- **Infants born October – March in most of the continental United States***
  - Mother did not receive RSV vaccine OR mother's RSV vaccination status is unknown: administer 1 dose nirsevimab within 1 week of birth in hospital or outpatient setting
  - Mother received RSV vaccine **less than 14 days** prior to delivery: administer 1 dose nirsevimab within 1 week of birth in hospital or outpatient setting
  - Mother received RSV vaccine **at least 14 days** prior to delivery: nirsevimab not needed but can be considered in rare circumstances at the discretion of healthcare providers (see special populations and situations at www.cdc.gov/vaccines/vpd/rsv/hcp/child-faqs.html)
- **Infants born April–September in most of the continental United States***
  - Mother did not receive RSV vaccine OR mother's RSV vaccination status is unknown: administer 1 dose nirsevimab shortly before start of RSV season*
  - Mother received RSV vaccine **less than 14 days** prior to delivery: administer 1 dose nirsevimab shortly before start of RSV season*
  - Mother received RSV vaccine **at least 14 days** prior to delivery: nirsevimab not needed but can be considered in rare circumstances at the discretion of healthcare providers(see special populations and situations at www.cdc.gov/vaccines/vpd/rsv/hcp/child-faqs.html)

Infants with prolonged birth hospitalization** (e.g., for prematurity) discharged October through March should be immunized shortly before or promptly after discharge.

Special situations

- **Ages 8–19 months with chronic lung disease of prematurity requiring medical support (e.g., chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) any time during the 6-month period before the start of the second RSV season; severe immunocompromise; cystic fibrosis with either weight for length <10th percentile or manifestation of severe lung disease (e.g., previous hospitalization for pulmonary exacerbation in the first year of life or abnormalities on chest imaging that persist when stable)**:**
  - 1 dose nirsevimab shortly before start of second RSV season*
- **Ages 8–19 months who are American Indian or Alaska Native:**
  - 1 dose nirsevimab shortly before start of second RSV season*
- **Age-eligible and undergoing cardiac surgery with cardiopulmonary bypass**:** 1 additional dose of nirsevimab after surgery. For additional details see special populations and situations at www.cdc.gov/vaccines/vpd/rsv/hcp/child-faqs.html

***Note:** While the timing of the onset and duration of RSV season may vary, nirsevimab may be administered October through March in most of the continental United States. Providers in jurisdictions with RSV seasonality that differs from most of the continental United States (e.g., Alaska, jurisdiction with tropical climate) should follow guidance from public health authorities (e.g., CDC, health departments) or regional medical centers on timing of administration based on local RSV seasonality. Although optimal timing of administration is just before the start of the RSV season, nirsevimab may also be administered during the RSV season to infants and children who are age-eligible.

****Note:** Nirsevimab can be administered to children who are eligible to receive palivizumab. Children who have received nirsevimab should not receive palivizumab for the same RSV season.

For further guidance, see www.cdc.gov/mmwr/volumes/72/wr/mm7234a4.htm and www.cdc.gov/vaccines/vpd/rsv/hcp/child-faqs.html

Respiratory syncytial virus vaccination (RSV [Abrysvo™])

Routine vaccination

- **Pregnant at 32 weeks 0 days through 36 weeks and 6 days gestation from September through January in most of the continental United States*:** 1 dose RSV vaccine (Abrysvo™). Administer RSV vaccine regardless of previous RSV infection.
  - Either maternal RSV vaccination or infant immunization with nirsevimab (RSV monoclonal antibody) is recommended to prevent respiratory syncytial virus lower respiratory tract infection in infants.
- **All other pregnant persons:** RSV vaccine not recommended.

There is currently no ACIP recommendation for RSV vaccination in subsequent pregnancies. No data are available to inform whether additional doses are needed in later pregnancies.

***Note:** Providers in jurisdictions with RSV seasonality that differs from most of the continental United States (e.g., Alaska, jurisdiction with tropical climate) should follow guidance from public health authorities (e.g., CDC, health departments) or regional medical centers on timing of administration based on local RSV seasonality.

Rotavirus vaccination (minimum age: 6 weeks)

Routine vaccination

- **Rotarix®:** 2-dose series at age 2 and 4 months
- **RotaTeq®:** 3-dose series at age 2, 4, and 6 months
- If any dose in the series is either **RotaTeq®** or unknown, default to 3-dose series.

Catch-up vaccination

- Do not start the series on or after age 15 weeks, 0 days.
- The maximum age for the final dose is 8 months, 0 days.
- For other catch-up guidance, see Table 2.

Tetanus, diphtheria, and pertussis (Tdap) vaccination (minimum age: 11 years for routine vaccination, 7 years for catch-up vaccination)

Routine vaccination

- **Age 11–12 years:** 1 dose Tdap (adolescent booster)
- **Pregnancy:** 1 dose Tdap during each pregnancy, preferably in early part of gestational weeks 27–36.

Note: Tdap may be administered regardless of the interval since the last tetanus- and diphtheria-toxoid-containing vaccine.

Catch-up vaccination

- **Age 13–18 years who have not received Tdap:** 1 dose Tdap (adolescent booster)
- **Age 7–18 years not fully vaccinated* with DTaP:** 1 dose Tdap as part of the catch-up series (preferably the first dose); if additional doses are needed, use Td or Tdap.
- **Tdap administered at age 7–10 years:**
  - **Age 7–9 years** who receive Tdap should receive the adolescent Tdap booster dose at age 11–12 years.
  - **Age 10 years** who receive Tdap do not need the adolescent Tdap booster dose at age 11–12 years.
- **DTaP inadvertently administered on or after age 7 years**:
  - **Age 7–9 years**: DTaP may count as part of catch-up series. Administer adolescent Tdap booster dose at age 11–12 years.
  - **Age 10–18 years**: Count dose of DTaP as the adolescent Tdap booster dose.
- For other catch-up guidance, see Table 2.

Special situations

- **Wound management** in persons age 7 years or older with history of 3 or more doses of tetanus-toxoid-containing vaccine: For clean and minor wounds, administer Tdap or Td if more than 10 years since last dose of tetanus-toxoid-containing vaccine; for all other wounds, administer Tdap or Td if more than 5 years since last dose of tetanus-toxoid-containing vaccine. Tdap is preferred for persons age 11 years or older who have not previously received Tdap or whose Tdap history is unknown. If a tetanus-toxoid-containing vaccine is indicated for a pregnant adolescent, use Tdap.
- For detailed information, see www.cdc.gov/mmwr/volumes/69/wr/mm6903a5.htm.

**Fully vaccinated* = 5 valid doses of DTaP OR 4 valid doses of DTaP if dose 4 was administered at age 4 years or older*

Varicella vaccination (minimum age: 12 months)

Routine vaccination

- 2-dose series at age 12–15 months, 4–6 years
- VAR or MMRV may be administered*
- Dose 2 may be administered as early as 3 months after dose 1 (a dose inadvertently administered after at least 4 weeks may be counted as valid)

***Note**: For dose 1 in children age 12–47 months, it is recommended to administer MMR and varicella vaccines separately. MMRV may be used if parents or caregivers express a preference.

Catch-up vaccination

- Ensure persons age 7–18 years without evidence of immunity (see *MMWR* at www.cdc.gov/mmwr/pdf/rr/rr5604.pdf) have a 2-dose series:
  - **Age 7–12 years**: Routine interval: 3 months (a dose inadvertently administered after at least 4 weeks may be counted as valid)
  - **Age 13 years and older**: Routine interval: 4–8 weeks (minimum interval: 4 weeks)
  - The maximum age for use of *MMRV* is 12 years.

Fig. 215.1, cont'd

Appendix Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger, United States, 2024

Guide to Contraindications and Precautions to Commonly Used Vaccines

Vaccines and other Immunizing Agents	Contraindicated or Not Recommended[1]	Precautions[2]
COVID-19 mRNA vaccines [Pfizer-BioNTech, Moderna]	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a component of an mRNA COVID-19 vaccine[4]	• Diagnosed non-severe allergy (e.g., urticaria beyond the injection site) to a component of an mRNA COVID-19 vaccine[4]; or non-severe, immediate (onset less than 4 hours) allergic reaction after administration of a previous dose of an mRNA COVID-19 vaccine • Myocarditis or pericarditis within 3 weeks after a dose of any COVID-19 vaccine • Multisystem inflammatory syndrome in children (MIS-C) or multisystem inflammatory syndrome in adults (MIS-A) • Moderate or severe acute illness, with or without fever
COVID-19 protein subunit vaccine [Novavax]	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a component of a Novavax COVID-19 vaccine[4]	• Diagnosed non-severe allergy (e.g., urticaria beyond the injection site) to a component of Novavax COVID-19 vaccine[4]; or non-severe, immediate (onset less than 4 hours) allergic reaction after administration of a previous dose of a Novavax COVID-19 vaccine • Myocarditis or pericarditis within 3 weeks after a dose of any COVID-19 vaccine • Multisystem inflammatory syndrome in children (MIS-C) or multisystem inflammatory syndrome in adults (MIS-A) • Moderate or severe acute illness, with or without fever
Influenza, egg-based, inactivated injectable (IIV4)	• Severe allergic reaction (e.g., anaphylaxis) after previous dose of any influenza vaccine (i.e., any egg-based IIV, ccIIV, RIV, or LAIV of any valency) • Severe allergic reaction (e.g., anaphylaxis) to any vaccine component[3] (excluding egg)	• Guillain-Barré syndrome (GBS) within 6 weeks after a previous dose of any type of influenza vaccine • Moderate or severe acute illness with or without fever
Influenza, cell culture-based inactivated injectable (ccIIV4) [Flucelvax Quadrivalent]	• Severe allergic reaction (e.g., anaphylaxis) to any ccIIV of any valency, or to any component[3] of ccIIV4	• Guillain-Barré syndrome (GBS) within 6 weeks after a previous dose of any type of influenza vaccine • Persons with a history of severe allergic reaction (e.g., anaphylaxis) after a previous dose of any egg-based IIV, RIV, or LAIV of any valency. If using ccIV4, administer in medical setting under supervision of health care provider who can recognize and manage severe allergic reactions. May consult an allergist. • Moderate or severe acute illness with or without fever
Influenza, recombinant injectable (RIV4) [Flublok Quadrivalent]	• Severe allergic reaction (e.g., anaphylaxis) to any RIV of any valency, or to any component[3] of RIV4	• Guillain-Barré syndrome (GBS) within 6 weeks after a previous dose of any type of influenza vaccine • Persons with a history of severe allergic reaction (e.g., anaphylaxis) after a previous dose of any egg-based IIV, ccIIV, or LAIV of any valency. If using RIV4, administer in medical setting under supervision of health care provider who can recognize and manage severe allergic reactions. May consult an allergist. • Moderate or severe acute illness with or without fever
Influenza, live attenuated (LAIV4) [Flumist Quadrivalent]	• Severe allergic reaction (e.g., anaphylaxis) after previous dose of any influenza vaccine (i.e., any egg-based IIV, ccIIV, RIV, or LAIV of any valency) • Severe allergic reaction (e.g., anaphylaxis) to any vaccine component[3] (excluding egg) • Children age 2–4 years with a history of asthma or wheezing • Anatomic or functional asplenia • Immunocompromised due to any cause including, but not limited to, medications and HIV infection • Close contacts or caregivers of severely immunosuppressed persons who require a protected environment • Pregnancy • Cochlear implant • Active communication between the cerebrospinal fluid (CSF) and the oropharynx, nasopharynx, nose, ear or any other cranial CSF leak • Children and adolescents receiving aspirin or salicylate-containing medications • Received influenza antiviral medications oseltamivir or zanamivir within the previous 48 hours, peramivir within the previous 5 days, or baloxavir within the previous 17 days	• Guillain-Barré syndrome (GBS) within 6 weeks after a previous dose of any type of influenza vaccine • Asthma in persons age 5 years old or older • Persons with underlying medical conditions other than those listed under contraindications that might predispose to complications after wild-type influenza virus infection, e.g., chronic pulmonary, cardiovascular (except isolated hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus) • Moderate or severe acute illness with or without fever

1. When a contraindication is present, a vaccine should **NOT** be administered. Kroger A, Bahta L, Hunter P. ACIP General Best Practice Guidelines for Immunization.
2. When a precaution is present, vaccination should generally be deferred but might be indicated if the benefit of protection from the vaccine outweighs the risk for an adverse reaction. Kroger A, Bahta L, Hunter P. ACIP General Best Practice Guidelines for Immunization.
3. Vaccination providers should check FDA-approved prescribing information for the most complete and updated information, including contraindications, warnings, and precautions. See Package inserts for U.S.-licensed vaccines.
4. See package inserts and FDA EUA fact sheets for a full list of vaccine ingredients. mRNA COVID-19 vaccines contain polyethylene glycol (PEG).

Fig. 215.1, cont'd

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Vaccines and other Immunizing Agents	Contraindicated or Not Recommended[1]	Precautions[2]
Dengue (DEN4CYD)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] • Severe immunodeficiency (e.g., hematologic and solid tumors, receipt of chemotherapy, congenital immunodeficiency, long-term immunosuppressive therapy or patients with HIV infection who are severely immunocompromised) • Lack of laboratory confirmation of a previous Dengue infection	• Pregnancy • HIV infection without evidence of severe immunosuppression • Moderate or severe acute illness with or without fever
Diphtheria, tetanus, pertussis (DTaP)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] • For DTaP only: Encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures) not attributable to another identifiable cause within 7 days of administration of previous dose of DTP or DTaP	• Guillain-Barré syndrome (GBS) within 6 weeks after previous dose of tetanus-toxoid–containing vaccine • History of Arthus-type hypersensitivity reactions after a previous dose of diphtheria-toxoid–containing or tetanus-toxoid–containing vaccine; defer vaccination until at least 10 years have elapsed since the last tetanus-toxoid-containing vaccine • For DTaP only: Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, progressive encephalopathy; defer DTaP until neurologic status clarified and stabilized • Moderate or severe acute illness with or without fever
Haemophilus influenzae type b (Hib)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] • Less than age 6 weeks	• Moderate or severe acute illness with or without fever
Hepatitis A (HepA)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] including neomycin	• Moderate or severe acute illness with or without fever
Hepatitis B (HepB)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] including yeast • *Pregnancy: Heplisav-B and PreHevbrio are not recommended due to lack of safety data in pregnant persons. Use other hepatitis B vaccines if HepB is indicated*[4].	• Moderate or severe acute illness with or without fever
Hepatitis A-Hepatitis B vaccine (HepA-HepB) [Twinrix]	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] including neomycin and yeast	• Moderate or severe acute illness with or without fever
Human papillomavirus (HPV)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] • *Pregnancy: HPV vaccination not recommended.*	• Moderate or severe acute illness with or without fever
Measles, mumps, rubella (MMR) Measles, mumps, rubella, and varicella (MMRV)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] • Severe immunodeficiency (e.g., hematologic and solid tumors, receipt of chemotherapy, congenital immunodeficiency, long-term immunosuppressive therapy or patients with HIV infection who are severely immunocompromised) • Pregnancy • Family history of altered immunocompetence, unless verified clinically or by laboratory testing as immunocompetent	• Recent (≤11 months) receipt of antibody-containing blood product (specific interval depends on product) • History of thrombocytopenia or thrombocytopenic purpura • Need for tuberculin skin testing or interferon-gamma release assay (IGRA) testing • Moderate or severe acute illness with or without fever • For MMRV only: Personal or family (i.e., sibling or parent) history of seizures of any etiology
Meningococcal ACWY (MenACWY) MenACWY-CRM [Menveo] MenACWY-TT [MenQuadfi]	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] • For Men ACWY-CRM only: severe allergic reaction to any diphtheria toxoid—or CRM197—containing vaccine • For MenACWY-TT only: severe allergic reaction to a tetanus toxoid-containing vaccine	• For MenACWY-CRM only: Preterm birth if less than age 9 months • Moderate or severe acute illness with or without fever
Meningococcal B (MenB) MenB-4C [Bexsero] MenB-FHbp [Trumenba]	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3]	• Pregnancy • For MenB-4C only: Latex sensitivity • Moderate or severe acute illness with or without fever
Meningococcal ABCWY (MenACWY-TT/MenB-FHbp) [Penbraya]	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] • Severe allergic reaction to a tetanus toxoid-containing vaccine	• Moderate or severe acute illness, with or without fever
Mpox [Jynneos]	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3]	• Moderate or severe acute illness, with or without fever
Pneumococcal conjugate (PCV)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] • Severe allergic reaction (e.g., anaphylaxis) to any diphtheria-toxoid-containing vaccine or its component[3]	• Moderate or severe acute illness with or without fever
Pneumococcal polysaccharide (PPSV23)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3]	• Moderate or severe acute illness with or without fever
Poliovirus vaccine, inactivated (IPV)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3]	• Pregnancy • Moderate or severe acute illness with or without fever
RSV monoclonal antibody (RSV-mAb)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[5]	• Moderate or severe acute illness with or without fever
Respiratory syncytial virus vaccine (RSV)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3]	• Moderate or severe acute illness with or without fever
Rotavirus (RV) RV1 [Rotarix] RV5 [RotaTeq]	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] • Severe combined immunodeficiency (SCID) • History of intussusception	• Altered immunocompetence other than SCID • Chronic gastrointestinal disease • RV1 only: Spina bifida or bladder exstrophy • Moderate or severe acute illness with or without fever
Tetanus, diphtheria, and acellular pertussis (Tdap) Tetanus, diphtheria (Td)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] • For Tdap only: Encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures) not attributable to another identifiable cause within 7 days of administration of previous dose of DTP, DTaP, or Tdap	• Guillain-Barré syndrome (GBS) within 6 weeks after a previous dose of tetanus-toxoid–containing vaccine • History of Arthus-type hypersensitivity reactions after a previous dose of diphtheria-toxoid–containing or tetanus-toxoid–containing vaccine; defer vaccination until at least 10 years have elapsed since the last tetanus-toxoid–containing vaccine • For Tdap only: Progressive or unstable neurological disorder, uncontrolled seizures, or progressive encephalopathy until a treatment regimen has been established and the condition has stabilized • Moderate or severe acute illness with or without fever
Varicella (VAR)	• Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component[3] • Severe immunodeficiency (e.g., hematologic and solid tumors, receipt of chemotherapy, congenital immunodeficiency, long-term immunosuppressive therapy or patients with HIV infection who are severely immunocompromised) • Pregnancy • Family history of altered immunocompetence, unless verified clinically or by laboratory testing as immunocompetent	• Recent (≤11 months) receipt of antibody-containing blood product (specific interval depends on product) • Receipt of specific antiviral drugs (acyclovir, famciclovir, or valacyclovir) 24 hours before vaccination (avoid use of these antiviral drugs for 14 days after vaccination) • Use of aspirin or aspirin-containing products • Moderate or severe acute illness with or without fever • If using MMRV, see MMR/MMRV for additional precautions

1. When a contraindication is present, a vaccine should NOT be administered. Kroger A, Bahta L, Hunter P. ACIP General Best Practice Guidelines for Immunization. www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html
2. When a precaution is present, vaccination should generally be deferred but might be indicated if the benefit of protection from the vaccine outweighs the risk for an adverse reaction. Kroger A, Bahta L, Hunter P. ACIP General Best Practice Guidelines for Immunization. www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html
3. Vaccination providers should check FDA-approved prescribing information for the most complete and updated information, including contraindications, warnings, and precautions. Package inserts for U.S.-licensed vaccines are available at www.fda.gov/vaccines-blood-biologics/approved-products/vaccines-licensed-use-united-states.
4. For information on the pregnancy exposure registries for persons who were inadvertently vaccinated with Heplisav-B or PreHevbrio while pregnant, please visit heplisavbpregnancyregistry.com or www.prehevbrio.com/#safety.
5. Full prescribing information for BEYFORTUS (nirsevimab-alip) www.accessdata.fda.gov/drugsatfda_docs/label/2023/761328s000lbl.pdf

Fig. 215.1, cont'd

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Table 215.7 Recommended Catch-Up Immunization Schedule for Children and Adolescents Who Start Late or Who Are More than 1 Month Behind United States, 2024.*

VACCINE	MINIMUM AGE FOR DOSE 1	MINIMUM INTERVAL BETWEEN DOSES			
		DOSE 1 TO DOSE 2	DOSE 2 TO DOSE 3	DOSE 3 TO DOSE 4	DOSE 4 TO DOSE 5
CHILDREN AGE 4 MONTHS THROUGH 6 YEARS					
Hepatitis B	Birth	**4 weeks**	**8 weeks *and* at least 16 weeks after first dose** minimum age for the final dose is 24 weeks		
Rotavirus	6 weeks Maximum age for first dose is 14 weeks, 6 days.	**4 weeks**	**4 weeks** maximum age for final dose is 8 months, 0 days		
Diphtheria, tetanus, and acellular pertussis	6 weeks	**4 weeks**	**4 weeks**	**6 months**	**6 months** A fifth dose is not necessary if the fourth dose was administered at age 4 years or older ***and*** at least 6 months after dose 3
Haemophilus influenzae type b	6 weeks	**No further doses needed** if first dose was administered at age 15 months or older. **4 weeks** if first dose was administered before the 1st birthday. **8 weeks (as final dose)** if first dose was administered at age 12 through 14 months.	**No further doses needed** if previous dose was administered at age 15 months or older **4 weeks** if current age is younger than 12 months ***and*** first dose was administered at younger than age 7 months ***and*** at least 1 previous dose was PRP-T (ActHib®, Pentacel®, Hiberix®), Vaxelis® or unknown **8 weeks *and* age 12 through 59 months (as final dose)** if current age is younger than 12 months ***and*** first dose was administered at age 7 through 11 months; **OR** if current age is 12 through 59 months ***and*** first dose was administered before the 1st birthday ***and*** second dose was administered at younger than 15 months; **OR** if both doses were PedvaxHIB® and were administered before the 1st birthday	**8 weeks (as final dose)** This dose only necessary for children age 12 through 59 months who received 3 doses before the 1st birthday.	
Pneumococcal conjugate	6 weeks	**No further doses needed** for healthy children if first dose was administered at age 24 months or older **4 weeks** if first dose was administered before the 1st birthday **8 weeks (as final dose for healthy children)** if first dose was administered at the 1st birthday or after	**No further doses needed** for healthy children if previous dose was administered at age 24 months or older **4 weeks** if current age is younger than 12 months ***and*** previous dose was administered at <7 months old **8 weeks (as final dose for healthy children)** if previous dose was administered between 7–11 months (wait until at least 12 months old); **OR** if current age is 12 months or older ***and*** at least 1 dose was administered before age 12 months	**8 weeks (as final dose)** This dose is only necessary for children age 12 through 59 months regardless of risk, or age 60 through 71 months with any risk, who received 3 doses before age 12 months.	
Inactivated poliovirus	6 weeks	**4 weeks**	**4 weeks** if current age is <4 years**6 months (as final dose)** if current age is 4 years or older	**6 months (minimum age 4 years for final dose)**	

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Table 215.7 Recommended Catch-Up Immunization Schedule for Children and Adolescents Who Start Late or Who Are More than 1 Month Behind United States, 2024.*—cont'd

VACCINE	MINIMUM AGE FOR DOSE 1	MINIMUM INTERVAL BETWEEN DOSES			
		DOSE 1 TO DOSE 2	DOSE 2 TO DOSE 3	DOSE 3 TO DOSE 4	DOSE 4 TO DOSE 5
CHILDREN AGE 4 MONTHS THROUGH 6 YEARS					
Measles, mumps, rubella	12 months	**4 weeks**			
Varicella	12 months	**3 months**			
Hepatitis A	12 months	**6 months**			
Meningococcal ACWY	2 months MenACWY-CRM 2 years MenACWY-TT	**8 weeks**	See Notes	See Notes	
CHILDREN AND ADOLESCENTS AGE 7 THROUGH 18 YEARS					
Meningococcal ACWY	Not applicable (N/A)	**8 weeks**			
Tetanus, diphtheria; tetanus, diphtheria, and acellular pertussis	7 years	**4 weeks**	**4 weeks** if first dose of DTaP/DT was administered before the 1st birthday**6 months (as final dose)** if first dose of DTaP/DT or Tdap/Td was administered at or after the 1st birthday	**6 months** if first dose of DTaP/DT was administered before the 1st birthday	
Human papillomavirus	9 years	**Routine dosing intervals are recommended.**			
Hepatitis A	N/A	**6 months**			
Hepatitis B	N/A	**4 weeks**	**8 weeks *and* at least 16 weeks after first dose**		
Inactivated poliovirus	N/A	**4 weeks**	**6 months** A fourth dose is not necessary if the third dose was administered at age 4 years or older ***and*** at least 6 months after the previous dose.	A fourth dose of IPV is indicated if all previous doses were administered at <4 years **OR** if the third dose was administered <6 months after the second dose.	
Measles, mumps, rubella	N/A	**4 weeks**			
Varicella	N/A	**3 months** if younger than age 13 years. **4 weeks** if age 13 years or older			
Dengue	9 years	**6 months**	6 months		

*Always use this table in conjunction with Figure 215.1 and the notes that follow it.
This table provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the section appropriate for the child's age.
For vaccination recommendations for persons ages 19 yr or older, see the Recommended Adult Immunization Schedule, 2024 https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html.
Courtesy U.S. Centers for Disease Control and Prevention, Atlanta, Georgia. 2024. https://www.cdc.gov/vaccines/schedules/hcp/imz/catchup.html#table-catchup.

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combined with other vaccines. Either Td vaccine or Tdap can be used for the decennial Td booster, for tetanus prophylaxis in wound management, or for additional required doses in the catch-up immunization schedule if a person has received at least one Tdap dose. One dose of Tdap vaccine is recommended for pregnant adolescents with each pregnancy, preferably between 27 and 36 weeks of gestation, regardless of the time since the last Tdap or Td. Current available data suggest that vaccinating earlier in the 27- through 36-week period will maximize passive antibody transfer to the infant. This recommendation was made in response to data predicting lack of infant protection when maternal Tdap had been received before pregnancy.

There are three licensed preparations of single-antigen **Hib** vaccines. The two monovalent vaccines conjugated to tetanus toxoid (PRP-T) are each given in a four-dose series at 2, 4, 6, and 12 through 15 months of age. The third Hib vaccine is conjugated to meningococcal outer membrane protein (PRP-OMP) and is recommended in a three-dose series at 2, 4, and 12 through 15 months of age. There also are several vaccines in which Hib is a component, in addition to single-antigen Hib conjugate vaccines (see Tables 215.8 and 215.9).

Influenza vaccine is recommended for all children beginning at 6 months of age, with a minimum age of 6 months for IIVs and 24 months for LAIV4. Various influenza vaccine preparations are FDA-licensed for different age-groups.* Children 6 months through 8 years of age being vaccinated for the first time should receive two doses at least 4 weeks apart. If such children only received a single dose of IIV before July 1 of the current season, they need two doses. Children who have received two doses in a prior season only need one dose annually thereafter. For additional guidelines, follow dosing instructions in the influenza policy statements, which are updated annually by both the CDC (https://www.cdc.gov/flu/professionals/acip/index.htm) and AAP (aapredbook.org). Influenza vaccine usually is given in October or November, although there are benefits even when administered as late as February or March because influenza seasons most frequently peak in February. People ≥9 years old should receive one dose of influenza vaccine annually. LAIV4 is recommended for the 2023-2024 season. Because of limited use of LAIV4, there have been no effectiveness estimates in the United States. Data from other countries have demonstrated similar protection from LAIV4 to that of standard-dose, egg-based IIV in children. Although there are no reports of additional safety risks for LAIV4 in children with immunodeficiencies, anatomic or functional asplenia, cochlear implants, or active cerebrospinal fluid leaks, it is not recommended in these populations because the vaccine is a live attenuated product (see Table 215.7). For more information see https://pediatrics.aappublications.org/content/146/4/e2020024588

IPV should be administered at 2, 4, and 6 through 18 months of age with a booster dose at 4 through 6 years. The final dose in the series should be administered on or after 4 years of age and at least 6 months after the previous dose. Four or more doses of IPV can be administered before age 4 years when a combination vaccine containing IPV is used. The final dose in the IPV series should still be administered at 4 years or older regardless of the number of previous doses, and the minimal interval from dose 3 to dose 4 is 6 months. For series that contain oral polio vaccine (OPV), the total number of doses needed to complete the series is the same as that recommended for the U.S. IPV schedule. Only documentation specifying receipt of trivalent OPV constitutes proof of vaccination according to the U.S. polio vaccination recommendations. This is important because since April 2016, trivalent OPV (tOPV) is no longer available with the type 2 serotype removed. Thus children vaccinated since that time only received the type 1 and 3 components and are not immune to type 2. In contrast, IPV contains all three polio serotypes. Only IPV is available in the United States. One lifetime IPV booster should be considered for adolescents 18 years old who are at increased risk of exposure to poliovirus and completed IPV primary series. For catch-up vaccine recommendations, see the recommended childhood immunization schedule at http://www.cdc.gov/vaccines/schedules/hcp/imz/catchup.html (see Table 215.7).

MMR should be administered at 12 through 15 months of age followed by a second dose at 4 through 6 years. Before all international travel, infants 6 through 11 months of age should receive one dose of MMR vaccine. These children should be revaccinated with the routinely recommended two doses of MMR vaccine beginning at 12 months of age. For children 12 months or older, administer two doses before international travel; the second dose should be administered at least 4 weeks after the first dose.

Two doses of **varicella** vaccine should be given, the first at 12 through 15 months of age and the second at 4 through 6 years. The second dose may be administered before 4 years of age provided at least 3 months have elapsed since the first dose. MMR and MMRV preparations are available. Ensure persons age 7-18 years without evidence of immunity have a two-dose series. The **quadrivalent MMRV** vaccine is preferred in place of separate MMR and varicella vaccines at the 4- to 6-year-old visit. For dose 1 in children age 12-47 months, it is recommended to administer MMR and varicella vaccines separately because of the slight increase in febrile seizures associated with the combined MMRV vaccine compared with simultaneous administration of the separate products. MMRV may be used if parents or caregivers express a preference.

Protection against pneumococcal disease can be provided by either conjugated or polysaccharide vaccines. Conjugated vaccines offer several benefits over polysaccharide vaccines (see Table 215.5). A four-dose series of either PCV15 or 20 is recommended at 2, 4, 6, and 12 to 15 months of age. In the latest immunization schedule, PCV15 and 20 are referenced. Use of either pneumococcal conjugate vaccines is recommended for all children age 2–23 months according to currently recommended PCV dosing and schedules. References to the previously available thirteen-valent (PCV13) have been removed. For children without high risk conditions, PCV20 is not indicated if they have received four doses of PCV13 or PCV15 or another age-appopriate complete PCV series. For guidance on determining which pneumococcal vaccines a patient needs and when, a mobile app has been created. (www.cdc.gov/vaccines/vpd/pneumo/hcp/pneumoapp.html. PPSV23 is recommended for select children with conditions that place them at risk for pneumococcal disease. When both PCV and PPSV23 are indicated, administer PCV first. PCV and PPSV23 should be administered during the same visit.

A two-dose series of MCV4 includes a recommended dose for *all* adolescents at 11 through 12 years of age followed by a second dose at 16 years. If the first dose is administered at 13 through 15 years of age, a booster dose should be administered at 16-18 years. No booster dose is needed if the first dose is administered at 16 years. In addition, MCV4 should be administered to people 2 months through 55 years of age with underlying conditions that place them at high risk of meningococcal disease. There are two licensed quadrivalent meningococcal vaccines and one pentavalent vaccine that additionally provides coverage against serogroup B disease. Each vaccine has a different minimum age for beginning vaccination with that product. In addition to the quadrivalent meningoccal vaccine, two other vaccines provide coverage against serogroup B meningoccal disease. Two to three doses of the meningococcal B (MenB) vaccines are recommended for persons >10 years old at increased risk of meningococcal disease. Further, consideration should be given to adolsecents not at increased risk (16-23 years, preferred age 16-18 years) based on shared clinical decision making, which involves patients and families coming together to discuss the potential benefits of vaccination (https://www.cdc.gov/vaccines/hcp/admin/downloads/isd-job-aid-scdm-mening-b-shared-clinical-decision-making.pdf).

Children 10 years of age or older may receive a single dose of the quadrivalent vaccine as an alternative to separate administration of MenACWY and MenB when both vaccines would be given on the same clinic day. The two licensed MenB vaccine products are not interchangeable. MCV4 vaccines may be administered simultaneously with MenB vaccines if indicated, but at a different anatomic site if feasible.

Hepatitis A vaccine, licensed for administration to children ≥12 months old, is recommended for universal administration to all children at 12 through 23 months of age and for certain high-risk groups. The two doses in the series should be separated by at least 6 months.

* See http://www.cdc.gov/flu/protect/vaccine/vaccines.htm and http://aapredbook.aappublications.org/site/news/vaccstatus.xhtml#flu.

Table 215.8 Combination Vaccines Licensed and Available in the United States

VACCINE PRODUCT (MANUFACTURER)*	TRADE NAME (YR LICENSED)	COMPONENTS	RECOMMENDED AGES	
			PRIMARY SERIES	BOOSTER DOSE
DTaP-IPV/Hib (Sanofi Pasteur)	Pentacel (2008)	DTaP-IPV + PRP-T	2, 4, and 6 mo	15-18 mo
DTaP-HepB-IPV (GlaxoSmithKline)	Pediarix (2002)	DTaP + HepB + IPV	2, 4, and 6 mo	
DTap-HepB-IPV-Hib (MSP Vaccine Company)	Vaxelis (2020)	DTaP + HepB+ IPV + Hib	2, 4, and 6 mo	
DTaP-IPV	Kinrix (2008), Quadracel (2015)	DTaP + IPV		Kinrix: For use as the fifth dose of DTaP and the fourth dose of IPV in children age 4-6 yr Quadracel: For use as the fifth dose in the DTaP series and as the fourth or fifth dose in the IPV series in children 4-6 yr of age
HepA-HepB (GlaxoSmithKline)	Twinrix (2001)	HepA + HepB	>18 yr of age; 0, 1, and 6 mo schedule	
MMRV (Merck & Co)	ProQuad (2005)	MMR + varicella	†	4-6 yr

*Dash (-) indicates that products are supplied in their final form by the manufacturer and do not require mixing or reconstitution by user; slash (/) indicates that products are mixed or reconstituted by user.
†Although ProQuad is available for the first dose (at 12-15 mo of age), the CDC recommends that MMR vaccine and varicella vaccine be administered separately for the first dose in this age-group unless the parent or caregiver expresses a preference for MMRV vaccine.
DTaP, Diphtheria and tetanus toxoids and acellular pertussis vaccine; HepA, hepatitis A vaccine; HepB, hepatitis B vaccine; IPV/Hib, trivalent inactivated polio vaccine and *Haemophilus influenzae* type b vaccine; MMRV, measles-mumps-rubella and varicella vaccine, PRP-T, H. influenzae type b capsular polysaccharide (polyribosyl-ribitol279 phosphate [PRP]) covalently bound to tetanus toxoid (PRP-T).
Adapted from Cohn AC, MacNeil JR, Clark TA, et al. Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices. *MMWR*. 2013;62(2):1–28.

Table 215.9 Vaccines Recommended for Children and Adolescents with Underlying Conditions or at High Risk

VACCINES	SPECIAL SITUATIONS
Pneumococcal conjugate (and PPSV23 in certain conditions)	Cerebrospinal fluid leak Chronic heart disease Chronic kidney disease (excluding maintenance dialysis and nephrotic syndrome, which are included in immunocompromising conditions) Chronic liver disease Chronic lung disease (including moderate persistent or severe persistent asthma) Cochlear implant Diabetes mellitus Immunocompromising conditions (on maintenance dialysis or with nephrotic syndrome; congenital or acquired asplenia or splenic dysfunction; congenital or acquired immunodeficiencies; diseases and conditions treated with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, Hodgkin disease, and solid organ transplant; HIV infection; and sickle cell disease and other hemoglobinopathies)
MCV4	Anatomic or functional asplenia (including sickle cell disease) Persistent complement component deficiency Complement inhibitor use Residents of or travelers to countries in African meningitis belt or pilgrims on the Hajj During outbreaks caused by a vaccine serogroup First-year college students who live in residential housing (if not previously vaccinated at age 16 yr or older) or military recruits HIV infection
MenB	Anatomic or functional asplenia (including sickle cell disease) Children with persistent complement component deficiency Complement inhibitor use During outbreaks caused by a vaccine serogroup
Hib	In addition to routine Hib vaccine recommendations. Persons at increased risk for Hib disease, including chemotherapy recipients and those with anatomic or functional asplenia (including sickle cell disease), HIV infection, immunoglobulin deficiency, or early component complement deficiency Recipients of hematopoietic stem cell transplant (HSCT) Elective splenectomy
Hep B	In addition to routine Hep B vaccine recommendations; infants born to HBsAg-positive mothers or mothers whose HBsAg status is unknown (administer vaccine within 12 hr of birth)
HPV	In addition to routine HPV vaccine recommendations; immunocompromising conditions, including HIV infection History of sexual abuse or assault
Tetanus	Wound management recommendations exist based on age, number of prior doses of tetanus-toxoid-containing vaccine, and type of wound.

From Centers for Disease Control and Prevention. Child and adolescent schedule. https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html

Persons who previously received one dose at age 12 months or older should receive dose 2 at least 6 months after dose 1. Unvaccinated persons through age 18 years should complete a two-dose series with a minimum interval of 6 months. Adolescents age 18 years or older may receive the combined HepA and HepB vaccine. Immunity against hepatitis A infection is particularly important in people with chronic liver disease and clotting factor disorders, in men who have sex with men, in those who use injection or noninjection drugs, in people who are homeless, exposed to hepatitis A virus at work or travel, and those in close contact with international adoptees. Before all international travel, infants 6 through 11 months of age should receive one dose of hepatitis A vaccine. These children should be revaccinated with the routinely recommended two doses of hepatitis A vaccine beginning at 12 months of age. For unvaccinated children 12 months or older, administer dose 1 as soon as travel is considered. Preferably two doses should be administered before international travel to countries with high or intermediate endemic hepatitis A; the second dose should be administered at least 6 months after the first dose.

The **9vHPV** vaccine is recommended at age 11 or 12 years, although some advocate for routinely administering it as early as 9 years of age. Catch-up HPV vaccination is recommended for all persons through age 18 years if not adequately vaccinated. For those who initiate the series before their 15th birthday, the recommended schedule is two doses of 9vHPV vaccine. The minimum interval is 5 months between the first and second dose. If the second dose is given at a shorter interval, a third dose should be administered a minimum of 12 weeks after the second dose and a minimum of 5 months after the first dose. For those initiating the series on or after their 15th birthday, the recommended schedule is three doses of 9vHPV vaccine. The minimum intervals are 4 weeks between the first and second dose, 12 weeks between the second and third dose, and 5 months between the first and third dose. For children with a history of sexual abuse or assault, the ACIP recommends routine HPV vaccination beginning at age 9 years. In males and females with primary or secondary immunocompromising conditions such as B-lymphocyte deficiencies, T-lymphocyte complete or partial defects, HIV, malignancy, transplantation, autoimmune disease, or immunosuppressive therapy, the ACIP recommends vaccination with three doses of 9vHPV (0, 1-2, and 6 months) because immune response to vaccination might be attenuated. 9vHPV may be used to continue or complete a vaccination series in patients who started with 4vHPV or 2vHPV, though no additional doses are recommended after completing the series with recommended dosing intervals using any HPV vaccine. If the vaccination schedule is interrupted, the series does not need to be restarted. HPV vaccination is not recommended until after pregnancy, but no intervention is needed if vaccinated while pregnant. Pregnancy testing is not needed before vaccination.

Two **rotavirus** vaccines are available: RotaTeq (RV5) and Rotarix (RV1). With both vaccines, the first dose can be administered as early as 6 weeks of age. Do not start the series on or after age 15 weeks, 0 days. The RV5 vaccine is administered in three doses at least 4 weeks apart. The RV1 vaccine is administered in two doses at least 4 weeks apart. If any dose in the series is either RotaTeq or unknown, default to a three-dose series. The maximum age for the final dose is 8 months, 0 days as stated in the immunization schedule.

A dengue vaccine (Dengvaxia) was approved by the FDA in May 2019 for use in children age 9-16 years living in dengue-endemic territories **AND** having laboratory confirmation of *previous* dengue infection. It is a three-dose series administered at 0, 6, and 12 months. Endemic areas include Puerto Rico, American Samoa, U.S. Virgin Islands, Federated States of Micronesia, Republic of Marshall Islands, and the Republic of Palau. For updated guidance on dengue-endemic areas and pre-vaccination laboratory testing see https://apps.who.int/mediacentre/factsheets/fs117/en/index.html. Dengvaxia is not approved for use in U.S. travelers who are visiting but not living in an area where dengue is endemic. See https://www.aappublications.org/news/2020/05/01/mmwr050120 for more information.

For those that are 18 years of age or older and at risk for Mpox infection, 2 doses of the Mpox vaccine are recommended. See https://www.cdc.gov/poxvirus/mpox/interim-considerations/jynneos-vaccine.html#:~:text=JYNNEOS%20is%20approved%20for%20the,22)%3A734%2D742) for more information.

To prevent RSV in infants, one dose of nirsevimab is recommended for infants younger than 8 months of age who were born shortly before or are entering their first RSV season (typically fall through spring) if: (1) the mother did not receive RSV vaccine during pregnancy, (2) the mother's RSV vaccination status is unknown, or (3) the infant was born within 14 days of maternal RSV vaccination. Additionally, a dose of nirsevimab is recommended for some children 8 to 19 months of age who are at increased risk for severe RSV disease and entering their second RSV season (https://www.cdc.gov/mmwr/volumes/72/wr/mm7234a4.htm#suggestedcitation).

The present schedule, excluding influenza vaccine, can require as many as 41 doses. Of the doses, more than half are recommended before 2 years of age. Influenza vaccination, starting at age 6 months, can add an additional 20 injections through 18 years. To reduce the injection burdens, several combination vaccines are available (see Table 215.8).

The recommended childhood and adolescent immunization schedule establishes a routine adolescent visit at 11 through 12 years of age. MCV4, a Tdap booster, and 9vHPV vaccine should be administered during this visit in addition to the COVID-19 vaccine if the child is 12 years of age or older. Influenza vaccine should be administered annually. In addition, the 11- to 12-year-old visit is an opportune time to review all the immunizations the adolescent has received previously, to provide any doses that were missed, and to review other age-appropriate preventive services. The 11- to 12-year visit establishes an important platform for incorporating other vaccines. Information on the current status of new vaccine licensure and recommendations for use is available.*

For children who are at least 1 month behind in their immunizations, catch-up immunization schedules are available for children 4 months through 18 years of age (http://www.cdc.gov/vaccines/schedules/hcp/imz/catchup.html) (see Table 215.7). Interactive immunization schedules are available for children from birth through 18 years of age at https://www2a.cdc.gov/vaccines/childquiz/. Only written/electronic, dated, authentic records should be accepted as evidence of immunization. In general, when in doubt, a person with unknown or uncertain immunization status should be considered "disease susceptible," and recommended immunizations should be initiated without delay on a schedule commensurate with the person's current age. No evidence suggests that administration of vaccines to already-immune recipients is harmful. A new addendum section has been added to list any ACIP recommendations that occur by majority vote and are approved by CDC Director after the 2024 immunization schedules are approved and published.

VACCINES RECOMMENDED IN SPECIAL SITUATIONS

Eight vaccines—PCV, PPSV23, MCV4, MenB, Flu, Hib, HepA, and HepB—are recommended for children and adolescents at increased risk for complications from vaccine-preventable diseases or children who have an increased risk for exposure to these diseases who are outside the age-groups for which these vaccines are normally recommended (PPSV23 and MenB are not routinely recommended for any age-group of children and are only used for children with high-risk conditions; Fig. 215.2 and Table 215.9). Specific recommendations for use of these vaccines in children with underlying conditions can be found in the recommended immunization schedule.

PCV15 or **PCV20** is recommended for children 24-71 months of age with specialized risk conditions that place them at high risk for pneumococcal disease. This recommendation includes children with sickle cell disease and other hemoglobinopathies, including hemoglobin SS, hemoglobin S-C, or hemoglobin S–β-thalassemia,

* http://aapredbook.aappublications.org/site/news/vaccstatus.xhtml and http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM093833

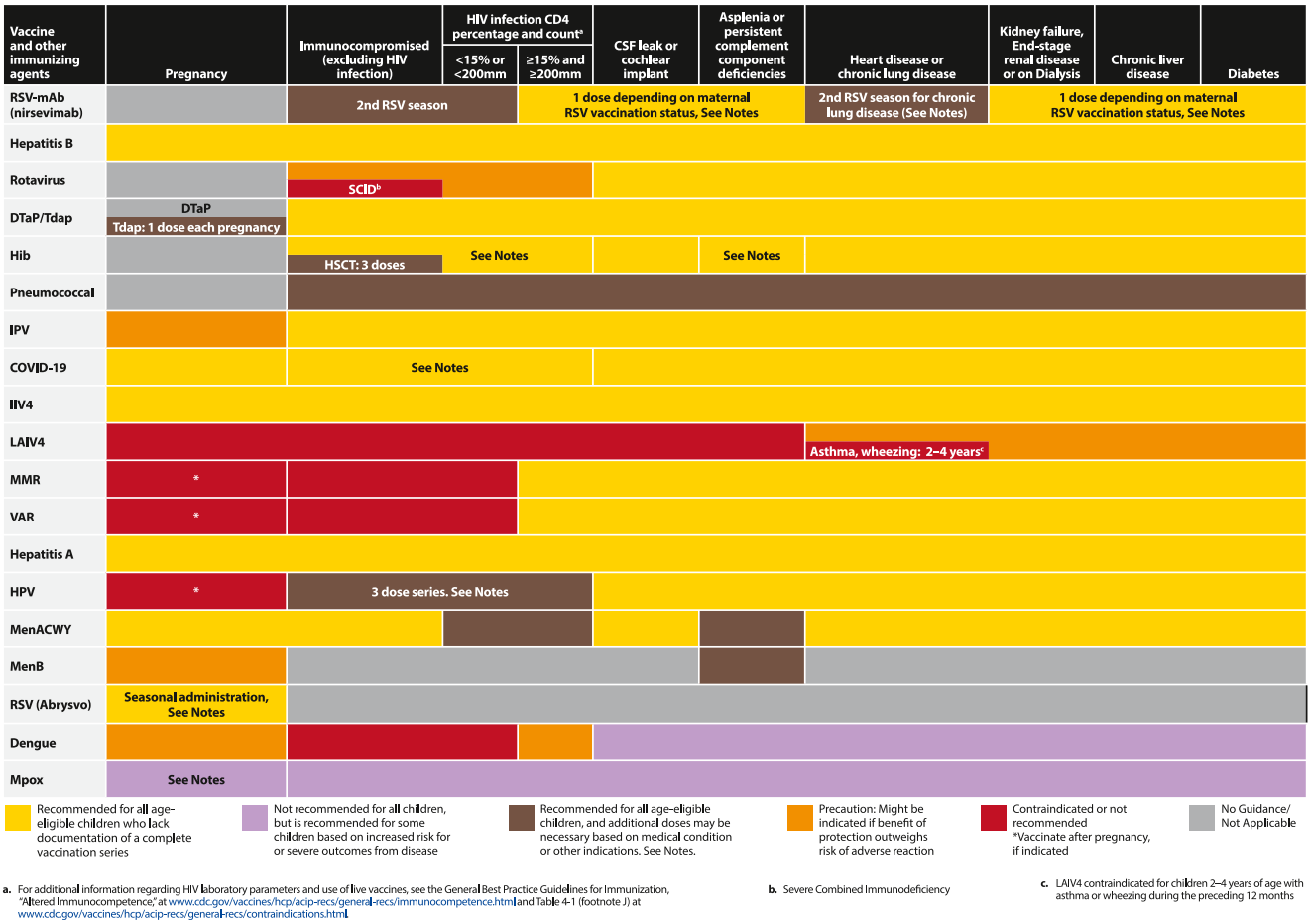

Fig. 215.2 Recommended child and adolescent immunization schedule by medical indication—United States, 2024. *Always use this figure in conjunction with Figure 215.1 and the notes that follow it. (Courtesy U.S. Centers for Disease Control and Prevention, Atlanta, Georgia. 2024. https://www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf.)*

or children who are functionally or anatomically asplenic; children with HIV infection; and children who have chronic disease (see Table 215.9 and Fig. 215.2). (For further recommendations on pneumococcal vaccine recommendations, see https://www.cdc.gov/vaccines/vpd/pneumo/hcp/who-when-to-vaccinate.html.)

Children at high risk for pneumococcal disease also should receive **PPSV23** to provide immunity to serotypes not contained in the 13- or 15-valent conjugate vaccine. PPSV23 should be administered on or after the second birthday and should follow completion of the PCV series by at least 8 weeks. Two doses of PPSV23 are recommended, with an interval of 5 years between doses. Immunization of children >5 years old with high-risk conditions can be performed with PCV15 or PCV20 and/or PPSV23, depending on the condition and vaccination history. When both PCV and PPSV23 are indicated, PCV should be administered first.

MCV4 is recommended for HIV-infected persons ≥2 months old, children with anatomic or functional asplenia (including sickle cell disease), children with persistent complement component deficiency (includes persons with inherited or chronic deficiencies in C3, C5-9, properdin, factor D, or factor H), or children taking a complement inhibitor (e.g., eculizumab or ravulizumab).

Meningococcal B (**MenB**) vaccine is recommended for persons ≥10 years old at increased risk of meningococcal disease. This includes people with complement deficiencies or anatomic or functional asplenia, people at increased risk because of serogroup B meningococcal disease outbreaks, and microbiologists who routinely are exposed to isolates of *Neisseria meningitidis*. Young adults age 16-23 (preferred range: 16-18 years) who are not at increased risk for meningococcal disease may be vaccinated with either of the two MenB vaccines, which are not interchangeable, to provide short-term protection against most strains of serogroup B meningococcal disease.

Hib vaccine and **HepA** vaccine are recommended for children with certain high-risk conditions. **HepB** is recommended for infants born to HBsAg-positive mothers or mothers whose HBsAg status is unknown (administer the vaccine within 12 hours of birth) (see Table 215.9).

In addition to vaccines in the recommended childhood and adolescent schedule, a variety of vaccines are available for children who will be **traveling** to areas of the world where certain infectious diseases are common (Table 215.10). Vaccines for travelers include typhoid fever, hepatitis A, hepatitis B, Japanese encephalitis, MCV4, cholera, rabies, and yellow fever, depending on the location and circumstances of travel. **Measles** is endemic in many parts of the world. Children 6-11 months old should receive a dose of MMR and hepatitis A vaccines before international travel outside of the United States. However, doses of MMR and hepatitis A vaccines received before 12 months should not be counted in determining compliance with the recommended two-dose MMR schedule. For unvaccinated children ≥12 months old, administer two doses before international travel following the recommended schedule. (Additional information on vaccines for international travel can be found at http://wwwnc.cdc.gov/travel/.)

Vaccine recommendations for children with **immunocompromising conditions**, either primary (inherited) or secondary (acquired), vary according to the underlying condition, the degree of immune deficit, the risk for exposure to disease, and the vaccine (Table 215.11 and see Fig. 215.2). Immunization of children who are

Table 215.10 Recommended Immunizations for International Travel*

IMMUNIZATIONS	LENGTH OF STAY	
	Brief, <1 mo	Long-Term / Residential, >1 mo
Review and complete age-appropriate childhood and adolescent schedule (see text for details) • DTaP, poliovirus, pneumococcal, and *Haemophilus influenzae* type b (Hib) vaccines may be given at 4-wk intervals if necessary to complete recommended schedule before departure. • Influenza • MMR: two additional doses given if <12 mo old at first dose • Meningococcal disease (MenACWY)† • Rotavirus • Varicella • Human papillomavirus (HPV) • Hepatitis A: two additional doses given if <12 mo old at 1st dose‡,§ • Hepatitis B§ • Tdap	+	+
Yellow fever#	+	+
Typhoid fever¶	+	+
Rabies**	±	±
Japanese encephalitis‡	±	+
Cholera‡‡	±	±

*See disease-specific chapters in the Centers for Disease Control and Prevention's *Yellow Book* for details. For further sources of information, see text.
†Recommended for regions of Africa with endemic infection and during local epidemics and required for travel to Saudi Arabia for the Hajj.
‡For infants age 6-11 mo, first dose is recommended before departure for all international travel. For unvaccinated children 12 mo and older, this vaccine is indicated for travelers to areas with intermediate or high endemic rates of hepatitis A virus infection.
§If there is insufficient time to complete 6-mo primary series, accelerated series can be given.
#For regions with endemic infection, see Health Information for International Travel (http://www.cdc.gov/travel). Because of the risk of serious adverse events after yellow fever vaccination, clinicians should only vaccinate people who (1) are at risk of exposure to yellow fever virus (YFV) or (2) require proof of vaccination to enter a country.
¶Indicated for travelers who will consume food and liquids in areas of poor sanitation.
**Indicated for people with high risk for animal exposure (especially to dogs) and for travelers to countries with endemic infection.
‡For regions with endemic infection (see Health Information for International Travel). For high-risk activities in areas experiencing outbreaks, vaccine is recommended, even for brief travel.
‡‡Cholera vaccine (CVD 103-HgR, Vaxchora) is recommended for adult (18-64 yr old) travelers to an area of active toxigenic *V. cholerae* O1 transmission.
+, Recommended; ±, consider; DTaP, diphtheria and tetanus toxoids and acellular pertussis.
Data from Centers for Disease Control and Prevention. Travelers' health. https://wwwnc.cdc.gov/travel.

Table 215.11 Vaccination of Persons with Primary and Secondary Immune Deficiencies

	PRIMARY			
CATEGORY	SPECIFIC IMMUNODEFICIENCY	CONTRAINDICATED VACCINES*	RISK-SPECIFIC RECOMMENDED VACCINES*	EFFECTIVENESS AND COMMENTS
B lymphocyte (humoral)	Severe antibody deficiencies (e.g., X-linked agammaglobulinemia and common variable immunodeficiency)	OPV[a] Smallpox[b] LAIV4 BCG Ty21a Yellow fever virus (YFV) and live-bacteria vaccines[c] No data for rotavirus vaccines	Annual IIV is the only vaccine given to patients receiving IG therapy; routine inactivated vaccines can be given if not receiving IVIG. Pneumococcal Hib (children 12-59 mo of age)	The effectiveness of any vaccine will be uncertain if it depends only on the humoral response (e.g., PPSV23). IG therapy interferes with the immune response to live vaccines MMR and VAR.
	Less severe antibody deficiencies (e.g., selective IgA deficiency and IgG subclass deficiency)	OPV[a] BCG YFV vaccine Other live vaccines[d] appear to be safe.	Vaccines should be given as on the annual immunization schedule for immunocompetent people.[e] PPSV23 should be given beginning at 2 yr of age.[f] Pneumococcal Hib (children 12-59 mo of age)	All vaccines are probably effective. Immune response may be attenuated.
T lymphocyte (cell-mediated and humoral)	Complete defects (e.g., SCID, complete DiGeorge syndrome)	All live vaccines[c,d,g]	Pneumococcal Hib (children 12-59 mo of age) and annual IIV	All inactivated vaccines are probably ineffective.
	Partial defects (e.g., most patients with DiGeorge syndrome, hyper-IgM syndrome, Wiskott-Aldrich syndrome, ataxia-telangiectasia)	All live vaccines[c,d,g]	Routine inactivated vaccines should be given.[e] PPSV23 should be given beginning at 2 yr of age.[f] Pneumococcal Hib (children 12-59 mo of age)	Effectiveness of any vaccine depends on degree of immune suppression.
	Interferon (IFN)-γ–interleukin (IL)-12 axis deficiencies	All live vaccines for IL-12/IL-12R deficiencies, IFN-γ, IFN-α, or STAT1 deficiencies	None	None

Table 215.11 Vaccination of Persons with Primary and Secondary Immune Deficiencies—cont'd

PRIMARY

CATEGORY	SPECIFIC IMMUNODEFICIENCY	CONTRAINDICATED VACCINES*	RISK-SPECIFIC RECOMMENDED VACCINES*	EFFECTIVENESS AND COMMENTS
Complement	Persistent complement, properdin, MBL, or factor B deficiency; secondary deficiency because taking eculizumab (Solaris)	None	PPSV23 should be given beginning at 2yr of age.[f] MCV series beginning in infancy.[h] MenB series beginning at 10 yr of age and Hib vaccine (children 12-59 mo of age)	All routine vaccines are probably effective.
Phagocytic function	Chronic granulomatous disease	Live-bacteria vaccines[c]	None	All inactivated vaccines are safe and probably effective. Live-virus vaccines are probably safe and effective.
	Phagocytic deficiencies that are undefined or accompanied by defect in T-cell and NK-cell dysfunction (e.g., Chédiak-Higashi syndrome, leukocyte adhesion defects, myeloperoxidase deficiency)	MMR, MMRV, OPV,[a] smallpox, LAIV4, Ty21a, YF, all bacteria vaccines	PPSV23 should be given beginning at 2yr of age.[f] MCV series beginning in infancy.[h]	All inactivated vaccines are safe and probably effective.

SECONDARY

SPECIFIC IMMUNODEFICIENCY	CONTRAINDICATED VACCINES*	RISK-SPECIFIC RECOMMENDED VACCINES*	EFFECTIVENESS AND COMMENTS
HIV/AIDS	OPV[a] Smallpox BCG Combined MMRV LAIV4 Withhold MMR, varicella, and zoster in severely immunocompromised persons. YF vaccine may have a contraindication or precaution depending on the indicators of immune function.[j]	PPSV23 should be given beginning at 2yr of age.[f] MCV series beginning in infancy.[h] HepB vaccine Consider Hib (if not administered in infancy).[l]	Rotavirus vaccine is recommended on standard schedule. MMR and VAR are recommended for HIV-infected children who are asymptomatic or only low-level immunocompromised.[k] All inactivated vaccines may be effective.
Generalized malignant neoplasm, transplantation, autoimmune disease, immunosuppressive or radiation therapy	Live-virus and live-bacteria vaccines, depending on immune status.[c,d,m]	PPSV23 should be given beginning at 2yr of age.[f] Annual IIV (unless receiving intensive chemotherapy or anti–B-cell antibodies). Hib vaccine may be indicated.[n]	Effectiveness of any vaccine depends on degree of immune suppression; inactivated standard vaccines are indicated if not highly immunosuppressed, but doses should be repeated after chemotherapy ends.
Asplenia (functional, congenital anatomic, surgical)	LAIV4	PPSV23 should be given beginning at 2yr of age.[f] MCV series beginning in infancy.[h] MenB series beginning at 10 yr of age. Hib (if not administered in infancy)[o]	All routine vaccines are probably effective.
Chronic renal disease	None	PPSV23 should be given beginning at 2yr of age.[f] HepB is indicated if not previously immunized.	All routine vaccines are probably effective.
CNS anatomic barrier defect (cochlear implant, congenital dysplasia of the inner ear, persistent CSF communication with naso-/oropharynx)	None	PPSV23 should be given beginning at 2yr of age.[f]	All standard vaccines are indicated.

*Other vaccines that are universally or routinely recommended should be given if not contraindicated.
[a]OPV is no longer available in the United States.
[b]This table refers to contraindications for nonemergency vaccination (i.e., ACIP recommendations).
[c]Live-bacteria vaccines: BCG and oral Ty21a *Salmonella* Typhi vaccine.
[d]Live-virus vaccines: MMR, MMRV, VAR, OPV, LAIV, YF, zoster, rotavirus, and vaccinia (smallpox). Smallpox vaccine is not recommended for children or the general public.
[e]Children who are delayed or underimmunized should be immunized with routinely recommended vaccines, according to age and catch-up schedule.
[f]PPSV23 is begun at 2 yr or older. If PCV13 is required, PCV13 doses should be administered first, followed by PPSV23 at least 8 wk later; a second dose of PPSV23 is given 5 yr after the first.
[g]Regarding T-lymphocyte immunodeficiency as a contraindication for rotavirus vaccine, data exist only for SCID.

Table 215.11 Vaccination of Persons with Primary and Secondary Immune Deficiencies—cont'd

[h]Age and schedule of doses depend on the product; repeated doses are required.
[i] Pneumococcal vaccine is not indicated for children with chronic granulomatous disease beyond age-based universal recommendations for PCV13. Children with chronic granulomatous disease are not at increased risk for pneumococcal disease.
[j]YF vaccine is contraindicated in HIV-infected children <6 yr old who are highly immunosuppressed. There is a precaution for the use of YF vaccine in asymptomatic HIV-infected children <6 yr with total lymphocyte percentage of 15–24%, and >6 yr old with $CD4^+$ T-lymphocyte counts of 200-499 cells/mm^3. Data from Centers for Disease Control and Prevention. Yellow fever vaccine: recommendations of the Advisory Committee on Immunization Practices, *MMWR Recomm Rep*. 2010;59(RR-07); 1–27.
[k]HIV-infected children should receive immunoglobulin after exposure to measles and may receive varicella vaccine if $CD4^+$ T-lymphocyte percentage is ≥15% for those <6 yr old or $CD4^+$ T-lymphocyte count ≥200 cells/mm^3 for those ≥6 yr old. People with perinatal HIV infection who were vaccinated with measles-, rubella-, or mumps-containing vaccine before the establishment of combination antiretroviral therapy (cART) should be considered unvaccinated and should receive two appropriately spaced doses of MMR vaccine once effective cART has been established (at least 6 mo with $CD4^+$ T lymphocytes ≥15% for children <6 yr old, or $CD4^+$ T-lymphocyte count ≥200 cells/mm^3 for children ≥6 yr old).
[l]For patients 5-18 yr old who have not received a Hib primary series and a booster dose or at least one Hib dose after age 14 mo.
[m]Withholding inactivated vaccines also is recommended with some forms of immunosuppressive therapy, such as anti-CD20 antibodies, induction or consolidation chemotherapy, or patients with major antibody deficiencies receiving immunoglobulins. Inactivated influenza vaccine is an exception, but consideration should be given to repeating doses of any inactivated vaccine administered during these therapies.
[n]For persons <60 mo old undergoing chemotherapy or radiation therapy who have not received a Hib primary series plus a booster dose or at least one Hib dose after age 14 mo.
[o]For persons >59 mo old who are asplenic and persons ≥15 mo who are undergoing elective splenectomy and who have not received a Hib primary series and a booster dose or at least one Hib dose after age 14 mo.
BCG, Bacille Calmette-Guérin vaccine; CNS, central nervous system; Hib, *Haemophilus influenzae* type b vaccine; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; IG, immunoglobulin; IIV, inactivated influenza vaccine; LAIV4, live-attenuated influenza vaccine; MMR, measles, mumps, rubella vaccine; MMRV, measles-mumps-rubella-varicella; MCV, quadrivalent meningococcal polysaccharide vaccine; MenB, serogroup B meningococcal vaccine; OPV, oral poliovirus vaccine (live); PPSV23, pneumococcal polysaccharide vaccine; SCID, severe combined immunodeficiency disease; VAR, varicella; YF, yellow fever.
Adapted from Immunization in Special Circumstances. In: Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2021–2024 Report of the Committee on Infectious Diseases*, 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021.

immunocompromised poses the following potential concerns: the incidence or severity of some vaccine-preventable diseases is higher, and therefore certain vaccines are recommended specifically for certain conditions; vaccines may be less effective during the period of altered immunocompetence and may need to be repeated when immune competence is restored; and because of altered immunocompetence, some children and adolescents may be at increased risk for an adverse event after receipt of a live-virus vaccine. Live-attenuated vaccines generally are contraindicated in immunocompromised persons. The exceptions include **MMR**, which may be given to a child with HIV infection provided the child is asymptomatic or symptomatic without evidence of severe immunosuppression, and **varicella** vaccine, which may be given to HIV-infected children if the $CD4^+$ lymphocyte count is at least 15% and the total $CD4^+$ cell count is >200/mm^3. MMRV is not recommended in these situations.

Altered immunocompetence is considered a precaution for rotavirus; however, the vaccine is contraindicated in children with severe combined immunodeficiency disease. Inactivated vaccines may be administered to immunocompromised children, although their effectiveness might not be optimal depending on the immune deficit. Children with complement deficiency disorders may receive all vaccines, including live-attenuated vaccines. In contrast, children with phagocytic disorders may receive both inactivated and live-attenuated viral vaccines but not live-attenuated bacterial vaccines.*

Corticosteroids can suppress the immune system. Children receiving corticosteroids (≥2 mg/kg/day or ≥20 mg/day of prednisone or equivalent) for ≥14 days should not receive live vaccines until therapy has been discontinued for at least 1 month. Children on the same dose levels but for <2 weeks may receive live-virus vaccines as soon as therapy is discontinued, although some experts recommend waiting 2 weeks after therapy has been discontinued. Children receiving lower doses of corticosteroids may be vaccinated while receiving therapy.

Children and adolescents with malignancy and those who have undergone solid organ or hematopoietic stem cell transplantation and immunosuppressive or radiation therapy should not receive live-virus and live-bacteria vaccines depending on their immune status. Children who have undergone chemotherapy for leukemia may need to be reimmunized with age-appropriate single doses of previously administered vaccines. Preterm infants generally can be vaccinated at the same chronological age as full-term infants according to the recommended childhood immunization schedule. An exception is the birth dose of HepB. When mother is HBsAg-negative, infants weighing ≥2 kg and who are medically stable should receive a birth dose within the first 24 hours of life. However, HepB should be deferred in infants weighing <2 kg at birth until chronological age 1 months or hospital discharge (whichever is earlier and even if weight is still <2 kg). All preterm, low-birthweight infants born to HBsAg-positive mothers should receive hepatitis B immunoglobulin (HBIG) and HepB vaccine (at separate anatomic sites) within 12 hours of birth. However, such infants should receive an additional three doses of vaccine starting at 30 days of age (see Fig. 215.1). Infants born to HBsAg-positive mothers should be tested for HBsAg and antibody at 9-12 months, or 1-2 months after completion of the HepB series if the series was delayed. If the test is negative for antibody against the surface antigen (anti-HBs), an additional dose of HepB is recommended with testing 1-2 months after the dose. If the child is still antibody negative, an additional two doses of vaccine should be administered.

If the mother's HBsAg status is unknown within 12 hours of birth, administer HepB vaccine regardless of birthweight. For infants weighing <2,000 g, administer HBIG in addition to HepB within 12 hours of birth. Determine the mother's HBsAg status as soon as possible and, if the mother is HBsAg-positive, also administer HBIG to infants weighing ≥2,000 g as soon as possible, but no later than 7 days of age.

Varicella-zoster immunoglobulin **(VariZIG)** is recommended for patients without evidence of immunity to varicella who are at high risk for severe varicella and complications, who have been exposed to varicella or herpes zoster, and for whom varicella vaccine is contraindicated. This includes immunocompromised patients without evidence of immunity, newborn infants whose mothers have signs and symptoms of varicella around the time of delivery (i.e., 5 days before to 2 days after), hospitalized premature infants born at ≥28 weeks of gestation whose mothers do not have evidence of immunity to varicella, hospitalized premature infants born at <28 weeks of gestation or who weigh ≤1,000 g at birth (regardless of their mother's evidence of immunity to varicella), and pregnant women without evidence of immunity.

The ACIP recommends the use of COVID-19 vaccines within the scope of the EUA or fully approved by the FDA based on a Biologics License Application for the particular vaccine. Interim ACIP recommendations for the use of COVID-19 vaccines can be found at https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/covid-19.html. COVID-19 vaccine and other routine vaccines may be administered on the same day. For more information about COVID-19 vaccines authorized for use in the United States, see https://www.cdc.gov/vaccines/covid-19/info-by-product/index.html. Rare serious adverse events have been reported after COVID-19 vaccination, including myocarditis in children older than 5 years of age. The ACIP continues to conclude that the benefits outweigh the risks for rare serious adverse events after COVID-19 vaccination.

*https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/a/immuno-table.pdf

Some children have situations that are not addressed directly in current immunization schedules. Physicians can use general rules to guide immunization decisions in some of these instances. General Best Practice Guidelines for Immunization (including contraindications and precautions) can be found at https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html. In general, vaccines may be given simultaneously on the same day, whether inactivated or live. Different inactivated vaccines can be administered at any interval between doses. However, because of theoretical concerns about viral interference, different live-attenuated vaccines (MMR, varicella), if not administered on the same day, should be given at least 1 month apart. An inactivated and a live vaccine may be spaced at any interval from each other.

Immunoglobulin does not interfere with inactivated vaccines. However, immunoglobulin can interfere with the immune response to measles vaccine and, by inference, to varicella vaccine. In general, immunoglobulin, if needed, should be administered at least 2 weeks after the measles vaccine. Depending on the dose of immunoglobulin received, MMR should be deferred for as long as 3-11 months. Immunoglobulin is not expected to interfere with the immune response to LAIV4 or rotavirus vaccines.

Certain adult (including pregnancy) immunizations are recommended to decrease the risk of infection in their children; these include influenza virus and pertussis (Tdap).

PRECAUTIONS AND CONTRAINDICATIONS

Observation of valid precautions and contraindications is critical to ensure that vaccines are used in the safest manner possible and to obtain optimal immunogenicity. When a child presents for immunization with a clinical condition considered a **precaution**, the physician must weigh benefits and risks to that individual child. If benefits are judged to outweigh risks, the vaccine or vaccines in question may be administered. A **contraindication** means the vaccine should not be administered under any circumstances.

A general contraindication for all vaccines is **anaphylactic reaction** to a prior dose. Anaphylactic hypersensitivity to vaccine constituents is also a contraindication. However, if a vaccine is essential, there are desensitizing protocols for some vaccines. The major constituents of concern are *egg proteins* for vaccines grown in eggs; *gelatin,* a stabilizer in many vaccines; and antimicrobial agents. The recommendations for persons with egg allergy were modified as follows: A previous severe allergic reaction to influenza vaccine is a contraindication to future receipt of any influenza vaccine. Persons with a history of egg allergy who have experienced only hives after exposure to egg should receive any flu vaccine appropriate for age and health status. Persons who had symptoms other than hives (e.g., angioedema, respiratory distress, need for emergency medical services or epinephrine) should receive any influenza vaccine appropriate for age and health status annually. If using an influenza vaccine other than Flublok or Flucelvax, administer in a medical setting under supervision of a healthcare provider who is able to recognize and manage severe allergic conditions. LAIV4 should not be used for persons with a history of severe allergic reaction to any component of the vaccine (excluding egg) or to a previous dose of any influenza vaccine. The measles and mumps components of MMR are grown in chick embryo fibroblast tissue culture. However, the amount of egg protein in MMR is so small that there are no special procedures for administering the vaccine to someone with a history of anaphylaxis after egg ingestion.

Vaccines should usually be deferred in children with moderate to severe acute illnesses, regardless of the presence of fever, until the child recovers. *However, children with mild illnesses may be vaccinated.* Studies of undervaccinated children have documented opportunities that were missed because mild illness was used as an invalid contraindication.

Complete tables of contraindications and precautions by vaccine can be found at https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html and as an appendix to the 2024 immunization schedule (https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html#appendix).

MEDICAL EXEMPTIONS

All 50 states, the District of Columbia, and Puerto Rico have regulations requiring verification of immunization for childcare and school attendance. This provides direct protection to the immunized population and indirect protection to those unable to be immunized. It also functions to improve timely immunization of children. Regulations also allow for medical exemption from immunization requirements in all 50 states, and the majority of states also have varied regulations that allow for nonmedical exemptions. Rare, medically recognized contraindications are important to observe. Nonmedical exemptions to immunization requirements include exemptions because of religious or philosophical beliefs. Persons with exemptions are at greater risk of vaccine-preventable diseases than the general population. When children with exemptions cluster, as can happen with nonmedical exemptions, the community may be at risk for outbreaks, leading to exposure of children who cannot be protected by vaccination to vaccine-preventable diseases, such as children too young for vaccination and those with medical contraindications. (For more information, see http://pediatrics.aappublications.org/content/early/2016/08/25/peds.2016-2145.)

IMPROVING IMMUNIZATION COVERAGE

Standards for child and adolescent immunization practices have been developed to support achievement of high levels of immunization coverage while providing vaccines in a safe and effective manner and educating parents about risks and benefits of vaccines (Table 215.12).

Pediatric vaccine uptake has decreased since the start of the COVID-19 pandemic resulting in decreased vaccination coverage. This identified decline may indicate that U.S. children and their communities face increased risks for outbreaks of vaccine-preventable diseases (Fig. 215.3).

Despite benefits that vaccines have to offer, many children are underimmunized as a result of not receiving recommended vaccines or not receiving them at the recommended ages. Much of the underimmunization problem can be solved through physician actions. Most children have a regular source of healthcare. However, missed opportunities to provide immunizations at healthcare visits include but are not limited to failure to provide all recommended vaccines that could be administered at a single visit during that visit, failure to provide immunizations to children outside of well child care encounters when contraindications are not present, and referral of children to public health clinics because of inability to pay for vaccines. Simultaneous administration of multiple vaccines is generally safe and effective. When the benefits of simultaneous vaccination are explained, many parents prefer such immunization to making an extra visit. Providing all needed vaccines simultaneously should be the standard of practice.

Only valid contraindications and precautions to vaccine administration should be observed. Ideally, immunizations should be provided during well child visits; however, if no contraindications exist, it is important to administer vaccines at other visits, particularly if the child is behind in the schedule. There is no good evidence that providing immunizations outside of well child care ultimately decreases the number of well child visits.

Financial barriers to immunization should be minimized. Participation in the **VFC** program allows physicians to receive vaccines at no cost for their eligible patients, which helps such patients get immunized in their medical home.

Several interventions have been shown to help physicians increase immunization coverage in their practices. Reminder systems for children before an appointment or recall systems for children who fail to keep appointments have repeatedly been demonstrated to improve coverage. Assessment and feedback are also important interventions. Many physicians overestimate the immunization coverage among patients they serve and thus are not motivated to make any changes in their practices to improve performance. Assessing the immunization coverage of patients served by an individual physician with feedback of results can be a major motivator for improvement. Often, public health departments can be contacted to provide the assessments and feedback. Alternatively, physicians can perform self-assessment. Review of approximately 60 consecutive charts of 2-year-old children may provide

Table 215.12 Standards for Child and Adolescent Immunization Practices

AVAILABILITY OF VACCINES
Vaccination services are readily available.
Vaccinations are coordinated with other healthcare services and provided in a medical home when possible.
Barriers to vaccination are identified and minimized.
Patient costs are minimized.
ASSESSMENT OF VACCINATION STATUS
Healthcare professionals review the vaccination and health status of patients at every encounter to determine which vaccines are indicated.
Healthcare professionals assess for and follow only medically accepted contraindications.
EFFECTIVE COMMUNICATION ABOUT VACCINE BENEFITS AND RISKS
Parents or guardians and patients are educated about the benefits and risks of vaccination in a culturally appropriate manner and in easy-to-understand language.*
Healthcare professionals offer strong and consistent recommendations for all universally recommended vaccines according to the current immunization schedule. They use presumptive language (e.g., these vaccines are routine) and deliver this recommendation in the same manner for all vaccines.
Healthcare professionals answer parents' or guardians' and patients' questions thoroughly and emphasize an unwavering commitment to the recommendation. If parents or guardians and patients are hesitant or refuse, healthcare professionals persevere and offer the vaccine again at the next most appropriate time.
PROPER STORAGE AND ADMINISTRATION OF VACCINES AND DOCUMENTATION OF VACCINATIONS
Healthcare professionals follow appropriate procedures for vaccine storage and handling.
Up-to-date, written vaccination protocols are accessible at all locations where vaccines are administered.
Persons who administer vaccines and staff who manage or support vaccine administration are knowledgeable and receive ongoing education.
Healthcare professionals simultaneously administer as many indicated vaccine doses as possible.
Vaccination records for patients are accurate, complete, and easily accessible.
Healthcare professionals report adverse events after vaccination promptly and accurately to the Vaccine Adverse Event Reporting System (VAERS) and are aware of a separate program, the National Vaccine Injury Compensation Program (VICP).
Healthcare professionals and personnel review the immunization timeline with parents or guardians and patients and schedule follow-up immunization visits before the family leaves the care setting.
All personnel who have contact with patients are appropriately vaccinated and communicate consistent messages about vaccines.
IMPLEMENTATION OF STRATEGIES TO IMPROVE VACCINATION COVERAGE
Systems are used to remind parents or guardians, patients, and healthcare professionals when vaccinations are due and to recall those who are overdue.
Office- or clinic-based patient record reviews and vaccination coverage assessments are performed annually.
Healthcare professionals practice community-based approaches.
Healthcare professionals understand cultural needs and disparities of different populations and use the most effective strategies for these populations.
Most healthcare visits (including acute care or sick visits) are viewed as opportunities to review immunization records, provide vaccines that are due, and catch up on missed vaccinations.

*Additional resources to help improve immunization rates include the following:
- Provider Resources for Vaccine Conversations with Parents from CDC, AAP, and American Academy of Family Physicians (www.cdc.gov/vaccines/hcp/conversations/index.html)
- American Academy of Pediatrics (AAP) Training Guide (https://shar.es/1JRNmJ)
- Centers for Disease Control and Prevention (CDC): *Pink Book,* Chapter 6: Vaccine administration (https://www.cdc.gov/vaccines/pubs/pinkbook/vac-admin.html) and quality improvement projects and educational materials (https://www.cdc.gov/vaccines/ed/index.html)
- Immunization Action Coalition: Suggestions to improve your immunization services (http://www.immunize.org/catg.d/p2045.pdf)

Adapted from National Vaccine Advisory Committee. Standards for child and adolescent immunization practices. *Pediatrics.* 2003;112:958–963; and Bernstein HH, Bocchini JA; AAP Committee on Infectious Diseases. The need to optimize adolescent immunization. *Pediatrics.* 2017;139(3):e20164186, and Practical approaches to optimize adolescent immunization. *Pediatrics.* 2017;139(3):e20164187.

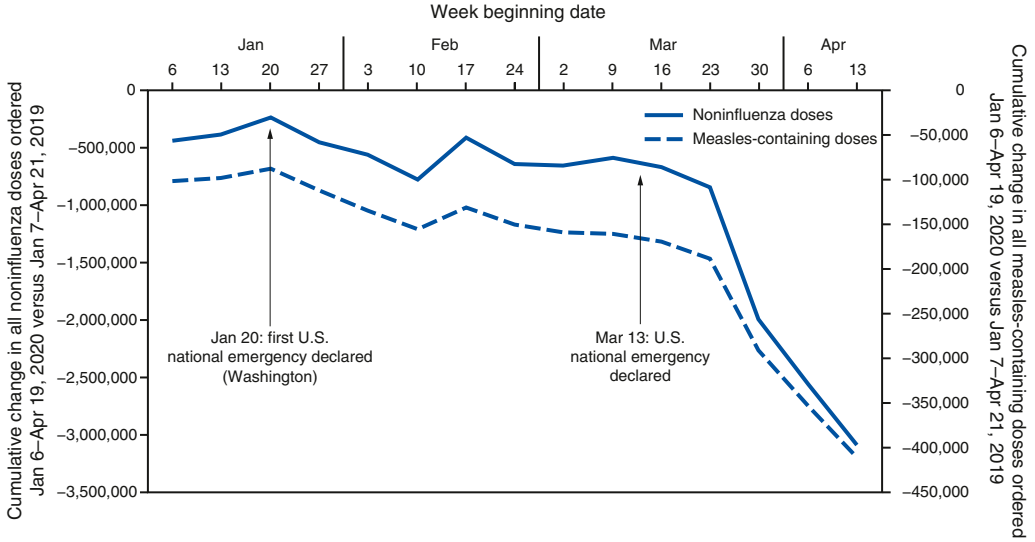

Fig. 215.3 Weekly changes in Vaccines for Children Program (VFC) provider orders* and Vaccine Safety Datalink (VSD) doses administered† for routine pediatric vaccines — United States, January 6–April 19, 2020. *VFC data represent the difference in cumulative doses of VFC-funded non-influenza and measles-containing vaccines ordered by healthcare providers at weekly intervals between Jan. 7–Apr. 21, 2019, and Jan. 6–Apr. 19, 2020; †VSD data depict weekly measles-containing vaccine doses administered by age-group (age ≤24 mo and >24 mo to 18 yr). *(From Santoli JM, Lindley MC, DeSilva MB, et al. Effects of the COVID-19 pandemic on routine pediatric vaccine ordering and administration – United States, 2020. MMWR Morb Mortal Wkly Rep. 2020;69:591–593.)*

a reasonable estimate of practice coverage. Another approach is to have a staff member review the chart of every patient coming in for a visit and placing immunization needs reminders on the chart for the physician. Electronic medical records can be designed to accomplish this goal.

VACCINE HESITANCY

The World Health Organization (WHO) characterized *vaccine hesitancy* as a delay in acceptance or refusal of vaccines despite availability of vaccination services. The COVID-19 pandemic has also changed the way outpatient care is being delivered across the United States. Because of COVID-19, providers face the additional challenges of maintaining and strengthening routine vaccinations. As communities are reopening, it is vitally important for providers to work with parents to ensure their children stay up to date on routine, universally recommended vaccines. The pandemic is a reminder of the threat of infectious diseases. Providers are well positioned to counsel parents about the value of vaccination. Uptake is highest when parents are aware that their child is due for specific vaccines and when they feel safe about their children receiving those vaccines. Factors implicated in vaccine hesitancy include complacency, convenience, and confidence. The percentage of children having a parent reporting they were "hesitant about childhood shots" was 25.8% in 2018 and 19.5% in 2019 (https://pediatrics.aappublications.org/content/146/6/e2020007609). Concerns about vaccine safety and questions about the necessity of vaccines are often cited as reasons for refusal. Vaccine-hesitant individuals are a heterogeneous group, and their individual concerns should be respected and addressed. Multiple studies have shown that the most important factor in persuading parents to accept vaccines remains the *one-on-one contact* with an informed, caring, and concerned pediatrician. Parents should be reassured that vaccines are tested thoroughly before licensure, that ongoing mechanisms of monitoring safety exist after licensure, and that the current vaccine schedule is the only recommended schedule. It is important to stress that serious disease can occur if a child and family are not immunized, because unvaccinated children put medically exempt children who live in that same area at risk, as well as some children who have been vaccinated (although most vaccines are highly effective, no vaccine is 100% effective). Parental education can be provided through reputable sources for vaccine information (see Table 215.8). (For more information, see http://pediatrics.aappublications.org/content/early/2016/08/25/peds.2016-2146.) Provider resources for vaccine conversations with parents are available at https://www.cdc.gov/vaccines/hcp/conversations/index.html.

Physician concerns about liability should be addressed by appropriate documentation of discussions in the chart. The Committee on Bioethics of the AAP has published guidelines for dealing with parents' refusal of immunization. Physicians also might want to consider having parents sign a **refusal waiver**. A sample refusal-to-vaccinate waiver can be found at http://www2.aap.org/immunization/pediatricians/pdf/refusaltovaccinate.pdf.

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215.1 International Immunization Practices

W. William Schluter, Kari Johansen, and Tracey Goodman

Given that the epidemiology of infectious diseases varies across countries and continents, it is necessary for vaccination programs to be adapted accordingly. The WHO's Strategic Advisory Group of Experts (SAGE) on immunization evaluates the scientific evidence available for the various vaccines and products and develops advice on global policies and strategies ranging from vaccine type, recommendations for vaccine delivery, links with other health interventions, and suggested vaccine research. Its remit includes all vaccine-preventable infectious diseases for all age-groups. The WHO SAGE recommendations are summarized in the WHO Vaccine Position papers that are updated regularly. The latest information for recommended routine immunizations for children up to 18 years of age, including recommended ages for the initiation of the primary series and dose intervals, as well as recommendations for subsequent booster doses are listed in Table 215.13.

The WHO policy recommendations are adapted by the Regional and National Immunization Technical Advisory Groups making recommendations to respective country governments. As a consequence, the immunization schedules and the types of vaccines, including the specific vaccine products used, vary substantially. Country-specific immunization schedules have been compiled and are available online (https://immunizationdata.who.int/listing.html?topic=vaccine-schedule). Availability and cost play a major role in the choice of vaccine products and schedules in many countries.

According to the WHO recommended schedule, all children should be protected against 12 vaccine-preventable infectious pathogens: *Bordetella pertussis*, *Clostridium tetani*, *Corynebacterium diphtheriae, Haemophilus influenzae* type b, hepatitis B virus, human papillomavirus (HPV), measles virus, *Mycobacterium tuberculosis*, poliovirus, rotavirus, rubella virus, and *Streptococcus pneumoniae* (see Table 215.13).

BIRTH DOSE VACCINES

At birth, hepatitis B vaccine is recommended for all children within 24 hours of birth to prevent perinatal transmission. Additionally, Bacille Calmette-Guérin (BCG) vaccine is recommended at birth in countries or settings with a high incidence of tuberculosis (TB) and/or high leprosy burden, and the first dose of bivalent oral polio vaccine containing poliovirus type 1 and 3 (bOPV) is recommended to be given at birth in polio-endemic countries and in countries at high risk for importation and subsequent spread of poliovirus.

Primary Infant Series

Infant immunization visits are recommended to begin from the age of 6-8 weeks, with an interval of 4-8 weeks between doses to complete the primary series for protection against hepatitis B, polio, diphtheria, pertussis, tetanus, rotavirus, and invasive bacterial infections caused by *H. influenzae* type b and *S. pneumoniae*. To reduce the number of injections, some of these vaccines are provided in combination vaccines. Rotavirus vaccines are provided orally and can be administered concomitantly with the injectable vaccines and OPV. It should be noted that for all countries using OPV, two doses of injectable IPV are recommended from 14 weeks of age with an interval of at least 4 months between doses.

Two doses of measles vaccines are recommended, with the first dose given at 9-12 months of age and the second dose in the second year of life. Only one dose of rubella given at 9 months of age is sufficient to provide >95% protection. However, when using a rubella-containing vaccine that is combined with measles, it is often easier to provide a second dose using the same MR or MMR vaccine product for both doses, dependent on availability. HPV vaccine is recommended for girls from 9-14 years of age.

Booster Doses

In addition to the three doses provided in infancy, three booster doses of combination diphtheria toxoid– and tetanus toxoid–containing vaccine should be provided during childhood and adolescence, at 12-23 months (using DTP-containing vaccine), 4-7 years (with DT or Td), and 9-15 years of age (with Td). Ideally, there should be at least 4 years between booster doses. Depending on disease epidemiology, booster doses may also be recommended for Hib and pneumococcal conjugate vaccines. For countries where DTP/DT/Td booster doses are not provided, maternal vaccination with tetanus-containing vaccine (TT or Td) is provided to protect against neonatal and maternal tetanus.

Vaccination Against Outbreak-Prone Diseases for Endemic Areas

Cholera, Japanese encephalitis, meningococcal conjugate, typhoid, and yellow fever vaccines may be recommended for infants, children, and adolescents living in endemic areas, as shown in Table 215.14.

Table 215.13 Summary of Recommended Routine Immunization for *All* Children Up to 18 Years Based on WHO Vaccine Position Papers (updated as of September 2020)

For the most recent version of the respective position papers, the summary tables and further details per vaccine, consult the reference provided here*:

VACCINE		AGE OF FIRST DOSE	NUMBER OF DOSES IN PRIMARY SERIES	INTERVAL BETWEEN DOSES			BOOSTER DOSE(S) AFTER PRIMARY SERIES	CONSIDERATIONS TO BE MADE
				FIRST TO SECOND	SECOND TO THIRD	THIRD TO FOURTH		
BCG		As soon as possible after birth	1	NA	NA	NA	NA	• Universal vs selective vaccination of high-risk groups • Co-administration with hepatitis B and OPV • Birth dose and HIV • Vaccination of older age-groups
Hepatitis B	Option 1	As soon as possible after birth (<24 hr)	3	4 wk (min) with DTPCV1	4 wk (min) with DTPCV2	NA	NA	• Premature and low birthweight infants • Co-administration with other vaccines • High-risk infants
	Option 2	As soon as possible after birth (<24 hr)	4	4 wk (min) with DTPCV1	4 wk (min) with DTPCV2	4 wk with DTPCV3	NA	
Rotavirus		6 wk (min)	2 or 3 (dependent on product used)	4 wk (min) with DTPCV2	For the three-dose schedule: 4 wk with DTPCV3	NA	NA	• Not recommended if child >24 mo old
DTP-containing vaccine (DTPCV)		6 wk (min)	3	4 wk (min) to 8 wk	4 wk (min) to 8 wk	NA	3 boosters with DTPCV at 12-23 mo, 4-7 yr (Td/DT), and 9-15 yr (Td)	• Co-administration with other vaccines/combination vaccines • Maternal immunization if needed
Hemophilus influenzae type b	Option 1	6 wk (min) to 59 mo (max)	3	4 wk (min) with DTPCV2	4 wk (min) with DTPCV3	NA	At least 6 mo after last dose	• Single dose if >12 mo of age • Not recommended for children >5 yr • Co-administration with other vaccines/combination vaccines
	Option 2	6 wk (min) to 59 mo (max)	2-3	8 wk (min) if only 2 doses 4 wk (min) if 3 doses	4 wk (min) if 3 doses	NA	At least 6 mo (min) after last dose	
Pneumococcal conjugate	Option 1 3p + 0	6 wk (min)	3	4 wk (min)	4 wk	NA		• Schedule options • HIV+ • Preterm neonate booster
	Option 2 2p + 1	6 wk (min)	2	8 wk (min)		NA	9-18 mo	
Poliovirus	Option 1 bOPV + IPV	bOPV 6 wk IPV 14 wk	5 (3 bOPV + 2 IPV)	bOPV 4 wk (min) with DTPCV2 IPV 4 mo (min)	bOPV 4 wk (min) with DTPCV3			• bOPV birth dose • Fractional dose • Transmission and importation criteria
	Option 2 IPV/bOPV sequential	8 wk (IPV first)	1-2 IPV 2 bOPV	4-8 wk	4-8 wk	4-8 wk		
	Option 3 IPV-only	8 wk	3	4-8 wk	4-8 wk		Under evaluation	• IPV booster needed for early schedule (i.e., first dose given <8 wk)

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Table 215.13 Summary of Recommended Routine Immunization for *All* Children Up to 18 Years Based on WHO Vaccine Position Papers (updated as of September 2020)—cont'd

VACCINE	AGE OF FIRST DOSE	NUMBER OF DOSES IN PRIMARY SERIES	INTERVAL BETWEEN DOSES			BOOSTER DOSE(S) AFTER PRIMARY SERIES	CONSIDERATIONS TO BE MADE
			FIRST TO SECOND	SECOND TO THIRD	THIRD TO FOURTH		
Measles	9 or 12 mo	2	4 wk (min)			NA	• Combination vaccines • HIV early vaccination • Pregnancy
Rubella	9 or 12 mo with measles-containing vaccine	1				NA	• Achieve and sustain 80% vaccination coverage • Combination vaccine • Pregnancy
HPV	As soon as possible from 9 yr of age (females only)	2	6 mo (min 5 mo)			NA	• Target 9- to 14-yr-old girls • Vaccination during pregnancy to be avoided • Older age >15 yr, HIV, and immunocompromised irrespective of age need three doses

DTPCV1, DTP-containing vaccine dose 1; NA, not applicable.
*https://who.int/teams/immunization-vaccines-and-biologicals/policies/who-recommendations-for-routine-immunization—summary-tables
Courtesy of the World Health Organization, Department of Immunization, Vaccines and Biologicals. https://cdn.who.int/media/docs/default-source/immunization/immunization_schedules/table_2_feb_2023_english.pdf?sfvrsn=3e27ab48_11

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Table 215.14 Summary of Recommended Routine Immunization for Children Residing in Endemic Areas, Belonging to Identified High-Risk Populations or in Countries with More Extensive Vaccination Programs Based on WHO Vaccine Position Papers (updated as of 2020)*

VACCINE		AGE OF FIRST DOSE	NUMBER OF DOSES IN PRIMARY SERIES	INTERVAL BETWEEN DOSES			BOOSTER DOSE(S) AFTER PRIMARY SERIES	CONSIDERATIONS (SEE FOOTNOTES FOR DETAILS)
				FIRST TO SECOND	SECOND TO THIRD	THIRD TO FOURTH		
RECOMMENDATIONS FOR CHILDREN RESIDING IN CERTAIN REGIONS								
Japanese encephalitis	Option 1. Inactivated Vero cell derived	6 mo	2	4 wk (generally)				Vaccine options Pregnancy Immunocompromised
	Option 2. Live attenuated	8 mo	1					
	Option 3. Live recombinant	9 mo	1					
Yellow fever		9-12 mo with measles-containing vaccine	1					
Tickborne encephalitis		>1 yr FSME-Immun and Encepur >3 yr TBE-Moscow and EnceVir	3	1-3 mo FSME-Immun and Encepur 1-7 mo TBE Moscow and EnceVir	5-12 mo FSME-Immun and Encepur 12 mo TBE Moscow and EnceVir		At least 1 every 3 yr	Definition of high-risk Vaccine options Timing of booster doses
RECOMMENDATIONS FOR CHILDREN IN SOME HIGH-RISK POPULATIONS								
Typhoid	Option 1. TCV (Typbar)	>6 mo	1					Definition of high risk
	Option 2. Vi PS	2 yr (min)	1					Definition of high risk
	Option 3. Ty21a	Capsules 5 yr	3 or 4	1 day	1 day	1 day	Every 3-7 yr	Definition of high risk
Cholera	Dukoral (WC-rBS)	2 yr	3 for 2-5 yr 2 >6 yr	>7 days to 6 wk	>7 days to 6 wk		Every 6 mo Every 2 yr	Minimum age Definition of high risk
	Shancol, Euvichol and mORCVAX	1 yr	2	14 days			After 2 yr	
Meningococcal	MenA conjugate	9-18 mo	1					Definition of high risk Vaccine options 2 doses if <9 mo with 8-wk interval
	MenC conjugate	>2-11 mo	2	8 wk			After 1 yr	Definition of high-risk Vaccine options
		>12 mo	1					
	Quadrivalent (ACWY)	9-23 mo >2 yr	2 1					Definition of high risk Vaccine options

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Table 215.14 Summary of Recommended Routine Immunization for Children Residing in Endemic Areas, Belonging to Identified High-Risk Populations or in Countries with More Extensive Vaccination Programs Based on WHO Vaccine Position Papers (updated as of 2020)*—cont'd

VACCINE	AGE OF FIRST DOSE	NUMBER OF DOSES IN PRIMARY SERIES	INTERVAL BETWEEN DOSES			BOOSTER DOSE(S) AFTER PRIMARY SERIES	CONSIDERATIONS (SEE FOOTNOTES FOR DETAILS)
			FIRST TO SECOND	SECOND TO THIRD	THIRD TO FOURTH		
Hepatitis A	1 yr	At least 1					Level of endemicity Vaccine options Definition of high-risk groups
Rabies	As required	2	7 days				Preexposure vs postexposure prophylaxis Definition of high-risk groups
Dengue (CYD-TDV)	9 yr	3	6 mo	6 mo			Prevaccination screening
RECOMMENDATIONS FOR CHILDREN RECEIVING VACCINATIONS IN IMMUNIZATION PROGRAMS WITH CERTAIN CHARACTERISTICS							
Seasonal influenza Inactivated	6 mo	2 (<9 yr) 1 (≥9 yr)	4 wk			Revaccinate annually, 1 dose	Priority risk groups, especially pregnant women Lower dosage for children 6-35 mo
Mumps	12-18 mo with measles-containing vaccine	2	1 mo min to school entry				Coverage criteria >80% Combination vaccines
Varicella	12-18 mo	1-2	4 wk to 3 mo per manufacturer recommendations				Achieve and sustain >80% coverage necessary Pregnancy Co-administration with other live vaccines

*https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/who-rcommendations-for-routine-immunization—summary-tables

Courtesy the World Health Organization, Department of Immunization, Vaccines and Biologicals. https://cdn.who.int/media/docs/default-source/immunization/immunization_schedules/table_2_feb_2023_english.pdf?sfvrsn=3e27ab48_11&download=true

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Table 215.15 International Vaccine Websites and Resources

ORGANIZATION	WEBSITE
PUBLIC HEALTH ORGANIZATIONS	
WHO recommendations for routine immunization	https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/who-recommendations-for-routine-immunization—summary-tables
WHO Vaccine Position Papers	https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/position-papers
WHO SAGE	https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/about
Global NITAG network systematic reviews	https://www.nitag-resource.org
WHO Regional Office for Africa	https://www.afro.who.int/
WHO Regional Office for the Americas or Pan American Health Organization	https://www.paho.org/en
WHO Regional Office for the Eastern Mediterranean	http://www.emro.who.int/index.html
WHO Regional Office for Europe	https://www.euro.who.int/en
WHO Regional Office for Southeast Asia	https://www.who.int/southeastasia
WHO Regional Office for the Western Pacific	https://www.who.int/westernpacific
Country-specific vaccination schedules	https://apps.who.int/immunization_monitoring/globalsummary
Canada provincial and territorial immunization schedule	https://www.canada.ca/en/public-health/services/provincial-territorial-immunization-information/provincial-territorial-routine-vaccination-programs-infants-children.html.
European Center for Disease Prevention and Control (ECDC)	https://www.ecdc.europa.eu/en
ECDC Vaccine Scheduler	https://vaccine-schedule.ecdc.europa.eu
Japan	https://www.jpeds.or.jp/uploads/files/2020%20English%20JPS%20Immunization%20Schedule.pdf
Mexico National Vaccination Schedule	https://www.gob.mx/salud/articulos/esquema-de-vacunacion.
UK immunization schedule	https://www.gov.uk/government/groups/joint-committee-on-vaccination-and-immunisation
UK Immunisation against infectious disease – the Green Book	https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book
Pan American Health Organization/WHO revolving fund for access to vaccines	https://www.paho.org/en/revolvingfund
UNICEF Supply Division	https://www.unicef.org/supply/vaccines
NONPROFIT GROUPS	
GAVI, the Alliance	http://www.gavialliance.org/
COVAX facility	https://www.gavi.org/covax-facility
Coalition for Epidemic Preparedness Innovations (CEPI)	https://cepi.net

Vaccine Supply and Production

Since 2000, the Global Alliance for Vaccines and Immunizations (GAVI, now known as *GAVI, The Vaccine Alliance*) has helped expand access to vaccines for infants, children, and adolescents in low-income countries by cost-sharing vaccine introduction and through market-sharing activities to expand vaccine production to drive down vaccine costs. There are other initiatives by the WHO and United Nations Children's Fund (UNICEF) that support pooled vaccine procurement to help expand access to vaccines in low- and middle-income countries. In many low- and middle-income countries, the private vaccine market is increasing. For relevant international vaccine websites and resources, see Table 215.15.

Vaccines are currently produced in many countries around the world, with India hosting the largest vaccine producers that serve many low- and middle-income countries. The number of countries with vaccine production capacity are expected to increase in the coming years as a result of the COVID-19 pandemic. Occasionally counterfeit vaccines have been identified, and therefore vigilant surveillance is needed to ensure safe and effective products reach the end consumer.

Vaccine Hesitancy and Demand

In addition to access, population willingness to accept vaccination is an important consideration influencing control of vaccine-preventable diseases. In 2019, the WHO declared vaccine hesitancy, which is the reluctance or refusal to accept vaccinations despite availability, as one of the top 10 threats to global health. Vaccination coverage for recommended vaccines varies between countries, and it is estimated that in 2022, 20.5 million children worldwide at the age of 1 year were considered unvaccinated or undervaccinated using DTP3 coverage data collected by UNICEF/WHO. Significant attempts to reach the unvaccinated and undervaccinated are underway, irrespective of the reasons.

Eradication and Elimination

After the success of the global eradication of smallpox, global eradication or regional disease elimination goals have been adopted for polio, measles, and rubella. In 1988 the World Health Assembly endorsed the goal of eradicating polio from the world by the end of 2000. Although that goal has not yet been reached, endemic wild poliovirus (WPV) transmission in 2023 is limited to two countries worldwide (Afghanistan and Pakistan). The principal eradication strategy has been the use of OPV both for routine immunization and mass supplemental immunization campaigns in endemic or high-risk areas, targeting all children <5 years of age for immunization, regardless of prior immunization status. In areas with low polio population immunity, the OPV virus can mutate over time to develop neurovirulence, similar to WPV. These mutated vaccine viruses are known as *vaccine-derived poliovirus* (VDPV). Since 2018, more paralytic cases have been caused by VDPVs than WPV. Once interruption of WPV transmission is achieved, the goal is to stop the use of OPV.

All six WHO regions have resolved to achieve measles elimination, and five (all but the Eastern Mediterranean region) have rubella elimination goals. In 2015, the Region of the Americas was the first region to achieve rubella elimination and has maintained that status since that time. Regional measles elimination in the Americas was verified in 2016 but was lost in 2018 when measles virus was reintroduced

and continued circulating for more than 12 months in Venezuela and Brazil. Though no other WHO region has achieved certification of regional measles or rubella elimination, national-level certification of elimination is continuing in all regions, with the European Region nearing regional elimination for both measles and rubella.

Goals to eliminate epidemics or to eliminate diseases as a public health problem have been adopted for other vaccine-preventable diseases that are not eradicable such as bacterial meningitis (*S. pneumoniae*, *N. meningitidis*), cervical cancer (HPV), cholera, hepatitis B, rabies, and tetanus (maternal and neonatal tetanus).

Vaccine Schedules in High-Income Countries

Immunization schedules in high-income countries are more variable than in low- and low-middle-income countries. In general, in high-income countries where disease incidence may be lower, doses of many vaccines are recommended to be given later than with the WHO recommended schedule. The infant primary series doses are usually given at 2, 3, and 4 months or at 2, 4, and 6 months (as in the United States) instead of starting early at 6 weeks of age. The first dose of measles-containing vaccines are often not administered until 12 months of age or later, with the second dose provided before school entry. Most middle- and high-income countries have moved to sequential IPV/OPV schedules or an IPV-only program with five or six recommended doses using combination vaccines.

Immunization recommendations for Canada are developed by the Canadian National Advisory Committee on Immunization (NACI) but vary by province. The Canadian schedule is similar to the U.S. immunization schedule, with a few exceptions. A birth dose of hepatitis B vaccine is not specifically recommended as it is in the United States, although some Canadian provinces do provide a birth dose. Conjugate meningococcal C vaccine is recommended in a one- or two-dose series, depending on the age at the time of administration (one dose if ≥12 months). In contrast to the United States, hepatitis A vaccine is not recommended in Canada as a routine pediatric immunization.

In Europe, there is significant variation in vaccines used and the immunization schedules recommended. The number of infectious diseases for which vaccines are offered vary between 12 and 17. As an example, an extensive immunization schedule is offered in the United Kingdom as recommended by the UK Joint Committee on Vaccine and Immunisation (JCVI). In 2023, it includes visits at 2, 3, and 4 months of age, when a combination DTaP-Hib-IPV-HepB vaccine is administered. Infants at high risk of developing hepatitis B infection from infected mothers are given doses of hepatitis B vaccine at birth, 4 weeks, and 1 year of age. MMR is recommended in a two-dose schedule at 12 and 40 months of age. During the second MMR visit, a booster of dTaP-IPV is provided. A Td/IPV booster is recommended at age 14 years. PCV13 is recommended at 3 and 12 months of age. Conjugate meningococcal C vaccine (MenC) is given in combination with a booster dose of Hib at 12 months, whereas MenB is offered at 2, 4, and 12 months of age, and conjugated MenACWY-135 is offered to adolescents at 14 years, with catch-up available up to 25 years of age. HPV vaccine is recommended for females and males at 12-13 years of age, with catch-up vaccination available up to 25 years of age. Rotavirus vaccination is offered at 2 and 3 months of age. Live attenuated influenza vaccine is provided to children 2-10 years of age. BCG is offered at birth in areas of the country with a TB incidence >40/100,000 or in families with a parent or grandparent born in a high-incidence country. As of June 2021, the UK schedule does not include the varicella and hepatitis A vaccines for universal childhood immunization.

Varicella vaccination has been initiated in 12 of the European Union countries, whereas hepatitis A vaccine is only offered routinely in a handful of these countries. However, hepatitis A is often provided to European children ahead of traveling to other regions of the world.

The 2020 Japanese immunization schedule differs from the U.S. schedule, in that a birth dose of hepatitis B vaccine is recommended only for infants born to mothers who test positive for HbsAg. The Japanese do not use MMR, instead recommending MR with mumps vaccine available on a voluntary basis. The recommendation for routine HPV vaccination was suspended in 2013 because of concerns about adverse events but was included for adolescent females in the 2020 schedule.

VACCINATION OF CHILDREN STARTING IMMUNIZATION OUTSIDE THE UNITED STATES

Some children come to the United States having started or completed international immunization schedules with vaccines produced outside the United States. In general, doses administered in other countries should be considered valid if administered at the same ages as recommended in the United States. For missing doses, age-inappropriate doses, lost immunization records, or other concerns, pediatricians have two options: administer or repeat missing or inappropriate doses, or perform serologic tests and, if they are negative, administer vaccines.

The childhood immunization schedule for China is unique because it recommends a sequential series for polio with IPV at 2 and 3 months of age, followed by OPV at 3 and 4 months of age. The infant primary series with diphtheria-tetanus-pertussis–containing vaccines is recommended at 3, 4, and 5 months of age. Similarly, China's schedule recommends one dose of MR vaccine at 8 months of age followed by one dose of MMR at 18 months.

India's childhood immunization schedule follows the WHO recommendations but includes two fractional doses (one fifth) of a full dose of IPV administered intradermally at 6 and 14 weeks.

Mexico recommends a schedule for pediatric immunization that is largely similar to the schedule in the United States. Some differences include that Mexico recommends the use of BCG and recommends HPV for females, but not males.

Vaccination Against Outbreak-Prone Diseases

Outbreaks spanning large geographical areas have affected several countries or continents caused by Ebola virus, influenza virus, circulating VDPV, and coronaviruses, including SARS-CoV-2 virus, have highlighted the need for preparedness to develop and assess in formal clinical trials and, if successful, rapidly produce vaccines to be used in outbreak response measures. For the Ebola virus outbreaks first identified in 2014 in West Africa and later in Democratic Republic of Congo, two new vaccines based on the recombinant vector-technology platform were developed, tested, and then used successfully in ring-vaccination outbreak vaccination campaigns.

The 2009 influenza A H1N1 pandemic triggered production of pandemic influenza vaccines (following the strain selection by WHO) by seasonal influenza vaccine producers worldwide, and adjuvants were used by several producers with the aim to be dose-sparing.

The eradication goal for polio and the chosen global strategy using a combination of OPV and IPV and the associated rare adverse event vaccine-induced paralytic polio have triggered development of a new oral poliovirus (nOPV) vaccine. This virus is more genetically stable and maintains an attenuation phenotype that will support the Global Polio Eradication Initiative during the final push to eliminate poliovirus globally, with the most immediate need in ongoing outbreak settings to control and eliminate circulating VDPVs.

The COVID-19 outbreak that started in late 2019 triggered unprecedented vaccine development, with clinical trials being conducted during the ongoing outbreak. Favorable short-term efficacy and safety data have resulted in the emergency use listing of eleven COVID-19 vaccines that were recommended by the WHO. The WHO vaccination recommendations had not been vaccine-product specific until the COVID-19 vaccines were made available. Since January 2021, each of the COVID-19 vaccine products has been recommended individually, because they are based on different technology production platforms and have been assessed in clinical trials including different age-groups and using different endpoints. Vaccination of children and adolescents 6 months of age and older is authorized for two mRNA vaccines. In June 2021, China was the first country globally that approved inactivated COVID-19 vaccines for children age 3-17 years. COVID-19 vaccines are made available globally either through direct contracts between vaccine producers and each country or through the COVAX facility, a global risk-sharing mechanism for pooled procurement and equitable distribution of COVID-19 vaccines.

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Chapter 216

Infection Prevention and Control

Kevin P. O'Callaghan and Julia S. Sammons

Infection prevention and control (IPC) programs are a critical and core component of ensuring patient and employee safety in pediatric healthcare systems. The scope of IPC programs is often large and requires a coordinated, well-resourced, multidisciplinary approach. At their heart, IPC programs are designed to prevent the **acquisition** and **transmission** of potentially pathogenic organisms within a healthcare setting. A robust regulatory and policy focus on the prevention of healthcare-associated infections (HAIs) is critical given their frequency. Data from the Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN) provides evidence that on any given day approximately 1 in 31 hospitalized patients experiences at least one HAI. Federal and state-level infrastructures that support HAI improvement efforts include the CDC NHSN, which operates a national surveillance system for HAIs, and the Joint Commission's 2022 National Patient Safety Goals. With improved surveillance and detection and focused improvement efforts, preventable events of harm (including HAIs) are now linked by many payors to reduced levels of reimbursement to offset costs associated with these events.

As our understanding of HAIs has developed over time with better surveillance metrics, reporting has expanded beyond the walls of hospitals to include HAIs occurring throughout healthcare systems. This scope includes infections in ambulatory surgical and medical settings, nursing homes, long-term acute care facilities, and even in patients' homes, especially with regard to medical device–associated infections. We have also expanded our understanding of epidemiologic risk factors, environmental pressures, and specific at-risk patient populations. Through a variety of avenues, IPC programs seek to eliminate transmission events and keep patients and employees safe.

TRANSMISSION IN THE HEALTHCARE SETTING

Fundamentally, transmission in the healthcare setting is multifaceted and multimodal. Patients, their family and caregivers, healthcare personnel, and others interact in a complex environment that is fraught with opportunity for transmission events to occur. Modern understanding of human microbiota informs us that all humans carry a plethora of microorganisms that could potentially be pathogenic in the right circumstances and in the right host. These colonizing microbiotas can be transmitted from one person to another in the healthcare setting through contaminated hands or medical equipment. The majority of infections that arise in healthcare settings occur from endogenous flora representing colonizing organisms. New HAIs require the presence of a number of independent but linked concepts, including a susceptible host, an infectious agent, a portal of entry, and modes of transmission.

Modes of transmission are a critical element of HAI prevention work and include **contact**, **droplet**, and **airborne**. Contact transmission occurs by direct contact with the patient or indirect contact with environmental surfaces or patient care items in the patient's environment that are contaminated with the offending microorganism (e.g., rotavirus). Droplet transmission occurs through large respiratory droplets, which are generated by coughing, sneezing, or talking and typically travel approximately 3 feet from an infectious person (e.g., influenza). These droplets are heavy and do not remain suspended in air for long periods. Airborne transmission occurs through small particles, which can remain suspended in air and can be widely dispersed by air currents (e.g., measles, tuberculosis). Although many infections can occur through transmission directly from an infectious host to a susceptible host, infections can also occur through contact with contaminated environments, whether through contaminated surfaces, fomites, or previously occupied air spaces.

PREVENTION STRATEGIES

Hand Hygiene

One of the most fundamental elements of infection prevention is hand hygiene; thus one of the most critical elements of an IPC program is hand hygiene education and auditing. Ignaz Semmelweis first postulated the effects of hand hygiene in 1847 when he noted epidemiologic differences in maternal mortality rates secondary to puerperal fever between physician- and midwife-delivered pregnancies. The critical difference was hand hygiene, and this proved to be a seminal finding in the field of infection prevention. Growing evidence of the importance of hand hygiene led to the first national hand hygiene guidelines in the 1980s and the development of international guidance on hand hygiene in healthcare. The World Health Organization (WHO) has developed an internationally used framework for hand hygiene education, called the *5 Moments for Hand Hygiene*. This program provides a structure for recognizing critical moments where hand hygiene can influence a transmission event, including before and after touching a patient, before a clean or aseptic procedure, after a body fluid exposure risk, and after touching patient surroundings (Table 216.1). Use of this or similar frameworks provides a structure for staff education around the practice of hand hygiene and serves as an auditing tool to assess rates of compliance with optimal practice.

Hand hygiene itself is the act of either handwashing (placing hands under running water and using friction with or without a soap product) or using a waterless hygiene product (e.g., alcohol-based foams or gels) to remove the burden of surface flora from the skin and nails of the hand. Alcohol-based hand hygiene products are widely available, are quick and easy to use, and allow for repeated in-the-moment use, such that they are the preferred method for hand hygiene for most healthcare situations. However, because they do not remove visible dirt or debris, handwashing with soap and water is recommended over alcohol-based products after dirty tasks when visible soiling is likely, such as after changing a diaper or using the restroom. Alcohol-based products are also not the preferred agents for certain hardy microbes such as norovirus or *Clostridioides difficile* spores, especially in outbreak settings.

Personal Protective Equipment

Personal protective equipment (PPE) is equipment worn to prevent or reduce exposure to potential hazards in the workplace, including infectious diseases. In the healthcare setting, PPE is targeted to prevent exposure of healthcare personnel's skin, eyes, respiratory tract, and mucous membranes to potential infectious agents but is also used to protect patients from the colonizing flora and respiratory secretions of healthcare personnel. Various types of PPE may be used in different settings, with the specific type of PPE tied to the **precautions** that are indicated for a specific patient and/or a specific pathogen. The five primary components of PPE include **gowns**, **gloves**, **masks**, **eye protection**, and **respirators (e.g., N95 or Powered Air-Purifying Respirator)**. Gowns can either be reusable (launderable) or disposable and are designed to prevent contamination of the provider's clothing, particularly from those infectious agents that are spread through a contact mechanism. Depending on the setting, gowns may be required to be resistant to liquid soaking in order to maximize their effectiveness.

Gloves are used most commonly as a component of standard precautions when performing a task where there is a reasonable expectation of soiling of the hands (e.g., changing a diaper or examining a wound). Importantly, glove use is not required for every moment of patient contact (e.g., routine physical exam), and glove use is not a substitute for effective hand hygiene in breaking the chain of transmission. Therefore gloves should never be used as the only element of infection prevention. Hand hygiene before donning of gloves and after removal of gloves is a critical and necessary step in breaking the chain of transmission.

Face masks and eye protection are intended to prevent exposure of a provider's mouth, nose, and eyes from expectorated and aerosolized pathogens. Protection of the eyes can include clear shields attached

Table 216.1 Recommendations for Application of Standard Precautions for Care of All Patients in All Healthcare Settings

COMPONENT	RECOMMENDATIONS
Hand hygiene	Before and after each patient contact, regardless of whether gloves are used. After contact with blood, body fluids, secretions, excretions, or contaminated items; immediately after removing gloves; before and after entering patient rooms. Alcohol-containing antiseptic hand rubs preferred except when hands are visibly soiled with blood or other proteinaceous material or if exposure to spores (e.g., *Clostridium difficile, Bacillus anthracis)* or nonenveloped viruses (norovirus) is likely to have occurred; in these cases, soap and water is required.
PERSONAL PROTECTIVE EQUIPMENT (PPE)	
Gloves	For touching blood, body fluids, secretions, excretions, or contaminated items; for touching mucous membranes and nonintact skin. Employ hand hygiene before and after glove use.
Gown	During procedures and patient-care activities when contact of clothing or exposed skin with blood, body fluids, secretions, or excretions is anticipated.
Mask, eye protection (goggles), face shield	During procedures and patient-care activities likely to generate splashes or sprays of blood, body fluids, or secretions, such as suctioning and endotracheal intubation, to protect healthcare personnel. For patient protection, use of a mask by the person inserting an epidural anesthesia needle or performing myelograms when prolonged exposure of the puncture site is likely to occur.
Soiled patient-care equipment	Handle in a manner that prevents transfer of microorganisms to others and to the environment. Wear gloves if equipment is visibly contaminated. Perform hand hygiene.
ENVIRONMENT	
Environmental control	Develop procedures for routine care, cleaning, and disinfection of environmental surfaces, especially frequently touched surfaces in patient-care areas.
Textiles (linens) and laundry	Handle in a manner that prevents transfer of microorganisms to others and the environment.
PATIENT CARE	
Injection practices (use of needles and other sharps)	Do not recap, bend, break, or manipulate used needles; if recapping is required, use a one-handed scoop technique only. Use needle-free safety devices when available, placing used sharps in puncture-resistant container. Use a sterile, single-use, disposable needle and syringe for each injection. Single-dose medication vials preferred when medications may be administered to more than one patient.
Patient resuscitation	Use mouthpiece, resuscitation bag, or other ventilation devices to prevent contact with mouth and oral secretions.
Patient placement	Prioritize for single-patient room if patient is at increased risk for transmission, is likely to contaminate the environment, is unable to maintain appropriate hygiene, or is at increased risk for acquiring infection or developing adverse outcome after infection.
Respiratory hygiene/cough etiquette (source containment of infectious respiratory secretions in symptomatic patients) beginning at initial point of encounter, such as triage or reception areas in emergency department or physician office	Instruct symptomatic persons to cover nose/mouth when sneezing or coughing; use tissues with disposal in no-touch receptacles. Employ hand hygiene after soiling of hands with respiratory secretions. Wear surgical mask if tolerated or maintain spatial separation (>3 ft if possible).

Adapted from Kimberlin DW, Brady MT, Jackson MA, et al., eds. *Red Book 2018–2021: Report of the Committee on Infectious Diseases,* 31st ed. Elk Grove Village, IL: American Academy of Pediatrics; 2018:148–150.

directly to surgical masks, separate face shields, or goggles, but protection of both forward-facing and lateral aspects of the ocular region is required.

In the setting of a true aerosolized pathogen, respirator use is indicated. Respirator masks include National Institute of Occupational Safety and Health (NIOSH)–approved N95s, so-called because they filter out up to 95% of particles in the air when used appropriately. Other respirator options that meet international standards include KN95 masks, but these may not meet NIOSH standards and should not be used in lieu of an N95. The use of fitted face mask respirators such as the N95 requires a fit-testing program to ensure that healthcare personnel are using a correctly sized and fitted mask at all times. Alternatives to a fitted respiratory mask include the powered air purifying respirator (PAPR), which uses a motor and fan to provide constant pressurized air flow from under a loosely fitting hood over the entire head.

Precautions and Isolation

Precautions and *isolation* are terms to describe in a specific patient-care setting which equipment, practices, and procedures should be used to best prevent against a transmission event related to a known or suspected pathogen.

Standard precautions are used in any setting in which patient care occurs to prevent transmission of a potential pathogen to or from a healthcare worker, regardless of suspected or confirmed infection status of the patient. These include consistent hand hygiene and use of barrier PPE (gown, glove, mask) as required based on risk of exposure

to blood and body fluids, including expectorations and respiratory secretions (e.g., routine use of mask and eye protection during endotracheal intubation).

Isolation procedures, or **transmission-based precautions**, are targeted to prevent transmission of known or suspected pathogens or in the setting of specific syndromes (e.g., infectious diarrhea, upper respiratory tract symptoms). **Contact isolation** typically includes gloves and gown in addition to standard precautions and is used to limit the spread of pathogens by direct contact with a patient (e.g., patients with norovirus). **Droplet isolation** includes protection of mucosal surfaces from expectorated large droplets and should include face mask and eye protection. Some pathogens may spread efficiently by both contact and droplet (e.g., rhinovirus), and thus these two isolation types may be combined as **droplet and contact**.

Airborne isolation is used for pathogens that are readily aerosolized and requires the use of eye protection and use of an appropriate respirator (either N95 or PAPR depending on the employee). Additionally, patients with airborne infections require placement in specialized airborne infection isolation rooms (AIIRs), which have specialized air handling that can maintain negative pressure compared with the surrounding environment and have increased air turnovers per unit time.

ENVIRONMENT, DISINFECTION, AND STERILIZATION

A critical component of preventing transmission of infectious pathogens in healthcare settings includes appropriate environmental cleaning, elimination of potential reservoirs, and disinfection and sterilization of medical equipment.

Maintaining cleanliness (and, where appropriate, sterility) of all patient care spaces, equipment, and medical devices requires an institutional focus on the environment of care that highlights accountability and highly reliable policies and procedures. For each individual healthcare worker, cleanliness of personal medical equipment used in patient care is key. This includes personal stethoscopes, which should be cleaned whenever they are visibly soiled and should be disinfected with an appropriate topical agent (e.g., alcohol) between each use. Similarly, shared patient devices such as thermometers, otoscopes, and ophthalmoscopes should either have disposable single-use covers or should have a cleaning protocol that is adhered to after each patient use.

Higher-level cleaning and disinfection, known as high-level disinfection, are required for reusable items that contact mucous membranes or nonintact skin (e.g., endoscopes), and sterilization is required for critical items that enter sterile tissue or the vascular system (e.g., surgical tools).

VISITATION AND PATIENT AND CAREGIVER MANAGEMENT

In pediatric healthcare settings, unlike adult settings, patients frequently are accompanied by parents, caregivers, and family members throughout their healthcare experience. Visitor and caregiver management is a critical tool in preventing healthcare transmission events in these settings. Limitation of total numbers of visitors at a bedside may be indicated in the setting of local or seasonal outbreaks of disease, such as during influenza season. Similarly, age-based limitations are commonly used to keep siblings of patients away from the healthcare setting, particularly during the winter respiratory viral season. Visitor screening at points of entry can be effective in identifying caregivers and siblings who may not be presenting for care but have evident symptoms of infection and may need to be excluded from the healthcare setting.

OCCUPATIONAL HEALTH AND CLINICIAN EDUCATION

Typically, infection prevention and control programs work closely with occupational or employee health programs because both departments have a responsibility for keeping healthcare workers safe from workplace hazards, including infection. Occupational health and IPC programs may work together to develop on-boarding requirements for vaccination for common diseases and programs for seasonal vaccination for influenza. Annual and as-needed education for healthcare workers is an important role of IPC programs, including education on best practices for hand hygiene, use of PPE, and promoting understanding of patient isolation categories.

SPECIAL POPULATIONS

Immunocompromised Hosts

Immunocompromised hosts include those patients with inborn disorders of immunity and patients with iatrogenically caused immune deficits (e.g., patients undergoing chemotherapy, solid organ, or bone marrow transplant or those using immune-modulating therapies). Immunocompromised hosts pose a special infection prevention problem, as they are typically more susceptible to infections that may be common and benign in other patients and more susceptible to infections that are highly unusual in hosts with intact immune systems, such as invasive mold.

The environment of care for these patients may have additional considerations over and above the norm. **Positive pressure ventilation** can be used to provide a protective environment for such patients during periods of highest risk (e.g., immediately after bone marrow transplantation). A focus on air handling capability, including high-efficiency particulate absorbing (HEPA) filtration, is critically important, especially in settings where construction or renovation is ongoing, as this increases the risk of aerosolization of fungal and mold spores.

Patients with Indwelling Medical Devices

Indwelling medical devices such as pacemakers, orthopedic hardware, intracranial shunts, and indwelling venous catheters pose a special infection risk because of disruption of normal immunologic barriers (e.g., skin) that can allow for communication between sterile and nonsterile spaces and because of the presence of foreign material, which can present a nidus for biofilm formation. IPC programs are frequently involved in quality improvement projects around the optimal insertion and maintenance of such devices, both in the healthcare setting and at home.

Surveillance and Reporting

In addition to the primary prevention work of an IPC program, another core element includes response to transmission events, which critically includes a surveillance and reporting mechanism. IPC programs typically monitor for events of infection within the healthcare setting, such as surgical site infection or new diagnoses of viral respiratory infection so as to generate data about current trends, detect clusters and outbreaks, and guide future policy. Most states require reporting of healthcare-associated events such as infections to a state- and/or federal-level body such as NHSN.

Preparedness, Bioresponse, and Public Health

An important additional element of IPC work is preparedness and planning for community-based outbreaks or epidemics that can affect healthcare operations. Planning for low-likelihood, high-risk pathogens such as Ebola virus requires a multidisciplinary planning team, including hospital operations, IPC, clinical teams, transport services, and others. Scheduled periodic retraining of a core group of healthcare workers can increase their comfort in managing the care of these patients and in decreasing the risk of PPE and isolation breaches that could lead to an event of transmission.

In addition to internal systemwide planning, interfacing with public health bodies is an important responsibility of IPC teams. This responsibility includes reporting of notifiable diseases (e.g., sexually transmitted infections [STIs], tuberculosis, measles), which may require a broader public health response in the community. In the absence of positive test results, individual clinician suspicion of a disease is frequently the initial trigger for public health notification, and so an understanding of reporting requirements is important for each healthcare worker.

IPC is increasingly a complex and specialized area of expertise within healthcare operations. However, at its heart it requires the active participation and commitment of every member of the healthcare team. As such, the best way to keep patients safe is to approach every moment of patient interaction as an opportunity to create a safe and clean environment of care.

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Chapter 217

Childcare and Communicable Diseases

Gail V. Carter-Hamilton and Susan E. Coffin

More than 20 million children <5 years old attend a childcare facility. These facilities can include part-day or full-day programs at nursery schools or preschools and full-day programs based in either a licensed childcare center or another person's home. Regardless of the age at entry, children entering childcare settings are more prone to infections, largely from the exposure to greater numbers of children.

Childcare facilities can be classified based on the number of children enrolled, ages of attendees, health status of the attendees, and type of setting. As defined in the United States, **childcare facilities** consist of childcare centers, small and large family childcare homes, and facilities for ill children or for children with special needs. Centers are licensed and regulated by state governments and care for a larger number of children than are typically cared for in family homes. In contrast, **family childcare homes** are designated as small (1-6 children) or large (7-12 children), may be full-day or part-day, and may be designed for either daily or sporadic attendance. Family childcare homes generally are not licensed or registered, depending on state requirements.

Although many children who attend childcare facilities are cared for in family childcare homes, most studies of infectious diseases in infants and toddlers have been conducted in childcare centers. Almost any organism has the potential to be spread and to cause disease in a childcare setting. Epidemiologic studies have established that children in childcare facilities are 2-18 times more likely to acquire a variety of infectious diseases than children not enrolled in childcare (Table 217.1).

Children who attend childcare facilities are more likely to receive more courses of antimicrobial agents for longer periods and to acquire antibiotic-resistant organisms. Transmission of infectious agents in group care depends on the age and immune status of the children, season, hygiene practices, crowding, and environmental characteristics of the facilities. The pathogen characteristics, including infectivity, survivability in the environment, and virulence, also influence transmission in childcare settings. Rates of infection, duration of illness, and risk for hospitalization tend to decrease among children in childcare facilities after the first 6 months of attendance and decline to levels observed among homebound children after 3 years of age. Adult caregivers are also at increased risk for acquiring and transmitting infectious diseases, particularly in the first year of working in these settings.

EPIDEMIOLOGY

Respiratory tract infections and **gastroenteritis** are the most common diseases associated with childcare. These infections occur in children and their household contacts and in childcare workers and can spread into the community. The severity of illness caused by a given respiratory and enteric pathogen depends on the person's underlying health status, the inoculum, and prior exposures to the pathogen, either by infection or immunization. Some organisms, such as hepatitis A virus (HAV), can cause subclinical disease in young children and produce overt and sometimes serious disease in older children and adults. Other diseases, such as otitis media and varicella, usually affect children rather than adults. Both infections and infestations of the skin and hair may be acquired through contact with contaminated linens or through close personal contact, which is inevitable in childcare settings.

RESPIRATORY TRACT INFECTIONS

Respiratory tract infections account for the majority of childcare-related illnesses. Children <2 years old who attend childcare centers have more upper and lower respiratory tract infections than do age-matched children not in childcare. The organisms responsible for these illnesses are similar to those that circulate in the community and include respiratory syncytial virus (RSV), parainfluenza viruses, influenza viruses, human metapneumoviruses, adenoviruses, rhinoviruses, endemic and epidemic coronaviruses, parvovirus B19, and *Streptococcus pneumoniae.*

Upper respiratory tract infections, including **otitis media**, are among the most common manifestations of these infections. The risk for developing otitis media is 2-3 times greater among children who attend childcare centers than among children cared for at home. Most prescriptions for antibiotics for children <3 years old in childcare are to treat otitis media. These children also are at increased risk for recurrent

Table 217.1 Infectious Diseases in the Childcare Setting

DISEASE	INCREASED INCIDENCE WITH CHILDCARE
RESPIRATORY TRACT INFECTIONS	
Otitis media	Yes
Sinusitis	Probably
Pharyngitis	Probably
Pneumonia	Yes
GASTROINTESTINAL TRACT INFECTIONS	
Diarrhea (rotavirus, norovirus, calicivirus, astrovirus, enteric adenovirus, *Giardia lamblia, Cryptosporidium, Shigella, Escherichia coli* O157:H7, and *Clostridium difficile*)	Yes
Hepatitis A	Yes
SKIN DISEASES	
Impetigo	Probably
Scabies	Probably
Pediculosis	Probably
Tinea (ringworm)	Probably
INVASIVE BACTERIA INFECTIONS	
Haemophilus influenzae type b	No*
Neisseria meningitidis	Probably
Streptococcus pneumoniae	Yes
ASEPTIC MENINGITIS	
Enteroviruses	Probably
HERPESVIRUS INFECTIONS	
Cytomegalovirus	Yes
Varicella-zoster virus	Yes
Herpes simplex virus	Probably
BLOOD-BORNE INFECTIONS	
Hepatitis B	Few case reports
HIV	No cases reported
Hepatitis C	No cases reported
VACCINE-PREVENTABLE DISEASES	
Measles, mumps, rubella, diphtheria, pertussis, tetanus	Not established
Polio	No
H. influenzae type b	No*
Varicella	Yes
Rotavirus	Yes
COVID-19	Yes

*Not in the post–vaccine era; *yes* in the pre–vaccine era.

otitis media, further increasing the use of antimicrobial agents in this population. Studies have demonstrated reductions in both otitis media and antibiotic use subsequent to pneumococcal vaccination implementation. Pharyngeal carriage of group A *Streptococcus* occurs earlier among children in childcare; systemic illness may occur including pneumonia, empyema, septic arthritis, or osteomyelitis. **Influenza** vaccination of younger infants reduces influenza infection and secondary sequelae in both the children and the adults who care for them in their home and in childcare settings. After adoption of the acellular pertussis vaccine, increases in clusters and outbreaks of infection caused by *Bordetella pertussis* have led to the recognition of less durable immunity, with older children and adults serving as reservoirs of infection.

Transmission of these organisms typically occurs through either direct or indirect contact with the respiratory droplets of an infected child. In childcare settings, contamination of surfaces occurs frequently as children mouth toys, drool, and cough or sneeze. Additionally, some respiratory pathogens are spread through large droplets that typically can travel 3-6 feet. However, intimate contact between children is a routine part of the play and care of young children, thus facilitating transmission. The most common surfaces from which airborne droplets can be spread are the hands, so the most efficient form of infection control in the childcare setting is good hand hygiene.

GASTROINTESTINAL TRACT INFECTIONS

Acute infectious **diarrhea** is 2-3 times more common among children in childcare than among children cared for in their homes. Outbreaks of diarrhea, which occur frequently in childcare centers, are usually caused by enteric viruses, such as norovirus, caliciviruses, enteric adenoviruses, and astroviruses, or by enteric parasites such as *Giardia lamblia* or *Cryptosporidium*. A dramatic and sustained decline in the burden of rotavirus infection has been demonstrated since introduction of the rotavirus vaccination program in 2006, and this trend is likely reflected in the population of children attending childcare and early childhood education programs. Bacterial **enteropathogens** such as *Shigella* and *Escherichia coli* O157:H7 and, less often *Campylobacter, Clostridium difficile,* and *Bacillus cereus* also have caused outbreaks of diarrhea in childcare settings. *Salmonella* rarely is associated with outbreaks of diarrhea in childcare settings because person-to-person spread of this organism is uncommon.

Outbreaks of **HAV infection** in children enrolled in childcare facilities have resulted in community-wide outbreaks. HAV infection is typically mild or asymptomatic in young children and often is identified only after symptomatic illness becomes apparent among either older children or adult contacts of children in childcare. Enteropathogens and HAV are transmitted in childcare facilities by the fecal-oral route and can also be transmitted through contaminated food or water. Children in diapers constitute a high risk for the spread of gastrointestinal infections through the fecal-oral route. As such, enteric illness and HAV infection are more common in centers that care for children who are not toilet-trained and where proper hygienic practices are not followed. The most common enteropathogens, such as norovirus and *G. lamblia,* are characterized by low infective doses and high rates of asymptomatic excretion among children in childcare, characteristics that facilitate transmission and outbreaks.

SKIN DISEASES

The most recognized skin infections or infestations in children in childcare are impetigo caused by *Staphylococcus aureus* or group A *Streptococcus*, pediculosis, scabies, tinea capitis, tinea corporis, and molluscum contagiosum. Many of these diseases are spread by contact with infected linens, clothing, hairbrushes, and hats and through direct personal contact; they more often affect children >2 years old. The magnitude of these infections and infestations in children in childcare is not known.

Parvovirus B19, which causes fifth disease (erythema infectiosum), is spread through the respiratory route and has been associated with outbreaks in childcare centers. The rash of fifth disease is a systemic manifestation of parvovirus B19 infection; the child is no longer contagious once the rash is present (see Chapter 298). The greatest health hazard is for pregnant women and immunocompromised hosts because of their respective risks for fetal loss and aplastic crisis.

INVASIVE ORGANISMS AND SYSTEMIC INFECTIONS

Before universal immunization, *Haemophilus influenzae* type b invasive disease was more common among children in childcare than children in homecare. Although the largest burden of invasive *H. influenzae* infection in the pediatric population still occurs in children <5 years old, infection is now primarily caused by nontypeable *H. influenzae* or non–type b encapsulated strains of *H. influenzae;* there have been no reported outbreaks of nontypeable or type b *H. influenzae* in >5 years in the United States.

Data suggest that the risk for primary disease caused by *Neisseria meningitidis* is higher among children in childcare than among children in homecare. Childcare attendance is also associated with nasopharyngeal carriage of penicillin-resistant *S. pneumoniae* and invasive pneumococcal disease, especially among children with a history of recurrent otitis media and use of antibiotics. Secondary spread of *S. pneumoniae* and *N. meningitidis* has been reported, indicating the potential for outbreaks to occur in this setting. Routine use of pneumococcal conjugate vaccine has decreased the incidence of invasive disease and reduced carriage of serotypes of *S. pneumoniae* contained in the vaccine both in the vaccinated child and in younger siblings. A vaccine against serogroup B meningococcus has been introduced for routine use in children <2 years old in the United Kingdom. It is anticipated that infant vaccination against meningococcus will be adopted in the near future. Outbreaks of aseptic meningitis have been reported among children in childcare centers and among their parents and their teachers.

HERPESVIRUSES

As many as 70% of diapered children who become infected with **cytomegalovirus** (CMV) shed virus in urine and saliva for prolonged periods. CMV-infected children often transmit the virus to other children with whom they have contact and to their care providers and their mothers at a rate of 8–20% per year. Transmission occurs as a result of contact with either saliva or urine. The overwhelming majority of primary infections with and reactivation of CMV in otherwise healthy children results in asymptomatic shedding of CMV; nonetheless, this shedding can pose a health risk for previously uninfected pregnant childcare providers or immunocompromised persons. A licensed CMV vaccine is not yet available, but research is ongoing, with recent trials demonstrating tolerability and immunogenicity of candidate CMV vaccines (see Chapter 302).

Varicella often is transmitted in childcare centers, but routine use of varicella vaccine has reduced this risk. Vaccinated children who become infected with varicella often have mild, atypical symptoms and signs of disease that can result in delayed recognition and spread of infection to susceptible contacts. The role of childcare facilities in the spread of **herpes simplex virus**, especially during episodes of gingivostomatitis, requires further clarification.

BLOOD-BORNE PATHOGENS

Hepatitis B virus (HBV) transmission has been reported rarely in childcare settings, and transmission of hepatitis C virus (HCV), hepatitis D virus (HDV), and HIV has not been reported in a childcare setting. However, it is impossible to identify every child who might have a blood-borne infection such as hepatitis B, C, or D, or HIV, and it is critical that standard precautions be observed routinely to reduce the risk for transmitting these viruses and other pathogens.

Concerns have been raised about the risk of HIV transmission in childcare settings and the acquisition of opportunistic infections by HIV-infected children who attend childcare, but experience has revealed that this risk is minimal. Children with HIV infection enrolled in childcare facilities should be kept up to date on their vaccines and monitored for exposure to infectious diseases.

Transmission of blood-borne pathogens can theoretically occur when there is contact between blood or body fluids and a mucous membrane or an open wound. Blood-borne pathogens are unlikely to spread by toddler **biting** in a group setting. Most bites do not break the skin, and if a bite does break the skin, the mouth of the biter does not stay on the victim long enough for blood to transfer from the biter to the victim. If there are concerns about transmission of HBV, HCV, or HIV infection, it is recommended to check the status of the biter rather than the bite victim as part of the initial evaluation process.

ANTIBIOTIC USE AND BACTERIAL RESISTANCE

Antibiotic resistance has become a major global problem and threatens the health of children who attend childcare facilities because the incidence of infection by organisms resistant to frequently used antimicrobial agents has increased dramatically. It is estimated that children in childcare are 2-4 times more likely to receive an antibiotic and that they receive longer courses of antibiotics compared with age-matched children in homecare. This frequency of antibiotic use combined with the propensity for person-to-person transmission of pathogens in a crowded environment has resulted in an increased prevalence of antibiotic-resistant bacteria in the respiratory and intestinal tracts, including *S. pneumoniae, H. influenzae, Moraxella catarrhalis, E. coli* O157:H7, and *Shigella* spp.

Methicillin-resistant *S. aureus* **(MRSA)** has historically been found primarily in the healthcare setting but is now prevalent in the community setting. Traditional childcare center attendance is cited as a risk factor for colonization with MRSA, and carriage is associated with increased risk of infection and transmission. Population-based surveillance has demonstrated a rise in both invasive and noninvasive MRSA infections in community settings over the past 2 decades. Currently, large-scale studies investigating the epidemiology of *S. aureus* in the childcare setting are limited.

PREVENTION

Written policies designed to prevent or to control the spread of infectious agents in a childcare center should be available and should be reviewed regularly. All programs should use a health consultant to help with development and implementation of infection prevention and control (IPC) policies (see Chapter 216). Standards for environmental and personal hygiene should include maintenance of current immunization records for both children and staff, appropriate policies for exclusion of ill children and caretakers, targeting of potentially contaminated areas for frequent cleaning, adherence to appropriate procedures for changing diapers, appropriate handling of food, management of pets, and surveillance for and reporting of communicable diseases. Staff whose primary function is preparing food should not change diapers. Appropriate and thorough **hand hygiene** is the most important factor for reducing infectious diseases in the childcare setting. Strategies for improving adherence to these standards should be implemented. Children at risk for introducing an infectious disease should not attend childcare until they are no longer contagious (Tables 217.2 and 217.3).

Routine vaccination is proven to improve the health of children in childcare settings. In the United States, there are 17 diseases and organisms against which all children should be immunized unless there are contraindications: diphtheria, pertussis, tetanus, measles, mumps, rubella, polio, hepatitis A and hepatitis B, varicella, *H. influenzae* type b, *S. pneumoniae,* rotavirus, *N. meningitidis,* influenza, COVID-19, and human papillomavirus (see Chapter 215). Rates of immunization among children in licensed childcare facilities are high, in part because of laws in almost all states that require age-appropriate immunizations of children who attend licensed childcare programs. Vaccines against influenza, *H. influenzae* type b, hepatitis B, rotavirus, varicella, *S. pneumoniae,* COVID-19, and hepatitis A are of particular benefit to children in childcare centers.

Childcare providers should receive all immunizations that are recommended routinely for adults, including tetanus and diphtheria toxoids and acellular pertussis (Tdap) booster, influenza, and COVID-19 vaccines and should have a preemployment health evaluation, with a tuberculin skin test or interferon-γ release blood assay. Local public health authorities should be notified of cases of reportable communicable disease that occur in children or providers in childcare settings.

STANDARDS

Every state has specific standards for licensing and reviewing childcare centers and family childcare homes. The American Academy of Pediatrics, American Public Health Association, and National Resource

Table 217.2 Disease- or Condition-Specific Recommendations for Exclusion of Children in Out-of-Home Childcare

CONDITION	MANAGEMENT OF CASE	MANAGEMENT OF CONTACTS
COVID-19	Return to class after 10 days from onset and no fever for at least 24 hr without antipyretics.	Varies and evolving but many include being tested ≥5 days from exposure, wearing a mask, checking for symptoms, stay at home if symptoms develop (see latest recommendations at CDC) (see also Chapter 311).
Clostridium difficile	Exclusion until stools are contained in the diaper or child is continent and stool frequency is no more than two stools above that child's normal frequency for the time the child is in the program. Stool consistency does not need to return to normal to be able to return to childcare. Neither test of cure nor repeat testing should be performed for asymptomatic children in whom *C. difficile* was diagnosed previously.	Symptomatic contacts should be excluded until stools are contained in the diaper or child is continent and stool frequency is no more than two stools above that child's normal frequency for the time the child is in the program. Testing is not required for asymptomatic contacts.
Hepatitis A virus (HAV) infection	Serologic testing to confirm HAV infection in suspected cases. Exclusion until 1 wk after onset of illness.	In facilities with diapered children, if one or more cases confirmed in child or staff attendees or two or more cases in households of staff or attendees, hepatitis A vaccine (HepA) or immune globulin intramuscular (IGIM) should be administered within 14 days of exposure to all unimmunized staff and attendees. In centers without diapered children, HepA or IGIM should be administered to unimmunized classroom contacts of index case. Asymptomatic IGIM recipients may return after receipt of IGIM.
Impetigo	No exclusion if treatment has been initiated and as long as lesions on exposed skin are covered.	No intervention unless additional lesions develop.
Measles	Exclusion until 4 days after beginning of rash and when the child is able to participate.	Immunize exposed children without evidence of immunity within 72 hr of exposure. Children who do not receive vaccine within 72 hr or who remain unimmunized after exposure should be excluded until at least 2 wk after onset of rash in the last case of measles.

Continued

Table 217.2 Disease- or Condition-Specific Recommendations for Exclusion of Children in Out-of-Home Childcare—cont'd

CONDITION	MANAGEMENT OF CASE	MANAGEMENT OF CONTACTS
Mumps	Exclusion until 5 days after onset of parotid gland swelling.	In outbreak setting, people without documentation of immunity should be immunized or excluded. Immediate readmission may occur after immunization. Unimmunized people should be excluded for 26 or more days after onset of parotitis in last case. A second dose of MMR vaccine (or MMRV, if age appropriate) should be offered to all students (including those in postsecondary school) and to all healthcare personnel born in or after 1957 who have only received one dose of MMR vaccine. A second dose of MMR also may be considered during outbreaks for preschool-age children who have received one MMR dose. People previously vaccinated with two doses of a mumps-containing vaccine who are identified by public health as at increased risk for mumps because of an outbreak should receive a third dose of a mumps-containing vaccine to improve protection against mumps disease and related complications.
Pediculosis capitis (head lice) infestation	Treatment at end of program day and readmission on completion of first treatment. Children should not be excluded or sent home early from school because of head lice, because this infestation has low contagion within classrooms.	Household and close contacts should be examined and treated if infested. No exclusion necessary.
Pertussis	Exclusion until completion of 5 days of the recommended course of antimicrobial therapy if pertussis is suspected. Children and providers who refuse treatment should be excluded until 21 days have elapsed from cough onset.	Immunization and chemoprophylaxis should be administered as recommended for household contacts. Symptomatic children and staff should be excluded until completion of 5 days of antimicrobial therapy. Untreated adults should be excluded until 21 days after onset of cough.
Rubella	Exclusion for 7 days after onset of rash for postnatal infection.	During an outbreak, children without evidence of immunity should be immunized or excluded for 21 days after onset of rash of the last case in the outbreak. Pregnant contacts should be evaluated.
Infection with *Salmonella* serotypes Typhi or Paratyphi	Exclusion until three consecutive stool cultures obtained at least 48 hr after cessation of antimicrobial therapy are negative, stools are contained in the diaper or child is continent, and stool frequency is no more than two stools above that child's normal frequency for the time the child is in the program.	When *Salmonella* serotype Typhi infection is identified in a child care staff member, local or state health departments may be consulted regarding regulations for length of exclusion and testing, which may vary by jurisdiction.
Infection with nontyphoidal *Salmonella* spp., *Salmonella* of unknown serotype	Exclusion until stools are contained in the diaper or child is continent and stool frequency is no more than two stools above that child's normal frequency for the time the child is in the program. Stool consistency does not need to return to normal to be able to return to childcare. Negative stool culture results *not* required for nonserotype Typhi or Paratyphi *Salmonella* spp.	Symptomatic contacts should be excluded until stools are contained in the diaper or child is continent and stool frequency is no more than two stools above that child's normal frequency for the time the child is in the program. Stool cultures are not required for asymptomatic contacts.
Scabies	Exclusion until after treatment given.	Close contacts with prolonged skin-to-skin contact should receive prophylactic therapy. Bedding and clothing in contact with skin of infected people should be laundered.
Infection with Shiga toxin–producing *Escherichia coli* (STEC), including *E. coli* O157:H7	Exclusion until two stool cultures (obtained at least 48 hr after any antimicrobial therapy, if administered, has been discontinued) are negative, stools are contained in the diaper or child is continent, and stool frequency is no more than two stools above that child's normal frequency. Some state health departments have less stringent exclusion policies for children who have recovered from less virulent STEC infection.	Meticulous hand hygiene; stool cultures should be performed for any symptomatic contacts. In outbreak situations involving virulent STEC strains, stool cultures of asymptomatic contacts may aid in controlling spread. Center(s) with cases should be closed to new admissions during STEC outbreak.
Shigellosis	Exclusion until treatment complete and one or more posttreatment stool cultures are negative for *Shigella* spp., stools are contained in the diaper or child is continent, and stool frequency is no more than two stools above that child's normal frequency for the time the child is in the program. Some states may require more than one negative stool culture.	Meticulous hand hygiene; stool cultures should be performed for any symptomatic contacts.

Table 217.2 Disease- or Condition-Specific Recommendations for Exclusion of Children in Out-of-Home Childcare—cont'd

CONDITION	MANAGEMENT OF CASE	MANAGEMENT OF CONTACTS
Staphylococcus aureus skin infections	Exclusion only if skin lesions are draining and cannot be covered with a watertight dressing.	Meticulous hand hygiene; cultures of contacts are not recommended.
Streptococcal pharyngitis	Exclusion until at least 12 hr after treatment has been initiated.	Symptomatic contacts of documented cases of group A streptococcal infection should be tested and treated if test results are positive.
Tuberculosis	Most children younger than 10 yr are not considered contagious. For those with active disease, exclusion until determined to be noninfectious by physician or health department authority. No exclusion for latent tuberculosis infection (LTBI).	Local health department personnel should be informed for contact investigation.
Varicella	Exclusion until all lesions have crusted or, in immunized people without crusts, until no new lesions appear within a 24-hr period.	For people without evidence of immunity, varicella vaccine should be administered, ideally within 3 days, but up to 5 days after exposure, or when indicated, varicella-zoster immune globulin (VariZIG) should be administered up to 10 days after exposure; if VariZIG is not available, intravenous immunoglobulin (IGIV) should be considered as an alternative. If vaccine cannot be administered and VariZIG/IGIV is not indicated, preemptive oral acyclovir or valacyclovir can be considered.

From Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2021–2024 Report of the Committee on Infectious Diseases*, 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021, Table 2.3, pp. 128–132.

Table 217.3 Recommendations for Inclusion or Exclusion of Childcare*

CHILDREN NEED NOT BE EXCLUDED FOR A MINOR ILLNESS UNLESS ANY OF THE FOLLOWING EXISTS:

- The illness prevents the child from participating comfortably in program activities.
- The illness results in a greater care need than the childcare staff can provide without compromising the health and safety of the other children.
- The child has any of the following conditions: fever, unusual lethargy, irritability, persistent crying, difficulty breathing, or other signs of possible severe illness.
- Diarrhea (defined as an increased number of stools compared with the child's normal pattern, with increased stool water and/or decreased form) that is not contained by diapers or toilet use.
- Vomiting two or more times in the previous 24 hours, unless the vomiting is determined to be caused by a noncommunicable condition and the child is not in danger of dehydration.
- Mouth sores associated with an inability of the child to control his or her saliva, unless the child's physician or local health department authority states that the child is noninfectious.
- Rash with fever or behavior change, until a physician has determined the illness to not be a communicable disease.
- Purulent conjunctivitis (defined as pink or red conjunctiva with white or yellow eye discharge, often with matted eyelids after sleep and eye pain or redness of the eyelids or skin surrounding the eye), until examined by a physician and approved to readmission, with or without treatment.
- Tuberculosis, until the child's physician or local health department authority states that the child is noninfectious.
- Impetigo, until 24 hours after treatment has been initiated.
- Streptococcal pharyngitis, until 24 hours after treatment has been initiated and unless the child has been afebrile for 24 hours.
- Head lice (pediculosis), until the morning after the first treatment.
- Scabies, until after treatment has been completed.
- Varicella, until the sixth day after the onset of rash or sooner if all lesions have dried and crusted.
- Pertussis (which is confirmed by laboratory or suspected based on symptoms of the illness or because of cough onset within 14 days of having face-to-face contact with a person in a household or classroom who has a laboratory-confirmed case of pertussis), until 5 days of appropriate antibiotic therapy (currently: erythromycin) has been completed (total course of treatment is 14 days).
- Mumps, until 9 days after onset of parotid gland swelling.
- Hepatitis A virus infection, until 1 week after onset of illness and jaundice, if present, has disappeared or until passive immunoprophylaxis (immune serum globulin) has been administered to appropriate children and staff in the program, as directed by the responsible health department.

Certain conditions do not constitute a prior reason for excluding a child from childcare unless the child would be excluded by the above criteria or the disease is determined by a health authority to contribute to transmission of the illness at the program. These conditions include the following: a symptomatic excretion of an enteropathogen; nonpurulent conjunctivitis (defined as pink conjunctiva with a clear, watery eye discharge and without fever, eye pain, or eyelid redness); rash without fever and without behavior change; cytomegalovirus infection; hepatitis B virus carrier state; and HIV infection.

*Child and caregiver-specific exclusion policies reflect the present state of knowledge.
From Centers for Disease Control and Prevention: https://dchealth.dc.gov/sites/default/files/dc/sites/doh/publication/attachments/Recommendations%20for%20Inclusion%20or%20Exclusion%20CDC.pdf

Center jointly publish comprehensive health and safety performance standards that can be used by pediatricians and other healthcare professionals to guide decisions about management of infectious diseases in childcare facilities (available at http://nrckids.org/CFOC). Additionally, the **National Association for the Education of Young Children (NAEYC)**, a professional organization supporting early childhood education efforts and volunteer accreditation, is gaining recognition as a resource for health and safety standards for childcare facilities (http://www.naeyc.org/). Specific standards set by all states can be reviewed at the U.S. Department of Health and Human Services' **National Center on Early Childhood Quality Assurance** website (https://childcareta.acf.hhs.gov/licensing).

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Chapter 218

Health Advice for Children Traveling Internationally

John C. Christenson and James G. Carlucci

Children are traveling internationally with increasing frequency and to more exotic destinations that pose unique injury and disease risks. Compared to adults, children are *less* likely to receive pretravel advice and *more* likely to be seen by a medical provider or be hospitalized on return for a travel-related illness. Primary care providers are confronted with the challenge of trying to ensure safe, healthy travel for their patients, whether travel is occurring for purposes of tourism, study abroad, visiting friends and relatives, or volunteerism. Whenever possible, health professionals are encouraged to consult with **travel medicine specialists**, especially when uncertain about pretravel advice, unique travel medicine vaccines (e.g., yellow fever, Japanese encephalitis, typhoid, rabies), and recommendations for malaria medications.

Travel medicine is a unique specialty, and experienced travel medicine practitioners provide specialized guidance on the infectious and noninfectious risks based on age, itinerary, duration, season, purpose of travel, and underlying traveler characteristics (health and vaccination status). A **pretravel consultation** includes the essential elements of (1) safety and preventive counseling against injuries and diseases, (2) routine, recommended, and required vaccinations, based on individual risk assessment, (3) counseling and medications for self-treatment of traveler's diarrhea, and (4) when indicated by itinerary, malaria chemoprophylaxis (Table 218.1).

In the United States, recommendations and vaccine requirements for travel to different countries are provided by the Centers for Disease Control and Prevention (CDC) and are available online at https://wwwnc.cdc.gov/travel/page/yellowbook-home (Table 218.2). Some travel vaccines and medications may not be recommended based on specifics of travel itinerary, trip duration, or patient characteristics. Alternatively, some vaccinations are not approved for younger children because of lack of data or limited immunologic response but may still confer potential benefit to the young traveler with off-label vaccine administration. In both scenarios, consultation or referral to a knowledgeable travel medicine practitioner is encouraged, especially if uncertainty exists regarding pretravel recommendations.

THE PEDIATRIC TRAVEL MEDICINE CONSULTATION

Parents of traveling children should seek medical consultation at least 1 month before departure to review the travel itinerary, obtain safety and preventive counseling, ensure adequate vaccinations (routine, recommended, and required), receive necessary medications for chronic health conditions, and obtain important medications for self-treatment of traveler's diarrhea and, when indicated, malaria chemoprophylaxis with counseling. Advice, vaccinations, and medications should be emphasized as important measures, with the provider goal of keeping the child healthy during travel rather than to discourage traveling.

Pediatric Travelers Visiting Friends and Relatives

Compared to most children traveling internationally, the **pediatric visiting-friends-and-relatives (VFR) traveler** is the most vulnerable population uniquely at risk for travel-related illnesses. VFR travelers may include immigrants, refugees, migrants, students, or displaced persons who are traveling back to their country of origin for the purposes of visiting friends and relatives. Pediatric VFR travelers are typically children accompanying their parents or family members back to their ancestral country, where relational, social, and cultural connections remain. Compared to tourist travelers, VFR travelers are more likely to travel for longer durations, visit more remote destinations, travel by higher-risk local transportation modes, experience closer contact with the local population, and use fewer insect, food, and water precautions. Adult and pediatric VFR travelers are also less likely to perceive a risk of travel-related illnesses, seek pretravel advice, receive travel immunizations, or use effective malaria prophylaxis on arrival in the destination country. VFR travel comprises ~60% of imported malaria in U.S. children (i.e., malaria acquired outside the United States), and pediatric VFR travelers are reported to be 25 times more likely than tourist travelers to acquire malaria. Among all travelers, unvaccinated pediatric VFR travelers remain at higher risk for contracting and having symptomatic illness caused by hepatitis A virus. Several studies suggest that VFR travelers are at disproportionate risk of acquiring typhoid fever and possibly tuberculosis as well.

SAFETY AND PREVENTIVE COUNSELING TOPICS

Health and Evacuation Insurance, Underlying Health Conditions, and Medications

Parents should be made aware that their medical insurance policy might not provide coverage for hospitalizations or medical emergencies in foreign countries and is unlikely to cover the high cost of an emergency medical evacuation. Supplemental **travel medical insurance** and **evacuation insurance** may be purchased and are especially recommended for prolonged travel itineraries, for remote destinations, and for children with higher-risk preexistent health conditions going to countries where inpatient care at a level comparable to the traveler's home country may not be available. Information regarding medical and evacuation insurance providers can be found at the U.S. Department of State International Travel advisory website (https://travel.state.gov/content/travel/en/international-travel/before-you-go/your-health-abroad/insurance-providers-overseas.html) and the CDC Travel Health website (https://wwwnc.cdc.gov/travel/page/insurance).

Parents of children with medical conditions should take with them a brief medical summary and a sufficient supply of prescription medications for their children, with bottles that are clearly identified by prescription labels. For children requiring care by specialists, an international directory for that specialty can be consulted. A directory of physicians worldwide who speak English and who have met certain qualifications is available from the International Society of Travel Medicine (https://www.istm.org). If medical care is needed urgently when abroad, sources of information include the U.S. embassy or consulate, hotel managers, travel agents catering to foreign tourists, and missionary hospitals.

A travel health kit consisting of prescription medications and nonprescription items, such as acetaminophen, an antihistamine, oral rehydration solution packets, antibiotic ointment, bandages, insect repellent (DEET or picaridin), and sunscreen, is highly recommended for all children. Children with persistent asthma should have bronchodilators and oral corticosteroids prescribed for treatment of any acute asthma exacerbations encountered during overseas travel. Children with a history of angioedema, anaphylaxis, or severe allergies to food or insects should have an epinephrine autoinjector (EpiPen) and antihistamines available for use during travel.

Parents and family members should be aware of the prevalence of *counterfeit medication* and lack of quality control of medications in many areas of the world, particularly in low- and middle-income countries. Critical medications, including insulin and newly prescribed antimalarials, should be purchased before international travel and packed in original prescription containers.

Safety and Injury Prevention

Motor vehicle accidents are a leading cause of traumatic injuries, hospitalizations, and deaths, both in pediatric and adult travelers. Differences in traffic patterns and regulations (e.g., right- vs. left-hand traffic and pedestrian right of way) should be emphasized to children, and the use of safety belts should be reinforced. When possible, child safety seats should be taken on the trip. Parents should also be aware of additional risks for small children that may exist overseas, such as open balconies, windows without screens or bars, exposed wires and electrical outlets, paint chips, pest and rodent poison, and stray animals.

Table 218.1 Checklist of Items to Address in the Pretravel Consultation

CATEGORY	ISSUES THAT SHOULD BE ADDRESSED
Patient risk assessment	Obtain history: itinerary, type of travel, personal medical history, age, underlying diseases, allergies, current medications, pregnancy status, previous vaccination status
Immunizations	Update routine immunizations Provide routine travel immunizations Provide destination-specific immunizations
Malaria prophylaxis	If indicated: Provide malaria education and advice; discuss bite-avoidance measures Prescribe antimalaria prophylaxis
Traveler's diarrhea	Prescribe oral rehydration therapy and loperamide (Imodium)* Prescribe appropriate antibiotic (see Table 218.4)
Prevention against mosquito bites	Give advice regarding mosquito-borne disease Discuss personal protection measures
Rabies prevention	Give advice regarding behavior near animals Discuss measures to take if bitten or scratched by an animal—seek urgent medical advice Administer vaccine when indicated
Prevention of sexually transmitted diseases	Provide education regarding safe sex
Zika virus	Discuss potential risk of congenital Zika syndrome for pregnant women or women/men planning to conceive after return from an endemic area

Some of the recommendations are indicated only for specific destinations or specific at-risk groups.
*Contraindicated in bacterial diarrhea, dysentery.
Modified from Matson KB, Siraj DS. Travel medicine. In Kellerman RD, Rakel DP, Heidelbaugh JJ, Lee EM, eds. *Conn's Current Therapy 2023*. Philadelphia: Elsevier; 2023: Table 2, p. 1474.

Water-related activities also are associated with significant injuries in pediatric travelers, and pools and oceanfronts are often unsupervised and without lifeguards at overseas destinations. Injuries to children on **flights** are also well-documented. Children should not sit in aisle seats, as they can be injured by aisle traffic, service carts, and falling objects from overhead storage bins.

Animal Contact

Among travelers, attacks from domestic or stray animals are much more likely to occur than attacks from wild animals. Wounds from animal bites present a risk for bacterial infections, tetanus, and rabies. **Dogs** are responsible for >95% of all **rabies** transmission in Asia, Africa, and Latin America. Globally, the World Health Organization (WHO) estimates that approximately 59,000 human deaths result from rabies each year, with the vast majority of cases occurring in South Asia, Southeast Asia, and Africa. Rabies transmission is reported less frequently after bites from cats and other carnivores, monkeys, and bats. Macaque monkeys native to Asia and North Africa can be found in urban centers and tourist sites and pose a risk for rabies and herpes B virus infections after bites and scratches.

Young children are more likely to be bitten and experience more severe facial wounds because of their short stature. They are at higher risk for rabies exposure from dogs and other animals during travel and require greater supervision. Parents should always encourage their children to report bite injuries and to avoid petting, feeding, or handling dogs, monkeys, and stray animals. Before travel, tetanus vaccinations need to be current for all travelers. Children, long-term travelers, expatriates, and all individuals likely to come into contact with animals in a rabies-endemic region (primarily Africa and South and Southeast Asia) should consider preexposure vaccination for rabies before international travel (see Rabies later). Bite or scratch wounds should be washed thoroughly and for a prolonged time (≥15 minutes) with copious water and soap. Local wound care will substantially reduce the risk of canine and other mammalian rabies transmission. Rabies **postexposure vaccination** and rabies immunoglobulin is likely indicated in most cases, and medical care should be sought emergently. Antibiotics (e.g., amoxicillin-clavulanate) may need to be administered to a child to prevent secondary infections, especially for animal bites involving the hands and head/neck areas.

ROUTINE CHILDHOOD VACCINATIONS REQUIRED FOR PEDIATRIC TRAVEL

Parents should allow at least 4 weeks before departure for optimal administration of vaccines to their children. All children who travel should be immunized according to the routine childhood immunization schedule with all vaccines appropriate for their age. The immunization schedule can be accelerated to maximize protection for traveling children, especially for unvaccinated or incompletely vaccinated children (see Fig. 215.1 in Chapter 215). Routine and catch-up childhood vaccine schedules can be found at the CDC website (https://www.cdc.gov/vaccines/schedules/).

Live-attenuated viral vaccines should be administered concurrently or ≥4 weeks apart to minimize immunologic interference. Intramuscular Immunoglobulin administration interferes with the immune response to measles immunization and possibly to varicella immunization. If a child requires measles or varicella immunization, the vaccines should be given either 2 weeks before or 3 months after immunoglobulin administration (longer with higher doses of intravenous immunoglobulin). Immunoglobulin does not interfere with the immune response to oral typhoid, poliovirus, or yellow fever vaccines.

Vaccine products produced in eggs (yellow fever, influenza) may be associated with hypersensitivity responses, including anaphylaxis in persons with known severe **egg sensitivity**. Screening by inquiring about adverse effects when eating eggs is a reasonable way to identify those at risk for anaphylaxis from receiving influenza or yellow fever vaccines. Although measles and mumps vaccines are produced in chick embryo cell cultures, children with egg allergy are at very low risk for anaphylaxis with these vaccines.

Diphtheria-Tetanus-Pertussis

Children traveling internationally should be fully vaccinated with diphtheria and tetanus toxoids and acellular pertussis (DTaP), having completed the fourth or fifth booster dose by 4-6 years of age. A single dose of an adolescent/adult preparation of tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccine is recommended at 11-12 years of age for those who have completed the recommended primary DTaP (or DTP) series.

Adolescents and adults should receive a single Tdap booster if >5 years have elapsed since the last dose, since a tetanus-containing booster (Td or Tdap) may not be readily available for tetanus-prone wounds during international travel or in remote settings (e.g., adventure travel, wilderness).

Haemophilus influenzae Type b

Haemophilus influenzae type b (Hib) remains a leading cause of meningitis in children 6 months to 3 years of age in many low- and middle-income countries. Before they travel, all unimmunized children <5 years old should be vaccinated against Hib (see Chapter 215). A single dose of Hib vaccine should also be administered to unvaccinated or

partially vaccinated children ≥5 years old if they have anatomic or functional asplenia, sickle cell disease, HIV infection, leukemia, malignancy, or other immunocompromising condition. Unvaccinated children >5 years old do not need vaccination unless they have a high-risk condition.

Hepatitis A

Hepatitis A is a routine childhood vaccine in the United States but requires special considerations in the traveling pediatric patient. Protection from hepatitis A in specific children may also involve the provision of immunoglobulin. For these reasons, hepatitis A vaccination is covered later in Specialized Pediatric Travel Vaccinations.

Hepatitis B

Hepatitis B can be a travel-associated infection. Hepatitis B is highly prevalent throughout much of the world, including areas of South America, sub-Saharan Africa, Eastern and Southeastern Asia, and most of the Pacific basin. In certain parts of the world, 8–15% of the population may be chronically infected. Disease can be transmitted by blood transfusions not screened for hepatitis B surface antigen, exposure to unsterilized needles, close contact with local children who have open skin lesions, and sexual exposure. Exposure to hepatitis B is more likely for travelers residing for prolonged periods in endemic areas. Partial protection may be provided by one or two doses, but ideally three doses should be given before travel. For unvaccinated adolescents, a three-dose hepatitis B vaccine series should be administered, with a minimum interval of 4 weeks between the first and second doses, 8 weeks between the second and third doses, and at least 16 weeks between the first and third doses.

All unvaccinated children and adolescents should receive the accelerated hepatitis B vaccine series before travel. Because one or two doses provide some protection, hepatitis B vaccination should be initiated even if the full series cannot be completed before travel.

Respiratory Viruses

Infections by respiratory viruses such as influenza and SARS-CoV-2 are well recognized as a cause of morbidity among adult and pediatric travelers. Disease caused by these viruses can be prevented through vaccination. The risk for exposure to influenza during international travel varies depending on the time of year, destination, and close contact with infected persons. During the peak of the SARS-CoV-2 pandemic, the use of lockdowns and quarantine, masks, and physical distancing used in many countries to control the spread of SARS-CoV-2 greatly altered the epidemiology of influenza and other respiratory viruses, resulting in few reported infections More recently, influenza appears to have returned to its "traditional" seasonality.

Influenza vaccination is recommended for all children older than 6 months of age and for adults. Vaccines against SARS-CoV-2 are also available (for persons ≥ 6 months of age) and are recommended to prevent severe disease, hospitalization, and death. **Oseltamivir** can be used to treat (and prevent) influenza infections. Antivirals are available to treat serious SARS-CoV-2 infections, especially for high-risk individuals.

There are no available vaccines effective against avian influenza strains such as influenza A H5N1 and H7N9, which have become a great concern worldwide. Because these strains of influenza virus are spread through contact with infected birds, precautions include avoiding direct contact with birds or surfaces with bird droppings, avoiding poultry farms or bird markets, eating only well-cooked poultry or products, and washing hands frequently. **Oseltamivir** is the antiviral of choice to treat infections caused by these viruses.

Measles-Mumps-Rubella

Measles is still endemic in many low- and middle-income countries and in some industrialized nations. It remains a leading cause of vaccine-preventable death in much of the world. Vaccine status for measles is important for all traveling children, particularly if they are traveling to low- and middle-income countries or areas with measles outbreaks. Measles vaccine, preferably in combination with mumps and rubella vaccines (MMR), should be given to all children at 12-15 months and at 4-6 years of age, unless there is a contraindication (see Chapter 215). In children traveling internationally, the second vaccination can be given as soon as 4 weeks after the first to induce immunity among those children who did not respond to the first MMR vaccine.

Children 6-12 months old traveling to low- and middle-income countries should be vaccinated early. The monovalent measles vaccine is not available in the United States, so MMR can be administered. Early vaccination (i.e., 6-12 months of age) will provide some immunity to measles, but antibody response may not be durable or lasting. Therefore any MMR vaccine administered before 12 months of age should not be counted toward the routine vaccination schedule; children vaccinated early for purposes of international travel must be revaccinated on or after their first birthday with two doses separated by at least 4 weeks. Infants <6 months old are generally protected by maternal antibodies (assuming the mother has previously been immunized against measles or had natural infection) and would not need early MMR vaccination before travel.

Pneumococcal Vaccines

Streptococcus pneumoniae is the leading cause of childhood **bacterial pneumonia** and is among the leading causes of bacteremia and bacterial meningitis in children in low- and middle-income and industrialized nations. Preparing a child to travel internationally includes routine or catch-up vaccination with 20-valent pneumococcal conjugate vaccine (PCV20) and, for children with certain high-risk conditions, use of 23-valent pneumococcal polysaccharide vaccine (PPSV23). A single dose of PCV20 should be administered to previously unvaccinated children 6-18 years old with underlying high-risk medical conditions, including anatomic or functional asplenia (including sickle cell disease), HIV infection, a congenital immunodeficiency or immunocompromising condition, chronic heart or lung disease, chronic renal failure or nephrotic syndrome, diabetes mellitus, cerebrospinal fluid leak, or cochlear implant. The Advisory Committee on Immunization Practices (ACIP) also recommends that high-risk children ≥2 years old receive the PPSV23 vaccine ≥8 weeks after their last PCV13 dose. ACIP recommendations on prevention of pneumococcal disease among infants and children using PCV13 and PPSV23 can be found at http://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/pneumo.html.

Polio Vaccine

Poliomyelitis (wild type) was eradicated from the Western Hemisphere in 1991. Polio remains endemic in two countries—Afghanistan and Pakistan—with additional surrounding countries at risk for importation of polio. Unfortunately, many other countries throughout the world, mainly Africa, are experiencing infections by vaccine-derived poliovirus. The poliovirus vaccination schedule in the United States is a four-dose, all-inactivated poliovirus (IPV) regimen (see Chapter 215). Traveling infants should begin the IPV series as early as 6 weeks of age (for an accelerated dosing schedule for children, see Fig. 215.1 and Table 215.1). Length of immunity conferred by IPV immunization is not known; a single booster dose of IPV is therefore recommended for previously vaccinated adolescents and adults traveling to polio-endemic areas if approximately 10 years have elapsed since they completed their primary series. Oral poliovirus vaccine is no longer available in the United States.

Varicella

All children ≥12 months old who have no history of varicella vaccination or chickenpox should be vaccinated unless there is a contraindication to vaccination (see Chapter 215). Unlike measles vaccine (see earlier), varicella vaccine is not approved or recommended for traveling children 6-12 months of age. Infants <6 months old are generally protected by maternal antibodies. All children now require two doses, the first at 12 months of age and the second at 4-6 years. The second dose can be given as soon as 3 months after the first dose. For unvaccinated children ≥13 years old, the first and second doses can be separated by 4 weeks.

SPECIALIZED PEDIATRIC TRAVEL VACCINATIONS

Table 218.2 summarizes the dosages and age restrictions of vaccines specifically given to children traveling internationally.

Cholera

Cholera is present in many low- and middle-income countries, but the risk for infection among travelers to these countries is extremely low. Travelers entering countries reporting cholera outbreaks are at minimal risk of acquiring cholera if they take adequate safe food and water precautions and practice frequent handwashing. No country or territory currently requires cholera vaccination as a condition for entry. Of note, a live-attenuated, single-dose oral suspension vaccine is licensed in the United States to prevent disease in travelers 2-64 years of age visiting endemic regions.

Hepatitis A Vaccination and Preexposure Immunoglobulin

Hepatitis A virus (HAV) is endemic in most of the world, and travelers are at risk, even if their travel is restricted to the usual tourist routes. HAV infection can result from eating shellfish harvested from sewage-contaminated waters, eating unwashed vegetables or fruits, or eating food prepared by an asymptomatic HAV carrier. Young children infected with hepatitis A are often asymptomatic but can transmit infection to unvaccinated older children and adults, who are more likely to develop clinical hepatitis. Few areas carry no risk of HAV infection, and therefore immunization is recommended for all travelers. Hepatitis A vaccine (HepA) is recommended in the United States for universal immunization of all children ≥12 months old, administered as two doses 6 months apart. A single dose of HepA vaccine given to travelers will provide adequate protection. Protective immunity develops within 2 weeks after the initial vaccine dose. A combined three-dose HepA and hepatitis B vaccine (Twinrix, GlaxoSmithKline) is available in the United States but is licensed for use only in individuals >18 years old. Pediatric combination hepatitis A–hepatitis B vaccine (HepA-HepB) (Twinrix-Junior, GlaxoSmithKline) is licensed for use in children 1-18 years old in Canada and Europe. In many countries, a combination hepatitis A–typhoid fever vaccine is available for persons >16 years of age.

Children <1 year old are at lower risk of clinical HAV infection, especially if they are breastfed or residing in areas with safe water for formula reconstitution. Some experts recommend use of preexposure intramuscular immunoglobulin for children <6 months who are traveling internationally to higher-risk destinations, particularly low-income destinations or regions where hygienic or sanitary conditions are limited. However, administration of immunoglobulin diminishes the immunogenicity of live-virus vaccines, in particular measles vaccine, that may be needed for infant travelers. Vaccination against measles should occur ≥2 weeks before any immunoglobulin administration, and a 3-month interval is suggested between immunoglobulin administration and subsequent measles immunization.

Because measles-endemic countries frequently overlap with higher-risk travel destinations for HAV infection, HepA vaccine is recommended for infant travelers 6-11 months of age. Several studies demonstrate that infants as young as 6 months will develop antibodies after HepA, especially if there are no interfering maternal antibodies from prior maternal vaccination or disease. There is potential for a more durable immune response to the HepA vaccination, especially in later infancy, when potential interfering maternal antibody concentrations are lower. If early HepA vaccination is given rather than immunoglobulin to infant travelers (age 6-11 months), it should not count toward the routine two-dose vaccine series. Similar to MMR vaccination, an informed decision should be made with the parents, balancing the risk of travel-associated disease and vaccine adverse events with the potential protective benefit to the traveling infant.

Japanese Encephalitis

Japanese encephalitis is a disease transmitted by mosquitoes in many areas of Asia, especially in rural farming areas. Although it is a leading cause of vaccine-preventable encephalitis in children in many Asian countries and parts of western Pacific countries, the risk of disease to nonimmune travelers is low. A map showing where Japanese encephalitis transmission occurs can be found at https://wwwnc.cdc.gov/travel/yellowbook/2024/infections-diseases/japanese-encephalitis.

Most human infections with **Japanese encephalitis virus (JEV)** are asymptomatic, and <1% of individuals develop clinical disease. With symptomatic disease, the fatality rate is 20–30%, and the incidence of neurologic or psychiatric sequelae in survivors is 30–50%. The risk of JEV disease for pediatric travelers is unknown, but among all travelers, it is estimated to be less than 1 case per 1 million travelers to Asia. However, if residing in a rural area with active JEV transmission in the rainy season, the risk may increase to 5-50 cases per 100,000 population per year. Risk of Japanese encephalitis neurologic disease after mosquito-bite transmission is thought to be higher in children than in adults. The disease occurs primarily from June to September in temperate zones and throughout the entire year in tropical zones. Vaccination is recommended for travelers planning visits >1 months to rural areas of Asia, where the disease is endemic, especially areas of rice or pig farming. Vaccination is recommended for shorter visits to such areas if the traveler will often be outdoors or where increased disease activity is reported. Risk for infection can be greatly reduced by following the standard precautions to avoid mosquito bites.

The inactivated Vero cell culture–derived Japanese encephalitis vaccine (Ixiaro) has replaced the older inactivated mouse brain–derived vaccine (JE-VAX), which is no longer manufactured. Japanese encephalitis vaccine efficacy is >95% in adults who receive two doses administered 7-28 days apart. The licensed range for Japanese encephalitis vaccine has been extended to include children as young as 2 months, with a dose administered on days 0 and 28.

Meningococcal Vaccines

Meningococcal vaccines currently available in the United States include two quadrivalent conjugate A/C/Y/W-135 vaccines, MenACWY-CRM (Menveo) and MenACWY-TT (MenQuadfi), and two meningococcal B vaccines (Bexsero, Trumenba).

Children traveling to those equatorial countries in sub-Saharan Africa (i.e., the "meningitis belt") where the incidence of meningococcal disease (especially group A) is highest should receive a *Neisseria meningitidis* quadrivalent vaccine, especially if travel is prolonged or occurs during the dry season of December to June. Risk is greatest in the meningitis belt of sub-Saharan Africa, with rates of meningococcal disease in endemic regions reaching up to 1,000 cases per 100,000 population per year. Vaccination programs for resident populations with a monovalent group A vaccine in highly endemic areas have resulted in a decrease in cases of invasive disease. In recent years, other serogrups have become more prevalent. Conjugate A/C/Y/W-135 vaccines are available to pediatric travelers ≥2 months of age, but the dosing schedule varies by product and age, as outlined in Table 218.2. Booster doses of conjugate A/C/Y/W-135 should occur every 3-5 years for travelers returning to endemic areas, depending on the age of the pediatric traveler. Providers may also want to consider meningococcal vaccination for other pediatric travelers, especially if there is remote or rural travel within low-income countries with limited healthcare access, because meningococcal outbreaks can occur anywhere in the world. Proof of receipt of quadrivalent meningococcal vaccination is also necessary for individuals traveling to Saudi Arabia for the annual Hajj or Umrah pilgrimage.

Serogroups A and C are most often associated with epidemics of meningitis in sub-Saharan Africa, especially in the meningitis belt of equatorial Africa during the dry season months (December to June). Serogroups Y and W-135 have also been found in meningococcal outbreaks. Serogroup B is associated with more sporadic cases of invasive meningococcal disease in industrialized countries, including the United States. Routine vaccination of travelers with meningococcal B vaccine is currently not recommended. Additional vaccine information on meningococcal vaccination regimens and booster intervals can be found at the CDC website (https://wwwnc.cdc.gov/travel/yellowbook/2024/infections-diseases/meningococcal-disease).

Rabies

Rabies is endemic in many countries in Africa, Asia, and Central and South America. Children are at particular risk because they are less likely to report bites and because facial bites are more common in children. Rabies has the potential for an extended latency period (months) and is uniformly fatal once the clinical symptoms emerge. **Preexposure prophylaxis** is recommended for ambulatory children with extended

Table 218.2 Travel Vaccine Summary Table

VACCINE	TRADE NAME (MFR)	AGE	DOSE	ROUTE	SCHEDULE	BOOSTER
Cholera CVD 103-HgR vaccine	Vaxchora (PaxVax)	18-64 yr	100 mL (reconstituted)	Oral	1 dose[1]	Undetermined[2]
Hepatitis A vaccine, inactivated	Havrix (GlaxoSmithKline)	1-18 yr	0.5 mL (720 ELISA units)	IM	0 and 6-12 mo	None
		≥19 yr	1.0 mL (1,440 ELISA units)	IM	0 and 6-12 mo	None
Hepatitis A vaccine, inactivated	Vaqta (Merck & Co., Inc.)	1-18 yr	0.5 mL (25 U)	IM	0 and 6-18 mo	None
		≥19 yr	1.0 mL (50 U)	IM	0 and 6-18 mo	None
Hepatitis B vaccine, recombinant with novel adjuvant (1018)	Heplisav-B (Dynavax Technologies Corp.)	>18	0.5 mL (20 μg HBsAg and 3,000 μg of 1018)	IM	0, 1 mo	None
Hepatitis B vaccine, recombinant[2,3]	Engerix-B (GlaxoSmithKline)	0-19 yr	0.5 mL (10 μg HBsAg)	IM	0, 1, 6 mo	None
		0-10 yr (accelerated)	0.5 mL (10 μg HBsAg)	IM	0, 1, 2 mo	12 mo
		11-19 yr (accelerated)	1 mL (20 μg HBsAg)	IM	0, 1, 2 mo	12 mo
		≥20 yr (primary)	1 mL (20 μg HBsAg)	IM	0, 1, 6 mo	None
		≥20 yr (accelerated)	1 mL (20 μg HBsAg)	IM	0, 1, 2 mo	12 mo
Hepatitis B vaccine, recombinant[2,3]	Recombivax HB (Merck & Co., Inc.)	0-19 yr (primary)	0.5 mL (5 μg HBsAg)	IM	0, 1, 6 mo	None
		11-15 yr (adolescent accelerated)	1 mL (10 μg HBsAg)	IM	0, 4-6 mo	None
		≥20 yr (primary)	1 mL (10 μg HBsAg)	IM	0, 1, 6 mo	None
Combined hepatitis A and hepatitis B vaccine	Twinrix (GlaxoSmithKline)	≥18 yr (primary)	1.0 mL (720 ELU HAV + 20 μg HBsAg)	IM	0, 1, 6 mo	None
		≥18 yr (accelerated)	1.0 mL (720 ELU HAV + 20 μg HBsAg)	IM	0, 7, and 21-30 days	12 mo
Japanese encephalitis vaccine, inactivated	Ixiaro (Valneva)	2 mo to 2 yr	0.25 mL	IM	0, 28 days	≥1 year after primary series[4]
		3-17 yr	0.5 mL	IM	0, 28 days	≥1 yr after primary series[4]
		18-65 yr	0.5 mL	IM	0, 7-28 days	≥1 yr after primary series[4]
		>65 yr	0.5 mL	IM	0, 28 days	≥1 yr after primary series[4]
Meningococcal polysaccharide tetanus toxoid conjugate vaccine (MenACWY-TT)[5]	MenQuadfi (Sanofi Pasteur)	≥2 yr	0.5 mL	IM	1 dose[6]	If at continued risk[7]
Meningococcal oligosaccharide diphtheria CRM_{197} conjugate vaccine (MenACWY-CRM)[5]	Menveo (GSK)	2-12 mo	0.5 mL	IM	0, 2, 4, 10 mo	If at continued risk[7]
		7-23 yr	0.5 mL	IM	0, 3 mo (second dose administered in second year of life)	
		≥2 yr	0.5 mL	IM	1 dose[6]	

Table 218.2 Travel Vaccine Summary Table—cont'd

VACCINE	TRADE NAME (MFR)	AGE	DOSE	ROUTE	SCHEDULE	BOOSTER
Polio vaccine, inactivated	IPOL (Sanofi Pasteur)	≥18 yr	0.5 mL	SC or IM	1 dose if patient has completed a pediatric series	Repeat boosters may be needed for long-term travelers to polio-affected countries; see Chapter 296
Rabies vaccine (human diploid cell)	Imovax (Sanofi Pasteur)	Any	1 mL	IM	Preexposure series: days 0, 7, and 21 or 28 days	None; see Chapter 320 for postexposure immunization
Rabies vaccine (purified chick embryo cell)	RabAvert (Novartis)	Any	1 mL	IM	Preexposure series: days 0, 7, and 21 or 28 days	None; see Chapter 320 for postexposure immunization
Typhoid vaccine (oral, live, attenuated)	Vivotif (PaxVax)	≥6 yr	1 capsule[8]	Oral	0, 2, 4, 6 days	Repeat primary series after 5 yr
Typhoid vaccine (Vi capsular polysaccharide)	Typhim Vi (Sanofi Pasteur)	≥2 yr	0.5 mL	IM	1 dose	2 yr
Yellow fever	YF-Vax (Sanofi Pasteur)	≥9 mo[9]	0.5 mL[10]	SC	1 dose	Not recommended for most[11]

[1]Must be administered in a healthcare setting.
[2]In a clinical trial, vaccine efficacy was 90% at 10 days postvaccination and declined to 80% at 3 months postvaccination in prevention of severe diarrhea after oral cholera challenge. Long- term immunogenicity is unknown. Clinicians advising travelers who are at continued or repeated risk over an extended period may consider revaccination, although the appropriate interval and efficacy are unknown.
[3]Consult the prescribing information for differences in dosing for hemodialysis and other immunocompromised patients.
[4]If potential for Japanese encephalitis virus exposure continues.
[5]If an infant is receiving the vaccine before travel, two doses may be administered as early as 8 wk apart.
[6]People with HIV, anatomic or functional asplenia, and persistent complement component deficiencies (C3, C5-9, properdin, factor D, and factor H or people taking eculizumab [Soliris]) should receive a two-dose primary series 8-12 wk apart.
[7]Revaccination with meningococcal conjugate vaccine (MenACWY-D or MenACWY-CRM) is recommended after 3 yr for children who received their last dose at <7 yr of age. Revaccination with meningococcal conjugate vaccine is recommended after 5 yr for people who received their last dose at ≥7 yr of age and every 5 yr thereafter for people who are at continued risk.
[8]Must be kept refrigerated at 35.6°F to 46.4°F (2°C to 8°C); administer with cool liquid no warmer than 98.6°F (37°C).
[9]Ages 6-8 mo and ≥60 yr are precautions and age <6 mo is a contraindication to the use of yellow fever vaccine.
[10]YF Vax is available in single-dose and multiple-dose (five-dose) vials.
[11]For full details regarding revaccination, see https://wwwnc.cdc.gov/travel/page/yellow-book-resources.
ACIP, Advisory Committee on Immunization Practices; ELU, ELISA units of inactivated HAV; HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; IM, intramuscular; U, units HAV antigen; SC, subcutaneous.
From Centers for Disease Control and Prevention (CDC). International travel with infants and children: Yellow Book 2024. Atlanta: CDC, 2024. https://wwwnc.cdc.gov/travel/yellowbook

travel to high-risk regions, especially expatriate children and younger children traveling to or living in rural areas where enzootic dog rabies is endemic. Rabies preexposure vaccination should also be considered for adventure travelers (e.g., hikers, bikers), individuals likely to come into contact with rabies vectors (e.g., students working with animal or bat conservation), or travelers with itineraries to rabies-endemic regions where timely, effective **postexposure prophylaxis** might not be available after an animal bite. Most animal bites in a rabies-endemic area should be considered a medical emergency, especially bites from stray dogs, other carnivores, and bats. Immediate and copious wound irrigation should be followed by prompt administration of appropriate postexposure rabies prophylaxis at a medical facility. Postexposure prophylaxis is required even for persons who received preexposure vaccination. Algorithms for preexposure and postexposure vaccination are the same regardless of patient age.

Numerous rabies vaccine formulations exist around the world. In the United States, two rabies vaccines are available: human diploid cell vaccine (HDCV; Imovax, Sanofi Pasteur, SA) and purified chick embryo cell vaccine (PCEC; RabAvert, Novartis). Preexposure prophylaxis is given intramuscularly (HDCV or PCEC) as two doses (1 mL) on days 0 and 7. For previously unvaccinated individuals, postexposure prophylaxis is given as four doses (1 mL) of HDCV or PCEC vaccine intramuscularly on days 0, 3, 7, and 14. A fifth dose is recommended at day 28 for immunocompromised individuals. For previously vaccinated individuals, only two doses (1 mL) intramuscularly on days 0 and 3 are recommended. Previously unvaccinated persons should also receive rabies immunoglobulin (RIG, 20 IU/kg), with as much of the dose as possible infiltrated around the wound site at the time of initial postexposure prophylaxis. Previously vaccinated persons do not require RIG. Unpurified or purified equine RIG preparations are still used in some low- and middle-income countries and are associated with a higher risk for severe reactions, including serum sickness and anaphylaxis. Purified cell culture–derived vaccines also are not always available abroad; travelers should be aware that any rabies vaccines derived from neural tissue carry an increased risk for adverse reactions, often with neurologic sequelae. If rabies prophylaxis is initiated abroad, neutralizing titers should be checked on return and immunization completed with a cell culture–derived vaccine. If rabies prophylaxis cannot be provided abroad, children with high-risk bites (e.g., stray dog) should be emergently transported to a site where they can receive prophylaxis, because the vaccinations should be started as soon as possible after the bite and ideally within 24 hours. Infants and

young children respond well to rabies vaccine, and both preexposure and postexposure vaccinations can be given at any age, using the same dose and schedule as adults. Individual travelers simultaneously receiving mefloquine or chloroquine may have limited immune reactions to intradermal (ID) rabies vaccine and should be vaccinated intramuscularly. The ID administration route is not currently recommended in the United States.

Tuberculosis

The risk for tuberculosis in the typical traveler is low. Pretravel and posttravel testing for tuberculosis is controversial and should be done on an individualized basis depending on the itinerary, duration, and activities (e.g., working in a hospital setting). Immunization with bacille Calmette-Guérin (BCG) is even more controversial. BCG vaccine has variable efficacy in reducing severe tuberculosis disease in infants and young children, is not available in the United States, and is generally not recommended for pediatric travelers. However, parents traveling with young children who plan to reside in countries with high endemic rates of tuberculosis may consider vaccination once in country to prevent disseminated disease. Infection with *Mycobacterium bovis* can be prevented through avoiding consumption of unpasteurized dairy products.

Typhoid

Salmonella Typhi infection, or **typhoid fever**, is common in many low- and middle-income countries in Asia, Africa, and Latin America (see Chapter 244). Typhoid vaccination is recommended for most children ≥2 years old who are traveling to the Indian subcontinent because the incidence of typhoid is 10-100 times higher for travelers to the Indian subcontinent than all other travel destinations. Vaccination should be strongly considered for other travelers to low- and middle-income countries, particularly if they are VFR travelers, lack access to reliable clean water and food, are traveling for a prolonged duration, or are adventurous eaters.

Two typhoid vaccines, the intramuscular (IM) Vi-polysaccharide vaccine and the oral Ty21a strain live-attenuated vaccine, are recommended for use in children in the United States. Both produce a protective response in 50–80% of recipients. The Ty21a vaccine may offer partial protection against *Salmonella* Paratyphi, another cause of enteric fever. Travelers who have had prior diagnoses of typhoid fever should still receive vaccination because past infection does not confer long-term immunity.

The IM Vi-polysaccharide vaccine is licensed for use in children ≥2 years old. It can be given any time before departure, but it should ideally be administered 2 weeks before travel, with a booster needed 2-3 years later. The oral Ty21a vaccine can only be used in children ≥6 years old and is given in four doses over 1 week. Enteric-coated capsules are to be swallowed with a cool or room-temperature drink, at least 1 hour before a meal, every other day until the four doses are completed. Oral typhoid capsules must remain refrigerated (not frozen). Capsules should never be broken open, because vaccine efficacy depends on capsules being swallowed whole in order to pass through the acidic stomach contents. The oral vaccine is associated with an immune response lasting 5-7 years (depending on national labeling). Antibiotics inhibit the immune response to the oral Ty21a vaccine; the vaccine should not be given within 72 hours of antibiotic treatment, and antibiotics should be avoided until 7 days after completing the vaccine series. Studies demonstrate that mefloquine, chloroquine, and atovaquone-proguanil can be given concurrently with the oral Ty21a vaccine without affecting the immunogenicity of the vaccine. Oral Ty21a vaccine should not be given to immunocompromised children; these children should receive the IM Vi-polysaccharide vaccine.

Yellow Fever

Yellow fever (see Chapter 316) is a mosquito-borne viral illness resembling other viral hemorrhagic fevers (see Chapter 317) but with more prominent hepatic involvement. Yellow fever is present in tropical areas of South America and Africa.

Yellow fever vaccination is indicated in children >9 months old traveling to an endemic area. Many countries require yellow fever vaccination by law for travelers arriving from endemic areas, and some African countries require evidence of vaccination from all entering travelers. Current recommendations can be obtained by contacting state or local health departments or the Division of Vector-Borne Infectious Diseases of the CDC (800-232-4636; https://wwwnc.cdc.gov/travel/yellowbook/2024/infections-diseases/yellow-fever.

Most countries accept a medical waiver for children who are too young to be vaccinated (i.e., <6 months of age) and for persons with a contraindication to vaccination. Children with asymptomatic HIV infection may be vaccinated if exposure to yellow fever virus (YFV) cannot be avoided.

Yellow fever vaccine (0.5 mL subcutaneously), a *live-attenuated vaccine* (17D strain) developed in chick embryos, is safe and highly effective in children >9 months old, but in young infants is associated with a greatly increased risk for vaccine-associated encephalitis (0.5-4/1,000) and other severe reactions. Yellow fever vaccine should *never* be given to infants <6 months old; infants 6-8 months old should be vaccinated only in consultation with the CDC or a travel medicine expert to assess the current epidemiology, travel itinerary and duration, and whether the risk of YFV exposure is greater than vaccine risks. In children >9 months old, adverse effects are rare, although vaccine-associated neurotropic and viscerotropic disease associated with the vaccine has been reported. The risk of these reactions is higher in those with thymic disease, altered immune status, multiple sclerosis, or age <9 months (neurotropic disease) or >60 years. Yellow fever vaccination is generally contraindicated in pregnancy and for nursing mothers, unless extended travel to a yellow fever–endemic area is unavoidable.

Children with immunodeficiency or an immunosuppressed state, a thymic disorder or dysfunction (e.g., DiGeorge syndrome), or a history of anaphylactic reactions to eggs *should not receive* yellow fever vaccine. Long-lived immunity develops with this vaccine, perhaps even lasting for a lifetime. Effective July 2016, the WHO and countries following international health regulations no longer require revaccination every 10 years (i.e., a single lifetime dose is now accepted); however, individuals traveling to high-risk areas with active yellow fever transmission and who anticipate frequent or prolonged stays should still consider being reimmunized every 10 years.

TRAVELER'S DIARRHEA

Ingestion of contaminated food or water makes travel-associated diarrhea the most common health complaint among international travelers. Traveler's diarrhea, characterized by a twofold or greater increase in the frequency of unformed bowel movements, occurs in as many as 40% of all travelers overseas (see Chapter 387.1). Children, especially those <3 years old, have a higher incidence of diarrhea, more severe symptoms, and more prolonged symptoms than adults, with a reported attack rate of 60% for those <3 years old in one study.

An important risk factor for traveler's diarrhea is the country of destination. High-risk areas (attack rates of 25–50%) include low- and middle-income countries of Latin America, Africa, the Middle East, and Asia. Intermediate risk occurs in Mediterranean countries, China, and Israel. Low-risk areas include North America, Northern Europe, Australia, and New Zealand. Fecal-oral diarrheal pathogens that children acquire during travel are similar to those acquired by adults and include enterotoxigenic and enteroaggregative *Escherichia coli*, *Campylobacter, Salmonella* (nontyphoidal serotypes predominate), and *Shigella* spp. Enteric protozoa are a much less common cause of traveler's diarrhea than bacterial pathogens; *Giardia lamblia* is the most likely protozoal cause of persistent diarrhea. Less common travel-associated protozoa include *Cryptosporidium* spp., *Entamoeba histolytica,* and *Cyclospora*. Viral infections, particularly rotavirus and norovirus infections, may also cause travel-associated diarrhea in children. Clinicians should be aware that not all diarrheal illness in children is food-borne or water-borne; for example, febrile children with malaria may also present with vomiting and/or nonbloody diarrhea and may be misdiagnosed as having traveler's diarrhea.

Guidance on Prevention of Traveler's Diarrhea

Food and water hygiene remain important measures to reduce the incidence of traveler's diarrhea in children. However, creating long lists of foods to avoid or offering the popular, simple advice of "Boil it, peel it, cook it, or forget it!" is generally an ineffective method of reducing traveler's diarrhea. Most studies show that these types of dietary directives are difficult to keep and may have little impact on the incidence of traveler's diarrhea. In adult studies, the risk of developing traveler's diarrhea appears to be more associated with *where a person eats rather than what they eat*. Eating in a relative's or friend's home is generally safer than eating in a restaurant, where restaurant kitchen hygiene and proper refrigeration may be lacking and employee handwashing may be sporadic.

In general, travel medicine providers can give some commonsense food and water advice to family travelers. Boiled or bottled water, hot beverages, and canned or bottled beverages are generally safe to consume. Ice should be avoided. In low- and middle-income countries, tap water is generally unsafe for drinking or brushing teeth. Boiling water for ≥1 minute (or 3 minutes at altitudes >2,000 meters) remains a reliable method of disinfecting water. Food that is thoroughly cooked and served hot is almost always safe to eat. Dry foods, such as pastry items, breads, and cookies, are generally safe to eat. Unpasteurized milk or other dairy products (cheese) should always be avoided. Breastfeeding should be encouraged for young children, especially infants <6 months old, to reduce exposure to contaminated water or formula. All children should be reminded to wash their hands before eating and after playing around soil or animals. Chemoprophylactic agents for traveler's diarrhea are not recommended for children.

Management of Traveler's Diarrhea

Dehydration is the greatest threat presented by a diarrheal illness in a small child. Parents should be made aware of the symptoms and signs of dehydration and given instructions on how to prepare and administer rehydration solutions. Prepackaged WHO **oral rehydration solution** packets, which are available at stores or pharmacies in almost all low- and middle-income countries, should be part of a child's travel kit. Oral rehydration solution should be mixed as directed with bottled or boiled water and given slowly, as tolerated, to the child while symptoms persist.

Antimotility agents such as diphenoxylate (Lomotil) and loperamide (Imodium) should be avoided in infants and young children. The American Academy of Pediatrics (AAP) does not recommend their routine use in acute gastroenteritis. Use of antimotility agents may be beneficial in older children and adolescents with afebrile, nonbloody traveler's diarrhea. In general, antimotility agents should not distract parents from giving frequent oral rehydration solution, because ongoing intestinal fluid losses likely continue despite a decrease in stooling. Bismuth subsalicylate for acute gastroenteritis should be avoided because of concern for toxicity and Reye syndrome.

Presumptive Antibiotic Treatment

Oral rehydration is the mainstay of treatment for pediatric traveler's diarrhea. However, antibiotics should be prescribed for the pediatric traveler, with parental instructions to start presumptive treatment early in the diarrheal illness (Tables 218.3 and 218.4). Systemic antibiotics can shorten the duration and severity of diarrheal illness, especially if presumptive antibiotics are initiated immediately after the onset of traveler's diarrhea. For children, the drug of choice is **azithromycin** (10 mg/kg once daily for up to 3 days, with a maximum daily dose of 500 mg). **Ciprofloxacin** (10 mg/kg per dose twice daily for up to 3 days, maximum dose of 500 mg twice daily) is an alternative but should not be prescribed for travelers to the Indian subcontinent or Southeast Asia, where fluoroquinolone resistance is common. Shiga toxin–producing *E. coli,* such as *E. coli* O157:H7, is an extremely uncommon cause of pediatric traveler's diarrhea in nonindustrialized countries, and the benefit of presumptive antibiotic therapy in traveling children, even with bloody diarrhea, typically outweighs the low risk of developing hemolytic-uremic syndrome. Parents need to be aware that the use of antibiotics for the treatment of traveler's diarrhea has been associated with colonization with highly resistant organisms such as extended-spectrum β-lactamase–producing Enterobacteriaceae. These organisms could later cause infections once back home.

Azithromycin is highly effective against most bacterial pathogens that cause traveler's diarrhea and is the preferred antibiotic among many travel experts. Azithromycin can be prescribed in powder form that can be reconstituted with safe water into a liquid suspension when needed. Amoxicillin, trimethoprim-sulfamethoxazole (cotrimoxazole), and erythromycin should *not* be prescribed for self-treatment of traveler's diarrhea, because of widespread resistance among diarrheal pathogens. Traveler's diarrhea that results in bloody stools, persistently high fevers, systemic chills and rigors, severe or localizing abdominal pain, or continued fluid losses should prompt additional medical evaluation.

Table 218.3 Traveler's Diarrhea Empiric Treatment Recommendations

Therapy of mild traveler's diarrhea: diarrhea that is tolerable, is not distressing, and does not interfere with planned activities.

- Antibiotic treatment is not recommended in patients with mild traveler's diarrhea.
- Loperamide or BSS may be considered in the treatment of mild traveler's diarrhea in older children.

Therapy of moderate traveler's diarrhea: diarrhea that is distressing or interferes with planned activities.

- Antibiotics may be used to treat cases of moderate traveler's diarrhea.
- Fluoroquinolones may be used to treat moderate traveler's diarrhea depending on resistance patterns of country or region.
- Azithromycin may be used to treat moderate traveler's diarrhea.
- Rifaximin may be used to treat moderate, noninvasive traveler's diarrhea.
- Loperamide may be used as adjunctive therapy for moderate to severe traveler's diarrhea. Antimotility agents alone are not recommended for patients with bloody diarrhea or those who have diarrhea and fever.
- Loperamide may be considered for use as monotherapy in moderate traveler's diarrhea in older children.

Therapy of severe traveler's diarrhea: diarrhea that is incapacitating or completely prevents planned activities: all dysentery is considered severe.

- Antibiotics should be used to treat severe traveler's diarrhea.
- Azithromycin is preferred to treat severe traveler's diarrhea.
- Fluoroquinolones may be used to treat severe, nondysenteric traveler's diarrhea depending on resistance patterns of country or region.
- Rifaximin may be used to treat severe, nondysenteric traveler's diarrhea.*
- Single-dose antibiotic regimens may be used to treat traveler's diarrhea.

*These treatment recommendations were developed before the approval of rifamycin SV in the United States. Because it is in the same category of antimicrobial drug as rifaximin and because they have the same mechanism of action, rifamycin SV can be considered as an alternative to rifaximin.

Modified from Centers for Disease Control and Prevention (CDC). International travel with infants and children: Yellow Book 2024. Atlanta: CDC, 2020. Box 2-04 and Table 2-10. https://wwwnc.cdc.gov/travel/yellowbook/2024/preparing/travelers-diarrhea#treatment

INSECT-BORNE INFECTIONS

Insect-borne infections for which traveling children are most at risk include malaria, dengue, chikungunya, yellow fever, Zika, and Japanese encephalitis, depending on the area of travel. **Malaria** is transmitted by nighttime biting *Anopheles* mosquitoes, whereas **dengue** occurs from mosquito species *(Culex, Aedes)* that are predominantly active during the day. Families should be encouraged to protect children against daytime and nighttime biting mosquitoes, because many regions of the world where malaria is found also have diseases transmitted by daytime

Table 218.4 Acute Diarrhea Adult Antibiotic Treatment Recommendations*

ANTIBIOTIC*	DOSE	DURATION
Azithromycin†,‡	1,000 mg	Single or divided dose§
	500 mg daily	3 days
Levofloxacin	500 mg daily	1-3 days§
Ciprofloxacin	750 mg	Single dose§
	500 mg bid	3 days
Ofloxacin	400 mg bid	1-3 days§
Rifamycin SV‖	388 mg bid	3 days
Rifaximin‖	200 mg tid	3 days

*See also Chapter 387.1. Lower weight-based dosing should be used where appropriate.
*Antibiotic regimens may be combined with loperamide 4 mg initially followed by 2 mg after each loose stool, not to exceed 16 mg in a 24-hr period. This is the adult dose of loperamide, which might be appropriate for older children and adolescents, but antimotility agents are generally not recommended for younger children, and if they are used then lower doses may be more appropriate.
†Use empirically as first-line in Southeast Asia or other areas if fluoroquinolone-resistant bacteria are suspected.
‡Preferred regimen for dysentery or febrile diarrhea.
§If symptoms are not resolved after 24 hr, continue daily dosing for up to 3 days.
‖Do not use if clinical suspicion for *Campylobacter, Salmonella, Shigella,* or other causes of invasive diarrhea. Use may be reserved for patients unable to receive fluoroquinolones or azithromycin.
From Centers for Disease Control and Prevention (CDC). International travel with infants and children: Yellow Book 2024. Atlanta: CDC, 2024. Table 2-09. https://wwwnc.cdc.gov/travel/yellowbook/2024/preparing/travelers-diarrhea#table 209

biting mosquitoes (dengue, Zika, chikungunya). Zika can also be sexually transmitted, so sexually active adolescents and young adults need to be advised on these additional risks when traveling to Zika-endemic regions. In addition to insect bite prevention using insect repellents, methods of contraception should be discussed with the traveler. Ticks, fleas, lice, and other arthropods are also known to transmit rickettsial, borrelial, and parasitic pathogens, but transmission can be prevented by close attention to measures to mitigate exposures that are appropriate when outdoors, close inspection for ticks once returning indoors, and use of insect repellents on skin and clothing with products containing DEET and permethrin, respectively.

Exposure to insect bites can be reduced by wearing appropriate attire and using insect repellents containing *N,N*-diethyl-*m*-toluamide (**DEET**) or picaridin. The AAP recommends avoiding DEET-containing repellents in children <2 months old. Rare cases of neurologic events have been reported in very young children with exposure to inappropriate, frequent applications of DEET-containing repellents (>10 times/day) or who licked off DEET. Concentrations of 25–30% DEET need be applied every 4-6 hours, as needed, whereas 5–7% DEET provides only 1-2 hours of protection time. DEET concentrations >40–50% do not confer a substantially longer protection time for children and are not recommended.

Picaridin is fragrance-free, effective, and generally well tolerated on exposed skin and faces. It has similar efficacy to DEET but with less inhalational or dermal irritation. Picaridin at concentrations of 20% or higher provides adequate protection against *Anopheles* mosquitoes that have potential to transmit malaria. When applying sunscreen and insect repellent, sunscreen should be applied first, followed by DEET or picaridin.

Spraying or treating clothing with **permethrin**, a synthetic pyrethroid, is a safe and effective method of further reducing insect bites in children. Permethrin can be applied directly to clothing, bed nets, shoes, and hats and should be allowed to dry fully before use. As an insecticide, permethrin should never be applied to skin. Permethrin-treated garments retain both repellency and insecticidal activity, even with repeated laundering. Clothing will eventually need to be retreated to maintain repellency, according to the product label. Bed nets, particularly permethrin-impregnated bed nets, also decrease the risk of insect bites, and their use is highly recommended in malarial areas.

MALARIA CHEMOPROPHYLAXIS

Malaria, a mosquito-borne infection, is the leading parasitic cause of death in children worldwide (see Chapter 334). Of the five *Plasmodium* species that infect humans, *Plasmodium falciparum* causes the greatest morbidity and mortality. Each year, >8 million U.S. citizens visit parts of the world where malaria is endemic (sub-Saharan Africa, Central and South America, India, Southeast Asia, Oceania). Children accounted for 15–20% of imported malaria cases in a WHO study in Europe. Given travel of young children with their families to endemic countries, physicians in industrialized countries are increasingly required to give advice on prevention, diagnosis, and treatment of malaria. **Risk factors** for severe malaria and death include inadequate adherence to chemoprophylaxis, delay in seeking diagnosis and medical care, and nonimmune status, but the case-fatality rate of imported malaria remains <1% in children from nonendemic countries. The CDC maintains updated information at https://wwwnc.cdc.gov/travel/yellowbook/2024/infections-diseases/malaria, as well as a malaria hotline for physicians (770-488-7788). It is important to check this updated information, because recommendations for prophylaxis and treatment are often modified as a result of changes in the risk for developing malaria in different areas of the world, changing *Plasmodium* resistance patterns, and the availability of new antimalarial medications.

Avoidance of mosquitoes and **barrier protection** from mosquitoes are an important part of malaria prevention for travelers to endemic areas. The *Anopheles* mosquito feeds from dusk to dawn. Travelers should remain in well-screened areas, wear clothing that covers most of the body, sleep under a bed net (ideally impregnated with permethrin), and use insect repellents with DEET during these hours. Parents should be discouraged from taking a young child on a trip that will entail evening or nighttime exposure in areas endemic for *P. falciparum*.

Chemoprophylaxis is the cornerstone of malaria prevention for nonimmune children and adults who travel to malaria-endemic areas *but is not a replacement for other protective measures*. Travelers often do not take malaria prophylaxis as prescribed or at all. They are more likely to use prophylactic antimalarial drugs if their physicians provide appropriate recommendations and education before departure. However, in one survey, only 14% of persons who sought medical advice obtained correct information about malaria prevention and prophylaxis. Families with children visiting friends and relatives are particularly less likely to take malaria prophylaxis or seek pretravel medical advice.

Resistance of *P. falciparum* to the traditional chemoprophylactic agent, **chloroquine**, is widespread, and in most areas of the world other agents must be used (Table 218.5). Factors that must be considered

Table 218.5 Antimalarial Chemoprophylaxis for Children

AREA	DRUG	ADULT DOSE	PEDIATRIC DOSE	ADVANTAGES	DISADVANTAGES	COMMENTS
Chloroquine-resistant area	Mefloquine*,†	250 mg salt (228 mg base) tablets One tablet weekly	Weight <10 kg: 5 mg salt (4.6 mg base)/kg/week	Once-weekly dosing	Bitter taste No pediatric formulation Side effects of sleep disturbance, vivid dreams	Children going to malaria-endemic area for ≥4 wk Children unlikely to take daily medication
			Weight 10-19 kg: ¼ tablet/week			
			Weight 20-30 kg: ½ tablet/week			
			Weight 31-45 kg: ¾ tablet/week			
			Weight >45 kg: 1 tablet/week			
	Doxycycline‡	100 mg tablet One tablet daily	2.2 mg/kg daily (max: 100 mg)	Known safety profile Readily available in most pharmacies	Prolonged (>21 days) courses should not be given to children <8 yr old Daily dosing Must take with food or causes stomach upset Photosensitivity Yeast superinfections	Children ≥8 yr old going to area for <4 wk who cannot take or cannot obtain atovaquone-proguanil
	Atovaquone-proguanil§ (Malarone)	250/100 adult tablet One tablet daily	Pediatric tablet: 62.5 mg atovaquone/25 mg proguanil	Pediatric tablet formulation available Generally well tolerated	Daily dosing Expensive Can cause stomach upset	Children going to malaria-endemic area for <4 wk
			Weight 5-8 kg: ½ pediatric tablet once daily			
			Weight >8-10 kg: ¾ pediatric tablet once daily			
			Weight >10-20 kg: 1 pediatric tablet once daily			
			Weight >20-30 kg: 2 pediatric tablets once daily			
			Weight >30-40 kg: 3 pediatric tablets once daily			
			Weight >40 kg: 1 adult tablet once daily			
Chloroquine-susceptible area	Chloroquine phosphate	500 mg salt (300 mg base) One tablet weekly	8.3 mg/kg salt (5 mg/kg base) weekly, up to maximum adult dose of 500 mg salt	Once-weekly dosing Generally well tolerated Safe in pregnancy	Bitter taste No pediatric formulation	Best medication for children traveling to areas with *Plasmodium falciparum* or *P. vivax* that is chloroquine susceptible
	Hydroxychloroquine	400 mg of salt (310 mg of base)	6.5 mg/kg of salt (5 mg/kg of base) once weekly, up to maximum adult dose of 400 mg of salt	Safe in pregnancy		Alternative when chloroquine is unavailable for travelers to areas with *P. falciparum* or *P. vivax* that is chloroquine susceptible

Continued

Table 218.5 Antimalarial Chemoprophylaxis for Children—cont'd

AREA	DRUG	ADULT DOSE	PEDIATRIC DOSE	ADVANTAGES	DISADVANTAGES	COMMENTS
Terminal prophylaxis (antirelapse therapy) for regions predominantly with *P. vivax* and *P. ovale*.	Primaquine	26.3 mg salt (15 mg base) tablets; 2 tablets once daily for 14 days after departure from malarious area.	0.8 mg/kg of salt form (0.5 mg/kg of base) once daily for 14 days after departure from malarious area	Reduce risk for relapses by *P. vivax* and *P. ovale*.	May cause hemolysis in persons with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Contraindicated in pregnancy and breastfeeding mothers.	Must confirm G6PD sufficiency before administration.
Short-term prophylaxis for regions with predominantly *Plasmodium vivax*	Primaquine	26.3 mg salt (15 mg base) tablets; 2 tablets. Begin 1-2 days before travel to malarious areas, continue for 7 days after leaving area.	0.8 mg/kg of salt form (0.5 mg/kg of base). Begin 1-2 days before travel to malarious areas, continue for 7 days after leaving area.	Reduce risk for relapses by *P. vivax*.	May cause hemolysis in persons with G6PD deficiency. Contraindicated in pregnancy and breastfeeding mothers.	Must confirm G6PD sufficiency before administration.
Terminal prophylaxis (antirelapse therapy) for regions predominantly with *P. vivax*	Tafenoquine **(Krintafel)**	150 mg tablets; ≥16 yr: 2 tablets, single dose	Not recommended	Single dose	May cause hemolysis in persons with G6PD deficiency. Contraindicated in pregnancy and breastfeeding mothers.	Must confirm G6PD sufficiency before administration.
Prophylaxis against all *Plasmodium* spp.	Tafenoquine **(Arakoda)**	100 mg tablets; ≥18 yr: 2 tablets, daily for 3 days before travel. Weekly during travel (starting 1 wk after last pretravel dose). Once 1 wk after travel	Not recommended	Effective against all *Plasmodium* spp.	May cause hemolysis in persons with G6PD deficiency. Contraindicated in pregnancy and breastfeeding mothers.	Must confirm G6PD sufficiency before administration.

*Chloroquine and mefloquine should be started 1-2 wk before departure and continued for 4 wk after last exposure.
†Mefloquine resistance exists in western Cambodia and along the Thailand-Cambodia and Thailand-Myanmar borders. Travelers to these areas should take doxycycline or atovaquone-proguanil. See text for precautions about mefloquine use.
‡Doxycycline should be started 1-2 days before departure and continued for 4 wk after last exposure. Do not use in children <8 yr old or in pregnant women.
§Atovaquone-proguanil (Malarone) should be started 1-2 days before departure and continued for 7 days after last exposure; should be taken with food or a milky drink. Not recommended in pregnant women, children who weigh <5 kg, and women breastfeeding infants who weigh <5 kg. Contraindicated in individuals with severe renal impairment (creatinine clearance <30 mL/min).
Drugs used for chloroquine-resistant areas can also be used in chloroquine-susceptible areas.

in choosing appropriate chemoprophylaxis medications and dosing schedules include age of the child, travel itinerary (including whether the child will be traveling to areas of risk within a particular country and whether chloroquine-resistant *P. falciparum* is present in the country), vaccinations being given, allergies or other known adverse reactions to antimalarial agents, and the availability of medical care during travel.

Children traveling to areas with chloroquine-resistant *P. falciparum* can be given mefloquine, atovaquone-proguanil, or doxycycline (if >8 years old) as malaria prophylaxis. For trips shorter than 4 weeks, atovaquone-proguanil is the preferred medication, because it is given for only a short period before and after travel. Atovaquone-proguanil or doxycycline is also preferred for travel of any duration to western Cambodia and the Thailand-Cambodia and Thailand-Myanmar borders because of mefloquine resistance in these areas. For periods of travel >4 weeks to all other areas with chloroquine-resistant *P. falciparum,* mefloquine is the preferred medication because it can be taken weekly.

Mefloquine is FDA approved only for children weighing >15 kg, but the CDC recommends mefloquine prophylaxis for all children regardless of weight because the risk for acquiring severe malaria outweighs the risk for potential mefloquine toxicity. Adults taking mefloquine prophylaxis have a 10–25% incidence of sleep disturbance and dysphoria and, less frequently, more serious neuropsychiatric symptoms. These side effects appear to be less common in children. Other potential side effects of mefloquine therapy include nausea and vomiting.

The lack of a liquid or suspension formulation for all antimalarial agents can make administration difficult. For children who cannot take tablets, parents should take a chloroquine or mefloquine prescription

to a compounding pharmacy, which can pulverize the tablets and place exact dosages into gel capsules. Parents can then open the gel capsules and sprinkle the powder into food. Disguising these medications, which have a bitter taste, is important; chocolate syrup has been used successfully as a vehicle for the medication. Persons with depression, neuropsychiatric disorders, seizure disorders, or cardiac conduction defects should not take mefloquine.

Atovaquone-proguanil fixed combination (Malarone) is an effective and safe chemoprophylaxis for travelers to chloroquine-resistant malaria-endemic areas. Adverse effects are infrequent and mild (abdominal pain, vomiting, and headache) and infrequently result in discontinuation of the medication. Atovaquone-proguanil prophylaxis must be taken every day with food, so it is better suited for prophylaxis during short periods of exposure. Recent data allow dosing down to 5 kg body weight, although the use of atovaquone-proguanil in children weighing 5-10 kg is considered off-label.

Daily **doxycycline** is an alternative chemoprophylaxis regimen for chloroquine-resistant *P. falciparum* malaria. Doxycycline has been used extensively and is highly effective. Use in children <8 years old should be avoided, as courses >21 days are usually required and safety data are limited in this age-group. Adverse effects (nausea, vomiting, photosensitivity, vaginal candidiasis) are relatively uncommon. Persons given doxycycline prophylaxis should be warned to decrease exposure to direct sunlight, wear protective clothing (long sleeves and brimmed hat), and use sunscreen to minimize the possibility of photosensitivity.

Primaquine has also been used successfully as chemoprophylaxis, especially in areas of high prevalence of *Plasmodium vivax* and *Plasmodium ovale,* but there are limited data about its use in nonimmune children. Primaquine prophylaxis for children should only be given in consultation with the CDC or a travel medicine specialist.

Chloroquine, chloroquine-proguanil, and azithromycin do not provide adequate protection for children traveling to a chloroquine-resistant malaria-endemic area.

In areas of the world where *P. falciparum* remains fully chloroquine-sensitive (Haiti, the Dominican Republic, Central America west of the Panama Canal, and some countries in the Middle East), weekly chloroquine is the drug of choice for malaria chemoprophylaxis. Updated information on chloroquine susceptibility and recommended malaria prophylaxis is available at https://wwwnc.cdc.gov/travel/yellowbook/2024/infections-diseases/malaria.

On leaving an area endemic for *P. vivax* or *P. ovale* after a prolonged visit (usually >3 months), travelers should consider terminal prophylaxis with primaquine (0.5 mg/kg base) daily, up to a maximum dose of 30 mg base or 52.6 mg salt, for 14 days, to eliminate extraerythrocytic forms of *P. vivax* and *P. ovale* and prevent relapses. Screening for glucose-6-phosphate dehydrogenase (G6PD) deficiency is mandatory before primaquine treatment, because primaquine is contraindicated in G6PD-deficient persons because it can cause severe hemolysis.

Small amounts of antimalarial drugs are secreted into breast milk. The amounts of transferred drug are not considered to be either harmful or sufficient to provide adequate prophylaxis against malaria. Prolonged infant exposure to doxycycline through breast milk is not advisable.

Self-treatment of presumptive malaria during travel remains controversial. It should never be substituted for seeking appropriate medical care, but it can be considered in special circumstances such as travel to remote areas, intolerance of prophylaxis, or refusal of chemoprophylaxis by the traveler. Self-treatment medication should be different from the prescribed chemoprophylaxis. The CDC or a travel medicine specialist should be consulted if self-treatment medication is being considered for a traveler.

THE RETURNING TRAVELER

Posttravel evaluations are part of travel medicine and continuing care. Physicians unfamiliar with diseases that occur in low- and middle-income countries often misdiagnose the cause of illness in a child returning from travel abroad. Among returning patients identified from the GeoSentinel Surveillance Network sites who were ill, the most common disorders (in descending order of frequency) included malaria, giardiasis, dengue fever, campylobacteriosis, cutaneous larva migrans, enteric fever, spotted fever (rickettsiosis), chikungunya fever, hepatitis A, and influenza. Returning pediatric travelers who are severely ill or with continued fevers should be seen in consultation with a pediatric travel medicine or infectious diseases specialist. The cause of fever may be suggested by the geographic area (Table 218.6) and incubation period (Table 218.7).

Among all persons returning from travel (children and adults), three major patterns of illness have been noted (Table 218.8). The etiology of each of these disease presentations in part depends on the country or geographic region visited (see Table 218.6). Table 218.9 provides suggestive clues to a diagnosis.

Table 218.6 Common Causes of Fever by Geographic Area

GEOGRAPHIC AREA	COMMON TROPICAL DISEASE-CAUSING FEVER	OTHER INFECTIONS CAUSING OUTBREAKS OR CLUSTERS IN TRAVELERS
Caribbean	Chikungunya, dengue, malaria (Haiti), Zika	Acute histoplasmosis, leptospirosis
Central America	Chikungunya, dengue, malaria (primarily *Plasmodium vivax*), Zika	Leptospirosis, histoplasmosis, coccidioidomycosis
South America	Chikungunya, dengue, malaria (primarily *P. vivax*), Zika	Bartonellosis, leptospirosis, enteric fever, histoplasmosis
Southcentral Asia	Dengue, enteric fever, malaria (primarily non–*P. falciparum*)	Chikungunya
Southeast Asia	Dengue, malaria (primarily non–*P. falciparum*)	Chikungunya, leptospirosis
Sub-Saharan Africa	Malaria (primarily *P. falciparum*), tick-borne rickettsiae (main cause of fever in southern Africa), acute schistosomiasis, dengue	

https://wwwnc.cdc.gov/travel/yellowbook/2024/posttravel-evaluation/general-approach-to-the-returned-traveler
From Centers for Disease Control and Prevention (CDC). International travel with infants and children: Yellow Book 2024. Wilson ME. Post-travel evaluation. Atlanta: CDC, 2024. Table 11-09.

Table 218.7 Common Infections by Incubation Period

DISEASE	USUAL INCUBATION PERIOD (RANGE)	DISTRIBUTION
INCUBATION <14 DAYS		
Chikungunya	2-4 days (1-14 days)	Tropics, subtropics
Dengue	4-8 days (3-14 days)	Topics, subtropics
Encephalitis, arboviral (Japanese encephalitis, tick-borne encephalitis, West Nile virus, other)	3-14 days (1-20 days)	Specific agents vary by region
Enteric fever (typhoid/paratyphoid)	7-18 days (3-60 days)	Especially in Indian subcontinent
Acute HIV	10-28 days (10 days to 6 weeks)	Worldwide
Influenza	1-3 days	Worldwide, can also be acquired while traveling
Legionellosis	5-6 days (2-10 days)	Widespread
Leptospirosis	7-12 days (2-26 days)	Widespread, most common in tropical areas
Malaria, *Plasmodium falciparum*	6-30 days (98% onset within 3 mo of travel)	Tropics, subtropics
Malaria, *Plasmodium vivax*	8 days to 12 mo (almost half have onset >30 days after completion of travel)	Widespread in tropics and subtropics
Spotted-fever rickettsiae	Few days to 2-3 wk	Causative species vary by region
Zika virus infection	3-14 days	Widespread in Latin America, endemic through much of Africa, Southeast Asia, and Pacific Islands
INCUBATION 14 DAYS TO 6 WEEKS		
Encephalitis, arboviral; enteric fever; acute HIV; leptospirosis; malaria	See above incubation periods for relevant diseases.	See above distribution for relevant diseases
Amebic liver abscess	Weeks to months	Most common in resource-poor countries
Hepatitis A	28-30 days (15-50 days)	Most common in resource-poor countries
Hepatitis E	26-42 days (2-9 wk)	Widespread
Acute schistosomiasis (Katayama syndrome)	4-8 wk	Most common in sub-Saharan Africa
INCUBATION >6 WK		
Amebic liver abscess, hepatitis E, malaria, acute schistosomiasis	See above incubation periods for relevant diseases.	See above distribution for relevant diseases
Hepatitis B	90 days (60-150 days)	Widespread
Leishmaniasis, visceral	2-10 mo (10 days to years)	Asia, Africa, Latin America, Southern Europe, and the Middle East
Tuberculosis	Primary, weeks; reactivation, years	Global distribution, rates, and levels of resistance vary widely

https://wwwnc.cdc.gov/travel/yellowbook/2024/posttravel-evaluation/general-approach-to-the-returned-traveler
From Centers for Disease Control and Prevention (CDC). International travel with infants and children: Yellow Book 2024. Fairley JK. General approach to the returned traveler. Atlanta: CDC, 2024. Table 11-02.

Fever is a particularly worrisome symptom. Children with a febrile/systemic illness after recent travel to a malarial destination should be promptly evaluated for malaria, especially if having traveled to sub-Sahara Africa and Papua New Guinea. *P. falciparum* malaria will generally present within 1-2 months after return from travel to a malaria-endemic area, but can occur within the first year after return. In contrast, symptoms of *P. vivax* or *P. ovale* malaria are typically later in onset after travel (i.e., several months), are milder in disease severity, and may occur in a relapsing pattern if undiagnosed or improperly treated. Other symptoms of malaria can be nonspecific and include chills, malaise, headache, myalgias, vomiting, diarrhea, cough, and possible seizures. Children are more likely than adults to have higher fevers and also gastrointestinal symptoms, hepatomegaly, splenomegaly, and severe anemia. Thrombocytopenia (without increased bleeding) and fever in a child returning from an endemic area are highly suggestive of malaria.

Thick and thin blood smears need to be performed for diagnosis *if* malaria is clinically suspected. If results are negative initially, two or more additional smears should be done 12-24 hours after the initial smears. The diagnostic yield of blood smears may be higher if obtained during a febrile episode. Rapid malaria antigen tests (BinaxNOW Malaria) are also available, are FDA-approved, and are sensitive for diagnosing *P. falciparum* malaria. At times, a polymerase chain reaction (PCR) assay is necessary to confirm the malarial parasite species. Treatment should be initiated immediately once the diagnosis is confirmed or empirically if presentation is severe with suspected malaria. Treatment should be determined in consultation with a pediatric infectious disease specialist and/or the CDC for updated information on the drugs of choice, which are similar to those for adults (see Chapter 334). Great caution should be used with young children, nonimmune patients, and pregnant patients with *P. falciparum* malaria, and hospitalization of these

Table 218.8 Patterns of Illness in Returning International Travelers

SYSTEMIC FEBRILE ILLNESS
Malaria
Dengue
Zika
Enteric fever (typhoid/paratyphoid)
Chikungunya virus
Spotted fever rickettsiae
Hepatitis A
Acute HIV
Leptospirosis
Measles
Infectious mononucleosis
Respiratory causes (pneumonia, influenza)
Undetermined fever source
ACUTE DIARRHEA
Campylobacter
Shigella spp.
Salmonella spp.
Diarrheagenic *Escherichia coli* (enterotoxigenic *E. coli,* enteroadherent *E. coli*—not tested for by routine stool culture methods)
Giardiasis (acute, persistent, or recurrent)
Entamoeba histolytica
Cryptosporidium spp.
Cyclospora cayetanensis
Presumed viral enteritis
DERMATOLOGIC MANIFESTATIONS
Rash with fever (dengue)
Arthropod-related dermatitis (insect bites)
Cutaneous larva migrans (*Ancylostoma braziliense*)
Bacterial skin infections—pyoderma, impetigo, ecthyma, erysipelas
Myiasis (tumbu and botfly)
Scabies
Tungiasis
Superficial mycosis
Animal bites
Leishmaniasis
Rickettsial diseases
Marine envenomation/dermatitis
Photoallergic dermatitis and phytophotodermatitis

Table 218.9 Common Clinical Findings and Associated Infections

COMMON CLINICAL FINDINGS	INFECTIONS TO CONSIDER AFTER TRAVEL
Fever and rash	Dengue, chikungunya, Zika, rickettsial infections, enteric fever (skin lesions may be sparse or absent), acute HIV infection, measles
Fever and abdominal pain	Enteric fever, amebic liver abscess
Undifferentiated fever and normal or low white blood cell count	Dengue, malaria, rickettsial infection, enteric fever, chikungunya, Zika
Fever and hemorrhage	Viral hemorrhagic fevers (dengue and others), meningococcemia, leptospirosis, rickettsial infections
Fever and arthralgia or myalgia, sometimes persistent	Chikungunya, dengue, Zika
Fever and eosinophilia	Acute schistosomiasis, drug hypersensitivity reaction, fascioliasis and other parasitic infections (rare)
Fever and pulmonary infiltrates	Common bacterial and viral pathogens, legionellosis, acute schistosomiasis, Q fever, leptospirosis
Fever and altered mental status	Cerebral malaria, viral or bacterial meningoencephalitis, African trypanosomiasis, scrub typhus
Mononucleosis syndrome	Epstein-Barr virus (EBV) infection, cytomegalovirus (CMV) infection, toxoplasmosis, acute HIV infection
Fever persisting >2 wk	Malaria, enteric fever, EBV infection, CMV infection, toxoplasmosis, acute HIV infection, acute schistosomiasis, brucellosis, tuberculosis, Q fever, visceral leishmaniasis (rare)
Fever with onset >6 wk after travel	*Plasmodium vivax* or *P. ovale* malaria, acute hepatitis (B, C, or E), tuberculosis, amebic liver abscess

From Centers for Disease Control and Prevention (CDC). International travel with infants and children: Yellow Book 2024. Wilson ME. Post-travel evaluation. Atlanta: CDC, 2024. Table 11-4. https://wwwnc.cdc.gov/travel/yellowbook/2024/posttravel-evaluation/general-approach-to-the-returned-traveler.

patients should be strongly considered until reliable improvement is observed.

Enteric (typhoid) fever should be considered in children with persistent or recurrent fevers, especially after return from the Indian subcontinent. Multiple blood cultures and a stool culture may both be necessary for diagnosis of enteric fever. **Dengue** is another cause of fever and systemic illness in ill travelers, particularly when returning from Southeast Asia, the Caribbean, Central and South America, or the Indian subcontinent. Many bacterial and protozoal causes of acute traveler's diarrhea may also result in fever and systemic symptoms in children. Additional travel-associated febrile, diarrheal, and dermatologic illnesses exist, of which the most common etiologies can be found in Tables 218.8 and 218.9.

THE ADOLESCENT TRAVELER

The preparation of an adolescent interested in traveling abroad can pose a challenge for most clinicians. Study abroad, gap year, humanitarian volunteer work, adventure, and tourism are among many reasons for travel to countries with limited resources. Although many travel-related problems discussed in this chapter are relevant to this group, other high-risk activities such as sexual intercourse, alcohol consumption, driving, use of illicit drugs, and adventure travel (e.g., mountain climbing, white water rafting, kayaking, biking) require special attention and discussion with the traveler and parents/guardians. Topics such as HIV exposure, sexually transmitted infections, sexual assault, and unplanned pregnancy may require specific preventive strategies such as condom use, contraception, and postexposure HIV prophylaxis.

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Chapter 219

Fever

Linda S. Nield and Deepak Kamat

Fever is defined as a rectal temperature ≥38°C (100.4°F), and a fever >40°C (104°F) is called **hyperpyrexia**. Traditionally, body temperature fluctuates in a defined normal range (36.6–37.9°C [97.9–100.2°F] rectally), so that the highest point is reached in the early evening and the lowest point is reached in the morning. Any abnormal rise in body temperature should be considered a symptom and sign of an underlying condition.

PATHOGENESIS

Body temperature is regulated by thermosensitive neurons located in the preoptic or anterior hypothalamus that respond to changes in blood temperature, as well as by cold and warm receptors located in skin and muscles. Thermoregulatory responses include redirecting blood to or from cutaneous vascular beds, increased or decreased sweating, regulation of extracellular fluid (ECF) volume by arginine vasopressin, and behavioral responses, such as seeking a warmer or cooler environmental temperature.

Three different mechanisms can produce fever: pyrogens, heat production exceeding heat loss, and defective heat loss. The first mechanism involves endogenous and exogenous pyrogens that raise the hypothalamic temperature set point. **Endogenous pyrogens** include the cytokines interleukin (IL)-1 and IL-6, tumor necrosis factor (TNF)-α, and interferon (IFN)-β and IFN-γ. Stimulated leukocytes and other cells produce lipids that also serve as endogenous pyrogens. The best-studied lipid mediator is prostaglandin E_2, which attaches to the prostaglandin receptors in the hypothalamus to produce the new temperature set point. Along with infectious diseases, drugs, malignancy, and inflammatory diseases can cause fever through the production of endogenous pyrogens. Some substances produced within the body are not pyrogens but are capable of stimulating endogenous pyrogens. Such substances include antigen-antibody complexes in the presence of complement components, lymphocyte products, bile acids, and androgenic steroid metabolites. **Exogenous pyrogens** come from outside the body and consist of mainly infectious pathogens and drugs. Microbes, microbial toxins, or other products of microbes are the most common exogenous pyrogens, which stimulate macrophages and other cells to produce endogenous pyrogens. **Endotoxin** is one of the few substances that can directly affect thermoregulation in the hypothalamus and stimulate endogenous pyrogen release. Many drugs cause fever, and the mechanism for increasing body temperature varies with the class of drug. Drugs that are known to cause fever include vancomycin, amphotericin B, and allopurinol.

Heat production exceeding heat loss is the second mechanism that leads to fever; examples include salicylate poisoning and malignant hyperthermia. **Defective heat loss**, the third mechanism, may occur in children with ectodermal dysplasia or victims of severe heat exposure.

ETIOLOGY

The causes of fever can be organized into four main categories: *infectious, inflammatory, neoplastic,* and *miscellaneous.* Self-limited viral infections (common cold, influenza, gastroenteritis) and uncomplicated bacterial infections (otitis media, pharyngitis, sinusitis) are the most common causes of acute fever. The body temperature rarely rises above potentially lethal levels (42°C [107.6°F]) in the neurologically intact child unless extreme hyperthermic environmental conditions are present or other extenuating circumstances exist, such as underlying malignant hyperthermia or thyrotoxicosis.

The pattern of the fever can provide clues to the underlying etiology. Viral infections typically are associated with a slow decline of fever over several days, whereas bacterial infections are often associated with a prompt resolution of fever after effective antimicrobial treatment. Although antimicrobials can result in rapid elimination of bacteria, if tissue injury has been extensive, the inflammatory response and fever can continue for days after all microbes have been eradicated.

Intermittent fever is an exaggerated circadian rhythm that includes a period of normal temperatures on most days; extremely wide fluctuations may be termed **septic** or **hectic fever**. **Sustained fever** is persistent and does not vary by >0.5°C (0.9°F)/day. **Remittent fever** is persistent and varies by >0.5°C/day. **Relapsing fever** is characterized by febrile periods separated by intervals of normal temperature; **tertian fever** occurs on the first and third days (malaria caused by *Plasmodium vivax*), and **quartan fever** occurs on the first and fourth days (malaria caused by *Plasmodium malariae*). Diseases characterized by relapsing fevers should be distinguished from infectious diseases that tend to relapse (Table 219.1). **Biphasic fever** indicates a single illness with two distinct periods (**camelback fever** pattern); poliomyelitis is the classic example. A biphasic course is also characteristic of other enteroviral infections, leptospirosis, dengue fever, yellow fever, Colorado tick fever, spirillary rat-bite fever (caused by *Spirillum minus*), and the African hemorrhagic fevers (Marburg, Ebola, and Lassa fevers). The term **periodic fever** is used narrowly to describe fever syndromes with a regular periodicity (cyclic neutropenia and periodic fever, aphthous

Table 219.1 Fevers Prone to Relapse

INFECTIOUS CAUSES
Acute rheumatic fever
Babesiosis
Blastomycosis
Brucellosis
Chronic meningococcemia
Coccidioidomycosis
Colorado tick fever
COVID-19/SARS-CoV-2 and MIS-C
Dengue fever
Epstein-Barr virus infection
Histoplasmosis
Leptospirosis
Lyme disease *(Borrelia burgdorferi)*
Lymphocytic choriomeningitis (LCM) infection
Malaria
Melioidosis *(Pseudomonas pseudomallei)*
Noninfluenza respiratory viral infection
Oroya fever *(Bartonella bacilliformis)*
Q fever *(Coxiella burnetii)*
Rat-bite fever (*Spirillum minus*)
Relapsing fever *(Borrelia recurrentis)*
Syphilis *(Treponema pallidum)*
Tuberculosis
Typhoid fever *(Salmonella typhi)*
Visceral leishmaniasis
Yellow fever
NONINFECTIOUS CAUSES
Behçet disease
Crohn disease
Leukocytoclastic vasculitis syndromes
Sweet syndrome
Systemic lupus erythematosus and other autoimmune disorders
Weber-Christian disease (panniculitis)
Others
PERIODIC FEVER SYNDROMES (SEE CHAPTER 204)
Cyclic neutropenia
Familial Mediterranean fever
Hyper–immunoglobulin D syndrome
Muckle-Wells syndrome
Periodic fever, aphthous stomatitis, pharyngitis, and adenopathy (PFAPA)
Tumor necrosis factor receptor–associated periodic syndrome [TRAPS])
Others

MIS-C, multisystem inflammatory syndrome in children.

stomatitis, pharyngitis, adenopathy) or more broadly to include disorders characterized by recurrent episodes of fever that do not follow a strictly periodic pattern (familial Mediterranean fever, TNF receptor–associated periodic syndrome [Hibernian fever], hyper-IgD syndrome, Muckle-Wells syndrome) (see Chapter 204). **Factitious fever**, or self-induced fever, may be caused by intentional manipulation of the thermometer or injection of pyrogenic material.

The **double quotidian fever** (or fever that peaks twice in 24 hours) is classically associated with juvenile idiopathic arthritis. In general, a single isolated fever spike is not associated with an infectious disease. Such a spike can be attributed to the infusion of blood products and some drugs, as well as some procedures or manipulation of a catheter on a colonized or infected body surface. Similarly, temperatures in excess of 41°C (105.8°F) are most often associated with a noninfectious cause. Causes for very high temperatures (>41°C [105.8°F]) include central fever (resulting from central nervous system dysfunction involving the hypothalamus or spinal cord injury), malignant hyperthermia, malignant neuroleptic syndrome, drug fever, or heat stroke. Temperatures that are lower than normal (<36°C [96.8°F]) can be associated with overwhelming sepsis but are more often related to cold exposure, hypothyroidism, autonomic instability, central nervous system lesions, or overuse of antipyretics.

CLINICAL FEATURES

The clinical features of fever can range from no symptoms to extreme malaise. Children might complain of feeling hot or cold, display facial flushing, and experience shivering. Fatigue and irritability may be evident. Parents often report that the child looks ill or pale and has a decreased appetite. The underlying etiology also produces accompanying symptoms. Although the underlying etiologies can manifest in varied ways clinically, there are some predictable features. For example, **fever with petechiae** in an ill-appearing patient indicates the high possibility of life-threatening conditions such as meningococcemia, Rocky Mountain spotted fever, or acute bacterial endocarditis. The unusual symptom of loss of smell and taste can accompany fever in COVID-19.

Changes in heart rate, most frequently tachycardia, accompany fever. Normally heart rate rises by 10 beats/min per 1°C (1.8°F) rise in temperature for children >2 months old. Relative tachycardia, when the pulse rate is elevated disproportionately to the temperature, is usually caused by noninfectious diseases or infectious diseases in which a toxin is responsible for the clinical manifestations. **Relative bradycardia** (temperature-pulse dissociation), when the pulse rate remains low in the presence of fever, can accompany typhoid fever, brucellosis, leptospirosis, or drug fever. Bradycardia in the presence of fever also may be a result of a conduction defect resulting from cardiac involvement with acute rheumatic fever, Lyme disease, viral myocarditis, or infective endocarditis.

EVALUATION

Most acute febrile episodes in a normal host can be diagnosed by a careful history and physical examination and require few, if any, laboratory tests. Because infection is the most likely etiology of acute fever, the evaluation should initially be geared to discovering an underlying infectious cause (Table 219.2 and Chapter 220). The details of the history should include the onset and pattern of fever and any accompanying signs and symptoms. The patient often displays signs or symptoms that provide clues to the cause of the fever. Exposures to other ill persons at home, daycare, and school should be noted, along with any recent travel, animal exposures, or medications. The past medical history should include information about underlying immune deficiencies or other major illnesses and receipt of childhood vaccines.

Physical examination should begin with a complete evaluation of vital signs, which should include pulse oximetry, because hypoxia may indicate lower respiratory infection. In the acutely febrile child, the physical examination should focus on any localized complaints, but a complete head-to-toe screen is recommended, because clues to the underlying diagnosis may be found. For example, palm and sole lesions may be discovered during a thorough skin examination and provide a clue for infection with coxsackievirus.

Table 219.2 Evaluation of Acute Fever

Thorough history: onset, other symptoms, exposures (daycare, school, family, pets, playmates, other ill individuals), travel, medications, other underlying disorders, immunizations
Physical examination: complete, with focus on localizing symptoms
Laboratory studies on a case-by-case basis:
- Blood: complete blood count, culture, C-reactive protein, procalcitonin, sedimentation rate
- Cerebrospinal fluid: cell count, culture, glucose, Gram stain, NAAT for herpes simplex virus, protein
- Nasopharyngeal: NAAT for respiratory viruses
- Pharyngeal: NAAT and culture for group A *Streptococcus*
- Stool: calprotectin, culture, NAAT for enteric pathogens
- Urine: culture, gross and microscopic analysis, NAAT for genital pathogens
- Others (such as chest radiograph or other radiologic imaging)

NAAT, Nucleic acid amplification test.

If a fever has an obvious cause, laboratory evaluation may not be required, and management is tailored to the underlying cause with as-needed reevaluation. If the cause of the fever is not apparent, further diagnostic evaluation should be considered on a case-by-case basis. The history of presentation and abnormal physical examination findings guide the evaluation. The child with respiratory symptoms and hypoxia may require a chest radiograph, rapid antigen testing for respiratory syncytial virus or influenza, or polymerase chain reaction (PCR) testing for SARS-CoV-2. The child with pharyngitis can benefit from PCR testing for group A *Streptococcus* and a throat culture. Dysuria, back pain, or a history of vesicoureteral reflux should prompt a urinalysis and urine culture, and bloody diarrhea should prompt a stool culture. A complete blood count and blood culture should be considered in the ill-appearing child, along with cerebrospinal fluid studies if the child has neck stiffness or if the possibility of meningitis is considered. Well-defined high-risk groups require a more extensive evaluation on the basis of age, associated disease, or immunodeficiency status and might warrant prompt antimicrobial therapy before a pathogen is identified. Fever in neonates and young infants (0-3 months old), fever in older children, and fever of unknown origin are discussed in Chapters 220, 221, and 222, respectively.

MANAGEMENT

Although fever is a common parental worry, no evidence supports the belief that high fever can result in brain damage or other bodily harm, except in rare instances of febrile status epilepticus and heat stroke. *Treating fever in self-limiting illnesses for the sole reason of bringing the body temperature back to normal is not necessary in the otherwise healthy child.* Most evidence suggests that fever is an adaptive response and should be treated only in select circumstances. In humans, increased temperatures are associated with decreased microbial replication and an increased inflammatory response. Although fever can have beneficial effects, it also increases oxygen consumption, carbon dioxide production, and cardiac output and can exacerbate cardiac insufficiency in patients with heart disease or chronic anemia (e.g., sickle cell disease), pulmonary insufficiency in patients with chronic lung disease, and metabolic instability in patients with diabetes mellitus or inborn errors of metabolism. Children between 6 months and 5 years of age are at increased risk for simple febrile seizures. *The focus of the evaluation and treatment of febrile seizures is aimed at determining the underlying cause of the fever.* Children with idiopathic epilepsy also often have an increased frequency of seizures associated with a fever. High fever during pregnancy may be teratogenic.

Fever with temperatures <39°C (102.2°F) in healthy children generally does not require treatment. However, as temperatures become higher, patients tend to become more uncomfortable, and treatment of fever is then reasonable. If a child is included in one of the high-risk groups previously discussed or if the child's caregiver is concerned that the fever is adversely affecting the child's behavior and causing discomfort, treatment may be given to hasten the resolution of the fever.

Other than providing symptomatic relief, antipyretic therapy does not change the course of infectious diseases. Encouraging good hydration is the first step to replacing fluids that are lost related to the increased metabolic demands and insensible losses of fever. Antipyretic therapy is beneficial in high-risk patients and patients with discomfort. **Hyperpyrexia** (>41°C [105.8°F]) indicates high probability of a hypothalamic disorder or central nervous system injury (hemorrhage, other etiology) and should be treated with antipyretics. Some studies show that hyperpyrexia may be associated with a significantly increased risk of serious bacterial infection, but other studies have not substantiated this relationship. The most common antipyretics are **acetaminophen 10-15 mg/kg/dose every 4 hours and ibuprofen in children >6 months old at 5-10 mg/kg/dose every 8 hours**. Antipyretics reduce fever by reducing production of prostaglandins. If used appropriately, antipyretics are safe; potential adverse effects include liver damage (acetaminophen) and gastrointestinal or kidney disturbances (ibuprofen). To reduce fever most safely, the caregiver should choose one type of medication and clearly record the dose and time of administration so that overdosage does not occur, especially if multiple caregivers are involved in the management. Physical measures such as tepid baths and cooling blankets are not considered effective to reduce fever. Evidence is also scarce for the use of complementary and alternative medicine interventions.

Fever caused by specific underlying etiologies resolves when the condition is properly treated. Examples include administration of intravenous immunoglobulin to treat Kawasaki disease or the administration of antibiotics to treat bacterial infections.

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Chapter 220

Fever Without a Focus in the Neonate and Young Infant

Laura Brower and Samir S. Shah

Fever is a common reason for neonates and young infants to undergo medical evaluation in the hospital or ambulatory setting. For this age-group (0-3 months), **fever without a focus** refers to a rectal temperature of 38°C (100.4°F) or greater without other presenting signs or symptoms. The evaluation of these patients can be challenging because of the difficulty distinguishing between a serious infection (bacterial or viral) and a self-limited viral illness. The etiology and evaluation of fever without a focus depend on the age of the child. Three age-groups are typically considered: neonates 0-28 days, young infants 29-90 days, and children 3-36 months.

ETIOLOGY AND EPIDEMIOLOGY

Serious bacterial infection (SBI) occurs in 7–13% of neonates and young infants with fever. In this group, the most common SBIs are urinary tract infection (UTI; 5–13%), bacteremia (1–2%), and meningitis (0.2–0.5%). The risk for SBI is highest in those appearing ill (in contrast to well appearing) and those with risk factors and is inversely related to postnatal age. The term **invasive bacterial infection (IBI)**, which refers to bacteremia and meningitis, recognizes that infants with UTIs may be managed differently (e.g., often with oral antibiotics) than those with bacteremia or meningitis. *Escherichia coli* is the most common organism causing SBI, followed by group B *Streptococcus* (GBS). The frequency of GBS infections has decreased as a consequence of increased screening of pregnant women and use of intrapartum antibiotic prophylaxis. Other, less common organisms include *Klebsiella* spp., *Enterococcus* spp., *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Staphylococcus aureus* (Table 220.1). *Listeria monocytogenes* is a rare cause of neonatal infections, potentially related to changes in public health education and improvements in food safety. Additional details about specific bacteria are available in the following chapters: *E. coli* (see Chapter 246), GBS (see Chapter 230), *S. pneumoniae* (see Chapter 228), *N. meningitidis* (see Chapter 237), *S. aureus* (see Chapter 227.1), and *L. monocytogenes* (see Chapter 234). Specific bacterial infections that can present with fever in this age-group, although often with symptoms other than isolated fever, include pneumonia (see Chapter 449), gastroenteritis (see Chapter 387), osteomyelitis (see Chapter 725), septic arthritis (see Chapter 726), omphalitis (see Chapter 144), cellulitis, and other skin and soft tissue infections (see Chapter 706).

Herpes simplex virus **(HSV)** infections (see Chapter 299) should also be considered in febrile neonates, particularly those under 28 days old, given the high rate of mortality and significant morbidity among survivors. Neonatal HSV is rare, with a prevalence of 0.2–0.3% among febrile neonates. Most of these infections are caused by HSV type 2, though HSV type 1 can also cause neonatal infection. Neonates with disseminated disease and skin, eye, and mouth (SEM) disease typically present at 5-12 days of life. Neonates with central nervous system (CNS) disease generally present at 16-19 days. Perinatally acquired HSV occasionally manifests beyond 28 days of age, although most cases beyond 28 days of age represent postnatal acquisition.

In febrile infants who *appear well,* viral illnesses are much more common than bacterial or serious viral infections. The most common viruses include respiratory syncytial virus (RSV; see Chapter 307), enteroviruses (see Chapter 297), influenza viruses (see Chapter 305), parainfluenza viruses (see Chapter 306), human metapneumovirus (see Chapter 308), adenovirus (see Chapter 309), parechoviruses (see Chapter 297), and rhinovirus (see Chapter 310).

CLINICAL MANIFESTATIONS

In neonates and young infants, bacterial and viral infections can present with isolated fever or nonspecific symptoms, making diagnosis of serious illnesses challenging. Some neonates and young infants will have signs of systemic illness at presentation, including abnormal temperature (hypothermia <36°C [96.8°F], fever ≥38°C [100.4°F]), abnormal respiratory examination (tachypnea >60 breaths/min, respiratory distress, apnea), abnormal circulatory examination (tachycardia >180 beats/min, delayed capillary refill >3 seconds, weak or bounding pulses), abnormal abdominal examination, abnormal neurologic

Table 220.1 Bacterial Pathogens in Neonates and Young Infants with Urinary Tract Infection, Bacteremia, or Meningitis

FREQUENCY	URINARY TRACT INFECTION	BACTEREMIA AND MENINGITIS
Common	*Escherichia coli*	*Escherichia coli* Group B *Streptococcus*
Less common	*Klebsiella* spp. *Enterococcus* spp.	*Listeria monocytogenes* *Streptococcus pneumoniae* *Staphylococcus aureus* *Klebsiella* spp.
Rare	Group B *Streptococcus* *Staphylococcus aureus* *Pseudomonas aeruginosa* *Enterobacter* spp. *Citrobacter* spp. *Proteus mirabilis*	*Neisseria meningitidis* *Salmonella* spp. *Enterobacter* spp. *Enterococcus* spp. *Cronobacter sakazakii* *Haemophilus influenzae* *Citrobacter*

Other than providing symptomatic relief, antipyretic therapy does not change the course of infectious diseases. Encouraging good hydration is the first step to replacing fluids that are lost related to the increased metabolic demands and insensible losses of fever. Antipyretic therapy is beneficial in high-risk patients and patients with discomfort. **Hyperpyrexia** (>41°C [105.8°F]) indicates high probability of a hypothalamic disorder or central nervous system injury (hemorrhage, other etiology) and should be treated with antipyretics. Some studies show that hyperpyrexia may be associated with a significantly increased risk of serious bacterial infection, but other studies have not substantiated this relationship. The most common antipyretics are **acetaminophen 10-15 mg/kg/dose every 4 hours and ibuprofen in children >6 months old at 5-10 mg/kg/dose every 8 hours**. Antipyretics reduce fever by reducing production of prostaglandins. If used appropriately, antipyretics are safe; potential adverse effects include liver damage (acetaminophen) and gastrointestinal or kidney disturbances (ibuprofen). To reduce fever most safely, the caregiver should choose one type of medication and clearly record the dose and time of administration so that overdosage does not occur, especially if multiple caregivers are involved in the management. Physical measures such as tepid baths and cooling blankets are not considered effective to reduce fever. Evidence is also scarce for the use of complementary and alternative medicine interventions.

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Chapter 220

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CLINICAL MANIFESTATIONS

In neonates and young infants, bacterial and viral infections can present with isolated fever or nonspecific symptoms, making diagnosis of serious illnesses challenging. Some neonates and young infants will have signs of systemic illness at presentation, including abnormal temperature (hypothermia <36°C [96.8°F], fever ≥38°C [100.4°F]), abnormal respiratory examination (tachypnea >60 breaths/min, respiratory distress, apnea), abnormal circulatory examination (tachycardia >180 beats/min, delayed capillary refill >3 seconds, weak or bounding pulses), abnormal abdominal examination, abnormal neurologic

Table 220.1 Bacterial Pathogens in Neonates and Young Infants with Urinary Tract Infection, Bacteremia, or Meningitis

FREQUENCY	URINARY TRACT INFECTION	BACTEREMIA AND MENINGITIS
Common	*Escherichia coli*	*Escherichia coli* Group B *Streptococcus*
Less common	*Klebsiella* spp. *Enterococcus* spp.	*Listeria monocytogenes* *Streptococcus pneumoniae* *Staphylococcus aureus* *Klebsiella* spp.
Rare	Group B *Streptococcus* *Staphylococcus aureus* *Pseudomonas aeruginosa* *Enterobacter* spp. *Citrobacter* spp. *Proteus mirabilis*	*Neisseria meningitidis* *Salmonella* spp. *Enterobacter* spp. *Enterococcus* spp. *Cronobacter sakazakii* *Haemophilus influenzae* *Citrobacter*

examination (lethargy, irritability, alterations in tone), or abnormal skin examination (rash, petechiae, cyanosis). Infants with **septic arthritis** or **osteomyelitis** may appear well except for signs around the involved joint or bone or may only manifest with *pseudoparalysis* (disuse) and *paradoxical irritability* (infant experiences pain during attempts to comfort the child).

DIAGNOSIS

Historically, all neonates <60 or <90 days of age were hospitalized; underwent laboratory evaluation of the blood, urine, and cerebrospinal fluid (CSF); and received empirical antibiotics. Additionally, some patients had stool cultures, had chest radiographs, had HSV evaluation, and/or received empirical antiviral agents. Under this approach, many infants without SBI or serious viral infection received evaluation, treatment, and hospitalization. Protocols were subsequently developed to identify infants at lower risk of SBI, who may be managed outside the hospital setting. The most current protocol is the American Academy of Pediatrics (AAP) guideline, which considers UTIs separately from bacteremia and meningitis (Table 220.2). Despite protocols, substantial variation continues to exist in the approach to and management

Table 220.2 Management of Fever Without Source in Infants 0-36 Months Old

GROUP	MANAGEMENT
Any toxic-appearing child 0–36 mo and temperature ≥38°C (100.4°F)	Hospitalize, cultures (blood, urine, CSF) plus other tests*, parenteral antibiotics
WELL-APPEARING CHILD	
Child <22 days and temperature ≥38°C (100.4°F)	Hospitalize, cultures (blood, urine, CSF) plus other tests*, parenteral antibiotics
Child 22–60 days and temperature ≥38°C (100.4°F)	**Three-Step Process** 1. Determine risk based on history, physical examination, and laboratory studies. Low risk: • Uncomplicated medical history • Well-appearing physical examination • Normal laboratory studies • Urine: negative leukocyte esterase and nitrite, ≤5 WBC/hpf centrifuged and <10 WBC/hpf uncentrifuged • Inflammatory markers: temperature ≤38.5°C, procalcitonin ≤0.5 ng/mL, CRP ≤20 mg/L, absolute neutrophil count ≤4,000-5,200/mm^3 • Stool studies if diarrhea (no RBC and <5 WBC/hpf) 2. If child *fulfills all low-risk criteria*, use age to determine need for LP, parenteral antimicrobials, and hospital observation. • **Age 22-28 days**: Obtain UA, blood culture, inflammatory markers. May perform LP. May administer parenteral antimicrobials. Observe in hospital. • **Age 29-60 days old**: Obtain UA, blood culture, inflammatory markers. Need not perform LP. Need not administer antimicrobials. Observe closely at home with follow-up within 24-36 hr. 3. If child does not fulfill all low-risk criteria, use age and lab results to determine need for LP, antimicrobials, and hospital observation. • **Age 22-28 days** with abnormal UA and normal inflammatory markers: May perform LP. Administer parenteral antimicrobials. Observe in hospital. • **Age 22-28 days** with abnormal inflammatory markers: Perform LP. If CSF pleocytosis, CSF uninterpretable, or abnormal UA, administer parenteral antimicrobials and observe in hospital. If CSF and UA are normal, may observe at home after parenteral antimicrobials or observe in the hospital with or without parenteral antimicrobials. • **Age 29-60 days** with abnormal UA and normal inflammatory markers: Administer oral antimicrobials. May observe closely at home with follow-up in 12-24 hr. • **Age 29-60 days** with abnormal inflammatory markers: May perform LP. If CSF pleocytosis, administer parenteral antimicrobials and observe in hospital. If CSF is normal, may administer parenteral or oral antimicrobials and may observe closely in hospital or at home. If CSF is not available or uninterpretable, administer parenteral antimicrobials and may observe closely in hospital or at home.
Child 2-36 mo and temperature 38–39°C (100.4–102.2°F)	Reassurance that diagnosis is likely self-limited viral infection, but advise return with persistence of fever, temperatures >39°C (102.2°F), and/or new signs and symptoms.
Child 2-36 mo and temperature >39°C (102.2°F)	**Two-Step Process** 1. Determine immunization status. 2. If received conjugate pneumococcal and *Haemophilus influenzae* type b vaccines, obtain urine studies (urine WBC, leukocyte esterase, nitrite, and culture) for all females, all males <6 mo old, all uncircumcised males <2 yr, and all children with recurrent urinary tract infections. If did not receive conjugate pneumococcal and *H. influenzae* type b vaccines, manage according to the 1993 Guidelines (see Baraff et al. *Ann Emerg Med.* 1993;22:1198–1210).

*Other tests may include chest radiograph, stool studies, herpes simplex and other virus polymerase chain reaction.
CSF, Cerebrospinal fluid; hpf, high-powered field; LP, lumbar puncture; RBC, red blood cell; UA, urinalysis; WBC, white blood cell.
Modified from Huppler A. Fever. In: Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Philadelphia: Elsevier; 2023: Table 52.5, p. 971; with data from Pantell RH, Roberts KB, Adams WG, et al. Evaluation and management of well appearing febrile infants 8 to 60 days old. *Pediatrics.* 2021;148(2):e2021052228.

of the febrile infant. *It must be emphasized that these criteria apply to the well-appearing child; those who appear critically ill (septic) require prompt evaluation, resuscitation, and empiric antibiotic therapy (within 1 hour).*

In the past, experts advocated that all neonates ≤28 days old undergo a complete evaluation for serious infection, receive empirical antimicrobials, and be hospitalized. In prior risk criteria, one allowed neonates ≤28 days to be designated as "low risk" and managed outside the hospital without antimicrobials. In one study, <1% of low-risk infants ≤28 days old had SBI; however, in another study applying the other criteria to neonates, 3–4% of those classified as low risk had SBI. In the current protocols, neonates 22-28 days who meet certain low-risk criteria can be managed outside the hospital; in one study, the risk of bacteremia in this age-group was lower than in infants <22 days (1.6% vs 3.3–5.3%).

Young febrile infants ≥29 days old who *appear ill* (with signs of systemic illness) require complete evaluation for serious infection, empiric antimicrobials, and hospitalization; however, well-appearing infants can be managed safely as outpatients using low-risk criteria as indicated in Table 220.2. With each of these approaches, infants must have a normal physical examination, must be able to reliably obtain close follow-up, and must meet certain laboratory and/or radiographic criteria. Based on these protocols, all infants meeting the previous criteria would undergo lumbar puncture (LP), whereas low-risk infants meeting other criteria and following the current protocols would not. There is substantial variation in clinical practice in the performance of LPs in well-appearing infants >28 days. When deciding whether to perform an LP in this age-group, clinicians should consider multiple factors, including the home situation and the ability to contact the family.

The protocols discussed in Table 220.2 were initially developed for use in the emergency department (ED). Infants evaluated in the office setting may warrant a different approach when a relationship between the physician and family already exists to facilitate clear communication and timely follow-up. In one large study of febrile infants <3 months old who were initially evaluated for fever in the office setting, clinicians hospitalized only 36% of infants but initiated antibiotics in 61 of the 63 infants with bacteremia or bacterial meningitis. These findings suggest that, with very close follow-up (including multiple in-person visits or frequent contacts by telephone), some febrile infants perceived to be at low risk for **invasive bacterial infection** (bacteremia and meningitis) on the basis of history, physical examination, and normal but limited laboratory testing can be managed in an office-based setting. It is important to note that 3% of infants with SBI did not initially receive empiric antibiotics, necessitating careful consideration of risks and benefits of selective rather than universal testing and empiric antibiotic treatment of febrile infants evaluated in the office setting.

Viral Respiratory Illness

Several studies have demonstrated a decreased risk of SBI in infants with positive testing for influenza, RSV, and other respiratory viral illnesses, although the risk of UTI remains significant. In one prospective study, the risk of SBI in neonates <28 days old was not altered by RSV status. Given these data, young febrile infants with bronchiolitis may not require LP, particularly if they can be closely observed or have close follow-up.

Urinary Tract Infection and Bacterial Meningitis

In the past, infants with abnormal findings on urinalysis (UA) would undergo complete evaluation for infection, including LP. In well-appearing infants >28 days old with an abnormal UA, some evidence suggests that the risk of bacterial meningitis is extremely low: <0.5%. For neonates 0-28 days, the risk of concomitant bacterial meningitis with UTI is 1–2%.

CSF pleocytosis in the absence of bacterial meningitis (i.e., **sterile pleocytosis**) has been reported in ~23% infants with UTI. The cause is uncertain, with some studies attributing this phenomenon to traumatic LPs or undetected viral infection rather than inflammation in the context of systemic illness.

LABORATORY DIAGNOSIS

Complete Blood Count

The peripheral complete blood cell count (CBC) and differential are frequently obtained by providers when evaluating febrile neonates and infants. The white blood cell (WBC) count alone cannot accurately predict SBI risk. In one series, isolated use of the WBC cutoffs of outside 5,000-15,000 WBCs/mm^3 would miss at least 33% of infants with bacteremia and 40% of those with meningitis. A prospective study found no increased risk of SBI in febrile, well-appearing infants with leukopenia (WBC count <5,000/mm^3). The WBC count combined with other factors may help determine an infant's risk of SBI, but it should not be used in isolation to predict infection risk. The absolute neutrophil count (ANC) has also been used in evaluating the risk of serious infection. Two recent large studies derived ANC cutoffs of greater than 4,000 and 5,200 per mm^3 for use in specific protocols; however, these protocols used ANC in conjunction with other markers.

Blood Culture

The ability to identify pathogens in the blood depends on the volume of blood, the timing of the blood culture in relation to antimicrobial administration, and, to a lesser degree, the number of blood cultures obtained. A negative blood culture does not exclude the possibility of bacterial meningitis; in one study, 38% of infants with culture-proven bacterial meningitis had negative blood cultures. For additional information on the time to positivity of blood cultures in neonates and young infants, see "Discharge from the Hospital."

Urinalysis

Different methods can assist in making a presumptive diagnosis of UTI while awaiting results of a urine culture. *Traditional* UA consists of dipstick biochemical analysis of urine for nitrites or leukocyte esterase (LE) and microscopic examination of the urine for WBCs and bacteria. One study found that the traditional UA had a higher negative predictive value (NPV) than dipstick alone (99.2% vs 98.7%), but that dipstick alone had a higher positive predictive value (PPV, 66.8% for dipstick alone vs 51.2% for traditional UA). *Enhanced* UA includes hemocytometer cell count (to decrease variability of urine cell counts) and Gram stain on uncentrifuged urine. The enhanced UA has a higher sensitivity but comparable specificity to traditional UA. However, the enhanced UA has not been studied in the most common protocols for evaluation of the febrile infant, and many institutions/office practices do not perform this test.

Cerebrospinal Fluid

CSF evaluation consists of culture and Gram stain, cell count, glucose, and protein. Polymerase chain reaction (PCR) testing may also be sent based on the clinical scenario, usually for enterovirus or HSV (some include bacterial pathogens). Normal CSF parameters vary by age of the infant and should be interpreted in combination with other clinical and historical risk factors, given that some infants with normal CSF parameters may rarely have CNS infections (Table 220.3). The CSF Gram stain can be a useful adjunct to other CSF parameters given the high specificity of the test (99.3–99.9%; i.e., relatively few false-positive results), although the range of reported sensitivity is much broader (67–94.1%).

The interpretation of CSF can be challenging in the setting of a traumatic LP, where the CSF is contaminated with peripheral blood. Some clinicians assume a ratio of WBCs to red blood cells (RBCs) of 1:500 in the CSF. Others advocate calculating the expected CSF WBCs based on the peripheral blood WBCs and RBCs and then using the observed-to-predicted ratio of CSF WBCs to aid in the identification of bacterial meningitis. This calculation assumes that the ratio of WBCs to RBCs in the peripheral blood remains constant after introduction into the CSF. Next-generation molecular testing is helpful in identifying the most

Table 220.3 Values of Cerebrospinal Fluid (CSF) Studies in Neonates and Infants by Age

CSF WHITE BLOOD CELL COUNTS	CELLS/MM³
Upper limit of normal by age*	
1-28 days	18
29-60 days	8.5
61-90 days	8.5
Upper limit of normal by age#	
0-28 days	15
29-60 days	9
90th percentile by age†	
0-7 days	26
8-28 days	8-9
29-56 days	6-8
95th percentile by age‡	
0-28 days	19
29-56 days	9
95th percentile by age#	
0-28 days	16
29-60 days	11

CSF PROTEIN	MG/DL
Upper limit of normal by age*	
1-28 days	131
29-60 days	105.5
61-90 days	71
Upper limit of normal by age#	
0-28 days	127
29-60 days	99

CSF PROTEIN	MG/DL
90th percentile by age†	
0-7 days	153
8-28 days	84-106
29-56 days	84-105
95th percentile by age§	
0-14 days	132
15-28 days	100
29-42 days	89
43-56 days	83
95th percentile by age#	
0-28 days	118
29-60 days	91

CSF GLUCOSE	MG/DL
Lower limit of normal by age*	
1-28 days	30
29-60 days	30.5
61-90 days	33.5
Lower limit of normal by age#	
0-28 days	25
29-60 days	27
10th percentile for infants 0-56 days†	38-43
10th percentile by age#	
0-28 days	37
29-60 days	39

*Data from Byington CL, Kendrick J, Sheng X. Normative cerebrospinal fluid profiles in febrile infants. *J Pediatr*. 2011;158(1):130–134. All infants had nontraumatic lumbar puncture (LP) and no evidence of bacterial or viral infection.

†Data from Chadwick SL, Wilson JW, Levin JE, Martin JM. Cerebrospinal fluid characteristics of infants who present to the emergency department with fever: establishing normal values by week of age. *Pediatr Infect Dis J*. 2011;30(4):e63–e67. All infants were excluded if they had identified viral or bacterial meningitis, positive blood or urine cultures, a ventriculoperitoneal shunt, recent neurosurgery/antibiotics/seizure, or a traumatic LP.

‡Data from Kestenbaum LA, Ebberson J, Zorc JJ, et al. Defining cerebrospinal fluid white blood cell count reference values in neonates and young infants. *Pediatrics*. 2010;125(2):257–264. Infants were excluded for traumatic LP, serious bacterial infection, congenital infection, seizure, presence of ventricular shunt, or positive CSF testing for enterovirus.

§Data from Shah SS, Ebberson J, Kestenbaum LA, et al. Age-specific reference values for cerebrospinal fluid protein concentration in neonates and young infants. *J Hosp Med*. 2011;6(1):22–27. Infants were excluded for traumatic LP, serious bacterial infection, congenital infection, seizure, presence of a ventricular shunt, positive CSF testing for enterovirus, or elevated serum bilirubin.

#Data from Thomson J, Sucharew H, Cruz AT, et al. Cerebrospinal fluid reference values for young infants undergoing lumbar puncture. *Pediatrics*. 2018;141(3):e20173405. Infants were excluded for missing any component of the CSF profile, traumatic LP, serious bacterial infection, viral CNS infection, non-CNS HSV disease, or prolonged hospital length of stay.

common bacterial and viral pathogens despite a traumatic LP; results are often available within a few hours.

One retrospective cohort study concluded that an observed/predicted CSF WBC ratio of ≤0.01 was helpful in predicting the absence of bacterial meningitis; however, another retrospective cohort study and one case series of traumatic LPs concluded that adjustment of CSF WBC count does not improve the accuracy of diagnosis of meningitis in patients with traumatic LPs. Clinicians may consider hospitalization and empirical antimicrobials in patients with traumatic LPs given the challenge of interpreting the CSF WBC count when there is blood contamination of the specimen.

Treatment with antibiotics before LP can complicate the interpretation of CSF cultures. CSF cultures are negative relatively rapidly after antibiotic administration, within 2 hours for *N. meningitidis* and 4-24 hours for *S. pneumoniae*. Next-generation molecular testing is not affected by prior antibiotic treatment, thus enhancing a diagnosis despite prior antibiotic therapy. In patients with bacterial meningitis, CSF glucose increases to normal range, often within 4-24 hours of antibiotic administration, whereas CSF protein concentrations, despite decreasing, remain abnormal for >24 hours after antibiotic administration. Changes in CSF WBC count and ANC are minimal in the first 24 hours of antibiotic therapy. Therefore CSF findings can provide relevant management information even in the setting of antibiotic administration before LP.

Herpes Simplex Virus Testing

No consensus exists on which neonates should be tested and empirically treated for HSV infection. Historical and clinical features that

should raise concern for HSV include exposure to individuals infected with HSV, particularly mothers with primary HSV infections or first-time genital infections, seizure or abnormal neurologic examination, vesicular rash, ill appearance, apnea, hypothermia, petechial rash/excessive bleeding, hepatic failure, or a history of a scalp electrode. However, neonates with HSV can present *without any high-risk* clinical or historical features, particularly with early isolated CNS disease. Published approaches to neonatal HSV include (1) testing and empirical treatment of all neonates <21 days old who are evaluated for infection; (2) testing and empirical treatment of neonates with the presence of high-risk clinical features for HSV; and (3) testing and empirical treatment for all neonates with high-risk features plus testing the CSF of all neonates <21 days old while deferring empirical acyclovir in those without high-risk features, unless the CSF HSV PCR test is positive.

The AAP Committee on Infectious Diseases recommends that neonates undergoing evaluation for HSV have the following laboratory studies performed: surface cultures or PCR of the conjunctiva, mouth or nasopharynx, rectum, and any vesicles; CSF PCR (sensitivity: 75–100%); whole blood PCR; and serum levels of alanine transaminase (ALT). HSV PCR testing of the mouth, conjunctiva, nasopharynx, rectum, and vesicles has been shown to be more sensitive than culture, with comparable specificity, although no direct comparisons have been performed in neonates.

Enterovirus Testing

Enterovirus is a common and typically benign cause of fever in febrile infants, although it can be difficult to distinguish from SBI on initial presentation. Enterovirus PCR testing of the CSF is a sensitive and rapid means to diagnose infection. One retrospective study of patients with CSF enterovirus testing found no cases of bacterial meningitis in patients with positive enterovirus PCR; this study did not include neonates ≤28 days old. Several studies have demonstrated shorter length of stay, fewer antibiotics, and lower cost among infants with positive CSF enterovirus test results. These results suggest that during local enterovirus seasons, and if PCR testing is available, testing for enterovirus may be of benefit in the evaluation of febrile infants and neonates. Some centers have implemented multiplex PCR panels, which permit testing for multiple viruses, including enterovirus and HSV (and bacteria) simultaneously.

Other Inflammatory Markers

Investigations have examined the utility of inflammatory markers such as C-reactive protein (CRP) and serum procalcitonin (PCT) in the diagnosis of SBI and, more specifically, IBI (bacteremia and meningitis) (see Table 220.2). One meta-analysis reported that PCT is superior to WBC count and CRP for the detection of IBI in children <3 years old, whereas another found that PCT was inferior to prediction rules in identifying SBI in young infants. A prospective multicenter cohort study of febrile infants 7-91 days old determined that the PCT was better at identifying patients with IBI than CRP, WBC count, or ANC. Building on these results, clinical prediction rules for febrile infants, such as the **Step-by-Step** approach, incorporate PCT and CRP, along with age ≤21 days, ill appearance, ANC >10,000/mm^3, and pyuria in a stepwise approach to determine which patients are at high risk for IBI; only 0.7% of infants who met none of those criteria had IBI. In the approach from the AAP, inflammatory markers are recommended for all infants 22 days and older as part of risk stratification. If available, this approach recommends PCT along with either CRP or ANC. If PCT is unavailable, then CRP, ANC, and elevation in temperature should be considered as markers of inflammation (see Table 220.2).

Other Diagnostic Studies

Older infants with positive RSV and influenza testing have a very low risk of SBI beyond UTI. One large case-based survey demonstrated decreased admission rates and antibiotic use for infants with positive respiratory viral tests, and another study demonstrated that implementation of a care algorithm incorporating viral testing led to a shorter length of stay and antibiotic course.

Chest radiographs are unlikely to be clinically useful in the evaluation of the febrile infant without respiratory symptoms. Studies that have examined routine use of radiographs have found limited utility because in infants without respiratory symptoms, most results will be normal and abnormal results can be difficult to interpret.

TREATMENT

Antimicrobials

Ill-appearing and high-risk infants and those <22 days old hospitalized for evaluation for SBI should receive antimicrobial therapy. Commonly used regimens include (1) a third-generation cephalosporin (typically cefepime or ceftazidime), (2) a third-generation cephalosporin and ampicillin, or (3) an aminoglycoside and ampicillin.

Ampicillin is the preferred treatment of GBS and covers *L. monocytogenes* and many *Enterococcus* spp. and some *E. coli*. For neonates 0-28 days, options 2 or 3 have been recommended, given the risk of *L. monocytogenes*. For young infants >28 days, option 1 (third-generation cephalosporin: ceftriaxone) is a reasonable choice. For ill-appearing infants or those with positive CSF Gram stains, additional antibiotics may include vancomycin or broad-spectrum antibiotics such as carbapenems. Local epidemiology and resistance patterns may assist in these choices. Neonates with concern for HSV should be empirically treated with high-dose acyclovir (60 mg/kg/day).

Treatment duration and route of antimicrobial administration depend on the infection. Additional details based on specific infections and organisms are available in the following chapters: meningitis (see Chapter 148), UTI (see Chapter 575), *E. coli* (see Chapter 246), GBS (see Chapter 230), and HSV (see Chapter 299).

Discharge from the Hospital

Traditionally, infants remained in the hospital receiving antimicrobial therapy until bacterial cultures were negative for 48 hours or even longer. Multiple studies have suggested that shorter culture observation periods (i.e., 24 or 36 hours) may be reasonable because most pathogens in the blood grow within this time frame when automated blood culture monitoring systems are used. In one multicenter retrospective cross-sectional study, 91% of blood cultures were positive by 24 hours and 96% by 36 hours. Fewer studies have evaluated the *time to positivity* of CSF and urine cultures, but in one large study of febrile infants 28-90 days old, all positive CSF cultures grew within 24 hours (median time to positivity, 18 hours). For blood cultures, 1.3% grew after 24 hours (median time to positivity, 16 hours), and for urine cultures, 0.9% grew after 24 hours (median time to positivity, 16 hours). In one multicenter study including infants <60 days old, 82% of CSF cultures were positive by 24 hours and 86% by 36 hours. For neonates undergoing evaluation for HSV, it is reasonable to await results of HSV testing before discharge to home. For patients with identified bacterial infections or HSV infections, the duration of the hospital stay will be determined by the specific pathogen and site of infection.

PROGNOSIS

Most well-appearing neonates and young infants with fever recover completely and relatively quickly, depending on the etiology of the fever. Most infection-related mortality and long-term morbidity result from HSV infection and bacterial meningitis. For HSV, reported mortality rates range from 27% to 31% for disseminated disease and from 4% to 6% for CNS disease. Of those who survive, 83% of patients with disseminated disease and 31% of those with CNS disease will have normal development at 12 months old. The mortality of bacterial meningitis varies by pathogen but ranges from 4% to 15%. In one study of children who had meningitis as infants, 84% had normal development at age 5 years.

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Chapter 221

Fever in the Older Child

Laura Brower and Samir S. Shah

Fever is the most common reason for a child to seek medical care. While most infants and children have benign viral causes of fever, a small proportion will have more serious infections. Unlike fever in young infants, pediatricians can rely more readily on symptoms and physical examination findings to establish a diagnosis in older children. Laboratory testing and radiographic studies are not routinely indicated but may be helpful when diagnostic uncertainty exists or the patient appears critically ill. Occult infections, such as urinary tract infection (UTI), may be present, and testing for such infections should be guided by demographic and contextual factors such as patient age, patient gender, and environmental exposures.

DIAGNOSIS

The many potential causes of fever in older infants and children can be broadly categorized into viral and bacterial infections, further organized by body region, as well as the less common inflammatory, oncologic, endocrine, and medication-induced causes (Table 221.1).

Viral Infections

Viral infections are the most common cause of fever, and the prevalence of specific viral infections varies by season. Typically, in the summer and early fall, enteroviruses (e.g., coxsackieviruses) predominate, usually presenting as hand-foot-and-mouth disease, herpangina, aseptic meningitis, or a variety of other manifestations. In the late fall and winter, viral upper and lower respiratory tract infections caused by respiratory viruses such as respiratory syncytial virus (RSV) and influenza and gastroenteritis caused by gastrointestinal (GI) viruses such as norovirus and rotavirus are common. Parainfluenza viruses are a common cause of **laryngotracheobronchitis (croup)** and occur primarily in the fall and spring, affecting mostly infants and toddlers. Varicella is a less common cause of fever than in the past because of childhood vaccination but still occurs, with the highest incidence in winter and early spring. Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 can cause fever alone or with either upper or lower respiratory tract symptoms in young children, though asymptomatic infections also occur.

Bacterial Infections

Common bacterial infections include acute **otitis media** and **streptococcal pharyngitis (strep throat)**. Acute otitis media is diagnosed by the presence of a bulging, erythematous, and nonmobile tympanic membrane upon insufflation. Streptococcal pharyngitis occurs most frequently in the late fall and winter and is uncommon before age 3 years. The presence of focal auscultatory findings, including crackles, suggests a lower respiratory tract infection, such as bacterial pneumonia, but may also be present among children with **bronchiolitis** and viral pneumonia. **Atypical pneumonia** caused by mycoplasma typically occurs in school-age children and is often associated with headache, sore throat, malaise, and low-grade fever. The presence of neck pain (especially with neck extension for those with retropharyngeal abscess), drooling, or muffled voice may indicate a deep neck infection such as a **retropharyngeal abscess**, which occurs in infants and young children, or a **peritonsillar abscess**, which typically affects older children. Skin and soft tissue infections such as cellulitis and abscess may also present with fever, with the buttocks a common area for abscesses in young children. Bone and joint infections such as **osteomyelitis** and **septic arthritis** may present with fever and refusal to bear weight or limp in the young child. Invasive bacterial infections, including **sepsis** and **bacterial meningitis**, must be considered in young children presenting with fever. Although uncommon, these infections are potentially life-threatening and require prompt recognition and treatment. Ill appearance, lethargy, and tachycardia are typically present among children with severe sepsis, and petechiae may be an early finding among children with meningococcemia or other invasive bacterial diseases. Figures 221.1 and 221.2 show age-related diagnoses and organisms producing bacterial sepsis in infants and children. Children with fever who are immunosuppressed, such as children receiving chemotherapy or those with sickle cell disease, are at higher risk for invasive bacterial infection.

Infants and children age 2-24 months merit special consideration because they have limited verbal skills, are at risk for occult bacterial infections, and may be otherwise asymptomatic except for fever (see Chapter 220).

Occult Urinary Tract Infection

Among children 2-24 months old without symptoms or physical examination findings that identify another focal source of infection, the prevalence of UTI may be as high as 5–10%. The highest risk of UTI occurs in females and uncircumcised males, with a very low rate of infection (<0.5%) in circumcised males. Table 221.2 lists clinical risk factors for UTI.

Occult Bacteremia

Occult bacteremia is defined as a positive blood culture for a pathogen in a well-appearing child without an obvious source of infection. In the 1990s, before vaccination programs against *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae*, up to 5% of young children age 2 to 24 (up to 36) months with fever ≥39°C (102.2°F) had occult bacteremia, most often caused by *S. pneumoniae*. Currently, the prevalence of occult bacteremia is far less than 1% in febrile, well-appearing young children. Most cases of pneumococcal occult bacteremia are transient, with a minority of these children developing new focal infections, sepsis, or other sequelae. Unimmunized and incompletely immunized young children remain at higher risk for occult bacteremia because of pneumococcus (see Chapter 228). Bacteremia caused by Hib or meningococcus should not be considered benign because subsequent serious invasive infection may rapidly follow the bacteremia.

GENERAL APPROACH

The general approach to fever in the older child begins with an assessment of the child's overall appearance and vital signs. A detailed history of the present illness and a thorough physical examination should be performed to identify the cause of the fever.

Overall Appearance and Vital Signs

Children who are ill or appear toxic or who have abnormal vital signs (e.g., tachycardia, tachypnea, hypotension) require rapid assessment, including a focused physical examination to evaluate for the possibility of an invasive bacterial infection. A more detailed history and physical exam can be performed in the well-appearing child.

Symptoms

A thorough history should be obtained from the caregiver (and patient, when appropriate), including a characterization of the fever and any other associated symptoms. The degree and duration of the fever should be assessed, and the method of taking the temperature should be ascertained (e.g., forehead, axillary, oral, rectal). For children with prolonged fever, it is important to determine whether the fever has been episodic or persistent. Patients with prolonged fever may harbor occult infections, UTI, or bone or soft tissue infections or may have an inflammatory or oncologic condition. Additionally, Kawasaki disease and multisystem inflammatory syndrome in children (MIS-C) should be considered among children with prolonged fever, and a careful evaluation for other stigmata associated with these conditions is warranted (see Chapter 208).

After characterizing the fever, it is important to ask systematically about the presence of symptoms that may identify an etiology for the fever, including symptoms of common viral infections such as rhinorrhea, cough, vomiting, and diarrhea. Additionally, symptoms should be elicited for each body system: headache, ear pain, sore throat, neck pain or swelling, difficulty breathing, chest pain, abdominal pain, rash or changes in skin color, extremity pain or difficulty with ambulation (including refusal to bear weight in a

Table 221.1 Etiologies of Fever in Children >2 Mo of Age

INFECTIOUS

Central Nervous System
Bacterial meningitis
Viral meningitis
Viral encephalitis
Epidural abscess
Brain abscess

Ear, Nose, and Throat
Acute otitis media
Mastoiditis
Viral upper respiratory infection (i.e., common cold)
Acute bacterial sinusitis
Acute streptococcal pharyngitis
Acute viral pharyngitis
Retropharyngeal abscess
Ludwig angina
Peritonsillar abscess
Herpangina
Herpes simplex virus gingivostomatitis
Acute bacterial lymphadenitis
Viral laryngotracheobronchitis (i.e., croup)
Bacterial tracheitis
Epiglottitis
Lemierre syndrome

Face and Ocular
Parotitis (viral and bacterial)
Erysipelas
Preseptal cellulitis
Orbital cellulitis

Lower Respiratory Tract
Acute viral bronchiolitis
Pneumonia (viral and bacterial)
Complicated pneumonia (e.g., empyema, pleural effusion)
Tuberculosis

Cardiac
Pericarditis
Myocarditis
Endocarditis

Gastrointestinal
Gastroenteritis (viral and bacterial)
Mesenteric adenitis
Acute appendicitis
Hepatitis
Pancreatitis
Gallbladder disease (e.g., cholecystitis, cholangitis)
Intraabdominal abscess

Genitourinary
Urinary tract infection/pyelonephritis
Renal abscess
Epididymitis
Pelvic inflammatory disease
Tubo-ovarian abscess

Skin, Soft Tissue, and Muscle
Viral exanthemas (e.g., varicella, coxsackievirus, roseola, measles)
Scarlet fever
Syphilis
Cellulitis
Abscess
Necrotizing fasciitis
Myositis (viral and bacterial and immune)

Bone and Joint
Osteomyelitis
Septic arthritis
Transient synovitis
Spondylodiscitis

Toxin Mediated
Toxic shock syndrome
Staphylococcal scalded skin syndrome

Invasive Bacterial Infections
Occult bacteremia
Bacterial sepsis
Bacterial meningitis
Disseminated gonococcal infection

Systemic Infection
EBV
CMV
HIV
Cat scratch disease
Brucellosis
Influenza
Others (see Chapter 222)

Vector-Borne (Tick, Mosquito)
Lyme disease
Rickettsiae (e.g., Rocky Mountain spotted fever
Ehrlichiosis
Arboviruses (e.g., West Nile virus)
Dengue fever

INFLAMMATORY
Kawasaki disease
Acute rheumatic fever
Systemic lupus erythematosus
Inflammatory bowel disease
Juvenile idiopathic arthritis
IgA vasculitis (Henoch-Schönlein purpura)
Other rheumatologic diseases (e.g., dermatomyositis)
Periodic fever syndromes
Serum-like sickness syndrome
Multisystem inflammatory syndrome in children (MIS-C)

ONCOLOGIC
Leukemia
Lymphoma
Solid tumors (e.g., neuroblastoma)

ENDOCRINE
Thyrotoxicosis/thyroid storm

MEDICATION INDUCED
Serotonin syndrome
Anticholinergic toxidrome (e.g., antihistamines)
Sympathomimetic toxidrome (e.g., cocaine)
Salicylate toxicity

OTHER
Hemophagocytic lymphohistiocytosis
Macrophage activation syndrome
Ectodermal dysplasia
Dysautonomia
Factitious

young child), and overall activity level. In older children, the presence of dysuria, urinary frequency, or back pain may indicate UTI. Assessment of oral intake and urine output is also critical because dehydration may accompany common childhood infections and is associated with higher rates of morbidity. The presence of weight loss or night sweats may indicate leukemia, lymphoma, or tuberculosis. Additionally, a thorough social history should be performed, inquiring about attendance at daycare, any travel, and any sick contacts at daycare, school, or in the household.

Physical Examination

A complete physical examination includes particular attention to body systems with associated symptoms (e.g., thorough exam of oropharynx for child with sore throat). A complete physical

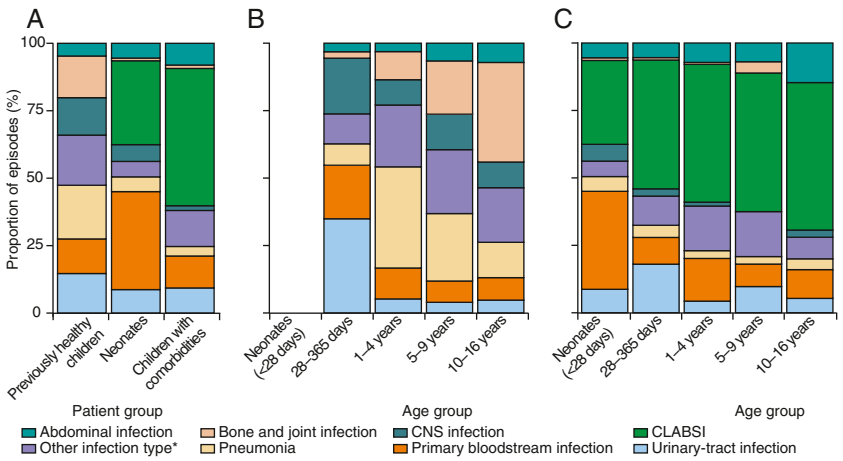

Fig. 221.1 Age distribution of sites of infection causing blood culture–proven bacterial sepsis in children. Sites of infection are shown for (A) the three patient groups together and separately for (B) previously healthy children ≥28 days old and (C) neonates and children with comorbidities ≥28 days old. CLABSI, Central line–associated bloodstream infection; CNS, central nervous system. *Skin infection, wound infection, endocarditis, toxic shock syndrome; ear, nose, and throat infection; other, nonspecified focal infection. *(From Agyeman PKA, Schlapbach LJ, Giannoni E, et al. Epidemiology of blood culture-proven bacterial sepsis in children in Switzerland: a population-based cohort study. Lancet Child Adolesc. 2017;1:124–133, Fig. 3.)*

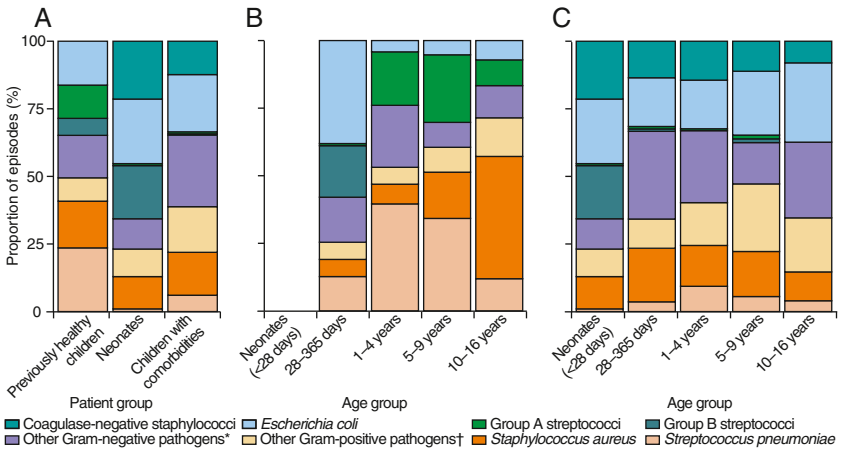

Fig. 221.2 Age distribution of pathogens causing blood culture–proven bacterial sepsis in children. Pathogens isolated in blood culture are shown for (A) the three patient groups together and separately for (B) previously healthy children ≥28 days old and (C) neonates and children with comorbidities ≥28 days old. **Pseudomonas aeruginosa, Klebsiella* spp., *Neisseria meningitidis, Haemophilus influenzae,* other gram-negative pathogens. †*Enterococcus* spp., viridans group streptococci, other gram-positive pathogens. *(From Agyeman PKA, Schlapbach LJ, Giannoni E, et al. Epidemiology of blood culture-proven bacterial sepsis in children in Switzerland: a population-based cohort study. Lancet Child Adolesc. 2017;1:124–133, Fig. 4.)*

examination is particularly important in young children <24 months old who have limited verbal skills to communicate localized pain. In older children the physical exam may proceed systematically from head to toe, but in younger children, who may be fearful of the exam, it is important to auscultate the heart and lungs first before proceeding to potentially painful or distressing aspects of the examination (e.g., inspection of ears or oropharynx). In addition to a careful evaluation of each body system, a complete examination should include an assessment of neck pain and mobility, which may be limited in children with **meningitis**. Additionally, the examiner should palpate carefully for the presence of **lymphadenopathy**, which may be present with infectious and oncologic causes of fever. Erythema and exudate of the tonsils with palatal petechiae suggest streptococcal pharyngitis. Erythema, bulging, and decreased mobility of the tympanic membrane are the cardinal signs of acute otitis media. Diffuse crackles and wheezes on auscultation of the lungs occur with acute viral bronchiolitis, whereas focal crackles or decreased breath sounds are more consistent with bacterial pneumonia. Focal tenderness in the right lower quadrant of the abdomen suggests **appendicitis**, and suprapubic tenderness may indicate UTI **(cystitis)**. Any focal bony tenderness may reflect a diagnosis of osteomyelitis, whereas erythema, swelling, and limitation of range of motion suggest a diagnosis of septic arthritis. Abnormal gait or pain with ambulation without focal findings may also reflect a bone or joint infection. A careful skin examination should also be performed. The presence of petechiae may suggest meningococcal or other invasive bacterial infection, whereas viral exanthems are typically associated with a blanching macular or maculopapular rash.

EVALUATION

Laboratory Testing

Laboratory testing is not routinely indicated in the well-appearing child without a focus of infection on examination. Urine testing should be considered based on the child's age, duration of fever, and risk factors for UTI (see Table 221.2). In general, the decision to perform laboratory testing should be guided by the overall appearance and vital signs of the child, the presence of specific symptoms or physical examination findings, and the child's age.

For children who are ill or appear toxic or who have vital sign abnormalities indicative of an invasive bacterial infection (tachycardia, hypotension), rapid laboratory evaluation should be performed. Testing may include a blood culture and possibly urine and cerebrospinal fluid (CSF) cultures, depending on the age of the child and the presence or absence of physical exam findings indicative of UTI or bacterial meningitis. Markers of inflammation, such as procalcitonin or C-reactive protein may also be considered. Complete blood counts (CBCs) identify leukocytosis or leukopenia, anemia, and thrombocytosis or thrombocytopenia. Children with infectious mononucleosis may have lymphocyte predominance and the presence of atypical lymphocytes. Children

who are immunosuppressed or who have a central venous catheter should also undergo diagnostic testing and receive prompt antimicrobial therapy, given their higher risk of invasive bacterial infection.

For well-appearing children with symptoms or signs indicative of a viral upper respiratory or GI infection, routine viral testing is not generally indicated. **Influenza** testing may be indicated within 48 hours of symptom onset in certain higher-risk populations, with immunosuppression, chronic respiratory or cardiac disease, sickle cell disease, hospitalization, and age <2 years influencing the decision to treat with an antiviral agent. Testing for **SARS-CoV-2** may be indicated based on local prevalence and symptoms (fever, cough, congestion, loss of taste or smell, shortness of breath, body aches, fatigue, headache, sore throat, nausea, vomiting, or diarrhea). Viral testing may also be useful with prolonged fever to identify a source of the fever and avoid extensive evaluation for inflammatory conditions such as Kawasaki disease or MIS-C.

Rapid strep testing of the oropharynx is indicated for children ≥3 years old with signs of streptococcal pharyngitis on examination. Although strep throat is uncommon in children <3 years old, this group should undergo rapid strep testing if they have signs of strep throat on exam and a household contact with streptococcal pharyngitis (see Chapter 229).

Febrile children 2 months to 2 years old with several of the risk factors for UTI listed in Table 221.2, particularly females and uncircumcised males, should undergo evaluation with urine dipstick, urine microscopy, and urine culture. Females and uncircumcised males 2-6 months old with high fever or fever that lasts ≥2 days may undergo urine testing even in the presence of respiratory tract infection, given the higher risk of UTI in this younger group (see Chapter 575).

Given the very low risk of occult bacteremia, routine performance of blood testing (e.g., CBC, blood culture) is not indicated in the vast majority of immunized children with fever. Unimmunized and underimmunized children <2 years old remain at higher risk of occult pneumococcal bacteremia, and CBC, blood culture, and/or inflammatory markers may be considered in this population in the absence of another source of infection.

Imaging

The presence of focal crackles or decreased breath sounds on auscultation in the febrile child is suggestive of **pneumonia**. Current guidelines recommend presumptive antibiotic treatment for pneumonia based on clinical grounds and reserve the use of chest radiography for children with hypoxemia or significant respiratory distress and for those who fail outpatient therapy. Chest radiography is indicated for hospitalized children to assess for complicated pneumonia, including **empyema**. The performance of other imaging should be dictated by physical exam findings. The presence of drooling and neck or throat pain in an infant or toddler may be suggestive of a retropharyngeal abscess, which is usually confirmed by imaging that may include a lateral radiograph of the soft tissue of the neck or computed tomography (CT) if clinical suspicion is high. Ultrasonography (US) may be performed to assess for **appendicitis** in children with fever and focal right lower quadrant pain or abdominal pain that is severe. However, definitive imaging, including CT or MRI, may be required if US is nondiagnostic or if clinical suspicion is high.

Table 221.2 Risk Factors for Urinary Tract Infection in Children

AMERICAN ACADEMY OF PEDIATRICS CLINICAL PRACTICE GUIDELINE* CHILDREN 2-24 MO OF AGE
Female Age <1 yr Temperature ≥39°C (102.2°F) Fever duration ≥2 days No obvious source of infection
Male *Uncircumcised males at higher risk* Temperature ≥39°C (102.2°F) Fever duration >1 day No obvious source of infection
UNIVERSITY OF PITTSBURGH UTICALC† CHILDREN 2-23 MO OF AGE
Age <12 mo Maximum temperature ≥39°C History of UTI Female or uncircumcised male Duration of fever ≥48 hr No other source of fever

*Adapted from Subcommittee on Urinary Tract Infection, et al. Urinary tract infection clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics*. 2011;128(3):595–610.

†Adapted from Shaikh N, Hoberman A, Hum SW, et al. Development and validation of a calculator for estimating the probability of urinary tract infection in young febrile children. *JAMA Pediatr*. 2018;172(6):550–556 and UTICalc Version 3.0, University of Pittsburgh 2021, https://uticalc.pitt.edu/

MANAGEMENT

General Management Principles

Management should be guided by the presence of specific symptoms by history or signs on physical examination. Based on the child's age and duration of fever, management may also be guided by focused diagnostic testing, such a urinalysis and selective urine culture testing among young febrile children (Fig. 221.3 and see Table 221.2). Supportive care, including the use of antipyretics and adequate hydration, should be reviewed with the patient and caregiver for all children with fever. Children with viral infections generally require supportive care only, except for children at higher risk of severe or complicated disease with **influenza virus** (see Chapter 305) or SARS-CoV-2 (see Chapter 311). Antibiotics should

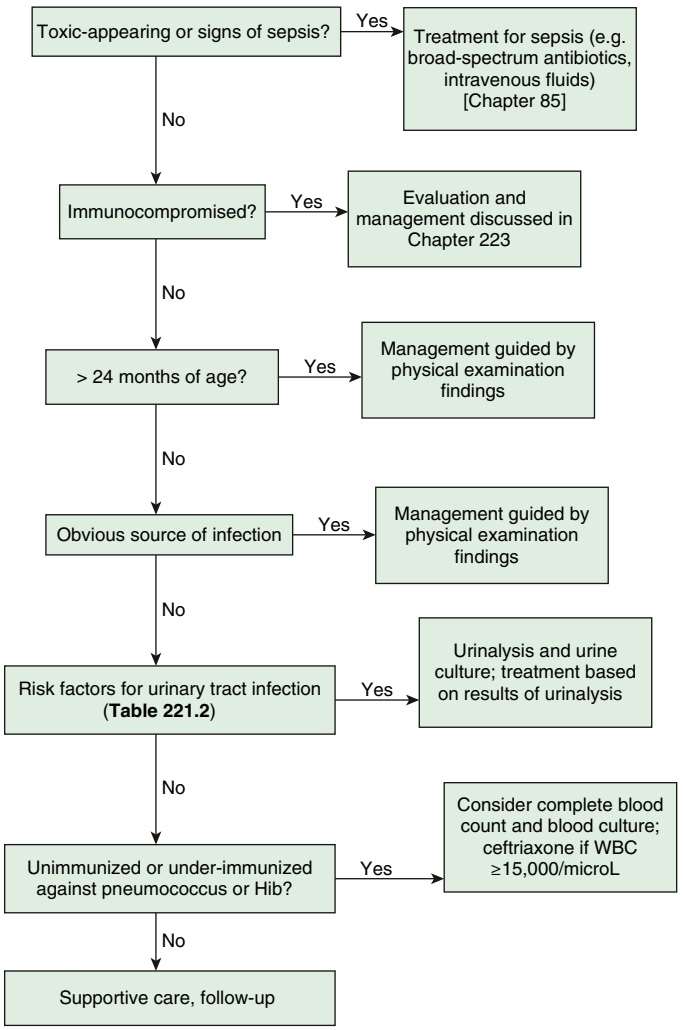

Fig. 221.3 Algorithm for evaluation and management of fever in infants and children >2 mo of age. Hib, *Haemophilus influenzae* type b; WBC, white blood cell count.

be reserved for children with evidence of bacterial infection on physical examination. A wait-and-see approach can be considered for children with acute **otitis media**, in whom a prescription for antibiotics can be provided to the family but instructions given to not fill the prescription unless severe or worsening symptoms develop (see Chapter 680). Oral antibiotics can be prescribed to young children with UTI, although children who cannot tolerate oral intake, are vomiting or dehydrated, or appear toxic require parenteral antibiotics and hospitalization.

Blood tests, including CBC and blood culture, should be considered to evaluate for occult **bacteremia** in the unimmunized child. One management strategy for these children is to administer a parenteral antibiotic (e.g., ceftriaxone) if leukocytosis (white blood cell count ≥15,000/μL), elevated absolute neutrophil count (≥10,000/μL), or elevated inflammatory markers (procalcitonin >0.5 ng/mL) are present while awaiting results of blood culture. Children who appear toxic or who have signs of either sepsis or bacterial meningitis require emergent treatment with parenteral antibiotics as well as adjunct therapies to support the child's hemodynamics (see Chapter 85).

Importantly, anticipatory guidance should be provided to all families of children with fever, including the criteria to return to care and the importance of fever control and adequate hydration.

Other Considerations

Children who are unimmunized or underimmunized are at higher risk of invasive bacterial infection, as are children who are immunocompromised. Management of fever in these children is described further in Chapter 223. Additionally, the approach to fever in the returning traveler should be focused on identifying commonly encountered infections based on the region of travel (see Chapter 218).

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Chapter 222

Fever of Unknown Origin

Andrew P. Steenhoff

Fever of unknown origin **(FUO)** is a diagnostic dilemma for pediatricians because it is often difficult to distinguish clinically between benign and potentially life-threatening causes. Pediatricians face the important challenge of not missing the diagnosis of a serious illness or an easily treatable condition that can result in increased morbidity. Fortunately, FUO is usually an uncommon presentation of a common disease, with most of these common diseases being easily treatable.

The classification of FUO is best reserved for children with a temperature >38°C (100.4°F) documented by a healthcare provider and for which the cause could not be identified after at least 8 days of evaluation (Table 222.1). It is important to differentiate FUO from **fever without a source (FWS)**. FWS is fever where the source has not yet been identified and is differentiated from FUO by the duration of the fever. FWS can progress to FUO if no cause is elicited after 7 days of evaluation.

ETIOLOGY

The many causes of FUO in children are infectious, rheumatologic (connective tissue or autoimmune), autoinflammatory, oncologic, neurologic, genetic, factitious, and iatrogenic processes (Table 222.2). Although oncologic disorders should be seriously considered, most children with malignancies do not have fever alone. The possibility of **drug fever** should be considered if the patient is receiving any drug. Drug fever is usually sustained and not associated with other symptoms. Discontinuation of the drug is associated with resolution of the fever, generally within 72 hours, although certain drugs, such as iodides, are excreted for a prolonged period, with fever that can persist for as long as 1 month after drug withdrawal.

Most fevers of unknown origin result from atypical presentations of common diseases. In some cases, the presentation as an FUO is characteristic of the disease (e.g., juvenile idiopathic arthritis), but the definitive diagnosis can be established only after prolonged observation, because initially there are no associated or specific findings on physical examination, and all laboratory results are negative or normal.

In the United States the systemic infectious diseases most commonly implicated in children with FUO are bacterial enterocolitis, including salmonellosis, as well as tuberculosis, rickettsial diseases, syphilis, Lyme disease, cat-scratch disease, atypical prolonged presentations of common viral diseases such as adenovirus infection, Epstein-Barr virus (EBV) infection, cytomegalovirus (CMV) infection, viral hepatitis, coccidioidomycosis, histoplasmosis, malaria, *Angiostrongylus cantonensis* infection, and toxoplasmosis. Less common infectious causes of FUO include tularemia, brucellosis, leptospirosis, and rat-bite fever. Acquired immunodeficiency syndrome (AIDS) alone is not usually responsible for FUO, although febrile illnesses often occur in patients with AIDS as a result of opportunistic infections (see Table 222.1).

Juvenile idiopathic arthritis (JIA) and **systemic lupus erythematosus** (SLE) are the connective tissue diseases most often associated with FUO. **Inflammatory bowel disease** (IBD) and **Kawasaki disease** are also frequently reported as causes of FUO. If **factitious fever** (inoculation of pyogenic material or manipulation of the thermometer by the patient or parent) is suspected, the presence and pattern of fever should be documented in the hospital. Prolonged and continuous observation of the patient, which can include electronic or video surveillance, is imperative. FUO lasting >6 months is uncommon in children and suggests granulomatous, autoinflammatory, or autoimmune disease. Repeat interval evaluation is required, including history, physical examination, laboratory evaluation, and imaging studies.

Historically, 90% of pediatric FUO cases in the United States had an identifiable cause: approximately 50% infectious, 10–20% collagen vascular, and 10% oncologic. Other studies had variable results: 20–44% infectious, 0–7% collagen vascular, 2–3% oncologic, and up to 67% undiagnosed. The reason for the paradoxical increase in undiagnosed cases of FUO ironically is likely caused by improved infectious and autoimmune diagnostic techniques. The advent of polymerase chain reaction (PCR), improved culture techniques, and better understanding of atypical viral and bacterial pathogenesis and autoimmune processes likely contribute to *earlier* diagnosis of these conditions and fewer children with these conditions *advancing* to the category of FUO. By contrast, causes of FUO remain primarily infectious in low and middle income settings where there is a higher infectious disease burden and advanced diagnostic techniques are more limited.

DIAGNOSIS

The evaluation of FUO requires a thorough history and physical examination supplemented by a few screening laboratory tests and additional laboratory and imaging evaluation informed by the history or abnormalities on examination or initial screening tests (see Table 222.2). Occasionally the **fever pattern** helps make a diagnosis (Fig. 222.1). Nonetheless, most diseases causing an FUO do not have a typical fever pattern.

History

A detailed fever history should be obtained, including onset, frequency, duration, response or nonresponse to therapy, recurrence, and associated symptoms. Repetitive chills and temperature spikes are common in children with **septicemia** (regardless of cause), particularly when associated with kidney disease, liver or biliary disease, infective endocarditis, malaria, brucellosis, rat-bite fever, or a loculated collection of pus.

The age of the patient is helpful in evaluating FUO. Children >6 years old often have a respiratory or genitourinary tract infection, localized infection (abscess, osteomyelitis), JIA, or rarely, leukemia. Adolescent patients are more likely to have IBD, autoimmune processes, lymphoma, or tuberculosis in addition to the causes of FUO found in younger children.

A history of exposure to wild or domestic **animals** should be solicited. The incidence of **zoonotic infections** in the United States is

be reserved for children with evidence of bacterial infection on physical examination. A wait-and-see approach can be considered for children with acute **otitis media**, in whom a prescription for antibiotics can be provided to the family but instructions given to not fill the prescription unless severe or worsening symptoms develop (see Chapter 680). Oral antibiotics can be prescribed to young children with UTI, although children who cannot tolerate oral intake, are vomiting or dehydrated, or appear toxic require parenteral antibiotics and hospitalization.

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Table 222.1 Summary of Definitions and Major Features of Four Subtypes of Fever of Unknown Origin (FUO)

FEATURE	CLASSIC FUO	HEALTHCARE-ASSOCIATED FUO	IMMUNE-DEFICIENT FUO	HIV-RELATED FUO
Definition	>38°C (100.4°F), >3 wk, >2 visits, or 1 wk in hospital	≥38°C (100.4°F), >1 wk, not present or incubating on admission	≥38°C (100.4°F), >1 wk, negative cultures after 48 hr	≥38°C (100.4°F), >3 wk for outpatients, >1 wk for inpatients, HIV infection confirmed
Patient location	Community, clinic, or hospital	Acute care hospital	Hospital or clinic	Community, clinic, or hospital
Leading causes	Cancer, infections, inflammatory conditions, undiagnosed, habitual hyperthermia	Healthcare-associated infections, postoperative complications, drug fever	Majority caused by infections, but cause documented in only 40–60%	HIV itself, typical and atypical mycobacteria, CMV, lymphomas, toxoplasmosis, cryptococcosis, immune reconstitution inflammatory syndrome (IRIS)
History emphasis	Travel, contacts, animal and insect exposure, medications, immunizations, family history, cardiac valve disorder	Operations and procedures, devices, anatomic considerations, drug treatment	Stage of chemotherapy, drugs administered, underlying immunosuppressive disorder	Drugs, exposures, risk factors, travel, contacts, stage of HIV infection
Examination emphasis	Fundi, oropharynx, temporal artery, abdomen, lymph nodes, spleen, joints, skin, nails, genitalia, rectum or prostate, lower-limb deep veins	Wounds, drains, devices, sinuses, urine	Skinfolds, IV sites, lungs, perianal area	Mouth, sinuses, skin, lymph nodes, eyes, lungs, perianal area
Investigation emphasis	Imaging, biopsies, sedimentation rate, skin tests	Imaging, bacterial cultures	CXR, bacterial cultures	Blood and lymphocyte count; serologic tests; CXR; stool examination; biopsies of lung, bone marrow, and liver for cultures and cytologic tests; brain imaging
Management	Observation, outpatient temperature chart, investigations, avoidance of empirical drug treatments	Depends on situation	Antimicrobial treatment protocols	Antiviral and antimicrobial protocols, vaccines, revision of treatment regimens, good nutrition
Time course of disease	Months	Weeks	Days	Weeks to months
Tempo of investigation	Weeks	Days	Hours	Days to weeks

CMV, Cytomegalovirus; CXR, chest radiograph; HIV, human immunodeficiency virus; IV, intravenous line.
Adapted from Mackowak PA, Durack DT. Fever of unknown origin. In: Mandell GL, Bennett, JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 7th ed. Philadelphia: Elsevier; 2010: Table 51-1.

increasing, and these infections are often acquired from pets that are not overtly ill. Immunization of dogs against specific disorders such as **leptospirosis** can prevent canine disease but does not always prevent the animal from carrying and shedding leptospires, which may be transmitted to household contacts. A history of ingestion of rabbit or squirrel meat might provide a clue to the diagnosis of oropharyngeal, glandular, or typhoidal **tularemia**. A history of tick bite or travel to tick- or parasite-infested areas should be obtained.

Any history of **pica** should be elicited. Ingestion of dirt is a particularly important clue to infection with *Toxocara canis* (visceral larva migrans) or *Toxoplasma gondii* (toxoplasmosis).

A history of unusual dietary habits or travel as early as the birth of the child should be sought. Tuberculosis, malaria, histoplasmosis, and coccidioidomycosis can reemerge years after visiting or living in an endemic area. It is important to identify prophylactic immunizations and precautions taken by the patient against ingestion of contaminated water or food during foreign travel. Rocks, dirt, and artifacts from geographically distant regions that have been collected and brought into the home as souvenirs can serve as vectors of disease.

A **medication** history should be pursued rigorously. This history should elicit information about nonprescription preparations and topical agents, including eyedrops, that may be associated with atropine-induced fever.

The genetic background of a patient also is important. Descendants of the Ulster Scots may have FUO because they are afflicted with nephrogenic diabetes insipidus. **Familial dysautonomia** (Riley-Day syndrome), a disorder in which hyperthermia is recurrent, is more common among Jews than among other population groups. Ancestry from the Mediterranean region should suggest **familial Mediterranean fever**. Both familial Mediterranean fever and hyper-IgD syndrome are inherited as autosomal recessive disorders. Tumor necrosis factor receptor–associated periodic syndrome and Muckle-Wells syndrome are inherited as autosomal dominant traits.

Pseudo-FUO is defined as successive episodes of benign, self-limited infections with fever that the parents perceive as one prolonged fever episode. This needs to be carefully ruled out before undertaking an unnecessary evaluation. Usually, pseudo-FUO starts with a well-defined infection (frequently viral) that resolves but is followed by other febrile viral illnesses that may be less well defined. Diagnosis of pseudo-FUO usually requires a careful history, focusing on identifying afebrile periods between febrile episodes. If pseudo-FUO is suspected and the patient does not appear ill, keeping a *fever diary* can be helpful.

Table 222.2 Etiology of Fever of Unknown Origin (FUO) in Children

ABSCESSES
Brain
Hepatic
Intraabdominal*
Odontogenic (dental)
Pelvic*
Perinephric and renal
Psoas
Rectal
Subphrenic

BACTERIAL DISEASES
Actinomycosis
Bartonella henselae (cat-scratch disease)*
Brucellosis
Campylobacter
Chlamydia
Francisella tularensis (tularemia)
Fusobacterium (Lemierre syndrome)
Leptospirosis
Listeria monocytogenes (listeriosis)
Lymphogranuloma venereum
Meningococcemia (chronic)
Mycoplasma pneumoniae
Psittacosis
Rat-bite fever (*Streptobacillus moniliformis*; streptobacillary form of rat-bite fever)
Salmonella
Tuberculosis*
Whipple disease
Yersiniosis

LOCALIZED INFECTIONS
Bacterial endocarditis*
Cholangitis
Ludwig angina
Mastoiditis
Osteomyelitis*
Pericarditis
Pneumonia
Pyelonephritis*
Sinusitis
Spondylodiskitis

SPIROCHETES
Borrelia burgdorferi (Lyme disease)
Leptospirosis
Rat-bite fever (*Spirillum minus*; spirillary form of rat-bite fever)
Relapsing fever *(Borrelia recurrentis, Borrelia miyamotoi)*
Syphilis

FUNGAL DISEASES
Blastomycosis (extrapulmonary)
Coccidioidomycosis (disseminated)
Cryptococcosis
Histoplasmosis (disseminated)

RICKETTSIAE-LIKE ORGANISMS
Anaplasmosis
Ehrlichiosis
Q fever
Rocky Mountain spotted fever
Tick-borne typhus

VIRUSES
Arboviruses
Chikungunya
Cytomegalovirus*
Epstein-Barr virus*
Hantavirus
Hepatitis viruses
HIV
Human herpesviruses (HHV-6 and HHV-7)
Lymphocytic choriomeningitis
Respiratory viruses (especially, adenovirus and enteroviruses)*
Zika virus

PARASITIC DISEASES
Amebiasis
Babesiosis
Baylisascaris
Malaria
Naegleria
Toxoplasmosis
Trichinosis
Trypanosomiasis
Visceral larva migrans *(Toxocara)*

RHEUMATOLOGIC DISEASES
Autoimmune hepatitis
Behçet syndrome
Chronic noninfectious osteomyelitis (CNO)
Juvenile dermatomyositis
Juvenile idiopathic arthritis* ± macrophage activation syndrome
Rheumatic fever
Systemic lupus erythematosus*
Vasculitis syndromes (granulomatous, nongranulomatous)

HYPERSENSITIVITY DISEASES
Drug fever, including DRESS
Hypersensitivity pneumonitis
Hypersensitivity vasculitis/reactive arthritis*
Serum sickness
Weber-Christian disease

NEOPLASMS
Atrial myxoma
Cholesterol granuloma
Hodgkin lymphoma
Inflammatory pseudotumor
Langerhans cell histiocytosis
Leukemia
Lymphoma*
Pheochromocytoma
Neuroblastoma
Wilms tumor

GRANULOMATOUS DISEASES
Crohn disease
Granulomatous hepatitis
Polyangiitis with granulomatosis
Sarcoidosis

FAMILIAL AND HEREDITARY DISEASES
Anhidrotic ectodermal dysplasia
Autoimmune lymphoproliferative syndrome (ALPS)
Autonomic neuropathies
Fabry disease
Familial dysautonomia
Familial Hibernian fever
Familial Mediterranean fever and the many other autoinflammatory (periodic fever) diseases (see Chapter 204)
Hypertriglyceridemia
Ichthyosis
Sickle cell crisis
Spinal cord/brain injury

MISCELLANEOUS
Addison disease
Allergic alveolitis
Castleman disease
Cyclic neutropenia
Diabetes insipidus (non-nephrogenic and nephrogenic)
Erythema multiforme
Factitious fever
Hemophagocytic lymphohistiocytosis (HLH)
Hypereosinophilia syndromes
Hypothalamic-central fever
Infantile cortical hyperostosis
Inflammatory bowel disease*
Kawasaki disease*
Kikuchi-Fujimoto disease
Metal fume fever
Multisystem inflammatory syndrome in children (MIS-C)
Pancreatitis
Poisoning
Pulmonary embolism
Rosai-Dorfman disease
Thrombotic thrombocytopenia purpura
Thrombophlebitis
Thyrotoxicosis, thyroiditis

*Most common identified causes of FUO in children.
DRESS, Drug reaction with eosinophilia and systemic symptoms.
Modified from Huppler AR. Fever. In: Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Philadelphia: Elsevier; 2023: Table. 52.9, pp. 980–981.

Physical Examination

A complete physical examination is essential to search for any clues to the underlying diagnosis, and often it is worthwhile to repeat a detailed examination on different days to detect signs that may have changed or been missed (Tables 222.3-222.5). The child's general appearance, including **sweating** during fever, should be noted. The continuing absence of sweat in the presence of an elevated or changing body temperature suggests dehydration caused by vomiting, diarrhea, or central or nephrogenic diabetes insipidus. It also should suggest anhidrotic ectodermal dysplasia, familial dysautonomia, or exposure to atropine.

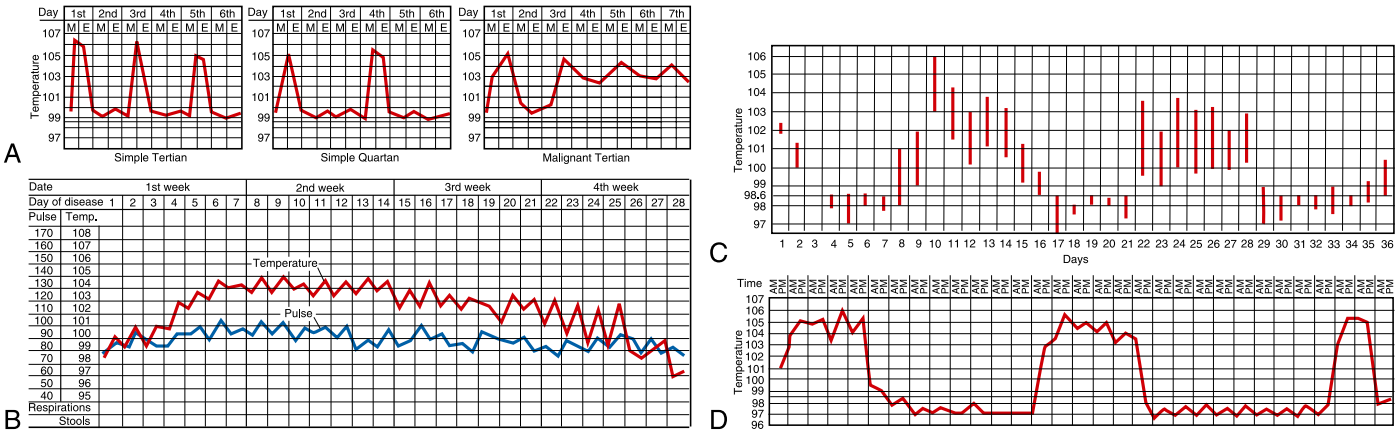

Fig. 222.1 Distinctive fever patterns. **A,** Malaria. **B,** Typhoid fever (demonstrating relative bradycardia). **C,** Hodgkin disease (Pel-Ebstein fever pattern). **D,** Borreliosis (relapsing fever pattern). *(From Woodward TE. The fever pattern as a clinical diagnostic aid. In Mackowiak PA, ed. Fever: Basic Mechanisms and Management, 2nd ed. Philadelphia: Lippincott-Raven; 1997:215–236.)*

Table 222.3 Subtle Physical Findings with Special Significance in Patients with Fever of Unknown Origin

BODY SITE	PHYSICAL FINDING	DIAGNOSIS
Head	Sinus tenderness	Sinusitis
Temporal artery	Nodules, reduced pulsations	Temporal arteritis
Oropharynx	Ulceration	Disseminated histoplasmosis, SLE, IBD, Behçet syndrome, periodic fever syndromes
	Tender tooth	Periapical abscess, sinus referred pain
	Loose teeth	Langerhans cell histiocytosis, leukemia
Fundi or conjunctivae	Choroid tubercle	Disseminated granulomatosis*
	Petechiae, Roth spots	Endocarditis
Thyroid	Enlargement, tenderness	Thyroiditis
Heart	Murmur	Infective or marantic endocarditis
	Relative bradycardia	Typhoid fever, malaria, leptospirosis, psittacosis, central fever, drug fever
Abdomen	Enlarged iliac crest lymph nodes, splenomegaly	Lymphoma, endocarditis, disseminated granulomatosis*
	Audible abdominal aortic or renal artery bruit	Large vessel vasculitis such as Takayasu arteritis
	Costovertebral tenderness	Chronic pyelonephritis, perinephric abscess
Rectum	Perirectal fluctuance, tenderness	Abscess
	Prostatic tenderness, fluctuance	Abscess
Genitalia	Testicular nodule	Periarteritis nodosa, cancer
	Epididymal nodule	Disseminated granulomatosis
Spine	Spinal tenderness	Vertebral osteomyelitis
	Paraspinal tenderness	Paraspinal collection
Lower extremities	Deep venous tenderness	Thrombosis or thrombophlebitis
Upper or lower extremities	Pseudoparesis	Syphilitic bone disease
Skin and nails	Petechiae, splinter hemorrhages, subcutaneous nodules, clubbing	Vasculitis, endocarditis

*Includes tuberculosis, histoplasmosis, coccidioidomycosis, sarcoidosis, granulomatosis with polyangiitis, and syphilis.
Adapted from Mackowak PA, Durack DT. Fever of unknown origin. In: Mandell GL, Bennett, JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 7th ed. Philadelphia: Elsevier; 2010: Table 51-8.

Table 222.4 Examples of Potential Diagnostic Clues to Infections Presenting as Fever of Unknown Origin

ETIOLOGY	HISTORICAL CLUES	PHYSICAL CLUES
Anaplasmosis	Transmitted by bite of *Ixodes* tick in association with outdoor activity in northern-central and eastern United States	Fever, headache, arthralgia, myalgia, pneumonitis, thrombocytopenia, lymphopenia, elevated liver enzymes
Babesiosis	Transmitted by bite of *Ixodes* tick in association with outdoor activity in northeastern United States	Arthralgias, myalgias, relative bradycardia, hepatosplenomegaly, anemia, thrombocytopenia, elevated liver enzymes
Bartonellosis	Recent travel to Andes Mountains (Oroya fever; *Bartonella bacilliformis*), association with homelessness in urban settings *(Bartonella quintana)* or scratch of infected kitten or feral cat *(Bartonella henselae)*	Conjunctivitis, retroorbital pain, anterior tibial bone pain, macular rash, nodular plaque lesions, regional lymphadenopathy
Blastomycosis	Contact with soil adjacent to Mississippi and Ohio River valleys, Saint Lawrence River in New York and Canada, and North American Great Lakes or exposure to infected dogs	Arthritis, atypical pneumonia, pulmonary nodules, and/or fulminant adult respiratory distress syndrome; verrucous, nodular, or ulcerative skin lesions; prostatitis
Brucellosis	Associated with contact or consumption of products from infected goats, pigs, camels, yaks, buffalo, or cows and with abattoir work	Arthralgias, hepatosplenomegaly, suppurative musculoskeletal lesions, sacroiliitis, spondylitis, uveitis, hepatitis, pancytopenia
Coccidioidomycosis	Exposure to soil or dust in southwestern United States	Arthralgias, pneumonia, pulmonary cavities, pulmonary nodules, erythema multiforme, erythema nodosum
Ehrlichiosis	Transmitted by bite of *Amblyomma, Dermacentor,* or *Ixodes* tick in association with outdoor activity in midwestern and southeastern United States	Pneumonitis, hepatitis, thrombocytopenia, lymphopenia
Enteric fever (*Salmonella enterica* serovar Typhi)	Recent travel to a low- or middle-income country (LMIC) with consumption of potentially contaminated food or water	Headache, arthritis, abdominal pain, relative bradycardia, hepatosplenomegaly, leukopenia
Histoplasmosis	Exposure to bat or blackbird excreta in roosts, chicken houses, or caves in region surrounding Ohio and Mississippi River valleys	Headache, pneumonia, pulmonary cavities, mucosal ulcers, adenopathy, erythema nodosum, erythema multiforme, hepatitis, anemia, leukopenia, thrombocytopenia
Leptospirosis	Occupational exposure among workers in sewers, rice and sugarcane fields, and abattoirs; recreational water sports and exposure to contaminated waters or infected dogs	Bitemporal and frontal headache, calf and lumbar muscle tenderness, conjunctival suffusion, hepatic and renal failure, hemorrhagic pneumonitis
Leishmaniasis (visceral disease)	Associated with recent travel to areas endemic for sand flies	Hepatosplenomegaly, lymphadenopathy, and hyperpigmentation of face, hand, foot, and abdominal skin (kala-azar)
Malaria	Recent travel to endemic areas in Asia, Africa, and Central/South America	Fever, headaches, nausea, emesis, diarrhea, hepatomegaly, splenomegaly, anemia
Psittacosis *(Chlamydia psittaci)*	Associated with contact with birds, especially psittacine birds	Fever, pharyngitis, hepatosplenomegaly, pneumonia, blanching maculopapular eruptions; erythema multiforme, marginatum, and nodosum
Q fever *(Coxiella burnetii)*	Associated with farm, veterinary, or abattoir work; consumption of unpasteurized milk; contact with infected sheep, goats, or cattle	Atypical pneumonia, hepatitis, hepatomegaly, relative bradycardia, splenomegaly
Rat-bite fever *(Streptobacillus moniliformis)*	Recent bite or scratch by rat, mouse, or squirrel; ingestion of food or water contaminated by rat excrement	Headaches, myalgias, polyarthritis, and maculopapular, morbilliform, petechial, vesicular, or pustular rash over the palms, soles, and extremities
Relapsing fever *(Borrelia recurrentis)*	Associated with poverty, crowding, and poor sanitation (louse-borne) or with camping (tick-borne), particularly in the Grand Canyon	High fever with rigors, headache, delirium, arthralgias, myalgias, and hepatosplenomegaly
Rocky Mountain spotted fever	Associated with outdoor activity in the South Atlantic or southeastern United States and exposure to *Dermacentor* tick bites	Headache, petechial rash involving the extremities, palms, and soles
Tuberculosis	Recent contact with tuberculosis; recent immigration from endemic country; work or residence in homeless shelters, correctional facilities, or healthcare facilities	Night sweats, weight loss, atypical pneumonia; on chest x-ray, hilar adenopathy is most common in younger children, with cavitary pulmonary lesions seen in youth.
Tularemia	Associated with bites by *Amblyomma* or *Dermacentor* ticks, deer flies, and mosquitoes or direct contact with tissues of infected animals such as rabbits, squirrels, deer, raccoons, cattle, sheep, and swine	Ulcerated skin lesions at a bite site, pneumonia, relative bradycardia, lymphadenopathy, conjunctivitis

Continued

Table 222.4 Examples of Potential Diagnostic Clues to Infections Presenting as Fever of Unknown Origin—cont'd

ETIOLOGY	HISTORICAL CLUES	PHYSICAL CLUES
Whipple disease (*Tropheryma whipplei*)	Potential association with exposure to sewage	Chronic diarrhea, arthralgia, weight loss, malabsorption, malnutrition

Adapted from Wright WF, Mackowiak PA. Fever of unknown origin. In: Bennett JE, Blaser MJ, Dolin R, et al., eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 8th ed. Philadelphia: Saunders; 2015: Table 56-9.

Table 222.5 Discriminating Features of Noninfectious Causes of Fever of Unknown Origin

CAUSES OF FEVER	EXPOSURE OR CONDITION	FEATURES	DIAGNOSTIC METHOD
Kikuchi-Fujimoto disease		Regional or generalized lymphadenopathy; elevated inflammatory markers	Biopsy or histology
Inflammatory pseudotumor	History of nonspecific illness (presumed host-controlled infection)	Insidious; malaise, weight loss, vague abdominal pain or tenderness; anemia; elevated inflammatory markers	Abdominal CT; biopsy or histology
Kawasaki disease (incomplete)		Asynchronous or incomplete features of Kawasaki disease; elevated inflammatory markers; thrombocytosis	Clinical constellation; echocardiogram
Juvenile idiopathic arthritis	Familial, sporadic	Hepatosplenomegaly, lymphadenopathy, exanthem; anemia, elevated inflammatory markers	Clinical constellation
Systemic lupus erythematosus	Familial, sporadic	Malaise, weight loss; then multisystem involvement (kidneys, joints, skin)	Serum antinuclear antibody, anti–double-stranded DNA, anti–smooth muscle antibody
Hemophagocytic lymphohistiocytosis	Familial, virus, or rheumatologic (macrophage activation syndrome) induced	Severe, rapidly progressive illness; hepatomegaly, lymphadenopathy, exanthem; cytopenias; extreme elevations of inflammatory markers	Ferritin, triglyceride levels, gene panel, other diagnostic criteria; erythrophagocytosis by macrophages; natural killer cell, $CD8^+$ T-lymphocyte dysfunction
Vasculitis syndromes	Familial, sporadic	Specific hallmarks (renal, neurologic, stomatitis or perianal ulcers, uveitis, pulmonary)	Clinical constellation; specific autoantibodies; biopsy or histology
Sarcoidosis	Geography; race	Fatigue, weight loss, leg pain; anemia; elevated inflammatory markers; mediastinal lymphadenopathy; uveitis	Clinical constellation; biopsy or histology; soluble interleukin-2 receptor level
Inflammatory bowel disease	Familial; sporadic	Linear growth failure, subtle gastrointestinal symptoms or abdominal tenderness; perirectal skin tag; iron-deficiency anemia; elevated inflammatory markers	Abdominal CT; barium study
Lymphoreticular malignancy		Weight loss, fatigue; nonarticular bone pain; lymphadenopathy; cytopenias	Bone marrow or tissue biopsy
Drug hypersensitivity	Prescription or nonprescription drug exposure	Preserved sense of well-being; exanthems; eosinophilia; organ dysfunction (renal, cardiac, pulmonary)	Clinical constellation; withdrawal of drug
Factitious fever or Munchausen syndrome by proxy	Predisposing parent-patient dynamic	Discordant temperature and vital signs; discordant parent-measured temperature and urine temperature; normal inflammatory markers	Clinical constellation; verification of temperature in medical setting
Hypothalamic dysfunction, diabetes insipidus, dysautonomia, or absent corpus callosum	Underlying condition; genetic syndrome; anatomic abnormality	Normal inflammatory markers; hypernatremia; no response to nonsteroidal antiinflammatory drugs	Clinical constellation; laboratory tests and imaging

Modified from Long SS, Prober CG, Fischer M, eds. *Principles and Practice of Pediatric Infectious Diseases*, 5th ed. Philadelphia: Elsevier; 2018: Table 15.2, p. 121.

The general activity of the patient and the presence or absence of rashes should also be noted.

A careful ophthalmic examination is important. Red, weeping eyes may be a sign of connective tissue disease, particularly polyarteritis nodosa. Palpebral **conjunctivitis** in a febrile patient may be a clue to measles, coxsackievirus infection, tuberculosis, infectious mononucleosis, lymphogranuloma venereum, or cat-scratch disease. In contrast, bulbar conjunctivitis in a child with FUO suggests Kawasaki disease or leptospirosis. Petechial conjunctival **hemorrhages** suggest infective endocarditis. Uveitis suggests sarcoidosis, JIA, SLE, Kawasaki disease,

Behçet disease, and vasculitis. **Chorioretinitis** suggests CMV, toxoplasmosis, and syphilis. **Proptosis** suggests an orbital tumor, thyrotoxicosis, metastasis (neuroblastoma), orbital infection, granulomatosis with polyangiitis, or orbital pseudotumor.

The ophthalmoscope should also be used to examine nail-fold capillary abnormalities that are associated with connective tissue diseases such as juvenile dermatomyositis and systemic scleroderma. Immersion oil or lubricating jelly is placed on the skin adjacent to the nailbed, and the capillary pattern is observed with the ophthalmoscope set on +40.

FUO is sometimes caused by **hypothalamic dysfunction**. A clue to this disorder is failure of pupillary constriction because of absence of the sphincter constrictor muscle of the eye. This muscle develops embryologically when hypothalamic structure and function also are undergoing differentiation.

Fever resulting from familial dysautonomia may be suggested by lack of tears, an absent corneal reflex, or a smooth tongue with absence of fungiform papillae. Tenderness to tapping over the sinuses or the upper teeth suggests sinusitis. Recurrent oral candidiasis may be a clue to various disorders of the immune system, especially involving the T lymphocytes. Hyperactive deep tendon reflexes can suggest thyrotoxicosis as the cause of FUO.

Hyperemia of the pharynx, with or without exudate, suggests streptococcal infection, EBV infection, CMV infection, toxoplasmosis, salmonellosis, tularemia, Kawasaki disease, gonococcal infection, or leptospirosis.

The muscles and bones should be palpated carefully. Point tenderness over a bone can suggest occult osteomyelitis or bone marrow invasion from neoplastic disease. Tenderness over the trapezius muscle may be a clue to subdiaphragmatic abscess. Generalized muscle tenderness suggests dermatomyositis, trichinosis, polyarteritis, Kawasaki disease, or *Mycoplasma* or arboviral infection.

Rectal examination can reveal perirectal lymphadenopathy or tenderness, which suggests a deep pelvic abscess, iliac adenitis, or pelvic osteomyelitis. A guaiac test should be obtained; occult blood loss can suggest granulomatous colitis or ulcerative colitis as the cause of FUO.

Laboratory Evaluation

The laboratory evaluation of the child with FUO and whether inpatient or outpatient are determined on a case-by-case basis. Hospitalization may be required for laboratory or imaging studies that are unavailable or impractical in an ambulatory setting, for more careful observation, or for temporary relief of parental anxiety. The **tempo** of diagnostic evaluation should be adjusted to the tempo of the illness; haste may be imperative in a critically ill patient, but if the illness is more chronic, the evaluation can proceed in a systematic manner and can be carried out in an outpatient setting. If there are no clues in the patient's history or on physical examination that suggest a specific infection or area of suspicion, it is unlikely that diagnostic studies will be helpful. In this common scenario, continued surveillance and repeated reevaluations of the child should be employed to detect any new clinical findings.

Although ordering a large number of diagnostic tests in every child with FUO according to a predetermined list is discouraged, certain studies should be considered in the evaluation. A complete blood cell count (CBC) with a white blood cell (WBC) differential and a urinalysis should be part of the initial laboratory evaluation. An absolute neutrophil count (ANC) of <5,000/μL is evidence against indolent bacterial infection other than typhoid fever. Conversely, in patients with a polymorphonuclear leukocyte (PMN) count of >10,000/μL or a nonsegmented PMN count of >500/μL, a severe bacterial infection is highly likely. Direct examination of the blood smear with Giemsa or Wright stain can reveal organisms of malaria, trypanosomiasis, babesiosis, or relapsing fever.

An erythrocyte sedimentation rate (ESR) >30 mm/hr indicates inflammation and the need for further evaluation for infectious, autoimmune, autoinflammatory, or malignant diseases, tuberculosis, Kawasaki disease, or autoimmune disease. A low ESR does not eliminate the possibility of infection or JIA. C-reactive protein (CRP) is another acute-phase reactant that becomes elevated and returns to normal more rapidly than the ESR. Experts recommend checking either ESR or CRP, because there is no evidence that measuring both in the same patient with FUO is clinically useful.

Blood cultures should be obtained aerobically. Anaerobic blood cultures have an extremely low yield and should be obtained only if there are specific reasons to suspect anaerobic infection. Multiple or repeated blood cultures may be required to detect bacteremia associated with infective endocarditis, osteomyelitis, or deep-seated abscesses. Polymicrobial bacteremia suggests factitious or self-induced infection or gastrointestinal (GI) pathology. The isolation of leptospires, *Francisella,* or *Yersinia* requires selective media or specific conditions not routinely used. Therefore it is important to inform the laboratory what organisms are suspected in a particular case. Urine culture should be obtained in all cases. Next-generation sequencing of tissue or whole blood or plasma may identify undetected or unculturable bacteria, fungi, or viruses.

Tuberculin skin testing (TST) should be performed with intradermal placement of 5 units of purified protein derivative that has been kept appropriately refrigerated. In children >2 years old, it is reasonable to test for tuberculosis using an interferon-γ release assay (IGRA).

Imaging studies of the chest, sinuses, mastoids, or GI tract may be indicated by specific historical or physical findings. Radiographic evaluation of the GI tract for IBD may be helpful in evaluating selected children with FUO and no other localizing signs or symptoms.

Examination of the bone marrow can reveal leukemia; metastatic neoplasm; mycobacterial, fungal, or parasitic infection; histiocytosis; hemophagocytosis; or storage diseases. If a bone marrow aspirate is performed, cultures for bacteria, mycobacteria, and fungi should be obtained.

Serologic tests can aid in the diagnosis of EBV infection, CMV infection, toxoplasmosis, salmonellosis, tularemia, brucellosis, leptospirosis, cat-scratch disease, Lyme disease, rickettsial disease, and on some occasions JIA. The clinician should be aware that the reliability and the sensitivity and specificity of these tests vary; for example, serologic tests for Lyme disease outside of reference laboratories have been generally unreliable.

MRI scans may be helpful in detecting abdominal abscesses and osteomyelitis, especially if the focus cannot be localized to a specific limb or multifocal disease is suspected. ^{18}F-fluorodeoxyglucose positron emission tomography (PET) combined with MRI or CT is a helpful imaging modality and contributed to an ultimate diagnosis in 48% of children in a Dutch study. Echocardiograms can demonstrate vegetation on the leaflets of heart valves, suggesting infective endocarditis. Ultrasonography (US) can identify intraabdominal abscesses of the liver, subphrenic space, pelvis, or spleen.

Total-body CT or MRI (both with contrast) is usually the first imaging study of choice; both permit detection of neoplasms and collections of purulent material without the use of surgical exploration or radioisotopes. CT and MRI are helpful in identifying lesions of the head, neck, chest, retroperitoneal spaces, liver, spleen, intraabdominal and intrathoracic lymph nodes, kidneys, pelvis, and mediastinum. CT- or US-guided aspiration or biopsy of suspicious lesions has reduced the need for exploratory laparotomy or thoracotomy. MRI is particularly useful for detecting osteomyelitis or myositis if there is concern about a specific limb. Diagnostic imaging can be helpful in confirming or evaluating a suspected diagnosis. With CT scans, however, the child is exposed to large amounts of radiation. PET-CT or MRI may help localize an occult tumor.

Biopsy is occasionally helpful in establishing a diagnosis of FUO. Bronchoscopy, laparoscopy, mediastinoscopy, and GI endoscopy can provide direct visualization and biopsy material when organ-specific manifestations are present. When employing any of the more invasive testing procedures, the risk/benefit ratio for the patient must always be considered before proceeding further. A diagnostic approach to an FUO is noted in Figure 222.2.

MANAGEMENT

The ultimate treatment of FUO is tailored to the underlying diagnosis. Fever and infection in children are not synonymous, and **antimicrobial agents** should only be used when there is evidence of infection, with avoidance of empirical trials of medication. An exception may be the use of antituberculous treatment in critically ill children with

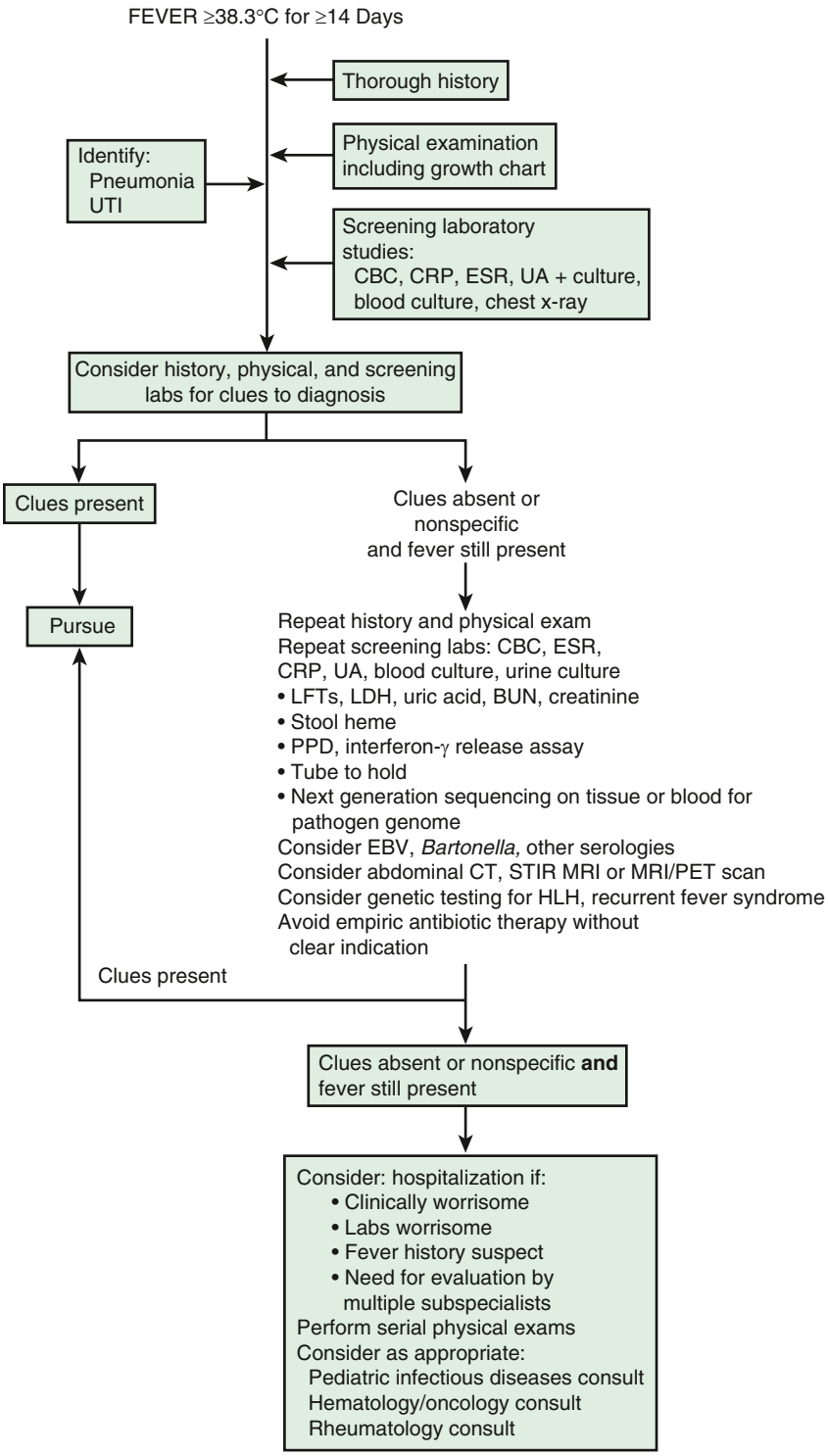

Fig. 222.2 Algorithmic approach to the evaluation of fever of unknown origin (FUO). EBV, Epstein-Barr virus; HLH, hemophagocytic lymphohistiocytosis; LDH, lactate dehydrogenase; LFT, liver function test; PPD, purified protein derivative; STIR, short tau inversion recovery rapid MRI; UTI, urinary tract infection. *(Modified from Huppler AR. Fever. In Kliegman RM, Toth H, Bordini BJ, Basel D, eds. Nelson Pediatric Symptom-Based Diagnosis, 2nd ed. Philadelphia: Elsevier; 2023, Fig. 52.2, p. 982.)*

suspected disseminated tuberculosis. Empirical trials of other antimicrobial agents may be dangerous and can obscure the diagnosis of infective endocarditis, meningitis, parameningeal infection, or osteomyelitis. After a complete evaluation, **antipyretics** may be indicated to control fever associated with adverse symptoms.

PROGNOSIS

Children with FUO have a better prognosis than adults. The outcome in a child depends on the primary disease process. In many cases, no diagnosis can be established, and fever abates spontaneously. In as many as 25% of children in whom fever persists, the cause of the fever remains unclear even after thorough evaluation.

In a series of 69 patients referred for "prolonged" unexplained fever, 10 were not actually having fever, and 11 had diagnoses that were readily apparent at the initial visit. The remaining 48 were classified as having FUO. The median duration of reported fever for these patients was 30 days. Fifteen received a diagnosis, and 10 (67%) had confirmed infections: acute EBV or CMV infection ($n = 5$; with 1 patient developing hemophagocytic lymphohistiocytosis), cat-scratch disease (3), and histoplasmosis (2). The other 5 patients had inflammatory conditions (systemic JIA, 2; IBD, 1), central fever (1), or malignancy (acute lymphoblastic leukemia, 1).

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Chapter 223

Infections in Immunocompromised Persons

Marian G. Michaels, Hey Jin Chong, and Michael Green

Infection develops when the host immune system fails to protect adequately against potential pathogens (see also Chapters 165, 166, and 180). For individuals with an intact immune system, infection occurs in the setting of naïveté to the microbe and absence of or inadequate preexisting microbe-specific immunity, or when protective barriers of the body such as the skin have been breached. Healthy children are able to meet the challenge of most infectious agents with an immunologic armamentarium capable of preventing significant disease. Once an infection begins to develop, an array of immune responses is set into action to control the disease and prevent it from reappearing. In contrast, immunocompromised children might not have this same capability. Depending on the level and type of immune defect, the affected child might not be able to contain the pathogen or develop an appropriate immune response to prevent recurrence.

Primary immunodeficiencies are compromised states that result from genetic defects affecting one or more arms of the immune system. **Acquired**, or **secondary**, **immunodeficiencies** may result from infection (e.g., infection with **HIV**), from malignancy, or as a consequence of immunomodulating or immunosuppressing medications. The latter include medications that affect T cells (corticosteroids, calcineurin inhibitors, tumor necrosis factor [TNF] inhibitors, chemotherapy), neutrophils (myelosuppressive agents, idiosyncratic or immune-mediated neutropenia), specific immunoregulatory cells (TNF blockers, interleukin-2 inhibitors), or all immune cells (chemotherapy). Perturbations of the mucosal and skin barriers or the normal microbial flora can also be characterized as secondary immunodeficiencies, predisposing the host to infections, if only temporarily.

The pathogens causing infections among *immunocompetent* hosts are also responsible for infections among children with *immunodeficiencies*. In addition, less virulent or opportunistic organisms, including normal skin flora, commensal bacteria of the oropharynx or gastrointestinal (GI) tract, environmental fungi, and common community viruses of low-level pathogenicity, can cause severe, life-threatening illnesses in immunocompromised patients (Table 223.1). Close communication with the diagnostic laboratory is critical to ensure that the laboratory does not disregard normal flora and organisms normally considered contaminants as being unimportant.

Table 223.1 Most Common Causes of Infections in Immunocompromised Children

BACTERIA, AEROBIC
Acinetobacter
Bacillus
Burkholderia cepacia
Citrobacter
Corynebacterium
Enterobacter spp.
Enterococcus faecalis
Enterococcus faecium
Escherichia coli
Klebsiella spp.
Listeria monocytogenes
Mycobacterium spp.
Neisseria meningitidis
Nocardia spp.
Pseudomonas aeruginosa
Staphylococcus aureus
Staphylococcus, coagulase-negative
Streptococcus pneumoniae
Streptococcus, viridans group
BACTERIA, ANAEROBIC
Bacillus
Clostridium
Fusobacterium
Peptococcus
Peptostreptococcus
Propionibacterium
Veillonella
FUNGI
Aspergillus
Candida albicans
Other *Candida* spp.
Cryptococcus neoformans
Fusarium spp.
Pneumocystis jirovecii
Zygomycoses *(Mucor, Rhizopus, Rhizomucor)*
VIRUSES
Adenoviruses
Cytomegalovirus
Epstein-Barr virus
Herpes simplex virus
Human herpesvirus 6
Polyomavirus (BK)
Respiratory and enteric community-acquired viruses
Varicella-zoster virus
PROTOZOA
Cryptosporidium parvum
Giardia lamblia
Toxoplasma gondii

223.1 Infections Occurring with Primary Immunodeficiencies

Marian G. Michaels, Hey Jin Chong, and Michael Green

Currently, more than 450 genes involving inborn errors of immunity have been identified, accounting for a wide array of diseases presenting with susceptibility to infection, allergy, autoimmunity, and autoinflammation, as well as malignancy (see Chapters 165 and 166).

ABNORMALITIES OF THE PHAGOCYTIC SYSTEM

Children with abnormalities of the phagocytic and neutrophil system have problems with bacteria and environmental fungi. Disease manifests as recurrent infections of the skin, mucous membranes, lungs, liver, and bones. Dysfunction of this arm of the immune system can be a result of inadequate numbers, abnormal movement properties, or aberrant function of neutrophils (see Chapter 168).

Neutropenia is defined as an absolute neutrophil count (ANC) of <1,000 cells/mm^3 and can be associated with significant risk for developing severe bacterial and fungal disease, particularly when prolonged or when the ANC is <500 cells/mm^3. Although acquired neutropenia secondary to bone marrow suppression from a virus or medication is common, practitioners should be cognizant of genetic causes of neutropenia. **Primary congenital neutropenia** most often manifests during the first year of life with cellulitis, perirectal abscesses, or stomatitis from *Staphylococcus aureus* or *Pseudomonas aeruginosa.* Episodes of severe disease, including bacteremia or meningitis, are also possible. Bone marrow evaluation shows a failure of maturation of myeloid precursors. Many of the neutropenic syndromes respond to colony-stimulating factor. Cyclic neutropenia can be associated with autosomal dominant inheritance or de novo sporadic gene variations

and manifests as fixed cycles of severe neutropenia between periods of normal granulocyte numbers. Often the ANC has normalized by the time the patient presents with symptoms, thus hampering the diagnosis. The cycles classically occur every 21 days (range: 14-36 days), with neutropenia lasting 3-6 days. Most often the disease is characterized by recurrent aphthous ulcers and stomatitis during the periods of neutropenia. However, life-threatening necrotizing myositis or cellulitis and systemic disease can occur, especially with *Clostridium septicum* or *Clostridium perfringens*.

Leukocyte adhesion deficiencies (LADs) are caused by defects of neutrophil aggregation and attachment to endothelial surfaces, rendering them unable to enter sites of infection (see Chapter 168). In the most severe form, there is a total absence of CD18, seen in LAD type 1, but genetic defects in fucose metabolism (LAD type 2) and FERMT3 (LAD type 3) have also been described. Generally, children with LAD have a history of delayed cord separation and recurrent infections of the skin, oral mucosa, and genital tract beginning early in life. Ecthyma gangrenosum also occurs. Because the defect involves leukocyte migration and adherence, the ANC in the peripheral blood is usually *extremely elevated,* but a key hallmark of LAD is that pus is not found at the site of infection. The mainstay of treatment is aggressive antibiotic use, with curative therapy being hematopoietic stem cell transplantation (HSCT).

Chronic granulomatous disease (CGD) is an inherited neutrophil dysfunction syndrome, which can be either X-linked or autosomal recessive, although spontaneous genetic changes can also occur (see Chapter 170). Neutrophils and other myeloid cells have defects in their nicotinamide-adenine dinucleotide phosphate oxidase function, decreasing superoxide production and thereby impairing intracellular killing. Accordingly, microbes that destroy their own hydrogen peroxide *(S. aureus, Serratia marcescens, Burkholderia cepacia, Nocardia* spp., *Aspergillus)* cause recurrent infections in these children. Less common but considered pathognomonic are *Granulibacter bethesdensis, Francisella philomiragia, Chromobacterium violaceum,* and *Paecilomyces* infections. Infections have a predilection to involve the lungs, liver, and bone. **Mulch pneumonitis** can be seen in patients with known CGD but also can be a unique presenting feature in adults with autosomal recessive CGD. Mulch pneumonitis can resemble hypersensitivity pneumonitis, and bronchoscopy may yield *Aspergillus* but often may not identify a clear organism. Treatment with antifungals and corticosteroids for the inflammation is recommended. *S. aureus* abscesses can occur in the liver despite prophylaxis. In addition, these children can present with recurrent abscesses affecting the skin, perirectal region, or lymph nodes. Sepsis can occur but is more common with certain gram-negative organisms such as *C. violaceum* and *F. philomiragia*.

Prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX), recombinant human interferon-γ, and oral antifungal agents with activity against *Aspergillus* spp., such as itraconazole or newer azoles, substantially reduces the incidence of severe infections. Patients with life-threatening infections are also reported to benefit from aggressive treatment with white blood cell transfusions along with antimicrobial agents directed against the specific pathogen. In addition, HSCT can be curative, and gene therapy trials are also a consideration. It is important to remember that patients with CGD do not make pus, and thus drainage alone for liver abscesses is not effective. Instead, patients should be treated with intravenous (IV) antibiotics as well as IV corticosteroids, with surgical resection considered if these measures fail.

DEFECTIVE SPLENIC FUNCTION, OPSONIZATION, OR COMPLEMENT ACTIVITY

Children who have congenital asplenia or splenic dysfunction associated with polysplenia or hemoglobinopathies, such as sickle cell disease, as well as those who have undergone splenectomy are at risk for serious infections from encapsulated bacteria and blood-borne protozoa such as *Plasmodium* and *Babesia.* Prophylaxis against bacterial infection with penicillin or amoxicillin should be considered for these patients, particularly children <5 years of age. The most common causative bacterial organisms include *Staphylococcus pneumoniae, Haemophilus influenzae* type b (Hib), and *Salmonella,* which can cause sepsis, pneumonia, meningitis, and osteomyelitis. Defects in the early complement components, particularly C2 and C3, may also be associated with severe infection from these bacteria. **Terminal complement defects** (C5, C6, C7, C8, and C9) are associated with recurrent infections with *Neisseria.* Patients with complement deficiency also have an increased incidence of autoimmune disorders. Vaccines for *S. pneumoniae,* Hib, and *N. meningitidis* should be administered to all children with abnormalities in opsonization or complement pathways (see Chapters 173 and 174).

B-CELL DEFECTS (HUMORAL IMMUNODEFICIENCIES)

Antibody deficiencies account for the majority of primary immunodeficiencies among humans (see Chapters 165 and 166). Patients with defects in the B-cell arm of the immune system fail to develop appropriate antibody responses, with abnormalities that range from complete **agammaglobulinemia** to isolated failure to produce antibody against a specific antigen or organism. Complete antibody deficiencies found in children with **X-linked agammaglobulinemia (XLA)** or other rarer autosomal recessive **agammaglobulinemia** predispose to infections with encapsulated organisms such as *S. pneumoniae* and Hib. Other bacteria can also be problematic in these children (see Table 223.1). Patients with XLA can also have neutropenia, with one case series showing 12 of 13 patients with XLA having neutropenia as part of the initial presentation. Because of the neutropenia, patients with XLA can present with *Pseudomonas* septicemia. Viral infections can also occur, with rotavirus leading to chronic diarrhea. Enteroviruses can disseminate and cause a chronic meningoencephalitis syndrome in these patients. Paralytic polio can develop after immunization with live polio vaccine. Protozoan infections such as giardiasis can be severe and persistent.

Children with agammaglobulinemia are usually asymptomatic until 5-6 months of age, when maternally derived antibody levels begin to wane. Around 6 months of age these children begin to develop recurrent episodes of otitis media, bronchitis, pneumonia, bacteremia, and meningitis. Many of these infections respond quickly to antibiotics, delaying the recognition of antibody deficiency, with studies showing some patients diagnosed in their teens. Children with B-cell defects can develop bronchiectasis over time after chronic or recurrent pulmonary infections and require lifelong IgG replacement therapy. Careful physical examination identifies lack of tonsils in these children, and lymphocyte subsets should confirm the lack of circulating B cells.

Selective IgA deficiency is the most common antibody deficiency and leads to a lack of production of secretory antibody at the mucosal membranes (see Chapter 166). Even though most patients have no increased risk for infections, some have mild to moderate disease at sites of mucosal barriers. Accordingly, recurrent sinopulmonary infection and GI disease are the major clinical manifestations. These patients also have an increased incidence of allergies and autoimmune disorders compared with the normal population.

Common variable immunodeficiency (CVID) is considered an antibody deficiency, with ~30% of cases found to have a monogenic cause. Diagnosis can be made in children over the age of 4, with low IgG as well as low IgM or IgA and lack of protective vaccine titers. These patients develop sinopulmonary and GI infections with common organisms, although they can have more severe presentations than their immunocompetent counterparts. They also have increased risk of autoimmunity and malignancy and often require IgG replacement.

Hyper-IgM syndrome encompasses a group of genetic defects associated with immunoglobulin class-switch recombination. The most common type is caused by a defect in the CD40 ligand on the T cell, leading to inability of the B cell to class-switch (see Chapter 166). Similar to other patients with humoral defects, these patients are at risk for bacterial sinopulmonary infections. However, unlike a true pure antibody defect, besides being important in T-cell–B-cell interactions, CD40 ligand is also important in the interaction between T cells and macrophages/monocytes, predisposing to opportunistic infections such as *Pneumocystis jirovecii* pneumonia (PJP) and *Cryptosporidium* intestinal infection.

T-CELL DEFECTS (CELL-MEDIATED IMMUNODEFICIENCIES)

Children with primary T-cell–mediated immunodeficiencies can present early in life and are susceptible to viral, fungal, and protozoan infections. Clinical manifestations include chronic diarrhea,

mucocutaneous candidiasis, and recurrent pneumonia, rhinitis, and otitis media. In thymic hypoplasia **(DiGeorge syndrome)**, hypoplasia or aplasia of the thymus and parathyroid glands occurs during fetal development in association with the presence of other congenital abnormalities. Hypocalcemia and cardiac anomalies can be the presenting features of DiGeorge syndrome, which should prompt evaluation of the T-cell system.

Chronic mucocutaneous candidiasis (CMC) is a group of immunodeficiencies leading to susceptibility to fungal infections of the skin, nails, oral cavity, and genitals. Most frequently caused by *Candida* spp., dermatophyte infections with *Microsporum, Epidermophyton,* and *Trichophyton* have also been described. Interestingly, patients with CMC do not have an increased risk for histoplasmosis, blastomycosis, or coccidioidomycosis. Despite chronic cutaneous and mucosal infection with *Candida* spp., these patients often lack a delayed hypersensitivity to skin tests for *Candida* antigen. Several gene defects have been identified in people with CMC, including *STAT1* gain-of-function pathologic gene variations, *IL17R* defects, *CARD9* deficiency, and *ACT1* deficiency. Although patients with CMC generally do not develop invasive candidiasis, patients with CMC as a feature of an inborn error or immunity certainly do develop invasive *Candida* infection. Endocrinopathies, autoimmunity, and life-threatening vascular abnormalities can be seen as well, making genetic testing important in the prognosis and management of patients with CMC.

COMBINED B-CELL AND T-CELL DEFECTS

Patients with defects in both the B-cell and T-cell components of the immune system have variable manifestations depending on the extent of the defect (see Chapter 165). Complete or almost complete immunodeficiency is found with **severe combined immunodeficiency disorder (SCID)**, whereas partial defects can be present in such states as **ataxia-telangiectasia**, **Wiskott-Aldrich syndrome**, **hyper-IgE syndrome**, and **X-linked lymphoproliferative disorder**. Rather than one disorder, SCID represents a heterogeneous group of genetic defects that present in the first year of life with recurrent and typically severe infections caused by a variety of bacteria, fungi, and viruses. Failure to thrive, chronic diarrhea, mucocutaneous or systemic candidiasis, PJP, or cytomegalovirus (CMV) infections are common early in life. Passive maternal antibody is relatively protective against the bacterial pathogens during the first few months of life, but thereafter patients are susceptible to both gram-positive and gram-negative organisms. Exposure to live-virus vaccines can also lead to disseminated disease; accordingly, the use of live vaccines (including rotavirus vaccine) is contraindicated in patients with suspected or proven SCID. Without stem cell transplantation or gene therapy, most affected children succumb to infections within the first year of life.

Children with **ataxia-telangiectasia** develop recurrent sinopulmonary infections from both bacteria and respiratory viruses and are particularly susceptible to chronic lung infections because of their immunodeficiency and their muscular weakness leading to poor airway clearance. In addition, these children experience an increased incidence of malignancies and neurologic complications, with most patients being wheelchair bound by the second decade of life. **Wiskott-Aldrich syndrome** is an X-linked recessive disease associated with eczema, thrombocytopenia, reduced number of CD3 lymphocytes, moderately suppressed mitogen responses, and impaired antibody response to polysaccharide antigens. Accordingly, infections with *S. pneumoniae* or Hib can be seen.

Hyper-IgE syndrome (HIES) is characterized by elevated levels of IgE, infections, and eczema, with the most common cause being the result of dominant negative gene variation in *STAT3*. Pathogenic gene variants in *TYK2, PGM3, ZNF341, CARD11,* and *IL6ST* have also been reported to cause this phenotype. Patients can present with recurrent episodes of *S. aureus* abscesses of the skin, lungs, and musculoskeletal system. These abscesses were initially described as "cold" in that they did not have the characteristic warmth and rubor typically seen in immunocompetent patients and thereby are easily missed, delaying therapy. Patients can also develop infections caused by *Candida* and, depending on the gene defect, severe viral infections. Patients with *STAT3* HIES should receive prophylaxis against *S. aureus* with aggressive management of eczema as well.

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223.2 Infections Occurring with Acquired Immunodeficiencies

Marian G. Michaels, Hey Jin Chong, and Michael Green

Immunodeficiencies can be secondarily acquired from infections or other underlying disorders, such as malignancy, cystic fibrosis, diabetes mellitus, sickle cell disease, or malnutrition. Immunosuppressive medications used to prevent rejection after organ transplantation, to prevent graft-versus-host disease (GVHD) after stem cell transplantation, or to treat malignancies may also leave the host vulnerable to infections. Similarly, medications used to control rheumatologic or other autoimmune diseases may be associated with an increased risk for developing infection. Surgical removal of the spleen likewise puts a person at increased risk for infections. Further, any process that disrupts the normal mucosal and skin barriers (e.g., burns, surgery, indwelling catheters) may lead to an increased risk for infection.

ACQUIRED IMMUNODEFICIENCY FROM INFECTIOUS AGENTS

Infection with HIV, the causative agent of **AIDS**, remains globally an important infectious cause of acquired immunodeficiency (see Chapter 322). Left untreated, HIV infection has profound effects on many parts of the immune system but in particular T-cell–mediated immunity that leads to susceptibility to the same types of infections as with primary T-cell immunodeficiencies.

Other organisms can also lead to temporary alterations of the immune system. Very rarely, transient neutropenia associated with community-acquired viruses can lead to significant disease with bacterial infections. Secondary infections can occur because of impaired immunity or disruption of normal mucosal immunity, as exemplified by the increased risk for pneumonia from *S. pneumoniae* or *S. aureus* after influenza infection and group A streptococcal cellulitis and fasciitis after varicella.

MALIGNANCIES

The immune systems of children with malignancies are compromised by the therapies used to treat the cancer and, at times, by direct effects of the cancer itself. The type, duration, and intensity of anticancer therapy remain the major risk factors for infections in these children and often affect multiple arms of the immune system. The presence of mucous membrane abnormalities, indwelling catheters, malnutrition, prolonged exposure to antibiotics, and frequent hospitalizations adds to the risk for infection in these children.

Even though several arms of the immune system can be affected, the major abnormality predisposing to infection in children with cancer is **neutropenia**. The depth and duration of neutropenia are the primary predictors of the risk of infection in children being treated for cancer. Patients are at particular risk for bacterial and fungal infections if the ANC decreases to <500 cells/mm^3, and the risk is highest in those with counts <100 cells/mm^3. Counts of >500 cells/mm^3 but <1,000 cells/mm^3 incur some increased risk for infection, but not nearly as great. The lack of neutrophils can lead to a diminution of inflammatory response, limiting the ability to localize sites of infection and potentially leaving fever as the only manifestation of infection. Accordingly, the absence of physical signs and symptoms does not reliably exclude the presence of infection, resulting in the need for empirical antibiotics (Fig. 223.1). Because patients with **fever and neutropenia** might only have subtle signs and symptoms of infection, the presence of fever warrants an intensive investigation, including a thorough physical examination with careful attention to the oropharynx, lungs, perineum and anus, skin, nailbeds, and intravascular catheter insertion sites (Table 223.2).

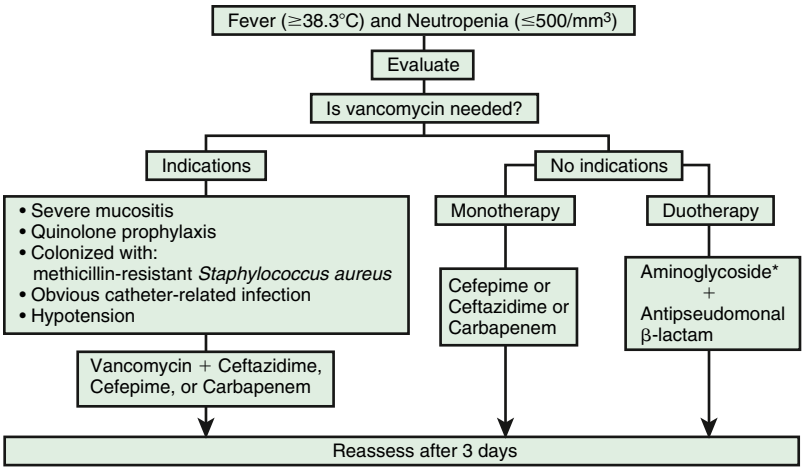

Fig. 223.1 Algorithm for the initial management of the febrile neutropenic patient. Monotherapy can be considered with cefepime, imipenem/cilastatin, meropenem, piperacillin-tazobactam, or ticarcillin–clavulanic acid. *Aminoglycoside antibiotics should be avoided if the patient is also receiving nephrotoxic, ototoxic, or neuromuscular blocking agents; has renal or severe electrolyte dysfunction; or is suspected of having meningitis (because of poor blood-brain perfusion). *(Adapted from Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2011;52:e56–e93.)*

A comprehensive laboratory evaluation, including a complete blood cell count, serum creatinine, blood urea nitrogen, and serum transaminases, should be obtained. Blood cultures should be taken from each port of any **central venous catheter** (CVC) and from a peripheral vein and repeated if the original culture is negative. Although peripheral vein sampling is often omitted with continued fevers and neutropenia, it should be obtained before the initial antibiotic administration and reconsidered in children with one or more positive cultures from a CVC, facilitating localization (line vs systemic) of the source of the infection. Other microbiologic studies should be done if there are associated clinical symptoms, including a nasal aspirate for viruses in patients with upper respiratory findings; stool for viruses such as rotavirus or norovirus and for *Clostridium difficile* toxin in patients with diarrhea; urinalysis and culture in young children or in older patients with symptoms of urgency, frequency, dysuria, or hematuria; and biopsy and culture of cutaneous lesions. Chest radiographs should be obtained in any patient with lower respiratory tract symptoms, although pulmonary infiltrates may be absent in children with severe neutropenia. Sinus films should be obtained for children >2 years of age if rhinorrhea is prolonged. Abdominal CT scans should also be considered in children with profound neutropenia and abdominal pain to evaluate for the presence of typhlitis. Chest CT scan should be considered for children not responding to broad-spectrum antibiotics who have continued fever and neutropenia for >96 hours. Although some have considered the use of fungal biomarkers (e.g., galactomannan, β-D-glucan, fungal polymerase chain reaction [PCR]), these assays have poor positive predictive values, and their use is not routinely recommended. Biopsies for cytology, Gram stain, and culture should be considered if abnormalities are found during endoscopic procedures or if lung nodules are identified radiographically.

Past studies demonstrated that before the routine institution of empirical antimicrobial therapy for fever and neutropenia, 75% of children with fever and neutropenia were ultimately found to have a documented site of infection, suggesting that most children with fever and neutropenia will have an underlying infection (see Table 223.2). Current data suggest that bacteremia is present in ~20% of febrile neutropenic pediatric patients with leukemia; ~90% have bacterial disease (Fig. 223.2). Currently, gram-positive cocci are the most common pathogens identified in these patients; however, gram-negative organisms such as *P. aeruginosa, Escherichia coli,* and *Klebsiella* can cause life-threatening infection and must be considered in the empirical treatment regimen. Other multidrug-resistant Enterobacterales are increasingly recovered in these children. Although coagulase-negative staphylococci often cause infections in these children in association with CVCs, these infections are typically indolent, and a short delay in treatment usually does not lead to a detrimental outcome. Other gram-positive bacteria, such as *S. aureus* and *S. pneumoniae,* can cause more fulminant disease and require prompt institution of therapy. Viridans streptococci are particularly important potential pathogens in patients with the oral mucositis that is often associated with use of cytarabine and in patients who experience selective pressure from treatment with certain antibiotics such as quinolones. Infection caused by this group of organisms can present with an acute septic shock syndrome. Also, patients with prolonged neutropenia are at increased risk for opportunistic fungal infections (fungemia or tissue invasion), with *Candida* spp. and *Aspergillus* spp. being the most commonly identified fungi. Other fungi that can cause serious disease in these children include zygomycetes, *Fusarium* spp., and dematiaceous molds. In patients with repeatedly negative blood cultures but persistent fevers, next-generation sequencing in blood or plasma may help identify bacterial, viral, fungal, or protozoan pathogens.

FEVER AND NEUTROPENIA

The use of empirical antimicrobial treatment as part of the management of fever and neutropenia decreases the risk of progression to sepsis, septic shock, acute respiratory distress syndrome, organ dysfunction, and death. In 2017 the International Pediatric Fever and Neutropenia Guideline Panel updated a comprehensive guideline for the management of neutropenic children with cancer or after HSCT (see Fig. 223.1).

First-line antimicrobial therapy should take into consideration the types of microbes anticipated and the local resistance patterns encountered at each institution as well as the level of risk for severe infection associated with a given patient. In addition, antibiotic choices may be limited by specific circumstances, such as the presence of drug allergy and renal or hepatic dysfunction. Guidelines for the management of fever and neutropenia in children with cancer and/or undergoing HSCT conclude that the use of oral antimicrobial therapy as either initial or stepdown therapy can be considered in low-risk children who can tolerate oral antibiotics and in whom careful monitoring can be ensured. However, the guideline emphasizes that oral medication use may present major challenges in children, including the availability of liquid formulations of appropriate antibiotics, cooperation of young children, and the presence of mucositis potentially interfering with absorption. Accordingly, decisions to implement this approach should be reserved for a select subset of these children presenting with fever and neutropenia and institutions with an appropriate infrastructure to follow them as outpatients.

The decision to initially use IV monotherapy versus an expanded regimen of antibiotics depends on the severity of illness of the patient, history of previous colonization with resistant organisms, and obvious presence of catheter-related infection. Glycopeptide addition (such as vancomycin) to the initial empirical regimen should be implemented if the patient has hypotension or other evidence of septic shock, an obvious catheter-related infection, a history of colonization with methicillin-resistant *S. aureus,* or the patient is at high risk for infection with viridans streptococci (severe mucositis, acute myelogenous leukemia, or prior use of quinolone prophylaxis). Otherwise, use of monotherapy with an antipseudomonal β-lactam, such as piperacillin-tazobactam, a fourth-generation cephalosporin, or a carbapenem can be considered. Ceftazidime should not be used as monotherapy if concern exists for gram-positive organisms or resistant gram-negative bacteria. The addition of a second anti–gram-negative bacterial agent (e.g., aminoglycoside) for empirical therapy can be considered in patients who are clinically unstable when multidrug-resistant organisms are suspected.

Table 223.2 Host Defense Defects and Common Pathogens by Time After Bone Marrow or Hematopoietic Stem Cell Transplantation

TIME PERIOD	HOST DEFENSE DEFECTS	CAUSES	COMMON PATHOGENS
Pretransplant	Neutropenia Abnormal anatomic barriers	Underlying disease Prior chemotherapy	Aerobic gram-negative bacilli
Preengraftment	Neutropenia Abnormal anatomic barriers	Chemotherapy Radiation Indwelling catheters	Aerobic gram-positive cocci Aerobic gram-negative bacilli *Candida* *Aspergillus* Herpes simplex virus (in previously infected patients) Community-acquired viral pathogens
Postengraftment	Abnormal cell-mediated immunity Abnormal anatomic barriers	Chemotherapy Immunosuppressive medications Radiation Indwelling catheters Unrelated cord blood donor	Gram-positive cocci Aerobic gram-negative bacilli Cytomegalovirus Adenoviruses Community-acquired viral pathogens *Pneumocystis jirovecii*
Late posttransplant	Delayed recovery of immune function (cell-mediated, humoral, and abnormal anatomic barriers)	Time required to develop donor-related immune function Graft-versus-host disease	Varicella-zoster virus *Streptococcus pneumoniae*

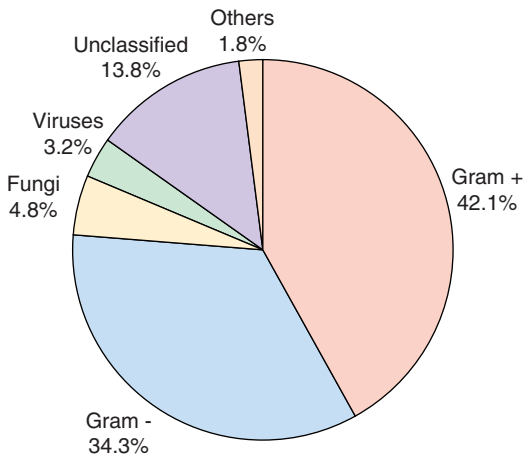

Fig. 223.2 Pathogens involved in the microbiologically documented infections in pediatric oncology patients with febrile neutropenia. *(From Boeriu E, Borda A, Dumitru D, et al. Diagnosis and management of febrile neutropenia n pediatric oncology patients – a systematic review. Diagnostics. 2022;12:1800.)*

Regardless of the regimen chosen initially, it is critical to evaluate the patient carefully and continually for response to therapy, development of secondary infections, and adverse effects. Management recommendations for these children are evolving. Patients who have negative blood cultures at 48 hours, who have been afebrile for at least 24 hours, and who have evidence of bone marrow recovery can have all antibiotics discontinued. However, if symptoms persist or evolve, IV antibiotics should be continued. Continuation of antibiotics in children whose fever has abated and who are clinically well but continue to have depression of neutrophils is more controversial. Pediatric guidelines advocate for discontinuing antibiotics in low-risk patients at 72 hours for children who have negative blood cultures and who have been afebrile for at least 24 hours regardless of bone marrow recovery, as long as careful follow-up is ensured.

Next-generation sequencing (NGS) during episodes of fever and neutropenia may enhance pathogen detection when blood cultures and other tests are negative. NGS has the advantage of detecting bacteria, fungi, viruses and polymicrobial infections. When fever persists despite empiric antibiotics, NGS results may help modify antimicrobial therapy based on the pathogens identified.

Patients without an identified etiology but with **persistent fever** should be reassessed daily. At day 3-5 of persistent fever and neutropenia, those remaining clinically well may continue on the same regimen, although consideration should be given to discontinuing vancomycin or double gram-negative bacterial coverage if they were included initially. Patients who remain febrile with clinical instability warrant escalation of therapy with the addition of a glycopeptide, if it was not included initially and risk factors exist, and modification of the empirical antibacterial regimen to cover potential antimicrobial resistance and anaerobic infections in these children. If fever persists for >96 hours, the addition of an **antifungal agent** with antimold activity should be considered, particularly for those at high risk for invasive fungal infection (those with acute myelogenous leukemia or relapsed acute lymphocytic leukemia or who are receiving highly myelosuppressive chemotherapies for other cancers or with allogeneic HSCT). Liposomal amphotericin products and echinocandins have been studied in children; voriconazole, itraconazole, and posaconazole have been successfully used in adults, with increasing experience in children. Azoles may have substantial drug-drug interactions; however, their use has not been thoroughly evaluated. Studies comparing caspofungin with liposomal amphotericin for children with malignancies and fever and neutropenia have shown that caspofungin is noninferior.

The use of **antiviral agents** in children with fever and neutropenia is not warranted without specific evidence of viral disease. Active herpes simplex or varicella-zoster lesions merit treatment to decrease the time of healing; even if these lesions are not the source of fever, they are potential portals of entry for bacteria and fungi. CMV is a rare cause of fever in children with cancer and neutropenia. If CMV infection is suspected, assays to evaluate viral load in the blood and organ-specific infection should be obtained. Ganciclovir, foscarnet, or cidofovir may be considered while evaluation is pending, although ganciclovir can cause bone marrow suppression and foscarnet and cidofovir can be nephrotoxic. If influenza is identified, specific treatment with an antiviral agent (oseltamivir, zanamivir) should be administered. The possibility of severe acute respiratory syndrome–coronavirus type 2 (SARS-CoV-2) infection should be evaluated by PCR, and treatment should be considered based on current recommendations and local availability of antiviral therapies.

The use of **hematopoietic growth factors** shortens the duration of neutropenia but has not been proved to reduce morbidity or mortality. Accordingly, guidelines do not endorse the routine use of hematopoietic growth factors in patients with established fever and neutropenia, although the recommendations do note that hematopoietic growth factors can be considered as prophylaxis in those with neutropenia at high risk for fever.

Prophylaxis with levofloxacin has been shown to decrease bacteremia for children with acute leukemia receiving intensive chemotherapy and may also be effective in those undergoing allogenic HSCT. However, monitoring for breakthrough bacteremia and for quinolone resistance is important.

FEVER WITHOUT NEUTROPENIA

Infections occur in children with cancer in the absence of neutropenia. Most often, these infections are viral in etiology. However, *P. jirovecii* can cause pneumonia regardless of the neutrophil count. Administration of prophylaxis against *Pneumocystis* is an effective preventive strategy and should be provided to all children undergoing active treatment for malignancy. First-line therapy remains TMP-SMX, with second-line alternatives including pentamidine, atovaquone, dapsone, or dapsone-pyrimethamine. Environmental fungi such as *Cryptococcus, Histoplasma,* and *Coccidioides* can also cause disease. *Toxoplasma gondii* is an uncommon but occasional pathogen in children with cancer. Infections caused by pathogens encountered in healthy children (*S. pneumoniae,* group A streptococcus) can also occur in children with cancer regardless of the granulocyte count.

TRANSPLANTATION

Transplantation of hematopoietic stem cells and solid organs (including heart, liver, kidney, lungs, pancreas, and intestines) is increasingly used as therapy for a variety of disorders. Children undergoing transplantation are at risk for infections caused by many of the same microbial agents that cause disease in children with primary immunodeficiencies. Although the types of infections after transplantation generally are similar among all recipients of these procedures, some differences exist between patients depending on the type of transplantation performed, the type and amount of immunosuppression given, and the child's preexisting immunity to specific pathogens.

Stem Cell Transplantation

Infections after HSCT can be classified as occurring during the **pretransplantation period**, **preengraftment period** (0-30 days after transplantation), **postengraftment period** (30-100 days), or **late posttransplantation period** (>100 days). Specific defects in host defenses predisposing to infection vary within each of these periods (see Table 223.2). In addition, risk is affected by type of transplant (autologous, allogeneic, T-cell depleted, cord blood) along with the quality of the donor-recipient match. Neutropenia and abnormalities in cell-mediated and humoral immune function occur predictably during specific periods after transplantation. In contrast, breaches of anatomic barriers caused by indwelling catheters and mucositis secondary to radiation or chemotherapy create defects in host defenses that may be present any time after transplantation.

Pretransplantation Period

Children come to HSCT with a heterogeneous history of underlying diseases, chemotherapy exposure, degree of immunosuppression, and previous infections. Approximately 12% of all infections among adult HSCT recipients occur during the pretransplantation period. These infections are often caused by aerobic gram-negative bacilli and manifest as localized infections of the skin, soft tissue, and urinary tract. Importantly, the development of infection during this period does not delay or adversely affect the success of engraftment.

Preengraftment Period

Bacterial infections predominate in the preengraftment period (0-30 days). **Bacteremia** is the most common documented infection and occurs in as many as 50% of all HSCT recipients during the first 30 days after transplantation. Bacteremia is typically associated with the presence of either mucositis or an indwelling catheter but may also be seen with pneumonia. Similarly, >40% of children undergoing HSCT experience one or more infections in the preengraftment period. Gram-positive cocci, gram-negative bacilli, yeast, and, less frequently, other fungi cause infection during this period. *Aspergillus* has been identified in 4–20% of HSCT recipients, most often after 3 weeks of neutropenia. Infections caused by the emerging fungal pathogens *Fusarium* and *Pseudallescheria boydii* are associated with the prolonged neutropenia during the preengraftment period.

Viral infections also occur during the preengraftment period. Among adults, reactivation of herpes simplex virus (HSV) is the most common viral disease observed, but this is less common among children. A history of HSV infection or seropositivity indicates the need for prophylaxis. Nosocomial exposure to community-acquired viral pathogens, including SARS-CoV-2, respiratory syncytial virus (RSV), influenza virus, adenovirus, rotavirus, and norovirus, represents another important source of infection during this period. There is growing evidence that community-acquired viruses cause increased morbidity and mortality for HSCT recipients during this period. Adenovirus is a particularly important viral pathogen that can occur early, although it typically presents after engraftment.

Postengraftment Period

The predominant defect in host defenses in the postengraftment period is altered cell-mediated immunity. Accordingly, organisms historically categorized as *opportunistic pathogens* predominate during this period. The risk is especially accentuated 50-100 days after transplantation, when host immunity is lost and donor immunity is not yet established. *P. jirovecii* presents during this period if patients are not maintained on appropriate prophylaxis. Reactivation of *T. gondii,* a rare cause of disease among HSCT recipients, can also occur after engraftment. Hepatosplenic candidiasis often presents during the postengraftment period, although seeding likely occurs during the neutropenic phase.

Cytomegalovirus (CMV) is an important cause of morbidity and mortality among HSCT recipients. Unlike patients undergoing solid organ transplantation (SOT), where primary infection from the donor causes the greatest harm, CMV reactivation in an HSCT recipient whose donor is naïve to the virus can also cause severe disease. Disease risk from CMV after HSCT is also increased in recipients of cord blood transplants or matched unrelated T-cell–depleted transplants and those with GVHD. **Adenovirus**, another important viral pathogen, has been recovered from up to 5% of adult and pediatric HSCT recipients and causes invasive disease in approximately 20% of cases. Children receiving matched unrelated donor organs or unrelated cord blood cell transplants have an incidence of adenovirus infection as high as 14% during this early postengraftment period. **Polyomaviruses** such as BK virus have been increasingly recognized as a cause of renal dysfunction and hemorrhagic cystitis after bone marrow transplantation. Infections with other herpesviruses (Epstein-Barr virus [EBV] and human herpesvirus 6) as well as community-acquired pathogens are associated with excess morbidity and mortality during this period, similar to the preengraftment period.

Late Posttransplantation Period

Infection is unusual after 100 days in the absence of chronic GVHD. However, the presence of chronic GVHD significantly affects anatomic barriers and is associated with defects in humoral, splenic, and cell-mediated immune function. Viral infections, including primary infection with or reactivation of varicella-zoster virus (VZV), are responsible for >40% of infections during this period. This may decrease over time, as the Oka varicella vaccine strain has a lower rate of reactivation than wild-type varicella. Pandemic SARS-CoV-2 has also been noted to have more severe outcomes in children after HSCT. Bacterial infections, particularly of the upper and lower respiratory tract, account for approximately 30% of infections. These infections may be associated with deficiencies in immunoglobulin production, especially IgG2. Fungal infections account for <20% of confirmed infections during the late posttransplantation period.

Solid Organ Transplantation

Factors predisposing to infection after organ transplantation include those that either existed before transplantation or are secondary to intraoperative events or posttransplantation therapies (Table 223.3). Some of these additional risks cannot be prevented, and some risks acquired during or after the operation depend on decisions or actions of members of the transplant team. Organ recipients are at risk for infection from potential exposure to pathogens in the donor organ. Although some donor-derived infections can be anticipated through donor screening, many pathogens are not routinely screened for, and strategies defining when and how to screen for all but a small subset of potential pathogens have not been identified or implemented. Similar to other children who have undergone surgical procedures, surgical site infections are a frequent cause of infection early after transplantation. Beyond this, the need for immunosuppressive agents to prevent rejection is the major factor predisposing to infection after transplantation. Despite efforts to

Table 223.3 Risk Factors for Infections After Solid Organ Transplantation in Children

PRETRANSPLANTATION FACTORS
Age of patient
Underlying disease, malnutrition
Specific organ transplanted
Previous exposures to infectious agents
Previous immunizations
Presence of infection in the donor
INTRAOPERATIVE FACTORS
Duration of transplant surgery
Exposure to blood products
Technical problems
Organisms transmitted with donor organ
POSTTRANSPLANTATION FACTORS
Immunosuppression
Induction immunosuppression type
Maintenance immunosuppression
Augmented treatment for rejection
Indwelling catheters
Nosocomial exposures
Community exposures

optimize immunosuppressive regimens to prevent or treat rejection with minimal impairment of immunity, all current regimens interfere with the ability of the immune system to prevent infection. The primary target of the majority of these immunosuppressive agents in organ recipients is the cell-mediated immune system, but regimens can and do impair many other aspects of the transplant recipient's immune system as well.

Timing

The timing of specific types of infections is generally predictable, regardless of which organ is transplanted. Infectious complications typically develop in one of three intervals: early (0-30 days after transplantation), intermediate (30-180 days), or late (>180 days); most infections present in the first 180 days after transplantation. Table 223.4 should be used as a general guideline to the types of infections encountered, but the timing of the presentation may be modified with the introduction of newer immunosuppressive therapies and by the use of prophylaxis.

Early infections are usually the result of a complication of the transplant surgery itself, the unexpected acquisition of a bacterial or fungal pathogen from the donor, or the presence of an indwelling catheter. In contrast, infections during the intermediate period typically result from a complication of the immunosuppression, which tends to be at its greatest intensity during the first 6 months after transplantation. This is the period of greatest risk for infections caused by opportunistic pathogens such as CMV, EBV, and *P. jirovecii*. Anatomic abnormalities, such as bronchial stenosis and biliary stenosis, that develop as a result of the transplant surgery can also predispose to recurrent infection in this period.

Infections developing late after transplantation typically result from uncorrected anatomic abnormalities, chronic rejection, or exposure to community-acquired pathogens. Augmented immunosuppression as treatment for late acute cellular rejection or chronic rejection can increase the risk for late presentations with CMV, EBV, and other potential opportunistic infections. Acquisition of infection from community-acquired pathogens such as RSV can result in severe infection secondary to the immunocompromised state of the transplant recipient during the early and intermediate periods. Compared with the earlier periods, community-acquired infections in the late period are usually benign because immunosuppression is typically maintained at significantly lower levels. However, certain pathogens such as VZV and EBV may be associated with severe disease even at this late period.

Bacterial and Fungal Infections

Although there are important graft-specific considerations for bacterial and fungal infections after transplantation, some principles are generally applicable to all transplant recipients. Bacterial and fungal infections after organ transplantation are usually a direct consequence of the surgery, a breach in an anatomic barrier, a foreign body, or an abnormal anatomic narrowing or obstruction. With the exception of infections related to the use of indwelling catheters, sites of bacterial infection tend to occur at or near the transplanted organ. Infections after abdominal transplantation (liver, intestine, or renal) usually occur in the abdomen or at the surgical wound. The pathogens are typically enteric gram-negative bacteria, *Enterococcus*, and occasionally *Candida*. Infections after thoracic transplantation (heart, lung) usually occur in the lower respiratory tract or at the surgical wound. Pathogens associated with these infections include *S. aureus* and gram-negative bacteria. Patients undergoing lung transplantation for cystic fibrosis

Table 223.4 Timing of Infectious Complications After Solid Organ Transplantation

EARLY PERIOD (0-30 DAYS)
Bacterial Infections
Gram-negative enteric bacilli
• Small bowel, liver, neonatal heart
Pseudomonas, Burkholderia, Stenotrophomonas, Alcaligenes
• Cystic fibrosis lung
Gram-positive organisms
• All transplant types
Fungal Infections
• All transplant types
Viral Infections
Herpes simplex virus
• All transplant types
Nosocomial respiratory viruses
• All transplant types
MIDDLE PERIOD (1-6 MO)
Viral Infections
Cytomegalovirus
• All transplant types
• Seronegative recipient of seropositive donor
Epstein-Barr virus
• All transplant types (small bowel the highest-risk group)
• Seronegative recipient
Varicella-zoster virus
• All transplant types
• Opportunistic infections
Pneumocystis jirovecii
• All transplant types
Toxoplasma gondii
• Seronegative recipient of cardiac transplant from a seropositive donor are highest risk group
Bacterial Infections
Pseudomonas, Burkholderia, Stenotrophomonas, Alcaligenes
• Cystic fibrosis lung
Gram-negative enteric bacilli
• Small bowel
LATE PERIOD (>6 MO)
Viral Infections
Epstein-Barr virus
• All transplant types, but less risk than middle period
Varicella-zoster virus
• All transplant types
Community-acquired viral infections
• All transplant types
Bacterial Infections
Pseudomonas, Burkholderia, Stenotrophomonas, Alcaligenes
• Cystic fibrosis lung
• Lung transplants with chronic rejection
Gram-negative bacillary bacteremia
• Small bowel
Fungal Infections
Aspergillus
• Lung transplants with chronic rejection

Adapted from Green M, Michaels MG. Infections in solid organ transplant recipients. In: Long SS, Prober CG, Fischer M, eds. *Principles and Practice of Pediatric Infectious Diseases*, 5th ed. Philadelphia: Elsevier; 2018: Table 95-1.

experience a particularly high rate of infectious complications because they are often colonized with *P. aeruginosa* or *Aspergillus* before transplantation. Even though the infected lungs are removed, the sinuses and upper airways remain colonized with these pathogens, and subsequent reinfection of the transplanted lungs can occur. Children receiving organ transplants are often hospitalized for long periods and receive many antibiotics; thus recovery of multidrug-resistant bacteria is common after all types of organ transplantation. Infections caused by *Aspergillus* are less common but occur after all types of organ transplantation and are associated with high rates of morbidity and mortality.

Viral Infections

Viral pathogens, especially herpesviruses, are a major source of morbidity and mortality after SOT. In addition, BK virus is a major cause of renal disease after kidney transplantation. Although SARS-CoV-2 has affected pediatric SOT recipients less than adult recipients, disease severity is increased compared with nonimmunosuppressed children. The patterns of disease associated with individual viral pathogens are generally similar among all organ transplant recipients. However, the incidence, mode of presentation, and severity differ according to the type of organ transplanted and, for many viral pathogens, pretransplant serologic status of the recipient.

Viral pathogens can be generally categorized as latent pathogens, which cause infection through reactivation in the host or acquisition from the donor (e.g., CMV, EBV) or as community-acquired viruses (e.g., SARS-CoV-2, RSV, influenza). For CMV and EBV, primary infection occurring after transplantation is associated with the greatest degree of morbidity and mortality. The highest risk is seen in a naïve host who receives an organ from a donor who previously was infected with one of these viruses. This mismatched state is frequently associated with severe disease. However, even if the donor is negative for CMV and EBV, primary infection can be acquired from a close contact or through blood products. Secondary infections (reactivation of a latent strain within the host or superinfection with a new strain) tend to result in milder illness unless the patient is highly immunosuppressed, which can occur in the setting of treatment of significant rejection.

CMV is one of the most commonly recognized transplant viral pathogens. Disease from CMV has decreased significantly with the use of preventive strategies, including antiviral prophylaxis, most commonly using ganciclovir or oral valganciclovir, as well as viral load monitoring to inform preemptive antiviral therapy. Some centers have implemented a sequential approach where surveillance viral load monitoring follows a relatively short period of chemoprophylaxis. Clinical manifestations of CMV disease can range from a syndrome of fatigue and fever to tissue-invasive disease that most often affects the liver, lungs, and GI tract.

Infection caused by **EBV** is another important complication of SOT. Clinical symptoms range from a mild mononucleosis syndrome to disseminated **posttransplant lymphoproliferative disorder (PTLD)**. EBV-associated PTLD is more common among children than adults, because primary EBV infection in the immunosuppressed host is more likely to lead to uncontrolled proliferative disorders, including posttransplant lymphoma.

Other viruses, such as adenovirus, also have the capacity to be donor associated, but appear to be less common. The unexpected development of donor-associated viral pathogens, including hepatitis B virus, hepatitis C virus, and HIV, is rare today because of intensive donor screening. However, the changing epidemiology of some viruses (e.g., dengue, chikungunya, Zika) raises concerns for the *donor-derived transmission* of these emerging viral pathogens.

Community-acquired viruses, including those associated with respiratory tract infection (SARS-CoV-2, RSV, influenza virus, adenovirus, parainfluenza virus) and GI infection (enteroviruses, norovirus, and rotavirus), can cause important disease in children after organ transplantation. In general, risk factors for more severe infection include young age, acquisition of infection early after transplantation, and augmented immune suppression. Infection in the absence of these risk factors frequently results in a clinical illness that is comparable to that seen in immunocompetent children. However, some community-acquired viruses, such as adenovirus, can be associated with graft dysfunction even when acquired late after transplantation.

Although children with SARS-CoV-2 infection after transplantation fare better than adult counterparts, they are at risk for more severe symptoms early after transplant and if they have comorbidities. Immunization remains one of the best preventive strategies against severe disease even though efficacy is less compared to nonimmunosuppressed children.

Opportunistic Pathogens

Children undergoing SOT are also at risk for symptomatic infections from pathogens that do not usually cause clinical disease in immunocompetent hosts. Although these typically present in the intermediate period, these infections can also occur late in patients, requiring prolonged and high levels of immunosuppression. *P. jirovecii* is a well-recognized cause of pneumonia after SOT, although routine prophylaxis has essentially eliminated this problem. *T. gondii* can complicate cardiac transplantations because of tropism of the organism for cardiac muscle and risk for donor transmission; less often, it complicates other types of organ transplantation.

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223.3 Prevention of Infection in Immunocompromised Persons

Marian G. Michaels, Hey Jin Chong, and Michael Green

Although infections cannot be completely prevented in children who have defects in one or more arms of their immune system, measures can be taken to decrease the risks for infection. Replacement immunoglobulin is a benefit to children with primary B-cell deficiencies. Interferon (IFN)-γ, TMP-SMX, and oral antifungal agents have long been used to reduce the number of infections occurring in children with CGD, although the relative benefit of INF-γ has been questioned. Children who have depressed cellular immunity resulting from primary diseases, advanced HIV infection, or immunosuppressive medications benefit from prophylaxis against *P. jirovecii.* Strategies for safe living for all children with immunocompromising conditions should be emphasized, including hand hygiene, avoidance of community members with communicable infections, and attention to local environmental risk factors. These strategies were stressed and employed during the era of pandemic SARS-CoV-2 circulation. Immunizations prevent many infections and are particularly important for children with compromised immune systems who do not have a contraindication or inability to respond. For children rendered immunocompromised because of medication or splenectomy, immunizations should be administered before treatment whenever possible. This timing allows for superior response to vaccine antigens, avoids the risk of live vaccines, which may be contraindicated depending on the immunosuppression, and importantly, provides protection before the immune system is compromised.

Although immunodeficient children are a heterogeneous group, some principles of prevention are generally applicable. The use of inactivated vaccines does not lead to an increased risk for adverse effects, although their efficacy may be reduced because of an impaired immune response. In most cases, children with immunodeficiencies should receive all the recommended inactivated vaccines. Live-attenuated vaccinations can cause disease in some children with immunologic defects, and therefore alternative immunizations should be used whenever possible, such as inactivated influenza vaccine rather than live-attenuated influenza vaccine or inactivated typhoid vaccine rather than the oral live typhoid vaccine for travelers. In general, live-virus vaccines should not be used in children with primary T-cell abnormalities; efforts should be made to ensure that close contacts are all immunized to decrease the risk of exposure. In some patients in whom wild-type viral infection can be severe, immunizations, even with live-virus vaccine, are warranted in the immunosuppressed child. For example, children with HIV infection and a CD4 level of >15% should receive vaccinations against measles and varicella. In addition, growing evidence suggests that select transplant recipients can safely receive live vaccines as well. Some vaccines should be given to children with immunodeficiencies in addition to routine

vaccinations. As an example, children with asplenia or splenic dysfunction should receive meningococcal vaccine and both the conjugate and the polysaccharide pneumococcal vaccines. Influenza and SARS-CoV-2 vaccination is recommended for all eligible individuals (>6 months old for influenza) and should be emphasized for immunocompromised children and all household contacts to minimize risk for transmission to the immunocompromised child.

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Chapter 224

Infection Associated with Medical Devices

Hana Hakim and Joshua Wolf

Use of implanted synthetic and prosthetic devices has revolutionized pediatric practice by providing long-term venous access, limb-salvage surgery, and successful treatment of hydrocephalus, urinary retention, and renal failure. However, infectious complications of these devices remain a major concern and account for a significant number of healthcare-acquired infections (HAIs) and attributable morbidity and mortality among hospitalized patients. Several federal and hospital programs in the United States and elsewhere focus on prevention initiatives to reduce device-related HAI rates, most frequently central line–associated bloodstream infection (CLABSI), catheter-associated urinary tract infection (CAUTI), and ventilator-associated pneumonia (VAP). HAIs are typically defined as infections that occur at least 2 days after admission to the hospital and that were not incubating at the time of admission. Device-associated infections are related to the development of **biofilms**, organized communities of microorganisms on the device surface protected from the immune system and from antimicrobial therapy. A number of factors are important to the development of infection, including host susceptibility, device composition, duration of implantation, and exposure to colonizing or contaminating organisms.

INTRAVASCULAR ACCESS DEVICES

Intravascular access devices range from short, stainless steel needles or plastic cannulae inserted for brief periods to multilumen, implantable, synthetic plastic catheters that are expected to remain in use for years. Infectious complications include local skin and soft tissue infections, such as exit site, tunnel tract, and device pocket infections, and **catheter-related bloodstream infections (CRBSIs)**. The use of central venous devices has improved the quality of life of high-risk patients but has also increased the risk of infection.

Catheter Types

Short-term peripheral cannulae are most often used in pediatric patients, and infectious complications occur infrequently. The rate of peripheral CRBSIs in children is <0.15%. Patient age <1 year, duration of use >144 hours (6 days), and some infusates are associated with increased risk for catheter-related infection. Catheter-associated phlebitis is more common (1–6%) but is rarely infective and can be treated conservatively by cannula removal.

Central venous catheters (CVCs), which terminate in a central vein such as the superior or inferior vena cava, are widely used in both adult and pediatric patients and are responsible for the majority of catheter-related infections. These catheters are frequently used in patients with chronic illnesses such as oncologic, gastrointestinal, and cardiovascular diseases and in critically ill patients, including neonates, who have many other risk factors for nosocomial infection. Patients in an intensive care unit (ICU) with a CVC in place have a fivefold greater risk for developing a nosocomial bloodstream infection than those without. Other risk factors that have been associated with increased incidence of CLABSIs include prolonged hospital stay, total parenteral nutrition, use of multiple concurrent CVCs or a CVC with multiple lumens, and use of short-term nontunneled CVC.

The use of peripherally inserted central catheters, which are inserted into a peripheral vein and terminate in a central vein, has increased in pediatric patients. Infection rates seem to be similar to long-term tunneled CVCs, ranging between 2.0 and 3.51 per 1,000 catheter-days, but other complications such as fracture, dislodgment, and occlusion are more common.

When prolonged intravenous (IV) access is required, a cuffed silicone rubber (Silastic) or polyurethane catheter may be inserted into the superior vena cava through the subclavian, cephalic, or jugular vein. The extravascular segment of the catheter passes through a subcutaneous (SC) tunnel before exiting the skin, usually on the superior aspect of the chest (e.g., Broviac or Hickman catheter). A cuff around the catheter near the exit site induces a fibrotic reaction to seal the tunnel. Totally implanted devices comprise a tunneled central catheter attached to an SC reservoir or port with a self-sealing silicone septum immediately under the skin that permits repeated percutaneous needle access.

The incidence of local (exit site, tunnel, and pocket) infection with long-term catheters is 0.2-2.8/1,000 catheter-days. The incidence of external tunneled CRBSI is 0.5-11.0/1,000 catheter-days. The incidence of CRBSI in implantable devices is much lower at 0.3-1.8/1,000 catheter-days; however, treatment with total parenteral nutrition (TPN) eliminates this risk reduction because of a much greater relative increase in infection rate in ports. The risk for CRBSI is increased among premature infants, young children, and TPN patients.

Catheter-Associated Skin and Soft Tissue Infection

A number of local infections can occur in the presence of a CVC. The clinical manifestations of local infection include erythema, tenderness, and purulent discharge at the exit site or along the SC tunnel tract of the catheter. **Exit site infection** denotes infection localized to the exit site, without significant tracking along the tunnel, often with purulent discharge. **Tunnel tract infection** indicates infection in the SC tissues tracking along a tunneled catheter, which may also include serous or serosanguineous discharge from a draining sinus along the path. **Pocket infection** indicates suppurative infection of an SC pocket containing a totally implanted device. Bloodstream infection may coexist with local infection.

The diagnosis of local infection is established clinically, but a Gram-stained smear and culture of any exit site drainage should be performed to identify the microbiologic cause. The source is usually contamination by skin or gastrointestinal flora, and the most common organisms are *Staphylococcus aureus,* coagulase-negative staphylococci, *Pseudomonas aeruginosa, Candida* spp., and mycobacteria. Green discharge is strongly suggestive of mycobacterial infection, and appropriate stains and culture should be performed.

Treatment of local infection related to a short-term CVC should include device removal. Exit site infection may resolve with device removal alone, but systemic symptoms should initially be managed with antimicrobial therapy. In the case of long-term CVCs, exit site infections usually respond to local care with topical or systemic antibiotics alone. However, tunnel or pocket infections require removal of the catheter and systemic antibiotic therapy in almost all cases. When a tunneled CVC is removed as a result of tunnel infection, the cuff should also be removed and sent for culture if possible. In cases of mycobacterial infection, wide surgical debridement of the tissues is usually required for cure.

Catheter-Related Bloodstream Infection

CRBSI occurs when microorganisms attached to the CVC are shed into the bloodstream, leading to bacteremia. The term **catheter-related bloodstream infection** is reserved for a bloodstream infection that is demonstrated by CVC tip culture or other techniques to have been caused by colonization of the device. In contrast, the more general term **central line–associated bloodstream infection (CLABSI)** is typically

used for surveillance and can refer to any bloodstream infection that occurs in a patient with a CVC, unless there is an identified alternative source. On the device, the organisms are embedded in biofilms as organized communities. Colonization may be present even in the absence of symptoms or positive cultures.

Organisms may contaminate the external surface of the CVC during insertion or the intraluminal surface through handling of the catheter hub or contaminated infusate. Most cases of CRBSI appear to be caused by intraluminal colonization, but external colonization may play a greater role in infections related to recently inserted (<30 days) catheters or in immunocompromised patients. In most populations, gram-positive cocci predominate, with about half of infections caused by coagulase-negative staphylococci. Gram-negative enteric bacteria are isolated in approximately 20–30% of episodes, and fungi account for 5–10% of episodes.

Fever without an identifiable focus is the most common clinical presentation of CRBSI; local soft tissue symptoms and signs are usually absent. Onset of fever or rigors during or soon after flushing of a catheter is highly suggestive of CRBSI. Symptoms and signs of complicated infection, such as septic thrombophlebitis, endocarditis, and ecthyma gangrenosum, may also be present.

Blood cultures collected before beginning antibiotic therapy are generally positive from both the CVC and the peripheral blood. It is important not to collect cultures unless infection is suspected, as blood culture contamination may occur and can lead to inappropriate therapy. To help interpret positive cultures with common skin contaminants, blood cultures should be collected from at least two sites, preferably including all lumens of a CVC, before initiation of antibiotic therapy.

Tests to differentiate CRBSI from other sources of bacteremia in the presence of a CVC include culture of the catheter tip, quantitative blood cultures, and **differential time to positivity** of blood cultures drawn from different sites. Definitive diagnosis of CRBSI can be important to identify those patients who might benefit from catheter removal. Although CVC tip culture can identify CRBSI, it precludes salvage of the catheter. The most readily available technique to confirm CRBSI without catheter removal is calculation of differential time to positivity between blood cultures drawn through a catheter and from a peripheral vein or separate lumen. During CRBSI, blood obtained through the responsible lumen will usually indicate growth at least 2-3 hours before peripheral blood or uncolonized lumens because of a higher intraluminal microorganism burden. Identical volumes of blood must be collected simultaneously from each site, and a continuously monitored blood culture system is required. Specificity of this test is good (94–100%), and sensitivity is good when a peripheral blood culture is available (approximately 90%) but poorer when comparing two lumens of a CVC (64%). Where available, quantitative blood culture showing at least a threefold higher number of organisms from central compared with peripheral blood is similarly diagnostic.

Treatment of CRBSI related to **long-term vascular access devices** (e.g., Hickman, Broviac, totally implantable devices) with systemic antibiotics is successful for many bacterial infections without removal of the device. Antibiotic therapy should be directed to the isolated pathogen and given for a total of 10-14 days from the date of blood culture clearance. Until pathogen identification and susceptibility testing are available, empirical therapy, based on local antimicrobial susceptibility data and usually including **vancomycin** plus an antipseudomonal aminoglycoside (e.g., gentamicin), penicillin (e.g., piperacillin-tazobactam), or cephalosporin (e.g., ceftazidime or cefepime), is generally indicated. An echinocandin or azole antifungal should be initiated if fungemia is suspected. Patients who have a recent history of CRBSI with a resistant organism treated without CVC removal who subsequently develop severe sepsis should generally receive initial empirical therapy directed against that organism, because relapse is common.

Antibiotic lock or dwell therapy, with administration of solutions of high concentrations of antibiotics or ethanol that remain in the catheter for up to 24 hours, has been proposed to improve outcomes when used as an adjuvant to systemic therapy. Antibiotic locks are recommended in patients receiving dialysis who may not have antibiotics frequently delivered through the CVC, but evidence does not suggest that routine use of lock therapy is beneficial in other patient populations, and it may cause harm. Ethanol lock therapy increases the risk of CVC occlusion, and lock therapy can result in delays to necessary CVC removal.

If blood cultures remain positive after 72 hours of appropriate therapy, or if a patient deteriorates clinically, the device should be removed. Failure of CRBSI salvage therapy is common and can be serious in infections caused by *S. aureus* (approximately 50%), *Candida* spp. (>70%), and *Mycobacterium* spp. (>70%). Other indications for removing a long-term catheter include severe sepsis, suppurative thrombophlebitis, and endocarditis. Prolonged therapy (4-6 weeks) is indicated for persistent bacteremia or fungemia after catheter removal, because this may represent unrecognized infective endocarditis or thrombophlebitis. The decision to attempt catheter salvage should weigh the risk and clinical impact of persistent or relapsed infection against the risk of surgical intervention.

CRBSI may be complicated by other intravascular infections such as septic thrombophlebitis or endocarditis. The presence of these conditions may be suggested by preexisting risk factors (e.g., congenital heart disease), signs and symptoms, or persistent bacteremia or fungemia 72 hours after device removal and appropriate therapy. Screening for these complications in otherwise low-risk children, even those with *S. aureus* infection, is not recommended, because the overall frequency is low, and the tests can be difficult to interpret and may lead to inappropriate therapy.

Prevention of Infection

Consistent implementation of evidence-based prevention bundles has been essential to reduce HAI CLABSI rates. Prevention of CLABSI starts with preinsertion planning for the type and number of CVC lumens and selection of the venous site for CVC insertion. Insertion bundle elements include meticulous hand hygiene, aseptic skin preparation using 2% chlorhexidine gluconate, and use of maximal sterile barrier precautions in an operating room–like environment. Maintenance bundles guide the daily safe care of CVCs to prevent infections, including protecting the CVC from gross contamination with excretions or body fluids, evidence-based techniques to access and scrub the CVC hub and connectors, and assessing and changing the CVC site dressing. Regular assessment of the need for the catheter should be part of the daily medical and nursing care team discussions. In general, children with external CVCs are discouraged from swimming because of concern of subsequent CRBSI. However, existing evidence regarding risk of CRBSI related to swimming is limited. It is important to educate patient caregivers about the potential risk and the importance of maintaining a secured CVC with water-resistant dressing if patients choose to swim. Catheters should routinely be removed as soon as they are no longer needed. Although prevalence of infection increases with prolonged duration of catheter use, routine replacement of a required CVC, either at a new site or over a guide wire, results in significant morbidity and is not recommended. Other practices that have been associated with reduction in CLABSI rates include use of a chlorhexidine-impregnated sponge at the exit site and daily bathing of ICU patients with 2% chlorhexidine gluconate. Use of antibiotic, taurolidine, or ethanol lock solutions; heparin with preservatives; and alcohol-impregnated caps, as well as antimicrobial-impregnated/coated catheters may be appropriate in high-risk populations. There is no evidence that routine replacement of short-term peripheral catheters prevents phlebitis or other complications in children, so they should only be replaced when clinically indicated (e.g., phlebitis, dysfunction, dislodgment).

URINARY CATHETERS

Urinary catheters are a frequent cause of HAIs, with approximately 14 infections per 1,000 admissions, resulting in increasing duration of hospitalization, cost of patient care, morbidity, and mortality. Rates of CAUTI are highest among ICU patients. As with other devices, microorganisms adhere to the urinary catheter surface and establish a biofilm that allows proliferation. The physical presence of the catheter reduces the normal host defenses by preventing complete emptying of the bladder, thus providing a medium for growth, distending the urethra, and blocking periurethral glands. Almost all patients catheterized

for >30 days develop bacteriuria. The mechanism of the infection can be either from organisms colonizing the patient's perineal or rectal area or from organisms contaminating the hands of healthcare providers or contaminating equipment such as a collection bag. The organism burden in CAUTI is typically ≥100,000 colony-forming units/mL. Lower thresholds may be used where there is a high index of suspicion, but these episodes usually represent colonization rather than infection. Urine culture should only be performed in catheterized patients when infection is suspected, because asymptomatic colonization is ubiquitous and may lead to overtreatment and subsequent development of bacterial resistance. Gram-negative bacilli and *Enterococcus* spp. are the predominant organisms isolated in CAUTI; coagulase-negative staphylococci are implicated in approximately 15% of cases. Symptomatic UTIs should be treated with antibiotics and catheter removal. Catheter colonization with *Candida* spp. is common but rarely leads to invasive infection, and treatment does not have a long-term impact on colonization. Treatment for asymptomatic candiduria or bacteriuria is not recommended, except in neonates, immunocompromised patients, and those with urinary tract obstruction.

All urinary catheters introduce a risk for infection and thus should be used only when necessary and for the minimum required duration. Existing evidence supports the benefit of using alternatives to indwelling urethral catheters to prevent CAUTI, including external catheters in male patients, intermittent catheterization, or suprapubic catheters in selected patients. Hand hygiene and aseptic technique are part of the insertion bundles of interventions aimed at preventing CAUTI. Evidence-based urinary catheter maintenance practices are essential to prevent hospital-acquired CAUTI, including perineal hygiene, a closed drainage system, maintenance of unobstructed urine flow, and keeping the collection bag below the level of the bladder. Technologic advances have led to the development of silver- or antibiotic-impregnated urinary catheters that are associated with lower rates of infection. Prophylactic antibiotics do not significantly reduce the infection rates for long-term catheters but clearly increase the risk for infection with antibiotic-resistant organisms.

MECHANICAL VENTILATORS

Endotracheal intubation and mechanical ventilation are lifesaving technologies to support patients with respiratory failure and patients undergoing surgical procedures. However, VAP has contributed to prolonged hospital stay and increased costs in patients in medical and surgical ICUs. VAP is more frequently reported in adult than in pediatric patients. The mechanism of VAP is through microaspiration of colonizing oropharyngeal organisms to the lower respiratory tract and its associated host inflammatory response. Common pathogens causing VAP include gram-negative bacilli (e.g., *Escherichia coli, Klebsiella pneumoniae, Enterobacter* spp., and *P. aeruginosa*) and gram-positive cocci (e.g., *S. aureus* and *Streptococcus* spp.). Risk factors for VAP include medications that increase gastric pH (e.g., H_2 blockers, antacids, proton pump inhibitors), decreased level of consciousness, use of paralytics or muscle relaxant agents, and prolonged intubation. Progressive or acute-onset respiratory deterioration requiring increased mechanical setting support in a patient who has been intubated for more than 2 days should raise the suspicion of VAP. Chest diagnostic imaging and cultures of lower respiratory specimens (e.g., endotracheal aspiration or bronchoalveolar lavage) should be considered.

Evidence-based practices to prevent VAP include use of noninvasive ventilation (e.g., continuous positive airway pressure [CPAP], bilevel positive airway pressure [BiPAP]) when possible to avoid endotracheal intubation and prevention of microaspiration by elevating the head of the bed, controlling cuff pressure, minimizing and early weaning of sedation, and maintaining closed ventilator circuits. Oral care with chlorhexidine gluconate for oropharyngeal decontamination has been included as an element in several VAP prevention bundles. Evidence regarding the efficacy and safety of other interventions such as use of probiotics or silver-coated endotracheal tubes has been inconclusive.

CEREBROSPINAL FLUID SHUNTS

Cerebrospinal fluid (CSF) shunting is required for the treatment of many children with **hydrocephalus**. The usual procedure uses a silicone rubber device with a proximal portion inserted into the ventricle, a unidirectional valve, and a distal segment that diverts the CSF from the ventricles to either the peritoneal cavity (**ventriculoperitoneal** [VP] shunt) or right atrium (**ventriculoatrial** [VA] shunt). The incidence of shunt infection ranges from 1% to 20% (average, 10%). The highest rates are reported in young infants, patients with prior shunt infections, and certain etiologies of hydrocephalus. Most infections result from intraoperative contamination of the surgical wound by skin flora. Accordingly, coagulase-negative staphylococci are isolated in more than half the cases. *S. aureus* is isolated in approximately 20% and gram-negative bacilli in 15% of cases.

Four distinct clinical syndromes have been described: colonization of the shunt, infection associated with wound infection, distal infection with peritonitis, and infection associated with meningitis. The most common type of infection is **colonization of the shunt**, with nonspecific symptoms that reflect shunt malfunction as opposed to frank infection. Symptoms associated with colonized VP shunts include lethargy, headache, vomiting, a full fontanel, and abdominal pain. Fever is often absent or may be low-grade (<39°C or 102.2°F). Symptoms usually occur within months of the surgical procedure. Colonization of a VA shunt results in more severe systemic symptoms, and specific symptoms of shunt malfunction are often absent. Septic pulmonary emboli, pulmonary hypertension, and infective endocarditis are frequently reported complications of VA shunt colonization. Chronic VA shunt colonization may cause hypocomplementemic glomerulonephritis from antigen-antibody complex deposition in the glomeruli, commonly called *shunt nephritis;* clinical findings include hypertension, microscopic hematuria, elevated blood urea nitrogen and serum creatinine levels, and anemia.

Diagnosis is by Gram stain, microscopy, biochemistry, and culture of CSF. CSF should be obtained by direct aspiration of the shunt before administration of antibiotics, because CSF obtained from either lumbar or ventricular puncture is often sterile. It is unusual to observe signs of ventriculitis, and CSF findings can be only minimally abnormal. Blood culture results are usually positive in VA shunt colonization but negative in cases of VP colonization.

Wound infection presents with obvious erythema, swelling, discharge, or dehiscence along the shunt tract and most often occurs within days to weeks of the surgical procedure. *S. aureus* is the most common isolate. In addition to the physical findings, fever is common, and signs of shunt malfunction eventually ensue in most cases.

Distal infection of VP shunts with **peritonitis** presents with abdominal symptoms, usually without evidence of shunt malfunction. The pathogenesis is likely related to perforation of the bowel at VP shunt placement or translocation of bacteria across the bowel wall. Thus gram-negative isolates predominate, and mixed infection is common. The infecting organisms are often isolated from only the distal portion of the shunt.

Common pathogens responsible for community-acquired **meningitis**, including *Streptococcus pneumoniae, Neisseria meningitidis,* and *Haemophilus influenzae* type b, cause bacterial meningitis in patients with shunts only rarely, and the clinical presentation is similar to that for acute bacterial meningitis in other children (see Chapter 643.1).

Treatment of shunt colonization includes removal of the shunt and systemic antibiotic therapy directed against the isolated organisms. Treatment without removal of the shunt is rarely successful and should not be routinely attempted. After collection of appropriate samples for culture, empirical therapy is usually with vancomycin plus an antipseudomonal agent with relatively good CSF penetration, such as ceftazidime or meropenem. Definitive therapy should be directed toward the isolate and should account for poor penetration of most antibiotics into the CSF across noninflamed meninges. Accordingly, intraventricular antibiotics may be indicated but are usually reserved unless there is evidence of treatment failure. If the isolate is susceptible, a parenteral antistaphylococcal penicillin with or without intraventricular vancomycin is the treatment of choice. If the organism is resistant to penicillins, systemic vancomycin and possibly intraventricular vancomycin are recommended. In gram-negative infections, a third-generation cephalosporin with or without an intraventricular aminoglycoside is

optimal. When using intraventricular antibiotics, monitoring CSF levels is necessary to avoid toxicity.

Removal of the colonized device is required for cure, and final replacement should be delayed until clearance of CSF cultures is documented. Many neurosurgeons immediately remove the shunt and place an external ventricular drain to relieve intracranial pressure (ICP), with a second-stage shunt replacement once CSF sterilization has been confirmed. Others opt initially to exteriorize the distal end of the shunt and replace the shunt in a single-stage procedure once CSF cultures remain sterile for 48-72 hours. Daily CSF cultures should be collected until clearance has been documented on two to three consecutive specimens, and antibiotics should be continued for at least 10 days after documented sterilization of the CSF. Gram-negative organisms may require a longer duration of therapy (up to 21 days). The CSF white cell count generally increases for the first 3-5 days of appropriate therapy, and that alone should not prompt concern for treatment failure. Distal shunt infection with peritonitis and wound infection are managed in a similar fashion.

Treatment of **bacterial meningitis** with typical community-acquired pathogens such as meningococcus or pneumococcus usually requires only systemic antibiotic therapy. Shunt replacement is not required in the absence of device malfunction, poor clinical response, persistent CSF culture positivity, or relapse of infection after antibiotic therapy.

Prevention of Infection

Prevention of shunt infection includes meticulous cutaneous preparation and surgical technique. Systemic and intraventricular antibiotics, antibiotic-impregnated shunts, and soaking the shunt tubing in antibiotics are used to reduce the incidence of infection, with varying success. Systemic prophylactic antibiotics given before and during shunt insertion can reduce the risk for infection and should be used routinely but should not be continued for more than 24 hours postoperatively. Antibiotic-impregnated catheters also appear to reduce the risk of infection and may be used in high-risk patients where the devices are available.

PERITONEAL DIALYSIS CATHETERS

During the first year of peritoneal dialysis for end-stage renal disease, 65% of children will have one or more episodes of peritonitis. Bacterial entry comes from luminal or periluminal contamination of the catheter or by translocation across the intestinal wall. Hematogenous infection is rare. Infants and young children who are in diapers are at highest risk for peritoneal dialysis catheter–associated infections. Infections can be localized at the exit site or associated with peritonitis, or both. Organisms responsible for peritonitis include coagulase-negative staphylococci (30–40%), *S. aureus* (10–20%), streptococci (10–15%), *E. coli* (5-10%), *Pseudomonas* spp. (5–10%), other gram-negative bacteria (5–15%), *Enterococcus* spp. (3–6%), and fungi (2–10%). *S. aureus* is more common in localized exit site or tunnel tract infections (42%). Most infectious episodes are caused by a patient's own flora, and carriers of *S. aureus* have increased rates of infection compared with noncarriers.

The clinical manifestations of peritonitis may be subtle and include low-grade fever with mild abdominal pain or tenderness. Cloudy peritoneal dialysis fluid may be the first and predominant sign. With peritonitis, the peritoneal fluid cell count is usually >100 white blood cells/μL. When peritonitis is suspected, the effluent dialysate should be submitted for a cell count, Gram stain, and culture. The Gram stain is positive in up to 40% of cases of peritonitis.

Patients with cloudy fluid and clinical symptoms should receive empirical therapy, preferably guided by results of a Gram stain. If no organisms are visualized, vancomycin and either an aminoglycoside or a third- or fourth-generation cephalosporin with antipseudomonal activity should be given by the intraperitoneal route. Blood levels should be measured for glycopeptides and aminoglycosides. Patients without cloudy fluid and with minimal symptoms may have therapy withheld pending culture results. Once the cause is identified by culture, changes in the therapeutic regimen may be needed. Oral **rifampin** may be added as adjunctive therapy for susceptible *S. aureus* isolates but should not be used as a standalone agent and must prompt consideration of drug interactions. Candidal peritonitis should be treated with catheter removal and intraperitoneal or oral **fluconazole** or an IV **echinocandin** such as caspofungin or micafungin, depending on the *Candida* spp.; catheter retention has been associated with almost inevitable relapse and higher risk of mortality in adult studies. The duration of therapy for peritonitis is a minimum of 14 days, with longer treatment of 21-28 days for episodes of *S. aureus, Pseudomonas* spp., and resistant gram-negative bacteria and 28-42 days for fungi. Repeat episodes of peritonitis with the same organism within 4 weeks of previous therapy should lead to consideration of catheter removal or attempt at salvage with administration of a fibrinolytic agent and a longer course of up to 6 weeks of antibiotic therapy.

In all cases, if the infection fails to clear after appropriate therapy or if a patient's condition is deteriorating, the catheter should be removed. Exit site and tunnel tract infections may occur independently of peritonitis or may precede it. Appropriate antibiotics should be administered on the basis of Gram stain and culture findings and are typically given systemically only, unless peritonitis is also present. Some experts recommend that the peritoneal catheter be removed if *Pseudomonas* spp. or fungal organisms are isolated.

Prevention of Infection

In addition to usual hygienic practices such as hand hygiene and aseptic care of the catheter exit site, regular application of **mupirocin** or **gentamicin** cream to the catheter exit site reduces exit site infections and peritonitis. Some practitioners recommend against the use of gentamicin cream because of the risk of infection with gentamicin-resistant bacteria. Systemic antibiotic prophylaxis should be considered at catheter insertion, if there is accidental contamination, and at dental procedures. Antifungal prophylaxis with oral nystatin or fluconazole should be considered during antibiotic therapy to prevent fungal infection.

IMPLANTABLE ORTHOPEDIC DEVICES

Implantable orthopedic devices are used infrequently in children. Orthopedic device infection most often follows introduction of microorganisms at surgery through airborne contamination or direct inoculation, hematogenous spread, breakdown of overlying skin, or contiguous spread from an adjacent infection. Early postoperative infection occurs within 2-4 weeks of surgery, with manifestations typically including fever, pain, and local symptoms of wound infection. Chronic infection presents >1 month after surgery and is often caused by organisms of low virulence that contaminated the implant at surgery or by failure of wound healing. Typical manifestations include pain and deterioration in function. Local symptoms such as erythema, swelling, or drainage may also occur. Acute hematogenous infections are most often observed ≥2 years after surgery and may be more common in children with immunocompromise. Options for treatment include conservative management with operative debridement and irrigation and retention of the prosthesis, followed by a 3- to 6-month course of antimicrobial therapy, or more radical intervention with removal and replacement of all hardware—as either a one- or two-stage exchange with a shorter course of antibiotic therapy (2-6 weeks). If the prosthesis is retained, suppressive oral antibiotic therapy may be considered after an initial treatment course, especially in patients who are undergoing intensive time-limited treatment such as chemotherapy. As with other long-term implanted devices, the most common organisms are coagulase-negative staphylococci and *S. aureus*. With prior antibiotic therapy, the prosthesis culture may be negative; in these situations, molecular techniques to identify the organism are available, but sensitivity and specificity are poorly understood.

Orthopedic hardware such as screws and plates are more commonly encountered in children than true implantable orthopedic devices. The management of infections associated with these kinds of hardware is similar to other orthopedic device infections, but because the hardware is typically temporary, it should generally be removed as soon as feasible.

Systemic antibiotic prophylaxis, antibiotic-containing bone cement, and operating rooms fitted with laminar airflow have been proposed to reduce infection. To date, results from clinical studies are conflicting.

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Section 3
Antibiotic Therapy

Chapter 225
Principles of Antibacterial Therapy

Mark R. Schleiss

Antibacterial therapy in infants and children presents many challenges. A daunting problem is the paucity of pediatric data regarding pharmacokinetics and optimal dosages; as a consequence, pediatric recommendations are frequently extrapolated from adult studies. A second challenge is the need for the clinician to consider important differences among pediatric age-groups with respect to the pathogenic species most often responsible for bacterial infections. Age-appropriate antibiotic dosing and toxicities must be considered, taking into account the developmental status and physiology of infants and children. Finally, the style of how a pediatrician uses antibiotics in children, particularly young infants, has some important differences compared with how antibiotics are used in adult patients.

Specific antibiotic therapy is optimally driven by a **microbiologic diagnosis**, predicated on isolation of the pathogenic organism from a sterile body site and supported by antimicrobial susceptibility testing. However, given the inherent difficulties that can arise in collecting specimens from pediatric patients and given the high risk of mortality and disability associated with serious bacterial infections in very young infants, much of pediatric infectious diseases practice is based on clinical diagnoses and **empirical** use of antibacterial agents, often administered before and/or without identification of the specific pathogen. Although there is an ever-increasing emphasis on **antimicrobial stewardship**, driven by the importance of using empirical therapy sparingly (to avoid selecting for resistant organisms), there are some settings in which antimicrobials must be administered before the presence of a specific bacterial pathogen is proven. This is particularly relevant to the care of the febrile or ill-appearing neonate or young infant under 30 days of age.

Several key considerations influence decision-making regarding the appropriate empirical use of antibacterial agents in infants and children. It is important to know the age-specific differential diagnosis with respect to likely pathogens. This information affects the choice of antimicrobial agent and also the dose, dosing interval, and route of administration (oral vs parenteral). A complete history and physical examination, combined with appropriate laboratory and radiographic studies, are necessary to identify specific diagnoses, information that in turn affects the choice, dosing, and degree of urgency of administration of antimicrobial agents. The vaccination history may confer reduced risk for some invasive infections (i.e., *Haemophilus influenzae* type b, *Streptococcus pneumoniae, Neisseria meningitidis*), but a history of vaccination does not necessarily eliminate risk. The threat of serious bacterial infection in pediatric practice is also affected by the child's immunologic status, which may be compromised by immaturity (neonates), underlying disease, and immunosuppressive medications used to treat other disorders (see Chapter 223). Infections in immunocompromised children may result from bacteria that are not considered pathogenic in immunocompetent children. The presence of foreign bodies (medical devices) also increases the risk of bacterial infections (see Chapter 224). The likelihood of central nervous system (CNS) involvement must be considered in all pediatric patients with serious bacterial infections, because many bacteremic pathogens in childhood carry a significant risk of hematogenous spread to the CNS.

The patterns of **antimicrobial resistance** in the community and for the potential causative pathogen being empirically covered must also be considered. Resistance to penicillin and cephalosporins is frequent among strains of *S. pneumoniae,* often necessitating the use of other classes of antibiotics. Similarly, the striking emergence of community-acquired methicillin-resistant *Staphylococcus aureus* **(MRSA)** infections has complicated antibiotic choices, both when this pathogen is isolated in culture and for empirical coverage of skin and soft tissue infections. Extended-spectrum β-lactamase **(ESBL)**–producing gram-negative bacteria (Enterobacteriaceae) have reduced the effectiveness of penicillins and cephalosporins. Furthermore, carbapenem-resistant Enterobacteriaceae **(CRE)** are an increasing problem among hospitalized patients, particularly in children with an epidemiologic connection to regions of the world, such as India, where such strains are frequently encountered.

Antimicrobial resistance occurs through many modifications of the bacterial genome (Tables 225.1 and 225.2). Mechanisms include enzyme inactivation of the antibiotic, decreased cell membrane permeability to intracellularly active antibiotics, efflux of antibiotics out of the bacteria, protection or alteration of the antibiotic target site, excessive production of the target site, and bypassing the antimicrobial site of action. CRISPR (clustered regularly interspaced short palindromic repeats) elements in bacteria have also been shown to be related to emergence of antimicrobial resistance. CRISPRs are detectable in many bacterial genomes, protecting their genomes from attack by foreign DNA during transformation, phage invasion, or plasmid insertion. The mechanism of protection is mediated by insertion of small sequences of the invading DNA between palindromic repeats within the CRISPR element. Upon re-exposure to similar DNA sequences from phage or invading bacteria, the existing sequence within the CRISPR is transcribed into a small RNA that associates with CRISPR-associated nucleases, blocking integration of the targeted foreign DNA. Deletion of CRISPR elements in *Enterococcus* is inversely related to antibiotic resistance, and CRISPR-deficient strains are selected for in the context of healthcare-associated infections. CRISPR deficiency allows for evolution of significantly larger genomes, and the attendant insertion of large sequences of DNA in turn enables expression of multiple antibiotic-resistance genes.

Antimicrobial resistance has reached *crisis proportions,* driven by the emergence of new resistance mechanisms (e.g., carbapenemases, including *Klebsiella pneumoniae*–associated carbapenemases, or **KPCs**) and by overuse of antibiotics, both in healthcare and in other venues, such as agribusiness and animal husbandry. This increase in antibiotic resistance has rendered some bacterial infections encountered in clinical practice virtually untreatable. Accordingly, there is an urgent need to develop new antimicrobials and to rediscover some older antibiotics that have been out of use in recent decades but still retain activity against resistant organisms. It is vital that practitioners use antibiotics only when truly indicated, with the narrowest feasible antimicrobial spectrum, to help thwart emergence of resistance. In addition, advocacy for **vaccines**, particularly conjugate pneumococcal vaccine, can also decrease the selective pressure that excessive antimicrobial use exerts on resistance.

Effective antibiotic action requires achieving therapeutic levels of the drug at the site of infection. Other factors to consider include the impact of pH on antibiotic activity; for example, an antibiotic may penetrate an abscess with adequate levels but may be inactive in the acidic milieu of the abscess cavity. Although measuring the level of antibiotic at the site of infection is not always possible, one may measure the serum level and use this level as a surrogate marker to achieve the desired effect at the tissue level. Various target serum levels are appropriate for different antibiotic agents and are assessed by the peak and trough serum levels and the area under the therapeutic drug level curve (Fig. 225.1). These levels in turn are a reflection of the route of administration, drug absorption (IM, PO), volume of distribution, and drug elimination half-life, as well as drug-drug interactions that might

enhance or impede enzymatic inactivation of an antibiotic or result in antimicrobial synergism or antagonism (Fig. 225.2).

AGE- AND RISK-SPECIFIC USE OF ANTIBIOTICS IN CHILDREN

Neonates

The causative pathogens associated with neonatal infections are typically acquired around the time of delivery. Thus empirical antibiotic selection must take into account the importance of these organisms (see Chapter 148). Among the causes of neonatal sepsis in infants, **group B *Streptococcus*** (GBS) is the most common. Although intrapartum antibiotic prophylaxis administered to women at increased risk for transmission of GBS to the infant has greatly decreased the incidence of this infection in neonates, particularly with respect to so-called *early-onset disease,* GBS infections are still frequently encountered in clinical practice (see Chapter 230). Gram-negative enteric organisms acquired from the maternal birth canal, in particular *Escherichia coli,* are also common causes of neonatal sepsis. Although less common, *Listeria monocytogenes* is an important pathogen to consider, in particular because this organism is intrinsically resistant to cephalosporin antibiotics, which are often used as empirical therapy for serious bacterial infections in young children. *Salmonella* bacteremia and **meningitis** on a global basis is a well-recognized infection in infants. All these organisms can be associated with meningitis in the neonate; therefore lumbar puncture should always be considered in the setting of bacteremic infections in this age-group, and antibiotic management should include agents capable of crossing the blood-brain barrier if meningitis cannot be excluded.

Older Children

Antibiotic choices in toddlers and young children were once driven by the high risk of this age-group to invasive disease caused by *H. influenzae* type b (**Hib**; see Chapter 240). With the advent of conjugate vaccines against Hib, invasive disease has declined dramatically. However, outbreaks still occur and have been observed in the context of parental refusal of vaccines. Therefore the use of antimicrobials that are active against Hib remains important in many clinical settings, particularly if meningitis is a consideration. Other important pathogens to consider in this age-group include *E. coli*, *S. pneumoniae, N. meningitidis,* and *S. aureus*. Strains of *S. pneumoniae* that are resistant to penicillin and cephalosporin antibiotics are frequently encountered in clinical practice. Similarly, MRSA is highly prevalent in children in the outpatient setting. Antibiotic resistance in *S. pneumoniae* and MRSA is a result of mutations that confer alterations in penicillin-binding proteins, the molecular targets of penicillin and cephalosporin activity (see Table 225.1).

Depending on the specific clinical diagnosis, other pathogens encountered among older children include *Moraxella catarrhalis*, nontypeable (nonencapsulated) strains of *H. influenzae*, and *Mycoplasma pneumoniae*, which cause upper respiratory tract infections and pneumonia; group A *Streptococcus*, which causes pharyngitis, skin and soft tissue infections, osteomyelitis, septic arthritis, and rarely, bacteremia with toxic shock syndrome; *Kingella kingae*, which causes bone and joint infections and bacteremia; viridians group streptococci and Enterococcus, which cause endocarditis; and *Salmonella* spp., which cause enteritis, bacteremia, osteomyelitis, and septic arthritis. Vector-borne bacterial infections, including infections with *Borrelia burgdorferi*, *Rickettsia rickettsii*, and *Anaplasma phagocytophilum*, are increasingly recognized in certain regions, with an emerging increase in prevalence related to global climate change. Zoonotic exposures, pet ownership, and uncommon dietary intake may suggest less common pathogens such as *Coxiella burnetii, Brucella abortus, Bartonella henselae, Yersinia pestis, L. monocytogenes,* and *Francisella tularensis,* all of which have unique antibiotic susceptibility profiles. These complexities

Table 225.1 Mechanisms of Resistance to β-Lactam Antibiotics

I. Alter target site (PBP)
  A. Decrease affinity of PBP for β-lactam antibiotic
    1. Modify existing PBP
      a. Create mosaic PBP
        (1) Insert nucleotides obtained from neighboring bacteria (e.g., penicillin-resistant *Streptococcus pneumoniae*)
        (2) Mutate structural gene of PBP(s) (e.g., ampicillin-resistant β-lactamase–negative *Haemophilus influenzae*)
    2. Import new PBP (e.g., *mecA* in methicillin-resistant *Staphylococcus aureus*)
II. Destroy β-lactam antibiotic
  A. Increase production of β-lactamases, carbapenemases
    1. Acquire more efficient promoter
      a. Mutate existing promoter
      b. Import new promoter
    2. Deregulate control of β-lactamase production
      a. Mutate regulator genes (e.g., *ampD* in "stably derepressed" *Enterobacter cloacae*)
  B. Modify structure of resident β-lactamase
    1. Mutate structural gene (e.g., ESBLs in *Klebsiella pneumoniae*)
  C. Import new β-lactamase(s) with different spectrum of activity
III. Decrease concentration of β-lactam antibiotic inside cell
  A. Restrict its entry (loss of porins)
  B. Pump it out (efflux mechanisms)

ESBLs, Extended-spectrum β-lactamases; PBP, penicillin-binding protein.
Adapted from Opal SM, Pop-Vicas A. Molecular mechanisms of antibiotic resistance in bacteria. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases,* 9th ed. Philadelphia: Elsevier; 2020: Table 18-4.

Table 225.2 Aminoglycoside-Modifying Enzymes*

ENZYMES	USUAL ANTIBIOTICS MODIFIED	COMMON GENERA
PHOSPHORYLATION		
APH(2″)	K, T, G	SA, SR
APH(3′)-I	K	E, PS, SA, SR
APH(3′)-III	K ± A	E, PS, SA, SR
ACETYLATION		
AAC(2′)	G	PR
AAC(3)-I	±T, G	E, PS
AAC(3)-III, -IV, or -V	K, T, G	E, PS
AAC(6′)	K, T, A	E, PS, SA
ADENYLATION		
ANT(2″)	K, T, G	E, PS
ANT(4′)	K, T, A	SA
BIFUNCTIONAL ENZYMES		
AAC(6′)-APH(2″)	G, Ar	SA, Ent
AAC(6′)-Ibcr	G, K, T, FQ*	E

*Aminoglycoside-modifying enzymes confer antibiotic resistance through three general reactions: N-acetylation, O-nucleotidylation, and O-phosphorylation. For each of these general reactions, there are several different enzymes that attack a specific amino or hydroxyl group. The nomenclature for these enzymes lists the molecular site where the modification occurs after the type of enzymatic activity. An aminoglycoside acetyltransferase (AAC) that acts at the 3′ site is designated AAC(3′).There may be more than one enzyme that catalyzes the same reaction, however, and Roman numerals may be necessary (e.g., AAC[3′]-IV).
A, Amikacin; AAC, aminoglycoside acetyltransferase; ANT, aminoglycoside nucleotidyltransferase; APH, aminoglycoside phosphotransferase; Ar, arbekacin, E, Enterobacteriaceae; Ent, enterococci, FQ, fluoroquinolone (acetylates the piperazine ring in some fluoroquinolones), G, gentamicin; K, kanamycin; PR, *Providencia-Proteus*; PS, pseudomonads; SA, staphylococci; SR, streptococci; T, tobramycin.
Adapted from Opal SM, Pop-Vicas A. Molecular mechanisms of antibiotic resistance in bacteria. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases,* 9th ed. Philadelphia: Elsevier; 2020: Table 18-5.

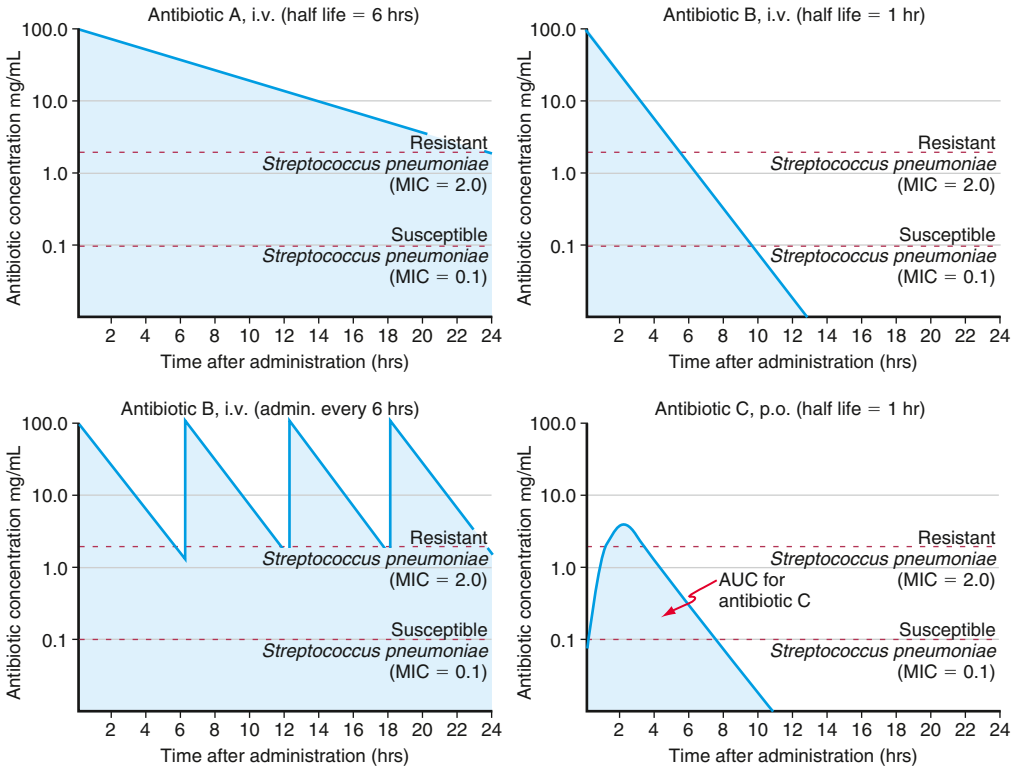

Fig. 225.1 Area under the curve (AUC; *shaded area*) for different antibiotics. The AUC provides a measure of antibiotic exposure to bacterial pathogens. The greatest exposure comes with antibiotics that have a long serum half-life and are administered parenterally (*upper left panel,* antibiotic A). The lowest exposure occurs with oral administration (*lower right panel,* antibiotic C). Dosing of antibiotic B once a day *(upper right panel)* provides far less exposure than dosing the same antibiotic every 6 hr *(lower left panel).* MIC, Minimal inhibitory concentration. *(From Pong AL, Bradley JS. Guidelines for the selection of antibacterial therapy in children. Pediatr Clin North Am. 2005;52:869–894.)*

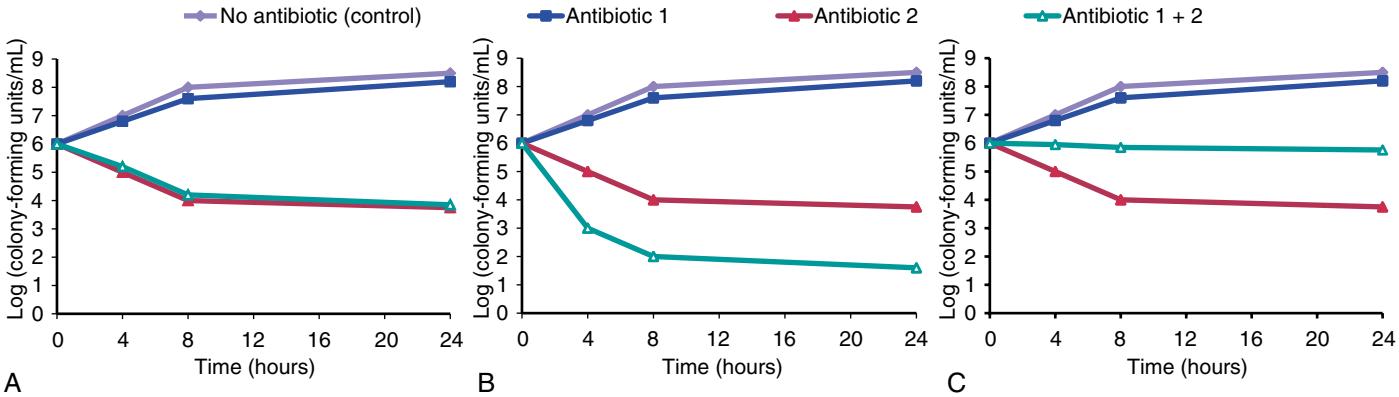

Fig. 225.2 Antibacterial effects of antibiotic combinations. **A,** Combination of antibiotics 1 and 2 is *indifferent;* killing by antibiotic 2 is unchanged when antibiotic 1 is added. **B,** Combination of antibiotics 1 and 2 results in *synergy;* killing by antibiotic 2 is significantly enhanced when antibiotic 1 is added at a subinhibitory concentration. **C,** Combination of antibiotics 1 and 2 is *antagonistic;* killing by antibiotic 2 is diminished in the presence of antibiotic 1. *(From Eliopoulos GM, Moellering RC Jr. Principles of anti-infective therapy. In: Bennett JF, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th ed. Philadelphia: Elsevier; 2015: Fig 17-1.)*

underscore the importance of formulation of a complete differential diagnosis in children with suspected severe bacterial infections, including an assessment of the severity of the infection in parallel with consideration of local epidemiologic disease trends. Knowledge of the antimicrobial susceptibility patterns in the community is also critically important in devising an antibiotic treatment strategy.

Immunocompromised and Hospitalized Patients

It is important to consider the risks associated with immunocompromising conditions (malignancy, solid organ or hematopoietic stem cell transplantation, immunodeficiencies) and the risks conferred by conditions leading to prolonged hospitalization (intensive care, trauma, burns). Influenza infection can also predispose to invasive bacterial infections, especially those caused by *S. aureus*. Measles infection is well-known to predispose to serious bacterial infection, particularly with *Mycobacteria*. Infection with SARS-CoV-2 can also be associated with bacterial and fungal opportunistic infections. Immunocompromised children are predisposed to develop a wide range of bacterial, viral, fungal, or parasitic infections. Prolonged hospitalization can lead to nosocomial infections, often associated with indwelling catheters and caused by highly antibiotic-resistant gram-negative enteric organisms. In addition to bacterial pathogens already discussed, *Pseudomonas aeruginosa* and enteric organisms, including *E. coli, K. pneumoniae, Enterobacter,* and *Serratia,* are important opportunistic pathogens in these settings.

The so-called *ESKAPE pathogens* are a group of six highly virulent and antibiotic-resistant organisms that are being increasingly recognized in hospitalized patients, including *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter* species. Selection of appropriate antimicrobials is challenging because of the diverse causes and scope of antimicrobial resistance exhibited by these organisms. Many strains of enteric

organisms have resistance because of ESBLs (see Table 225.1). Class B metallo-β-lactamases (also known as *New Delhi metallo-β-lactamases*) that hydrolyze all β-lactam antibiotics except aztreonam and KPCs that confer resistance to carbapenems are increasingly being described. CRE are different from other multidrug-resistant microorganisms in that they are susceptible to few (if any) antibacterial agents.

Other modes of antimicrobial resistance exist that complicate management of common hospital-acquired infections. *P. aeruginosa* encodes proteins that function as efflux pumps to eliminate multiple classes of antimicrobials from the cytoplasm or periplasmic space. In addition to these gram-negative pathogens, infections caused by *Enterococcus faecalis* and *E. faecium* are inherently difficult to treat. Isolates of *E. faecalis* are typically susceptible to ampicillin, whereas most *E. faecium* are resistant to ampicillin, with resistance mediated by alterations in either the stoichiometry or sequence of a specific penicillin binding protein (PBP). These organisms may cause urinary tract infection (UTI) or infective endocarditis in immunocompetent children and may be responsible for a variety of syndromes in immunocompromised patients, especially in the setting of prolonged intensive care. The emergence of infections caused by **vancomycin-resistant enterococcus (VRE)** has further complicated antimicrobial selection in high-risk patients and has necessitated the development of newer antimicrobials that target these highly resistant gram-positive bacteria.

Infections Associated with Medical Devices

A special situation affecting antibiotic use is the presence of an indwelling medical device, such as a venous catheter, ventriculoperitoneal shunt, stent, or other catheter (see Chapter 224). In addition to *S. aureus,* coagulase-negative staphylococci are a major consideration. Coagulase-negative staphylococci seldom cause serious disease in the absence of risk factors such as indwelling catheters. Empirical antibiotic regimens must take this risk into consideration. In addition to appropriate antibiotic therapy, removal or replacement of the colonized prosthetic material is usually required for cure.

ANTIBIOTICS, INCLUDING NEWER AGENTS AND THERAPIES COMMONLY USED IN PEDIATRIC PRACTICE

Table 225.3 lists selected antibiotic medications, including recently licensed agents. Not all agents have formal pediatric indications, but dosage considerations for infants and children are provided, as available.

Penicillins

Although there has been ever-increasing emergence of resistance to penicillins, these agents remain valuable and are commonly used for management of many pediatric infectious diseases.

Penicillins remain the drugs of choice for pediatric infections caused by group A and group B streptococci, *Treponema pallidum* (syphilis), *L. monocytogenes,* and *N. meningitidis.* The **semisynthetic penicillins** (nafcillin, cloxacillin, dicloxacillin) are useful for management of susceptible (non-MRSA) staphylococcal infections. The **aminopenicillins** (ampicillin, amoxicillin) were developed to provide broad-spectrum activity against gram-negative organisms, including *E. coli* and *H. influenzae,* but the emergence of resistance (typically mediated by a β-lactamase) has limited their utility in many clinical settings. The **carboxypenicillins** (ticarcillin) and **ureidopenicillins** (piperacillin, mezlocillin, azlocillin) also have bactericidal activity against most strains of *P. aeruginosa.*

Resistance to penicillin is mediated by a variety of mechanisms (see Table 225.1). The production of β-lactamase is a common mechanism exhibited by many organisms that may be overcome, with variable success, by including a β-lactamase inhibitor in the therapeutic formulation with the penicillin. Such combination products (ampicillin-sulbactam, amoxicillin-clavulanate, ticarcillin–clavulanic acid [no longer available in the United States], piperacillin-tazobactam) are potentially very useful for management of resistant isolates, but only if the resistance is β-lactamase mediated. Notably, MRSA and *S. pneumoniae* mediate resistance to penicillins through mechanisms other than β-lactamase production, rendering these combination agents of little value for the management of these infections. Cephalosporin (ceftazidime/avibactam, ceftolozane/tazobactam) and carbapenem (meropenem/vaborbactam, and imipenem/relebactam) antibiotics combined with β-lactamase inhibitors have also been recently licensed by the FDA (described later). In addition, the FDA has recently approved a novel β-lactam-β-lactamase inhibitor combination, sulbactam-durlobactam (SUL-DUR), designed specifically for the treatment of carbapenem-resistant *Acinetobacter baumannii* infections, in particular, those associated with hospital-acquired and ventilator-associated pneumonias.

Table 225.4 lists adverse reactions to penicillins.

Cephalosporins

Cephalosporins differ structurally from penicillins insofar as the β-lactam ring exists as a six-member ring, compared with the five-member ring structure of the penicillins. These agents are widely used in pediatric practice, both in oral and parenteral formulations (Table 225.5). The **first-generation cephalosporins** (e.g., cefazolin, a parenteral formulation, and cephalexin, an oral equivalent) are commonly used for management of skin and soft tissue infections caused by susceptible strains of *S. aureus* and group A streptococcus. The **second-generation cephalosporins** (e.g., cefuroxime, cefoxitin) have better activity against gram-negative bacterial infections than first-generation cephalosporins and are used to treat respiratory tract infections, UTIs, and skin and soft tissue infections. A variety of orally administered second-generation agents (cefaclor, cefprozil, loracarbef, cefpodoxime) are commonly used in the outpatient management of sinopulmonary infections and otitis media. The agents cefoxitin and cefotetan are also referred to as **cephamycins**, because they were originally isolated from actinomycetes (although synthetic versions also have been developed). The **third-generation cephalosporins** (cefotaxime [no longer available], ceftriaxone, and ceftazidime) are typically used for serious pediatric infections, including meningitis and sepsis. Oral third-generation cephalosporins have been developed, including cefixime, ceftibuten, cefdinir, cefpodoxime, and cefditoren. Ceftazidime is highly active against most strains of *P. aeruginosa,* making this a useful agent for febrile, neutropenic oncology patients. The FDA approved the combination of ceftazidime and the novel β-lactamase inhibitor avibactam in 2015. Current indications include complicated intraabdominal infections and UTIs. The combination may also be useful for the treatment of infection caused by KPCs. Pediatric experience is limited. Ceftriaxone should not be mixed or reconstituted with a calcium-containing product, such as Ringer or Hartmann solution or parenteral nutrition containing calcium, because particulate formation can result. Cases of fatal reactions with ceftriaxone-calcium precipitates in the lungs and kidneys in neonates have been reported.

Cefepime is a **fourth-generation cephalosporin** and has activity against *P. aeruginosa* along with good activity against methicillin-susceptible *S. aureus*. Phase 3 studies of two new formulations of cefepime (one combined with a β-lactamase inhibitor, taniborbactam, and the other with a penicillanic acid sulfone β-lactamase inhibitor, enmetazobactam) are ongoing. *Cefpirome* is a fourth-generation cephalosporin with activity against *P. aeruginosa* and methicillin-sensitive *S. aureus* (MSSA) and is licensed for complicated UTIs and ventilator-associated pneumonia in adults, but no data on pediatric use are available. *Ceftizoxime* is a fourth-generation cephalosporin that is no longer in use in the United States. *Cefiderocol* is a novel cephalosporin that is classified as a *siderophore* antibiotic and is used for treatment of resistant gram-negative organisms, particularly *P. aeruginosa,* associated with complicated UTIs. It also recently received FDA approval for the treatment of hospital-acquired bacterial pneumonia caused by resistant gram-negative organisms. Its mechanism of action involves binding to iron, followed by active transport into bacterial cells. It was the first siderophore antibiotic to be approved by the FDA. It is approved for ages 18 and older, so pediatric experience is limited. Some classification schemes have classified it as a fourth-generation cephalosporin.

Table 225.3 Selected Antibacterial Medications (Antibiotics)*

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Amikacin sulfate Amikin Injection: 50 mg/mL, 250 mg/mL	**Aminoglycoside antibiotic active against gram-negative bacilli, especially *Escherichia coli, Klebsiella, Proteus, Enterobacter, Serratia,* and *Pseudomonas*** Neonates: Postnatal age ≤7 days, weight 1,200-2,000 g: 7.5 mg/kg q12-18h IV or IM; weight >2,000 g: 10 mg/kg q12h IV or IM; postnatal age >7 days, weight 1,200-2,000 g: 7.5 mg/kg q8-12h IV or IM; weight >2,000 g: 10 mg/kg q8h IV or IM Children: 15-25 mg/kg/24 hr divided q8-12h IV or IM Adults: 15 mg/kg/24 hr divided q8-12h IV or IM	*Cautions:* Anaerobes, *Streptococcus* (including *S. pneumoniae*) are resistant. May cause ototoxicity and nephrotoxicity. Monitor renal function. Drug eliminated renally. Administered IV over 30-60 min. *Drug interactions:* May potentiate other ototoxic and nephrotoxic drugs. *Target serum concentrations:* Peak 25-40 mg/L; trough <10 mg/L.
Amoxicillin Amoxil, Polymox Capsule: 250, 500 mg Tablet: chewable: 125, 250 mg Suspension: 125 mg/5 mL, 250 mg/5 mL Drops: 50 mg/mL	**Penicillinase-susceptible β-lactam: gram-positive pathogens except *Staphylococcus;* susceptible gram-negatives, including *Salmonella, Shigella, Neisseria* species, *E. coli,* and *Proteus mirabilis*** Children: 20-50 mg/kg/24 hr divided q8-12h PO; higher dose of 80-90 mg/kg 24 hr PO for otitis media Adults: 250-500 mg q8-12h PO	*Cautions:* Rash, diarrhea, abdominal cramping. Drug eliminated renally. *Drug interaction:* Probenecid.
Amoxicillin-clavulanate Augmentin Oral Tablet: 250, 500, 875 mg Tablet, chewable: 125, 200, 250, 400 mg Suspension: 125 mg/5 mL, 200 mg/5 mL, 250 mg/5 mL, 400 mg/5 mL	**β-Lactam (amoxicillin) combined with β-lactamase inhibitor (clavulanate) enhances amoxicillin activity against penicillinase-producing bacteria. *S. aureus* (not methicillin-resistant organism), *Streptococcus, Haemophilus influenzae, Moraxella catarrhalis, E. coli, Klebsiella, Bacteroides fragilis*** Neonates: 30 mg/kg/24 hr divided q12h PO Children: 20-45 mg/kg 24 hr divided q8-12h PO; higher dose 80-90 mg/kg/24 hr PO for otitis media	*Cautions:* Drug dosed on amoxicillin component. May cause diarrhea, rash. Drug eliminated renally. *Drug interaction:* Probenecid. *Comment:* Higher dose may be active against penicillin-tolerant/resistant *S. pneumoniae.*
Ampicillin Polycillin, Omnipen Capsule: 250, 500 mg Suspension: 125 mg/5 mL, 250 mg/5 mL, 500 mg/5 mL Injection Oral	**β-Lactam with same spectrum of antibacterial activity as amoxicillin** Neonates: Postnatal age ≤7 days weight ≤2,000 g: 50 mg/kg/24 hr IV or IM q12h (meningitis: 100 mg/kg/24 hr divided q12h IV or IM); weight >2,000 g: 75 mg/kg/24 hr divided q8h IV or IM (meningitis: 150 mg/kg/24 hr divided q8h IV or IM). Postnatal age >7 days weight <1,200 g: 50 mg/kg/24 hr IV or IM q12h (meningitis: 100 mg/kg/24 hr divided q12h IV or IM); weight 1,200-2,000 g: 75 mg/kg/24 hr divided q8h IV or IM (meningitis: 150 mg/kg/24 hr divided q8hr IV or IM); weight >2,000 g: 100 mg/kg/24 hr divided q6h IV or IM (meningitis: 200 mg/kg/24 hr divided q6h IV or IM) Children: 100-200 mg/kg/24 hr divided q6h IV or IM (meningitis: 200-400 mg/kg/24 hr divided q4-6h IV or IM) Adults: 250-500 mg q4-8h IV or IM	*Cautions:* Less bioavailable than amoxicillin, causing greater diarrhea. *Drug interaction:* Probenecid.
Ampicillin-sulbactam Unasyn Injection	**β-Lactam (ampicillin) and β-lactamase inhibitor (sulbactam) enhances ampicillin activity against penicillinase-producing bacteria: *S. aureus, H. influenzae, M. catarrhalis, E. coli, Klebsiella, B. fragilis*** Children: 100-200 mg/kg/24 hr divided q4-8h IV or IM Adults: 1-2 g q6-8h IV or IM (max daily dose: 8 g)	*Cautions:* Drug dosed on ampicillin component. May cause diarrhea, rash. Drug eliminated renally. *Note:* Higher dose may be active against penicillin-tolerant/resistant *S. pneumoniae.* *Drug interaction:* Probenecid.
Azithromycin Zithromax Tablet: 250 mg Suspension: 100 mg/5 mL, 200 mg/5 mL	**Azalide antibiotic with activity against *S. aureus, Streptococcus, H. influenzae, Mycoplasma, Legionella, Chlamydia trachomatis, Babesia microti*** Children: 10 mg/kg PO on day 1 (max dose: 500 mg) followed by 5 mg/kg PO q24h for 4 days Group A streptococcus pharyngitis: 12 mg/kg/24 hr PO (max dose: 500 mg) for 5 days Adults: 500 mg PO on day 1, followed by 250 mg for 4 days Uncomplicated *C. trachomatis* infection: single 1 g dose PO	*Note:* Very long half-life permitting once-daily dosing. No metabolic-based drug interactions (unlike erythromycin and clarithromycin), limited GI distress. Shorter-course regimens (e.g., 1-3 days) under investigation. For a 3-day course of therapy, use dose of (10 mg/kg/24 hr × 3 days); single-dose therapy, 30 mg/kg (not for streptococcal pharyngitis).
Aztreonam Azactam Injection	**β-Lactam (monobactam) antibiotic with activity against gram-negative aerobic bacteria, Enterobacteriaceae, and *Pseudomonas aeruginosa*** Neonates: Postnatal age ≤7 days weight ≤2,000 g: 60 mg/kg/24 hr divided q12h IV or IM; weight >2,000 g: 90 mg/kg/24 hr divided q8h IV or IM; postnatal age >7 days weight <1,200 g: 60 mg/kg/24 hr divided q12h IV or IM; weight 1,200-2,000 g: 90 mg/kg/24 hr divided q8h IV or IM; weight >2,000 g: 120 mg/kg/24 hr divided q6-8h IV or IM Children: 90-120 mg/kg/24 hr divided q6-8h IV or IM. For cystic fibrosis, up to 200 mg/kg/24 hr IV Adults: 1-2 g IV or IM q8-12h (max dose: 8 g/24 hr)	*Cautions:* Rash, thrombophlebitis, eosinophilia. Renally eliminated. *Drug interaction:* Probenecid.

Continued

Table 225.3 Selected Antibacterial Medications (Antibiotics)*—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Cefadroxil Generic Capsule: 500 mg Tablet: 1,000 mg Suspension: 125 mg/5 mL, 250 mg/5 mL, 500 mg/5 mL	First-generation cephalosporin active against *S. aureus, Streptococcus, E. coli, Klebsiella*, and *Proteus* Children: 30 mg/kg/24 hr divided q12h PO (max dose: 2 g) Adults: 250-500 mg q8-12h PO	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Long half-life permits q12-24h dosing. *Drug interaction:* Probenecid.
Cefazolin Ancef, Kefzol Injection	First-generation cephalosporin active against *S. aureus, Streptococcus, E. coli, Klebsiella*, and *Proteus* Neonates: Postnatal age ≤7 days 40 mg/kg/24 hr divided q12h IV or IM; >7 days 40-60 mg/kg/24 hr divided q8h IV or IM Children: 50-100 mg/kg/24 hr divided q8h IV or IM Adults: 0.5-2g q8h IV or IM (max dose: 12 g/24 hr)	*Caution:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Does not adequately penetrate CNS. *Drug interaction:* Probenecid.
Cefdinir Omnicef Capsule: 300 mg Oral suspension: 125 mg/5 mL	Extended-spectrum, semisynthetic cephalosporin Children 6 mo-12 yr: 14 mg/kg/24 hr in 1 or 2 doses PO (max dose: 600 mg/24 hr) Adults: 600 mg q24h PO	*Cautions:* Reduce dosage in renal insufficiency (creatinine clearance <60 mL/min). Avoid taking concurrently with iron-containing products and antacids because absorption is markedly decreased; take at least 2 hr apart. *Drug interaction:* Probenecid.
Cefepime Maxipime Injection	Expanded-spectrum, fourth-generation cephalosporin active against many gram-positive and gram-negative pathogens, including *P. aeruginosa* and many multidrug-resistant pathogens Children: 100-150 mg/kg/24 hr q8-12h IV or IM Adults: 2-4 g/24 hr q12h IV or IM	*Adverse events:* Diarrhea, nausea, vaginal candidiasis. Cautions: β-lactam safety profile (rash, eosinophilia). Renally eliminated. *Drug interaction:* Probenecid.
Cefiderocol Fetroja Injection 1 g vials	Expanded-spectrum, classified in some classifications as a fourth-generation cephalosporin; novel siderophore antibiotic; mechanism of action is mediated by binding to iron, followed by active transport into bacterial cells Indicated for treatment of complicated urinary tract infections, including pyelonephritis, caused by susceptible gram-negative microorganisms and for hospital-acquired and ventilator-associated pneumonia Adults: 2 g IV q8hr for 7-14 days Children: dose not established	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Not indicated for meningitis (in contrast with cefepime).
Cefixime Suprax Oral Tablet: 200, 400 mg Suspension: 100 mg/5 mL	Third-generation cephalosporin active against streptococci, *H. influenzae, M. catarrhalis, Neisseria gonorrhoeae, Serratia marcescens*, and *Proteus vulgaris* No antistaphylococcal or antipseudomonal activity Children: 8 mg/kg/24 hr divided q12-24h PO Adults: 400 mg/24 hr divided q12-24h PO	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Does not adequately penetrate CNS. *Drug interaction:* Probenecid.
Cefoperazone sodium Cefobid Injection	Third-generation cephalosporin active against many gram-positive and gram-negative pathogens Neonates: 100 mg/kg/24 hr divided q12h IV or IM Children: 100-150 mg/kg/24 hr divided q8-12h IV or IM Adults: 2-4 g/24 hr divided q8-12h IV or IM (max dose: 12 g/24 hr)	*Cautions:* Highly protein-bound cephalosporin with limited potency reflected by weak antipseudomonal activity. Variable gram-positive activity. Primarily hepatically eliminated in bile. *Drug interaction:* Disulfiram-like reaction with alcohol.
Cefotaxime sodium Claforan Injection	Third-generation cephalosporin active against gram-positive and gram-negative pathogens. No antipseudomonal activity Neonates: ≤7 days: 100 mg/kg/24 hr divided q12h IV or IM; >7 days: weight <1,200 g 100 mg/kg/24 hr divided q12h IV or IM; weight >1,200 g: 150 mg/kg/24 hr divided q8h IV or IM Children: 150 mg/kg/24 hr divided q6-8h IV or IM (meningitis: 200 mg/kg/24 hr divided q6-8h IV) Adults: 1-2 g q8-12h IV or IM (max dose: 12 g/24 hr)	
Cefotetan disodium Cefotan Injection	Second-generation cephalosporin active against *S. aureus, Streptococcus, H. influenzae, E. coli, Klebsiella, Proteus*, and *Bacteroides*. Inactive against *Enterobacter* Children: 40-80 mg/kg/24 hr divided q12h IV or IM Adults: 2-4 g/24 hr divided q12h IV or IM (max dose: 6 g/24 hr)	*Cautions:* Highly protein-bound cephalosporin, poor CNS penetration; β-lactam safety profile (rash, eosinophilia), disulfiram-like reaction with alcohol. Renally eliminated (~20% in bile).

Table 225.3 Selected Antibacterial Medications (Antibiotics)*—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Cefoxitin sodium Mefoxin Injection	**Second-generation cephalosporin active against *S. aureus, Streptococcus, H. influenzae, E. coli, Klebsiella, Proteus*, and *Bacteroides*. Inactive against *Enterobacter*** Neonates: 70-100 mg/kg/24 hr divided q8-12h IV or IM Children: 80-160 mg/kg/24 hr divided q6-8h IV or IM Adults: 1-2 g q6-8h IV or IM (max dose: 12 g/24 hr)	*Cautions:* Poor CNS penetration; β-lactam safety profile (rash, eosinophilia). Renally eliminated. Painful given intramuscularly. *Drug interaction:* Probenecid.
Cefpirome Cefrom Keiten Broact Cefir	**Fourth-generation cephalosporin; indicated for complicated urinary tract infections, including pyelonephritis, caused by susceptible gram-negative microorganisms; indicated for hospital-acquired and ventilator-associated pneumonia** Adults: 2 g IV q 8hr for 7-14 days Children: Dose not established	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Not indicated for meningitis (in contrast with cefepime).
Cefpodoxime proxetil Vantin Tablet: 100 mg, 200 mg Suspension: 50 mg/5 mL, 100 mg/5 mL	**Third-generation cephalosporin active against *S. aureus, Streptococcus, H. influenzae, M. catarrhalis, N. gonorrhoeae, E. coli, Klebsiella*, and *Proteus*** **No antipseudomonal activity** Children: 10 mg/kg/24 hr divided q12h PO Adults: 200-800 mg/24 hr divided q12h PO (max dose: 800 mg/24 hr) Uncomplicated gonorrhea: 200 mg PO as single-dose therapy	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Does not adequately penetrate CNS. Increased bioavailability when taken with food. *Drug interaction:* Probenecid; antacids and H_2 receptor antagonists may decrease absorption.
Cefprozil Cefzil Tablet: 250, 500 mg Suspension: 125 mg/5 mL, 250 mg/5 mL	**Second-generation cephalosporin active against *S. aureus, Streptococcus, H. influenzae, E. coli, M. catarrhalis, Klebsiella*, and *Proteus* spp.** Children: 30 mg/kg/24 hr divided q8-12h PO Adults: 500-1,000 mg/24 hr divided q12h PO (max dose: 1.5 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Good bioavailability; food does not affect bioavailability. *Drug interaction:* Probenecid.
Ceftaroline fosamil Teflaro Injection 400 mg/vial (20 mg/mL reconstituted) 600 mg/vial (30 mg/mL reconstituted)	**Fifth-generation cephalosporin active against *S. aureus* (including MRSA when used for skin and soft tissue infection), *S. pyogenes, S. agalactiae, E. coli, K. pneumoniae, H. influenzae,* and *K. oxytoca*** Children: skin/skin structure infections *or* community-acquired pneumonia, 24 mg/kg/24 hr divided q8h IV (2-23 mo old) ×5-14 days; 36 mg/kg/24 hr divided q8h IV (weight ≤33 kg) ×5-14 days; 400 mg q8h IV (weight >33 kg) Adults: 600 mg q12h IV	*Caution:* β-Lactam safety profile (rash, eosinophilia). *Drug interaction:* Probenecid.
Ceftazidime Fortaz, Ceptaz, Tazicef, Tazidime Injection	**Third-generation cephalosporin active against gram-positive and gram-negative pathogens, including *P. aeruginosa*** Neonates: Postnatal age ≤7 days: 100 mg/kg/24 hr divided q12h IV or IM; >7 days weight ≤1,200 g: 100 mg/kg/24 hr divided q12h IV or IM; weight >1,200 g: 150 mg/kg/24 hr divided q8h IV or IM Children: 150 mg/kg/24 hr divided q8h IV or IM (meningitis: 150 mg/kg/24 hr IV divided q8h) Adults: 1-2 g q8-12h IV or IM (max dose: 8-12 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Increasing pathogen resistance developing with long-term, widespread use. *Drug interaction:* Probenecid.
Ceftazidime/avibactam Avycaz Injection (2 g/0.5 g)/vial: 2.5 g Equivalent to 2.635 g of ceftazidime and 0.551 g of avibactam sodium	**Third-generation cephalosporin active against gram-positive and gram-negative pathogens, including *P. aeruginosa;* addition of β-lactamase; inhibits *K. pneumoniae* carbapenemases and AmpC-type β-lactamases that are resistant to β-lactamases, tazobactam, and clavulanic acid** **Useful for complicated intraabdominal infections, urinary tract infections, and pneumonia** Adults: 2.5 g (2 g/0.5 g) IV q8h infused over 2 hr for 7-14 days Children: 3 mo to <2 yr: 62.5 mg/kg (ceftazidime 50 mg/kg and avibactam 12.5 mg/kg) IV q8h for 5-14 days 2 yr to <18 yr: 62.5 mg/kg (ceftazidime 50 mg/kg and avibactam 12.5 mg/kg) IV q8h for 5-14 days; not to exceed 2.5 g (ceftazidime 2 g and avibactam 0.5 g)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Increasing pathogen resistance developing with long-term, widespread use. *Drug interaction:* Probenecid.

Continued

Table 225.3 Selected Antibacterial Medications (Antibiotics)*—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Ceftolozane/tazobactam Zerbaxa Injection	**Fifth-generation cephalosporin (with β-lactamase inhibitor) indicated for complicated intraabdominal infections; acute pyelonephritis; complicated urinary tract infections; hospital-acquired and ventilator-associated bacterial pneumonia** Adults: Community-acquired pneumonia, skin and soft tissue infections 600 mg IV q12 h ×5-7 days Children: Birth to <2 mo: 6 mg/kg IV q8h ×5-14 days 2 mo to <2 yr: 8 mg/kg IV q8h ×5-14 days 2 yr to <18 yr (≤33 kg): 12 mg/kg IV q8h ×5-14 days 2 yr to <18 yr (>33 kg): 400 mg q8h OR 600 mg q12h IV ×5-14 days	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. *Drug interaction:* Probenecid.
Ceftriaxone sodium Rocephin Injection	**Third-generation cephalosporin widely active against gram-positive and gram-negative pathogens** **No antipseudomonal activity** Neonates: 50-75 mg/kg q24h IV or IM Children: 50-75 mg/kg q24h IV or IM (meningitis: 75 mg/kg dose once then 80-100 mg/kg/24 hr divided q12-24h IV or IM) Adults: 1-2 g q24h IV or IM (max dose: 4 g/24 hr) Gonorrhea: 500 mg IM, single dose	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Eliminated via kidney (33–65%) and bile; can cause sludging. Long half-life and dose-dependent protein binding favors q24h rather than q12h dosing. Can add 1% lidocaine for IM injection. *Drug interaction:* Probenecid. In neonates, co-administration with calcium-containing products can result in severe precipitation and attendant embolic complications.
Cefuroxime (cefuroxime axetil for oral administration) Ceftin, Kefurox, Zinacef Injection Suspension: 125 mg/5 mL Tablet: 125, 250, 500 mg	**Second-generation cephalosporin active against *S. aureus, Streptococcus, H. influenzae, E. coli, M. catarrhalis, Klebsiella,* and *Proteus*** Neonates: 40-100 mg/kg/24 hr divided q12h IV or IM Children: 200-240 mg/kg/24 hr divided q8h IV or IM; PO administration: 20-30 mg/kg/24 hr divided q8-12h PO Adults: 750-1,500 mg q8h IV or IM (max dose: 6 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Food increases PO bioavailability. *Drug interaction:* Probenecid.
Cephalexin Keflex, Keftab Capsule: 250, 500 mg Tablet: 500 mg, 1 g Suspension: 125 mg/5 mL, 250 mg/5 mL, 100 mg/mL drops	**First-generation cephalosporin active against *S. aureus, Streptococcus, E. coli, Klebsiella,* and *Proteus*** Children: 25-100 mg/kg/24 hr divided q6-8h PO Adults: 250-500 mg q6h PO (max dose: 4 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. *Drug interaction:* Probenecid.
Cephradine Velosef Capsule: 250, 500 mg Suspension: 125 mg/5 mL, 250 mg/5 mL	**First-generation cephalosporin active against *S. aureus, Streptococcus, E. coli, Klebsiella,* and *Proteus*** Children: 50-100 mg/kg/24 hr divided q6-12h PO Adults: 250-500 mg q6-12h PO (max dose: 4 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. *Drug interaction:* Probenecid.
Ciprofloxacin Cipro Tablet: 100, 250, 500, 750 mg Injection Ophthalmic solution and ointment Otic suspension Oral suspension: 250 and 500 mg/5 mL	**Quinolone antibiotic active against *P. aeruginosa, Serratia, Enterobacter, Shigella, Salmonella, Campylobacter, N. gonorrhoeae, H. influenzae, M. catarrhalis,* some *S. aureus,* and some *Streptococcus*** Neonates: 10 mg/kg q12h PO or IV Children: 15-30 mg/kg/24 hr divided q12h PO or IV; cystic fibrosis: 20-40 mg/kg/24 hr divided q8-12h PO or IV Adults: 250-750 mg q12h; 200-400 mg IV q12h PO (max dose: 1.5 g/24 hr)	*Cautions:* Concerns of joint destruction in juvenile animals but not seen in humans; tendonitis, superinfection, dizziness, confusion, crystalluria, some photosensitivity. *Drug interactions:* Theophylline; magnesium-, aluminum-, or calcium-containing antacids; sucralfate; probenecid; warfarin; cyclosporine.
Clarithromycin Biaxin Tablet: 250, 500 mg Suspension: 125 mg/5 mL, 250 mg/5 mL	**Macrolide antibiotic with activity against *S. aureus, Streptococcus, H. influenzae, Legionella, Mycoplasma,* and *C. trachomatis*** Children: 15 mg/kg/24 hr divided q12h PO Adults: 250-500 mg q12h PO (max dose: 1 g/24 hr)	*Cautions:* Adverse events less than erythromycin; GI upset, dyspepsia, nausea, cramping. *Drug interactions:* Same as erythromycin: astemizole, carbamazepine, terfenadine, cyclosporine, theophylline, digoxin, tacrolimus.
Clindamycin Cleocin Capsule: 75, 150, 300 mg Suspension: 75 mg/5 mL Injection Topical solution, lotion, and gel Vaginal cream	**Protein synthesis inhibitor active against most gram-positive aerobic and anaerobic cocci except *Enterococcus*** Neonates: Postnatal age ≤7 days weight <2,000 g; 10 mg/kg/24 hr divided q12h IV or IM; weight >2,000 g: 15 mg/kg/24 hr divided q8h IV or IM; >7 days weight <1,200 g: 10 mg/kg/24 hr IV or IM divided q12h; weight 1,200-2,000 g: 15 mg/kg/24 hr divided q8h IV or IM; weight >2,000 g: 20 mg/kg/24 hr divided q8h IV or IM Children: 10-40 mg/kg/24 hr divided q6-8h IV, IM, or PO Adults: 150-600 mg q6-8h IV, IM, or PO (max dose: 5 g/24 hr IV or IM or 2 g/24 hr PO)	*Cautions:* Diarrhea, nausea, *Clostridium difficile*–associated colitis, rash. Administer slow IV over 30-60 min. Topically active as an acne treatment.

Table 225.3 Selected Antibacterial Medications (Antibiotics)*—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Cloxacillin sodium Tegopen Capsule: 250, 500 mg Suspension: 125 mg/5 mL	**Penicillinase-resistant penicillin active against *S. aureus* and other gram-positive cocci except *Enterococcus* and coagulase-negative staphylococci** Children: 50-100 mg/kg/24 hr divided q6h PO Adults: 250-500 mg q6h PO (max dose: 4 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Primarily hepatically eliminated; requires dose reduction in renal disease. Food decreases bioavailability. *Drug interaction:* Probenecid.
Colistin (colistimethate sodium; polymyxin E) Injection Inhalation	**Treatment of multidrug-resistant gram-negative organisms (*Enterobacteriaceae* including extended-spectrum β-lactamase– and carbapenemase-producing strains)** Children: 2.5-5 mg/kg/day divided in 2-4 divided doses IV Adults: 300 mg/day in 2-4 divided doses IV	*Cautions:* Nephrotoxicity (~3% in young children; higher rates in adolescents and adults); adjust dose for renal insufficiency; neurotoxicity (headaches, paresthesia, ataxia). *Drug interactions:* Should not be administered concomitantly with polymyxins or aminoglycosides.
Co-trimoxazole (trimethoprim-sulfamethoxazole; TMP-SMX) Bactrim, Cotrim, Septra, Sulfatrim Tablet: SMX 400 mg and TMP 80 mg Tablet DS: SMX 800 mg and TMP 160 mg Suspension: SMX 200 mg and TMP 40 mg/5 mL Injection	**Antibiotic combination with sequential antagonism of bacterial folate synthesis with broad antibacterial activity: *Shigella, Legionella, Nocardia, Chlamydia, Pneumocystis jiroveci*** **Dosage based on TMP component** Children: 6-20 mg TMP/kg/24 hr or IV divided q12h PO *Pneumocystis carinii* pneumonia: 15-20 mg TMP/kg/24 hr divided q12h PO or IV *P. carinii* prophylaxis: 5 mg TMP/kg/24 hr or 3 times/wk PO Adults: 160 mg TMP q12h PO	*Cautions:* Drug dosed on TMP (trimethoprim) component. Sulfonamide skin reactions: rash, erythema multiforme, Stevens-Johnson syndrome, nausea, leukopenia. Renal and hepatic elimination; reduce dose in renal failure. *Drug interactions:* Protein displacement with warfarin, possibly phenytoin, cyclosporine.
Dalbavancin Dalvance 500 mg/vial (20 mg/mL after reconstitution) Injection	**Glycopeptide antibiotic; bacteriocidal; disrupts cell wall synthesis** Indicated for acute bacterial skin and skin structure infections caused by susceptible gram-positive bacteria; active against MRSA Adult dose: 1-dose regimen of 1,500 mg IV or 2-dose regimen of 1000 mg IV followed 1 wk later by 500 mg IV; infuse IV over 30 min Pediatric dose: Not approved for use in children	Rapid IV infusion, as with other glycopeptide antibacterial agents, can cause reactions, including upper body flushing, urticaria, pruritus, back pain, and rash; stopping or slowing infusion may result in cessation of these reactions.
Daptomycin Cubicin Injection	**Disrupts bacterial cell membrane function, causing depolarization leading to inhibition of protein, DNA, and RNA synthesis, which results in bacterial cell death** **Active against enterococci (including glycopeptide-resistant strains), staphylococci (including MRSA), streptococci, and corynebacteria. Approved for skin and soft tissue infections** **Acceptable for bacteremia and right-sided endocarditis with susceptible strains** Adults: In skin and soft tissue infections, 4 mg/kg daptomycin IV once daily. For *S. aureus* bacteremia or right-sided endocarditis, 6 mg/kg IV once daily Children: For skin/skin structure infections, 12-23 mo, 10 mg/kg IV q24h; 2-6 yr, 9 mg/kg IV q24h; 7-11 yr, 7 mg/kg q24h; 12-17 yr, 5 mg/kg q24h, all for up to 14 days. For staphylococcal bacteremia, 1-6 yr, 12 mg/kg q24h; 7-11 yr, 9 mg/kg q24h; 12-17 yr, 7 mg/kg q24h; all for up to 42 days. For staphylococcal endocarditis, 1-5 yr, 10 mg/kg IV q24h for at least 6 wk; ≥6 yr, 6 mg/kg IV q24h for at least 6 wk	*Cautions:* Should not be used for pneumonia because drug inactivated by surfactants. Associated with rash, renal failure, anemia, and headache. Is reported to cause myopathy, rhabdomyolysis, and eosinophilic pneumonia. *Drug interactions:* Should not be administered with statins.
Delafloxacin Baxdela Injection Oral Injection, lyophilized powder for reconstitution 300 mg/vial (equivalent to 433 mg delafloxacin meglumine) Tablet, 450 mg (equivalent to 649 mg delafloxacin meglumine)	**Fluoroquinolone class of drugs; active against MSSA, MRSA, CoNS, and streptococci; retains activity against fluoroquinolone-resistant *S. aureus* strains.** **Approved for skin and soft tissue infections and community-acquired pneumonia.** Adults: 300 mg IV q12h for 5-14 days OR 300 mg IV q12h, then switch to a 450-mg tablet PO q12h for 5-14 days OR 450 mg PO q12h for 5-14 days Children: No dosage established	Similar to ciprofloxacin.

Continued

Table 225.3 Selected Antibacterial Medications (Antibiotics)*—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Demeclocycline Declomycin Tablet: 150, 300 mg Capsule: 150 mg	**Tetracycline active against most gram-positive cocci except *Enterococcus*, many gram-negative bacilli, anaerobes, *Borrelia burgdorferi* (Lyme disease), *Mycoplasma*, and *Chlamydia*** Children: 8-12 mg/kg/24 hr divided q6-12h PO Adults: 150 mg PO q6-8h Syndrome of inappropriate antidiuretic hormone secretion: 900-1,200 mg/24 hr or 13-15 mg/kg/24 hr divided q6-8h PO with dose reduction based on response to 600-900 mg/24 hr	*Cautions:* Teeth staining, possibly permanent (if administered <8 yr old) with prolonged use; photosensitivity, diabetes insipidus, nausea, vomiting, diarrhea, superinfections. *Drug interactions:* Aluminum-, calcium-, magnesium-, zinc- and iron-containing food, milk, dairy products may decrease absorption.
Dicloxacillin Dynapen, Pathocil Capsule: 125, 250, 500 mg Suspension: 62.5 mg/5 mL	**Penicillinase-resistant penicillin active against *S. aureus* and other gram-positive cocci except *Enterococcus* and coagulase-negative staphylococci** Children: 12.5-100 mg/kg/24 hr divided q6h PO Adults: 125-500 mg q6h PO	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Primarily renal (65%) and biliary (30%) elimination. Food may decrease bioavailability. *Drug interaction:* Probenecid.
Doripenem Doribax Injection	**Carbapenem antibiotic with broad-spectrum activity against gram-positive cocci and gram-negative bacilli, including *P. aeruginosa* and anaerobes** Children: dose unknown Adults: 500 mg q8h IV	*Cautions:* β-Lactam safety profile; does not undergo hepatic metabolism. Renal elimination (70–75%); dose adjustment for renal failure. *Drug interactions:* Valproic acid, probenecid.
Doxycycline Vibramycin, Doxy Injection Capsule: 50, 100 mg Tablet: 50, 100 mg Suspension: 25 mg/5 mL Syrup: 50 mg/5 mL	**Tetracycline antibiotic active against most gram-positive cocci except *Enterococcus*, many gram-negative bacilli, anaerobes, *B. burgdorferi* (Lyme disease), *Mycoplasma*, and *Chlamydia*** Children: 2-5 mg/kg/24 hr divided q12-24h PO or IV (max dose: 200 mg/24 hr) Adults: 100-200 mg/24 hr divided q12-24h PO or IV	*Cautions:* Teeth staining, possibly permanent (<8 yr old) with prolonged use; photosensitivity, nausea, vomiting, diarrhea, superinfections. *Drug interactions:* Aluminum-, calcium-, magnesium-, zinc-, iron-, kaolin-, and pectin-containing products, food, milk, dairy products may decrease absorption. Carbamazepine, rifampin, and barbiturates may decrease half-life.
Eravacycline Xerava 50 mg single-dose vials	**Tetracycline-class antibiotic (glycylcycline) active against Enterobacteriaceae, including extended spectrum β-lactamase producers; streptococci (including VRE); staphylococci (including MRSA); and CRE** Indicated for treatment of complicated intraabdominal infections in adults Dose: 1 mg/kg IV q12h ×4-14 days; infuse IV over ~60 min	Contraindications similar to other tetracyclines, including photosensitivity; pseudotumor cerebri; concerns for discoloration of tooth enamel in children under 8 yr of age.
Erythromycin E-Mycin, Ery-Tab, Eryc, Ilosone Estolate 125, 500 mg Tablet EES: 200 mg Tablet base: 250, 333, 500 mg Suspension: estolate 125 mg/5 mL, 250 mg/5 mL, EES 200 mg/5 mL, 400 mg/5 mL Estolate drops: 100 mg/mL; EES drops: 100 mg/2.5 mL Available in combination with sulfisoxazole (Pediazole), dosed on erythromycin content	**Bacteriostatic macrolide antibiotic most active against gram-positive organisms, *Corynebacterium diphtheriae*, and *Mycoplasma pneumoniae*** Neonates: Postnatal age ≤7 days: 20 mg/kg/24 hr divided q12h PO; >7 days weight <1,200 g: 20 mg/kg/24 hr divided q12h PO; weight >1,200 g: 30 mg/kg/24 hr divided q8h PO (give as 5 mg/kg/dose q6h to improve feeding intolerance) Children: Usual max dose: 2 g/24 hr Base: 30-50 mg/kg/24 hr divided q6-8h PO Estolate: 30-50 mg/kg/24 hr divided q8-12h PO Stearate: 20-40 mg/kg/24 hr divided q6h PO Lactobionate: 20-40 mg/kg/24 hr divided q6-8h IV Gluceptate: 20-50 mg/kg/24 hr divided q6h IV; usual max dose: 4 g/24 hr IV Adults: Base: 333 mg PO q8h; estolate/stearate/base: 250-500 mg q6h PO	*Cautions:* Motilin agonist leading to marked abdominal cramping, nausea, vomiting, and diarrhea. Associated with hypertrophic pyloric stenosis in young infants. Many different salts with questionable tempering of GI adverse events. Rare cardiac toxicity with IV use. Dose of salts differs. Topical formulation for treatment of acne. *Drug interactions:* Antagonizes hepatic CYP 3A4 activity: astemizole, carbamazepine, terfenadine, cyclosporine, theophylline, digoxin, tacrolimus.
Gentamicin Garamycin Injection Ophthalmic solution, ointment, topical cream	**Aminoglycoside antibiotic active against gram-negative bacilli, especially *E. coli, Klebsiella, Proteus, Enterobacter, Serratia,* and *Pseudomonas*** Neonates: Postnatal age ≤7 days weight 1,200-2,000 g: 2.5 mg/kg q12-18h IV or IM; weight <2,000 g: 2.5 mg/kg q12h IV or IM; postnatal age >7 days weight 1,200-2,000 g: 2.5 mg/kg q8-12h IV or IM; weight >2,000 g: 2.5 mg/kg q8h IV or IM Children: 2.5 mg/kg/24 hr divided q8-12h IV or IM; alternatively, may administer 5-7.5 mg/kg/24 hr IV once daily Intrathecal: Preservative-free preparation for intraventricular or intrathecal use: neonate: 1 mg/24 hr; children: 1-2 mg/24 hr intrathecal; adults: 4-8 mg/24 hr Adults: 3-6 mg/kg/24 hr divided q8h IV or IM	*Cautions:* Anaerobes, *S. pneumoniae,* and other *Streptococcus* are resistant. May cause ototoxicity and nephrotoxicity. Monitor renal function. Drug eliminated renally. Administered IV over 30-60 min. *Drug interactions:* May potentiate other ototoxic and nephrotoxic drugs. *Target serum concentrations:* Peak 6-12 mg/L; trough >2 mg/L with intermittent daily dose regimens only.

Table 225.3 Selected Antibacterial Medications (Antibiotics)*—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Imipenem-cilastatin Primaxin Injection	**Carbapenem antibiotic with broad-spectrum activity against gram-positive cocci and gram-negative bacilli, including *P. aeruginosa* and anaerobes. No activity against *Stenotrophomonas maltophilia*** Neonates: Postnatal age ≤7 days weight <1,200 g: 20 mg/kg q18-24h IV or IM; weight >1,200 g: 40 mg/kg divided q12h IV or IM; postnatal age >7 days weight 1,200-2,000 g: 40 mg/kg q12h IV or IM; weight >2,000 g: 60 mg/kg q8h IV or IM Children: 60-100 mg/kg/24 hr divided q6-8h IV or IM Adults: 2-4 g/24 hr divided q6-8h IV or IM (max dose: 4 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia), nausea, seizures. Cilastatin possesses no antibacterial activity; reduces renal imipenem metabolism. Primarily renally eliminated. *Drug interaction:* Possibly ganciclovir.
Imipenem/relebactam (imipenem/cilastatin/relebactam) Recarbrio 500 mg/500 mg/250 mg per vial (i.e., 1.25 g/vial)	**Carbapenem antibiotic similar to imipenem/cilastatin; addition of relebactam restores activity against *K. pneumoniae* isolates that encode KPCs; is indicated for treatment of complicated urinary tract infections and complicated intraabdominal infections and hospital-acquired/ventilator-associated bacterial pneumonia in adults 18 yr of age and older** Adults: 1.25 g IV q6h ×4-14 days Children: No dosing information available	*Cautions:* β-Lactam safety profile (rash, eosinophilia), nausea, seizures. Cilastatin possesses no antibacterial activity; reduces renal imipenem metabolism. Primarily renally eliminated.
Linezolid Zyvox Tablet: 400, 600 mg Oral suspension: 100 mg/5 mL Injection: 100 mg/5 mL	**Oxazolidinone antibiotic active against gram-positive cocci (especially drug-resistant organisms), including *Staphylococcus, Streptococcus, E. faecium,* and *Enterococcus faecalis*. Interferes with protein synthesis by binding to 50S ribosome subunit** Children: 10 mg/kg q12h IV or PO Adults: Pneumonia: 600 mg q12h IV or PO; skin infections: 400 mg q12h IV or PO	*Adverse events:* Myelosuppression, pseudomembranous colitis, nausea, diarrhea, headache, peripheral and optic neuropathy. *Drug interaction:* Probenecid.
Loracarbef Lorabid Generic Capsule: 200 mg Suspension: 100 mg/5 mL, 200 mg/5 mL	**Carbacephem very closely related to cefaclor (second-generation cephalosporin) active against *S. aureus, Streptococcus, H. influenzae, M. catarrhalis, E. coli, Klebsiella,* and *Proteus*** Children: 30 mg/kg/24 hr divided q12h PO (max dose: 2 g) Adults: 200-400 mg q12h PO (max dose: 800 mg/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. *Drug interaction:* Probenecid.
Meropenem Merrem Injection	**Carbapenem antibiotic with broad-spectrum activity against gram-positive cocci and gram-negative bacilli, including *P. aeruginosa* and anaerobes** **No activity against *S. maltophilia*** Children: 60 mg/kg/24 hr divided q8h IV; meningitis: 120 mg/kg/24 hr (max dose: 6 g/24 hr) q8h IV Adults: 1.5-3 g q8h IV	*Cautions:* β-Lactam safety profile; appears to possess less CNS excitation than imipenem; 80% renal elimination. *Drug interaction:* Probenecid.
Meropenem/vaborbactam Vabomere 1 g/1 g vials	**Carbapenem antibiotic with broad-spectrum activity against gram-positive cocci and gram-negative bacilli, including *P. aeruginosa* and anaerobes** **Vaborbactam protects meropenem from degradation by certain serine β-lactamases including *K. pneumoniae* carbapenemases (KPCs); added to enhance activity for complicated urinary tract infections, including pyelonephritis caused by *E. coli, K. pneumoniae,* and *E. cloacae* species complex in adults ≥18 yr** Adults: 4 g (meropenem [2 g]/vaborbactam [2 g]) IV q8h for up to 14 days; infuse over 3 hr.	*Cautions:* β-Lactam safety profile; appears to possess less CNS excitation than imipenem; 80% renal elimination. *Drug interaction:* Probenecid.
Metronidazole Flagyl, Metro I.V., Topical gel, vaginal gel Injection Tablet: 250, 500 mg	**Highly effective in the treatment of infections caused by anaerobes. Oral therapy of *C. difficile* colitis** Neonates: weight <1,200 g: 7.5 mg/kg/48 hr PO or IV; postnatal age ≤7 days weight 1,200-2,000 g: 7.5 mg/kg/24 hr q24h PO or IV; weight 2,000 g: 15 mg/kg/24 hr divided q12h PO or IV; postnatal age <7 days weight 1,200-2,000 g: 15 mg/kg/24 hr divided q12h PO or IV; weight >2,000 g: 30 mg/kg/24 hr divided q12 h PO or IV Children: 30 mg/kg/24 hr divided q6-8h PO or IV Adults: 30 mg/kg/24 hr divided q6h PO or IV (max dose: 4 g/24 hr)	*Cautions:* Dizziness, seizures, metallic taste, nausea, disulfiram-like reaction with alcohol. Administer IV slow over 30-60 min. Adjust dose with hepatic impairment. *Drug interactions:* Carbamazepine, rifampin, phenobarbital may enhance metabolism; may increase levels of warfarin, phenytoin, lithium.
Mezlocillin sodium Mezlin Infection	**Extended-spectrum penicillin active against *E. coli, Enterobacter, Serratia,* and *Bacteroides;* limited antipseudomonal activity** Neonates: Postnatal age ≤7 days: 150 mg/kg/24 hr divided q12h IV; >7 days: 225 mg/kg divided q8h IV Children: 200-300 mg/kg/24 hr divided q4-6h IV; cystic fibrosis 300-450 mg/kg/24 hr IV Adults: 2-4 g/dose q4-6h IV (max dose: 12 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia); painful given intramuscularly; each gram contains 1.8 mEq sodium. Interferes with platelet aggregation with high doses; increases noted in liver function test results. Renally eliminated. Inactivated by β-lactamase enzyme. *Drug interaction:* Probenecid.

Continued

Table 225.3 Selected Antibacterial Medications (Antibiotics)*—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Mupirocin Bactroban Ointment	**Topical antibiotic active against *Staphylococcus* and *Streptococcus*** Topical application: Nasal (eliminate nasal carriage) and to the skin 2-4 times daily	*Caution:* Minimal systemic absorption because drug metabolized within the skin.
Nafcillin sodium Nafcil, Unipen Injection Capsule: 250 mg Tablet: 500 mg	**Penicillinase-resistant penicillin active against *S. aureus* and other gram-positive cocci, except *Enterococcus* and coagulase-negative staphylococci** Neonates: Postnatal age ≤7 days weight 1,200-2,000 g: 50 mg/kg/24 hr divided q12h IV or IM; weight >2,000 g: 75 mg/kg/24 hr divided q8h IV or IM; postnatal age >7 days weight 1,200-2,000 g: 75 mg/kg/24 hr divided q8h; weight >2,000 g: 100 mg/kg/24 hr divided q6-8h IV (meningitis: 200 mg/kg/24 hr divided q6h IV) Children: 100-200 mg/kg/24 hr divided q4-6h IV Adults: 4-12 g/24 hr divided q4-6h IV (max dose: 12 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia), phlebitis; painful given intramuscularly; oral absorption highly variable and erratic (not recommended). *Adverse effect:* Neutropenia.
Nalidixic acid NegGram Tablet: 250, 500, 1,000 mg Suspension: 250 mg/5 mL	**First-generation quinolone effective for short-term treatment of lower UTIs caused by *E. coli, Enterobacter, Klebsiella*, and *Proteus*** Children: 50-55 mg/kg/24 hr divided q6h PO; suppressive therapy: 25-33 mg/kg/24 hr divided q6-8h PO Adults: 1 g q6h PO; suppressive therapy: 500 mg q6h PO	*Cautions:* Vertigo, dizziness, rash. Not for use in systemic infections. *Drug interactions:* Liquid antacids.
Neomycin sulfate Mycifradin Tablet: 500 mg Topical cream, ointment Solution: 125 mg/5 mL	**Aminoglycoside antibiotic used for topical application or orally before surgery to decrease GI flora (nonabsorbable) and hyperammonemia** Infants: 50 mg/kg/24 hr divided q6h PO Children: 50-100 mg/kg/24 hr divided q6-8h PO Adults: 500-2,000 mg/dose q6-8h PO	*Cautions:* In patients with renal dysfunction because small amount absorbed may accumulate. *Adverse events:* Primarily related to topical application, abdominal cramps, diarrhea, rash. Like any aminoglycoside, ototoxicity and nephrotoxicity occur if absorbed.
Nitrofurantoin Furadantin, Furan, Macrodantin Capsule: 50, 100 mg Extended-release capsule: 100 mg Macrocrystal: 50, 100 mg Suspension: 25 mg/5 mL	**Effective in treatment of lower UTIs caused by gram-positive and gram-negative pathogens** Children: 5-7 mg/kg/24 hr divided q6h PO (max dose: 400 mg/24 hr); suppressive therapy 1-2.5 mg/kg/24 hr divided q12-24h PO (max dose: 100 mg/24 hr) Adults: 50-100 mg/24 hr divided q6h PO	*Cautions:* Vertigo, dizziness, rash, jaundice, interstitial pneumonitis. Do not use with moderate to severe renal dysfunction. *Drug interactions:* Liquid antacids.
Ofloxacin Ocuflox 0.3% ophthalmic solution: 1, 5, 10 mL Floxin 0.3% otic solution: 5, 10 mL	**Quinolone antibiotic for treatment of conjunctivitis or corneal ulcers (ophthalmic solution) and otitis externa or chronic suppurative otitis media (otic solution) caused by susceptible gram-positive, gram-negative, anaerobic bacteria, or *C. trachomatis*** *Child >1-12 yr:* Conjunctivitis: 1-2 drops in affected eye(s) q2-4h for 2 days, then 1-2 drops qid for 5 days Corneal ulcers: 1-2 drops q30min while awake and at 4-hr intervals at night for 2 days, then 1-2 drops hourly for 5 days while awake, then 1-2 drops q6h for 2 days Otitis externa (otic solution): 5 drops into affected ear bid for 10 days Chronic suppurative otitis media: treat for 14 days *Child >12 yr and adults:* Ophthalmic solution doses same as for younger children. Otitis externa (otic solution): Use 10 drops bid for 10 or 14 days as for younger children	*Adverse events:* Burning, stinging, eye redness (ophthalmic solution), dizziness with otic solution if not warmed.
Omadacycline Nuzyra Injection 100 mg/single-dose vial Oral 150 mg tablet	**New subclass of tetracyclines; active against MSSA, MRSA CoNS, streptococci, including pneumococcus, and enterococci, including VRE** Adults: 200 mg IV once OR 100 mg IV × 2 doses OR 300 mg PO × 2 doses Follow with maintenance dosing starting on day 2: Maintenance dose 100 mg IV qday OR 300 mg PO qday Treatment duration: 7-14 days Children: No dosing information available	Omadacycline has comparable adverse events to other tetracyclines such as tooth discoloration, enamel hypoplasia, and inhibition of bone growth. However, no cases of photosensitivity were observed in phase 3 studies.

Table 225.3 Selected Antibacterial Medications (Antibiotics)*—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Oxacillin sodium Prostaphlin Injection Capsule: 250, 500 mg Suspension: 250 mg/5 mL	**Penicillinase-resistant penicillin active against *S. aureus* and other gram-positive cocci, except *Enterococcus* and coagulase-negative staphylococci** Neonates: Postnatal age ≤7 days weight 1,200-2,000 g: 50 mg/kg/24 hr divided q12h IV; weight >2,000 g: 75 mg/kg/24 hr IV divided q8h IV; postnatal age >7 days weight <1,200 g: 50 mg/kg/24 hr IV divided q12h IV; weight 1,200-2,000 g: 75 mg/kg/24 hr divided q8h IV; weight >2,000 g: 100 mg/kg/24 hr IV divided q6h IV Infants: 100-200 mg/kg/24 hr divided q4-6h IV Children: PO 50-100 mg/kg/24 hr divided q4-6h IV Adults: 2-12 g/24 hr divided q4-6h IV (max dose: 12 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia) Moderate oral bioavailability (35–65%). Primarily renally eliminated *Drug interaction:* Probenecid *Adverse effect:* Neutropenia
Penicillin G Injection Tablets	**Penicillin active against most gram-positive cocci; *S. pneumoniae* (resistance is increasing), group A *Streptococcus*, and some gram-negative bacteria (e.g., *N. gonorrhoeae, N. meningitidis*)** Neonates: Postnatal age ≤7 days weight 1,200-2,000 g: 50,000 units/kg/24 hr divided q12h IV or IM (meningitis: 100,000 U/kg/24 hr divided q12h IV or IM); weight >2,000 g: 75,000 U/kg/24 hr divided q8h IV or IM (meningitis: 150,000 U/kg/24 hr divided q8h IV or IM); postnatal age >7 days weight ≤1,200 g: 50,000 U/kg/24 hr divided q12h IV (meningitis: 100,000 U/kg/24 hr divided q12h IV); weight 1,200-2,000 g: 75,000 U/kg/24 hr q8h IV (meningitis: 225,000 U/kg/24 hr divided q8h IV); weight >2,000 g: 100,000 U/kg/24 hr divided q6h IV (meningitis: 200,000 U/kg/24 hr divided q6h IV) Children: 100,000-250,000 units/kg/24 hr divided q4-6h IV or IM (max dose: 400,000 U/kg/24 hr) Adults: 2-24 million units/24 hr divided q4-6h IV or IM	*Cautions:* β-Lactam safety profile (rash, eosinophilia), allergy, seizures with excessive doses particularly in patients with marked renal disease. Substantial pathogen resistance. Primarily renally eliminated *Drug interaction:* Probenecid
Penicillin G, benzathine Bicillin Injection	**Long-acting repository form of penicillin effective in treatment of infections responsive to persistent, low penicillin concentrations (1-4 wk) (e.g., group A *Streptococcus* pharyngitis, rheumatic fever prophylaxis)** Neonates weighing >1,200 g: 50,000 units/kg IM once Children: 300,000-1.2 million units/kg q3-4wk IM (max dose: 1.2-2.4 million units/dose) Adults: 1.2 million units IM q3-4wk	*Cautions:* β-Lactam safety profile (rash, eosinophilia), allergy. Administer by IM injection only. Substantial pathogen resistance. Primarily renally eliminated. *Drug interaction:* Probenecid.
Penicillin G, procaine Crysticillin Injection	**Repository form of penicillin providing low penicillin concentrations for 12 hr** Neonates with weight >1,200 g: 50,000 units/kg/24 hr IM Children: 25,000-50,000 units/kg/24 hr IM for 10 days (max dose: 4.8 million units/dose) Gonorrhea: 100,000 units/kg (max dose: 4.8 million units/24 hr) IM once with probenecid 25 mg/kg (max dose: 1 g) Adults: 0.6-4.8 million units q12-24h IM	*Cautions:* β-Lactam safety profile (rash, eosinophilia) allergy. Administer by IM injection only. Substantial pathogen resistance. Primarily renally eliminated. *Drug interaction:* Probenecid.
Penicillin V Pen VK, V-Cillin K Tablet: 125, 250, 500 mg Suspension: 125 mg/5 mL, 250 mg/5 mL	**Preferred oral dosing form of penicillin, active against most gram-positive cocci; *S. pneumoniae* (resistance is increasing), other streptococci, and some gram-negative bacteria (e.g., *N. gonorrhoeae, N. meningitidis*)** Children: 25-50 mg/kg/24 hr divided q4-8h PO Adults: 125-500 mg q6-8h PO (max dose: 3 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia), allergy, seizures with excessive doses particularly in patients with renal disease. Substantial pathogen resistance. Primarily renally eliminated. Inactivated by penicillinase. *Drug interaction:* Probenecid.
Piperacillin Pipracil Injection	**Extended-spectrum penicillin active against *E. coli, Enterobacter, Serratia, P. aeruginosa,* and *Bacteroides*** Neonates: Postnatal age ≤7 days 150 mg/kg/24 hr divided q8-12h IV; >7 days; 200 mg/kg divided q6-8h IV Children: 200-300 mg/kg/24 hr divided q4-6h IV; cystic fibrosis: 350-500 mg/kg/24 hr IV Adults: 2-4 g/dose q4-6h (max dose: 24 g/24 hr) IV	*Cautions:* β-Lactam safety profile (rash, eosinophilia); painful given intramuscularly; each gram contains 1.9 mEq sodium. Interferes with platelet aggregation/serum sickness–like reaction with high doses; increases in liver function test results. Renally eliminated. Inactivated by penicillinase. *Drug interaction:* Probenecid.
Piperacillin-tazobactam Zosyn Injection	**Extended-spectrum penicillin (piperacillin) combined with a β-lactamase inhibitor (tazobactam) active against *S. aureus, H. influenzae, E. coli, Enterobacter, Serratia, Acinetobacter, P. aeruginosa,* and *Bacteroides*** Children: 300-400 mg/kg/24 hr divided q6-8h IV or IM Adults: 3.375 g q6-8h IV or IM	*Cautions:* β-Lactam safety profile (rash, eosinophilia); painful given intramuscularly; each gram contains 1.9 mEq sodium. Interferes with platelet aggregation, serum sickness–like reaction with high doses, increases in liver function test results. Renally eliminated. *Drug interaction:* Probenecid.

Continued

Table 225.3 Selected Antibacterial Medications (Antibiotics)*—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Plazomicin Zemdri 500 mg/10 mL (50 mg/mL) vials Each vial contains plazomicin sulfate equivalent to 500 mg plazomicin free base	**Aminoglycoside active against resistant Enterobacteriaceae, including CRE** Adults: 15 mg/kg IV q24hr infused over 30 min Duration of therapy should be guided by the severity of infection and the patient's clinical status for up to 7 days; usual duration 4-7 days Children: no pediatric dose established	May cause ototoxicity and nephrotoxicity. Monitor renal function. Drug eliminated renally. *Drug interactions:* May potentiate other ototoxic and nephrotoxic drugs.
Quinupristin/dalfopristin Synercid IV injection: powder for reconstitution, 10 mL contains 150 mg quinupristin, 350 mg dalfopristin	**Streptogramin antibiotic (quinupristin) active against vancomycin-resistant *E. faecium* (VRE) and methicillin-resistant *S. aureus* (MRSA). Not active against *E. faecalis*** Children and adults: VRE: 7.5 mg/kg q8h IV for VRE; skin infections: 7.5 mg/kg q12h IV	*Adverse events:* Pain, edema, or phlebitis at injection site; nausea; diarrhea. *Drug interactions*: Synercid is a potent inhibitor of CYP 3A4.
Sulfadiazine Tablet: 500 mg	**Sulfonamide antibiotic primarily indicated for treatment of lower UTIs caused by *E. coli, P. mirabilis,* and *Klebsiella*** Toxoplasmosis: Neonates: 100 mg/kg/24 hr divided q12h PO with pyrimethamine 1 mg/kg/24 hr PO (with folinic acid) Children: 120-200 mg/kg/24 hr divided q6h PO with pyrimethamine 2 mg/kg/24 hr divided q12h PO ≥3 days, then 1 mg/kg/24 hr (max dose: 25 mg/24 hr) with folinic acid Rheumatic fever prophylaxis: weight ≤30 kg: 500 mg/24 hr q24h PO; weight >30 kg: 1 g/24 hr q24h PO	*Cautions:* Rash, Stevens-Johnson syndrome, nausea, leukopenia, crystalluria. Renal and hepatic elimination; avoid use with renal disease. Half-life: ~10 hr. *Drug interactions:* Protein displacement with warfarin, phenytoin, methotrexate.
Sulfamethoxazole Gantanol Tablet: 500 mg Suspension: 500 mg/5 mL	**Sulfonamide antibiotic used for treatment of otitis media, chronic bronchitis, and lower UTIs caused by susceptible bacteria** Children: 50-60 mg/kg/24 hr divided q12h PO Adults: 1 g/dose q12h PO (max dose: 3 g/24 hr)	*Cautions:* Rash, Stevens-Johnson syndrome, nausea, leukopenia, crystalluria. Renal and hepatic elimination; avoid use with renal disease. Half-life: ~12 hr. Initial dose often a loading dose (doubled). *Drug interactions:* Protein displacement with warfarin, phenytoin, methotrexate.
Sulfisoxazole Gantrisin Tablet: 500 mg Suspension: 500 mg/5 mL Ophthalmic solution, ointment	**Sulfonamide antibiotic used for treatment of otitis media, chronic bronchitis, and lower UTIs caused by susceptible bacteria. Also used for *Nocardia*** ***Plasmodium falciparum* resistant to chloroquine, toxoplasmosis in combination with pyrimethamine (sulfadiazine preferred).** Children: 120-150 mg/kg/24 hr divided q4-6h PO (max dose: 6 g/24 hr) Adults: 4-8 g/24 hr divided q4-6h PO	*Cautions:* Rash, Stevens-Johnson syndrome, nausea, leukopenia, crystalluria. Renal and hepatic elimination; avoid use with renal disease. Half-life: ~7-12 hr. Initial dose often a loading dose (doubled). *Drug interactions:* Protein displacement with warfarin, phenytoin, methotrexate.
Tedizolid Sivextro 200 mg vial 200 mg tablet	**Oxazolidinone agent; indicated for skin and soft tissue/skin structure infections caused by susceptible gram-positive organisms; active against MSSA, MRSA, streptococci, enterococci** Adults: 200 mg PO/IV qday for 6 days Children: Indicated for acute bacterial skin and skin structure infections in patients age ≥12 yr <12 yr: Safety and efficacy not established 12-18 yr: 200 mg PO/IV qday for 6 days	Similar to linezolid. Adverse events may include myelosuppression, pseudomembranous colitis, nausea, diarrhea, headache, peripheral and optic neuropathy.
Tigecycline Tygacil Injection	**Tetracycline-class antibiotic (glycylcycline) active against Enterobacteriaceae, including extended spectrum β-lactamase producers; streptococci (including VRE); staphylococci (including MRSA); and anaerobes** Children: unknown Adults: 100 mg loading dose followed by 50 mg q12h IV	*Cautions:* Pregnancy; children <8 yr old; photosensitivity; hypersensitivity to tetracyclines; hepatic impairment (~60% hepatic clearance). *Drug interaction:* Warfarin; mycophenolate mofetil.
Tobramycin Nebcin, Tobrex Injection Ophthalmic solution, ointment Inhalation capsule (28 mg); inhalation solution (60 mg/mL; 75 mg/mL)	**Aminoglycoside antibiotic active against gram-negative bacilli, especially *E. coli, Klebsiella, Enterobacter, Serratia, Proteus,* and *Pseudomonas*** Can be administered by inhalational route Neonates: Postnatal age ≤7 days, weight 1,200-2,000 g: 2.5 mg/kg q12-18h IV or IM; weight >2,000 g: 2.5 mg/kg q12h IV or IM; postnatal age >7 days, weight 1,200-2,000 g: 2.5 mg/kg q8-12h IV or IM; weight >2,000 g: 2.5 mg/kg q8h IV or IM Children: 2.5 mg/kg/24 hr divided q8-12h IV or IM. Alternatively, may administer 5-7.5 mg/kg/24 hr IV. Preservative-free preparation for intraventricular or intrathecal use: neonate, 1 mg/24 hr; children, 1-2 mg/24 hr; adults, 4-8 mg/24 hr Adults: 3-6 mg/kg/24 hr divided q8h IV or IM	*Cautions: S. pneumoniae*, other streptococcus, and anaerobes are resistant. May cause ototoxicity and nephrotoxicity. Monitor renal function. Drug eliminated renally. Administered IV over 30-60 min. *Drug interactions:* May potentiate other ototoxic and nephrotoxic drugs. *Target serum concentrations:* Peak 6-12 mg/L; trough <2 mg/L.

Table 225.3 Selected Antibacterial Medications (Antibiotics)*—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Trimethoprim Proloprim, Trimpex Tablet: 100, 200 mg	**Folic acid antagonist effective in prophylaxis and treatment of *E. coli, Klebsiella, P. mirabilis,* and *Enterobacter* UTIs; *P. carinii* pneumonia** Children: For UTI: 4-6 mg/kg/24 hr divided q12h PO Children >12 yr and adults: 100-200 mg q12h PO. *P. carinii* pneumonia (with dapsone): 15-20 mg/kg/24 hr divided q6h for 21 days PO	*Cautions:* Megaloblastic anemia, bone marrow suppression, nausea, epigastric distress, rash. *Drug interactions:* Possible interactions with phenytoin, cyclosporine, rifampin, warfarin.
Vancomycin Vancocin, Lyphocin Injection Capsule: 125 mg, 250 mg Suspension	**Glycopeptide antibiotic active against most gram-positive pathogens including staphylococci (including MRSA and coagulase-negative staphylococci), *S. pneumoniae* including penicillin-resistant strains, *Enterococcus* (resistance is increasing), and *C. difficile*–associated colitis** Neonates: Postnatal age ≤7 days, weight <1,200 g: 15 mg/kg/24 hr divided q24h IV; weight 1,200-2,000 g: 15 mg/kg/24 hr divided q12-18h IV; weight >2,000 g: 30 mg/kg/24 hr divided q12h IV; postnatal age >7 days, weight <1,200 g: 15 mg/kg/24 hr divided q24h IV; weight 1,200-2,000 g: 15 mg/kg/24 hr divided q8-12h IV; weight >2,000 g: 45 mg/kg/24 hr divided q8h IV Children: 45-60 mg/kg/24 hr divided q8-12h IV; *C. difficile*–associated colitis; 40-50 mg/kg/24 hr divided q6-8h PO	*Cautions:* Ototoxicity and nephrotoxicity, particularly when co-administered with other ototoxic and nephrotoxic drugs. Infuse IV over 45-60 min. Cutaneous and systemic side effects can be observed with rapid IV infusions, fever, chills, phlebitis (central line is preferred for infusions). Renally eliminated. *Target serum concentrations:* Peak (1 hr after 1 hr infusion) 30-40 mg/L; trough 5-10 mg/L.

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.
CNS, Central nervous system; GI, gastrointestinal; IM, intramuscular/ly; IV, intravenous/ly; PO, oral/ly; UTIs, urinary tract infections.

Table 225.4 Adverse Reactions to Penicillins

TYPE OF REACTION	FREQUENCY (%)	OCCURS MOST FREQUENTLY WITH
ALLERGIC Immunoglobulin E antibody	0.04-0.015	Penicillin G
Anaphylaxis*		
Early urticaria* (<72 hr)		
Cytotoxic antibody	Rare	Penicillin G
Hemolytic anemia*		
Antigen-antibody complex disease	Rare	Penicillin G
Serum sickness*		
Delayed hypersensitivity	2-5	Ampicillin, amoxicillin
Contact dermatitis*		
IDIOPATHIC	2-5	Ampicillin
Skin rash		
Fever		
Late-onset urticaria		
GASTROINTESTINAL Diarrhea	3-11	Ampicillin
Clostridioides difficile (formerly *Clostridium difficile*)–associated colitis	Rare	Ampicillin
HEMATOLOGIC Hemolytic anemia	Rare	Penicillin G
Neutropenia	10-17	Penicillin G, nafcillin, oxacillin†
Platelet dysfunction	43-73	Piperacillin
HEPATIC Elevated serum aspartate transaminase	0.01-22	Flucloxacillin, oxacillin

Continued

Table 225.4 Adverse Reactions to Penicillins—cont'd

TYPE OF REACTION	FREQUENCY (%)	OCCURS MOST FREQUENTLY WITH
ELECTROLYTE DISTURBANCE		
Hypokalemia	Rare	Nafcillin, oxacillin
Hyperkalemia, acute	Rare	Penicillin G
NEUROLOGIC		
Seizures	Rare	Penicillin G
Bizarre sensations (Hoigné syndrome)	Rare	Procaine penicillin
RENAL		
Interstitial nephritis*	Variable	Any penicillin

*Reaction can occur with any of the penicillins.
†With prolonged therapy.
Adapted from Doi Y. Penicillins and β-lactamase inhibitors. In Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 9th ed. Philadelphia: Elsevier; 2020: Table 20-7.

Table 225.5 Classification of Parenteral and Oral Cephalosporins

CEPHALOSPORINS	FIRST GENERATION	SECOND GENERATION	CEPHAMYCINS	THIRD GENERATION	FOURTH GENERATION	FIFTH GENERATION (MRSA ACTIVE)
Parenteral	Cefazolin (Ancef, Kefzol)	Cefamandole (Mandol)*	Cefmetazole (Zefazone)*	Cefoperazone (Cefobid)*	Cefepime (Maxipime)	Ceftaroline (Teflaro)
	Cephalothin (Keflin, Seffin)*	Cefonicid (Monocid)*	Cefotetan (Cefotan)	Cefotaxime (Claforan)	Cefpirome (Cefrom)	Ceftobiprole (Zeftera)*
	Cephapirin (Cefadyl)*	Cefuroxime (Kefurox, Zinacef)	Cefoxitin (Mefoxin)	Ceftazidime (Fortaz)	Cefiderocol (Fetroja; Siderophore antibiotic)	Ceftolozane (combined with tazobactam; Zerbaxa)
	Cephradine (Velosef)*			Ceftizoxime (Cefizox)*		
				Ceftriaxone (Rocephin)		
				Moxalactam*		
				Ceftazidime-avibactam (Avycaz)		
Oral	Cefadroxil (Duricef, Ultracef) Cephalexin (Keflex, Biocef, Keftab) Cephradine (Velosef)*	Cefaclor (Ceclor)* Cefprozil (Cefzil) Cefuroxime axetil (Ceftin) Loracarbef (Lorabid)*		Cefdinir (Omnicef) Cefditoren (Spectracef) Cefixime (Suprax) Cefpodoxime (Vantin) Ceftibuten (Cedax)		

*Not currently available in the United States.
Adapted from Lepak AJ, Andes DR. Cephalosporins. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 9th ed. Philadelphia: Elsevier; 2020: Table 21-1.

A **fifth-generation cephalosporin** called *ceftaroline* has been licensed. Ceftaroline is the active metabolite of the prodrug ceftaroline fosamil (which is the agent administered to the patient). Ceftaroline is a broad-spectrum cephalosporin with bactericidal activity against resistant gram-positive organisms, including MRSA, and common gram-negative pathogens. It has FDA approval and is licensed for use in children. Ceftaroline is indicated for MRSA in the treatment of skin and soft tissue infections. It is also licensed for treatment of community-acquired pneumonia but is not indicated for MRSA pneumonia. Ceftaroline's activity is attributed to its ability to bind to PBP 2a with higher affinity than other β-lactams. Another fifth-generation cephalosporin with a similar spectrum of activity, *ceftobiprole,* has been approved for use in Canada and the European Union. A third fifth-generation cephalosporin, *ceftolozane,* has been licensed. It is a derivative of ceftazidime with improved activity against *Pseudomonas* spp. It is not stable against most ESBLs or carbapenemases. It is marketed in combination with the β-lactam inhibitor tazobactam to improve its activity against β-lactamase–producing Enterobacteriaceae. Experience with children is limited.

Table 225.6 lists adverse reactions to cephalosporins.

Carbapenems

The carbapenem group of antibiotics includes imipenem (formulated in combination with cilastatin), meropenem, ertapenem, and doripenem. The basic structure of these agents is similar to that of β-lactam antibiotics, and these drugs have a similar mechanism of

Table 225.6 Potential Adverse Effects of Cephalosporins

TYPE	SPECIFIC	FREQUENCY
Hypersensitivity	Rash	1–3%
	Urticaria	<1%
	Serum sickness	<1%
	Anaphylaxis	0.01%
Gastrointestinal	Diarrhea	1–19%
	Nausea, vomiting	1–6%
	Transient transaminase elevation	1–7%
	Biliary sludge	20–46%*
Hematologic	Eosinophilia	1–10%
	Neutropenia	<1%
	Thrombocytopenia	<1–3%
	Hypoprothrombinemia	<1%
	Impaired platelet aggregation	<1%
	Hemolytic anemia	<1%
Renal	Interstitial nephritis	<1–5%
Central nervous system	Seizures	<1%
	Encephalopathy	<1%
False-positive laboratory	Coombs positive	3%
	Glucosuria	Rare
	Serum creatinine	Rare
Other	Drug fever	Rare
	Disulfiram-like reaction†	Rare
	Superinfection	Rare
	Phlebitis	Rare
	Calcium-antibiotic precipitation*	Unknown; can be associated with embolic events

*Ceftriaxone.
†Cephalosporins with thiomethyl tetrazole ring (MTT) side chain.
Adapted from Craig WA, Andes DR. Cephalosporins. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases,* 9th ed. Philadelphia: Elsevier; 2020: Table 21-6.

action. The carbapenems provide the broadest spectrum of antibacterial activity of any licensed class of antibiotics and are active against gram-positive, gram-negative, and anaerobic organisms. Among the carbapenems, **meropenem** is the only agent licensed for treatment of pediatric meningitis. Importantly, MRSA and *E. faecium* are *not* susceptible to carbapenems. Carbapenems also tend to be poorly active against *Stenotrophomonas maltophilia,* rendering their use for cystic fibrosis patients who are infected with this organism problematic. Ertapenem is poorly active against *P. aeruginosa* and *Acinetobacter* species and should be avoided when these pathogens are encountered. Although imipenem-cilastatin is the first carbapenem approved for clinical use and the carbapenem with the greatest clinical experience, this antibiotic unfortunately has a propensity to cause seizures in children, particularly in the setting of intercurrent meningitis. Accordingly, meropenem is typically more suitable for pediatric use, where meningitis is commonly a consideration. Carbapenems have also been combined with β-lactamase inhibitors. One example is **meropenem/vaborbactam,** where the β-lactamase inhibitor vaborbactam extends the spectrum of activity to include some ESBL- and carbapenemase-producing bacteria. No dosage recommendations exist as yet for pediatric use. Another example is **imipenem/relebactam** (imipenem/cilastatin/relebactam), which is approved for complicated urinary tract and intraabdominal infections and for ventilator-associated pneumonia.

Other carbapenems in various stages of clinical trials include benapenum, panipenem, biapenem, razupenem, and tomopenem. Tebipenem pivoxil is an orally available prodrug of tebipenem, a carbapenem with activity against multidrug-resistant gram-negative pathogens, including quinolone-resistant and ESBL-producing Enterobacteriaceae. Sulopenem/sulopenem etzadroxil/probenecid is an oral carbapenem combination. Sulopenem etzadroxil is an oral prodrug form of sulopenem, a thiopenem with broad-spectrum antibacterial activity against most gram-positive and gram-negative bacteria, not including *P. aeruginosa*. Probenecid is included to prolong half-life. Panipenem is a combination agent coformulated with betamipron, which inhibits renal uptake of panipenem (analogous to imipenem/cilastatin). Panipenem, biapenem, and tebipenem/pivoxil are licensed in Japan. There is minimal experience with pediatric dosing for all of these newer carbapenems.

Glycopeptides

Glycopeptide antibiotics include **vancomycin** and **teicoplanin**, the less commonly available analog. These agents are bactericidal and act by inhibiting cell wall biosynthesis. The antimicrobial activity of the glycopeptides is limited to gram-positive organisms, including *S. aureus,* coagulase-negative staphylococci, pneumococcus, enterococci, *Bacillus,* and *Corynebacterium.* Vancomycin is frequently employed in pediatric practice and is of particular value for serious infections, including meningitis, caused by MRSA and penicillin- and cephalosporin-resistant *S. pneumoniae.* Vancomycin is also commonly used for infections in the setting of fever and neutropenia in oncology patients, in combination with other antibiotics (see Chapter 223), and for infections associated with indwelling medical devices (see Chapter 224). Oral formulations of vancomycin are occasionally used to treat pseudomembranous colitis caused by *Clostridium difficile* infections; intrathecal therapy may also be used for selected CNS infections. Vancomycin must be administered with care because of its propensity to produce **vancomycin infusion syndrome**, which is a reversible adverse effect that is rare in young children and can typically be readily managed by slowing the rate of drug infusion.

Newer FDA-approved glycopeptide antibiotics include telavancin, dalbavancin, and oritavancin; pediatric experience is limited. **Telavancin** is indicated for skin and skin structure infections caused by *S. aureus* (including MRSA), group A streptococcus, and *E. faecalis* (vancomycin-susceptible isolates only). It is also approved for hospital-acquired (including ventilator-associated) pneumonia caused by *S. aureus*. The recommended adult dose for skin and soft tissue infections, and for nosocomial pneumonia, is 10 mg/kg intravenously (IV) every 24 hours for 7-21 days. Telavancin appears to be more nephrotoxic than vancomycin and has been associated with prolongation of the QT interval. **Dalbavancin**'s unique characteristic is its long half-life, 150-250 hours. In adults with normal renal function, the dose is 1000 mg IV, followed 1 week later by 500 mg IV. This agent can be considered when MRSA is confirmed or strongly suggested. Dalbavancin is not active against vancomycin-resistant *S. aureus*. It is FDA-approved for bacterial skin and soft tissue infections. **Oritavancin** is a vancomycin derivative with indications similar to those of dalbavancin. It has a half-life of approximately 250 hours. The dosage for adults is a single 1200-mg dose administered IV over 3 hours. The FDA has approved dalbavancin and oritavancin for the treatment of acute bacterial skin and skin structure infections caused by gram-positive bacteria, including MRSA. **Cefilavancin** is a unique agent spanning two antimicrobial classes in a single agent. It is a covalently linked glycopeptide-cephalosporin heterodimer antibiotic that is highly active against gram-positive bacteria and is in a phase 3 study.

Aminoglycosides

Aminoglycoside antibiotics include streptomycin, kanamycin, gentamicin, tobramycin, netilmicin, and amikacin. The most commonly used aminoglycosides in pediatric practice are **gentamicin** and **tobramycin**. They exert their action by inhibiting bacterial protein synthesis. Although they are most often used to treat gram-negative infections, the aminoglycosides are broad-spectrum agents, with activity against *S. aureus* and synergistic activity against GBS, *L. monocytogenes,* viridans streptococci, *Corynebacteria jeikeium*, *P. aeruginosa,* coagulase-negative staphylococci, and enterococci when co-administered with a β-lactam agent. Aminoglycoside use has decreased with the development of alternatives, but they still play a key role in pediatric practice in the management of neonatal sepsis, UTIs, gram-negative bacterial sepsis, and complicated intraabdominal infections; infections in cystic fibrosis patients (including both parenteral and aerosolized forms of therapy); and oncology patients with fever and neutropenia. Aminoglycosides, in particular streptomycin, are also important in the management of *Francisella tularensis, Mycobacterium tuberculosis,* and nontuberculous mycobacterial infections.

Toxicities of aminoglycoside therapy include nephrotoxicity and ototoxicity (cochlear and/or vestibular), and serum levels as well as renal function and hearing should be monitored in patients on long-term therapy. Toxicities of aminoglycosides may be reduced by the use of once-daily dosing regimens with appropriate monitoring of serum levels. Hypokalemia, volume depletion, hypomagnesemia, and other nephrotoxic drugs may increase the renal toxicity of aminoglycosides. A rare complication of aminoglycosides is **neuromuscular blockade**, which may occur in the presence of other neuromuscular blocking agents and in the setting of infant botulism.

A novel aminoglycoside, **plazomicin**, has recently been approved by the FDA for adult use. It was designed to evade all of the clinically relevant aminoglycoside-modifying enzymes (Table 225.2) responsible for aminoglycoside resistance. It is approved for complicated UTIs, including pyelonephritis caused by *E. coli*, *K. pneumoniae*, *Proteus mirabilis,* and *Enterobacter cloacae.* FDA approval is pending for bloodstream infections caused by multidrug-resistant *Enterobacteriaceae*, including CRE.

Tetracyclines

The tetracyclines (tetracycline hydrochloride, doxycycline, minocycline, demeclocycline, eravacycline, omadacycline, and minocycline) are bacteriostatic antibiotics that exhibit their antimicrobial effect by binding to the bacterial 30S ribosomal subunit, inhibiting protein translation. These agents have a broad spectrum of antimicrobial activity against gram-positive and gram-negative bacteria, rickettsia, and some parasites. The oral bioavailability of these agents facilitates oral dosing for many infections, including Rocky Mountain spotted fever, anaplasmosis, ehrlichiosis, Lyme disease, and malaria. Tetracyclines must be prescribed judiciously to children <9 years old, because they can cause staining of teeth, hypoplasia of dental enamel, and abnormal bone growth in this age-group.

Tigecycline, a semisynthetic derivative of minocycline, is a parenteral agent of a new antibiotic class **(glycylcyclines)** and is licensed in the United States. It has a broader spectrum of activity (bacteriostatic) than traditional tetracyclines but retains the side effect profile of tetracyclines. Tigecycline is active against tetracycline-resistant gram-positive and gram-negative pathogens, including MRSA and possibly VRE, but not *Pseudomonas.* **Demeclocycline** is an orally administered tetracycline with a similar antimicrobial spectrum as other agents in this class. A novel tetracycline derivative, **eravacycline** (a fluorocycline), has recently been approved for treatment of complicated intraabdominal infections in adults and has the broadest spectrum of any tetracycline, including MRSA and CRE. **Omadacycline** is another new tetracycline that is similar to that of other tetracyclines, functioning as an inhibitor of bacterial protein synthesis, but has activity against bacterial strains expressing the two main forms of tetracycline resistance, specifically, antibiotic efflux and ribosomal protection.

Complications of tetracyclines include eosinophilia, leukopenia and thrombocytopenia (tetracycline), pseudotumor cerebri, anorexia, emesis and nausea, hepatitis, photosensitivity, and a hypersensitivity reaction (urticaria, asthma exacerbation, facial edema, dermatitis) as well as a systemic lupus erythematosus–like syndrome (most common with minocycline). The FDA has issued a "black box" warning regarding tigecycline based on a meta-analysis of 10 studies that showed increased mortality among patients receiving this drug.

A salutary side effect of **demeclocycline** has been identified; it is occasionally used as an off-label treatment of hyponatremia resulting from the syndrome of inappropriate antidiuretic hormone (ADH). The mechanism of action appears to be inhibition of adenylyl cyclase activation after ADH binds to renal vasopressin receptors.

Sulfonamides

Trimethoprim and the sulfonamides are bacteriostatic agents that inhibit the bacterial folate synthesis pathway, in the process impairing both nucleic acid and protein synthesis. Sulfonamides interfere

with the synthesis of dihydropteroic acid from paraaminobenzoic acid, whereas trimethoprim acts at a site further downstream, interfering with synthesis of tetrahydrofolic acid from dihydrofolic acid. The sulfonamides are available in both parenteral and oral formulations. Although there have historically been a large number of sulfonamide antibiotics developed for clinical use, relatively few remain available for pediatric practice. The most important agent is the combination of **trimethoprim-sulfamethoxazole** (TMP-SMX), used for treatment of UTIs. TMP-SMX has also emerged as a commonly prescribed agent for staphylococcal skin and soft tissue infections, because this antibiotic generally retains activity against MRSA. TMP-SMX also plays a unique role in immunocompromised patients, as a prophylactic and therapeutic agent for *Pneumocystis jiroveci* infection. Other common sulfonamides include **sulfisoxazole**, which is useful in the management of UTIs, and **sulfadiazine**, which is a drug of choice in the treatment of toxoplasmosis.

Recently, a novel sulfonamide, **iclaprim**, demonstrated noninferiority to vancomycin in the treatment of complicated skin and soft tissue infections. Iclaprim is a diaminopyrimidine with a 20-fold higher affinity for the target molecule for sulfonamides, dihydrofolate reductase, than trimethoprim. It was granted orphan drug status by the FDA for treatment of *S. aureus* infection in patients with cystic fibrosis but has not been formally approved for general use.

Macrolides

The macrolide antibiotics most often used in pediatric practice include **erythromycin**, **clarithromycin**, and **azithromycin**. This class of antimicrobials exerts its antibiotic effect through binding to the 50S subunit of the bacterial ribosome, producing a block in elongation of bacterial polypeptides. Clarithromycin is metabolized to 14-hydroxy clarithromycin, and this active metabolite also has potent antimicrobial activity. The spectrum of antibiotic activity includes many gram-positive bacteria. Unfortunately, resistance to these agents among *S. aureus* and group A streptococcus is fairly widespread, limiting the usefulness of macrolides for many skin and soft tissue infections and for streptococcal pharyngitis. Azithromycin and clarithromycin have demonstrated efficacy for otitis media. All macrolide members have an important role in the management of pediatric respiratory infections, including atypical pneumonia caused by *M. pneumoniae, Chlamydophila pneumoniae,* and *Legionella pneumophila,* as well as infections caused by *Bordetella pertussis.*

Telithromycin, a ketolide antibiotic derived from erythromycin, was initially FDA-approved for the treatment in adults of mild to moderate community-acquired pneumonia, acute exacerbations of chronic bronchitis, and acute sinusitis, having good activity against the agents causing these infections (*S. pneumoniae*, *M. pneumoniae, C. pneumoniae,* and *L. pneumophila* for community-acquired pneumonia; *M. catarrhalis* and *H. influenzae* for sinusitis). Reports of liver failure and myasthenia gravis from telithromycin prompted the withdrawal of the drug from the market. **Solithromycin** is a related next-generation oral and IV fluoroketolide in phase 3 clinical development for the treatment of community-acquired pneumonia.

Drug interactions are common with erythromycin and to a lesser extent with clarithromycin. These agents can inhibit the CYP 3A4 enzyme system, resulting in increased levels of certain drugs, such as astemizole, cisapride, statins, pimozide, and theophylline. Itraconazole may increase macrolide levels, whereas rifampin, carbamazepine, and phenytoin may decrease macrolide levels. There are few reported adverse drug interactions with azithromycin. Cross-resistance may develop between a macrolide and the subsequent use of clindamycin.

Lincosamides

The prototype of the lincosamide class of antibiotics is **clindamycin**, which acts at the ribosomal level to exert its antimicrobial effect. The 50S subunit of the bacterial ribosome is the molecular target of this agent. Its spectrum of activity includes gram-positive aerobes and anaerobes. Clindamycin has no significant activity against gram-negative organisms. An important role for clindamycin has emerged in the management of MRSA infections. Because of its outstanding penetration into body fluids (excluding the CNS) and tissues and bone, clindamycin can be used for therapy of serious infections caused by MRSA. Clindamycin is also useful in the management of invasive group A streptococcus infections and in the management of many anaerobic infections, often in combination with a β-lactam. A form of **inducible clindamycin resistance** is exhibited by some strains of MRSA; therefore consultation with the clinical microbiology laboratory is necessary before treating a serious MRSA infection with clindamycin. Pseudomembranous colitis, a common complication of clindamycin therapy in adults, is seldom observed in pediatric patients. Clindamycin also plays an important role in the treatment of malaria and babesiosis (when co-administered with quinine), *P. jiroveci* pneumonia (when co-administered with primaquine), and toxoplasmosis.

Quinolones

The **fluoroquinolones** (ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin, besifloxacin [ophthalmic suspension], ofloxacin, and delafloxacin) are antimicrobials that inhibit bacterial DNA replication by binding to the topoisomerases of the target pathogen, inhibiting the bacterial enzyme DNA gyrase. This class has broad-spectrum activity against both gram-positive and gram-negative organisms. Some fluoroquinolones exhibit activity against penicillin-resistant *S. pneumoniae* as well as MRSA. These agents uniformly show excellent activity against gram-negative pathogens, including the Enterobacteriaceae and respiratory tract pathogens such as *M. catarrhalis* and *H. influenzae.* Quinolones are also highly active against pathogens associated with atypical pneumonia, particularly *M. pneumoniae* and *L. pneumophila.*

Although these agents are not approved for use in children, there is a reasonable body of evidence that the fluoroquinolones are generally safe, well tolerated, and effective against a variety of bacterial infections frequently encountered in pediatric practice. Parenteral quinolones are appropriate for critically ill patients with gram-negative infections. The use of oral quinolones in stable outpatients may also be reasonable for treatment of infections that would otherwise require parenteral antibiotics (e.g., *P. aeruginosa* soft tissue infections such as osteochondritis) or selected genitourinary tract infections. However, these agents should be reserved for situations when no other oral antibiotic alternative is feasible. In 2013 the FDA changed the warning labels for the fluoroquinolones to better describe the associated risk of permanent peripheral neuropathy. Additional risks include tendonitis, arrhythmias, and retinal detachment. Moreover, in situations of overuse (e.g., typhoid fever, gonococcal infection), organisms have been demonstrated to rapidly develop resistance. The FDA has advised against the use of quinolones for uncomplicated infections such as sinusitis and bronchitis. Thus use of fluoroquinolones in pediatric practice should still be approached with continued caution, and consultation with an expert is recommended.

Streptogramins and Oxazolidinones

The emergence of highly resistant gram-positive organisms, in particular VRE, has necessitated development of new classes of antibiotics. One such class especially useful for resistant gram-positive infections is the streptogramins. The currently licensed agent in this category is **dalfopristin-quinupristin**, which is available in a parenteral formulation. It is appropriate for treatment of MRSA, coagulase-negative staphylococci, penicillin-susceptible and penicillin-resistant *S. pneumoniae,* and vancomycin-resistant *E. faecium* but not *E. faecalis.*

Another licensed class of antibiotics for highly resistant gram-positive infections is the oxazolidinone class. The prototype in this group is **linezolid**, available in both oral and parenteral formulations and approved for use in pediatric patients. Its mechanism of action involves inhibition of ribosomal protein synthesis. It is indicated for MRSA, VRE, coagulase-negative staphylococci, and penicillin-resistant

S. pneumoniae. A related drug, **tedizolid phosphate**, is also FDA-approved for acute bacterial skin and skin structure infections. It is more potent in vitro than linezolid against MRSA and may be associated with less myelosuppression. It is available in both IV and oral formulations.

There is little information on streptogramins and oxazolidinones in the treatment of CNS infections, and neither class is approved for pediatric meningitis. Linezolid can cause significant anemia and thrombocytopenia and is a monoamine oxidase inhibitor.

A novel oxazolidinone, **contezolid acefosamil** (MRX-4), was recently approved for use in China. It is an orally active prodrug of the active antimicrobial metabolite, contezolid (MRX-I), an oxazolidinone that shows potent in vitro activity against various multidrug-resistant gram-positive bacteria, including MRSA. It also has activity against *M. tuberculosis*.

Daptomycin

Daptomycin is a novel member of the cyclic lipopeptide class of antibiotics. Its spectrum of activity includes virtually all gram-positive organisms, including *E. faecalis* and *E. faecium* (including VRE) and *S. aureus* (including MRSA). The structure of daptomycin is a 13-member amino acid peptide linked to a 10-carbon lipophilic tail, which results in a novel mechanism of action of disruption of the bacterial membrane through the formation of transmembrane channels. These channels cause leakage of intracellular ions, leading to depolarization of the cellular membrane and inhibition of macromolecular synthesis. A theoretical advantage of daptomycin for serious infections is its bactericidal activity against MRSA and enterococci. It is administered intravenously; experience in children is limited. Myopathy and elevations in creatine phosphokinase have been described. An FDA warning has been issued linking some cases of eosinophilic pneumonitis to the use of daptomycin. Daptomycin is inactivated by surfactant and should not be used to treat pneumonia.

Miscellaneous Agents

Metronidazole, which functions by disruption of DNA synthesis, has a unique role as an antianaerobic agent and also possesses antiparasitic and anthelmintic activity. In 2017 a related drug, **benznidazole**, was approved through the FDA's orphan drug Accelerated Approval Pathway. This antiprotozoal agent inhibits the synthesis of DNA, RNA, and proteins within *Trypanosoma cruzi* and is approved for adult and pediatric use for Chagas disease. **Rifampin** is a rifamycin antibiotic that inhibits bacterial RNA polymerase and has a major role in the management of tuberculosis. It is also of value in the management of other bacterial infections in pediatric patients, usually used as a second (synergistic) agent in the treatment of *S. aureus* infections or to eliminate nasopharyngeal colonization of Hib or *N. meningitidis*. **Rifabutin** is a related drug that has an off-label indication for treatment of tuberculosis, an orphan drug indication for Crohn disease, and an indication for prevention or treatment of disseminated *Mycobacterium avium* complex disease in patients with HIV or immune deficiency. **Rifaximin** is a *nonabsorbed rifamycin* that has been used as an adjunct agent to treat patients with multiple recurrences of *C. difficile* infection. **Fidaxomicin** is a first-in-class member of a new category of narrow-spectrum macrocyclic antibiotic drugs. It is an RNA polymerase inhibitor with activity against *C. difficile* infection.

The emerging crisis in antimicrobial resistance has also necessitated the rediscovery of antimicrobial agents seldom used in clinical practice in recent decades, such as **colistin** (colistimethate sodium), a member of the polymyxin family of antibiotics (polymyxin E). The general structure of polymyxins consists of a cyclic peptide with hydrophobic tails. After binding to lipopolysaccharide in the outer membrane of gram-negative bacteria, polymyxins disrupt both outer and inner membranes, leading to cell death. Colistin is broadly active against the Enterobacteriaceae family, including *P. aeruginosa*. It is also active against ESBL- and carbapenemase-producing strains. Toxicities are chiefly renal and neurologic.

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Chapter 226

Antimicrobial Stewardship

Kathleen Chiotos and Jeffrey S. Gerber

Antibiotics are the most common class of medications prescribed to pediatric outpatients, and over 50% of pediatric inpatients receive antibiotics during their hospitalization. It is estimated that between 25% and 50% of antibiotic prescriptions are inappropriate in drug choice, dose, or duration or are unnecessary altogether.

THE NEED FOR ANTIMICROBIAL STEWARDSHIP: HARMS FROM OVERUSE

There are many negative consequences of antibiotic overuse, including contributing to the dramatic rise in **antibiotic resistance** observed over the past 30 years, which has led to antibiotic resistance being named by the World Health Organization (WHO) as one of the top 10 threats to human health. Antibiotics also carry with them a risk of individual patient-level harm, including development of ***Clostridioides difficile* infection** and **antibiotic adverse events**. For example, 21% of antibiotic courses among pediatric inpatients are complicated by an adverse event, and each additional day of antibiotic therapy is associated with 7% greater odds of experiencing an adverse event. Among pediatric outpatients receiving broad- versus narrow-spectrum antibiotics for acute respiratory tract infections, adverse events are significantly more common in patients treated with broad-spectrum therapy. Finally, an emerging area of research is the **deleterious impact of antibiotics on the developing microbiome** and its potential influence on future disease states, including childhood obesity, asthma, and other allergic diseases. Collectively, these data highlight the importance of judicious antibiotic prescribing, both on a societal and individual patient level.

DEFINING ANTIMICROBIAL STEWARDSHIP AND AN ANTIMICROBIAL STEWARDSHIP PROGRAM

Antimicrobial stewardship is defined as coordinated interventions designed to improve the use of antimicrobial agents, such that dose, duration of therapy, and route of administration are optimized. The goal of these actions is to achieve the best clinical outcome for the patient, while minimizing the development of antimicrobial resistance and risk of adverse events. **It is paramount to recognize that simply reducing antimicrobial use is *not* a primary goal of antimicrobial stewardship.** However, because inappropriate antibiotic use is so common, optimization often results in de-escalation from a broader to a narrower spectrum of therapy or discontinuing antibiotics altogether.

Antimicrobial stewardship programs (ASPs) are multidisciplinary teams designed to improve the safety and quality of patient care by deploying these coordinated interventions. ASPs are often led or co-led by infectious diseases trained physicians and clinical pharmacists and work in collaboration with the infection prevention and control department, the clinical microbiology laboratory, and numerous stakeholder groups, including hospital leadership, clinicians, nurses, and pharmacy. Multiple studies have demonstrated reductions in antibiotic use, decreasing rates of *C. difficile* infections, and cost avoidance after the implementation of ASPs, with variable impact on local antibiotic resistance rates. With this growing evidence base and the crisis of antimicrobial resistance, ASPs are now a Standard from The Joint Commission and a Centers for Medicare and Medicaid Services (CMS) Condition of Participation. **Several guidelines provide evidence-based recommendations for implementation of an ASP, including the joint Infectious Diseases Society of America (IDSA) and**

Society for Healthcare Epidemiology of America (SHEA) guideline, the Centers for Disease Control and Prevention (CDC) Core Elements of Hospital Antibiotic Stewardship Programs, the CDC Core Elements of Outpatient Antibiotic Stewardship, and the WHO Practical Toolkit for Antimicrobial Stewardship Programmes in Healthcare Facilities in Low- and Middle-Income Countries.

INPATIENT ANTIMICROBIAL STEWARDSHIP STRATEGIES

Core elements of inpatient antimicrobial stewardship include hospital leadership commitment; accountability through appointment of a leader or coleaders; pharmacy expertise; implementation of actions or interventions to improve antibiotic use (Table 226.1); tracking

Table 226.1 Summary of Inpatient Antimicrobial Stewardship Interventions

ACTION	DESCRIPTION
PRIORITY ACTIONS	
Preauthorization	Clinician must contact the stewardship program to obtain approval for use of the antimicrobial before prescribing (see also text and Table 226.2).
Prospective audit and feedback	Antimicrobials are reviewed by the stewardship program after 48-72 hr and recommendations for optimization are provided at that point (see also text and Table 226.2).
Facility-specific treatment guidelines	These local guidelines should establish clear recommendations for commonly encountered infections based on published data or national guidelines, local susceptibility data, formulary options, and patient mix. These guidelines should address diagnostic testing, empiric treatment, and definitive treatment and should be developed in collaboration with clinician stakeholders.
ADDITIONAL ACTIONS	
Antibiotic "time-outs"	A "time-out" occurs after a set duration of antimicrobial therapy (e.g., 48-72 hr) and involves a clinician-led reassessment of the need for and choice of antibiotics. This differs from prospective audit and feedback in that the review is led by the frontline clinician, not the stewardship program. Time-outs may augment prospective audit and feedback led by the ASP but should not be considered an equivalent substitute.
Assessing penicillin allergy	Although penicillin allergies are reported in 10–15% of hospitalized patients, less than 1% are true serious allergies. Patients with penicillin allergy labels receive broader-spectrum antibiotics than would otherwise be recommended, and penicillin allergy labels may be associated with worse clinical outcomes. Clinicians or stewardship personnel may be able to "delabel" patients through performing a history and/or administering a challenge dose of penicillin or amoxicillin.
Documentation of antibiotic indications in orders or prescriptions	Requiring documentation of an indication for antibiotics can improve antibiotic prescribing practices. In addition, this facilitates other interventions, such as audit with feedback, where knowledge of the intended indication is needed.
Intravenous to oral antibiotic therapy	Transitioning from intravenous to oral therapy when an oral antibiotic is available can reduce the duration of hospitalization, need for long-term intravenous access, and improve patient satisfaction.
Pharmacist-based interventions	Pharmacists are uniquely positioned to optimize antibiotic use through making recommendations for optimal antibiotic dosing and administration (e.g., extended infusions of β-lactam antibiotics, therapeutic drug monitoring for vancomycin and aminoglycosides, identifying duplicative therapy such as overlapping anaerobic coverage, and detection/prevention of antibiotic-related drug-drug interactions).
Time-sensitive automatic stop orders	Including a stop date in antibiotic orders, after which the antimicrobial order is removed from the patient's active medication orders, can promote timely discontinuation of antibiotics. This may be particularly valuable for antibiotics where durations are short and well-defined (e.g., surgical prophylaxis).
Selective reporting of susceptibility testing results	Microbiology labs can partner with stewardship programs to report select antibiotics that are consistent with hospital guidelines or use "cascade" reporting in which susceptibilities to broader-spectrum agents are reported only if resistance to narrower-spectrum drugs is demonstrated.
Comments in microbiology reports	Comments in microbiology reports may guide prescribers to making appropriate antibiotic decisions, for example, by indicating bacterial growth may reflect contamination or guiding providers to using specific preferred antibiotics.
Rapid diagnostic tests for bacterial diagnostics	Molecular diagnostic tests (for example, tests using PCR, microarrays, or mass spectroscopy) may allow more rapid identification of organisms or resistance determinants than traditional culture-based techniques. When implemented together with real-time stewardship program guidance, assays performed on positive blood cultures may reduce time to optimal antibiotic therapy and improve patient outcomes.
Nursing-based interventions	Key opportunities to engage bedside nurses in stewardship activities include optimizing the appropriate collection of microbiology cultures, encouraging intravenous to oral transitions, and prompting antibiotic timeouts.

PCR, Polymerase chain reaction.
Adapted from Centers for Disease Control and Prevention. Core Elements of Hospital Antibiotic Stewardship Programs. Atlanta, GA: US Department of Health and Human Services, CDC; 2019. Available at https://www.cdc.gov/antibiotic-use/core-elements/hospital.html

Table 226.2 Comparing Preauthorization and Prospective Audit and Feedback

PREAUTHORIZATION	PROSPECTIVE AUDIT AND FEEDBACK
Allows stewardship oversight from the point of antimicrobial initiation.	Stewardship oversight focuses on antimicrobial duration, de-escalation, or discontinuation.
Requires dedicated and expert personnel for "real-time" phone calls or electronic communication through at least the majority of the day.	Resource intensive, particularly if done hospital-wide, but can be scaled to available resource (e.g., focused on a single unit).
Opportunity to counsel provider on optimal diagnostic testing before starting antimicrobials.	Culture and susceptibility testing may be available at the time the intervention is made, such that recommendations for definitive therapy can be made.
Requires a coordinated process including providers, pharmacy, and the stewardship program to ensure approved antimicrobials are dispensed promptly and that antimicrobial requests that are declined are not dispensed.	Prescribers may or may not follow the recommendations made by the stewardship program.
May be seen as a threat to autonomy and/or having the potential to delay therapy.	Generally well-received by providers, with high adherence to recommendations reported.
Only the antimicrobials that are restricted are affected and only at the point of initiation.	More flexibility for the stewardship team regarding the timing of interventions, as well as the potential to act on all antimicrobials prescribed to an individual patient during a single discussion.

antibiotic use, resistance, and *C. difficile* rates; reporting antibiotic use and resistance metrics to prescribers and hospital leaders; and education.

Prospective Audit and Feedback Versus Preauthorization

Two broad approaches to antimicrobial stewardship are supported by the IDSA/SHEA guideline and the CDC Core Elements: preauthorization and prospective audit and feedback. Preauthorization is a strategy in which the clinician must contact the ASP and secure approval for use of the antimicrobial before prescribing the drug. In contrast, prospective audit and feedback is performed by the ASP 48-72 hours after the start of antimicrobial therapy, and recommendations for antimicrobial de-escalation, discontinuation, transition from intravenous to oral therapy, change in dose, or changes in duration are made. Each of these approaches has pros and cons (Table 226.2), and ASPs generally adapt these broad strategies to the local context and availability of resources, often using a hybrid approach. "Handshake stewardship" is a specific type of audit and feedback where recommendations from the ASP are delivered face-to-face to prescribers; this approach has the advantage of developing collaborative relationships but is resource intensive and therefore may not be feasible in all settings. Regardless of which strategy is used, it is critical that ASPs view the interaction with the prescriber as an opportunity to collaboratively optimize antimicrobial therapy and that the guidance provided is evidence-based and, whenever available, aligned with local clinical practice guidelines.

Development and Implementation of Local Guidelines

Creation of evidence-based **local guidelines** containing recommendations for empiric and definitive therapy for common infectious diseases diagnoses and syndromes is a key activity of ASPs. In pediatrics, key target conditions include community-acquired pneumonia, urinary tract infections, intraabdominal infections, skin and soft tissue infections, and neonatal and pediatric sepsis. Coproduction of these guidelines with relevant stakeholders, including prescribing clinicians, offers a unique opportunity to broadly improve antimicrobial prescribing through standardization of evidence-based practices. Because the approach is agreed upon a priori, adhering to these recommendations may also be more appealing to prescribers relative to more "top-down" approaches, where the ASP is either unilaterally authorizing antimicrobial use or providing directive feedback.

Education

While educational interventions alone are insufficient to improve antimicrobial use, education is critical to the success of ASPs and should be integrated along with other strategies. Education can take place in many forms, including at the point of an individual prescriber-steward interaction during preauthorization or prospective audit and feedback; as part of the implementation of a new local treatment guideline or other specific improvement intervention; or as a stand-alone or recurring lecture focused on a topic of relevance, preferably one deemed important to the learners.

OUTPATIENT ANTIMICROBIAL STEWARDSHIP STRATEGIES

The majority of antibiotic use in children occurs in the outpatient setting. Effective outpatient antimicrobial stewardship is therefore critical and requires approaches distinct from the individual-level preauthorization and prospective audit with feedback that form the foundation of inpatient antimicrobial stewardship. Relative to hospital-based stewardship, fewer studies have been conducted in outpatient settings to inform best practices. However, the CDC provides four elements to guide outpatient stewardship efforts, which include commitment to optimizing antibiotic prescribing, including appointment of an accountable leader; actions for policy and practice; tracking and reporting antibiotic use; and education and expertise.

Commitment

In addition to commitment on the part of practice or system leadership, **a written and publicly displayed commitment poster** stating that the individual clinician will only prescribe antibiotics when they are indicated is a powerful tool to reduce unnecessary antibiotic prescribing in the ambulatory setting. This strategy is particularly appealing, as it requires minimal resources to implement and may not only influence provider behavior but also stimulate a discussion between provider and patient around the importance of judicious antibiotic use. In addition, clear communication across clinic providers and staff to ensure this message is consistent and practices are aligned is paramount.

Actions to Improve Antibiotic Prescribing

As with hospital-based stewardship programs, development and implementation of **local guidelines** to inform antibiotic prescribing for relevant conditions is a key strategy for ambulatory stewardship programs. Target conditions in this setting include acute respiratory tract infections, such as pharyngitis, sinusitis, otitis media, and community-acquired pneumonia, given that these conditions account for the vast majority of ambulatory antibiotic use and are associated with significant variation in antibiotic prescribing practices across clinics. A number of strategies have been used to optimize adherence to such guidelines, including audit with feedback at the practice or provider level, clinician education, and computerized decision support. An additional evidence-based practice that may improve antibiotic use in the outpatient setting for specific conditions is use of **delayed prescriptions**, namely, prescriptions provided to patients with mild infections likely to improve without antibiotics at the time of the clinic visit, with instructions to fill the prescription only if symptoms worsen or fail to improve. Delayed prescribing is endorsed by the American Academy of Pediatrics for acute otitis media and acute sinusitis. This type of

"contingency plan" may contribute to patient and parent acceptance of an initial recommendation against antibiotics.

Education

Education is also a fundamental element of outpatient stewardship. In contrast to education in the inpatient setting, which focuses on clinicians, education in the ambulatory setting additionally requires a focus on the patient and family, as well as teaching providers to promote optimal communication. For example, a commonly cited challenge to judicious antibiotic prescribing in the pediatric outpatient setting is a perception on the part of providers that antibiotic prescriptions are strongly desired by parents, even in situations where bacterial infections are unlikely. **However, several studies have refuted this notion and instead suggest that communication of both "positive" treatment recommendations (e.g., specific measures to take to improve symptoms) and "negative" treatment recommendations (e.g., recommendations against using antibiotics when they are not indicated, antibiotic adverse events) is a driver of parent satisfaction and desired by parents.**

TRACKING AND REPORTING ANTIMICROBIAL USE MEASURES

Quantifying antimicrobial use and reporting it to key stakeholders, including clinicians and hospital leadership, are key elements for both inpatient and outpatient stewardship efforts.

Antimicrobial Use Measures

Most antimicrobial stewardship measures are process measures. **The preferred metric for inpatient antimicrobial use is antimicrobial days of therapy (DOTs) per 1,000 patient days.** Each antimicrobial prescribed on each hospital day counts as one DOT, independent of the number of doses the patient receives in the day. For example, if a patient with an intraabdominal infection receives ceftriaxone and metronidazole on the same day, each drug contributes 1 DOT and the total DOT is 2. If instead, this patient received meropenem alone, just 1 DOT would be recorded. DOT/1,000 patient days is a metric particularly useful to track antimicrobial use over time or in response to a specific stewardship intervention and can be measured for an individual drug, a specific unit, or throughout the hospital. Limitations of the measure are that it does not measure the appropriateness of therapy or spectrum of activity, and as demonstrated in the previous example, multidrug regimens will contribute a greater number of DOTs even if the spectrum of the combination of drugs is narrower than the single drug. Finally, DOT/1,000 patient days does not account for differences in patient complexity, illness severity, or comorbid conditions, a limitation that should be considered when making comparisons across units or hospitals.

Antibiotic use measures in the outpatient setting can include individual- or facility-level tracking of antibiotic prescriptions in all visits, or in visits with a certain diagnosis or collection of diagnoses. Metrics could include the proportion of visits in which antibiotics were prescribed, the appropriateness of the antibiotic choice (e.g., broad- versus narrow-spectrum, compliance with local guidelines), and/or the correct duration of antibiotics for a given condition. **Individual-level measures are preferred**, as they facilitate audit and feedback based on individual performance, as well as peer comparisons, strategies that have been used successfully to improve adherence to evidence-based guidelines for antibiotic use in the outpatient setting.

Outcome Measures

The impact of reductions in antimicrobial use through implementation of ASPs or specific interventions should ideally be linked to clinical outcomes. In practice, however, specific outcomes can be difficult to identify, particularly in children where adverse outcomes attributable to antibiotics are uncommon (e.g., *C. difficile* infection) or resource intensive to measure (e.g., drug adverse events, patient-reported outcomes). Improvement in antibiotic resistance rates over time is an appealing hospital-level measure, but improvement occurs slowly and is influenced by multiple factors other than inpatient antibiotic use, including infection prevention and control practices and outpatient prescribing patterns. Other outcome measures that may be considered include revisits, readmissions, or hospital length of stay, though few studies have evaluated these outcomes, which may be confounded by multifactorial influences. Importantly, because antibiotic exposure has been clearly linked to development of antibiotic resistance, *C. difficile* infection, and other adverse drug events, decreases in antibiotic use process measures without a worsening of clinical outcomes are relevant and should be considered sufficient for defining success, even if the reduction in antibiotic use does not result in improved clinical outcomes.

SUMMARY

Antimicrobial stewardship is an important element of patient safety and quality that is the responsibility of all clinicians prescribing antimicrobials. Formal ASPs can guide these local efforts, and abundant evidence demonstrates the positive impact of these programs on improving antibiotic use in both the inpatient and ambulatory settings. Key needs in the field of pediatric antimicrobial stewardship include development of risk-adjusted antibiotic use measures for benchmarking across centers; development of measures to quantify antibiotic-associated harm; incorporating perspectives from nursing and patients/families; and adapting stewardship strategies and organizational structures successful in acute care hospitals to other settings.

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Section 4

Gram-Positive Bacterial Infections

Chapter 227

Staphylococcus

Carol M. Kao, Patrick J. Reich, and Stephanie A. Fritz

Staphylococci are hardy, aerobic, gram-positive bacteria that grow in pairs and clusters and are ubiquitous as normal flora of humans and present on fomites and in dust. They are resistant to heat and drying and may be recovered from nonbiologic environments weeks to months after contamination. Strains are classified as *Staphylococcus aureus* if they are coagulase positive or as one of the many species of **coagulase-negative staphylococci** (e.g., *S. epidermidis, S. lugdunensis, S. saprophyticus, S. haemolyticus*). *S. aureus* has many virulence factors that mediate various serious diseases, whereas coagulase-negative staphylococci tend to be less pathogenic unless an indwelling foreign body (e.g., intravascular catheter) is present. *S. aureus* strains resistant to β-lactam antibiotics, typically referred to as **methicillin-resistant *Staphylococcus aureus* (MRSA)**, are a significant problem in both community and hospital settings.

227.1 *Staphylococcus aureus*

Carol M. Kao, Patrick J. Reich, and Stephanie A. Fritz

S. aureus is the most common cause of skin and soft tissue infections (SSTIs). **Bacteremia** (primary or secondary) is common and can be associated with, or can result in, musculoskeletal infection (osteomyelitis, pyomyositis, septic arthritis), pneumonia, endocarditis, and rarely meningitis. **Toxin-mediated diseases**, including food poisoning,

staphylococcal scarlet fever, scalded skin syndrome, and toxic shock syndrome (TSS), are caused by certain *S. aureus* strains.

ETIOLOGY

S. aureus strains produce a wide spectrum of virulence factors. These factors contribute to pathogenesis in human disease by protecting the organism from host defenses, causing local tissue damage, and affecting noninfected sites through toxin elaboration.

Most strains of *S. aureus* possess factors that protect the organism from host defenses. The microbial surface components recognizing adhesive matrix molecules **(MSCRAMMs)** are a family of cell wall–anchored proteins with a broad spectrum of virulence properties, including host tissue and cell adhesion and invasion, biofilm formation, and evasion of the host immune response. Many staphylococci produce a loose extracellular polysaccharide that promotes formation of **biofilms**, which may interfere with opsonophagocytosis. Production of clumping factor and coagulase differentiates *S. aureus* from coagulase-negative staphylococci. **Clumping factor** interacts with fibrinogen to create large clumps of organisms, interfering with effective phagocytosis. **Coagulase** causes plasma to clot by interacting with fibrinogen and may have an important role in abscess formation. **Protein A** is located on the outermost coat of the cell wall and can absorb serum immunoglobulins, preventing opsonization and thus inhibiting phagocytosis. The **chemotaxis inhibiting protein of *S. aureus* (ChIPS)** and **extracellular adherence protein (Eap)** interfere with the native host immune response by inhibiting leukocyte chemotaxis. The staphylococcal enzyme **catalase** inactivates hydrogen peroxide, promoting intracellular survival.

Many strains of *S. aureus* produce substances that cause local tissue destruction. A number of immunologically distinct **hemolysins** that act on cell membranes and cause tissue necrosis have been identified (α-toxin, β-hemolysin, δ-hemolysin). The leukocidins (LukAB, LukDE, Panton-Valentine leucocidin) are pore-forming cytotoxins resulting in increased cell membrane permeability and eventual cell death. Strains of *S. aureus* that produce **Panton-Valentine leukocidin** are associated with more severe and invasive skin disease, necrotizing pneumonia, and osteomyelitis. Many strains of *S. aureus* release one or more exotoxins. **Exfoliatins A and B** are serologically distinct proteins that produce localized (bullous impetigo) or generalized (scalded skin syndrome, staphylococcal scarlet fever) dermatologic manifestations (see Chapter 706).

S. aureus can produce >20 distinct **enterotoxins** (types A-V). Ingestion of preformed enterotoxin, particularly types A or B, can result in **food poisoning**, resulting in vomiting and diarrhea and, in some cases, profound hypotension.

Toxic shock syndrome toxin-1 (TSST-1) is associated with **toxic shock syndrome (TSS)**, related to menstruation and focal staphylococcal infection (see Chapter 227.2). TSST-1 is a superantigen that induces production of interleukin (IL)-1 and tumor necrosis factor (TNF), resulting in hypotension, fever, and multisystem involvement. Focal infections associated with enterotoxins A or B also may be associated with nonmenstrual TSS.

S. aureus also possesses intrinsic factors that can contribute to pathogenesis, including proteins that promote adhesion to fibrinogen, fibronectin, collagen, and other human proteins. Expression of proteins that mediate antibiotic resistance is also of critical importance. Although historically sensitive to penicillin, *S. aureus* isolates now almost universally produce **penicillinase** or **β-lactamase**, which inactivates many β-lactams at the molecular level and represents the major resistance mechanism against many penicillin and some cephalosporin antibiotics. Thus treatment of *S. aureus* with β-lactam antibiotics requires either a penicillinase-resistant β-lactam ring (e.g., antistaphylococcal penicillins such as oxacillin or nafcillin) or combination with a β-lactamase inhibitor (e.g., ampicillin-sulbactam). Production of altered **penicillin-binding proteins (PBPs)** in the bacterial cell wall mediates resistance to penicillinase-resistant antibiotics; an **altered PBP-2A**, encoded by the gene *mecA,* is responsible for the methicillin, cephalosporin, and carbapenem resistance of MRSA isolates.

EPIDEMIOLOGY

S. aureus is a significant cause of morbidity and mortality, particularly in pediatric healthcare-associated infections including infections of the bloodstream, surgical sites, and respiratory tract. Genetically distinct strains of MRSA are termed *community-associated MRSA* (CA-MRSA); USA300 is the predominant pulsotype circulating in the United States. These strains led to an epidemic of SSTIs, and occasionally necrotizing invasive infections, in healthy individuals without the traditional healthcare-associated risk factors for MRSA. Ambulatory visits for purulent SSTIs rose from 5 million to 11 million annually between 2000 and 2013 but have since plateaued and even declined in some populations. Additionally, the incidence of invasive nosocomial MRSA infections (e.g., bacteremia) has also declined; however, the incidence of SSTIs and bloodstream infections caused by MSSA has increased.

Approximately 20–40% of healthy individuals carry at least one strain of *S. aureus* in the anterior nares at any given time, with intermittent carriage occurring in up to 70% of individuals. In children, the oropharynx, umbilicus, inguinal folds, and rectum are also important reservoirs of *S. aureus* carriage. Many neonates are colonized within the first 2 months of life, usually by a maternal strain. The prevalence of colonization with MRSA in the general pediatric population ranges from 2% to 10%, with higher prevalence in some locales and in children with significant healthcare exposure and chronic medical conditions.

S. aureus is acquired and transmitted through close person-to-person contact and contact with contaminated objects or environmental surfaces. *S. aureus* colonization poses a risk for subsequent *S. aureus* infection. In community settings, populations traditionally at high risk for *S. aureus* infection have included athletes, military personnel, young children, veterinarians, injection drug users, and inmates in correctional facilities. However, given the high colonization prevalence in the community, *S. aureus* infections commonly occur in individuals with no identifiable risk factors. In the outpatient setting, SSTI is the most common entity caused by *S. aureus*, accounting for 8 million annual ambulatory visits.

Households are an important reservoir for *S. aureus* transmission because of close personal contact among colonized family members. Increased disease frequency occurs among household contacts of *S. aureus*–colonized or –infected individuals. Additionally, *S. aureus* can persist on environmental surfaces over time. Contamination of environmental surfaces such as hand towels, television remote controls, and bed linens can further perpetuate transmission among household members and is a risk factor for recurrent infection. Thus preventive strategies are aimed at decreasing the burden of *S. aureus* carriage in affected individuals and household members, as well as targeted household environmental surfaces.

PATHOGENESIS

Except in the case of food poisoning resulting from ingestion of preformed enterotoxins, disease associated with *S. aureus* typically begins with colonization. Subsequent disease manifestations in susceptible individuals results either directly from tissue invasion or from injury caused by various toxins and enzymes produced by the organism (Fig. 227.1).

The most significant risk factor for the development of infection is **disruption of intact skin**, including breaches from wounds, skin diseases such as eczema, epidermolysis bullosa, insect bites, burns, ventriculoperitoneal shunts, and central venous catheter placement. Additional risk factors include immunodeficiency and malnutrition, although infection can also occur in otherwise healthy children. Viral infections of the respiratory tract, especially influenza virus infection, may predispose to secondary bacterial infection with staphylococci.

Congenital defects in chemotaxis (hyper-IgE syndromes, Chédiak-Higashi, and Wiskott-Aldrich syndromes) and defective phagocytosis and killing (neutropenia, chronic granulomatous disease) increase the risk for staphylococcal infections. Patients with HIV infection have neutrophils that are defective in their ability to kill *S. aureus* in vitro. Young infants with invasive infection or individuals with *recurrent* pyogenic infection should be evaluated for immune defects, especially those involving neutrophil dysfunction. Poor mucus clearance in children with cystic fibrosis frequently leads to chronic pulmonary staphylococcal colonization and persistent inflammation in these patients.

Infants may acquire type-specific humoral immunity to staphylococci transplacentally. Older children and adults develop antibodies to staphylococci as a result of colonization or minor infections. Antibody

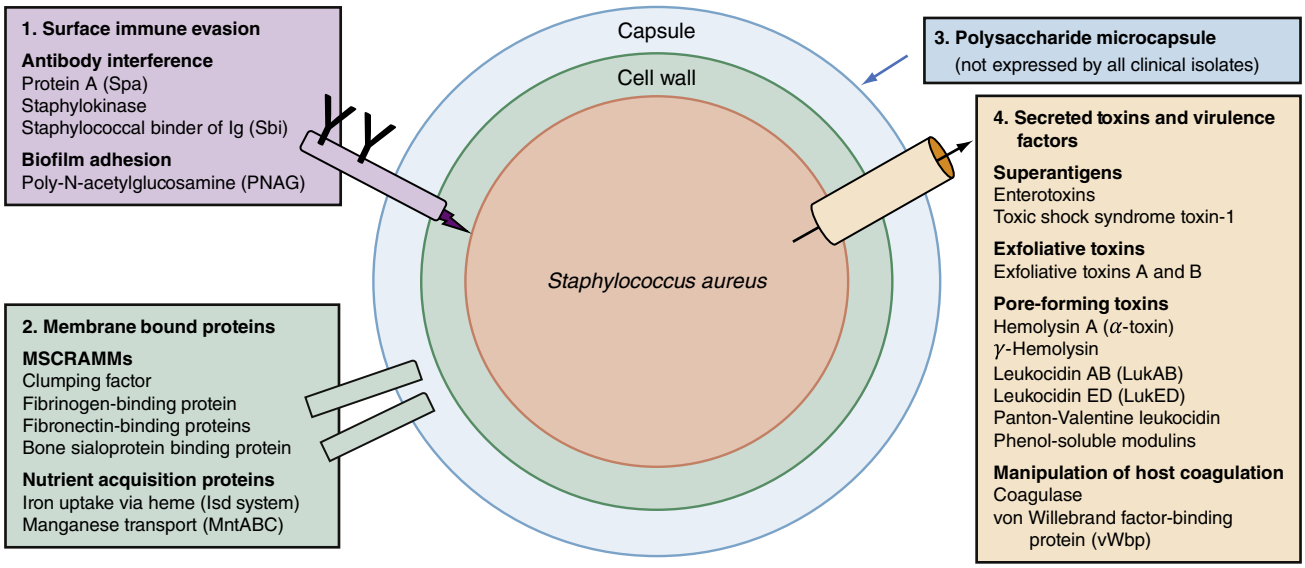

Fig. 227.1 Schematic of virulence factors and relevant surface adhesins of *Staphylococcus aureus*. YY, Immunoglobulin-binding site; MSCRAMMs, microbial surface components that recognize adhesive matrix molecules. *(From Thomsen I, Creech CB. Staphylococcus aureus. In Long SS, Prober CG, Fischer M, Kimberlin DW, eds. Principles and Practice of Pediatric Infectious Diseases, 6th ed. Philadelphia: Elsevier; 2023, Fig. 115.1, p. 711.)*

to the various *S. aureus* toxins appears to protect against those specific toxin-mediated diseases, but humoral immunity does not necessarily protect against focal or disseminated *S. aureus* infection with the same organisms.

CLINICAL MANIFESTATIONS

S. aureus has the potential to invade any tissue. Disease severity is influenced by local suppuration, systemic dissemination with metastatic infection, or systemic effects of toxin production.

Newborn

S. aureus is an important cause of neonatal infections (see Chapter 148).

Skin

S. aureus is an important cause of **pyogenic** skin infections, including impetigo contagiosa, ecthyma, bullous impetigo, folliculitis, furuncles (boils), carbuncles (multiple coalesced boils), and paronychia. **Toxigenic** infection with skin manifestations include staphylococcal scalded skin syndrome and staphylococcal scarlet fever. *S. aureus* is a frequent cause of superinfection of underlying dermatologic conditions, such as eczema, hidradenitis suppurativa, or insect bites. Skin abscesses caused by CA-MRSA commonly affect the lower extremities and buttocks. Up to 70% of individuals with SSTI will experience a recurrent infection. *S. aureus* is also an important cause of traumatic and surgical wound infections and can cause deep soft tissue involvement, including cellulitis and, rarely, necrotizing fasciitis.

Respiratory Tract

Infections of the upper respiratory tract (otitis media, sinusitis) caused by *S. aureus* are rare, in particular considering the frequency with which the anterior nares are colonized. *S. aureus* sinusitis is relatively common in children with cystic fibrosis or defects in leukocyte function and may be the only focus of infection in some children with TSS. Suppurative **parotitis** is a rare infection, but *S. aureus* is a common cause. A membranous **tracheitis** that complicates viral croup may result from infection with *S. aureus,* although other organisms may also be responsible.

Pneumonia caused by *S. aureus* is uncommon but can present with rapidly progressive respiratory failure. Children may present with recent flulike illness (see Chapter 449). Hematogenous pneumonia may be secondary to septic emboli from right-sided endocarditis or septic thrombophlebitis, with or without intravascular devices. Inhalation pneumonia is caused by alteration of mucociliary clearance, leukocyte dysfunction, or bacterial adherence initiated by a viral infection. Common symptoms and signs include high fever, abdominal pain, tachypnea, dyspnea, and localized or diffuse bronchopneumonia or lobar disease. In particular, USA300 strains of *S. aureus* often cause a **necrotizing pneumonitis** that may be associated with early development of empyema, pneumatoceles, pyopneumothorax, and bronchopleural fistulas (Fig. 227.2). Chronic pulmonary infection with *S. aureus* contributes to progressive pulmonary dysfunction in children with cystic fibrosis (see Chapter 454).

Bacteremia and Sepsis

S. aureus bacteremia and sepsis may be primary or secondary because of a localized infection such as an infected central venous catheter or thrombus, bone, or skin and soft tissue. Risk factors for *S. aureus* bacteremia include presence of a central venous catheter, immunodeficiency, malnutrition, recent MRSA STTI, and recent surgery. The onset may be acute and marked by nausea, vomiting, myalgia, fever, and chills.

Prolonged *S. aureus* bacteremia is associated with an increased risk of developing complications such as septic emboli, thrombi, and metastatic foci of infection. Methicillin resistance, musculoskeletal infection, endovascular infection, and delayed intervention for source control are risk factors for prolonged bacteremia. In general, removal of an infected central venous catheter is recommended because of the difficulty clearing *S. aureus* bacteremia in these patients.

A positive blood culture for MRSA or methicillin-sensitive *S. aureus* (MSSA) should always be considered pathogenic, and antistaphylococcus treatment should be initiated with vancomycin or daptomycin with a β-lactam until antimicrobial susceptibility is available. In the absence of an obvious source (isolated bacteremia), endocarditis must be considered. MSSA bacteremia should be treated with a β-lactam such as cefazolin or oxacillin, given poorer outcomes in children treated with vancomycin. Although vancomycin has been traditionally used as first-line treatment of MRSA bacteremia in children, daptomycin and ceftaroline, a β-lactam and fifth-generation cephalosporin, can also be considered. The duration of antibiotic therapy depends on the age and presence of associated infections. In general, 7-14 days of intravenous therapy is appropriate for uncomplicated bacteremia; however, additional studies are needed to determine the optimal duration in children. Repeat blood cultures should be obtained until negative for 2 days to document clearance of bacteremia. Prolonged positive blood cultures while on therapy suggest endocarditis, an infected thrombus, abscess formation, foreign body (central lines, bone prosthesis, or internal fixation of fractures), or other factors leading to poor source control. Whole body MRI or PET-MRI scanning may detect unrecognized metastatic foci. Infectious disease consultation has been shown to improve cure rates and outcomes in children with *S. aureus* bacteremia, including decreased mortality and decreased recurrence of bacteremia.

Muscle
Localized staphylococcal abscesses in muscle, sometimes without septicemia, have been called **pyomyositis**. This disorder is reported most frequently from tropical areas and is termed *tropical pyomyositis,* but also occurs in the United States in otherwise healthy children. Multiple abscesses occur in 30–40% of cases, most commonly affecting the pelvic and lower extremity muscles. History may include prior trauma at the site of the abscess. More commonly, pyomyositis results from seeding secondary to bacteremia, often near the site of osteomyelitis. Surgical drainage and appropriate antibiotic therapy are essential.

Bones and Joints
S. aureus is the most common cause of osteomyelitis and suppurative arthritis in children, most commonly the result of hematogenous seeding and, less often, from a contiguous focus of infection or through inoculation from trauma or a surgical procedure (see Chapters 725 and 726).

Central Nervous System
Meningitis caused by *S. aureus* is uncommon; it is associated with penetrating cranial trauma and neurosurgical procedures (craniotomy, cerebrospinal fluid [CSF] shunt placement) and, less frequently, with endocarditis, parameningeal foci (epidural or brain abscess), prematurity, complicated sinusitis, diabetes mellitus, or malignancy. The CSF profile of *S. aureus* meningitis is indistinguishable from that in other forms of bacterial meningitis (see Chapter 643.1).

Heart
S. aureus is a common cause of acute endocarditis on native valves and results in high rates of morbidity and mortality. Left-sided endocarditis is most common. The clinical presentation can be indolent with symptoms such as malaise, weight loss, or myalgias, and the typical signs of endocarditis are often not present in children (see Chapter 486).

Kidney
S. aureus is a common cause of renal and perinephric abscess, usually of hematogenous origin. Pyelonephritis and cystitis caused by *S. aureus* are unusual (see Chapter 575).

Toxic Shock Syndrome
S. aureus, more commonly MSSA than MRSA, is the principal cause of TSS, which should be suspected in anyone with fever, shock, and/or a diffuse erythroderma (see Chapter 227.2).

Intestinal Tract
Staphylococcal enterocolitis may rarely follow overgrowth of normal bowel flora by *S. aureus,* which can result from broad-spectrum oral antibiotic therapy. Diarrhea is associated with blood and mucus. Peritonitis associated with *S. aureus* in patients receiving long-term ambulatory peritoneal dialysis usually involves the catheter tunnel.

Food poisoning may be caused by ingestion of *preformed* enterotoxins produced by staphylococci in contaminated foods (see Chapter 387). The source of contamination is often colonized or infected food workers. Approximately 2-7 hours after ingestion of the toxin, sudden, severe vomiting begins. Watery diarrhea may develop, but fever is absent or low grade. Symptoms rarely persist >12-24 hours. Rarely, shock and death may occur.

DIAGNOSIS
The diagnosis of *S. aureus* infection depends on isolation of the organism in culture from the site of infection, such as cellulitis aspirates, abscess cavities, blood, bone, or joint aspirates, or other sites of infection. In patients with musculoskeletal infection, ~50% of children will have blood cultures that yield *S. aureus*. Thus surgical debridement or an aspirate or biopsy obtained by interventional radiology can maximize recovery of the organism, which is important for targeted antibiotic selection. Tissue samples or fluid aspirates in a syringe provide the best culture material. Because of the high prevalence of MRSA and the severity of *S. aureus* infections, it is important to obtain cultures before starting antibiotic treatment. The organism can be grown readily in liquid and on solid media. After isolation, identification is made on the basis of Gram stain and coagulase, clumping factor, and catalase activity. Molecular techniques and mass spectrometry are used to supplement traditional identification and antibiotic susceptibility methods. These technologies may allow for rapid species identification from positive blood cultures and simultaneously identify genetic patterns associated with methicillin resistance, such as presence of the *mecA* gene produced by MRSA. Diagnosis of *S. aureus* food poisoning is usually made on the basis of epidemiologic and clinical findings.

Differential Diagnosis
Many of the clinical entities caused by *S. aureus* can also be caused by other bacterial pathogens, and consideration of the differential diagnosis is particularly important when making empirical antibiotic choices before definitive identification of the offending pathogen. Skin lesions caused by *S. aureus* may be indistinguishable from those caused by group A streptococci, although *S. aureus* usually expands slowly and is more likely to be suppurative, whereas group A streptococci are prone to spread more rapidly and can be very aggressive. Fluctuant skin and soft tissue lesions also can be caused by other organisms, including *Mycobacterium tuberculosis,* atypical mycobacteria, *Nocardia*, *Bartonella henselae* (cat-scratch disease), *Francisella tularensis,* and various fungi. *S. aureus* pneumonia is often suspected in very ill-appearing children or after failure to improve with standard treatment that does not cover *Staphylococcus,* or on the basis of chest radiographs that reveal pneumatoceles, pyopneumothorax, or lung abscess (see Fig. 227.2). Other etiologies of cavitary pneumonias include group A streptococci, *Klebsiella pneumoniae,* and *M. tuberculosis*. In bone and joint infections, culture is the only reliable way to differentiate *S. aureus* from other etiologies, including group A streptococci and, in young children, *Kingella kingae*.

TREATMENT
Antibiotic therapy alone is rarely effective in individuals without source control of the focus of infection. Loculated collections of purulent material should be relieved by incision and drainage. Foreign bodies (e.g., orthopedic instrumentation, ventricular shunts, central venous catheters) should be removed, if possible. Therapy always should be initiated with an antibiotic consistent with the local staphylococcal susceptibility patterns, severity, and anatomic site of infection. For most patients with serious *S. aureus* infection, initial intravenous (IV) treatment is usually recommended, and transition to oral therapy can be considered based on clinical response and source of infection.

Treatment of *S. aureus* osteomyelitis (Chapter 725), meningitis (Chapter 643.1), and endocarditis (Chapter 486) is discussed in the respective chapters on these diagnoses.

Initial treatment for serious infections thought to be caused by **methicillin-susceptible *S. aureus* (MSSA)** should include a semisynthetic penicillin (e.g., nafcillin, oxacillin) or a first-generation cephalosporin (e.g., cefazolin). Penicillin and ampicillin are not appropriate, because >90% of all staphylococci isolated, regardless of source, are resistant to these agents. Addition of a β-lactamase inhibitor (clavulanic acid, sulbactam, tazobactam) to a penicillin-based drug also confers antistaphylococcal activity but has no effect on MRSA. The spectrum of these β-lactam/β-lactamase inhibitor agents (which includes gram-negative bacteria and anaerobes) can be an advantage when broad empirical coverage is needed, but narrower coverage should be selected once *S. aureus* is identified. *Antistaphylococcal penicillins and most cephalosporins do not provide activity against MRSA.*

Vancomycin is typically selected for initial treatment for penicillin-allergic individuals and those with suspected serious infections caused by MRSA. Although serum level monitoring has traditionally been used for patients receiving vancomycin, this method is no longer recommended for severe MRSA infections. Instead, calculating the ratio of area under the curve (AUC) over 24 hours to the minimum inhibitory concentration (MIC) as the primary predictor of vancomycin activity is currently recommended. Monitoring for nephrotoxicity is also important while on vancomycin therapy. Vancomycin intermediate *S. aureus* strains (VISAs), defined as having an MIC of vancomycin greater than 2 μg/mL, and, rarely, vancomycin-resistant strains of *S. aureus* (VRSA, MIC of vancomycin >16 μg/mL) have also been reported, mostly in patients being treated with vancomycin. For critically ill patients with

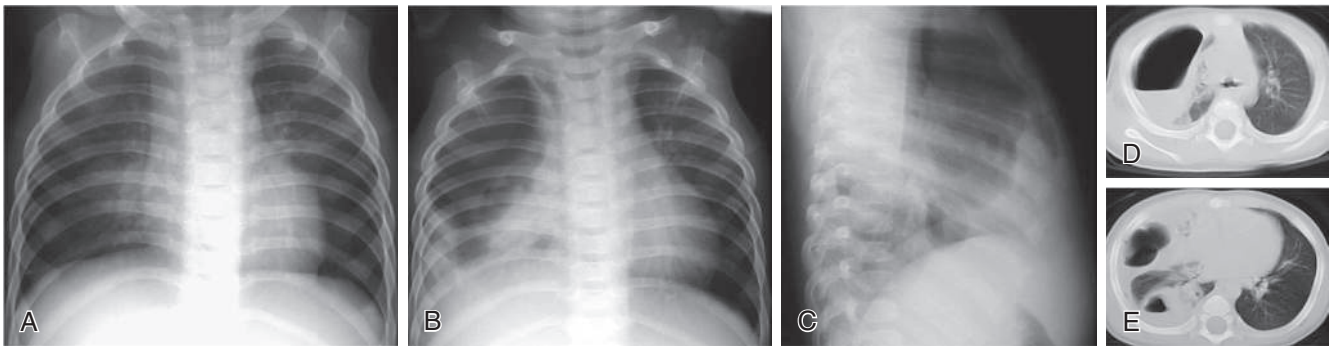

Fig. 227.2 Progressive methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia with pneumatoceles in a previously healthy 9-mo-old male. Chest radiographic findings spanning 4 days showed a perihilar right lower lobe infiltrate (**A**) progressing to a worsening infiltrate and large hydropneumothorax with mediastinal shift (**B** and **C**) despite appropriate therapy. Axial CT of the chest without contrast (lung windows) showed partial loculation of hydropneumothorax, multilobar consolidation, pneumatoceles, and atelectasis (**D** and **E**). Video-assisted thoracoscopic surgery (VATS) was performed, and a chest tube was placed for 3 days. MRSA was isolated from pleural fluid. After 2 weeks of clindamycin therapy, the chest radiograph had only minor abnormalities. *(Courtesy Dr. Sarah S. Long.)*

suspected *S. aureus* infection, empirical therapy with both vancomycin and a β-lactam (cefazolin or nafcillin) should be considered until culture results are available. Initial treatment with IV **clindamycin** followed by a transition to oral clindamycin can be considered in bone, joint, and soft tissue infection; however, not all strains of MSSA or MRSA are susceptible to clindamycin. Inducible clindamycin resistance in isolates initially reported as susceptible must be ruled out by D-test or molecular methods. Clindamycin is bacteriostatic and should not be used to treat endocarditis, persistent bacteremia, or CNS infections caused by *S. aureus*. Given that the mechanism of action of clindamycin involves inhibition or protein synthesis, many experts use clindamycin as an adjunctive agent to treat *S. aureus* toxin–mediated illnesses (e.g., TSS) to inhibit toxin production.

Although the broad-spectrum carbapenems (meropenem, ertapenem, and imipenem) have activity against MSSA, they have no activity against MRSA. As a result, carbapenems are rarely used for empirical therapy of possible staphylococcal infection and are too broad in most cases for use in identified MSSA infections. **Linezolid**, **daptomycin**, and **ceftaroline** are useful for serious *S. aureus* infections, providing excellent coverage of MRSA and MSSA (Table 227.1). A number of novel antistaphylococcal antibiotics have emerged for use in resistant or refractory MSSA and MRSA infection in adults that may be required for pediatric therapy in select patients under the guidance of a pediatric infectious disease specialist. These include the lipoglycopeptides, including **telavancin**, **oritavancin**, and **dalbavancin**, which are structurally related to vancomycin but have very long half-lives and broad activity against gram-positive organisms. **Rifampin** or **gentamicin** in addition to a β-lactam or vancomycin are recommended for prosthetic-valve endocarditis, although patients need to be monitored closely for adverse side effects; their use as combined therapy for other infections is not recommended.

In many infections, after an initial period of parenteral therapy, patients may be transitioned to oral antimicrobials to complete the course of treatment after determination of antimicrobial susceptibilities. Oral antimicrobials can be used as initial treatment in less severe infections (e.g., skin abscess). **Cephalexin** (25-100 mg/kg/24 hr divided 3-4 times daily PO) and cefadroxil (30 mg/kg/24 hr divided 2 times daily PO for noninvasive infections, 50-60 mg/kg/24 hr divided 2 times daily PO for osteoarticular infections) are absorbed well orally (PO) and are effective against MSSA. (Variable cefadroxil dosing regimens have been described, ranging from 30-150 mg/kg/day divided 2-4 times daily PO.) **Amoxicillin-clavulanate** (40-80 mg amoxicillin/kg/24 hr divided 3 times daily PO) is also effective when a broader spectrum of coverage is required. Clindamycin (30-40 mg/kg/24 hr divided 3-4 times daily PO) is highly absorbed from the intestinal tract and is frequently used for empirical coverage when both MRSA and MSSA are possible and for susceptible MRSA infections or for MSSA in penicillin/cephalosporin-allergic patients. Compliance with oral clindamycin may be limited in small children because of poor palatability of liquid formulations. **Trimethoprim-sulfamethoxazole** (TMP-SMX) may be an effective oral antibiotic for many strains of both MSSA and MRSA for SSTI. Oral linezolid is an option for severe MRSA infections that have improved but require ongoing therapy when more common options are not tolerated or are ineffective because of resistance patterns. The duration of linezolid therapy is typically limited to 2-3 weeks given toxicities such as myelosuppression and peripheral and optic neuropathy with prolonged courses. Despite in vitro susceptibility of *S. aureus* to ciprofloxacin and other quinolone antibiotics, these agents should *not* routinely be used in serious staphylococcal infections, because their use is associated with rapid development of resistance.

The **duration** of antibiotic therapy depends on the anatomic site and severity of infection and response, as determined by the clinical response and, in some cases, radiologic and laboratory findings.

PROGNOSIS

Untreated *S. aureus* septicemia is associated with a high fatality rate, which has been reduced significantly by appropriate antibiotic treatment. *S. aureus* pneumonia can be fatal at any age but is more likely to be associated with high morbidity and mortality in young infants or in patients whose therapy has been delayed. Prognosis also may be influenced by numerous host factors, including nutrition, immunologic competence, and the presence or absence of other debilitating diseases.

PREVENTION

S. aureus is transmitted primarily by direct contact. Strict attention to **hand hygiene** is the most effective measure for preventing the spread of staphylococci between individuals (see Chapter 216). Hospital surveillance programs to identify nosocomial acquisition of *S. aureus* colonization and/or infection are common, particularly in neonatal intensive care units. Clusters of nosocomial cases may be defined by molecular typing, and if associated with a singular molecular strain, investigation to identify any potential point sources (e.g., a colonized healthcare worker or contaminated environmental reservoir) should occur.

As *S. aureus* colonization often predisposes to infection, a number of protocols are aimed at **decolonization**, which is the application of topical antimicrobials to the skin and/or nares to eradicate *S. aureus* colonization. In healthcare settings, decolonization is often performed among vulnerable populations to prevent nosocomial infections. In community settings, decolonization is often recommended for patients with recurrent *S. aureus* skin infections. Decolonization regimens often involve combinations of decontaminating baths (hypochlorite, 1 tsp common bleach solution per gallon of water, or chlorhexidine 4% soap), nasal mupirocin twice daily for at least 5 days, and enhanced hygiene measures, including frequent laundering of household linens and targeted decontamination of frequently touched household surfaces. Although success is not universal, recurrent infections may be reduced, particularly when eradication is done in both the patient and household contacts, especially those with history of SSTI. Most cases of mild, recurrent disease will resolve in time without these measures.

Because of the potential severity of infections with *S. aureus* and concerns about emerging resistance, much work has focused on

Table 227.1 Parenteral Antimicrobial Agent(s) for Treatment of Serious *Staphylococcus aureus* Infections

SUSCEPTIBILITY	ANTIMICROBIALS	COMMENTS
I. INITIAL EMPIRICAL THERAPY (ORGANISM OF UNKNOWN SUSCEPTIBILITY)		
Drugs of choice	Vancomycin + nafcillin/oxacillin or cefazolin	For **life-threatening infections** (e.g., septicemia, endocarditis, CNS infection); linezolid, daptomycin, or ceftaroline could be substituted depending on the clinical scenario and site of infection
	Vancomycin	For **non–life-threatening infection** without signs of severe sepsis (e.g., skin infection, cellulitis, osteomyelitis, pyarthrosis) when prevalence of MRSA infection in the community is >20% of all *S. aureus* infections
	Cefazolin or nafcillin/oxacillin	For **non–life-threatening infection** when low likelihood of MRSA is suspected
	Clindamycin	For non–life-threatening infection without signs of severe sepsis when rates of MRSA infection in the community is substantial (>20% of all *S. aureus* infections) and prevalence of clindamycin resistance is low
II. METHICILLIN-SUSCEPTIBLE, PENICILLIN-RESISTANT *S. AUREUS*		
Drugs of choice	Cefazolin or oxacillin/nafcillin	May change to oral therapy after infection is controlled in low-risk situations
Alternatives (depending on susceptibility results)	Clindamycin	Only for patients with a serious penicillin allergy and clindamycin-susceptible strain
	Vancomycin	Only for penicillin- and cephalosporin-allergic patients
	Ampicillin + sulbactam	When broader coverage, including gram-negative organisms and/or anaerobes is required
III. METHICILLIN-RESISTANT *S. AUREUS* (MRSA)		
Drugs of choice	Vancomycin (some combine with a β-lactam) (some may begin with ceftaroline)	Linezolid, daptomycin, or ceftaroline* could be substituted or added depending on the clinical scenario, site of infection, or persistent bacteremia
Alternatives: susceptibility testing results available before alternative drugs are used	Clindamycin (if susceptible)	
	Trimethoprim-sulfamethoxazole	
	Doxycycline	

*Linezolid, daptomycin, and ceftaroline are agents with activity and efficacy against multidrug-resistant, gram-positive organisms, including *S. aureus*. Because experience with these agents in children is limited, consultation with an infectious diseases specialist should be considered before use. Daptomycin is ineffective for treatment of pneumonia, as it is inactivated by pulmonary surfactant.

developing a staphylococcal vaccine for use in high-risk patients, but to date, clinical trials have been disappointing. Because *S. aureus* is frequently a co-infection in severe influenza infections, an indirect preventive impact against staphylococcal pneumonia and tracheitis may be achieved through annual influenza vaccination.

To prevent *S. aureus* food poisoning, cooked foods should be eaten immediately or refrigerated within 2 hours of preparation to prevent multiplication of *S. aureus* that may have contaminated the food (see Chapter 387). Treatment is supportive.

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227.2 Toxic Shock Syndrome

Carol M. Kao, Patrick J. Reich, and Stephanie A. Fritz

Toxic shock syndrome (TSS) is an acute and potentially severe illness characterized by fever, hypotension, diffuse erythroderma with subsequent desquamation on the hands and feet, and multisystem involvement.

ETIOLOGY

TSS is caused by TSST-1–producing and some enterotoxin-producing strains of *S. aureus,* which may colonize the skin or mucous membranes or cause focal sites of staphylococcal infection.

EPIDEMIOLOGY

TSS continues to occur in the United States in men, women, and children, with the highest rates in menstruating women 15-25 years of age.

Nonmenstrual TSS is associated with *S. aureus*–infected nasal packing and wounds, sinusitis, tracheitis, pneumonia, empyema, abscesses, burns, osteomyelitis, and primary bacteremia. The majority of strains of *S. aureus* associated with TSS are methicillin susceptible. Most strains of USA300, the predominant clone of community-associated MRSA in the United States, do not possess the genes expressing the most common TSS superantigens; however, MRSA-associated TSS can occur.

PATHOGENESIS

The primary toxin associated with TSS is TSST-1, although a significant proportion of nonmenstrual TSS is caused by one or more staphylococcal enterotoxins. These toxins act as **superantigens**, which trigger cytokine release, causing massive loss of fluid from the intravascular space and end-organ cellular injury. Epidemiologic and in vitro studies suggest that these toxins are selectively produced in a clinical environment consisting of a neutral pH, a high P_{CO_2}, and an aerobic P_{O_2}, which are the conditions found in abscesses and the vagina with tampon use during menstruation. The risk factors for symptomatic disease include a nonimmune host who is colonized with a toxin-producing organism that is exposed to focal growth conditions (menstruation plus tampon use or abscess) that in turn induce toxin production. Some hosts may have a varied cytokine response to TSST-1 exposure, helping to explain a spectrum of severity of TSS that may include staphylococcal scarlet fever. The overall mortality rate of treated patients is 3–5% when treated early.

Approximately 90% of adults have antibody to TSST-1 without a history of clinical TSS, suggesting that most individuals are colonized at some point with a toxin-producing organism at a site (e.g., anterior nares) where low-grade or inactive toxin exposure results in an immune response without disease.

CLINICAL MANIFESTATIONS

The diagnosis of TSS is based on clinical manifestations (Table 227.2). Milder cases and those with incomplete clinical characteristics may be common, particularly if the nidus of infection is addressed quickly (e.g., removal of a tampon or nasal packing). The onset of classic TSS is abrupt, with high fever, vomiting, and diarrhea, and is accompanied by sore throat, headache, and myalgias. A diffuse erythematous rash (sunburn-like or scarlatiniform) appears within 24 hours and may be associated with hyperemia of pharyngeal, conjunctival, and vaginal mucous membranes. A strawberry tongue is common. Symptoms may include alterations in the level of consciousness, oliguria, and hypotension, which in severe cases may progress to shock and disseminated intravascular coagulation. Complications, including acute respiratory distress syndrome (ARDS), myocardial dysfunction, and renal failure, are commensurate with the degree of shock. Recovery occurs within 7-10 days and is associated with desquamation, particularly of the palms and soles; hair and nail loss have also been observed after 1-2 months. Immunity to the toxins is slow to develop, so recurrences can occur, especially if there is inadequate antibiotic treatment and/or recurrent tampon use. Many cases of apparent scarlet fever without shock may be caused by TSST-1–producing *S. aureus* strains.

DIAGNOSIS

There is no specific laboratory test, and diagnosis depends on meeting certain clinical and laboratory criteria in the absence of an alternative diagnosis (see Fig. 227.2). Appropriate tests reveal involvement of multiple organ systems, including the hepatic, renal, muscular, gastrointestinal, cardiopulmonary, and central nervous systems. Bacterial cultures of the associated focus (vagina, abscess) before administration of antibiotics usually yield *S. aureus,* although this is not a required element of the definition.

Table 227.2 Toxic Shock Syndrome (Other Than Streptococcal) (TSS) 2011 Case Definition

CLINICAL CRITERIA

1. Fever: temperature ≥102.0°F (≥38.9°C)
2. Rash: diffuse macular erythroderma
3. Desquamation: 1-2 weeks after onset of rash
4. Hypotension: systolic blood pressure ≤90 mm Hg for adults or less than fifth percentile by age for children age less than 16 years
5. Multisystem involvement (three or more of the following organ systems):
   - Gastrointestinal: vomiting or diarrhea at onset of illness
   - Muscular: severe myalgia or creatine phosphokinase level at least twice the upper limit of normal
   - Mucous membrane: vaginal, oropharyngeal, or conjunctival hyperemia
   - Renal: blood urea nitrogen or creatinine at least twice the upper limit of normal for laboratory or urinary sediment with pyuria (≥5 leukocytes per high-power field) in the absence of urinary tract infection
   - Hepatic: total bilirubin, alanine aminotransferase enzyme, or aspartate aminotransferase enzyme levels at least twice the upper limit of normal for laboratory
   - Hematologic: platelets less than 100,000/mm^3
   - Central nervous system: disorientation or alterations in consciousness without focal neurologic signs when fever and hypotension are absent

LABORATORY CRITERIA FOR DIAGNOSIS

Negative results on the following tests, if obtained:

- Blood or cerebrospinal fluid cultures (blood culture may be positive for *Staphylococcus aureus*)
- Negative serologies for Rocky Mountain spotted fever, leptospirosis, or measles

CASE CLASSIFICATION

Probable

A case that meets the laboratory criteria and in which four of the five clinical criteria described above are present

Confirmed

A case that meets the laboratory criteria and in which all five of the clinical criteria described above are present, including desquamation, unless the patient dies before desquamation occurs

From Centers for Disease Control and Prevention: https://ndc.services.cdc.gov/case-definitions/toxic-shock-syndrome-2011/

Differential Diagnosis

Group A streptococci can cause a similar TSS-like illness, termed **streptococcal TSS** (see Chapter 229), which is often associated with severe streptococcal sepsis or a focal streptococcal infection such as cellulitis, necrotizing fasciitis, or pneumonia.

Kawasaki disease closely resembles TSS clinically but is usually not as severe or rapidly progressive. Both conditions are associated with fever unresponsive to antibiotics, hyperemia of mucous membranes, and an erythematous rash with subsequent desquamation. However, many of the clinical features of TSS are rare in Kawasaki disease, including diffuse myalgia, vomiting, abdominal pain, diarrhea, azotemia, hypotension, ARDS, and shock (see Chapter 208). Kawasaki disease typically occurs in children <5 years old. Measles, scarlet fever, Rocky Mountain spotted fever, leptospirosis, toxic epidermal necrolysis, and bacterial sepsis must also be considered in the differential diagnosis.

TREATMENT

Identification and drainage/removal of any focal source of infection (e.g., abscess, tampon, nasal packing), when present, is essential. Recommended antibiotic therapy for TSS should include the combination of a β-lactamase–resistant antistaphylococcal antibiotic (nafcillin, oxacillin, or cefazolin) *plus* clindamycin to reduce toxin production. Although TSS is most often caused by MSSA, clinicians should consider use of vancomycin in addition to the β-lactam in areas where MRSA rates are very high, when hospital-acquired MRSA is suspected, and when the clinical picture overlaps with staphylococcal sepsis.

TSS often requires intensive supportive care, including aggressive fluid replacement to prevent or treat hypotension, renal failure, and cardiovascular collapse. Inotropic agents may be needed to treat shock; intravenous immunoglobulin may be helpful in severe cases.

PREVENTION

The risk for acquiring menstrual TSS is low (1-2 cases/100,000 menstruating women). Changing tampons at least every 8 hours is recommended. If a fever, rash, or dizziness develops during menstruation, any tampon should be removed immediately and medical attention sought. Avoidance of tampon use with subsequent menstrual cycles may also reduce the risk for recurrent menstrual TSS.

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227.3 Coagulase-Negative Staphylococci

Carol M. Kao, Patrick J. Reich, and Stephanie A. Fritz

At present, there are approximately 50 identified species of coagulase-negative staphylococci **(CoNS)** affecting or colonizing humans. *Staphylococcus epidermidis* and, less often, *Staphylococcus hominis, S. haemolyticus,* and others are widely distributed on the skin and are significant causes of nosocomial infection, particularly in the bloodstream of neonatal and immunocompromised hosts, in surgical patients, and in those with indwelling catheters and other medical devices. *Staphylococcus saprophyticus* is a common cause of urinary tract infection (UTI). *Staphylococcus lugdunensis* and *Staphylococcus schleiferi* can cause severe infection similar to *S. aureus* and have been increasingly recognized as important pathogens since improved species identification with matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectrometry in clinical microbiology laboratories.

EPIDEMIOLOGY

In the United States, CoNS may be the most common cause of hospital-acquired infection, particularly in neonatal intensive care units (NICUs). In many instances, growth of CoNS from clinical specimens represents contamination from skin rather than a cause of true disease, posing significant challenges for clinicians and infection prevention specialists. CoNS are normal inhabitants of the human skin, throat,

mouth, vagina, and urethra. *S. epidermidis* is the most common and persistent species, representing 65–90% of staphylococci present on the skin and mucous membranes. Colonization, sometimes with strains acquired during hospitalization, precedes infection. Alternatively, direct inoculation during surgery may initiate infection of CSF shunts, prosthetic valves, or indwelling vascular lines.

PATHOGENESIS

CoNS produce an exopolysaccharide protective biofilm, particularly on indwelling medical devices, that surrounds the organism and may enhance adhesion to foreign surfaces, resist phagocytosis, and impair penetration of antibiotics. However, the low virulence of CoNS usually requires the presence of another factor for development of clinical disease. Of these, the most significant is the presence of an indwelling catheter or other medical device, including central venous catheters (CVCs), hemodialysis shunts and grafts, CSF shunts (meningitis), peritoneal dialysis catheters (peritonitis), pacemaker wires and electrodes (local infection), prosthetic cardiac valves (endocarditis), and prosthetic joints (septic arthritis). Other risk factors for the development of infection include immature or compromised immunity and significant exposure to antibiotics.

CLINICAL MANIFESTATIONS

Bacteremia

CoNS, specifically *S. epidermidis,* are the most common cause of nosocomial bacteremia, usually in association with central vascular catheters. In neonates, CoNS bacteremia, with or without a CVC, can manifest as localized disease in the CNS, lungs, skin, heart, bones, and joints, or even as sepsis or necrotizing enterocolitis. Persistent positive blood cultures despite adequate antimicrobial therapy is common, particularly when catheters are not removed. In older children with intact immune systems, CoNS bacteremia is indolent and is not usually associated with overwhelming septic shock.

Endocarditis

Infection of native heart valves or the right atrial wall may occur secondary to an infected thrombosis at the end of a central line. *S. epidermidis* and other CoNS may rarely produce native valve subacute endocarditis in previously healthy hosts without a CVC. CoNS is a common cause of prosthetic valve endocarditis, presumably a result of inoculation at surgery. Infection of the valve sewing ring, with abscess formation and dissection, produces valve dysfunction or obstruction, dehiscence, or arrhythmias (see Chapter 486). *S. lugdunensis* has been increasingly associated with severe endocardial infection in adults but remains an uncommon cause in children.

Central Venous Catheter Infection

CVCs become infected through the exit site and subcutaneous tunnel, which provide a direct path to the bloodstream. *S. epidermidis* is the most frequent pathogen, in part because of its high rate of cutaneous colonization. Line sepsis is usually manifested as fever and leukocytosis; tenderness and erythema may be present at the exit site or along the subcutaneous tunnel. Catheter thrombosis may complicate line sepsis. Disease severity with CoNS is often less severe than other etiologies of line infection.

Cerebrospinal Fluid Shunts

CoNS, introduced at surgery, is the most common pathogen associated with CSF shunt meningitis. Most infections (70–80%) occur within 2 months of the operation and manifest as signs of meningeal irritation, fever, increased intracranial pressure (headache, vomiting), or peritonitis from the intraabdominal position of the distal end of the shunt tubing.

Urinary Tract Infection

S. saprophyticus is a common cause of primary UTIs in sexually active females. Manifestations are similar to those characteristics of UTI caused by *Escherichia coli* (see Chapter 575). CoNS also cause asymptomatic UTI in hospitalized patients with urinary catheters and after urinary tract surgery or transplantation.

DIAGNOSIS

Because *S. epidermidis* is a common skin inhabitant and may contaminate poorly collected blood cultures, differentiating bacteremia from contamination is often difficult. True bacteremia should be suspected if blood cultures grow rapidly (within 15 hours of incubation in a continuously monitored blood culture system), more than one blood culture is positive with the same CoNS strain, cultures from both the blood and another sterile site are positive, and clinical and laboratory signs and symptoms compatible with CoNS sepsis are present and subsequently resolve with appropriate therapy. Growth of CoNS from a blood culture in a neonate or patient with an intravascular catheter should be considered evidence of true bacteremia until careful review of the foregoing criteria and evaluation of the patient. Before initiating presumptive antimicrobial therapy in such patients, it is always prudent to draw two separate blood cultures to facilitate subsequent interpretation if CoNS is grown. Molecular and mass spectrometry assays similar to those used for identification of *S. aureus* allow for rapid identification of CoNS in positive blood cultures.

TREATMENT

Because most CoNS strains are resistant to methicillin (with the exception of *S. lugdunensis* and *S. saprophyticus,* which are generally methicillin susceptible), **vancomycin** is the initial drug of choice. Resistance to vancomycin has rarely been reported with *S. haemolyticus*. For patients with indwelling medical devices, the addition of rifampin to vancomycin may increase antimicrobial efficacy because of good penetration of this antibiotic into biofilms. Other antibiotics with good in vitro activity against CoNS may be considered in certain circumstances. These include linezolid, ceftaroline, and daptomycin. Removal of an infected catheter is ideal. However, this is not always possible because of the therapeutic requirements of the underlying disease (e.g., nutrition for short bowel syndrome, chemotherapy for malignancy). A trial of IV vancomycin (potentially with the addition of rifampin) with the retained catheter can be attempted to preserve the use of the central line, as long as systemic manifestations of infection are not severe. Antibiotic therapy given through an infected CVC and the use of antibiotic locks in conjunction with systemic therapy may increase the likelihood of curing CoNS line sepsis without line removal. Prosthetic heart valves and CSF shunts usually need to be removed to adequately treat the infection.

Peritonitis caused by *S. epidermidis* in patients on continuous ambulatory peritoneal dialysis is an infection that may be treated with IV or intraperitoneal antibiotics without removing the dialysis catheter. If the organism is resistant to methicillin, vancomycin adjusted for renal function is appropriate therapy. Unlike most CoNS, *S. saprophyticus* is usually methicillin susceptible, and UTIs can typically be treated with a first-generation cephalosporin (cephalexin), amoxicillin–clavulanic acid, or TMP-SMX.

PROGNOSIS

Most episodes of CoNS bacteremia respond successfully to antibiotics and removal of any foreign material that is present. Poor prognosis is associated with malignancy, neutropenia, and infected prosthetic or native heart valves. CoNS infections increase the morbidity, duration of hospitalization, and mortality among patients with underlying complicated illnesses.

PREVENTION

Iatrogenic morbidity and resource use caused by contaminated blood cultures can be reduced by following recommended strategies to prevent CVC-associated bloodstream infections during catheter insertion and maintenance. These strategies include basic techniques such as central line care "bundles," which incorporate good hand hygiene, decontamination of hubs and ports before access, minimizing frequency of access, and frequent replacement of external connections and infusion materials. Antibiotic-impregnated catheters can be considered when other preventive measures have failed.

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Chapter 228

Streptococcus pneumoniae (Pneumococcus)

Kacy A. Ramirez and Timothy R. Peters

Streptococcus pneumoniae (pneumococcus) is an important pathogen that results in more than 1 million children deaths each year. Childhood invasive pneumococcal disease is prevalent and typically severe, causes numerous clinical syndromes, and is a major cause of life-threatening pneumonia, bacteremia, endocarditis, and meningitis; it may also cause sinusitis, otitis media, and bone and joint infections. Antimicrobial resistance in pneumococcus is a major public health problem, with 15–30% of isolates worldwide classified as **multidrug resistant** (**MDR**; resistant to at least three classes of antibiotics). Pneumococcal polysaccharide-protein conjugate vaccines (**PCVs**) developed for infants have been highly successful in the control of disease caused by virulent vaccine-specific serotypes. Epidemiologic surveillance reveals a dynamic pneumococcal ecology with emergence of highly virulent MDR serotypes. Ongoing vaccine development and distribution efforts remain the best approach to control this threat to childhood health.

ETIOLOGY

S. pneumoniae is a gram-positive, lancet-shaped, polysaccharide encapsulated diplococcus, occurring occasionally as individual cocci or in chains; >90 serotypes have been identified by type-specific capsular polysaccharides. Antisera to some pneumococcal polysaccharides cross-react with other pneumococcal types, defining serogroups (e.g., 6A and 6B). Encapsulated strains cause most serious disease in humans. Capsular polysaccharides impede phagocytosis. Virulence is related in part to capsule size, but pneumococcal types with capsules of the same size can vary widely in virulence.

On solid media, *S. pneumoniae* forms unpigmented, umbilicated colonies surrounded by a zone of incomplete (α) hemolysis. *S. pneumoniae* is bile soluble (i.e., 10% deoxycholate) and optochin sensitive. *S. pneumoniae* is closely related to the viridans groups of *Streptococcus mitis,* which typically overlap phenotypically with pneumococci. The conventional laboratory definition of pneumococci continues to rely on bile and optochin sensitivity, although considerable confusion occurs in distinguishing pneumococci and other α-hemolytic streptococci. Pneumococcal capsules can be microscopically visualized and typed by exposing organisms to type-specific antisera that combine with their unique capsular polysaccharide, rendering the capsule refractile (Quellung reaction). Specific antibodies to capsular polysaccharides confer protection on the host, promoting opsonization and phagocytosis. Additionally, $CD4^+$ T cells have a direct role in antibody-independent immunity to pneumococcal nasopharyngeal colonization. Conjugated PCVs promote T-cell immunity and protect against pneumococcal colonization, in contrast to the pneumococcal polysaccharide vaccine (PPSV23) that is used in adults and certain high-risk pediatric populations and that does not affect nasopharyngeal colonization.

EPIDEMIOLOGY

Most healthy individuals carry (colonized) various *S. pneumoniae* serotypes in their upper respiratory tract; >90% of children between 6 months and 5 years of age harbor *S. pneumoniae* in the nasopharynx at some time. A single serotype usually is carried by a given individual for an extended period (45 days to 6 months). Carriage does not consistently induce local or systemic immunity sufficient to prevent later reacquisition of the same serotype. Rates of pneumococcal carriage peak during the first and second year of life and decline gradually thereafter. Carriage rates are highest in institutional settings and during the winter and are lowest in summer. Nasopharyngeal carriage of pneumococci is common among young children attending out-of-home care, with rates of 21–59% in point prevalence studies.

Before the introduction of heptavalent pneumococcal conjugate vaccine **(PCV7)** in 2000, serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F caused most invasive childhood pneumococcal infections in the United States. The introduction of PCVs resulted in a marked decrease in **invasive pneumococcal infections (IPIs)** in children. By 2005, however, IPIs began to increase slightly because of an increase in non-PCV7 serotypes, particularly serotype 19A. **Serotype replacement** can result from expansion of existing nonvaccine serotypes and from vaccine-type pneumococci acquiring the polysaccharide capsule of a nonvaccine serotype **(serotype switching)**. Since the introduction of PCV13 in 2010 in the United States, there has been a decline in IPIs caused by new vaccine serotypes, including 19A. Nonetheless, 19A remains an important cause of meningitis. Indirect protection of unvaccinated persons has occurred since PCV introduction, and this *herd protection* is likely a result of decreases in nasopharyngeal carriage of virulent pneumococcal vaccine serotypes.

S. pneumoniae is the most frequent cause of bacteremia, bacterial pneumonia, and bacterial meningitis and among the most common causes of otitis media and sinusitis in children. The decreased ability in children <2 years old to produce antibody against the T-cell–independent polysaccharide antigens and the high prevalence of colonization may explain an increased susceptibility to pneumococcal infection and the decreased effectiveness of polysaccharide vaccines. Children at increased risk of pneumococcal infections include those with sickle cell disease, asplenia, deficiencies in humoral (B-cell) immunity, deficiencies in complement-mediated immunity, toll like receptor deficiencies, HIV infection, certain malignancies (e.g., leukemia, lymphoma), chronic heart, lung, or renal disease (particularly nephrotic syndrome), cerebrospinal fluid (CSF) leak, and cochlear implants. Table 228.1 lists other high-risk groups. Some American Indian, Alaska Native, and African American children may also be at increased risk. Children <5 years old in out-of-home daycare are at increased risk (approximately twofold higher) of experiencing IPIs than other children. Males are more frequently affected than females. Because immunocompetent vaccinated children have had fewer episodes of IPI, the proportion of infected children with immunologic risk factors has increased (estimated at 20%).

Pneumococcal disease usually occurs sporadically but can be spread from person to person by respiratory droplet transmission. *S. pneumoniae* is an important cause of secondary bacterial pneumonia in patients with influenza. During influenza epidemics and pandemics, most deaths result from bacterial pneumonia, and pneumococcus is the predominant bacterial pathogen isolated in this setting. Pneumococcal co-pathogenicity may be important in disease caused by other respiratory viruses as well.

PATHOGENESIS

Invasion of the host is affected by a number of factors. Nonspecific defense mechanisms, including the presence of other bacteria in the nasopharynx, may limit multiplication of pneumococci. Aspiration of secretions containing pneumococci is hindered by the epiglottic reflex and by respiratory epithelial cell cilia, which move infected mucus toward the pharynx. Similarly, normal ciliary flow of fluid from the middle ear through the eustachian tube and sinuses to the nasopharynx usually prevents infection with nasopharyngeal flora, including pneumococci. Interference with these normal clearance mechanisms by allergy, viral infection, or irritants (e.g., smoke) may allow colonization and subsequent infection with these organisms in otherwise normally sterile sites.

Virulent pneumococci are intrinsically resistant to phagocytosis by alveolar macrophages. Pneumococcal disease frequently is facilitated by viral respiratory tract infection, which may produce mucosal injury, diminish epithelial cell ciliary activity, and depress the function of

Table 228.1 Children at Increased Risk of Invasive Pneumococcal Infection

RISK GROUP	CONDITION
Immunocompetent children	Chronic heart disease* Chronic lung disease† Chronic kidney disease (excluding dialysis and nephrotic syndrome) Chronic liver disease Diabetes mellitus Cerebrospinal fluid leaks Cochlear implant
Children with immunocompromising conditions	HIV infection Maintenance dialysis or nephrotic syndrome Congenital or acquired asplenia or splenic dysfunction Congenital or acquired immunodeficiencies Sickle cell disease and other hemoglobinopathies Congenital immunodeficiency‡ Diseases and conditions treated with immunosuppressive drugs or radiation therapy, including malignant neoplasm, leukemia, lymphoma, and Hodgkin disease, or solid organ transplantation

*Particularly cyanotic congenital heart disease and cardiac failure.
†Including moderate persistent or severe persistent asthma.
‡Includes humoral or T lymphocyte deficiency; complement deficiencies, particularly C1, C2, C3 and C4 deficiency; and phagocytic disorders (excluding chronic granulomatous disease).
Adapted from Kobayashi M, Farrar JI, Gierke R, et al. Use of 15-valent pneumococcal conjugate vaccine among U.S. children: updated recommendations of the Advisory Committee on Immunization Practices -- United States, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(4):1174-1181; and Centers for Disease Control and Prevention. ACIP updates: Recommendations for use of 20-valent pneumococcal conjugate vaccine in children—United States, 2023. *MMWR Morb Mortal Wkly Rep*. 2023;72(39):1072.

alveolar macrophages and neutrophils. Phagocytosis may be impeded by respiratory secretions and alveolar exudate. In the lungs and other tissues, the spread of infection is facilitated by the antiphagocytic properties of the pneumococcal capsule. Surface fluids of the respiratory tract contain only small amounts of immunoglobulin G (IgG) and are deficient in complement. During inflammation, there is limited influx of IgG, complement, and neutrophils. Phagocytosis of bacteria by neutrophils may occur, but normal human serum may not opsonize pneumococci and facilitate phagocytosis by alveolar macrophages. In tissues, pneumococci multiply and spread through the lymphatics or bloodstream or, less often, by direct extension from a local site of infection (e.g., sinuses). In bacteremia the severity of disease is related to the number of organisms in the bloodstream and to the integrity of specific host defenses. A poor prognosis correlates with very large numbers of pneumococci and high concentrations of capsular polysaccharide in the blood and CSF.

Invasive pneumococcal disease is 30- to 100-fold more prevalent in children with sickle cell disease and other hemoglobinopathies and in children with congenital or surgical asplenia than in the general population. This risk is greatest in infants <2 years old, the age when antibody production to most serotypes is poor. The increased frequency of pneumococcal disease in asplenic persons is related to both deficient opsonization of pneumococci and absence of clearance by the spleen of circulating bacteria. Children with sickle cell disease also have deficits in the antibody-independent properdin (alternative) pathway of complement activation in addition to functional asplenia. Both complement pathways contribute to antibody-independent and antibody-dependent **opsonophagocytosis** of pneumococci. With advancing age (e.g., >5 years), children with sickle cell disease produce anticapsular antibody, augmenting antibody-dependent opsonophagocytosis and greatly reducing, but not eliminating, the risk of severe pneumococcal disease. Deficiency of many of the complement components (e.g., C2 and C3) is associated with recurrent pyogenic infection, including *S. pneumoniae* infection. The efficacy of phagocytosis also is diminished in patients with B- and T-cell immunodeficiency syndromes (e.g., agammaglobulinemia, severe combined immunodeficiency) or loss of immunoglobulin (e.g., nephrotic syndrome) and is largely caused by a deficiency of opsonic anticapsular antibody. These observations suggest that opsonization of pneumococci depends on the alternative complement pathway in antibody-deficient persons and that recovery from pneumococcal disease depends on the development of anticapsular antibodies that act as opsonins, enhancing phagocytosis and killing of pneumococci. Children with HIV infection also have high rates of IPI similar to or greater than rates in children with sickle cell disease, although rates of invasive pneumococcal disease decreased after the introduction of highly active antiretroviral therapy (HAART).

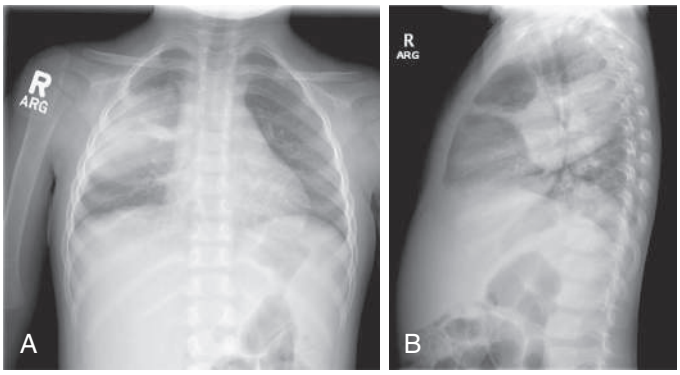

Fig. 228.1 Bacterial "round" pneumonia caused by *Streptococcus pneumoniae* in 2-yr-old child with a 2-day history of cough, high fever, leukocytosis, and back pain.

CLINICAL MANIFESTATIONS

The signs and symptoms of pneumococcal infection are related to the anatomic site of disease. Common clinical syndromes include otitis media (see Chapter 680), sinusitis (see Chapter 429), pneumonia (Fig. 228.1) (see Chapter 449), and sepsis (see Chapter 85). Before routine use of PCVs, pneumococci caused >80% of bacteremia episodes in infants 3-36 months old with fever without an identifiable source (i.e., occult bacteremia). Bacteremia may be followed by meningitis (see Chapter 643), osteomyelitis (see Chapter 725), suppurative (septic) arthritis (see Chapter 726), endocarditis (see Chapter 486), and, rarely, brain abscess (see Chapter 644). Primary peritonitis (see Chapter 419.1) may occur in children with peritoneal effusions caused by nephrotic syndrome and other ascites-producing conditions. Local complications of infection may occur, causing empyema, pericarditis, mastoiditis, epidural abscess, periorbital cellulitis, or meningitis. Hemolytic-uremic syndrome (see Chapter 533.4) and disseminated intravascular coagulation also occur as rare complications of pneumococcal infections. Epidemic conjunctivitis caused by nonencapsulated or encapsulated pneumococci occurs as well.

DIAGNOSIS

The diagnosis of pneumococcal infection is established by recovery of *S. pneumoniae* from the site of infection or the blood/sterile body fluid. Although pneumococci may be found in the nose or throat of patients with otitis media, pneumonia, septicemia, or meningitis, cultures of these locations are generally not helpful for diagnosis, because they are not indicative of causation. Blood cultures should be obtained in children with pneumonia, meningitis, endocarditis, arthritis, osteomyelitis, peritonitis, pericarditis, or gangrenous skin lesions. Because of the implementation of universal vaccination with PCVs, there has been a substantial decrease in the incidence of occult bacteremia, but blood

cultures should still be considered in febrile patients with clinical toxicity or significant leukocytosis. Leukocytosis often is pronounced, with total white blood cell (WBC) counts frequently >15,000/μL. In severe cases of pneumococcal disease, WBC count may be low.

Pneumococci can be identified in body fluids as gram-positive, lancet-shaped diplococci. Early in the course of pneumococcal meningitis, many bacteria may be seen in relatively acellular CSF. With methods of continuously monitored blood culture systems, the average time to isolation of pneumococcal organisms is 14-15 hours. Multiplex real-time polymerase chain reaction (PCR) assays are specific and more sensitive than culture of CSF and blood, particularly in patients who have recently received antimicrobial therapy. Antigen detection of C-polysaccharide in urine may be useful in adults with pneumococcal pneumonia but lacks specificity in children who may have positive results with asymptomatic colonization. Antigen immunochromatographic or PCR assays on pleural fluid are not routinely used but could be considered.

TREATMENT

Antimicrobial resistance among *S. pneumoniae* continues to be a serious healthcare concern, especially for the widely used β-lactams, macrolides, and fluoroquinolones. Serotypes 6A, 6B, 9V, 14, 19A, 19F, and 23F are the most common serotypes associated with resistance to penicillin. Consequently, the introduction of the 7- and 13-valent pneumococcal conjugate vaccines (**PCV7** and **PCV13**) has altered antimicrobial resistance patterns. By 2014, only ~5% of pneumococcal strains were penicillin nonsusceptible. However, pneumococcal serotypes 11A, 35F, and 35B have contributed to steady erosion of pneumococcal antibiotic susceptibility to penicillin, third-generation cephalosporins, fluoroquinolones, and carbapenems.

Resistance in pneumococci to penicillin and cephalosporins is defined by the minimum inhibitory concentration (MIC) and clinical syndrome. Pneumococci are considered *susceptible, intermediate,* or *resistant* to various antibacterial agents based on specific MIC breakpoints. For patients with pneumococcal meningitis, penicillin-susceptible strains have MICs ≤0.06 μg/mL, and penicillin-resistant strains have MICs ≥0.12 μg/mL. For patients with nonmeningeal pneumococcal infections, breakpoints are higher; in particular, penicillin-susceptible strains have MICs ≤2 μg/mL, and penicillin-resistant strains have MICs ≥8 μg/mL. For patients with meningitis, ceftriaxone-susceptible strains have MICs ≤0.5 μg/mL, and resistant strains have MICs ≥2.0 μg/mL. For patients with nonmeningeal pneumococcal disease, breakpoints are higher, and ceftriaxone-susceptible strains have MICs ≤1 μg/mL, and resistant strains have MICs ≥4 μg/mL. In cases when pneumococcus is resistant to erythromycin but sensitive to clindamycin, *a D-test should be performed* to determine whether clindamycin resistance can be induced; if the D-test is positive, clindamycin should not be used to complete treatment of the patient. More than 30% of pneumococcal isolates are resistant to trimethoprim-sulfamethoxazole (TMP-SMX); levofloxacin resistance is low but has also been reported. All isolates from children with severe infections should be tested for antibiotic susceptibility, given widespread pneumococcal MDR strains. Resistance to vancomycin has not been seen at this time, but vancomycin-tolerant pneumococci that are killed at a slower rate have been reported, and these tolerant pneumococci may be associated with a worse clinical outcome. Linezolid is an oxazolidinone antibacterial with activity against MDR gram-positive organisms, including pneumococcus, and has been used in the treatment of MDR pneumococcal pneumonia, meningitis, and severe otitis media. Despite early favorable studies, use of this drug is limited by myelosuppression and high cost, and linezolid resistance in pneumococcus is reported.

Children ≥1 month old with suspected pneumococcal meningitis should be treated with combination therapy using **vancomycin** (60 mg/kg/24 hr divided every 6-8 hr IV) and high-dose **ceftriaxone** (100 mg/kg/24 hr divided every 12 hr IV). Proven pneumococcal meningitis can be treated with penicillin alone or ceftriaxone alone if the isolate is penicillin susceptible. If the organism is nonsusceptible (i.e., intermediate or full resistance) to penicillin but susceptible to ceftriaxone, pneumococcal meningitis can be treated with ceftriaxone alone. However, if the organism is nonsusceptible to penicillin and to ceftriaxone, pneumococcal meningitis should be treated with combination vancomycin plus ceftriaxone, not with vancomycin alone, and consideration should be given to the addition of **rifampin**. Some experts recommend use of corticosteroids in pneumococcal meningitis early in the course of disease, but data demonstrating clear benefit in children are lacking.

The 2011 Infectious Diseases Society of America guidelines recommend **amoxicillin** as first-line therapy for previously healthy, appropriately immunized infants and preschool children with mild to moderate, uncomplicated community-acquired pneumonia. **Ampicillin** or **penicillin G** may be administered to the fully immunized infant or school-age child admitted to a hospital with uncomplicated community-acquired pneumonia when local epidemiologic data document lack of substantial high-level penicillin resistance for invasive *S. pneumoniae*. Empirical therapy with parenteral ceftriaxone should be prescribed for hospitalized infants and children who are not fully immunized, in regions where local epidemiology of invasive pneumococcal strains documents widespread penicillin resistance, or for infants and children with life-threatening infection, including those with empyema. Non–β-lactam agents, such as vancomycin, have not been shown to be more effective than ceftriaxone in the treatment of pneumococcal pneumonia, given the degree of drug resistance currently seen in the United States.

Higher doses of amoxicillin (80-90 mg/kg/24 hr) have been successful in the treatment of otitis media caused by relatively penicillin-resistant pneumococcal strains. If the patient has failed initial antibiotic therapy, alternative agents should be active against penicillin-nonsusceptible pneumococcus as well as β-lactamase–producing *Haemophilus influenzae* and *Moraxella catarrhalis*. These include high-dose oral amoxicillin-clavulanate (in the 14:1 formulation to reduce the risk of diarrhea), oral cefdinir, cefpodoxime, or cefuroxime or a 3-day course of daily intramuscular (IM) ceftriaxone if patients fail oral therapy. Empirical treatment of pneumococcal disease should be based on knowledge of susceptibility patterns in specific communities.

For individuals with a non–type I allergic reaction to penicillin, cephalosporins (standard dosing) can be used. For type I allergic reactions (immediate, anaphylactic) to β-lactam antibiotics, clindamycin and levofloxacin are preferred alternatives depending on the site of infection (e.g., clindamycin may be effective for pneumococcal infections other than meningitis). TMP-SMX may also be considered for susceptible strains but should be avoided in the absence of susceptibility results. Erythromycin and related macrolides (e.g., azithromycin, clarithromycin) should be avoided given high rates of resistance.

PROGNOSIS

Prognosis depends on the integrity of host defenses, virulence and numbers of the infecting organism, age of the host, site and extent of the infection, and adequacy of treatment. The mortality rate for pneumococcal meningitis is approximately 10% in most studies. Pneumococcal meningitis results in sensorineural hearing loss in 20–30% of patients and can cause other serious neurologic sequelae, including paralysis, epilepsy, blindness, and intellectual deficits.

Invasive pneumococcal disease is associated with various primary immunodeficiency states, leading some to suggest screening for immune defects in all or some patients with invasive diseases. In the absence of other risk factors (see Table 228.1), screening for immune defects (complement, B-cell, toll-like receptor, asplenia) may be indicated for patients with recurrent invasive disease, infection by a serotype covered by vaccination in a fully vaccinated child, children ≥2 years of age, or in some centers all patients with invasive disease.

PREVENTION

The highly successful PCVs have resulted in a marked decrease in IPIs in children. PCVs provoke protective antibody responses in 90% of infants given these vaccines at 2, 4, and 6 months of age, and greatly enhanced responses (e.g., immunologic memory) are apparent after vaccine doses given at 12-15 months of age (Table 228.2). In a large

Table 228.2 Comparison of Pneumococcal Vaccines Licensed in United States*

CARRIER PROTEIN	PNEUMOCOCCAL CAPSULAR POLYSACCHARIDES	MANUFACTURER
Diphtheria CRM_{197} protein	**4, 6B, 9V, 14, 18C, 19F, 23F**	Wyeth Lederle (PCV7, Prevnar)
Diphtheria CRM_{197} protein	1, 3, **4,** 5, 6A, **6B,** 7F, **9V, 14, 18C,** 19A, **19F, 23F**	Wyeth Lederle (PCV13, Prevnar 13)
Diphtheria CRM_{197} protein	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 32F	Merck Sharp and Dohme (PCV15, Prevnar 15)
Diphtheria CRM_{197} protein	1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, 32F	Merck Sharp and Dohme (PCV20, Prevnar 20)
None	1, 2, 3, **4,** 5, **6B,** 7F, 8, 9N, **9V,** 10A, 11A, 12F, **14,** 15B, 17F, **18C,** 19A, **19F,** 20, 22F, **23F,** 33F	Sanofi Pasteur MSD (PPSV23, Pneumovax II)

*PCV7 serotypes in **bold**.

Table 228.3 Recommended Routine Vaccination Schedule for 15- or 20-Valent Pneumococcal Conjugate Vaccine (PCV15 or 20) Among Infants and Children Who Have Not Received Previous Doses of Conjugate Vaccines, by Age at First Dose—United States, 2010

AGE AT FIRST DOSE (MO)	PRIMARY PCV15 OR PCV20 SERIES*	PCV15 OR PCV20 BOOSTER DOSE†
2-6	3 doses	1 dose at age 12-15 mo
7-11	2 doses	1 dose at age 12-15 mo
12-23	2 doses	—
24-59 (healthy children)	1 dose	—
24-71 (children with certain chronic diseases or immunocompromising conditions‡)	2 doses	—

*The minimum interval between doses is 8 wk except for children vaccinated at age <12 mo, for whom the minimum interval between doses is 4 wk. The minimum age for administration of the first dose is 6 wk.
†Given at least 8 wk after the previous dose.
‡See Table 228.1. If two doses of PCV15 are used, then 1 dose of PPSV23 vaccine is given ≥8 weeks later.
Adapted from Kobayashi M, Farrar JI, Gierke R, et al. Use of 15-valent pneumococcal conjugate vaccine among U.S. children: updated recommendations of the Advisory Committee on Immunization Practices -- United States, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(4):1174-1181; and Centers for Disease Control and Prevention. ACIP updates: Recommendations for use of 20-valent pneumococcal conjugate vaccine in children—United States, 2023. *MMWR Morb Mortal Wkly Rep*. 2023;72(39):1072.

clinical trial, PCV7 was shown to reduce invasive disease caused by vaccine serotypes by up to 97% and to reduce invasive disease caused by all serotypes, including serotypes not in the vaccine, by 89%. Children who received PCV7 had 7% fewer episodes of acute otitis media and underwent 20% fewer tympanostomy tube placements than unvaccinated children. After PCV13, a 98% reduction in IPIs caused by vaccine serotypes has been seen, particularly in children <5 years old. The number of pneumococcal isolates and percentage of isolates with high-level penicillin resistance from cultures taken from children with otitis media or mastoiditis for clinical indications decreased, largely related to decreases in serotype 19A. Rates of hospitalization for pneumococcal pneumonia among U.S. children decreased after PCV13 introduction. The number of cases of pneumococcal meningitis in children remain unchanged, but the proportion of PCV13 serotypes has decreased significantly. In addition, pneumococcal conjugate vaccines significantly reduce nasopharyngeal carriage of vaccine serotypes. PCVs have significantly decreased rates of invasive pneumococcal disease in children with sickle cell disease, and studies suggest substantial protection for HIV-infected children and splenectomized adults. Adverse events after the administration of PCV have included local swelling and redness and slightly increased rates of fever when used in conjunction with other childhood vaccines.

Currently, the predominant non-PCV13 serotypes are 22F, 12F, 33F, 24F, 15C, 15B, 23B, 10A, 11A, 35B, 35F, and 38. Serotypes 12F and 24F have high invasive disease potential, with the latter responsible for a rebound in incidence of pneumococcal meningitis since 2015. Serotypes 11A, 35F, and 35B in nasopharyngeal and middle ear samples are increasingly resistant to antibiotics. PCV15 or PCV20, which have replaced PCV13, do not contain serotypes 24 or 35, but PCV20 includes 11A and 12F.

Immunologic responsiveness and efficacy after administration of pneumococcal polysaccharide vaccines (PPSV23) is unpredictable in children <2 years old. PPSV23 contains purified polysaccharide of 23 pneumococcal serotypes responsible for >95% of invasive disease. The clinical efficacy of PPSV23 is controversial, and studies have yielded conflicting results.

Immunization with PCV15 or PCV20 is recommended for all infants on a schedule for primary immunization, in previously unvaccinated infants, and for transition for those partially vaccinated (Table 228.3). High-risk children ≥2 years old, such as those with asplenia, sickle cell disease, some types of immune deficiency (e.g., antibody deficiencies), HIV infection, cochlear implant, CSF leak, diabetes mellitus, and chronic lung (including moderate persistent or severe persistent asthma), heart, liver, or kidney disease (including nephrotic syndrome) or immunocompromising conditions, such as asplenia, sickle cell disease, some types of immune deficiency (e.g., antibody deficiencies), HIV infection, etc., may also benefit from PPSV23 administered after 2 years of age after priming with the scheduled doses of PCV15 or 20. Thus it is recommended that children 2 years of age and older with these conditions receive supplemental vaccination with PPSV23. A second dose of PPSV23 is recommended 5 years after the first dose of PPSV23 for persons ≥2 years old who have immunocompromising conditions including sickle cell disease and functional or anatomic asplenia. Additional doses of PPSV23 are not required, however, if the patient has ever received PCV20. Additional

TABLE 228.4 CDC Advisory Committee on Immunization Practices Recommendations for Use of PCV in Children, June 2023

AGE AND RISK GROUP	RECOMMENDATIONS
Children age <24 mo	• Use of either PCV15 or PCV20 is recommended for all children age 2–23 mo according to previously recommended PCV dosing and schedules. • If only PCV13 is available when the child is scheduled to receive a PCV, PCV13 may be given as previously recommended. • If a child started the PCV series with PCV13, the child may complete the series with PCV15 or PCV20 without giving additional doses; the PCV series does not need to be restarted. • For children who have received all recommended dosing and schedules with PCV13 or PCV15, a supplemental dose of PCV20 is not indicated.
Healthy children age 24–59 mo with an incomplete PCV vaccination status*	• A single dose of either PCV15 or PCV20 is recommended. • A supplemental dose of PCV15 or PCV20 is not indicated for healthy children who have received 4 doses of PCV13 or who completed another age-appropriate PCV13 schedule.
Children age 24–71 mo with any risk condition†	• Use either PCV15 or PCV20 according to previously recommended PCV dosing and schedules. • If only PCV13 is available when the child is scheduled to receive a PCV, PCV13 may be given as previously recommended.
Children age 2–18 yr with any risk condition who completed a recommended PCV series before age 6 yr	• Completed series includes ≥1 dose of PCV20: ○ No additional doses of any pneumococcal vaccine are indicated. ○ This recommendation may be updated as additional data become available. • Completed series using PCV13 or PCV15 (no PCV20): ○ Either a single dose of PCV20 or PPSV23 using previously recommended dosing and schedules is recommended to complete the recommended vaccine series.
Children age 6–18 yr with any risk condition with no previous PCV13, PCV15, or PCV20 vaccination	• For children age 6–18 yr with any risk condition who have not received any dose of PCV (PCV13, PCV15, or PCV20) a single dose of either PCV15 or PCV20 is recommended. • If the child has previously received PCV7 and/or PPSV23, a single dose of either PCV15 or PCV20 is recommended ≥8 wk after the most recent dose of pneumococcal vaccination. ○ PCV15 should be followed by a dose of PPSV23 if not previously given. ○ PCV20 does not need to be followed by a dose of PPSV23.
Children who have received HSCT	• Children who received HSCT are recommended to receive three doses of PCV20, 4 wk apart starting 3–6 mo after HSCT. • A fourth PCV20 dose is recommended ≥6 mo after the third PCV20 dose, or ≥12 mo after HSCT, whichever is later. • HSCT recipients who have started their pneumococcal vaccine series with PCV13 or PCV15 may complete their 4-dose pneumococcal vaccine series with PCV20 without giving extra doses. • If PCV20 is not available, three doses of PCV15, 4 wk apart starting 3–6 mo after HSCT, followed by a dose of PPSV23 ≥12 mo after HSCT may be given. • For patients with chronic graft-versus-host disease who are receiving PCV15, a fourth dose of PCV15 can be given in place of PPSV23 since these children are less likely to respond to PPSV23. A patient's clinical team is best positioned to determine the appropriate timing of vaccination.

*Routine use of PCV is not recommended for healthy children age ≥5 yr.

†Risk conditions include: cerebrospinal fluid leak; chronic heart disease; chronic kidney disease (excluding maintenance dialysis and nephrotic syndrome, which are included in immunocompromising conditions); chronic liver disease; chronic lung disease (including moderate persistent or severe persistent asthma); cochlear implant; diabetes mellitus; immunocompromising conditions (on maintenance dialysis or with nephrotic syndrome; congenital or acquired asplenia or splenic dysfunction; congenital or acquired immunodeficiencies; diseases and conditions treated with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, Hodgkin disease, and solid organ transplant; HIV infection; and sickle cell disease or other with these conditions who received PCV13 or PCV15 are also recommended to receive 23-valent pneumococcal polysaccharide vaccine.

PCV, pneumococcal conjugate vaccine; PCV13, 13-valent PCV; PCV15, 15-valent PCV; PCV20, 20-valent PCV; PPSV23, 23-valent pneumococcal polysaccharide vaccine; HSCT, hematopoietic stem cell transplant.

From Centers for Disease Control and Prevention. ACIP updates: Recommendations for use of 20-valent pneumococcal conjugate vaccine in children—United States, 2023. *MMWR Morb Mortal Wkly Rep*. 2023;72(39):1072. (Table 1).

recommendations have been made for at-risk children 6-18 years old (Table 228.4).

Immunization with pneumococcal vaccines also may prevent pneumococcal disease caused by nonvaccine serotypes that are serotypically related to a vaccine strain. However, because current vaccines do not eliminate all pneumococcal invasive infections, penicillin prophylaxis is recommended for children at high risk of invasive pneumococcal disease, including children with asplenia or sickle cell disease. Oral penicillin V potassium (125 mg twice daily for children <3 years old; 250 mg twice daily for children ≥3 years old) decreases the incidence of pneumococcal sepsis in children with sickle cell disease. Once-monthly IM benzathine penicillin G (600,000 units every 3-4 weeks for children weighing <60 lb; 1,200,000 units every 3-4 weeks for children weighing ≥60 lb) may also provide prophylaxis. Erythromycin may be used in children with penicillin allergy, but its efficacy is unproven. Prophylaxis in sickle cell disease has been safely discontinued after the fifth birthday in children who have received all recommended pneumococcal vaccine doses and who had not experienced invasive pneumococcal disease. Prophylaxis is often administered for at least 2 years after splenectomy or up to 5 years of age. Efficacy in children >5 years old and adolescents is unproven. If oral antibiotic prophylaxis is used, strict compliance must be encouraged.

Given the rapid emergence of penicillin-resistant pneumococci, especially in children receiving long-term, low-dose therapy, prophylaxis cannot be relied on to prevent disease. High-risk children with fever should be promptly evaluated and treated regardless of vaccination or penicillin prophylaxis history.

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Chapter 229

Group A *Streptococcus*

Stanford T. Shulman and Ami B. Patel

Group A *Streptococcus* **(GAS)**, also known as *Streptococcus pyogenes,* is a common cause of infections of the upper respiratory tract **(pharyngitis)** and the skin **(impetigo, pyoderma)** in children. Less frequently, GAS causes perianal cellulitis, vaginitis, septicemia, pneumonia, empyema, endocarditis, pericarditis, osteomyelitis, suppurative arthritis, myositis, cellulitis, omphalitis, and other infections. This organism also causes distinct clinical entities **(scarlet fever** and **erysipelas)**, as well as streptococcal **toxic shock syndrome** and monomicrobial **necrotizing fasciitis**. GAS is also the cause of at least two potentially serious nonsuppurative complications: **rheumatic fever** (see Chapters 229.1 and 487) and **acute glomerulonephritis** (see Chapter 559.4).

ETIOLOGY

Group A streptococci are gram-positive, coccoid-shaped bacteria that tend to grow in chains. Streptococci are broadly classified by their hemolytic activity on mammalian (typically sheep) red blood cells. The zone of complete hemolysis that surrounds colonies grown on blood agar distinguishes β-hemolytic (complete hemolysis) from α-hemolytic (green or partial hemolysis) and γ (nonhemolytic) species. The β-hemolytic streptococci can be divided into groups by a group-specific polysaccharide **(Lancefield C carbohydrate)** located in the bacterial cell wall. More than 20 serologic groups are identified, designated by the letters A through V, although only A through D are medically important. Serologic grouping by the Lancefield method is precise, but group A organisms can be identified more readily by any of a number of latex agglutination, coagglutination, molecular assays or enzyme immunoassays. Group A strains can also be distinguished from other groups by differences in sensitivity to bacitracin, as other groups are generally resistant to this antibiotic.

GAS can be subdivided into at least 220 serotypes on the basis of the **M protein** antigen, which is located on the cell surface and in fimbriae that project from the outer surface of the cell. Currently, a molecular approach to M-typing GAS isolates using the polymerase chain reaction (PCR) is based on sequencing the terminal portion of the *emm* gene of GAS that encodes the M protein. This *emm* typing system correlates with known serotypes and *emm* types. The *emm* types can be grouped into *emm* clusters that share structural and binding properties. It is important to note that immunity is largely based on type-specific opsonic anti-M antibody.

M/*emm* typing is valuable for epidemiologic studies; specific GAS diseases tend to be associated with certain M types. Types 1, 12, 28, 4, 3, and 2 (in that order) are the most common causes of uncomplicated streptococcal pharyngitis in the United States. M types usually associated with pharyngitis rarely cause skin infections, and the M types associated with skin infections rarely cause pharyngitis. A few **pharyngeal** GAS strains (e.g., M type 12) are associated with glomerulonephritis, but many more **skin** GAS strains (e.g., M types 49, 55, 57, and 60) are considered nephritogenic. Several pharyngeal serotypes (e.g., M types 1, 3, 5, 6, 18, and 29), but no proven skin strains, are associated with **acute rheumatic fever** in North America.

EPIDEMIOLOGY

Humans are the natural reservoir for GAS. These bacteria are highly communicable and can cause disease in normal individuals of all ages who do not have type-specific immunity against the particular serotype involved. Disease in neonates is uncommon in developed countries, probably because of maternally acquired antibody. The incidence of **pharyngitis** is highest in children 5-15 years of age, especially in young school-age children. Acute streptococcal pharyngitis is uncommon in children younger than 3 years, and testing is generally not recommended. These infections are most common in the northern regions of the United States, especially during winter and early spring. Children with untreated acute pharyngitis spread GAS by salivary droplets and nasal discharge. Transmission is favored by close proximity; therefore schools, military barracks, and homes are important environments for spread. GAS has the potential to be an important upper respiratory tract pathogen and to produce outbreaks of disease in the daycare setting. Foods contaminated by GAS occasionally cause explosive outbreaks of pharyngotonsillitis. The incubation period for pharyngitis is usually 2-5 days. Children are usually no longer infectious within 24 hours of starting appropriate antibiotic therapy. Chronic pharyngeal carriers of GAS rarely transmit this organism to others.

Streptococcal pyoderma (impetigo, pyoderma) occurs most frequently during the summer in temperate climates, or year-round in warmer climates, when the skin is exposed and abrasions and insect bites are more likely to occur (see Chapter 727). Colonization of healthy skin by GAS usually precedes the development of impetigo. Because GAS cannot penetrate intact skin, impetigo and other skin infections usually occur at the site of open lesions (insect bites, traumatic wounds, burns). Although impetigo serotypes may colonize the throat, spread is usually from skin to skin, not via the respiratory tract. Fingernails and the perianal region can harbor GAS and play a role in disseminating impetigo. Multiple cases of impetigo in the same family are common. Both impetigo and pharyngitis are more likely to occur among children living in crowded homes and in poor hygienic circumstances.

The incidence of **severe invasive** GAS infections, including bacteremia, pneumonia and empyema, osteomyelitis, septic arthritis, retropharyngeal abscess, lymphadenitis, streptococcal **toxic shock syndrome**, **scarlet fever**, and **necrotizing fasciitis**, has increased in recent decades. The incidence appears to be highest in very young and elderly persons. Before the routine use of varicella vaccine, varicella was the most commonly identified risk factor for invasive GAS infection in children. Other risk factors include diabetes mellitus, HIV infection, intravenous drug use, and chronic pulmonary or chronic cardiac disease. The portal of entry is unknown in almost 50% of cases of severe invasive GAS infection; in most cases, it is believed to be skin or, less often, mucous membranes. Severe invasive disease rarely follows clinically apparent GAS pharyngitis. Invasive GAS disease was reported in many children's hospitals in multiple countries during the COVID-19 pandemic. It is unclear why this has happened, but masking, social distancing, and school closures may have reduced exposure to common viral pathogens or colonization with GAS, resulting in more severe infection when mask and social distancing have stopped and schools have reopened. Co-infection with respiratory viruses (respiratory syncytial virus [RSV], other) may predispose to more severe infection.

PATHOGENESIS

The virulence of GAS depends primarily on the **M protein**, and strains rich in M protein resist phagocytosis in fresh human blood, whereas M-negative strains do not. M protein stimulates the production of protective opsonophagocytic antibodies that are type specific, protecting against infection with a homologous M type but much less so against other M types. Therefore multiple GAS infections attributable to various M types are common during childhood and adolescence. By adult life, individuals are probably immune to many of the common M types in the environment.

GAS produces a large variety of extracellular enzymes and toxins, including erythrogenic toxins, known as **streptococcal pyrogenic exotoxins**. Streptococcal pyrogenic exotoxins A, C, and SSA, alone or in combination, are responsible for the **rash of scarlet fever** and are elaborated by streptococci that contain a particular bacteriophage. These exotoxins stimulate the formation of specific antitoxin antibodies that provide immunity against the scarlatiniform rash but not against other streptococcal infections. Pathogenic variants in genes that are promoters of several virulence genes, including pyrogenic exotoxins, as well as several newly discovered exotoxins, appear to be involved in the

pathogenesis of invasive GAS disease, including streptococcal toxic shock syndrome.

The importance of other streptococcal toxins and enzymes in human disease is not yet established. Many of these extracellular substances are antigenic and stimulate antibody production after an infection. However, these antibodies do not confer immunity. The measurement of select toxins and antibodies is useful for establishing evidence of a recent streptococcal infection to aid in the diagnosis of postinfectious illnesses. Tests for antibodies against streptolysin O (anti–streptolysin O) and DNase B (anti–DNase B) are the most frequently used antibody determinations.

CLINICAL MANIFESTATIONS

The most common infections caused by GAS involve the respiratory tract and the skin and soft tissues.

Respiratory Tract Infections

GAS is an important cause of acute **pharyngitis** (see Chapter 430) and pneumonia, often with empyema (see Chapter 449).

Scarlet Fever

Scarlet fever is GAS pharyngitis associated with a characteristic rash, which is caused by an infection with **pyrogenic exotoxin** (erythrogenic toxin)–producing GAS in individuals who do not have antitoxin antibodies. It is now encountered less often and is less virulent than in the past, but the incidence is cyclic, depending on the prevalence of toxin-producing strains and the immune status of the population. The modes of transmission, age distribution, and other epidemiologic features are otherwise similar to those for GAS pharyngitis.

The scarlet fever rash appears within 24-48 hours after the onset of symptoms, although it may appear with the first signs of illness (Fig. 229.1A). It often begins around the neck and spreads over the trunk and extremities. The rash is a diffuse, finely papular, erythematous eruption producing bright-red discoloration of the skin, which blanches on pressure. It is often accentuated in the creases of the elbows, axillae, and groin (Pastia lines). The skin has a goose-pimple appearance and feels rough. The cheeks are often erythematous with perioral pallor. After 3-4 days, the rash begins to fade and is followed by **desquamation**, initially on the face, progressing caudally, and often resembling a mild sunburn. Occasionally, sheetlike desquamation may occur around the free margins of the fingernails, the palms, and the soles. Examination of the pharynx of a patient with scarlet fever reveals essentially the same findings as with GAS pharyngitis. In addition, the tongue is usually coated and the papillae are swollen (see Fig. 229.1B). After desquamation, the reddened papillae are prominent, giving the tongue a strawberry appearance (see Fig. 229.1C).

Typical scarlet fever is not difficult to diagnose; the milder form with equivocal pharyngeal findings can be confused with viral exanthems, Kawasaki disease, and drug eruptions. Staphylococcal infections are occasionally associated with a scarlatiniform rash. A history of recent exposure to a GAS infection is helpful. Identification of GAS in the pharynx confirms the diagnosis.

Impetigo

Impetigo (or pyoderma) has traditionally been classified into two clinical forms: bullous and nonbullous (see Chapter 706.1). **Nonbullous impetigo** is the more common form and is a superficial infection of the skin that appears first as a discrete papulovesicular lesion surrounded by a localized area of redness. The vesicles rapidly become purulent and covered with a thick, confluent, amber-colored crust that gives the appearance of having been stuck onto the skin. The lesions may occur anywhere but are most common on the face and extremities. If untreated, nonbullous impetigo is a mild but chronic illness, often spreading to other parts of the body, but occasionally self-limited. Regional **lymphadenitis** is common. Nonbullous impetigo is generally not accompanied by fever or other systemic signs or symptoms. Impetiginized excoriations around the nares are seen with active GAS infections of the nasopharynx, particularly in young children. However, impetigo is rarely associated with overt streptococcal infection of the upper respiratory tract.

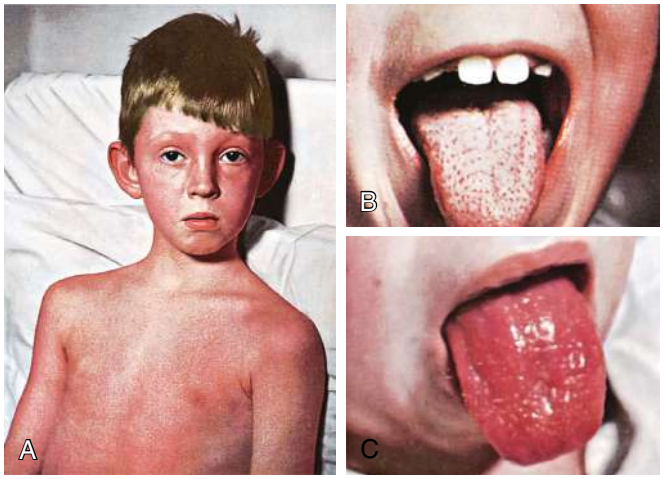

Fig. 229.1 Scarlet fever. **A,** Punctate, erythematous rash (second day). **B,** White strawberry tongue (first day). **C,** Red strawberry tongue (third day). *(Courtesy Dr. Franklin H. Top, Professor and Head of the Department of Hygiene and Preventive Medicine, State University of Iowa, College of Medicine, Iowa City, IA; and Parke, Davis & Company's Therapeutic Notes. From Gershon AA, Hotez PJ, Katz SL. Krugman's Infectious Diseases of Children, 11th ed. Philadelphia: Mosby; 2004, Plate 53.)*

Bullous impetigo is less common and occurs most often in neonates and young infants. It is characterized by flaccid, transparent bullae usually <3 cm in diameter on previously untraumatized skin. The usual distribution involves the face, buttocks, trunk, and perineum.

Although *Staphylococcus aureus* has traditionally been accepted as the sole pathogen responsible for bullous impetigo, there has been confusion about the organisms responsible for nonbullous impetigo. In most episodes of nonbullous impetigo, either GAS or *S. aureus* (or both) is isolated. Earlier investigations suggested that GAS was the causative agent in most cases of nonbullous impetigo and that *S. aureus* was only a secondary invader. However, *S. aureus* has emerged as the causative agent in most cases of nonbullous impetigo. Culture of the lesions is the only way to distinguish nonbullous impetigo caused by *S. aureus* from that caused by GAS.

Erysipelas

Erysipelas is a relatively rare acute GAS infection involving the deeper layers of the skin and the underlying connective tissue. The skin in the affected area is edematous, highly erythematous, and very tender. The erythema associated with erysipelas is very bright, which differentiates it from the dusky appearance of necrotizing fasciitis. Superficial blebs may be present. The most characteristic finding is a sharply defined, slightly elevated border. At times, reddish streaks of lymphangitis project out from the margins of the lesion. The onset is abrupt, and signs and symptoms of a systemic infection, such as high fever and sepsis, are often present. Cultures obtained by needle aspirate of the advancing margin of the inflamed area often reveal the causative agent.

Perianal Dermatitis

Perianal dermatitis, also called *perianal cellulitis* or **perianal streptococcal disease**, is a distinct clinical entity characterized by well-demarcated, perianal erythema associated with anal pruritus, painful defecation, and occasionally blood-streaked stools. Most children are 2-7 years old (range: 18 days-12 years). Physical examination reveals flat, pink to beefy-red perianal erythema with sharp margins extending

as far as 2 cm from the anus. Erythema may involve the vulva and vagina. Lesions may be very tender and, particularly when chronic, may fissure and bleed. Systemic symptoms and fever are unusual. Culture or a rapid streptococcal test of a perianal swab will yield GAS or detect antigen.

Vaginitis

GAS is a common cause of vaginitis in prepubertal girls (see Chapter 586). Patients usually have a serous discharge with marked erythema and irritation of the vulvar area, accompanied by discomfort in walking and in urination.

Severe Invasive Disease

Invasive GAS infection is defined by isolation of GAS from a normally sterile body site and includes three overlapping clinical syndromes. **GAS toxic shock syndrome (TSS)** is differentiated from other types of invasive GAS infections by the presence of shock and multiorgan system dysfunction early in the course of the infection (Table 229.1). The second syndrome is **GAS necrotizing fasciitis**, characterized by extensive local necrosis of subcutaneous soft tissues and skin. The third syndrome is the group of **focal and systemic infections** that do not meet the criteria for TSS or necrotizing fasciitis and includes bacteremia with sepsis with no identified focus, meningitis, pneumonia and empyema, peritonitis, puerperal sepsis, osteomyelitis, suppurative arthritis, myositis, and surgical wound and other infections. GAS TSS, necrotizing fasciitis, and focal and systemic infections can be present in any combination.

The pathogenic mechanisms responsible for severe, invasive GAS infections, including streptococcal TSS and necrotizing fasciitis, have yet to be defined completely, but an association with **streptococcal pyrogenic exotoxins** is strongly suspected. At least two of the three original streptococcal pyrogenic exotoxins (A and C) and potentially other as yet unidentified toxins produced by GAS act as **superantigens**, which stimulate intense activation and proliferation of T lymphocytes and macrophages, resulting in the production of large quantities of proinflammatory cytokines. These cytokines are capable of inducing shock and tissue injury and appear to mediate many of the clinical manifestations of severe, invasive GAS infections.

DIAGNOSIS OF GAS PHARYNGITIS

When deciding whether to perform a diagnostic test on a patient presenting with acute pharyngitis, the clinical and epidemiologic findings should be considered. A history of close contact with a well-documented case of GAS pharyngitis is helpful, as is an awareness of a high prevalence of GAS infections in the community. The signs and symptoms of streptococcal and nonstreptococcal pharyngitis overlap too broadly to allow the requisite diagnostic precision on clinical grounds alone. The clinical diagnosis of GAS pharyngitis cannot be made with reasonable accuracy even by the most experienced physicians, and laboratory confirmation is required, except for patients with overt viral signs and symptoms (e.g., rhinorrhea, cough, mouth ulcers, hoarseness), who generally do not need a GAS diagnostic test performed, as GAS is highly unlikely.

Culture of a throat swab on a sheep blood agar plate is effective for documenting the presence of GAS and for confirming the clinical diagnosis of acute GAS pharyngitis. When performed correctly, a single throat swab has a sensitivity of 90–95% for detecting the presence of GAS in the pharynx.

The significant disadvantage of culturing a throat swab on a blood agar plate is the delay (overnight or longer) in obtaining the culture result. **Streptococcal rapid antigen detection** tests are available for the identification of GAS directly from throat swabs. Their advantage over culture is the speed in providing results, often <10-15 minutes. Rapid identification and treatment of patients with streptococcal pharyngitis can reduce the risk for spread of GAS, allowing the patient to return to school or work sooner, and can reduce the acute morbidity of this illness.

Almost all currently available rapid antigen detection tests have excellent specificity of >95% compared with blood agar plate cultures. False-positive test results are quite unusual, and therefore therapeutic decisions can be made with confidence on the basis of a positive test result. Unfortunately, the sensitivity of most of these tests is 70–90% when compared with blood agar plate culture. Therefore a negative rapid test does not completely exclude the presence of GAS, and a confirmatory throat culture should be performed in children and adolescents, but not necessarily in adults, who are at exceptionally low risk for developing acute rheumatic fever. Definitive studies are not available to determine whether some rapid antigen detection tests are significantly more sensitive than others or whether any of these tests is sensitive enough to be used routinely in children and adolescents without throat culture confirmation of negative test results. Some experts believe that physicians who use a rapid antigen detection test without culture backup should compare the results with that specific test to those of throat cultures to confirm adequate sensitivity in their practice.

In point-of-care settings and laboratories testing for GAS pharyngitis, culture methods are being replaced by rapid antigen and molecular assays. These molecular assays include PCR methods and **nucleic acid amplification tests** using isothermal loop amplification. Some of these methods have been reported to have a sensitivity of up to 100% and specificity of >96% compared to culture or PCR. This very high sensitivity may lead to higher numbers of positive results, which in turn may contribute to identification of more patients with asymptomatic GAS colonization and unnecessary antibiotic therapy. Therefore it is important that the appropriate clinical context to perform these highly sensitive tests be considered. However, the benefit of faster results, sometimes <10 minutes, which ensures more expedited initiation of appropriate antibiotic therapy for patients with GAS pharyngitis, may be of value.

GAS infection can also be diagnosed retrospectively on the basis of an elevated or increasing streptococcal antibody titer. The **anti–streptolysin O** assay is the streptococcal antibody test most often used. The test is not specific for group A infection because streptolysin O also is produced by groups C and G streptococci. The anti–streptolysin O response can be feeble after streptococcal skin infection. In contrast, the anti–DNase B responses are generally present after either skin or throat infections. A significant antibody increase is usually defined as an increase in titer of two or more dilution increments (≥ fourfold rise) between the acute-phase and convalescent-phase specimens, regardless of the actual height of the antibody titer. Physicians frequently misinterpret streptococcal antibody titers because of a failure to appreciate that the normal levels of these antibodies are substantially higher among school-age children than adults. Both the traditional anti–streptolysin O and the anti–DNase B tests are neutralization assays. Newer tests use **latex agglutination** or nephelometric assays. Unfortunately, these newer tests often have not been well standardized against the traditional neutralization assays. Physicians should be aware of these potential problems when interpreting the results of streptococcal serologic testing.

Table 229.1 Definition of Streptococcal Toxic Shock Syndrome

CLINICAL CRITERIA
Hypotension *plus* two or more of the following: Renal impairment Coagulopathy Hepatic involvement Adult respiratory distress syndrome Generalized erythematous macular rash Soft tissue necrosis
DEFINITE CASE
Clinical criteria *plus* group A *Streptococcus* from a normally sterile site
PROBABLE CASE
Clinical criteria *plus* group A *Streptococcus* from a nonsterile site

Differential Diagnosis

Viruses are the most common cause of acute pharyngitis in children. Respiratory viruses such as influenza virus, parainfluenza virus, rhinovirus, coronavirus, adenovirus, and RSV are frequent causes of acute pharyngitis. Other viral causes of acute pharyngitis include enteroviruses and herpes simplex virus. Epstein-Barr virus is a frequent cause of acute pharyngitis that is often accompanied by other clinical findings of infectious mononucleosis (e.g., splenomegaly, generalized lymphadenopathy). Systemic infections with other viral agents, including cytomegalovirus, rubella virus, measles virus, and HIV, may be associated with acute pharyngitis.

GAS is by far the most common cause of *bacterial* pharyngitis, accounting for 15–30% of cases of acute pharyngitis in children and a lower proportion in adults. Groups C and G β-hemolytic streptococcus also cause acute pharyngitis, typically in teens and young adults (see Chapter 231). *Arcanobacterium haemolyticum* and *Fusobacterium necrophorum* are additional, less common causes. *Neisseria gonorrhoeae* can occasionally cause acute pharyngitis in sexually active adolescents and adults. Other bacteria, such as *Francisella tularensis* and *Yersinia enterocolitica,* as well as mixed infections with anaerobic bacteria (Vincent angina), are very rare causes of acute pharyngitis. *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* have been implicated as causes of acute pharyngitis, particularly in adults. *Corynebacterium diphtheriae* is a serious cause of pharyngitis but is very rare in areas with universal immunization (see Chapter 233). Although other bacteria (e.g., *S. aureus, Haemophilus influenzae, Streptococcus pneumoniae*) are frequently cultured from the throats of children with acute pharyngitis, their etiologic role in pharyngitis has not been established, because they are often isolated from healthy children.

GAS pharyngitis is the only common cause of acute pharyngitis for which antibiotic therapy is definitely indicated. Therefore when confronted with a patient with acute pharyngitis, the clinical decision that usually needs to be made is whether or not the pharyngitis is attributable to GAS.

TREATMENT OF GAS PHARYNGITIS

Timely antibiotic therapy for patients with GAS pharyngitis can prevent **acute rheumatic fever** (RF), shorten the clinical course of the illness, reduce transmission of the infection to others, and prevent suppurative complications. *For the patient with classic scarlet fever, antibiotic therapy should be started immediately, but for the majority of patients, who present with much less distinctive findings, treatment should be withheld until there is laboratory confirmation by throat culture, molecular assay, or rapid antigen detection test.* Rapid antigen detection tests, because of their high degree of specificity, allow initiation of antibiotic therapy immediately for the patient with a positive test result.

GAS is exquisitely sensitive to penicillin and cephalosporins, and resistant strains have never been encountered. Penicillin or amoxicillin is therefore the drug of choice (except in patients who are allergic to penicillins) for pharyngeal infections and for suppurative complications. Oral penicillin V (250 mg/dose 2 or 3 times daily [bid-tid] for children weighing ≤60 lb and 500 mg/dose bid-tid for children >60 lb) is recommended but must be taken for a full 10 days, even though symptomatic improvement may occur within 2-3 days. Penicillin V (phenoxymethylpenicillin) is preferred over penicillin G, because it may be given without regard to mealtime. The major concern with all forms of oral therapy is the risk that the drug will be discontinued before the 10-day course has been completed. Therefore when oral treatment is prescribed, the necessity of completing a full course of therapy must be emphasized. If the parents seem unlikely to comply with oral therapy because of family disorganization, difficulties in comprehension, or other reasons, parenteral therapy with a single intramuscular (IM) injection of benzathine penicillin G (600,000 IU for children weighing ≤60 lb and 1.2 million IU for children >60 lb) is the most efficacious and often the most practical method of treatment. Disadvantages include soreness around the site of injection, which may last for several days, and potential for injection into nerves or blood vessels if not administered correctly. The local reaction is diminished when the refrigerated drug is warmed to room temperature and when benzathine penicillin G is combined in a single injection with procaine penicillin G, although it is necessary to ensure that an adequate dose of benzathine penicillin G is administered.

In several comparative clinical trials, once-daily amoxicillin (50 mg/kg, maximum: 1,000 mg) for 10 days has been demonstrated to be as effective in treating GAS pharyngitis as amoxicillin administered orally multiple times per day. This somewhat broader-spectrum agent has the advantage of once-daily dosing, which may enhance adherence. In addition, amoxicillin is relatively inexpensive and is considerably more palatable than penicillin V suspension.

A 10-day course of a narrow-spectrum oral cephalosporin is recommended for most **penicillin-allergic** individuals. It has been suggested that a 10-day course with an oral cephalosporin is superior to 10 days of oral penicillin in eradicating GAS from the pharynx. Analysis of these data suggests that the difference in eradication is mainly the result of a higher rate of eradication of GAS carriage included unintentionally in these clinical trials. Some penicillin-allergic persons (up to 10%) are also allergic to cephalosporins, and these agents should be avoided in patients with immediate (anaphylactic-type) hypersensitivity to penicillin. Most oral broad-spectrum cephalosporins are considerably more expensive than penicillin or amoxicillin and are more likely to select for antibiotic-resistant flora.

Oral clindamycin is an appropriate agent for treating penicillin-allergic patients, and resistance to clindamycin among GAS isolates in the United States is currently <6%. An oral macrolide (erythromycin or clarithromycin) or azalide (azithromycin) is also an appropriate agent for patients allergic to penicillins. Ten days of therapy is indicated except for azithromycin, which is given at 12 mg/kg on day 1 and then 6 mg/kg on days 2-5. Erythromycin is associated with substantially higher rates of gastrointestinal side effects than the other agents. In recent years, macrolide resistance rates among pharyngeal isolates of GAS in most areas of the United States have been approximately 5–10%. Sulfonamides and the tetracyclines are not recommended for treatment of GAS pharyngitis. However, studies showed that trimethoprim-sulfamethoxazole (TMP-SMX) is highly active in vitro against GAS and was comparable to IM penicillin for GAS impetigo in clinical trials.

Most oral antibiotics must be administered for the conventional 10 days to achieve maximal pharyngeal eradication rates of GAS and prevention of RF, but certain newer agents are reported to achieve comparable bacteriologic and clinical cure rates when given for ≤5 days. However, definitive results from comprehensive studies are not available to allow full evaluation of these proposed shorter courses of oral antibiotic therapy, which therefore cannot be recommended at this time. In addition, these antibiotics have a much broader spectrum than penicillin and are generally more expensive, even when administered for short courses.

The majority of patients with GAS pharyngitis respond clinically to antimicrobial therapy, and GAS is eradicated from the pharynx. Posttreatment throat cultures are indicated only in the relatively few patients who remain symptomatic, whose symptoms recur, or who have had RF or rheumatic heart disease and are therefore at unusually high risk for recurrence.

Treatment of GAS Skin Infections

Antibiotic therapy for a patient with nonbullous impetigo can prevent local extension of the lesions, spread to distant infectious foci, and transmission of the infection to others. However, the ability of antibiotic therapy to prevent poststreptococcal glomerulonephritis has not been definitively demonstrated. Patients with a few superficial, isolated lesions and no systemic signs can be treated with topical antibiotics. **Mupirocin** is a safe and effective agent that has become the topical treatment of choice. If there are widespread lesions or systemic signs, oral therapy with coverage for both GAS and *S. aureus* is needed. With the rapid emergence of methicillin-resistant *S. aureus* in many communities, one should consider using clindamycin alone or a combination

of TMP-SMX and amoxicillin as first-line therapy. Oral cefuroxime is an effective treatment of perianal streptococcal disease.

Treatment of Invasive GAS Infection

Theoretical considerations and experimental data suggest that intravenous clindamycin is a more effective agent for the treatment of severe, invasive GAS infections than IV penicillin. However, because approximately 4–6% of GAS isolates in the United States are resistant to clindamycin, clindamycin initially should be used in combination with penicillin for these infections until susceptibility to clindamycin has been established. If **necrotizing fasciitis** is suspected, immediate surgical exploration may be required to identify a deep soft tissue infection that should be debrided immediately. Patients with **streptococcal TSS** require rapid and aggressive fluid replacement, management of respiratory or cardiac failure, if present, and anticipatory management of multiorgan system failure. Limited data suggest that intravenous immune globulin (IVIG) is effective as adjunctive therapy in the management of streptococcal TSS.

COMPLICATIONS

Suppurative complications from the spread of GAS to adjacent structures were extremely common in the preantibiotic era. Cervical lymphadenitis, peritonsillar abscess, retropharyngeal abscess, otitis media, mastoiditis, and sinusitis still occur in children in whom the primary illness has gone unnoticed or in whom treatment of the pharyngitis has been inadequate. GAS pneumonia can also occur.

Acute rheumatic fever (see Chapter 229.1) and acute poststreptococcal **glomerulonephritis** (see Chapter 559.4) are both nonsuppurative sequelae of infections with GAS that occur after an asymptomatic latent period. These complications occur after the initial GAS infection resolves and involves sites distal to the initial GAS infection site. These sequelae are thought to be the result of the immune response and not of direct GAS infection. Acute RF and acute glomerulonephritis differ in their clinical manifestations, epidemiology, and potential morbidity. In addition, acute glomerulonephritis follows a GAS infection of either the upper respiratory tract or the skin, but acute RF is only proven to follow an infection of the upper respiratory tract. Some investigators have suggested that in some highly endemic areas, particularly in New Zealand and Australia, GAS skin infection may trigger acute RF, but this remains controversial.

PROGNOSIS

The prognosis for appropriately treated GAS pharyngitis is excellent, and complete recovery is the rule. When therapy is instituted within 9 days of the onset of symptoms and continued for the full course, acute RF is almost always prevented. There is no comparable evidence that acute poststreptococcal glomerulonephritis can be prevented once pharyngitis or pyoderma with a nephritogenic strain of GAS has occurred. In rare instances, particularly in neonates or in children whose response to infection is compromised, fulminant pneumonia, septicemia, and death may occur despite usually adequate therapy.

PREVENTION

The only specific indication for long-term use of an antibiotic to prevent GAS infections is for patients with a history of acute RF and/or rheumatic heart disease. Mass prophylaxis is generally not feasible except possibly to reduce the number of infections during epidemics of impetigo and to control epidemics of pharyngitis in military populations and in schools. Because the ability of antimicrobial agents to prevent GAS infections is limited, a group A streptococcal vaccine would offer the possibility of a more effective approach.

Several candidate vaccines are in development, including a 30-valent M protein–based recombinant vaccine, another recombinant vaccine that includes several conserved non–M protein epitopes that induce protective antibody, and an M-protein vaccine that includes an epitope in a highly conserved region of M protein to provide broad immunity. All these vaccines are in relatively early stages of development.

Poststreptococcal Reactive Arthritis

Poststreptococcal reactive arthritis (PSRA) describes a syndrome characterized by the onset of acute arthritis after an episode of GAS pharyngitis in a patient whose illness does not fulfill the Jones Criteria for diagnosis of acute RF. It is still unclear whether this entity represents a distinct syndrome or is a variant of acute RF. Although PSRA usually involves the large joints, similar to the arthritis of acute RF, it may also involve small peripheral joints and the axial skeleton and is typically nonmigratory, a characteristic distinct from the arthritis of acute RF. The latent period between the antecedent episode of GAS pharyngitis and PSRA may be considerably *shorter* (usually <10 days) than that typically seen with acute RF (usually 14-21 days). In contrast to the arthritis of acute RF, PSRA *does not* respond dramatically to therapy with aspirin or other nonsteroidal antiinflammatory drugs (NSAIDs). In addition, fewer patients with PSRA than with acute RF have a temperature >38°C (100.4°F). Even though no more than half of PSRA patients with throat culture have GAS isolated, all have serologic evidence of a recent GAS infection. Because a very small proportion of patients with PSRA have been reported to develop valvular heart disease subsequently, these patients should be carefully observed for several months for clinical evidence of carditis. Some recommend that these patients receive secondary antistreptococcal prophylaxis for up to 1 year. If clinical evidence of carditis is not observed at that point, the prophylaxis can be discontinued. If valvular disease is detected, the patient should be classified as having had acute RF and should continue to receive secondary prophylaxis appropriate for RF patients.

Pediatric Autoimmune Neuropsychiatric Disorders Associated with *Streptococcus pyogenes*

Pediatric autoimmune neuropsychiatric disorders associated with *S. pyogenes* **(PANDAS)** is a term proposed for a group of neuropsychiatric disorders (originally obsessive-compulsive disorder [OCD], tic disorder, and Tourette syndrome, or only OCD or feeding abnormality) for which a possible relationship with GAS infections has been hypothesized (see Chapter 37). *This relationship has not been proved.* It has been proposed that this subset of patients with OCDs may produce autoimmune antibodies in response to a GAS infection that cross-react with brain tissue, similar to the autoimmune response believed to be responsible for the manifestations of **Sydenham chorea**. It has also been suggested that secondary prophylaxis that prevents recurrences of rheumatic fever, including Sydenham chorea, might also be effective in preventing exacerbations of OCDs in these patients, but clinical trials have not confirmed this. It has also been proposed that these patients may benefit from immunoregulatory therapy such as plasma exchange or IVIG, but these unproven modalities should only be used in a clinical research trial. That PANDAS may represent an extension of the spectrum of acute RF is intriguing, but it should be considered only as a yet-unproven hypothesis. Until carefully designed and well-controlled studies have established a causal relationship between neurobehavioral abnormalities and GAS infections, routine diagnostic laboratory testing for GAS and antistreptococcal antibodies, long-term antistreptococcal prophylaxis, or immunoregulatory therapy (e.g., IVIG, plasma exchange) to treat exacerbations of this disorder clearly are not recommended (see Chapter 37). It has also been suggested that a broad spectrum of infectious agents may have the ability to trigger exacerbations in children with these neurobehavioral disorders, which have been termed *pediatric acute-onset neuropsychiatric syndrome* (PANS), but this remains highly controversial.

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229.1 Rheumatic Fever

Stanford T. Shulman and Ami B. Patel

See also Chapter 487.

Overwhelming evidence supports the link between antecedent GAS pharyngitis and **acute rheumatic fever** (RF) and **rheumatic heart disease**. As many as two thirds of patients with an acute episode of RF have a history of an upper respiratory tract infection several weeks before; the peak age and seasonal incidence of acute RF closely parallel that of GAS pharyngitis. Patients with acute RF almost always have serologic evidence of a recent GAS infection. Their antibody titers are usually *considerably higher* than those seen in patients with uncomplicated GAS infections. Outbreaks of GAS pharyngitis in closed communities, such as boarding schools or military bases, may be followed by community outbreaks of acute RF. Antimicrobial therapy that eliminates GAS from the pharynx also prevents initial episodes of acute RF, and long-term, continuous antibiotic prophylaxis that prevents GAS pharyngitis also prevents recurrences of acute RF.

Not all serotypes of GAS can cause RF. When some GAS strains (e.g., M type 4) caused acute pharyngitis in a very susceptible rheumatic population, there were no recurrences of RF. In contrast, episodes of pharyngitis caused by other serotypes in the same population led to frequent recurrences of acute RF, suggesting that the latter organisms were rheumatogenic. The concept of *rheumatogenicity* is further supported by the observation that although serotypes of GAS frequently associated with skin infection can be isolated also from the upper respiratory tract, they rarely cause recurrences of RF in individuals with a previous history of RF or first episodes of RF. In addition, certain serotypes of GAS (M types 1, 3, 5, 6, 18, and 29) are more frequently isolated from patients with acute RF than are other serotypes.

EPIDEMIOLOGY

The annual incidence of acute RF in some developing countries exceeds 50 per 100,000 children, and very high rates are also seen in ethnic minority populations within Australia and New Zealand. Worldwide, **rheumatic heart disease** remains the most common form of acquired heart disease in all age-groups, accounting for up to 50% of all cardiovascular disease and 50% of all cardiac admissions in many developing countries. Striking differences in the incidence of acute RF and rheumatic heart disease among different ethnic groups are often evident within the same country; these differences are partially related to differences in socioeconomic status, and there is a genetic basis for increased susceptibility.

In the United States at the beginning of the 20th century, acute RF was a leading cause of death among children and adolescents, with annual incidence rates of 100-200 per 100,000 population. In addition, rheumatic heart disease was a leading cause of heart disease among adults <40 years old. At that time, as many as 25% of pediatric hospital beds in the United States were occupied by patients with acute RF or its complications. By the 1940s, the annual incidence of acute RF had decreased to 50 per 100,000 population, and over the next 4 decades, the decline in incidence accelerated rapidly. By the early 1980s, the annual incidence in some areas of the United States was as low as 0.5 per 100,000 population, and rates of acute RF since the 1980s have declined substantially. This sharp decline in the incidence of acute RF has been observed in other industrialized countries as well.

The explanation for this dramatic decline in the incidence of acute RF and rheumatic heart disease in the United States and other industrialized countries is not clear but is likely related in large part to a *decline in circulating rheumatogenic strains causing acute pharyngitis*. Historically, acute RF was associated with poverty and overcrowding, particularly in urban areas. Much of the decline in the incidence of acute RF in industrialized countries during the preantibiotic era was probably the result of improved living conditions. Of the various manifestations of poverty, crowding, which facilitates the spread of GAS infections, is most closely associated with the incidence of acute RF. The decline in incidence of acute RF in industrialized countries over the past 4 decades is also attributable to the greater availability of medical care and to the widespread use of antibiotics. Antibiotic therapy of GAS pharyngitis is important in preventing initial attacks and, particularly, recurrences of the disease. In addition, the decline in the United States is attributed to a shift in the prevalent strains of GAS causing pharyngitis from mostly rheumatogenic to nonrheumatogenic.

Certain rheumatogenic serotypes (types 1, 3, 5, 6, and 18) that were isolated less often during the 1970s and early 1980s dramatically reappeared during rheumatic fever outbreaks, and their appearance in selected communities was probably a major factor. GAS that are associated with rheumatogenicity often form highly mucoid colonies on throat culture plates.

In addition to the specific characteristics of the infecting strain of GAS, the risk of developing acute RF also depends on various host factors. The incidence of both initial attacks and recurrences of acute RF peaks in children 5-15 years old, the age of greatest risk for GAS pharyngitis. Patients who have had an attack of acute RF tend to have recurrences, and the clinical features of the recurrences tend to mimic those of the initial attack. In addition, there appears to be a genetic predisposition to acute RF. Studies in twins show a higher concordance rate of acute RF in monozygotic than in dizygotic twin pairs. Preliminary studies from Oceania in a population with high rates of rheumatic heart disease have identified an allele of interest that increases one's risk of rheumatic heart disease.

PATHOGENESIS

The **cytotoxicity theory** suggests that a GAS toxin is involved in the pathogenesis of acute RF and rheumatic heart disease. GAS produces a number of enzymes that are cytotoxic for mammalian cardiac cells, such as streptolysin O, which has a direct cytotoxic effect on mammalian cells in tissue culture. A major problem with the cytotoxicity hypothesis is its inability to explain the substantial latent period (usually 10-21 days) between GAS pharyngitis and onset of acute RF.

An **immune-mediated pathogenesis** for acute RF and rheumatic heart disease has been suggested by its clinical similarity to other illnesses with an immunopathogenesis and by the latent period between the GAS infection and acute RF. The immunologic cross-reactivity of several GAS cellular and extracellular epitopes with cardiac antigenic epitopes also lends support to the hypothesis of molecular mimicry. Common epitopes are shared between certain GAS components (e.g., M protein, cell membrane, group A cell wall carbohydrate, capsular hyaluronate) and specific mammalian tissues (e.g., heart valve, sarcolemma, brain, joint).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The current **Jones Criteria**, as revised in 2015 by the American Heart Association (AHA), are intended for diagnosis of the *initial* attack of acute RF and *recurrent* attacks (Table 229.2). There are **five major and four minor criteria** and a requirement for evidence of recent GAS infection. The 2015 revision includes separate criteria for **low-risk populations** (defined as those with incidence ≤2 per 100,000 school-age children per year or all-age rheumatic heart disease prevalence of ≤1 per 1,000 population) and **moderate/high-risk populations** (defined as those with higher incidence or prevalence rates). Virtually all of the United States, Canada, and Western Europe are low-risk, whereas moderate/high-risk populations include Maoris in New Zealand, aborigines in Australia, Pacific Islanders, and most developing countries. Diagnosis of a first attack or recurrent attack of acute RF can be established when a patient fulfills **two major or one major and two minor criteria and has evidence of preceding GAS infection**. Diagnosis of recurrent acute RF can also be made only in the moderate/high-risk population by the presence of three minor criteria with evidence of preceding GAS infection. In the 2015 Jones Criteria, a major change from previous versions expands the definition of the major criterion **carditis** to include *subclinical evidence* (e.g., in the absence of a murmur, echocardiographic evidence of mitral regurgitation [MR] meeting specific criteria to distinguish physiologic from

Table 229.2 Guidelines for the Diagnosis of an Initial or Recurrent Attack of Rheumatic Fever (Jones Criteria, Updated 2015)[1–5]

MAJOR MANIFESTATIONS	MINOR MANIFESTATIONS	SUPPORTING EVIDENCE OF ANTECEDENT GROUP A STREPTOCOCCAL INFECTION
Carditis Polyarthritis Erythema marginatum Subcutaneous nodules Chorea	**Clinical features:** Arthralgia Fever **Laboratory features:** Elevated acute-phase reactants: Erythrocyte sedimentation rate C-reactive protein Prolonged P-R interval	Positive throat culture or rapid streptococcal antigen test Elevated or increasing streptococcal antibody titer

[1]**Initial attack**: Two major manifestations or one major and two minor manifestations plus evidence of recent GAS infection. **Recurrent attack**: Two major, or one major and two minor, or three minor manifestations (the latter only in the moderate/high-risk population), plus evidence of recent GAS infection (see text).
[2]**Low-risk population** is defined as acute rheumatic fever (ARF) incidence <2 per 100,000 school-age children per year or all-age rheumatic heart disease (RHD) prevalence of <1 per 1,000 population. **Moderate/high-risk population** is defined as ARF incidence >2 per 100,000 school-age children per year or all-age RHD prevalence of >1 per 1,000 population.
[3]Carditis is now defined as clinical and/or subclinical (echocardiographic valvulitis). See Table 229.3.
[4]Arthritis (major) refers only to polyarthritis in low-risk populations but also to monoarthritis or polyarthralgia in moderate/high-risk populations.
[5]Minor criteria for moderate/high-risk populations only include monoarthralgia (polyarthralgia for low-risk populations), fever of >38°C (>38.5°C in low-risk populations), and ESR >30 mm/hr (>60 mm/hr in low-risk populations).
From Gewitz MH, Baltimore RS, Tani LY, et al. Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. *Circulation*. 2015;131(20):1806–1818.

pathologic MR) (see Table 487.1). Areas in which the Jones Criteria differ in low-risk from moderate/high-risk populations relate to the major criterion of **arthritis** and the minor criteria of arthralgia, definition of fever, and elevated inflammatory markers (see Table 229.2 and text that follows). These changes are designed to make it easier to fulfill the Jones Criteria in patients from moderate/high-risk populations. Even with strict application of the criteria, overdiagnosis and underdiagnosis of acute RF may occur. The diagnosis of acute RF can be made without strict adherence to the Jones Criteria in three circumstances: (1) when chorea occurs as the only major manifestation of acute RF, (2) when indolent carditis is the only manifestation in patients who first come to medical attention only months after the apparent onset of acute RF, and (3) in a limited number of patients with recurrence of acute RF in particularly high-risk populations.

The Five Major Criteria

Migratory Polyarthritis

Arthritis occurs in approximately 75% of patients with acute RF and typically involves larger joints, particularly the knees, ankles, wrists, and elbows. Involvement of the spine, small joints of the hands and feet, or hips is uncommon. Rheumatic joints are classically hot, red, swollen, and exquisitely tender, with even the friction of bedclothes being uncomfortable. The pain can precede and can appear to be disproportionate to the objective findings. The joint involvement is characteristically migratory in nature; that is, a severely inflamed joint can become normal within 1-3 days without treatment, even as one or more other large joints become involved. Severe arthritis can persist for several weeks in untreated patients. Monoarticular arthritis is unusual unless antiinflammatory therapy is initiated prematurely, aborting the progression of the migratory polyarthritis. If a child with fever and arthritis is suspected to have acute RF, it is frequently useful to withhold antiinflammatory medications like salicylates or NSAIDs and observe for migratory progression. A dramatic response to even low doses of salicylates is another characteristic feature of the arthritis, and the absence of such a response should suggest an alternative diagnosis.

Rheumatic arthritis is almost never deforming. Synovial fluid in acute RF usually has 10,000-100,000 white blood cells/μL with a predominance of neutrophils, protein level of approximately 4 g/dL, normal glucose level, and formation of a good mucin clot. Frequently, arthritis is the earliest manifestation of acute RF and may correlate temporally with peak antistreptococcal antibody titers. There is often an inverse relationship between the severity of arthritis and the severity of cardiac involvement. In moderate/high-risk populations only, monoarthritis in the absence of prior inflammatory therapies, or even polyarthralgia without frank objective signs of arthritis, can fulfill this major criterion. Before **polyarthralgia** should be considered a major criterion in the moderate/high-risk population, other potential causes should be excluded.

Carditis

A major change in the 2015 revision of the Jones Criteria is the acceptance of **subclinical carditis** (defined as without a murmur of valvulitis but with echocardiographic evidence of valvulitis) or **clinical carditis** (with a valvulitis murmur) as fulfilling the major criterion of carditis in all populations. The echocardiographic features of subclinical carditis must meet those included in Table 487.1 in Chapter 487 to distinguish pathologic from physiologic degrees of valve regurgitation. Silent or latent rheumatic heart disease describes echocardiographic evidence of rheumatic heart disease in individuals with no known history of acute RF and no clinical symptoms. In endemic regions, active surveillance via screening echocardiography has emerged as a potential strategy to detect *asymptomatic subclinical* rheumatic heart disease.

Carditis and resultant chronic rheumatic heart disease are the most serious manifestations of acute RF and account for essentially all the associated morbidity and mortality. Rheumatic carditis is characterized by **pancarditis**, with active inflammation of the myocardium, pericardium, and endocardium (see Chapter 487). Cardiac involvement during acute RF varies in severity from fulminant, potentially fatal exudative pancarditis to mild, transient cardiac involvement. **Endocarditis** (valvulitis) is a universal finding in rheumatic carditis, whereas the presence of pericarditis or myocarditis is variable. Myocarditis and/or pericarditis without clinical evidence of endocarditis almost never is rheumatic carditis; alternative etiologies (especially viral) need to be sought. Most rheumatic heart disease is isolated mitral valvular disease or combined aortic and mitral valvular disease. Isolated aortic or right-sided valvular involvement is quite uncommon. Serious and long-term illness is related entirely to the severity of valvular heart disease as a consequence of a single attack or recurrent attacks of acute RF. Valvular insufficiency is characteristic of both acute and convalescent stages of acute RF, whereas mitral and/or aortic valvular stenosis usually appears years or even decades after the acute illness. However, in developing countries, where acute RF often occurs at a younger age, mitral stenosis and aortic stenosis may develop sooner after acute RF than in developed countries and can occur in young children.

Acute rheumatic carditis usually presents as tachycardia and cardiac murmurs, with or without evidence of myocardial or pericardial

involvement. Moderate to severe rheumatic carditis can result in cardiomegaly and heart failure with hepatomegaly and peripheral and pulmonary edema. Echocardiographic findings include pericardial effusion, decreased ventricular contractility, and aortic and/or mitral regurgitation. **Mitral regurgitation** is characterized typically by a high-pitched apical holosystolic murmur radiating to the axilla. In patients with significant MR, this may be associated with an apical mid-diastolic murmur of relative mitral stenosis. Aortic insufficiency is characterized by a high-pitched decrescendo diastolic murmur at the left sternal border.

Carditis occurs in approximately 50–60% of all cases of acute RF. Recurrent attacks of acute RF in patients who had carditis with their initial attack are associated with high rates of carditis with increasing severity of cardiac disease. The major consequence of acute rheumatic carditis is chronic, progressive valvular disease, particularly valvular stenosis, which can require surgical intervention.

Chorea

Sydenham chorea occurs in approximately 10–15% of patients with acute RF and usually presents as an isolated, frequently subtle, movement disorder. Emotional lability, incoordination, poor school performance, uncontrollable movements, and facial grimacing are characteristic, all *exacerbated* by stress and *disappearing* with sleep. Chorea occasionally is unilateral (hemichorea). The latent period from acute GAS infection to chorea is usually substantially longer than for arthritis or carditis and can be months. The onset can be insidious, with symptoms being present for several months before recognition. Clinical maneuvers to elicit features of chorea include (1) demonstration of *milkmaid's grip* (irregular contractions and relaxations of the muscles of the fingers while squeezing the examiner's fingers), (2) spooning and pronation of the hands when the patient's arms are extended, (3) wormian darting movements of the tongue on protrusion, and (4) examination of handwriting to evaluate fine motor movements. Diagnosis is based on clinical findings with supportive evidence of GAS antibodies. However, in the usual patient with a long latent period from the inciting streptococcal infection to onset of chorea, antibody levels have often declined to normal. Although the acute illness is distressing, chorea rarely, if ever, leads to permanent neurologic sequelae.

Erythema Marginatum

Erythema marginatum is a rare (approximately 1% of patients with acute RF) but characteristic rash of acute RF. It consists of erythematous, serpiginous, macular lesions with pale centers that are not pruritic (Fig. 229.2). It occurs primarily on the trunk and extremities, but not on the face, and it can be accentuated by warming the skin.

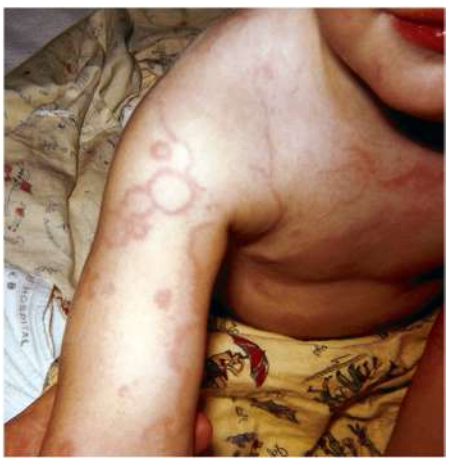

Fig. 229.2 Polycyclic red borders of erythema marginatum in a febrile child with acute rheumatic fever. *(From Schachner LA, Hansen RC, eds. Pediatric Dermatology, 3rd ed. Philadelphia: Mosby; 2003:808.)*

Subcutaneous Nodules

Subcutaneous nodules are a rare (≤1% of patients with acute RF) finding and consist of firm nodules approximately 0.5-1 cm in diameter along the extensor surfaces of tendons near bony prominences. There is a correlation between the presence of these nodules and significant rheumatic heart disease.

Minor Criteria

These are more *nonspecific* than major criteria, and the 2015 revised Jones Criteria have included some changes from the previous criteria. The first of the two clinical **minor criteria** involve joint manifestations (only if arthritis is not used as a major criterion) and is defined as *polyarthralgia* in low-risk populations and *monoarthralgia* in moderate/high-risk populations. The second clinical minor manifestation is fever, defined as *at least 38.5°C* in low-risk populations and *at least 38.0°C* in moderate/high-risk populations. The two laboratory minor criteria are (1) elevated acute-phase reactants, defined as erythrocyte sedimentation rate (ESR) at least 60 mm/hr and/or C-reactive protein (CRP) at least 3.0 mg/dL (30 mg/L) in low-risk populations and ESR at least 30 mm/hr and/or CRP at least 3.0 mg/dL (30 mg/L) in moderate/high-risk populations and (2) prolonged P-R interval on ECG (unless carditis is a major criterion). However, a prolonged P-R interval alone does not constitute evidence of carditis or predict long-term cardiac sequelae.

Recent Group A *Streptococcus* Infection

An absolute requirement for the diagnosis of acute RF is supporting evidence of a recent GAS infection. Acute RF typically develops 10-21 days after an acute episode of GAS pharyngitis at a time when clinical findings of pharyngitis are no longer present and when only 10–20% of patients still harbor GAS in the throat. One third of patients with acute RF have no history of an antecedent clinically symptomatic pharyngitis. Therefore evidence of an antecedent GAS infection is usually based on elevated or rising serum antistreptococcal antibody titers. If only a single antibody is measured (usually anti–streptolysin O), only 80–85% of patients with acute RF have an elevated titer; however, 95–100% have an elevation if three different antibodies (anti–streptolysin O, anti–DNase B, anti-hyaluronidase) are measured. Therefore when acute RF is suspected clinically, multiple antibody tests should be performed. Except for chorea, the clinical findings of acute RF generally coincide with peak antistreptococcal antibody responses. Most patients with chorea have elevation of antibodies to at least one GAS antigen. However, in patients with a long latent period from the inciting GAS infection, antibody levels may have declined to within the normal range. The diagnosis of acute RF should *not* be made in those patients with elevated or increasing streptococcal antibody titers who do not fulfill the Jones Criteria.

Differential Diagnosis

The differential diagnosis of RF includes many infectious and noninfectious illnesses (Table 229.3). When children present with arthritis, a collagen vascular disease must be considered. **Juvenile idiopathic arthritis** (JIA) must be distinguished from acute RF. Children with JIA tend to be younger and usually have less joint pain relative to their other clinical findings than those with acute RF. Spiking fevers, nonmigratory arthritis, lymphadenopathy, and splenomegaly are more suggestive of JIA than acute RF. The response to salicylate therapy is also much less dramatic with JIA than with acute RF. **Systemic lupus erythematosus** (SLE) can usually be distinguished from acute RF by antinuclear antibodies in SLE. Other causes of arthritis such as pyogenic arthritis, malignancies, serum sickness, Lyme disease, sickle cell disease, and reactive arthritis related to gastrointestinal infections (e.g., *Shigella, Salmonella, Yersinia*) should also be considered. Poststreptococcal reactive arthritis is discussed earlier (see Chapter 229).

When **carditis** is the sole major manifestation of suspected acute RF, viral myocarditis, viral pericarditis, Kawasaki disease, and infective endocarditis should also be considered. Patients with infective

Table 229.3 Differential Diagnosis of Acute Rheumatic Fever

ARTHRITIS	CARDITIS	CHOREA
Juvenile idiopathic arthritis	Viral myocarditis	Huntington chorea
Reactive arthritis (e.g., *Shigella, Salmonella, Yersinia*)	Viral pericarditis	Wilson disease
Serum sickness	Infective endocarditis	Systemic lupus erythematosus
Sickle cell disease	Kawasaki disease	Tic disorder
Malignancy	Congenital heart disease	Hyperactivity
Systemic lupus erythematosus	Mitral valve prolapse	Encephalitis (infectious or autoimmune)
Lyme disease (*Borrelia burgdorferi*)	Innocent murmurs	
Pyogenic arthritis	MIS-C	
Poststreptococcal reactive arthritis	Lyme disease	

MIS-C, Multisystem inflammatory syndrome in children (COVID-19).

endocarditis may present with both joint and cardiac manifestations. These patients can usually be distinguished from patients with acute RF by blood cultures and the presence of extracardiac findings (e.g., hematuria, splenomegaly, splinter hemorrhages). When **chorea** is the sole major manifestation of suspected acute RF, Huntington chorea, Wilson disease, SLE, and various encephalitides should also be considered.

TREATMENT

All patients with acute RF should be placed on bed rest and monitored closely for evidence of **carditis**. They can be allowed to ambulate when the signs of acute inflammation have improved. However, patients with carditis require longer periods of bed rest.

Antibiotic Therapy

Once the diagnosis of acute RF has been established and regardless of the throat culture results, the patient should receive 10 days of orally administered penicillin or amoxicillin or a single IM injection of benzathine penicillin to ensure eradication of GAS from the upper respiratory tract. If penicillin allergic, 10 days of erythromycin, 5 days of azithromycin, or 10 days of clindamycin is indicated. After this initial course of antibiotic therapy, long-term antibiotic prophylaxis for secondary prevention should be instituted (see later).

Antiinflammatory Therapy

Antiinflammatory agents (e.g., salicylates, corticosteroids) should be withheld if arthralgia or atypical arthritis is the only clinical manifestation of presumed acute RF. Premature treatment with one of these agents may interfere with the development of the characteristic migratory polyarthritis and thus obscure the diagnosis of acute RF. Acetaminophen can be used to control pain and fever while the patient is being observed for more definite signs of acute RF or for evidence of another disease.

Patients with typical migratory polyarthritis and those with carditis without cardiomegaly or congestive heart failure should be treated with oral salicylates. The usual dose of aspirin is 50-70 mg/kg/day in four divided doses orally (PO) for 3-5 days, followed by 50 mg/kg/day in four divided doses PO for 2-3 weeks and half that dose for another 2-4 weeks. Determination of the serum salicylate level is not necessary unless the arthritis does not respond or signs of salicylate toxicity (tinnitus, hyperventilation) develop. There is no evidence that NSAIDs are more effective than salicylates.

Patients with carditis and more than minimal cardiomegaly and/or congestive heart failure should receive corticosteroids. The usual dose of prednisone is 2 mg/kg/day in four divided doses for 2-3 weeks, followed by half the dose for 2-3 weeks, and then tapering of the dose by 5 mg/24 hr every 2-3 days. When prednisone is being tapered, aspirin should be started at 50 mg/kg/day in four divided doses for 6 weeks to prevent rebound of inflammation. Supportive therapies for patients with moderate to severe carditis include digoxin, fluid and salt restriction, diuretics, and oxygen. The cardiac toxicity of digoxin is enhanced with myocarditis.

Termination of the antiinflammatory therapy may be followed by the reappearance of clinical manifestations or of elevation in ESR and CRP (rebound). It may be prudent to increase salicylates or corticosteroids until near-normalization of inflammatory markers is achieved.

Sydenham Chorea

Because chorea often occurs as an isolated manifestation after the resolution of the acute phase of the disease, antiinflammatory agents are usually not indicated. Sedatives may be helpful early in the course of chorea; phenobarbital (16-32 mg every 6-8 hours PO) is the drug of choice. If phenobarbital is ineffective, haloperidol (0.01-0.03 mg/kg/24 hr divided twice daily PO) or chlorpromazine (0.5 mg/kg every 4-6 hours PO) should be initiated. Some patients may benefit from a few-week course of corticosteroids.

COMPLICATIONS

The arthritis and chorea of acute RF resolve completely without sequelae. Therefore the long-term sequelae of RF are essentially limited to the heart (see Chapter 487).

The AHA has published updated recommendations regarding the use of prophylactic antibiotics to prevent infective endocarditis (see Chapter 486). The AHA recommendations no longer suggest routine endocarditis prophylaxis for patients with rheumatic heart disease who are undergoing dental or other procedures. However, the maintenance of optimal oral healthcare remains an important component of an overall healthcare program. For the relatively few patients with rheumatic heart disease in whom infective endocarditis prophylaxis remains recommended, such as those with a prosthetic valve or prosthetic material used in valve repair, the current AHA recommendations should be followed (see Chapter 486). These recommendations advise using an agent other than a penicillin to prevent infective endocarditis in those receiving penicillin prophylaxis for RF because oral α-hemolytic streptococci are likely to have developed resistance to penicillin.

PROGNOSIS

The prognosis for patients with acute RF depends on the clinical manifestations present at the initial episode, the severity of the initial episode, and the prevention of recurrences. Approximately 50–70% of patients with carditis during the initial episode of acute RF recover with no residual heart disease; the more severe the initial cardiac involvement, the greater the risk for residual heart disease. Patients without carditis during the initial episode are less likely to have carditis with recurrent attacks, but there is a stepwise increase in cardiac involvement as the number of episodes increases. In contrast, patients with carditis during the initial episode are very likely to have carditis with recurrences, and the risk for permanent heart damage increases with each recurrence. Patients who have had acute RF are susceptible to recurrent attacks after reinfection of the upper respiratory tract with GAS, with approximately 50% risk with each GAS pharyngitis. Therefore these patients require long-term continuous chemoprophylaxis.

Table 229.4 Chemoprophylaxis for Recurrences of Acute Rheumatic Fever (Secondary Prophylaxis)

DRUG	DOSE	ROUTE
Penicillin G benzathine	600,000 IU for children weighing ≤60 lb and 1.2 million IU for children >60 lb, every 4 wk*	Intramuscular
or		
Penicillin V	250 mg, twice daily	Oral
or		
Sulfadiazine or sulfisoxazole	500 mg once daily for patients weighing ≤60 lb	Oral
	1000 mg once daily for patients weighing >60 lb	
FOR PEOPLE WHO ARE ALLERGIC TO PENICILLIN AND SULFONAMIDE DRUGS		
Macrolide or azalide	Variable	Oral

*In high-risk situations, administration every 3 wk is recommended.
Adapted from Gerber MA, Baltimore RS, Eaton CB, et al. Prevention of rheumatic fever and diagnosis and treatment of acute streptococcal pharyngitis: a scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young. *Circulation*. 2009;119:1541–1551.

Before antibiotic prophylaxis was available, 75% of patients who had an initial episode of acute RF had one or more recurrences in their lifetime. These recurrences were a major source of morbidity and mortality. The risk of recurrence is highest in the first 5 years after the initial episode and decreases with time.

Approximately 20% of patients who present with isolated chorea who are not given secondary prophylaxis develop rheumatic heart disease within 20 years. Therefore patients with chorea, even in the absence of other manifestations of RF, require long-term antibiotic prophylaxis (Table 229.4).

PREVENTION

Prevention of both initial and recurrent episodes of acute RF depends on controlling GAS infections of the upper respiratory tract. Prevention of initial attacks **(primary prevention)** depends on identification and eradication of GAS causing acute pharyngitis. A New Zealand study in a population with very high rates of acute RF showed that a school-based GAS pharyngitis screening and management program using oral amoxicillin substantially decreased pharyngeal GAS prevalence and rates of acute RF. Individuals who have already suffered an attack of acute RF are particularly susceptible to recurrences of RF with any subsequent GAS upper respiratory tract infection, whether or not they are symptomatic. Therefore these patients should receive continuous antibiotic prophylaxis to prevent recurrences **(secondary prevention)**.

Primary Prevention

Appropriate antibiotic therapy instituted before the ninth day of symptoms of acute GAS pharyngitis is highly effective in preventing the first attacks of acute RF. However, approximately 30% of patients with acute RF do not recall a preceding episode of pharyngitis and did not seek therapy.

Secondary Prevention

Secondary prevention is directed at preventing acute GAS pharyngitis in patients at substantial risk of recurrent acute RF. Secondary prevention requires continuous antibiotic prophylaxis, which should begin as soon as the diagnosis of acute RF has been made and immediately after a full course of antibiotic therapy has been completed. Because patients who have had carditis with their initial episode of acute RF are at higher risk for having carditis with recurrences and for sustaining additional cardiac damage, they should receive long-term antibiotic prophylaxis well into adulthood and perhaps for life (see Table 229.4 and Table 229.5).

Patients who did not have carditis with their initial episode of acute RF have a relatively low risk for carditis with recurrences. Antibiotic prophylaxis should continue in these patients until the patient reaches 21 years of age or until 5 years have elapsed since the last RF attack, whichever is longer. The decision to discontinue prophylactic antibiotics should be made only after careful consideration of potential risks and benefits and of epidemiologic factors such as the risk for exposure to GAS infections.

Table 229.5 Duration of Prophylaxis for People Who Have Had Acute Rheumatic Fever: AHA Recommendations

CATEGORY	DURATION
Rheumatic fever without carditis	5 yr or until 21 yr of age, whichever is longer
Rheumatic fever with carditis but without residual heart disease (no valvular disease*)	10 yr or until 21 yr of age, whichever is longer
Rheumatic fever with carditis and residual heart disease (persistent valvular disease*)	10 yr or until 40 yr of age, whichever is longer; sometimes lifelong prophylaxis

*Clinical or echocardiographic evidence.
Adapted from Gerber MA, Baltimore RS, Eaton CB, et al. Prevention of rheumatic fever and diagnosis and treatment of acute streptococcal pharyngitis: a scientific statement from the American Heart Association (AHA) Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young. *Circulation*. 2009;119:1541–1551.

The regimen of choice for secondary prevention is a single IM injection of benzathine penicillin G (600,000 IU for children weighing ≤60 lb and 1.2 million IU for those >60 lb) every 4 weeks (see Table 229.4). In certain high-risk patients and in certain areas of the world where the incidence of RF is particularly high, use of benzathine penicillin G every 3 weeks may be necessary because serum concentrations of penicillin may decrease to marginally effective levels after 3 weeks. In the United States, administration of benzathine penicillin G every 3 weeks is recommended only for those who have recurrent acute RF despite adherence to a 4-week regimen. In compliant patients, continuous oral antimicrobial prophylaxis can be used. Penicillin V (250 mg twice daily) and sulfadiazine or sulfisoxazole (500 mg for those weighing ≤60 lb or 1,000 mg for those >60 lb, once daily) are equally effective when used in such patients. For the exceptional patient who is allergic to both penicillin and sulfonamides, a macrolide (erythromycin or clarithromycin) or azalide (azithromycin) may be used. Table 229.5 notes the duration of secondary prophylaxis.

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Chapter 230

Group B *Streptococcus*

Thomas A. Hooven

Group B *Streptococcus* **(GBS)**, or *Streptococcus agalactiae,* is a major cause of **neonatal bacterial sepsis** worldwide. Although advances in prevention strategies have led to a decline in the incidence of neonatal disease, GBS remains a dangerous pathogen for neonates, pregnant women, and nonpregnant adults.

ETIOLOGY

Group B streptococci are facultative, anaerobic, gram-positive cocci that form chains or diplococci in broth and small, gray-white or orange-tinged colonies on solid medium. GBS is definitively identified by demonstration of the Lancefield group B carbohydrate antigen, such as with latex agglutination techniques widely used in clinical laboratories. Presumptive identification can be established on the basis of a narrow zone of β-hemolysis on blood agar, resistance to bacitracin and trimethoprim-sulfamethoxazole (TMP-SMX), lack of hydrolysis of bile esculin, and elaboration of CAMP factor (named for the discoverers, Christie, Atkins, and Munch-Petersen), an extracellular protein that, in the presence of the β toxin of *Staphylococcus aureus,* produces a zone of enhanced hemolysis on sheep blood agar. Individual GBS strains are serologically classified according to the presence of one of the structurally distinct capsular polysaccharides, which are important virulence factors and stimulators of antibody-associated immunity. Ten GBS capsular types have been identified: types Ia, Ib, II, III, IV, V, VI, VII, VIII, and IX.

EPIDEMIOLOGY

GBS emerged as a prominent neonatal pathogen in the late 1960s. For the next 2 decades, the incidence of neonatal GBS disease remained fairly constant, affecting 1.0-5.4 per 1,000 liveborn infants in the United States. Two patterns of disease were seen: **early-onset disease**, which presents at <7 days of age, and **late-onset disease**, which presents at ≥7 days of age. Since the early 1990s, widespread implementation of **maternal intrapartum antibiotic prophylaxis** has led to a striking decrease in the incidence of early-onset neonatal GBS disease in the United States, from 1.7 to 0.19 per 1,000 live births in recent years. This strategy has *not* had a significant effect on the incidence of late-onset disease, which has remained stable at approximately 0.3-0.4 per 1,000 live births (Fig. 230.1). The incidence of neonatal GBS disease is higher in premature and low birthweight infants, although most cases occur in full-term infants. Rates of both early- and late-onset disease are higher in Black infants.

Colonization by GBS in healthy adults is common. Vaginal or rectal colonization occurs in up to approximately 30% of pregnant women and is the usual source for GBS transmission to newborn infants. In the absence of maternal antibiotic prophylaxis, approximately 50% of infants born to colonized women acquire GBS colonization, and 1–2% of infants born to colonized mothers develop early-onset disease. Heavy maternal colonization increases the risk for infant colonization and development of early-onset disease. Additional risk factors for early-onset disease include prolonged rupture of membranes, intrapartum fever, prematurity, maternal bacteriuria during pregnancy, and previous delivery of an infant who developed GBS disease. Risk factors for late-onset disease are less well defined. Whereas late-onset disease may follow vertical transmission, horizontal acquisition from nursery or other community sources (such as family, healthcare providers, or environmental exposure) has also been described.

GBS is also an important cause of invasive disease in adults. GBS may cause urinary tract infections, bacteremia, endometritis, chorioamnionitis, and wound infection in pregnant and parturient women. In nonpregnant adults, especially those with underlying medical conditions such as diabetes mellitus, cirrhosis, or malignancy, GBS may cause serious infections such as bacteremia, skin and soft tissue infections, bone and joint infections, endocarditis, pneumonia, and meningitis. In the era of maternal chemoprophylaxis, most invasive GBS infections occur in nonpregnant adults. Unlike neonatal disease, the incidence of invasive GBS disease in adults has increased substantially, roughly tripling between 1990 and 2016.

The serotypes most frequently associated with neonatal GBS disease are types Ia, III, and V. Strains of serotype III are the most common subtype isolated from colonized pregnant women and are also the most frequent cause of invasive disease among newborns and adults. Global epidemiologic studies have revealed regional variation in subtype prevalence, some of which may reflect local dietary and healthcare practices.

PATHOGENESIS

A major risk factor for the development of early-onset neonatal GBS infection is maternal vaginal or rectal colonization by GBS. Infants acquire GBS by ascending infection or during passage through the birth canal. Fetal aspiration of infected amniotic fluid may occur. The incidence of early-onset GBS infection increases with the duration of rupture of membranes. Infection may also occur through transcellular passage across intact membranes. In cases of late-onset infection, GBS may be vertically transmitted or acquired later from maternal or nonmaternal sources.

Several bacterial factors are implicated in the pathogenesis of invasive GBS disease, primarily the type-specific **capsular polysaccharide**. Strains that are associated with invasive disease in humans elaborate more capsular polysaccharide than do colonizing isolates. All GBS capsular polysaccharides are high molecular weight polymers composed of repeating oligosaccharide subunits that include a short side chain terminating in *N*-acetylneuraminic acid **(sialic acid)**. Studies of type III GBS show that the sialic acid component of the capsular polysaccharide prevents activation of the alternative complement pathway in the absence of type-specific antibody. Sialylated capsular polysaccharide on the GBS surface also interacts with sialic acid–binding lectins or siglecs on human leukocytes to dampen inflammatory gene activation. Thus the capsular polysaccharide appears to exert a virulence effect by protecting the organism from opsonophagocytosis in the nonimmune host and by downregulating leukocyte activation. In addition, type-specific virulence attributes are suggested by the fact that type III strains are implicated in most cases of late-onset neonatal GBS disease and meningitis. Type III strains are taken up by brain endothelial cells

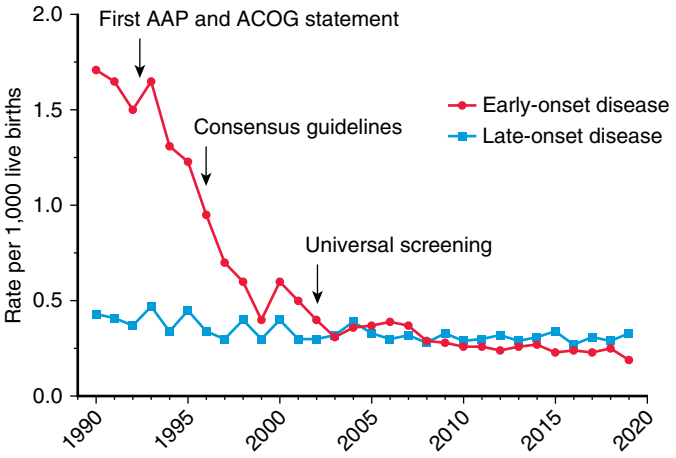

Fig. 230.1 Incidence of early- and late-onset invasive group B streptococcal (GBS) disease–active bacterial core surveillance areas, 1990-2019, and activities for prevention of GBS disease. AAP, American Academy of Pediatrics; ACOG, American College of Obstetricians and Gynecologists. *(Adapted from Jordan HT, Farley MM, Craig A, et al. Revisiting the need for vaccine prevention of late-onset neonatal group B streptococcal disease: a multistate, population-based analysis. Pediatr Infect Dis J. 2008;27:1057–1064.)*

more efficiently in vitro than are strains of other serotypes, although studies using acapsular mutant strains demonstrate that the capsule by itself does not facilitate cellular invasion. A single clade of type III GBS is highly associated with late-onset disease and meningitis. This clonal group, ST-17, produces a surface-anchored protein called *hypervirulent GBS adhesin* **(HvgA)** that is not present in other GBS isolates. HvgA contributes to GBS adherence to intestinal and endothelial cells and mediates invasion into the central nervous system (CNS) in an experimental infection model in mice. Other putative GBS virulence factors include GBS surface proteins, which may play a role in adhesion to host cells; C5a peptidase, which is postulated to inhibit the recruitment of polymorphonuclear cells to sites of infection; β-hemolysin/cytolysin, which has been associated with cell injury in vitro; and hyaluronidase, which has been postulated to act as a spreading factor in host tissues.

In a classic study of pregnant women colonized with type III GBS, those who gave birth to healthy infants had higher levels of capsular polysaccharide-specific antibody than those who gave birth to infants who developed invasive disease. In addition, there is a high correlation between antibody titer to GBS type III in the mother and titer in the paired infants. These observations indicate that transplacental transfer of maternal antibody is critically involved in neonatal immunity to GBS. Optimal immunity to GBS also requires an intact complement system. The classical complement pathway is an important component of GBS immunity in the absence of specific antibody; in addition, antibody-mediated opsonophagocytosis may proceed by the alternative complement pathway. These and other results indicate that anticapsular antibody can overcome the prevention of C3 deposition on the bacterial surface by the sialic acid component of the type III capsule.

The precise steps between GBS colonization and invasive disease remain unclear. In vitro studies showing GBS entry into alveolar epithelial cells and pulmonary vasculature endothelial cells suggest that GBS may gain access to the bloodstream by invasion from the alveolar space, perhaps after intrapartum aspiration of infected amniotic fluid. β-hemolysin/cytolysin may facilitate GBS entry into the bloodstream after inoculation into the lungs. Other studies have demonstrated intestinal GBS colonization preceding invasive disease among newborns, suggesting translocation across the intestinal wall as a pathogenic mechanism.

GBS induces the release of proinflammatory cytokines. The group B antigen and the peptidoglycan component of the GBS cell wall are potent inducers of tumor necrosis factor-α release in vitro, whereas purified type III capsular polysaccharide is not. Even though the capsule plays a central role in virulence through avoidance of immune clearance, the capsule does not directly contribute to cytokine release and the resultant inflammatory response.

The complete genome sequences of hundreds of GBS strains have been reported, facilitating a genomic approach to better understanding GBS. Analysis of these sequences shows that GBS is closely related to *Streptococcus pyogenes* and *Streptococcus pneumoniae.* Many known and putative GBS virulence genes are clustered in the genome in pathogenicity islands that also contain mobile genetic elements, suggesting that interspecies acquisition of genetic material plays an important role in genetic diversity.

CLINICAL MANIFESTATIONS

Two syndromes of neonatal GBS disease are distinguishable on the basis of age at presentation, epidemiologic characteristics, and clinical features (Table 230.1). **Early-onset neonatal GBS disease** presents within the first 6 days of life and is often associated with maternal obstetric complications, including chorioamnionitis, prolonged rupture of membranes, and premature labor. Infants may appear ill at the time of delivery, and most infants become ill within 24 hours of birth. In utero infection may result in septic abortion or immediate distress after birth. More than 80% of early-onset GBS disease presents as sepsis; pneumonia and meningitis are other common manifestations. Asymptomatic bacteremia is uncommon but can occur. In symptomatic patients, nonspecific signs such as hypothermia or fever, irritability, lethargy, apnea, and bradycardia may be present. Respiratory signs are prominent regardless of the presence of pneumonia and include cyanosis, apnea, tachypnea, grunting, flaring, and retractions. A fulminant course with hemodynamic abnormalities, including tachycardia, acidosis, and shock, may ensue. Persistent fetal circulation may develop. Clinically and radiographically, pneumonia associated with early-onset GBS disease is difficult to distinguish from **respiratory distress syndrome**. Patients with meningitis often present with nonspecific findings as described for sepsis or pneumonia, with more specific signs of CNS involvement initially absent.

Late-onset neonatal GBS disease presents at ≥7 days of life. Most cases occur within the first 3 months of life, but later presentations are also possible. Like early-onset disease, late-onset illness usually manifests as bacteremia (45–65%), often accompanied by meningitis (25–35%). Focal infections involving bone and joints, skin and soft tissue, the urinary tract, or lungs may also be seen. Cellulitis and adenitis are often localized to the submandibular or parotid regions. In contrast to early-onset disease, maternal obstetric complications are not risk factors for the development of late-onset GBS disease. Infants with late-onset disease are often less severely ill on presentation than infants with early-onset disease, and the disease is often less fulminant.

Invasive GBS disease in children beyond early infancy is uncommon. Bacteremia without a focus is the most common syndrome associated with childhood GBS disease beyond early infancy. Focal infections may include meningitis, pneumonia, endocarditis, and bone and joint infections.

DIAGNOSIS

A major challenge is distinguishing between respiratory distress syndrome and invasive neonatal GBS infection in preterm infants because the two illnesses share clinical and radiographic features. Severe apnea, early onset of shock, abnormalities in the peripheral leukocyte count, and greater lung compliance may be more likely in infants with GBS disease. Other neonatal pathogens, including *Escherichia coli* and *Listeria monocytogenes,* may cause illness that is clinically indistinguishable from that caused by GBS.

Table 230.1 Characteristics of Early- and Late-Onset Group B *Streptococcus* Disease

	EARLY-ONSET DISEASE	LATE-ONSET DISEASE
Age at onset	0-6 days	7-90 days
Increased risk after obstetric complications	Yes	No
Common clinical manifestations	Sepsis, pneumonia, meningitis	Bacteremia, meningitis, osteomyelitis, other focal infections
Common serotypes	Ia, III, V	Ia, III
Case fatality rate	4.5%	3.3%

Adapted from Seale AC, Bianchi-Jassir F, Russell NJ, et al. Estimates of the burden of Group B streptococcal disease worldwide for pregnant women, stillbirths, and children. *Clin Infect Dis.* 2017;65(Suppl 2):S200–S219.

The diagnosis of invasive GBS disease is established by isolation and identification of the organism from a normally sterile site, such as blood, urine, or cerebrospinal fluid (CSF). Isolation of GBS from gastric or tracheal aspirates or from skin or mucous membranes indicates colonization and is not diagnostic of invasive disease. CSF should be examined in all neonates suspected of having sepsis because specific CNS signs are often absent in the presence of meningitis, especially in early-onset disease. Antigen detection methods that use group B polysaccharide–specific antiserum, such as latex particle agglutination, are available for testing of urine, blood, and CSF, but these tests are less sensitive than culture. Moreover, antigen is often detected in urine samples collected by bag from otherwise healthy neonates who are colonized with GBS on the perineum or in the rectum. Commercially available methods for polymerase chain reaction (PCR) amplification of GBS-specific DNA sequences from blood or CSF samples are increasingly available, allowing earlier presumptive diagnosis than traditional culture. When possible, PCR-based diagnosis should be verified with a sterilely obtained culture; however, in certain cases the PCR result may be more accurate than the culture. A common example is a PCR performed on CSF sampled from an infant who has already received empiric antibiotic therapy, in which case the culture may remain negative despite the persistence of PCR-detectable GBS DNA. Test results must therefore be interpreted in the context of a patient's specific clinical history.

LABORATORY FINDINGS

Frequently present are abnormalities in the peripheral white blood cell count, including an increased or decreased absolute neutrophil count, elevated band count, increased ratio of bands to total neutrophils, or leukopenia. An elevated C-reactive protein level has been investigated as a potential early marker, but this test is nonspecific and cannot be used in isolation to diagnose GBS disease. Findings on chest radiograph are often indistinguishable from those of respiratory distress syndrome and may include reticulogranular patterns, patchy infiltrates, generalized opacification, pleural effusions, or increased interstitial markings. GBS meningitis is diagnosed based on a positive microbiologic test (culture or PCR), usually in combination with elevated CSF protein levels, leukocytic infiltration, and hypoglycorrhachia (decreased CSF glucose concentration).

TREATMENT

Penicillin G is the treatment of choice for confirmed GBS infection. Empirical therapy of neonatal sepsis that could be caused by GBS generally includes ampicillin and an aminoglycoside, both for the need for broad coverage pending organism identification and for synergistic bactericidal activity. Once GBS has been definitively identified and a good clinical response has occurred, therapy may be completed with penicillin alone. Especially in patients with meningitis, high doses of penicillin (450,000-500,000 units/kg/day) or ampicillin (300 mg/kg/day) are recommended because of the relatively high mean inhibitory concentration (MIC) of penicillin for GBS and the potential for a high initial CSF inoculum. The duration of therapy varies according to the site of infection and should be guided by clinical circumstances (Table 230.2). Extremely ill near-term patients with respiratory failure have been successfully treated with extracorporeal membrane oxygenation.

Although some experts recommend that, in culture-proven meningitis, additional CSF be sampled at 24-48 hours to determine whether sterility has been achieved, there is no strong evidence to support this practice. A repeat lumbar puncture, preferably paired with intracranial imaging such as MRI or CT, may be considered in patients with persistent neurologic symptoms after initiation of appropriately dosed antibiotics. The purpose in such a case is to rule out the presence of an abscess or other focal nidus of infection that may be escaping effective antibiotic exposure.

For **recurrent neonatal GBS disease**, standard intravenous antibiotic therapy recommendations for the infant should be followed. GBS recurrence can be caused by contaminated breast milk. Therefore breastfed infants with more than one episode of GBS infection should receive formula or pasteurized breast milk until expressed breast milk can be cultured for the presence of GBS. If breast milk contamination is confirmed, the mother should be counseled to consider a 5- to 7-day course of amoxicillin or rifampin to eradicate GBS carriage, followed by retesting of the milk.

Table 230.2 Recommended Duration of Therapy for Manifestations of Group B *Streptococcus* Disease

TREATMENT	DURATION
Bacteremia without a focus	10 days
Uncomplicated meningitis	14 days
Ventriculitis	At least 4 wk
Septic arthritis or osteomyelitis	3-4 wk

Data from the American Academy of Pediatrics. Group B streptococcal infections. In Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2021-2024 Report of the Committee on Infectious Diseases*, 32nd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2021:707–713.

PROGNOSIS

Studies from the 1970s and 1980s showed that up to 30% of infants surviving GBS meningitis had major long-term neurologic sequelae, including developmental delay, spastic quadriplegia, microcephaly, seizure disorder, cortical blindness, or deafness. A study of infants who survived GBS meningitis diagnosed from 1998 through 2006 found that 19% had severe **neurologic impairment** and 25% had mild to moderate impairment at long-term follow-up. Periventricular leukomalacia and severe developmental delay may result from GBS disease and accompanying shock in premature infants, even in the absence of meningitis. The outcome of focal GBS infections outside the CNS is generally favorable.

In 2015, a global survey on the impact of GBS disease found the case fatality rates associated with early- and late-onset neonatal GBS disease in developed countries were 4.5% and 3.3%, respectively. Case fatality rates were higher in developing countries. Mortality is higher in premature infants; one study reported a case fatality rate of 30% in infants at gestational age <33 weeks and 2% in those ≥37 weeks. The case fatality rate in children age 3 months to 14 years was 9% and was 11.5% in nonpregnant adults.

PREVENTION

Persistent morbidity and mortality from perinatal GBS disease despite advances in neonatal care have spurred intense investigation into modes of prevention. Two basic approaches to GBS prevention have been investigated: elimination of colonization from the mother or infant (chemoprophylaxis) and induction of protective immunity (immunoprophylaxis).

Chemoprophylaxis

Administration of antibiotics to pregnant women *before* the onset of labor does not reliably eradicate maternal GBS colonization and is not an effective means of preventing neonatal GBS disease. **Interruption of neonatal colonization is achievable through administration of antibiotics to the mother during labor.** Infants born to GBS-colonized women with premature labor or prolonged rupture of membranes who were given **intrapartum chemoprophylaxis** had a substantially lower rate of GBS colonization (9% vs 51%) and early-onset disease (0% vs 6%) than did the infants born to women who were not treated. Maternal postpartum febrile illness was also decreased in the treatment group.

In the mid-1990s, guidelines for chemoprophylaxis were issued that specified administration of intrapartum antibiotics to women identified as *high risk* by either culture-based or risk factor–based criteria. These guidelines were revised in 2002 after epidemiologic data indicated the superior protective effect of the **culture-based** approach in the prevention of neonatal GBS disease, and further revised guidelines

were issued in 2010 and 2020. According to current recommendations, **vaginorectal GBS screening cultures or PCR testing (where available) should be performed for all pregnant women at 36 0/7 to 37 6/7 weeks of gestation, except for those with GBS bacteriuria during the current pregnancy or a previous infant with invasive GBS disease**. Any woman with a positive prenatal screening culture, GBS bacteriuria during pregnancy, or a previous infant with invasive GBS disease should receive intrapartum antibiotics. Women whose culture status is unknown (culture not done, incomplete, or results unknown) and present in labor with a substantial risk of preterm birth, prolonged rupture of membranes (≥18 hr), or intrapartum fever (≥38°C [100.4°F]) should also receive intrapartum chemoprophylaxis (Table 230.3). **Routine intrapartum prophylaxis is not recommended for women with GBS colonization undergoing planned cesarean delivery who have not begun labor or had rupture of membranes.**

Penicillin remains the preferred agent for **maternal chemoprophylaxis** because of its narrow spectrum and the universal penicillin susceptibility of GBS isolates associated with human infection (Fig. 230.2). Ampicillin is an acceptable alternative. If amnionitis is suspected, broad-spectrum antibiotic therapy that includes an agent active against GBS should replace GBS prophylaxis. Occasional GBS isolates have demonstrated increased MICs to penicillin and other β-lactam antibiotics in association with mutations in penicillin-binding proteins. However, the clinical significance of these higher MIC values is unclear.

Table 230.3 Summary and References for GBS Prevention/Treatment Guidelines

AT-RISK POPULATION	KEY PREVENTION/ TREATMENT PRACTICES	PRACTICE GUIDELINE GOVERNING BODY
Women with history of a previous neonate with invasive GBS disease	Administer IAP during labor*	ACOG
Women with GBS bacteriuria during current pregnancy	Administer IAP during labor*	ACOG
Women with uncomplicated pregnancy	Perform prospective GBS colonization screening at 36 0/7 to 37 6/7 weeks of gestation	ACOG
	Administer IAP to colonized women during labor*	
	Women who present in term labor with unknown GBS status may qualify for IAP depending on additional clinical details	
Mothers with PROM, preterm labor, preterm intraamniotic infection, and unknown GBS colonization status	Administer IAP	ACOG
Term or late preterm (>34 wk) newborns with risk factors for GBS infection	For persistent clinical symptoms consistent with sepsis, obtain a blood culture and start empiric antibiotics with anti-GBS activity	AAP *Redbook* AAP *Pediatrics*
	In the absence of clinical symptoms, three possible approaches are available: 1. Categorical risk-based management 2. Use of an online Bayesian sepsis risk calculator to guide management 3. Serial observation of the infant	
Preterm newborns ≤34 wk with risk factors for GBS	For persistent clinical symptoms consistent with sepsis, obtain a blood culture and start empiric antibiotics with anti-GBS activity	AAP *Redbook* AAP *Pediatrics*
	If delivery followed spontaneous preterm labor, PROM, or concern for intraamniotic infection, obtain a blood culture and administer empiric antibiotics	
	If delivery followed induction of labor and there was concern for intraamniotic infection or if IAP was indicated but not provided, obtain a blood culture and administer empiric antibiotics	
Infants with signs of late-onset GBS disease	For empiric therapy of late-onset GBS disease in those who are not critically ill and in whom meningitis is not suspected, initial empiric therapy with ampicillin plus either gentamicin or cefotaxime is appropriate. If meningitis is suspected, ampicillin plus cefotaxime is recommended	AAP *Redbook*

*Infants born by cesarean section for maternal indications with no preceding labor or ROM: postnatal management should be guided by the newborn's clinical status and subsequent risk of GBS exposure.

AAP, American Academy of Pediatrics; ACOG, American College of Obstetrics and Gynecology; IAP, Intrapartum antibiotic prophylaxis; PROM, Preterm rupture of membranes

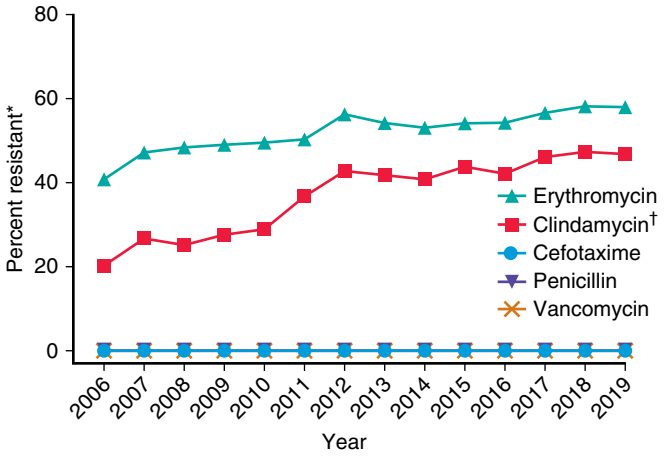

Fig. 230.2 GBS antibiotic resistance rates measured through Centers for Disease Control and Prevention active bacterial core surveillance, 2006-2019. *Resistant includes those isolates intermediate or fully resistant to antibiotics tested. †Before 2011, only constitutive resistance to clindamycin was tested. In 2011 and beyond, both constitutive and inducible resistance to clindamycin were tested. *(Courtesy Centers for Disease Control and Prevention.)*

For women who report a penicillin allergy but who have not undergone formal sensitivity testing, the American College of Obstetrics and Gynecology recommends allergy skin testing, which can be performed safely during pregnancy. Because of frequent resistance of GBS to clindamycin (up to 46%), first-generation cephalosporins (such as cefazolin) should be used for intrapartum chemoprophylaxis for penicillin-intolerant women with a low risk of anaphylaxis. For penicillin-allergic women at high risk for anaphylaxis, clindamycin should be used only if isolates are demonstrated to be susceptible. Vancomycin should be used if isolates are resistant to, or demonstrate inducible resistance to, clindamycin or if clindamycin susceptibility is unknown.

In 2019, the American Academy of Pediatrics (AAP) published updated guidelines with recommendations for prevention of early-onset GBS disease in newborns with risk factors (see Table 230.3). These replaced earlier prevention guidelines released by the AAP and Centers for Disease Control and Prevention. A key point of these revised recommendations is that **newborns with risk factors for GBS disease (such as inadequately treated maternal colonization or preterm delivery) who have persistent signs of infection after birth (beyond those attributable to transitional physiology) should undergo a laboratory evaluation that includes a blood culture and should receive empiric antibiotic therapy until infection has been ruled out**. For asymptomatic or minimally symptomatic infants born after 35 0/7 weeks of gestation, the extent of newborn evaluation and the decision to institute empiric antibiotics may be guided by one of **three systems for risk assessment**: a categorical decision chart based on the presence or absence of specific risk factors, repeated clinical evaluations, or a validated online "sepsis calculator" tool, developed from large datasets, which can estimate a newborn's risk of early-onset disease based on historical factors and clinical presentation. **For infants born before 35 0/7 weeks of gestation, the AAP recommends a blood culture and empiric antibiotics in all cases where spontaneous preterm labor, preterm rupture of the membranes, or any concern of intraamniotic infection preceded birth. Empiric treatment is also recommended in any case of a vaginal delivery before 35 0/7 weeks in which maternal chemoprophylaxis was indicated but not administered** (see Table 230.3).

Increasingly, there is recognition that decisions about whether to start empiric antibiotics for well-appearing infants with sepsis risk factors must also take into consideration the local resources available for systematic, serial examination. In medical environments where well-trained staff are available for careful, repeated observations of the newborn for 36-48 hours after birth, the threshold for initiating empiric antibiotics may be higher than sites where serial examinations are not possible. Of note, in the era of maternal chemoprophylaxis, most cases of early-onset disease are seen in infants born to women with negative prenatal screening cultures. Data from a large epidemiologic study indicate that the administration of maternal intrapartum antibiotics does not change the clinical spectrum or delay the onset of clinical signs in infants who developed GBS disease despite maternal prophylaxis.

A significant concern with maternal intrapartum chemoprophylaxis has been that large-scale antibiotic use among parturient women might lead to increased rates of antimicrobial resistance or infection in infants with organisms other than GBS, but this has not been borne out. In a population-based study of early-onset neonatal infection from 2005 to 2014, the incidence of early-onset sepsis both overall and caused by *E. coli* remained stable. At present, the substantial decline in early-onset neonatal GBS disease favors continued broad-scale intrapartum chemoprophylaxis, but continued surveillance is required.

A limitation of the maternal chemoprophylaxis strategy is that intrapartum antibiotic use is unlikely to have an impact on late-onset neonatal disease, miscarriages, or stillbirths attributed to GBS or adult GBS disease. In addition, with wider implementation of maternal chemoprophylaxis, an increasing percentage of early-onset neonatal disease has been detected in patients born to women with negative cultures, that is, false-negative screens.

Maternal Immunization

Human studies demonstrate that transplacental transfer of naturally acquired maternal antibody to the GBS capsular polysaccharide protects newborns from invasive GBS infection and that efficient transplacental passage of vaccine-induced GBS antibodies occurs. Conjugate vaccines composed of the GBS capsular polysaccharides coupled to carrier proteins have been produced for human use. In early clinical trials, conjugate GBS vaccines were well tolerated and induced levels of functional antibodies well above the range believed to be protective in >90% of recipients. A trivalent vaccine containing three subtypes of GBS capsule polysaccharide coupled to CRM_{197} was safely administered to pregnant women in a phase 2 clinical trial, eliciting functionally active type-specific antibodies that were efficiently transported to the fetus remaining detectable in the newborn. A more recent hexavalent vaccine candidate led to protective antibodies against six GBS capsular subtypes in experimental animal pregnancy models and generated robust antibody elaboration in nonpregnant adults in a phase 1/2 trial. Vaccines containing GBS surface proteins have been considered as a means to provide serotype-independent GBS protection, and availability of whole genome sequencing has enabled identification of vaccine protein candidates.

A successful GBS maternal vaccine administered before or during pregnancy should lead to transplacental passage of vaccine-induced antibody that protects the fetus and newborn against infection by several GBS serotypes. Such a vaccine would eliminate the need for cumbersome cultures during pregnancy, circumvent the various risks associated with large-scale antibiotic prophylaxis, likely have an impact on both early- and late-onset disease, and provide a prevention strategy in middle- and low-income countries, where maternal chemoprophylaxis may not be feasible. Intrapartum chemoprophylaxis will likely remain an important aspect of prevention, particularly for women in whom opportunities for GBS immunization are missed and for infants born so early that levels of transplacentally acquired antibodies may not be high enough to be protective.

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Chapter 231

Non–Group A or B *Streptococci*

David B. Haslam

The genus *Streptococcus* is exceptionally diverse and includes the major human pathogens *Streptococcus pyogenes* (group A *Streptococcus Streptococcus agalactiae* (group B *Streptococcus*), and *Streptococcus pneumoniae* (Table 231.1). Other important pathogens include large-colony species bearing groups C and G Lancefield antigens and numerous small-colony variants that may or may not express Lancefield carbohydrate antigen included among the viridans streptococci (see Table 231.1). This chapter focuses on *Streptococcus dysgalactiae* subspecies *equisimilis* (SDSE), commonly known as "group C and G streptococci," while Chapter 228 discusses *S. pneumoniae* and Chapter 232 discusses enterococci.

All members of the genus *Streptococcus* are gram-positive, catalase-negative organisms. Lancefield carbohydrate antigen, hemolytic activity, and colony morphology have classically been used to further distinguish and classify streptococci. These features provide a useful framework for the clinician and are still the most commonly used classification schema. However, grouping based on these phenotypic features does not precisely correlate with genetic relatedness, and it is becoming clear that disease propensity is better correlated with sequence homology than Lancefield grouping or hemolytic activity.

In this chapter, groups C and G streptococci refer exclusively to the large colony-forming organisms, often called *S. pyogenes–like,* as their microbiologic and clinical features tend to mimic those of group A *Streptococcus*. Despite their different Lancefield antigens, the large-colony-forming C and G streptococci are grouped together as SDSE. The remaining large-colony group C streptococci, predominantly animal pathogens, are grouped as *S. dysgalactiae* subspecies *dysgalactiae*. Nonhuman group G isolates are often considered part of a single species designated *Streptococcus canis* and are genetically distinct from the SDSE group G organisms.

The groups C and G streptococci share a number of virulence factors with *S. pyogenes,* including the production of streptolysin O, M protein, streptococcal pyrogenic exotoxin B, and hyaluronidase. The M protein is similar to that of *S. pyogenes* and may account for the postinfectious glomerulonephritis that is occasionally seen after infection with these organisms. A toxic shock–like syndrome associated with groups C and G streptococcal infection has been related to M protein type and production of a pyrogenic exotoxin by SDSE.

SDSE are common habitants of the pharynx, being detected in up to 5% of asymptomatic children. Other potential sites of colonization include the skin and gastrointestinal tract. Colonization of the vagina is reported and may be the source of occasional SDSE isolated from the umbilicus of healthy neonates.

Clinical manifestations of disease caused by SDSE overlap those of *S. pyogenes*. In children, these organisms are implicated most commonly in pharyngitis. The true role of these organisms as a cause of pharyngitis is difficult to determine because asymptomatic colonization is common. Nevertheless, several epidemics of SDSE pharyngitis have been reported, including foodborne outbreaks. A large study from Sweden recently demonstrated similar rates of detection of *S. pyogenes* (15%) and SDSE (14%) in children with pharyngitis. *S. pyogenes* was most prevalent in young children, whereas SDSE predominated in older children and adolescents. The clinical presentation of SDSE is indistinguishable from *S. pyogenes*–associated pharyngitis. Isolated case reports have described SDSE pneumonia in children, which is commonly complicated by abscess formation, empyema, and bacteremia. Additional respiratory infections include rare reports of epiglottitis and sinusitis.

SDSE are a significant cause of skin and soft tissue infections. As with *S. pyogenes,* lymphangitis can complicate superficial infections caused by SDSE. Necrotizing fasciitis caused by SDSE is being described with increasing frequency. Musculoskeletal infections, particularly pyogenic arthritis, occasionally are caused by SDSE. Pediatric cases are uncommon but may be increasing in incidence.

Table 231.1 Relationship of Large-Colony Streptococci Identified by Hemolysis and Lancefield Grouping to Sites of Colonization and Disease

	GROUP A *STREPTOCOCCUS* (*S. pyogenes*)	GROUP B *STREPTOCOCCUS* (*S. agalactiae*)	OTHER β-HEMOLYTIC *STREPTOCOCCI*	*VIRIDANS STREPTOCOCCI*
Hemolysis	β	β	β	α
Lancefield group	A	B	C-H, K-V Especially C and G	
Species or strains	M types (>180)	Serotypes (Ia, Ib, II, III, IV, V, VI, VII, and VIII)	*S. dysgalactiae* subspecies *equisimilis* *S. dysgalactiae* subspecies *dysgalactiae* *S. canis*	*Streptococcus bovis* *Streptococcus mitis* *Streptococcus mutans* *Streptococcus sanguis* Many others
Normal flora	Pharynx, skin, anus	Gastrointestinal and genitourinary tract	Pharynx, skin, gastrointestinal and genitourinary tracts	Pharynx, nose, skin, genitourinary tract
Common human diseases	Pharyngitis, tonsillitis, erysipelas, impetigo, septicemia, wound infections, necrotizing fasciitis, cellulitis, meningitis, pneumonia, scarlet fever, toxic shock–like syndrome, rheumatic fever, acute glomerulonephritis	Puerperal sepsis, chorioamnionitis, endocarditis, neonatal sepsis, meningitis, osteomyelitis, pneumonia	Wound infections, cellulitis, necrotizing fasciitis, pneumonia, endocarditis, brain abscess, sepsis, nosocomial infections, opportunistic infections	Endocarditis, human bite infections

α, Partial hemolysis; β, complete hemolysis; γ, no hemolysis (nonhemolytic).

Reactive arthritis has been described after SDSE infection; however, unlike *S. pyogenes,* the association between SDSE infection and acute rheumatic fever has not clearly been defined, and antibiotic prophylaxis is not recommended after reactive arthritis with this organism.

Endocarditis, bacteremia, brain abscess, and toxic shock syndrome caused by SDSE have all been described but are uncommon in children. These infections generally occur in children with immune deficits or in adolescents after delayed recognition of sinusitis.

These organisms can cause neonatal septicemia similar to early-onset group B streptococcal disease. Risk factors include prematurity and prolonged rupture of membranes. Respiratory distress, hypotension, apnea, bradycardia, and disseminated intravascular coagulation may be seen, and associated maternal infection is common. Neonatal toxic shock syndrome associated with SDSE has also been described.

Treatment of SDSE infections is similar to that of *S. pyogenes.* These organisms retain susceptibility to penicillin and other β-lactams. Other agents with reliable activity include linezolid, daptomycin, and vancomycin, though occasional isolates demonstrate tolerance to vancomycin. Clindamycin and macrolides have poor bactericidal activity against these organisms, and resistance rates are significant. Resistance to quinolones is reported, and up to 70% of SDSE are resistant to tetracycline.

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Chapter 232

Enterococcus

David B. Haslam

Enterococcus has long been recognized as a pathogen in select populations and has become a common and particularly troublesome cause of hospital-acquired infection in recent years. Enterococci were formerly classified with *Streptococcus bovis* and *Streptococcus equinus* as Lancefield group D streptococci but are now placed in a separate genus and are notorious for their propensity to cause infection in compromised hosts and frequent resistance to antibiotics.

ETIOLOGY

Enterococci are gram-positive, catalase-negative facultative anaerobes that grow in pairs or short chains. Most are nonhemolytic (also called γ-hemolytic) on sheep blood agar, although some isolates have α- or β-hemolytic activity. Enterococci are distinguished from most Lancefield groupable streptococci by their ability to grow in bile and hydrolyze esculin. They are able to grow in 6.5% NaCl and hydrolyze L-pyrrolidonyl-β-naphthylamide, features used by clinical laboratories to distinguish enterococci from group D streptococcus. Identification at the species level is enabled by differing patterns of carbohydrate fermentation.

EPIDEMIOLOGY

Enterococci are normal inhabitants of the gastrointestinal tract of humans and organisms throughout the animal kingdom, suggesting they are highly evolved to occupy this niche. Oral secretions and dental plaque, the upper respiratory tract, skin, and vagina may also be colonized by these organisms. *Enterococcus faecalis* is the predominant enterococcal species, with colonization commonly occurring in the first week of life. By the time of adulthood, *E. faecalis* colonization is nearly ubiquitous. *Enterococcus faecium* colonization is less consistent, although approximately 25% of adults harbor this organism. Disruption of the normal intestinal microbiota by antibiotic exposure or hematopoietic stem cell transplantation markedly enriches for fecal enterococcal abundance and dramatically increases the risk of subsequent bloodstream infection (BSI).

E. faecalis accounts for approximately 80% of enterococcal infections, with almost all of the remaining infections caused by *E. faecium.* Only rarely are other species, such as *Enterococcus gallinarum* and *Enterococcus casseliflavus,* associated with invasive infection, but these organisms are notable for their intrinsic low-level vancomycin resistance. Whole genome sequencing suggests that the patient's indigenous flora is the source of enterococcal infection in most cases. However, direct spread from person to person or from contaminated medical devices may occur, particularly within newborn nurseries and intensive care units, where nosocomial spread has resulted in hospital outbreaks.

PATHOGENESIS

Enterococci are not aggressively invasive organisms, usually causing disease only in children with damaged mucosal surfaces or an impaired immune system. Their dramatic emergence as a cause of nosocomial infection is predominantly a result of their resistance to antibiotics commonly used in the hospital setting. Hospital-associated enterococci generally lack CRISPR (clustered regularly interspaced short palindromic repeats) elements that defend against phage-mediated horizontal gene transfer, an important source of antimicrobial-resistance genes. Secreted and cell-surface molecules are implicated in pathogenesis. Adhesion-promoting factors such as the surface protein Eps likely account for the propensity of these organisms to cause endocarditis and urinary tract infections (UTIs). The ability to form biofilms likely facilitates the colonization of urinary and vascular catheters. Other proposed virulence factors include cytolysin, aggregation substance, gelatinase, and extracellular superoxide.

Antimicrobial Resistance

Enterococci are highly resistant to cephalosporins and semisynthetic penicillins such as nafcillin, oxacillin, and methicillin. They are moderately resistant to extended-spectrum penicillins such as ticarcillin and carbenicillin. Ampicillin and penicillin are the most active β-lactams against these organisms. Some strains of *E. faecalis* and *E. faecium* demonstrate decreased resistance to β-lactam antibiotics because of mutations in one of the penicillin-binding proteins. In addition, occasional strains of *E. faecalis* produce a plasmid-encoded β-lactamase similar to that found in *Staphylococcus aureus.* These isolates are completely resistant to penicillins, necessitating the combination of a penicillin plus a β-lactamase inhibitor or the use of imipenem or vancomycin. Any active drug may be insufficient if used alone for serious infections wherein high bactericidal activity is desired (Tables 232.1 and 232.2).

All enterococci have intrinsic low-level resistance to aminoglycosides because these antibiotics are poorly transported across the *Enterococcus* cell wall. Concomitant use of a cell wall–active agent, such as a β-lactam or glycopeptide antibiotic, improves the permeability of the cell wall for the aminoglycosides, resulting in synergistic killing. However, some isolates demonstrate high-level resistance, defined as mean inhibitory concentration (MIC) >2,000 μg/mL and a result of modification or inactivation of aminoglycoside agents. Strains demonstrating high-level resistance and even some isolates with moderate-level resistance are not affected synergistically by aminoglycosides and cell wall–active antibiotics.

Table 232.1 Intrinsic Resistance Mechanisms Among Enterococci

ANTIMICROBIAL	MECHANISM
Ampicillin, penicillin	Altered binding protein
Aminoglycoside (low level)	Decreased permeability, altered ribosomal binding
Clindamycin	Altered ribosomal binding
Erythromycin	Altered ribosomal binding
Tetracyclines	Efflux pump
Trimethoprim-sulfamethoxazole	Utilize exogenous folate

Table 232.2 Acquired Resistance Mechanisms Among Enterococci

ANTIMICROBIAL	MECHANISM
Ampicillin, penicillin (high level)	Mutation of PBP5
Aminoglycoside (high level)	Enzyme modification
Quinolones	DNA gyrase mutation
Chloramphenicol	Efflux pump
Glycopeptide	Altered cell wall binding
Quinupristin/dalfopristin	Ribosomal modification, efflux pump
Linezolid	Point mutation
Daptomycin	Unknown

Resistance to almost all other antibiotic classes, including tetracyclines, macrolides, and glycopeptides, has been described among the enterococci, necessitating individual susceptibility testing for these antibiotics when their use is considered. Despite apparent susceptibility in vitro, trimethoprim-sulfamethoxazole has poor activity in vivo and should not be used as the primary agent against enterococcal infections.

Vancomycin has traditionally been effective against *Enterococcus* isolates, but resistance to vancomycin, defined as MIC >32 μg/mL, and other glycopeptides, including teicoplanin, is increasingly common. The emergence of vancomycin-resistant *Enterococcus* (VRE) has become a major challenge in the care of hospitalized patients. In particular, mortality in patients with VRE BSIs is considerable, and treatment is complicated by frequent resistance of VRE to most other antibiotic classes. High-level vancomycin resistance (MIC ≥64 μg/mL) can be transferred by way of conjugation and usually results from plasmid-mediated transfer of the *vanA* gene. High-level resistance is most common among *E. faecium* but is increasingly seen among *E. faecalis* isolates. Moderate-level resistance (MIC 8-256 μg/mL) results from a chromosomal homolog of *vanA* known as *vanB.* Isolates that harbor the *vanB* gene are only moderately resistant to vancomycin and initially demonstrate susceptibility to teicoplanin, although resistance can emerge during therapy. Resistance to newer agents, including linezolid and daptomycin, is rare thus far. Linezolid resistance is a result of mutations in the 26S ribosomal subunit, whereas daptomycin resistance is associated with pathogenic variants in genes required for membrane synthesis and repair.

CLINICAL MANIFESTATIONS

Enterococcus infections traditionally occurred predominantly in newborn infants; infection in older children is increasingly common. Most enterococcal infections occur in patients with breakdown of normal physical barriers such as the gastrointestinal tract, skin, or urinary tract. Other risk factors for enterococcal infection include prolonged hospitalization, indwelling vascular catheters, prior use of antibiotics, and compromised immunity.

Neonatal Infections

Enterococcus accounts for up to 15% of all neonatal bacteremia and septicemia. Like group B streptococcus infections, enterococcal infections are seen in two distinct settings in neonatal patients. Early-onset infection (<7 days of age) may mimic early-onset group B streptococcus septicemia but tends to be milder. Early-onset enterococcal sepsis most often occurs in full-term infants who are otherwise healthy. Late-onset infection (≥7 days of age) is associated with risk factors such as extreme prematurity, presence of an intravascular catheter, or necrotizing enterocolitis or follows an intraabdominal surgical procedure. Symptoms in late-onset disease are more severe than those in early-onset disease and include apnea, bradycardia, and deteriorating respiratory function. Focal infections such as scalp abscess and catheter infection are commonly associated. Mortality rates range from 6% in early-onset septicemia to 15% in late-onset infections associated with necrotizing enterocolitis.

Enterococci are an occasional cause of meningitis. In neonates in particular, meningitis usually occurs as a complication of septicemia. Alternatively, the organism may gain access to the central nervous system by way of contiguous spread, such as through a neural tube defect or in association with an intraventricular shunt. Enterococcal meningitis can be associated with minimal abnormality of cerebrospinal fluid.

Infections in Older Children

Enterococcus rarely causes UTIs in healthy children but accounts for approximately 15% of cases of nosocomially acquired UTIs in both children and adults. Presence of an indwelling urinary catheter is the major risk factor for nosocomial UTIs. *Enterococcus* is frequently isolated in intraabdominal infections after intestinal perforation or surgery. The significance of enterococci in polymicrobial infections has been questioned, although reported mortality rates are higher when intraabdominal infections include enterococci. *Enterococcus* is increasingly common as a cause of nosocomial bacteremia; these organisms accounted for approximately 10% of nosocomial BSIs in children, ranking second only to coagulase-negative staphylococci. Predisposing factors for enterococcal bacteremia and endocarditis include an indwelling central venous catheter, gastrointestinal surgery, immunodeficiency, and cardiovascular abnormalities. Risk factors for vancomycin-resistant enterococcal bacteremia include prolonged mechanical ventilation, immunosuppression, and recent vancomycin exposure.

TREATMENT

Treatment of invasive enterococcal infections must recognize that these organisms are resistant to antimicrobial agents frequently used as empirical therapy. In particular, cephalosporins should not be relied upon in situations where *Enterococcus* is known or suspected to be involved. In general, in the immunocompetent host, minor localized infections caused by susceptible *Enterococcus* can be treated with ampicillin alone. Antibiotics containing β-lactamase inhibitors (clavulanate or sulbactam) provide advantage only for the very few organisms whose resistance is caused by the production of β-lactamase. In uncomplicated UTIs, nitrofurantoin is efficacious when the organism is known to be sensitive to this antibiotic.

Invasive infections such as sepsis and meningitis have traditionally been treated with a combination of penicillin or ampicillin and an aminoglycoside when the isolate is susceptible. Recent experience suggests that adjunctive aminoglycosides may increase the risk of nephrotoxicity without improving outcomes in uncomplicated BSIs. Vancomycin can be substituted for the penicillins in allergic patients but should be used with an aminoglycoside because vancomycin alone is not bactericidal. Endocarditis from strains possessing high-level aminoglycoside resistance may relapse even after prolonged therapy. Continuous-infusion penicillin or the combination of ampicillin plus ceftriaxone has been proposed for treatment of these infections in adults, yet ultimately valve replacement may be necessary. In patients with catheter-associated enterococcal bacteremia, the catheter should be removed promptly in most cases, although salvage of infected lines has occurred with the combined use of ampicillin or vancomycin with an aminoglycoside.

Treatment of Vancomycin-Resistant Enterococci

The treatment of serious infections caused by multiresistant, vancomycin-resistant strains is particularly challenging. The two most commonly used antibiotics are linezolid and daptomycin. Linezolid, an oxazolidinone antibiotic that inhibits protein synthesis, is bacteriostatic against most *E. faecium* and *E. faecalis* isolates, including vancomycin-resistant isolates. Response rates to linezolid are generally over 90%, including cases of bacteremia and sepsis, and this antibiotic is currently the only drug approved by the FDA for treatment of VRE infections. Anecdotal reports reveal the success of linezolid in treating meningitis caused by VRE. Unfortunately, as seen with other antibiotics, linezolid resistance is documented, and nosocomial spread of resistant organisms can occur. Linezolid frequently causes reversible bone marrow suppression after prolonged use and is associated with rare occurrences of lactic acidosis and irreversible peripheral neuropathy.

Serotonin syndrome may be seen in patients taking concomitant selective serotonin uptake inhibitor antidepressants. Newer oxazolidinones include tedizolid, which has better in vitro activity against enterococci and appears to have favorable pharmacokinetic and toxicity profiles when compared to linezolid.

Daptomycin is a cyclic lipopeptide that is rapidly bactericidal against a broad range of gram-positive organisms. The antibiotic inserts into the bacterial cell wall, causing membrane depolarization and cell death. It has been approved for the treatment of adults with serious skin and soft tissue infections, right-sided endocarditis, and bacteremia caused by susceptible organisms. Most strains of VRE (both *E. faecium* and *E. faecalis*) are susceptible to daptomycin in vitro, and daptomycin has become the first-line agent for VRE treatment in many centers. However, treatment failures occur when administered at the standard dose of 6 mg/kg/day, necessitating higher treatment doses in patients with severe invasive infections. Furthermore, daptomycin dosages may need to be higher in children when compared with adults because of more rapid renal clearance. The addition of a β-lactam antibiotic, such as ampicillin or ceftaroline, may enhance activity of daptomycin and provide benefit over daptomycin alone for severe VRE infections, including endocarditis. Daptomycin has unreliable activity in the lung and therefore should not be used as a sole agent to treat pneumonia. Resistance of both *S. aureus* and *Enterococcus* to daptomycin has rarely been described, sometimes arising during therapy.

Several studies and meta-analyses have suggested that clinical outcomes of invasive VRE infection are similar when linezolid and daptomycin are used. However, infection-related mortality remains significant, especially among adults, and alternative or combination therapies continue to be explored.

Ceftaroline, a fifth-generation cephalosporin with activity against methicillin-resistant *S. aureus,* has activity against many *E. faecalis* strains but is inadequate when used alone for the treatment of *E. faecium*.

Newer tetracyclines have been developed with activity against VRE, including tigecycline, omadacycline, and eravacycline. Tigecycline is approved for use in complicated intraabdominal and skin and soft tissue infections but fails to achieve high serum concentrations and may be associated with treatment failure for VRE BSIs. Gastrointestinal side effects are common with tigecycline and may be intolerable. Experience with omadacycline and eravacycline in treatment of pediatric patients with VRE infection is lacking.

Lipoglycopeptides are a newer class of antibiotics that possess a core structure similar to vancomycin with the addition of a lipid substituent. Lipoglycopeptides include telavancin, dalbavancin, and oritavancin. Only oritavancin has reliable activity against VRE, but resistance may develop, and thus far clinical experience in children is limited.

PREVENTION

Strategies for preventing enterococcal infections include timely removal of urinary and intravenous catheters and debridement of necrotic tissue. Infection control strategies, including surveillance cultures, patient and staff cohorting, and strict gown and glove isolation, are effective at decreasing colonization rates with VRE. Unfortunately, these organisms may persist on inanimate objects such as stethoscopes, complicating efforts to limit their nosocomial spread. In order to prevent the emergence and spread of vancomycin-resistant organisms, the Centers for Disease Control and Prevention has developed a series of guidelines for prudent vancomycin use. Antibiotics with broad activity against anaerobic organisms are also thought to contribute to colonization with VRE, suggesting that prudent use of such antibiotics may also help limit spread of VRE. Decolonization strategies have been attempted but are generally ineffective in eradicating skin or gastrointestinal carriage of VRE. In particular, antimicrobial therapy is not indicated for this purpose. The role of probiotic agents in eliminating VRE colonization is currently unclear but may be a useful adjunct to prudent antimicrobial usage and other infection control interventions in limiting nosocomial spread of VRE.

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Chapter 233

Diphtheria (*Corynebacterium diphtheriae*)

Amruta Padhye and Stephanie A. Fritz

Diphtheria is an acute toxic infection caused by toxin-producing strains of *Corynebacterium diphtheriae* and, less often, by toxin-producing strains of *Corynebacterium ulcerans.* Non–toxin-producing *C. diphtheriae* can also cause disease, although less severe. *C. ulcerans* is more often isolated from animal sources and can cause human disease similar to *C. diphtheriae*.

Although respiratory and cutaneous presentations of diphtheria are the most common, mortality is substantially higher with respiratory diphtheria. Classic respiratory diphtheria caused by toxigenic *Corynebacterium* species is the main focus of World Health Organization (WHO) case surveillance. In the United States, the case definition was modified in 2019, and currently toxigenic cases of diphtheria, including respiratory and nonrespiratory (e.g., skin, wound, conjunctiva, ear, genital mucosa) forms, are reportable to the Centers for Disease Control and Prevention (CDC).

ETIOLOGY

Corynebacteria are aerobic, nonencapsulated, non–spore-forming, mostly nonmotile, pleomorphic, gram-positive bacilli. *C. diphtheriae* is by far the most frequently isolated agent of diphtheria. Toxigenic *C. ulcerans* can cause mastitis in cattle and respiratory infections in animals and can spread to humans through close contact with secretions. It can cause cutaneous and respiratory illnesses that are clinically indistinguishable from diphtheria in humans. Person-to-person transmission of *C. ulcerans* is possible, though not well established. A selective medium (e.g., cystine-tellurite blood agar or Tinsdale agar) that inhibits growth of competing organisms is required for isolation and, when reduced by *C. diphtheriae,* renders colonies gray-black. Differentiation of *C. diphtheriae* from *C. ulcerans* is based on urease activity; *C. ulcerans* is urease-positive. Four *C. diphtheriae* biotypes *(mitis, intermedius, belfanti, gravis)* are capable of causing diphtheria and are differentiated by colony morphology, hemolysis, and fermentation reactions. The ability of either *C. diphtheriae* or *C. ulcerans* to produce diphtheritic toxin results from acquisition of a lysogenic corynebacteriophage, which encodes the diphtheritic toxin gene and confers diphtheria-producing potential in these strains. Demonstration of diphtheritic toxin production by the modified Elek test, an agar immunoprecipitin technique, alone or in conjunction with polymerase chain reaction (PCR) testing for carriage of the toxin gene, is necessary to confirm disease. Toxigenic and nontoxigenic strains are indistinguishable by colony type, microscopic features, or biochemical test results.

EPIDEMIOLOGY

Unlike other diphtheroids (coryneform bacteria), which are ubiquitous in nature, *C. diphtheriae* is an exclusive inhabitant of human mucous membranes and skin. Spread is primarily by respiratory droplets, direct contact with respiratory secretions of symptomatic individuals, or exudate from infected skin lesions. Asymptomatic respiratory tract carriage is important in transmission. In areas where diphtheria is endemic, 3–5% of healthy individuals can carry toxigenic organisms, but carriage is exceedingly rare in nonendemic areas. Skin infection and skin carriage are silent reservoirs of *C. diphtheriae,* and organisms can remain viable in dust or on fomites for up to 6 months.

In the 1920s, >125,000 diphtheria cases and 10,000 diphtheria-related deaths were reported annually in the United States, with the highest fatality

rates among very young and elderly persons. The incidence then began to decrease and, with widespread use of diphtheria toxoid in the United States after World War II, declined steadily through the late 1970s. From 1996 to 2018, only 14 cases of respiratory diphtheria, including 1 fatal case, were reported in the United States, an average of ≤1 case annually. During this same period, five cases of culture-confirmed respiratory diphtheria-like illness caused by toxigenic *C. ulcerans* were also identified.

Despite the worldwide decrease in disease incidence, diphtheria remains endemic in many developing countries with poor immunization rates against diphtheria. Since the introduction of toxoid immunization, the disease has shifted from affecting children <15 years old to adults who lack natural exposure to toxigenic *C. diphtheriae* in the vaccine era and have low rates of booster immunization. The largest outbreak of diphtheria in the developed world since the 1960s occurred from 1990 to 1996 in the newly independent countries of the former Soviet Union, involving >150,000 cases in 14 countries. Of these, >60% of cases occurred in individuals >14 years old. Case fatality rates ranged from 3% to 23% by country. Factors contributing to the epidemic included a large population of underimmunized adults, decreased childhood immunization rates, population migration, crowding, and failure to respond aggressively during early phases of the epidemic. Cases of diphtheria among travelers from these endemic areas were transported to many countries in Europe.

WHO surveillance reports indicate that most cases of diphtheria worldwide occur in the Southeast Asia and Africa regions, reporting more than 10,000 cases worldwide in 2020. India contributes a substantial proportion to the global burden of diphtheria, with an average of over 4,000 cases annually reported to the WHO in the past decade.

Although diphtheria was reduced from a major cause of childhood death to a medical rarity in the Western Hemisphere in the early 20th century, recurring reminders of the fragility of this success, particularly in conflict areas, emphasize the need to continue vigorous promotion of those same control principles across the global community. The largest diphtheria outbreak in the refugee setting occurred when the Rohingya people were displaced from Myanmar to Bangladesh in 2017, eventually lasting over 2 years and with 7064 cases and 45 deaths reported as of November 2019. Along with outbreaks in Venezuela, Haiti, Yemen, and more recently Nigeria, these are stark reminders of the threat of re-emergence that vaccine-preventable diseases pose. Improving surveillance, vaccination coverage, and public awareness of the disease are key for control of disease during outbreaks.

When diphtheria was common, **cutaneous diphtheria** accounted for more than 50% of reported *C. diphtheriae* isolates in the United States. This indolent local infection, compared with mucosal infection, is associated with more prolonged bacterial shedding, greater contamination of the environment, and increased transmission to the pharynx and skin of close contacts. Outbreaks are associated with homelessness, crowding, poverty, alcoholism, poor hygiene, contaminated fomites, underlying dermatosis, and introduction of new strains from exogenous sources. It is no longer a tropical or subtropical disease; 1,100 *C. diphtheriae* infections were documented in a Seattle neighborhood (the site of the last major U.S. outbreak) from 1971 to 1982; 86% were cutaneous, and 40% involved toxigenic strains. The incidence of *C. diphtheriae* isolates from cutaneous infections has risen dramatically over the past decade. Cutaneous diphtheria is an important source of toxigenic *C. diphtheriae* in the United States, and its importation from endemic areas is frequently the source of subsequent sporadic cases of respiratory tract diphtheria. Between 2015 and 2018, the CDC confirmed four cases of cutaneous diphtheria from toxin-producing *C. diphtheriae* in U.S. residents returning from travel to endemic areas. Cutaneous diphtheria caused by *C. ulcerans* from travel to tropical countries or animal contact has also been increasingly reported.

In Europe, increasing reports of respiratory and systemic infections have been attributed to *C. ulcerans;* animal contact is the predominant risk factor. In the United Kingdom, from 2008 to 2017, of the 33 toxigenic cases of diphtheria, just over half of the cases were caused by *C. diphtheriae,* and the remainder were caused by *C. ulcerans*. Most of the *C. diphtheriae* cases were cutaneous, while the *C. ulcerans* cases were equally respiratory and cutaneous. Travel to an endemic area was the major risk factor for *C. diphtheriae* acquisition, while contact with a companion animal was the major factor associated with acquisition of *C. ulcerans*. Incomplete vaccination status was strongly associated with the risk of hospitalization and death.

PATHOGENESIS

Both toxigenic and nontoxigenic strains of *C. diphtheriae* cause skin and mucosal infection and can rarely cause invasive disease, including endocarditis and bacteremia. The organism usually remains in the superficial layers of skin lesions or respiratory tract mucosa, inducing a local inflammatory reaction. The major virulence of the organism lies in its ability to produce a potent polypeptide exotoxin, the diphtheritic toxin, which inhibits protein synthesis and causes local tissue necrosis and the resultant local inflammatory response. Within the first few days of respiratory tract infection (usually in the pharynx), a dense necrotic coagulum of organisms, epithelial cells, fibrin, leukocytes, and erythrocytes forms, initially white and advancing to become a gray-brown, leather-like, adherent **pseudomembrane** (*diphtheria* is Greek for leather). Removal is difficult and reveals a bleeding, edematous submucosa. Paralysis of the palate and hypopharynx is an early local effect of diphtheritic toxin. Toxin absorption can lead to systemic manifestations: kidney tubule necrosis, thrombocytopenia, cardiomyopathy, and demyelination of nerves. Because the latter two complications can occur 2-10 weeks after mucocutaneous infection, the pathophysiology in some cases is suspected to be immunologically mediated. Among infected adults in the Seattle outbreak, 3% with cutaneous infections and 21% with symptomatic nasopharyngeal infection demonstrated toxic myocarditis, neuropathy, or obstructive respiratory tract complications. All had received at least 20,000 units of equine antitoxin at the time of hospitalization.

CLINICAL MANIFESTATIONS

The manifestations of *C. diphtheriae* infection are influenced by the anatomic site of infection, the immune status of the host, and the production and systemic distribution of toxin. Although 98% of infections occur in the respiratory tract, other sites include cutaneous, conjunctival, ear, and vaginal mucosa.

New estimates of epidemiologic and clinical aspects of diphtheria from a comprehensive update by Truelove et al., with systematic reviews including recent literature, are summarized in Figure 233.1.

Respiratory Tract Diphtheria

The pharynx or tonsils is the most common location of infection in the respiratory tract (75–94%), followed by the larynx (25%). Although the incubation period has traditionally been regarded to be 2-5 days (range 1-10 days), emerging data suggest that the median time from infection to onset of prodromal symptoms is only 1.4 days. An estimated 80% of untreated symptomatic cases progress to membranous diphtheria in an average of 2-3 days after symptom onset. In tonsillar and **pharyngeal diphtheria**, sore throat is the universal early symptom. Only half of patients have fever, and fewer have dysphagia, hoarseness, malaise, or headache. Mild pharyngeal injection is followed by unilateral or bilateral tonsillar membrane formation, which can extend to involve the uvula (which may cause toxin-mediated paralysis), soft palate, posterior oropharynx, hypopharynx, or glottic areas (Fig. 233.2). Underlying soft tissue edema and enlarged lymph nodes can cause a bull-neck appearance. The degree of local extension correlates directly with profound prostration, bull-neck appearance, and fatality caused by airway compromise or toxin-mediated complications (Fig. 233.3). In infants, infection of the anterior nares is more common and causes serosanguineous, purulent, erosive rhinitis with membrane formation. Shallow ulceration of the external nares and upper lip is characteristic.

The characteristic adherent pseudomembrane, extension beyond the faucial area, dysphagia, and relative lack of fever help differentiate diphtheria from **exudative pharyngitis** caused by *Streptococcus pyogenes* or Epstein-Barr virus. Vincent angina, infective phlebitis with thrombosis of the jugular veins (Lemierre syndrome), and mucositis in patients undergoing cancer chemotherapy are usually differentiated by the clinical setting. Infection of the larynx, trachea, and bronchi

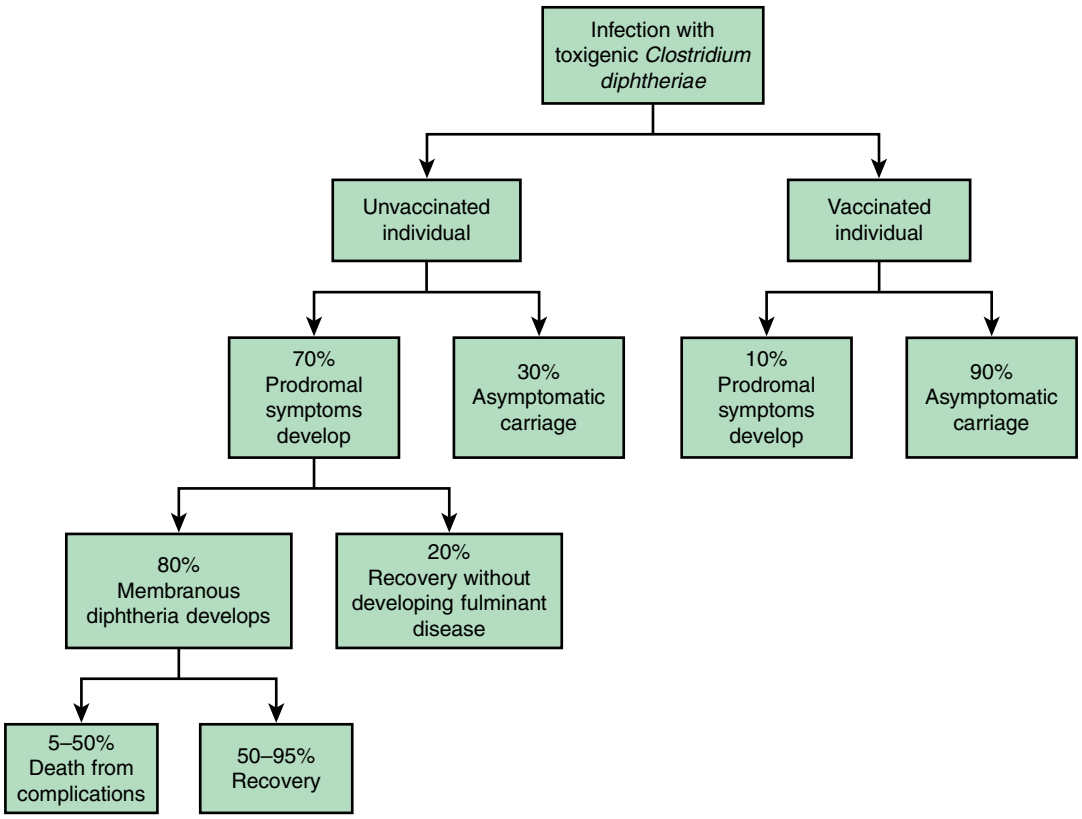

Fig. 233.1 Clinical manifestations of *Clostridium diphtheriae* infection among unvaccinated and vaccinated individuals. Among unvaccinated individuals infected with toxigenic *C. diphtheriae*, prodromal symptoms develop in ~70%, of whom 80% develop membranous diphtheria. Of those with membranous diphtheria, case fatality can be as high as 5–50%. Among vaccinated individuals infected with toxigenic *C. diphtheriae*, the toxoid vaccine provides protection from symptoms; 10% develop prodromal symptoms, whereas 90% become asymptomatic carriers. These symptomatic vaccinated individuals have a lower risk of severe disease and death and are more likely to recover. *(Adapted from Truelove SA, Keegan LT, Moss WJ, et al. Clinical and epidemiological aspects of diphtheria: a systematic review and pooled analysis. Clin Infect Dis. 2020;71[1]:89–97.)*

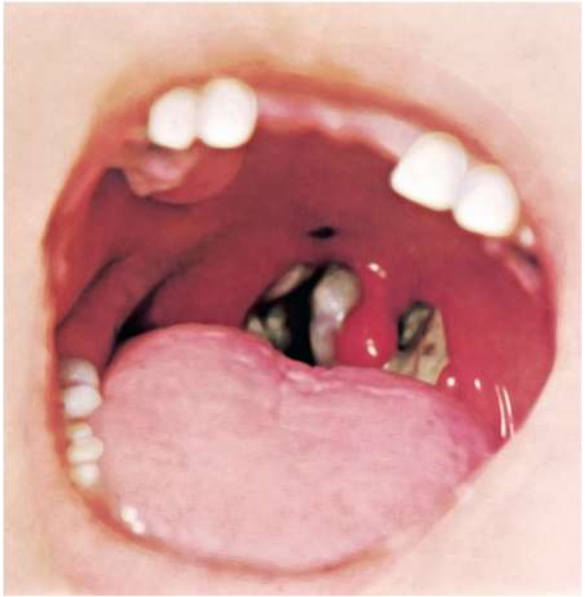

Fig. 233.2 Tonsillar diphtheria. *(Courtesy Franklin H. Top, MD, Professor and Head of the Department of Hygiene and Preventive Medicine, State University of Iowa, College of Medicine, Iowa City, IA; and Parke, Davis & Company's Therapeutic Notes.)*

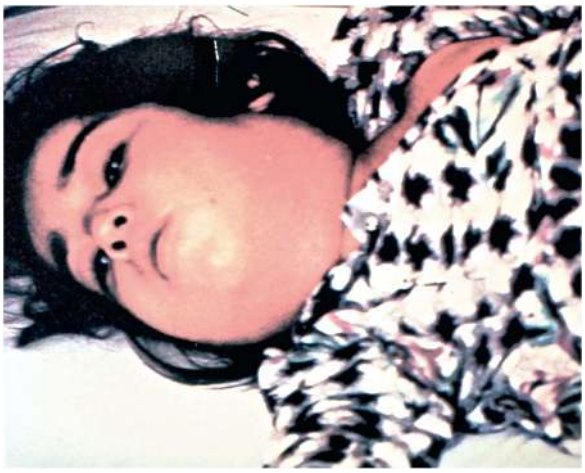

Fig. 233.3 Diphtheria. Bull-neck appearance of diphtheritic cervical lymphadenopathy. *(From the Centers for Disease Control and Prevention [CDC]. Public health image library [PHIL], image #5325. Available at:* https://phil.cdc.gov/Details.aspx?pid=5325.*)*

can be primary or a secondary extension from the pharyngeal infection, presenting with hoarseness, stridor, dyspnea, and croupy cough. Differentiation from bacterial epiglottitis, severe viral laryngotracheobronchitis, and staphylococcal or streptococcal tracheitis hinges partially on the relative paucity of other signs and symptoms in patients with diphtheria and primarily on visualization of the adherent pseudomembrane at laryngoscopy and intubation.

Patients with laryngeal diphtheria are at significant risk for suffocation because of local soft tissue edema and airway obstruction by the diphtheria membrane. This progression of airway obstruction in laryngeal infection within 1-2 weeks after symptom onset is responsible for 60–65% of overall deaths. Establishment of an artificial airway and resection of the pseudomembrane can be lifesaving, but further obstructive complications are common, and systemic toxic complications are inevitable.

Cutaneous Diphtheria

Classic cutaneous diphtheria is an indolent, nonprogressive infection characterized by a superficial, ecthyma-like, nonhealing ulcer with a gray-brown membrane. Diphtheria skin infections cannot always be differentiated from streptococcal or staphylococcal impetigo, and these conditions frequently coexist. In most cases, a primary process, such as dermatosis, laceration, burn, bite, or impetigo, becomes secondarily infected with *C. diphtheriae.* Extremities are more often affected than the trunk or head. Pain, tenderness, erythema, and exudate are typical. Local hyperesthesia or hypesthesia is unusual. Respiratory tract colonization or symptomatic infection with toxic complications occurs in the minority of patients with cutaneous diphtheria.

Infection at Other Sites

C. diphtheriae occasionally causes mucocutaneous infections at other sites, such as the ear (otitis externa), the eye (purulent and ulcerative conjunctivitis), and the genital tract (purulent and ulcerative vulvovaginitis). The clinical setting, ulceration, membrane formation, and submucosal bleeding help differentiate diphtheria from other bacterial and viral causes. Rare cases of septicemia are described and are universally fatal. Sporadic cases of endocarditis occur, and clusters among intravenous drug users have been reported in several countries; the skin was the probable portal of entry, and almost all strains were nontoxigenic. Sporadic cases of pyogenic arthritis, mainly from nontoxigenic strains, have been reported in adults and children. Diphtheroids isolated from sterile body sites should not be routinely dismissed as contaminants without careful consideration of the clinical setting.

DIAGNOSIS

Specimens for culture should be obtained from the nose and throat and any other mucocutaneous lesion. A portion of membrane should be removed and submitted for culture along with underlying exudate. The laboratory must be notified to use selective medium. *C. diphtheriae* survives drying. If obtained in a remote area, a dry swab specimen can be placed in a silica gel pack and sent to the laboratory. Evaluation of a direct smear using Gram stain or specific fluorescent antibody is unreliable. Culture isolates of coryneform organisms should be identified to the species level, and toxigenicity and antimicrobial susceptibility tests should be performed for *C. diphtheriae* isolates. It is recommended that all isolates be sent to a reference laboratory. In the United States, the CDC's Pertussis and Diphtheria Laboratory provides support to local and state health departments needing assistance with isolation, identification, and subtyping of *C. diphtheriae* and *C. ulcerans.*

COMPLICATIONS

Respiratory tract obstruction by pseudomembranes may require bronchoscopy or intubation and mechanical ventilation. Two other tissues usually remote from sites of *C. diphtheriae* infection can be significantly affected by **diphtheritic toxin**: the heart and the nervous system.

Toxic Cardiomyopathy

Toxic cardiomyopathy occurs in 10–25% of patients with respiratory diphtheria, resulting in death in 35–60% of cases with this complication and responsible for 20–25% of deaths overall. Subtle signs of myocarditis can be detected in most patients, especially the elderly, but the risk for significant complications correlates directly with the extent and severity of exudative local oropharyngeal disease, along with a delay in administration of antitoxin. The first evidence of cardiac toxicity characteristically occurs 7-14 days after the onset of respiratory symptoms but can appear acutely as early as the first week of illness, a poor prognostic sign, or as late as the sixth week. Tachycardia disproportionate to fever is common and may be evidence of cardiac toxicity or autonomic nervous system dysfunction. A prolonged P-R interval and changes in the ST-T wave on an electrocardiographic tracing are relatively frequent findings; dilated and hypertrophic cardiomyopathy detected by echocardiogram has been described. Single or progressive cardiac **dysrhythmias** can occur, including first-, second-, and third-degree heart block. Temporary transvenous pacing may improve outcomes. Atrioventricular dissociation and ventricular tachycardia are also described, the latter having a high associated mortality. Heart failure may appear insidiously or acutely. Elevation of the serum aspartate transaminase concentration closely parallels the severity of myonecrosis. Severe dysrhythmia portends death. Histologic postmortem findings are variable: little or diffuse myonecrosis with acute inflammatory response. Recovery from toxic myocardiopathy is usually complete, although survivors of more severe dysrhythmias can have permanent conduction defects.

Toxic Neuropathy

Neurologic complications occur in 20–25% of untreated cases, resulting in death in 50% of cases who develop them and responsible for 15% of deaths overall. They parallel the severity of primary infection and are multiphasic in onset. Acutely or 2-3 weeks after onset of oropharyngeal inflammation, hyperesthesia and local **paralysis** of the soft palate typically occur. Weakness of the posterior pharyngeal, laryngeal, and facial nerves may follow, causing a nasal quality in the voice, difficulty in swallowing, and risk for aspiration. **Cranial neuropathies** characteristically occur in the fifth week, leading to oculomotor and ciliary paralysis, which can cause strabismus, blurred vision, or difficulty with accommodation. Symmetric demyelinating **polyneuropathy** has onset 10 days to 3 months after oropharyngeal infection and causes principally motor deficits with diminished deep tendon reflexes. Nerve conduction velocity studies and cerebrospinal fluid findings in diphtheritic polyneuropathy are indistinguishable from those of Guillain-Barré syndrome. Paralysis of the diaphragm may ensue. Complete neurologic recovery is likely, but rarely vasomotor center dysfunction 2-3 weeks after onset of illness can cause hypotension or cardiac failure.

Recovery from myocarditis and neuritis is often slow but usually complete. Corticosteroids do not diminish these complications and are not recommended.

TREATMENT

Specific diphtheria **antitoxin** is the mainstay of therapy and should be administered as soon as possible, without delay on the basis of clinical diagnosis. Because it neutralizes only free toxin, antitoxin efficacy diminishes with elapsed time after the onset of mucocutaneous symptoms. Equine diphtheria antitoxin is available in the United States only from the CDC. Physicians treating a case of suspected diphtheria should contact the CDC Emergency Operations Center at 1-770-488-7100 after consulting with their state health department. Antitoxin is available from CDC under expanded access investigational new drug application protocol. Antitoxin is administered as a single empirical dose of 20,000-100,000 units based on the degree of severity, site, and duration of illness. Skin testing for hypersensitivity must be performed before administration of antitoxin. Patients with positive sensitivity testing or with a history of hypersensitivity reaction to horse equine protein should be desensitized. Antitoxin is probably of no value for local manifestations of cutaneous diphtheria, but its use is prudent because toxic sequelae can occur. Commercially available intravenous immunoglobulin preparations contain low titers of antibodies to diphtheria toxin; their use for therapy of diphtheria is not proven or approved. Antitoxin is not recommended for asymptomatic carriers.

The role of **antimicrobial therapy** is to halt toxin production, treat localized infection, and prevent transmission of the organism

to contacts. Although *C. diphtheriae* is usually susceptible to various agents in vitro, including penicillins, erythromycin, clindamycin, rifampin, and tetracycline, only erythromycin or penicillin are recommended for treatment. Erythromycin is marginally superior to penicillin for eradication of nasopharyngeal carriage. Resistance to erythromycin is common in populations where the drug has been used broadly, and resistance to penicillin has also been reported. Appropriate therapy is **erythromycin** (40-50 mg/kg/day divided every 6 hours by mouth [PO] or intravenously [IV]; maximum 2 g/day), **aqueous crystalline penicillin G** (150,000 - 250,000 units/kg/day divided every 6 hr IV or intramuscularly [IM], up to 2-3 million units/day), or **procaine penicillin** (300,000 units every 12 hr IM for those ≤10 kg in weight; 600,000 units every 12 hr IM for those >10 kg in weight) for 14 days. Once oral medications are tolerated, oral erythromycin (see dosing above) or penicillin V (50 mg/kg/day, divided every 6 hr, maximum 2 g per day) may be used for the remaining duration of therapy. *Antibiotic therapy is not a substitute for antitoxin therapy.* Some patients with cutaneous diphtheria have been treated for 7-10 days. Elimination of the organism should be documented by negative results of at least two successive cultures of specimens from the nose and throat (or skin) obtained at least 24 hours apart, collected 24 hours after completion of antimicrobial therapy. Treatment with erythromycin should be repeated if either culture yields *C. diphtheriae.*

Individuals untreated with antibiotics, including those with either symptomatic or asymptomatic infection, remain colonized with *C. diphtheriae* for an average of 18.5 days, with 5% remaining colonized longer than 48 days. With antibiotic treatment, they clear *C. diphtheriae* colonization within an average of 5.2 days, reducing the duration of infectiousness by 2 weeks.

SUPPORTIVE CARE

Droplet precautions are instituted for patients with pharyngeal diphtheria; for patients with cutaneous diphtheria, **contact precautions** are observed until the results of specimen cultures taken after cessation of therapy are negative. Cutaneous wounds are cleaned thoroughly with soap and water. Bed rest is essential during the acute phase of disease, usually for ≥2 weeks until the risk for symptomatic cardiac damage has passed, with return to physical activity guided by the degree of toxicity and cardiac involvement.

PROGNOSIS

The prognosis for patients with diphtheria depends on the virulence of the organism (subspecies *gravis* has the highest fatality rate), patient age, immunization status, site of infection, and speed of administration of the antitoxin. Mechanical obstruction from laryngeal diphtheria or bull-neck diphtheria and the complications of myocarditis account for most diphtheria-related deaths. The case fatality ratio for untreated, never-vaccinated cases is 29%, improving to 10% with antitoxin treatment. The risk of fatality increases with every day of delayed antitoxin treatment. Children age <5 years are more likely to die from symptomatic infection than adults >20 years of age, whereas children 5-19 years of age are less likely to die from infection than adults age >20 years. At recovery, administration of diphtheria toxoid is indicated to complete the primary series or booster doses of immunization, because not all patients develop antibodies to diphtheria toxin after infection.

PREVENTION

Protection against serious disease caused by imported or indigenously acquired *C. diphtheriae* depends on immunization. In the absence of a precisely determined minimum protective level for diphtheria antitoxin, the presumed minimum is 0.01-0.10 IU/mL. In outbreaks, 90% of individuals with clinical disease have had antibody values <0.01 IU/mL, and 92% of asymptomatic carriers have had values >0.1 IU/mL. In serosurveys in the United States and Western Europe, where almost universal immunization during childhood has been achieved, 25% to >60% of adults lack protective antitoxin levels, with typically very low levels in elderly persons. A serosurvey in the United States (1988–1994) indicated that 60% of the overall population had protective immunity against diphtheria; however, this level of protection declined from 80% in persons age 12-19 years to about 30% in persons age 60-69 years.

All suspected diphtheria cases should be reported to local and state health departments. Investigation is aimed at preventing secondary cases in exposed individuals and at determining the source and carriers to halt spread. The serial interval, or time between symptom onset of the infector/infectee pair, is a median of 5.9 days, with 5% of intervals <0.8 days and 5% longer than 21 days.

Asymptomatic Case Contacts

All household contacts and people who have had intimate respiratory or habitual physical contact with a patient are closely monitored for illness for 7 days. Cultures of the nose, throat, and any cutaneous lesions are performed. Antimicrobial prophylaxis is presumed effective and is administered regardless of immunization status, using a single injection of benzathine penicillin G (600,000 units IM for patients weighing <30kg, or 1,200,000 units IM for patients weighing ≥30 kg or adults,) or erythromycin (40-50 mg/kg/day divided every 6 hr PO for 7-10 days; max 1 g/day). Diphtheria toxoid vaccine, in age-appropriate form, is given to immunized individuals who have not received a booster dose within 5 years. Children who have not received their fourth dose should be vaccinated. Those who have received fewer than three doses of diphtheria toxoid or who have uncertain immunization status should be immunized with an age-appropriate preparation on a primary schedule.

Asymptomatic Carriers

When an asymptomatic carrier is identified, antimicrobial prophylaxis is given for 10-14 days, and an age-appropriate preparation of diphtheria toxoid vaccination is administered immediately if a booster has not been given within 1 year. Droplet precautions (respiratory tract colonization) or contact precautions (cutaneous colonization only) are observed until at least two subsequent cultures obtained at least 24 hours apart, collected 24 hours after cessation of therapy, have negative results.

Repeat cultures are performed about 2 weeks after completion of therapy for cases and carriers; if results are positive, an additional 10-day course of oral erythromycin should be given and follow-up cultures performed. Susceptibility testing of isolates should be performed, as erythromycin resistance is reported. Neither penicillin nor erythromycin eradicates carriage in 100% of individuals. In one report, a single course of therapy failed in 21% of carriers. Transmission of diphtheria in modern hospitals is rare. Only those who have an unusual contact with respiratory or oral secretions should be managed as contacts. Investigation of the casual contacts of patients and carriers or persons in the community without known exposure has yielded extremely low carriage rates and is not routinely recommended.

Vaccine

Universal immunization with diphtheria toxoid throughout life, designed to provide constant protective antitoxin antibody levels and to reduce severity of *C. diphtheriae* disease, is the only effective control measure. Although immunization does not preclude subsequent respiratory or cutaneous carriage of toxigenic *C. diphtheriae,* it decreases local tissue spread, prevents toxic complications, diminishes transmission of the organism, and provides herd immunity when at least 80–85% of a population is immunized.

Full vaccination is highly effective in preventing symptomatic disease (87% with three or more doses, increasing to 99% with five doses), severe disease (defined as local and systemic symptoms plus a major complication; 81%), and death (93%). Even though vaccines do not prevent colonization, they reduce transmission by 60%, likely through reduced symptomatic shedding. Asymptomatic carriers are still able to transmit infection, albeit at only 24% the rate of symptomatic cases. In an outbreak setting, both vaccination and antibiotic treatment to clear colonization are necessary to interrupt transmission. Although full vaccination coverage can interrupt transmission in only 27% of outbreak settings, this figure increases to 70% when rapid antibiotic treatment is initiated in 90% of symptomatic cases.

The COVID-19 pandemic resulted in disruptions in immunization services in 2020, leading to 3.5 million children missing their first dose of diphtheria, tetanus, and pertussis vaccine (DTP) as compared with 2019. Global annual vaccination coverage for first-dose DTP vaccine decreased from 90% in 2019 to 87% in 2020; third-dose DTP vaccine

decreased from 86% in 2019 to 83% in 2020. The impact this will have on the resurgence of vaccine-preventable infections is yet to be determined.

Diphtheria toxoid is prepared by formaldehyde treatment of toxin, standardized for potency and adsorbed to aluminum salts, enhancing immunogenicity. Two preparations of diphtheria toxoids are formulated according to the *limit of flocculation* (Lf) content, a measure of the quantity of toxoid. The pediatric (6 months to 6 years) preparations (i.e., **DTaP** [diphtheria and tetanus toxoids with acellular pertussis vaccine] and **DT** [diphtheria and tetanus toxoids vaccine]) contain 6.7-25.0 Lf units of diphtheria toxoid per 0.5 mL dose; tetanus toxoid with vaccines for ≥7 years (Td [tetanus and diphtheria toxoid vaccine] and **Tdap** [diphtheria and tetanus toxoids with acellular pertussis vaccine]) contain no more than 2-2.5 Lf units of toxoid per 0.5 mL dose. The *higher-potency* (D) formulation of toxoid is used for primary series and booster doses for children through 6 years of age, given its superior immunogenicity and minimal reactogenicity. For individuals ≥7 years old, Td or Tdap is recommended for the primary series and booster doses because the lower concentration of diphtheria toxoid is adequately immunogenic and increasing the content of diphtheria toxoid heightens reactogenicity with increasing age.

For children 6 weeks to 6 years of age, five 0.5-mL doses of diphtheria-containing (D) vaccine (DTaP preferred) are given in the primary series, including doses at 2, 4, and 6 months of age, and a fourth dose, an integral part of the primary series, at 15-18 months. Dose 4 may be administered as early as age 12 months if at least 6 months have elapsed since dose 3. A booster dose is given at 4-6 years of age (unless the fourth primary dose was administered at ≥4 years). For persons ≥7 years to 18 years not previously immunized for diphtheria, three 0.5-mL doses of *lower-level* diphtheria-containing (d) vaccine are given in a primary series of two doses at least 4 weeks apart and a third dose 6 months after the second dose. The first dose should be Tdap, and subsequent doses can be Td or Tdap.

A booster dose, consisting of Tdap, is recommended at 11-12 years of age. Tdap may be administered regardless of the interval since the last tetanus- and diphtheria-toxoid-containing vaccine. Adolescents 13-18 years old who have not received Tdap at 11-12 years should receive a single dose of Tdap, then a Td or Tdap booster every 10 years. Pregnant women should receive a single dose of Tdap during every pregnancy, preferably during gestational weeks 27-36. Adults who have never received Tdap should receive a single dose of Tdap, regardless of when they last got Td. A Td or Tdap booster should be given every 10 years.

Updated recommendations allow for use of either Td or Tdap vaccine in situations where previously only Td was recommended. This includes the decennial Td booster, tetanus prophylaxis for wound management, and for additional required doses in the catch-up immunization schedule if a person has received at least one Tdap dose.

The only contraindication to tetanus and diphtheria toxoid is a history of neurologic or severe hypersensitivity reaction after a prior dose. For children <7 years old in whom pertussis immunization is contraindicated, DT is used. Those whose immunization is begun with DTaP or DT before 1 year of age should have a total of five 0.5-mL doses of diphtheria-containing (D) vaccines by 6 years of age. For those whose immunization is begun at around 1 year old, the primary series is three 0.5-mL doses of diphtheria-containing (D) vaccine, with a booster given at 4-6 years, unless the third dose was given after the fourth birthday.

There is no association of DT or Td with seizures. Local adverse effects alone do not preclude continued use. The rare patient who experiences an Arthus-type hypersensitivity reaction or a temperature >39.4°C (103°F) after a dose of Td usually has high serum tetanus antitoxin levels and should not be given Td more frequently than every 10 years, even if the patient sustains a significant tetanus-prone injury.

The DT or Td preparation can be given concurrently with other vaccines. Meningococcal and pneumococcal conjugate vaccines containing diphtheria toxoid or a variant of diphtheria toxin, CRM197 protein, are not substitutes for diphtheria toxoid immunization and do not affect reactogenicity.

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Chapter 234

Listeria monocytogenes

Ashley C. Howard and Thomas S. Murray

Listeriosis in humans is caused principally by *Listeria monocytogenes,* 1 of 17 species of the genus *Listeria* that are widely distributed in the environment and throughout the food chain. Human infections can usually be traced to an animal reservoir. Infection usually occurs at the extremes of age. In the pediatric population, perinatal infections predominate and usually occur secondary to maternal infection or colonization. Outside the newborn period, disease is most often encountered in *immunosuppressed* (usually T-cell deficiencies) children and adults and in elderly persons. For most people the major risk for infection with *Listeria* is **food-borne transmission**. In the United States, food-borne outbreaks are caused by improperly processed dairy products and contaminated vegetables and principally affect the same individuals at risk for sporadic disease.

ETIOLOGY

Members of the genus *Listeria* are facultatively anaerobic, non–spore-forming, motile, gram-positive bacilli that are catalase positive. The 17 *Listeria* species are divided into two genomically distinct groups on the basis of DNA-DNA hybridization studies. One group contains the species *L. grayi,* and 10 others discovered since 2009 are considered nonpathogenic. The second group contains six species: the nonhemolytic species *L. innocua*, *L. welshimeri,* and *L. marthii* and the hemolytic species *L. monocytogenes, L. seeligeri,* and *L. ivanovii. L. ivanovii* is pathogenic primarily in animals, and the vast majority of both human and animal disease is caused by *L. monocytogenes*.

Subtyping of *L. monocytogenes* isolates for epidemiologic purposes is now performed predominately with whole genome sequencing. This demonstrates the clonal structure of populations of *L. monocytogenes* as well as the sharing of populations between human and animal sources. **Subtyping** is an important component of determining whether cases are connected or sporadic but usually requires collaboration with a specialized laboratory.

Historically, selected biochemical tests, together with the demonstration of *tumbling motility,* an umbrella-type formation below the surface in semisolid medium, hemolysis, and a typical cyclic adenosine monophosphate test, are usually sufficient to establish a presumptive identification of *L. monocytogenes*. Once growth is present, *L. monocytogenes* can now be rapidly identified with matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectrometry.

EPIDEMIOLOGY

L. monocytogenes is widespread in nature, has been isolated throughout the environment, and is associated with epizootic disease and asymptomatic carriage in >42 species of wild and domestic animals and 22 avian species. Epizootic disease in large animals (e.g., sheep, cattle) is associated with abortion and "circling disease," a form of basilar meningitis. *L. monocytogenes* is isolated from sewage, silage, and soil, where it survives for >295 days. Human-to-human transmission rarely occurs except in maternal-fetal transmission. The annual incidence of listeriosis decreased by 36% between 1996 and 2004 and has remained level since then, estimated between two and five cases per year per million people. However, **food-borne outbreaks** continue to occur. The rate of *Listeria* infections varies among states. Epidemic human listeriosis has been associated with food-borne transmission in several large outbreaks, especially in association with aged soft cheeses; improperly pasteurized milk and milk products; contaminated raw and ready-to-eat beef, pork, and poultry and packaged meats and

salads; and vegetables, both fresh and frozen, harvested from farms where the ground is contaminated with the feces of colonized animals. In 2017-2018, the largest *Listeria* outbreak ever recorded occurred in South Africa with >900 cases and 200 deaths related to a processed contaminated meat product, "polony." U.S. food-borne outbreaks from 2019 to 2020 included deli meats and cheeses, packaged hard boiled eggs, and enoki mushrooms. The ability of *L. monocytogenes* to grow at temperatures as low as 4°C (39.2°F) increases the risk for transmission from aged soft cheeses and stored contaminated food. Listeriosis is an uncommon but important recognized etiology of neonatal sepsis and meningitis. Small clusters of nosocomial person-to-person transmission have occurred in hospital nurseries and obstetric suites. Sporadic endemic listeriosis is less well characterized. Likely routes include food-borne infection and zoonotic spread. **Zoonotic transmission** with cutaneous infections occurs in veterinarians and farmers who handle sick animals.

Reported cases of listeriosis are clustered at the extremes of age. Some studies show higher rates in males and a seasonal predominance in the late summer and fall in the Northern Hemisphere. In the United States, there is an increased risk of infection in nonpregnant non-Hispanic Asians, non-Hispanic Blacks, and Hispanics compared with non-Hispanic Whites. Outside the newborn period and during pregnancy, disease is usually reported in patients with underlying immunosuppression, with a 100-300 times increased risk in HIV-infected persons and in the elderly population (Table 234.1). In a prospective cohort study for listeriosis, 82.5% of participants had at least one immunocompromising condition, and those with bacteremia and neurolisteriosis disease were found to have a fivefold increased risk of death if there was an underlying malignancy.

The incubation period, which is defined only for common-source food-borne disease, is 21-30 days but in some cases may be longer. Asymptomatic carriage and fecal excretion are reported in 1–5% of healthy persons and 5% of abattoir workers, but duration of excretion, when studied, is short (<1 month).

PATHOLOGY

One of the major concepts of *Listeria* pathology and pathogenesis is its ability to survive as an intracellular pathogen. *Listeria* incites a mononuclear response and elaboration of cytokines, producing multisystem disease, particularly pyogenic meningitis. Granulomatous reactions and microabscess formation develop in many organs, including the liver, lungs, adrenals, kidneys, central nervous system (CNS), and notably the placenta. Animal models demonstrate *translocation,* the transfer of intraluminal organisms across intact intestinal mucosa. Histologic examination of tissues, including the placenta, shows granulomatous inflammation and microabscess formation. Intracellular organisms can often be demonstrated with special stains.

Table 234.1 Types of *Listeria monocytogenes* Infections

Listeriosis in pregnancy
Neonatal listeriosis
Early onset
Late onset
Food-borne outbreaks/febrile gastroenteritis
Listeriosis in normal children and adults (rare)
Focal *Listeria* infections (e.g., meningitis, endocarditis, pneumonia, liver abscess, osteomyelitis, septic arthritis)
Listeriosis in immunocompromised persons
Lymphohematogenous malignancies
Collagen vascular diseases
Diabetes mellitus
HIV infection
Transplantation
Renal failure with peritoneal dialysis
Listeriosis in elderly persons

PATHOGENESIS

Listeria organisms usually enter the host through the gastrointestinal (GI) tract. Gastric acidity provides some protection, and drugs that raise gastric pH may promote infection. Studies of intracellular and intercellular spread of *L. monocytogenes* have revealed a complex pathogenesis. Four pathogenic steps are described: internalization, escape from the vacuole, nucleation of actin filaments, and cell-to-cell spread. **Listeriolysin O**, a hemolysin, mediates lysis of vacuoles and is responsible for the zone of hemolysis around colonies on blood-containing solid media. In cell-to-cell spread, locomotion proceeds via polymerization of actin filaments, which extrude the bacteria in pseudopods, which in turn are internalized by adjacent cells, necessitating escape from a double-membrane vacuole. This mechanism protects intracellular bacteria from the humoral arm of immunity and is responsible for the well-known requirement of T-cell–mediated activation of monocytes by lymphokines for clearance of infection and establishment of immunity. The significant risk for listeriosis in patients with depressed T-cell immunity speaks for the role of this arm of the immune system. The role of opsonizing antibody in protecting against infection is unclear. In addition, siderophores scavenge iron from the host, enhancing growth of the organism and likely explaining the relatively high risk of listeriosis in iron overload syndromes.

CLINICAL MANIFESTATIONS

The clinical presentation of listeriosis depends greatly on the age of the patient and the circumstances of the infection.

Listeriosis in Pregnancy

Pregnant women have increased susceptibility to *Listeria* infections (approximately 20 times higher than nonpregnant women), probably because of a relative impairment in cell-mediated immunity. *L. monocytogenes* has been grown from placental and fetal cultures of pregnancies ending in spontaneous abortion. The usual presentation in the second and third trimesters is a flulike illness that may result in seeding of the uterine contents by bacteremia. Rarely is maternal listeriosis severe, but meningitis in pregnancy has been reported. Recognition and treatment at this stage are associated with normal pregnancy outcomes, but the fetus may not be infected even if listeriosis in the mother is not treated. In other instances, placental listeriosis develops with infection of the fetus that may be associated with stillbirth or premature delivery. Delivery of an infected premature fetus is associated with very high infant mortality. Disseminated disease is apparent at birth, often with a diffuse pustular rash. Infection in the mother usually resolves without specific therapy after delivery, but postpartum fever and infected lochia may occur.

Neonatal Listeriosis

Two clinical presentations are recognized for neonatal listeriosis: early-onset neonatal disease (<5 days, usually within 1-2 days of birth), which is a predominantly **septicemic** form, and late-onset neonatal disease (>5 days, mean 14 days of life), which is a predominantly **meningitic** form (Table 234.2). The principal characteristics of the two presentations resemble the clinical syndromes described for group B *Streptococcus* (see Chapter 230).

Early-onset disease occurs with milder transplacental or ascending infections from the female genital tract. There is a strong association with recovery of *L. monocytogenes* from the maternal genital tract, obstetric complications, prematurity, and neonatal sepsis with multiorgan involvement, including rash, but without CNS localization (Fig. 234.1). The mortality rate is approximately 20–30%.

The epidemiology of **late-onset disease** is poorly understood. Onset is usually after 5 days but before 30 days of age. Affected infants frequently are full-term, and the mothers are culture negative and asymptomatic. The presenting syndrome is usually purulent meningitis with parenchymal brain involvement, which, if adequately treated, has a mortality rate of <20%.

Table 234.2 Characteristic Features of Early- and Late-Onset Neonatal Listeriosis

EARLY ONSET (<5 DAYS)	LATE ONSET (≥5 DAYS)
Positive result of maternal *Listeria* culture	Negative results of maternal *Listeria* culture
Obstetric complications	Uncomplicated pregnancy
Premature delivery	Term delivery
Low birthweight	Normal birthweight
Neonatal sepsis	Neonatal meningitis
Mean age at onset 1.5 days	Mean age at onset 14.2 days
Mortality rate <30%	Mortality rate <20% Nosocomial outbreaks

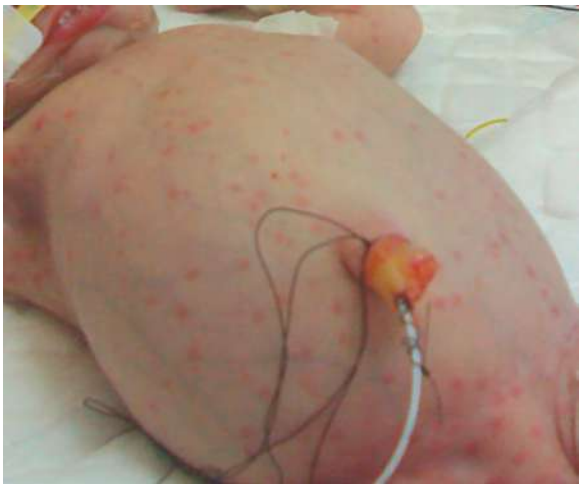

Fig. 234.1 *Listeria monocytogenes.* The generalized maculopapular rash present at birth disappeared within a few hours of life. *(From Benitez-Segura I, Fiol-Jaume M, Balliu PR, Tejedor M. Listeria monocytogenes: generalized maculopapular rash may be the clue. Arch Dis Child Fetal Neonatal Ed. 2013;98[1]:F64, Fig. 1.)*

Postneonatal Infections

Listeriosis beyond the newborn period may rarely occur in otherwise healthy children but is most often encountered in association with underlying malignancies (especially lymphomas) or immunosuppression. When associated with food-borne outbreaks, disease may cause GI symptoms or any of the *Listeria* syndromes. The clinical presentation is usually meningitis, less commonly sepsis, and rarely other CNS involvement, such as cerebritis, meningoencephalitis, brain abscess, spinal cord abscess, or a focus outside the CNS, such as suppurative arthritis, osteomyelitis, endocarditis, peritonitis (associated with peritoneal dialysis), or liver abscess. It is not known whether the frequent GI signs and symptoms result from enteric infection because the mode of acquisition is often unknown.

DIAGNOSIS

Listeriosis should be included in the differential diagnosis of infections in pregnancy, of neonatal sepsis and meningitis, and of sepsis or meningitis in older children who have underlying malignancies (lymphomas), are receiving immunosuppressive therapy, or have undergone transplantation. The diagnosis is established by culture of *L. monocytogenes* from blood or cerebrospinal fluid (CSF). Cultures from the maternal cervix, vagina, lochia, and placenta, if possible, should be obtained when intrauterine infections lead to premature delivery or early-onset neonatal sepsis. Cultures from closed-space infections may also be useful. It is helpful to alert the laboratory to suspected cases so that *Listeria* isolates are not discarded as contaminating diphtheroids.

Histologic examination of the placenta is also useful. Molecular assays are now commercially available to detect *L. monocytogenes* from CNS samples and directly from positive blood culture bottles. Serodiagnostic tests are not useful.

Differential Diagnosis

Listeriosis is indistinguishable clinically from neonatal sepsis and meningitis caused by other organisms. The presence of increased peripheral blood monocytes suggests listeriosis. Monocytosis or lymphocytosis may be modest or striking. Beyond the neonatal period, *L. monocytogenes* CNS infection is associated with fever, headache, seizures, and signs of meningeal irritation. The brainstem may be characteristically affected. The white blood cell concentration may vary from normal to slightly elevated, and the CSF laboratory findings are variable and less striking than in the more common causes of bacterial meningitis. Polymorphonuclear leukocytes or mononuclear cells may predominate, with shifts from polymorphonuclear to mononuclear cells in sequential lumbar puncture specimens. The CSF glucose concentration may be normal, but a low level mirrors the severity of disease. The CSF protein concentration is moderately elevated. *L. monocytogenes* is isolated from the blood in 40–75% of cases of meningitis caused by the organism. Deep focal infections from *L. monocytogenes,* such as endocarditis, osteomyelitis, and liver abscess, are also indistinguishable clinically from such infections from more common organisms. Cutaneous infections should be suspected in patients with a history of contact with animals, especially products of conception.

TREATMENT

The emergence of multiantibiotic resistance mandates routine susceptibility testing of all isolates. The recommended therapy is **ampicillin** (100-200 mg/kg/day divided every 6 hours intravenously [IV]; 300-400 mg/kg/day divided every 6 hours IV if meningitis is present), alone or in combination with an **aminoglycoside** (2.0-3.0 mg/kg/day IV divided every 8-24 hours depending on postnatal age). The aminoglycoside enhances the bactericidal activity and is generally recommended in cases of endocarditis and meningitis. The adult dose is ampicillin 4-6 g/day divided every 6 hours plus an aminoglycoside. The ampicillin dose is doubled if meningitis is present. Special attention to dosing is required for neonates, who require longer dosing intervals because of the longer half-lives of the antibiotics in their bodies. *L. monocytogenes* is not susceptible to the cephalosporins, including third-generation cephalosporins. If these agents are used for empirical therapy for neonatal sepsis or meningitis in a newborn, ampicillin must be added for possible *L. monocytogenes* infection. Vancomycin, vancomycin plus an aminoglycoside, and trimethoprim-sulfamethoxazole are alternatives to ampicillin. The duration of therapy is usually 2-3 weeks, with 3 weeks recommended for immunocompromised persons and patients with meningitis. A longer course is needed for endocarditis, brain abscess, and osteomyelitis. Antibiotic treatment is unnecessary for gastroenteritis without invasive disease.

PROGNOSIS

Early gestational listeriosis may be associated with abortion or stillbirth, although maternal infection with sparing of the fetus has been reported. There is no convincing evidence that *L. monocytogenes* is associated with repeated spontaneous abortions in humans. The mortality rate is >50% for premature infants infected in utero, 30% for early-onset neonatal sepsis, 15% for late-onset neonatal meningitis, and <10% in older children with prompt institution of appropriate antimicrobial therapy. Mental retardation, hydrocephalus, and other CNS sequelae are reported in survivors of *Listeria* meningitis.

Table 234.3 Prevention of Food-Borne Listeriosis

GENERAL RECOMMENDATIONS TO PREVENT *LISTERIA* INFECTION

FDA recommendations for washing and handling food:

- Rinse raw produce, such as fruits and vegetables, thoroughly under running tap water before eating, cutting, or cooking. Even if the produce will be peeled, it should still be washed first.
- Scrub firm produce, such as melons and cucumbers, with a clean produce brush.
- Dry the produce with a clean cloth or paper towel.
- Separate uncooked meats and poultry from vegetables, cooked foods, and ready-to-eat foods.

Keep your kitchen and environment cleaner and safer:

- Wash hands, knives, countertops, and cutting boards after handling and preparing uncooked foods.
- Be aware that *Listeria monocytogenes* can grow in foods in the refrigerator. Use an appliance thermometer, such as a refrigerator thermometer, to check the temperature inside your refrigerator. The refrigerator should be 4.5°C (40°F) or lower and the freezer −17.8°C (0°F) or lower.
- Clean up all spills in your refrigerator promptly, especially juices from hot dog and lunch meat packages, raw meat, and raw poultry.
- Clean the inside walls and shelves of your refrigerator with hot water and liquid soap, then rinse.

Cook meat and poultry thoroughly:

- Thoroughly cook raw food from animal sources, such as beef, pork, or poultry, to a safe internal temperature. For a list of recommended temperatures for meat and poultry, visit the safe minimum cooking temperatures chart at http://www.FoodSafety.gov.

Store foods safely:

- Use precooked or ready-to-eat food as soon as you can. Do not store the product in the refrigerator beyond the use-by date; follow USDA refrigerator storage time guidelines:
  - Hot dogs: store opened package no longer than 1 wk and unopened package no longer than 2 wk in the refrigerator.
  - Luncheon and deli meat: store factory-sealed, unopened package no longer than 2 wk. Store opened packages and meat sliced at a local deli no longer than 3-5 days in the refrigerator.
- Divide leftovers into shallow containers to promote rapid, even cooling. Cover with airtight lids or enclose in plastic wrap or aluminum foil. Use leftovers within 3-4 days.

Choose safer foods:

- Do not drink raw (unpasteurized) milk, and do not eat foods that have unpasteurized milk in them.

RECOMMENDATIONS FOR PERSONS AT HIGHER RISK*

In addition to the recommendations listed above, include:

Meats

- Do not eat hot dogs, luncheon meats, cold cuts, other deli meats (e.g., bologna) or fermented or dry sausages unless they are heated to an internal temperature of 73.9°C (165°F) or until steaming hot just before serving.
- Avoid getting fluid from hot dog and lunch meat packages on other foods, utensils, and food preparation surfaces, and wash hands after handling hot dogs, luncheon meats, and deli meats.
- Pay attention to labels. Do not eat refrigerated pâté or meat spreads from a deli or meat counter or from the refrigerated section of a store. Foods that do not need refrigeration, such as canned or shelf-stable pâté and meat spreads, are safe to eat. Refrigerate after opening.

Cheeses

- Do not eat soft cheese such as feta, queso blanco, queso fresco, brie, Camembert, blue-veined, or panela (queso panela) unless it is labeled as made with pasteurized milk. Make sure the label says "*Made With Pasteurized Milk.*"

Seafood

- Do not eat refrigerated smoked seafood, unless it is contained in a cooked dish, such as a casserole, or unless it is a canned or shelf-stable product.
- Refrigerated smoked seafood, such as salmon, trout, whitefish, cod, tuna, and mackerel, is most often labeled as "nova-style," "lox," "kippered," "smoked," or "jerky."
  - These fish are typically found in the refrigerator section or sold at seafood and deli counters of grocery stores and delicatessens.
- Canned and shelf-stable tuna, salmon, and other fish products are safe to eat.

Follow this general FDA advice for melon safety:

- Consumers and food preparers should wash their hands with warm water and soap for at least 20 sec before and after handling any whole melon, such as cantaloupe, watermelon, or honeydew.
- Scrub the surface of melons, such as cantaloupes, with a clean produce brush under running water and dry them with a clean cloth or paper towel before cutting. Be sure that your scrub brush is sanitized after each use to avoid transferring bacteria between melons.
- Promptly consume cut melon or refrigerate promptly. Keep your cut melon refrigerated ≤4.5°C (40°F) (0–1.1°C [32–34°F] is best) for no more than 7 days.
- Discard cut melons left at room temperature for >4 hours.

*Including pregnant women, persons with a weakened immune system, and older adults.
FDA, Food and Drug Administration; USDA, U.S. Department of Agriculture.
Adapted from Centers for Disease Control and Prevention: *Listeria* (listeriosis): prevention. http://www.cdc.gov/listeria/prevention.html.

PREVENTION

Listeriosis can be prevented by pasteurization and thorough cooking of foods. Irradiation of meat products may also be beneficial. Consumption of unpasteurized or improperly processed dairy products should be avoided, especially aged soft cheeses, uncooked and precooked meat products that have been stored at 4°C (39.2°F) for extended periods, and unwashed vegetables (Table 234.3). This avoidance is particularly important during pregnancy and for immunocompromised persons. Infected domestic animals should be avoided when possible. Education regarding risk reduction is aimed particularly at pregnant women and people being treated for cancer.

Careful handwashing is essential to prevent nosocomial spread within obstetric and neonatal units. Immunocompromised patients given prophylaxis with trimethoprim-sulfamethoxazole are protected from *Listeria* infections. Cases, and especially outbreaks, should be reported immediately to public health authorities so that timely investigation can be initiated in order to interrupt transmission from the contaminated source.

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Chapter 235

Actinomyces

Hamid Bassiri

TAXONOMY AND MICROBIOLOGY

Members of the phylum Actinobacteria are common soil and water gram-positive bacteria with high guanine and cytosine DNA content and play important roles in the decomposition of organic materials. A proportion of Actinobacteria form filamentous and branching structures (similar to *Nocardia* spp.) that resemble fungal mycelia; these are included in the class Actinomycetia. The genus *Actinomyces* (which translates literally to "ray fungus") belongs to the order Actinomycetales (along with *Mycobacteria* and *Nocardia*) and family Actinomycetaceae and constitutes several microaerophilic to facultatively anaerobic nonmotile species that are fastidious and slow growing.

More than 50 species of *Actinomyces* have been identified using 16S rRNA sequencing, with more than half of these species associated with human infection. ***Actinomyces israelii*** is the predominant species causing human actinomycosis. Other species associated with infection include but are not limited to *A. odontolyticus, A. meyeri, A. naeslundii, A. graevenitzii, A. neuii,* and *A. turicensis.*

PATHOGENESIS AND EPIDEMIOLOGY

Actinomyces are commensal organisms of the human oropharynx and gastrointestinal and urogenital tracts, and infections by these organisms (termed **actinomycosis**) typically emanate from these anatomic sites. The hallmark of actinomycosis is contiguous spread that fails to respect tissue or fascial planes. As such, these infections can extend to contiguous structures and form abscesses and chronically suppurative granulomatous infections and sinus tracts. Cicatricial healing can then ensue, from which the organism can further spread by burrowing along fascial planes, causing deeply communicating scarred sinus tracts. Sites of infection show dense cellular infiltrates and suppuration that form many interconnecting abscesses and sinus tracts. Bacteremia and infections of more distal sites (such as endocarditis, pericarditis, and central nervous system [CNS] infections) have also been documented. Notably, polymicrobial infections are typical, especially with copathogens such as *Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans,* as well as *Fusobacterium, Clostridia, Eikenella, Enterococcus, Bacteroides,* and *Peptostreptococcus* spp.

Knowledge regarding the epidemiology of actinomycosis is limited to case reports and case series. Based on these reports, actinomycosis appears to affect people of all ages, with no racial or ethnic predilection, seasonality, or occupational associations. Actinomycosis occurs in immunocompetent and immunocompromised hosts. However, pediatric actinomycosis only represents approximately 3% of reported cases. Risk factors in children include trauma, dental caries, debilitation, and poorly controlled diabetes. Although actinomycosis is not a common opportunistic infection, disease has been associated with corticosteroid use, leukemia, renal failure, congenital immunodeficiencies, HIV infection, and solid organ or hematopoietic stem cell transplantation.

Given the sites of colonization, the most common presentations of *Actinomyces* infections include cervicofacial, abdominal/pelvic, and thoracic regions (in order of frequency). Importantly, certain medical interventions can result in mucosal barrier injuries and infection. For instance, use of intrauterine contraceptive devices can predispose to pelvic actinomycosis, and aspiration events, poor dentition, and recent dental procedures can result in involvement of the thoracic region. However, more than one third of patients do not have an identifiable antecedent event that would explain the onset of actinomycosis. Importantly, actinomyces infections are not contagious.

DIAGNOSIS

Diagnosis of actinomycosis relies on identification of the organism in tissues of affected areas via culture, molecular methods, and/or histopathology. However, growth in cultures can take up to 2-3 weeks, and up to 50% of cultures may reveal no growth because of prior antibiotic exposure, failure to maintain anaerobic conditions during sample transport, or inadequate incubation.

The presence of **sulfur granules** on macroscopic or microscopic evaluation (Fig. 235.1) of involved tissue is suggestive of actinomycosis. Despite their name, these granules are not composed of sulfur, instead deriving this designation because of their typical yellow color on macroscopic appearance; they can also be white, gray, or brown. Similar granules can be formed by *Nocardia brasiliensis, Streptomyces madurae* (which can cause mycetomas), and *Staphylococcus aureus* (which can cause botryomycosis). Microscopically, these granules appear on hematoxylin-eosin or Gomori methenamine silver stains as masses of gram-positive, branching, filamentous rods surrounded by the host immune cells (e.g., polymorphonuclear neutrophils) and a milieu of eosinophilic staining inert material, often referred to as the **Splendore-Hoeppli phenomenon**. Notably, *A. meyeri* is nonbranching and *A. odontolyticus* does not form sulfur granules.

Nocardia are indistinguishable from *Actinomyces* on Gram stain, but *Nocardia* take up the modified acid-fast stain, whereas *Actinomyces* spp. do not. Although suggestive of actinomycosis, sulfur granules are often absent, and thus additional testing such as cultures are necessary for the diagnosis. Affected tissues can be cultured on

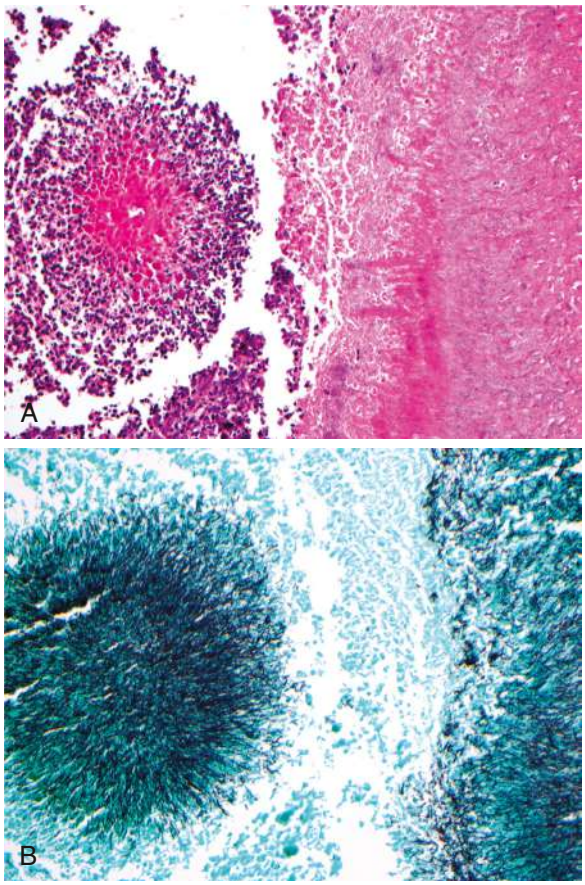

Fig. 235.1 Actinomycosis. **A,** Small cluster of *Actinomyces* on left, with sulfur granule and surrounding mixed inflammation demonstrating the Splendore-Hoeppli phenomenon (×200). **B,** Gomori methenamine silver stain of the same field, highlighting the filamentous forms (×200). *(From Johnson MM. Ear, nose, and throat infections. In: Kradin RL, ed. Diagnostic Pathology of Infectious Disease, 2nd ed. Philadelphia: Elsevier; 2018: Fig. 7.6.)*

brain-heart infusion agar incubated at 37°C anaerobically and aerobically to reveal organisms within the lines of streak at 24-48 hours. *A. israelii* colonies appear as loose masses of delicate, branching filaments with a characteristic spider-like growth. Unfortunately, even under the right conditions, it is challenging to grow *Actinomyces,* and the yield of different culturing techniques varies by species. Additionally, conventional biochemical testing for speciation is complex and may result in misclassifications. The evolution of diagnostic tools such as 16S rRNA sequence analysis and matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectrometry has improved the accuracy of speciation of cultured organisms and highlighted the potential for detection of *Actinomyces* directly from the involved tissue without culture.

Importantly, actinomycosis is usually, if not always, **polymicrobial** in nature. In a large study of >650 cases, infection with *Actinomyces* was identified in pure culture in only 1 case. Cultures usually also identify other endogenous flora, including members of the **HACEK group**, which includes *Haemophilus* spp. (typically *H. aphrophilus, H. parainfluenzae,* or *H. paraphrophilus*), *A. actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella kingae. A. actinomycetemcomitans* is a fastidious, gram-negative bacillus that is part of the oral flora and has been implicated in periodontal disease. Other bacteria frequently isolated concomitantly in human actinomycosis include *Fusobacterium, Bacteroides, Capnocytophaga,* and aerobic and anaerobic streptococci.

CT or MRI of involved areas is often employed in the initial patient evaluation. Imaging evidence of an invasive process spreading across tissue planes and ignoring anatomic boundaries is highly suggestive of actinomycosis. Furthermore, imaging can be helpful in establishing the extent of the infection, guiding subsequent diagnostic and therapeutic interventions, and monitoring for disease resolution.

COMMON CLINICAL PRESENTATIONS

Cervicofacial Actinomycosis

Cervicofacial disease is the most common form of pediatric actinomycosis and often manifests as a neck or submandibular mass that persists for weeks to months. Less than half of patients will have associated pain, and less than one third of patients will have fever. A minority of patients will report dysphagia or have a draining sinus (Fig. 235.2). Less frequently, cervicofacial actinomycosis manifests clinically as an acute pyogenic infection with a tender, fluctuant mass with trismus, firm swelling, and fistulas with drainage containing sulfur granules. Bone is not involved early in the disease, but periostitis, mandibular osteomyelitis, or perimandibular abscess may subsequently develop. Infection may spread through sinus tracts to cranial bones, possibly leading to meningitis. The ability of *Actinomyces* to burrow through tissue planes, including the periosteum, is a key difference between actinomycosis and nocardiosis. Whereas predisposing factors for cervicofacial actinomycosis are not well defined for children, adult cases are often preceded by a history of oral trauma, oral surgery, dental procedures, or caries, facilitating entry of organisms into cervicofacial tissues.

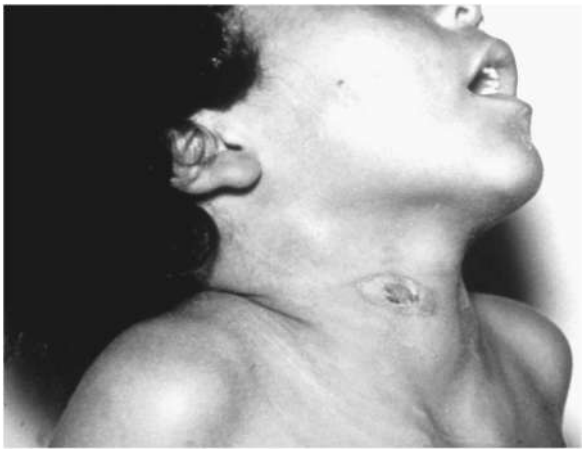

Fig. 235.2 A 2-yr-old male with HIV infection who has cervicofacial actinomycosis and a draining fistula.

Abdominal and Pelvic Actinomycosis

Of all the forms of actinomycosis, delayed diagnosis is most typical for abdominal and pelvic infection. A disruption of the mucosa of the gastrointestinal (GI) tract (e.g., acute GI perforation, abdominal trauma, prior abdominal surgery) is often postulated as the inciting event for adult-onset abdominopelvic actinomycosis. In pediatric patients, however, medical history sometimes fails to identify prior evidence of mucosal barrier injury. In a contemporary pediatric case series of abdominal and pelvic actinomycosis, prior abdominal surgery (all appendectomies) was reported in only 21% of patients and dental caries in 11%. In two thirds to three fourths of patients, the presenting signs are abdominal pain and a palpable mass on physical exam. Fever accompanies the abdominal pain in more than half of cases, with weight loss in almost one third. As with other forms of actinomycosis, abdominopelvic infection can spread across tissue planes by contiguous extension involving any tissue or organ, including muscle, solid abdominopelvic viscera, and walls of the intestinal tract. Imaging studies may reveal a mass with invasion of tissue planes, leading to misdiagnosis of malignancies, inflammatory bowel disease with fistulae, or abdominal tuberculosis. Genitourinary actinomycosis is often associated with use of intrauterine contraceptive devices (IUDs) in adults and can mimic gynecologic tumors, but these infections are quite rare in adolescents. Because of delays in diagnosis, more than one third of pediatric cases present with draining sinus fistulae.

Thoracic Actinomycosis

Thoracic actinomycosis may present with cough, chest pain, hemoptysis, and fever. In a retrospective review of reported pediatric cases of thoracic infection, almost half presented with a chest wall mass. Additional symptoms such as cough, fever, chest pain, and weight loss were reported in <40% of patients. Radiographic imaging may reveal hilar lymphadenopathy, endobronchial infection, tumor-like lesions, diffuse pneumonia, pleural effusions, or abscesses with or without cavitation and parenchymal lung destruction. These abscesses can also form sinus tracts to the diaphragm or mediastinum, which are often pathognomonic for actinomycosis. Other complications include bony destruction of adjacent ribs, sternum, and vertebral bodies. Multiple lobe involvement of the lungs is occasionally found. Importantly, evidence of thoracic actinomycosis can be found incidentally on radiographs ordered for noninfectious concerns. The variation in presentation and indolent nature of thoracic actinomycosis often delay the diagnosis.

Other Forms of Actinomycosis

CNS actinomycosis is often the result of hematogenous spread to the brain parenchyma from a distant site but can also ensue from contiguous spread from a cervicofacial lesion. The former often results in multiple brain abscesses. **Laryngeal** actinomycosis rarely has been reported in older teenagers. Oropharyngeal colonization with *Actinomyces* may be involved in the development of obstructive tonsillar hypertrophy. Severe forms of **periodontitis**, particularly localized juvenile periodontitis, are associated with *Actinomyces,* especially in adolescents. *Actinomyces* has a propensity for infecting heart valves, a process that results in subacute endocarditis, with fever present in less than half of cases.

DIFFERENTIAL DIAGNOSIS

Actinomycosis has been referred to as a "great imitator" with presentations that mimic appendicitis, pseudoappendicitis caused by *Yersinia enterocolitica,* amebiasis, malignancy, and inflammatory bowel disease. Actinomycosis must be differentiated from other chronic infections,

including tuberculosis, nocardiosis, polymicrobial bacterial infections, and fungal infections.

TREATMENT

Most cases of actinomycosis can be managed with antibiotics, although surgery can be adjunctive and may shorten the duration of antibiotic use. Routine susceptibility testing is not typically performed, as most *Actinomyces* spp. are susceptible to penicillin. Accordingly, penicillin G is the drug of choice for parenteral therapy, and penicillin V or amoxicillin is the preferred enteral antibiotic. Because actinomycosis is often found to be polymicrobial in nature, use of combination β-lactam/β-lactamase inhibitors (e.g., ampicillin-sulbactam or amoxicillin-clavulanate) may be warranted, especially if there is an initial poor response. In particular, ***A. actinomycetemcomitans*** is a copathogen in at least 30% of cases of actinomycosis. Failure to recognize this organism and treat it adequately has resulted in clinical relapse and deterioration.

Treating actinomycosis in a patient with a penicillin allergy can be challenging, as there is variation in susceptibility by *Actinomyces* spp. to other antibiotic classes; alternatives generally include cephalosporins, carbapenems, macrolides, and tetracyclines. Despite being anaerobic, a large percentage of *Actinomyces* are not susceptible to metronidazole, and isolates are variably susceptible to clindamycin. Fluoroquinolones and aminoglycosides have little to no activity against *Actinomyces* spp. Infectious disease specialists should be consulted to guide antibiotic usage in patients with penicillin allergy or deep-seated infections such as brain abscesses, endocarditis, or osteomyelitis. Commercially available sensitivity testing methods are available and can be employed in patients with severe disease or poor response to initial therapy.

No definitive comparative effectiveness data exist to guide the optimal route and duration of therapy. For severe or extensive infections, most experts recommend initial parenteral administration of antibiotics for 4-6 weeks and then transitioning to enteral therapy upon documentation of clinical improvement. The exceptions include endocarditis and CNS disease, which generally require parenteral administration for the entire course of therapy. In cases of mild or limited disease, enteral antibiotics could be considered even at initiation. Given concern for relapses, antibiotics are often continued for several months, with total durations ranging between 2-6 months for mild/limited disease and 6-12 months for severe/extensive disease. Shorter courses of antibiotic therapy can result in relapses, especially in cases of thoracic actinomycosis without surgical debridement. Longer courses up to 18 months have also been used in invasive disease and in immunocompromised patients. At the same time, courses of antibiotic therapy <3 months have been used successfully in cases of local disease, especially after surgical resection. Close follow-up and monitoring are indicated in patients treated with short courses of antibiotics. The total duration of treatment is often ultimately dictated by the location of the infection and follow-up clinical exams and imaging.

Traditionally, an adjunctive surgical intervention was thought to be necessary for a successful outcome. However, in some case series a subset of patients have responded well to medical management alone. In the setting of significant abscesses and/or sinus tracts, a surgical approach to establish source control and, if possible, completely resect involved issue can hasten clinical improvement. The morbidity of the surgical procedure needs to be weighed against the potential benefits for each patient.

PROGNOSIS

The prognosis is excellent with early diagnosis, prompt initiation of antibiotic therapy, adherence to a prolonged course of antibiotics, and adequate surgical debridement, if necessary. Despite a good overall prognosis, permanent scarring can still develop. Although actinomycosis can present in immunocompetent children, disseminated or recalcitrant actinomycosis should raise suspicion for immunodeficiency.

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Chapter 236

Nocardia

Coralee Del Valle Mojica

Various *Nocardia* species have been identified causing localized and disseminated disease in children and adults. These organisms are predominantly opportunistic pathogens infecting immunocompromised individuals, but cases in immunocompetent hosts are increasingly reported. Infection caused by these bacteria is termed *nocardiosis,* which consists of acute, subacute, or chronic suppurative manifestations.

ETIOLOGY

Nocardia spp. are a complex group of environmental, gram-positive bacteria that belong to aerobic actinomycetes. They can grow on diverse media (e.g., blood agar, brain-heart infusion agar, Lowenstein-Jensen media, buffered charcoal-yeast extract [BCYE], Sabouraud dextrose agar) and have been referred to as bacteria that masquerade as fungi, sometimes misdirected to the mycology or mycobacteriology section of clinical laboratories for identification. Colonies can appear as early as 48 hours, but typically growth of *Nocardia* is slower than in other bacteria and may take 1-2 weeks. Growth appears as waxy, folded, or heaped colonies at the edges, and yield is best achieved in conditions that include a temperature of 37°C (98.6°F) with 10% carbon dioxide. However, many isolates of *Nocardia* are thermophilic and will grow at temperatures up to 50°C (122°F). Microscopically, *Nocardia* spp. are weakly gram-positive, rod-shaped, filamentous bacteria. For some isolates, there may be alternating areas of gram-positive and gram-negative staining, giving a beaded appearance often described with *Nocardia*. These organisms are also weakly acid-fast, and the modified Kinyoun acid-fast staining technique can be helpful to identify organisms from clinical specimens such as a tissue biopsy or bronchoalveolar lavage (BAL).

To date, more than 80 species of *Nocardia* have been described and 50 species have been identified to be human pathogens. The distribution of *Nocardia* spp. causing disease varies across studies, partly because of revisions in taxonomic classification over time. A retrospective study looking at isolates in the United States from 1995 to 2004 reported *N. nova, N. brasiliensis,* and *N. farcinica* as the most common species. In contrast, a more recent study from China reported *N. otitidiscaviarum* as the most common species, and a systematic review from Iran from 1992 to 2021 reported *N. asteroides* and *N. cyriacigeorgica* as the two most common species. Species identification can be critical for optimal clinical outcomes because of variability in virulence strategies and antibiotic-resistance profiles. Traditional approaches to speciation require biochemical processing that can be laborious and inefficient. Techniques such as 16S rDNA polymerase chain reaction (PCR) or matrix-assisted laser desorption/ionization (MALDI) time of flight (TOF) mass spectrometry are now considered the gold standard.

EPIDEMIOLOGY

Once thought to be a rare human disease, nocardiosis is being recognized more frequently and has been diagnosed in people of all ages. Pediatric patients with compromised cellular immunity are at particular risk, including children receiving immune suppression after solid organ or stem cell transplantation, chemotherapy for malignancy, prolonged corticosteroid therapy, children with poorly controlled HIV infection, or those with a primary immunodeficiency, especially chronic granulomatous disease. Notably, nocardiosis has been described in patients without an identified immune defect, although in these clinical scenarios, other predisposing factors such as bronchiectasis are often present.

Due to the lack of a national reporting system for *Nocardia* infections and the molecular advances impacting the classification of this organism, measuring the incidence of the disease remains a challenge. Current knowledge of nocardiosis incidence in the United States is based on a historical survey of 171 infectious diseases physicians from 1974 and isolates received at the CDC reference laboratory, estimating 500-1000 cases annually. Prevalence estimates in high-risk populations have been reported to be less than 1%, with conflicting reports about the trends of infections in different geographic locations around the world.

PATHOGENESIS

Nocardia organisms are environmental saprophytes that are ubiquitous in soil and decaying vegetable matter and have been isolated from soil worldwide. Infection can be acquired via inhalation or direct cutaneous inoculation, including after arthropod and cat bites. From 70% to 80% of *Nocardia* infections originate in the pulmonary parenchyma, with 10–25% being primary cutaneous disease.

Nocardia can disseminate from the primary site of infection to any organ or any musculoskeletal location. Dissemination after primary lung infection is common, occurring in 15–50% of patients; those with an underlying immunocompromised condition are more likely to have disseminated disease. The central nervous system (CNS) is the most concerning and most common secondary site of infection, complicating as much as 25% of pulmonary disease. Although rare, isolated CNS disease has been described. Whereas most cases are the result of environmental exposure, *Nocardia* species diversity in the hospital environment has been reported as a reservoir for the development of nosocomial infections.

CLINICAL AND RADIOGRAPHIC MANIFESTATIONS

The clinical presentation can be nonspecific, with fever reported in approximately 60% of patients, cough in 30%, and dyspnea in 25%. Extrapulmonary signs and symptoms can correspond to the site of infection. In particular, neurologic deficit has been reported in up to 25% of all cases and in more than 50% of patients with CNS involvement. Neurologic complaints can include headache, confusion or altered mental status, weakness, and speech impairment. Renal nocardiosis can cause dysuria, hematuria, or pyuria, and gastrointestinal (GI) involvement may be associated with nausea, vomiting, diarrhea, abdominal distention, or melena. Skin infection can manifest with nodular lymphangitis (Fig. 236.1). Mycetoma is a chronic, progressive infection developing days to months after inoculation, usually on a distal location on the limbs. Musculoskeletal, endovascular, and ocular infections have also been reported.

Given the nonspecific symptoms and signs of nocardiosis (with the exception of cutaneous lesions), radiographic imaging is often necessary to define the location and extent of disease. Pulmonary infection can appear as a consolidation consistent with typical bacterial pneumonia or even as a necrotizing pneumonia with or without a pleural effusion. Single or multiple nodules and cavitary lesions have also been described. Cavitary lesions are more common in patients with an underlying immunocompromising condition. CNS disease can take the form of meningitis or focal lesions. Meningitis presents as neutrophil- or lymphocyte-predominant pleocytosis, elevated cerebrospinal fluid protein, and hypoglycorrhachia. For focal lesions, CT or MRI of the brain often reveals single- or multiple-ring enhancing lesions. Similar to the brain, when other organs or soft tissues are involved, CT or MRI also typically reveals single- or multiple-ring enhancing lesions, suggestive of an abscess or abscesses.

DIAGNOSIS

Microbiologic evidence is necessary to confirm the diagnosis of nocardiosis. In one systematic review, blood cultures were the only positive microbiologic specimen in 38% of cases, thus serving as an important noninvasive diagnostic test for nocardiosis. In the remaining patients, an invasive procedure such as bronchoscopy, tissue biopsy, or abscess aspiration is necessary to procure specimens for diagnostic testing. Histopathologic staining of such material can reveal beaded, weakly gram-positive or modified acid-fast filamentous bacteria. Histopathology can also show delicately branching bacteria with a proclivity to fragment.

Molecular methodologies, specifically gene sequencing, have become the most accurate for definitively identifying *Nocardia* to the species level. Speciation of *Nocardia* is becoming increasingly reliant on 16S rDNA PCR or MALDI-TOF technologies, with a specificity of 74% and a sensitivity of 88% in a multicenter study assessing the performance of 16S sequencing in 68 patients with proven or probable nocardiosis. Given that *Nocardia* spp. can colonize the respiratory airway, a sputum or BAL culture that yields a *Nocardia* species is not itself confirmatory of nocardiosis. However, a positive microbiologic test for a *Nocardia* species from one of these specimens in conjunction with the clinical and radiographic findings is strongly supportive of nocardiosis.

When a diagnosis of nocardiosis is made, strong consideration should be given to evaluation for disseminated disease, even in the absence of signs or symptoms, especially in the immunocompromised host. Although data are limited, most experts agree that, at a minimum, MRI of the brain should be performed in the immunocompromised host with nocardiosis.

TREATMENT

The choice, dose, and duration of antimicrobial treatment depend on the site and extent of infection, immune status of the patient, initial clinical response, and species and susceptibility testing of the *Nocardia* isolate. Several therapeutic options exist for the treatment of nocardiosis; however, there are no comparative effectiveness studies to inform the optimal therapeutic regimen. **Trimethoprim-sulfamethoxazole (TMP-SMX)** is the sulfonamide formulation that is recommended, although sulfadiazine and sulfisoxazole have been used. Increasing recognition of resistance to TMP-SMX across and within *Nocardia* spp. highlights the importance of speciation of *Nocardia* isolates and of performing sensitivity testing in a certified microbiology laboratory. TMP-SMX resistance rates as high as 42% have been reported. Administration of TMP-SMX as prophylaxis against *Pneumocystis jirovecii* pneumonia is not always protective against nocardiosis, and thus clinicians should not exclude this diagnosis from the differential in patients receiving TMP-SMX prophylaxis.

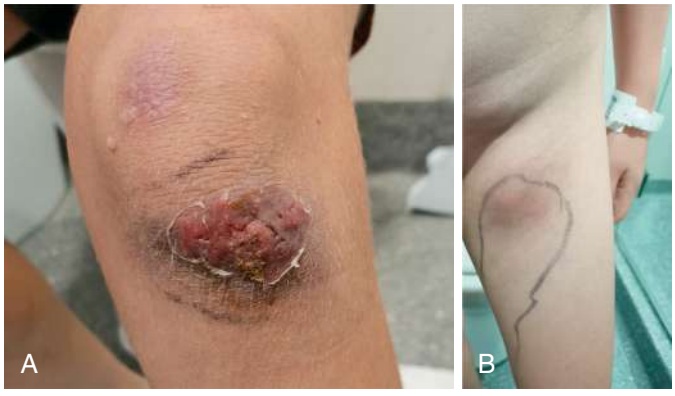

Fig. 236.1 A 9-yr-old healthy child with infected knee laceration (A) 10 days after falling onto concrete in his school playground, complicated by nodular lymphangitis (B). *(From Williams PCM, Bartlett AW, Palasanthiran P, McMullan B. A not so innocuous playground fall: lymphocutaneous nocardiosis in an immunocompetent boy. Arch Dis Child. 2022;107[3]:257–258, Figs. 1 and 2.)*

Other antibacterial agents with in vitro activity against *Nocardia* spp. include but are not limited to **amikacin, amoxicillin-clavulanate, ceftriaxone, ciprofloxacin, clarithromycin, imipenem, linezolid, and minocycline**. A recent study profiling the antimicrobial susceptibility pattern of a diverse range of *Nocardia* revealed that among 146 isolates, the susceptibilities were 100% to linezolid, 96% to amikacin, 94% to TMP-SMX, and 76% to imipenem. A similar retrospective study conducted in the United States from 1995 to 2004 revealed that 42% of the isolates were resistant to TMP-SMX. Therefore while awaiting sensitivity testing in patients with *Nocardia* isolated from a clinical specimen, it may be reasonable to administer linezolid empirically, taking into account local susceptibility data. Subsequent therapeutic decisions should be guided by final sensitivity results and consideration of the site of infection and pharmacokinetics of the available agents. It is not clear whether parenteral administration is superior to enteral formulations. However, most experts support the use of parenteral therapy for more severe disease, including endocarditis and CNS disease.

In vitro and in vivo animal models have suggested the benefit of combination regimens for the treatment of nocardiosis. There are no clinical data to confirm the need for combination therapy; however, based on the preclinical data, there is expert support for using combination therapy in CNS nocardiosis, in disseminated disease, and in children with an underlying immunocompromising condition. A variety of combination therapies have been suggested, with many experts favoring TMP-SMX, amikacin, and a carbapenem or third-generation cephalosporin. Since data on combination therapy are limited, antibiotic choices should primarily be guided by sensitivity testing of the clinical *Nocardia* isolate.

Surgical drainage of abscesses can be helpful in hastening resolution of nocardiosis. However, no comparative data have documented improvement in overall outcomes with adjunctive surgical intervention, and success has been reported with medical management alone in resolving deep-seated abscesses, even in the CNS. A literature review showed that among patients with CNS nocardiosis, 1-year overall mortality was approximately 20%, limited by cases lost to follow-up. Among patients who were treated with a combination of antibiotics and neurosurgical procedures, mortality was lower (7%). Therefore the decision to intervene surgically needs to be balanced with the potential consequences of a surgical procedure to drain an abscess. Intraventricular antibiotics have been reported.

The necessary duration of therapy for nocardiosis varies depending on the clinical presentation and the status of the patient. The optimal duration is uncertain, but long-term therapy is common because of the propensity for relapse. Historically, superficial cutaneous infection has been treated for 3 months, pulmonary or systemic nocardiosis has been treated for 6-12 months, and CNS infection has been treated for at least 12 months. These intervals should only be considered as a guide for expected therapeutic durations. The ultimate duration should be dictated by clinical and radiographic resolution of disease.

PROGNOSIS

Historically, nocardiosis has been associated with significant mortality. Fortunately, more recent reports have documented an improved rate of complete cure to approximately 80%. Predictably, attributable case fatality rates vary by disease entity. There is no attributable case fatality associated with cutaneous disease, but 10–20% attributable case fatality has been assigned to disseminated and visceral disease. CNS disease has the highest attributable case fatality rates, reaching 25%. Importantly, much of the data on case fatality rates are informed by predominantly adult cohorts, and thus there may be fewer fatal outcomes in children. Nonetheless, early diagnosis and intervention are important to reduce the morbidity and mortality of nocardiosis, especially in immunocompromised patients at increased risk for disseminated disease.

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Section 5

Gram-Negative Bacterial Infections

Chapter 237

Neisseria meningitidis (Meningococcus)

Manish Sadarangani

Neisseria meningitidis (the meningococcus) is a commensal of the human nasopharynx in approximately 10% of the population and, on rare occasions, enters the bloodstream to cause devastating invasive disease such as meningitis and meningococcal septicemia (meningococcemia). Although a rare endemic disease in most countries, the epidemiology of meningococcal disease varies widely over time and in different geographic regions, with both hyperendemic and epidemic disease patterns occurring. Onset of disease in susceptible individuals may be very rapid, within hours, and the case fatality rate is high, especially among those presenting with septic shock, despite access to modern critical care. Individual susceptibility is known to involve a complex relationship among environmental, host, and bacterial factors, and prevention of meningococcal disease through behavior modification (e.g., avoiding tobacco smoke) and vaccination offers the best prospect for control.

ETIOLOGY

N. meningitidis is a gram-negative, fastidious, encapsulated, oxidase-positive, aerobic diplococcus. Differences in the chemistry of the polysaccharide capsule allow definition of 12 (previously thought to be 13) serologically distinct meningococcal capsular groups, of which 6, designated A, B, C, W (previously designated W135), X, and Y, are responsible for almost all cases of disease. Meningococcal strains may be subclassified on the basis of antigenic variation in two porin proteins found in the outer membrane, **PorB** (serotype) and **PorA** (serosubtype), and **lipopolysaccharide** (immunotype), using serology. Serologic typing is being replaced by molecular typing methods, which target genes under immune selection to provide **antigen sequence typing** (based on amino acid variation in various surface proteins, including PorA and FetA). Sequencing of antigen genes (e.g., *porA, fHbp, nadA, nhba*) is an important means of monitoring pressure on meningococcal populations by protein-based vaccines containing these antigens. Because meningococci readily exchange genetic material, typing based on a few antigens cannot provide an accurate picture of relatedness of strains, an important goal in monitoring epidemiology. **Multilocus sequence typing**, which types meningococci using variation in seven housekeeping genes, has been widely used to map the distribution of genetic lineages of meningococci (http://pubmlst.org/neisseria/) and provides a clearer picture of the genetic and epidemiologic relatedness of strains. To provide still better definition of genetic variation, in some countries, including the United Kingdom, **whole genome sequencing** is used to type meningococci and appears set to replace both antigen and multilocus sequence typing as costs continue to fall. The application of molecular approaches to epidemiology has established that (1) endemic meningococcal disease is caused by genetically heterogeneous strains, although only a small number of genetic lineages are associated with the majority of cases of invasive disease, and (2) outbreaks are usually clonal, caused by single strains.

EPIDEMIOLOGY

Meningococci are transmitted during close contact through aerosol droplets or exposure to respiratory secretions, as by kissing. The organism does not survive for long periods in the environment. Enhanced rates of mucosal colonization and increased disease risk are associated with activities that increase the likelihood of exposure to a new strain or increase proximity to a carrier, thus facilitating transmission, including kissing, bar patronage, binge drinking, attendance at nightclubs, men having sex with men, and living in freshman college dormitories. Factors that damage the nasopharyngeal mucosa, such as smoking and respiratory viral infection (notably influenza), are also associated with increased rates of carriage and disease, perhaps by driving upregulation of host adhesion molecules that are receptors for meningococci. Carriage is unusual in early childhood and peaks during adolescence and young adulthood.

Meningococcal disease is a global problem, but disease rates vary by a factor of 10- to 100-fold in different geographic locations at one point in time and in the same location at different times. Most cases of meningococcal disease are sporadic, but small outbreaks (usually in schools or colleges, representing <3% of U.S. cases), **hyperendemic** disease (increased rates of disease persisting for a decade or more as a result of a single clone), and epidemic disease are all recognized patterns. However, over the past decade, rates of meningococcal disease have declined in most industrialized countries, partly through introduction of immunization programs and possibly aided by widespread legislation against smoking in public places. The arrival of hyperinvasive lineages and their eventual decline through development of natural immunity is recognized as a major driver of changes in disease rates over time. The U.S. disease rate was 1.1 cases per 100,000 population in 1999 but had fallen to 0.11 per 100,000 by 2019 (Fig. 237.1). By contrast, the rate of disease in Ireland in 1999 was >12 per 100,000, and rates of 1,000 per 100,000 have been described during epidemic disease in sub-Saharan Africa. Disease caused by dominant hyperendemic clones has been recognized in the past 2 decades in Oregon, United States; Quebec, Canada; Normandy, France; and across New Zealand. Laboratory data underreport meningococcal disease incidence rates because up to 50% of cases are not culture confirmed, particularly where prehospital antibiotics are recommended for suspected cases. In the United Kingdom, polymerase chain reaction (PCR) methods are used routinely for diagnosis of suspected cases, doubling the number of confirmed cases.

The highest rate of meningococcal disease occurs in infants <1 year old, probably as a result of *immunologic inexperience* (antibody that recognizes meningococcal antigens is naturally acquired during later childhood), immaturity of the alternative and lectin complement pathways, and perhaps the poor responses made by infants to bacterial polysaccharides. In the absence of immunization, incidence rates decline through childhood, except for a peak of disease among adolescents and young adults, which may be related to increased opportunity for exposure from social activities. The incidence of meningococcal disease is increased among persons with HIV infection.

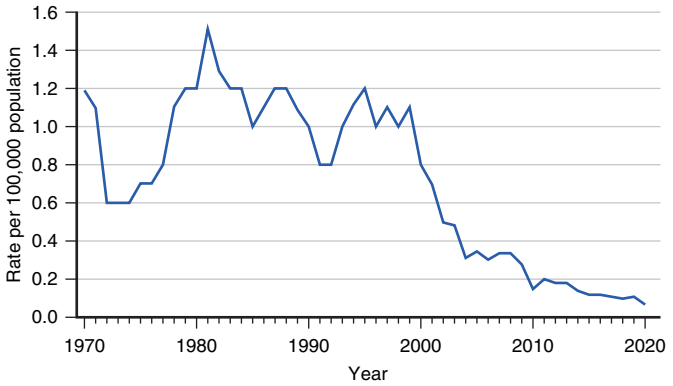

Fig. 237.1 Rate of meningococcal disease, by year—United States, 1970–2020. *(Modified from Cohn AC, MacNeil JR, Clark TA, et al; Centers for Disease Control and Prevention. Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep 2013;62[RR-2]:1–28, updated with data from the CDC meningococcal surveillance data tables: https://www.cdc.gov/meningococcal/surveillance/surveillance-data.html#figure01.)*

In the United States, most cases of disease in the first 5 years of life are caused by capsular **group B** strains. After age 5 years, disease cases are mostly distributed among capsular groups C, W, and Y. In most other industrialized countries, capsular group B strains predominate at all ages, in part because of introduction of routine capsular **group C** meningococcal conjugate vaccine among infants and/or toddlers. For unclear reasons, disease in children caused by group Y strains was uncommon in the United States before the 1990s and then began to increase. Rates of disease caused by this capsular group have also increased in several other countries but are declining in the United States. Disease caused by capsular **group W** strains has increased in the United Kingdom and in other countries in Europe and Australia as a result of a hyperinvasive clone, which appears to have originated in Latin America.

Large outbreaks of capsular **group A** meningococcal disease occurred during and immediately after the First World War and Second World War in both Europe and the United States, but since the 1990s, almost all cases caused by capsular group A strains have occurred in Eastern Europe, Russia, and developing countries. The highest incidence of capsular group A disease has occurred in a band across sub-Saharan Africa, the *meningitis belt,* with annual endemic rates of 10-25 per 100,000 population. For more than a century, this region has experienced large capsular group A epidemics every 7-10 years, with annual rates as high as 1,000 per 100,000 population. The onset of cases in the sub-Saharan region typically begins during the dry season, possibly related to drying and damage to the nasopharyngeal mucosa; subsides with the rainy season; and may reemerge the following dry season. Rates of capsular group A meningococcal disease are currently falling across this region as a result of a mass vaccine implementation targeting strains bearing the A polysaccharide. However, both endemic and epidemic meningococcal disease in this region is also caused by capsular groups C, W, and X strains. Capsular group A and **group X** are infrequent causes of disease in other areas of the world, although both A and W strains have been associated with outbreaks among pilgrims returning from the Hajj.

PATHOGENESIS AND PATHOPHYSIOLOGY

Colonization of the nasopharynx by *N. meningitidis* is the first step in either carriage or invasive disease. Disease usually occurs 1-14 days after acquisition of the pathogen. Initial contact of meningococci with host epithelial cells is mediated by pili, which may interact with the host CD46 molecule or an integrin. Close adhesion is then mediated by Opa and Opc binding to carcinoembryonic antigen (CEA) cell adhesion molecule receptors and integrins, respectively. Subsequent internalization of meningococci by epithelial cells is followed by transcytosis through to the basolateral tissues and dissemination into the bloodstream. Immunoglobulin A_1 protease secreted by invasive bacteria degrades secretory IgA on the mucosal surface, circumventing this first-line host defense mechanism.

Once in the bloodstream, meningococci multiply rapidly to high levels to cause septicemia (**meningococcemia**). Patients with a higher bacterial load have a more rapid clinical deterioration and longer period of hospitalization, as well as a higher risk of death and permanent sequelae. Resistance to complement-mediated lysis and phagocytosis is largely mediated by the polysaccharide capsule and **lipopolysaccharide (LPS)**. Outer membrane vesicles released from the surface of the organism contain LPS, outer membrane proteins, periplasmic proteins, and phospholipid and play a major role in the inflammatory cascade that leads to severe disease.

Much of the tissue damage is caused by host immune mechanisms activated by meningococcal components, in particular LPS. During invasive disease LPS is bound to a circulating plasma protein known as *LPS-binding protein.* The host receptor complex for LPS consists of toll-like receptor (TLR)-4, CD14, and myeloid differentiation protein 2. Binding of LPS to TLR-4, which is upregulated on circulating leukocytes during septicemia, results in activation of a number of different cell types. An intense inflammatory reaction results from secretion of proinflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin

(IL)-1β, IL-6, IL-8, and granulocyte-macrophage colony-stimulating factor, levels of which are closely associated with plasma levels of LPS. The major antiinflammatory cytokines IL-1Rα, IL-2, IL-4, and IL-12 and transforming growth factor-β are present at very low levels. Both high and low levels have been observed for IL-10 and interferon-γ.

The pathophysiologic events that occur during meningococcal septicemia are largely related to microvascular injury. This injury leads to increased vascular permeability and capillary leak syndrome, pathologic vasoconstriction and vasodilation, disseminated intravascular coagulation (DIC), and profound myocardial dysfunction. Increased vascular permeability can lead to dramatic fluid loss and severe hypovolemia. **Capillary leak syndrome** with or without aggressive fluid resuscitation (which is essential in severe cases) leads to pulmonary edema and respiratory failure. Initial vasoconstriction is a compensatory mechanism in response to hypovolemia and results in the clinical features of pallor and cold extremities. After resuscitation, some patients experience **warm shock**, that is, intense vasodilation with bounding pulses and warm extremities, despite persistent hypotension and metabolic acidosis. Virtually all antithrombotic mechanisms appear to be dysfunctional during meningococcal sepsis, leading to a procoagulant state and DIC. All these factors contribute to depressed myocardial function, but there is also a direct negative cytokine effect on myocardial contractility, thought to be largely mediated by IL-6. Hypoxia, acidosis, hypoglycemia, hypokalemia, hypocalcemia, and hypophosphatemia are all common features in severe septicemia and further depress cardiac function. Some patients become unresponsive to the positive inotropic effects of catecholamines and require high levels of inotropic support during intensive care management. These processes result in impairment of microvascular blood flow throughout the body and ultimately lead to **multiorgan failure**, which is responsible for much of the mortality.

After invasion of the circulation, meningococci may also penetrate the blood-brain barrier and enter the cerebrospinal fluid (CSF), facilitated by pili and possibly Opc. Once there, bacteria continue to proliferate, and LPS and other outer membrane products can stimulate a proinflammatory cascade similar to that observed in the blood. This leads to upregulation of specific adhesion molecules and recruitment of leukocytes into the CSF. Central nervous system damage occurs directly by meningeal inflammation and indirectly by circulatory collapse and causes a high rate of neurologic sequelae in affected patients. Death can occur from cerebral edema, which leads to **increased intracranial pressure (ICP)** and cerebral or cerebellar herniation.

Immunity

There is an inverse correlation between the incidence of disease and the prevalence of complement-dependent **serum bactericidal antibody (SBA)**. The level of SBA is highest at birth and among adults and lowest in children between 6 months and 2 years of age, when the highest incidence of disease occurs. Such antibodies are naturally elicited by asymptomatic carriage of pathogenic and nonpathogenic *Neisseria,* such as *Neisseria lactamica,* and other antigenically related gram-negative bacteria. A similar relationship was described for capsular groups A, B, and C. Vaccine trials support these earlier findings. For the meningococcal capsular group C conjugate vaccine, an SBA titer ≥1:8 correlated strongly with postlicensure vaccine effectiveness. For capsular group B disease, the data are less certain, but the proportions of capsular group B vaccine recipients with more than fourfold rises in SBA after vaccination or SBA titers ≥1:4 have been correlated with clinical effectiveness in studies of outer membrane vesicle vaccines. These cutoffs are therefore currently used for regulatory approval of new meningococcal vaccines. The strong association between disease risk and genetic variation in human complement factor H further supports the importance of complement-mediated protection against disease.

There is evidence that mechanisms other than complement-dependent bactericidal antibodies may be important in determining protection against meningococcal disease. Disease in individuals with complement deficiency has a different age distribution, has less severe clinical features, and often involves unusual capsular groups. In particular, complement deficiency does not appear strongly related to an increased risk of capsular group B disease. Alternative surrogate markers of protection include the opsonophagocytic assay and antibody avidity, but no studies have attempted to link these laboratory tests with vaccine efficacy or even population protection, as has been found with SBA.

Host Factors

Host susceptibility is strongly related to age, as previously described, indicating that immunologic responsiveness and/or naïveté in infancy and early childhood are key determinants of risk. **Complement** is a key factor in protection against meningococcal disease. Individuals with inherited deficiencies of properdin, factor D, or terminal complement components have up to a 1,000-fold higher risk for development of meningococcal disease than complement-sufficient people. The risk of meningococcal disease is also increased in patients with acquired complement deficiencies associated with diseases such as nephrotic syndrome, systemic lupus erythematosus (SLE), and hepatic failure and in patients treated with eculizumab, a monoclonal antibody against complement protein C5.

Among those with complement deficiencies, meningococcal disease is more prevalent during late childhood and adolescence, when carriage rates are higher than in children <10 years old; meningococcal infections in these patients may be recurrent. Although meningococcal disease can occasionally be overwhelming in patients with late complement component deficiency, cases are more typically described as being less severe than in complement-sufficient persons (with properdin deficiency being the exception), perhaps reflecting that these cases are often caused by unusual capsular groups. In one study, one third of individuals with meningococcal disease caused by capsular groups X, Y, and W had a complement deficiency. Although protective against early infection, extensive complement activation and bacteriolysis may contribute to the pathogenesis of severe disease once bacterial invasion has occurred.

The sibling risk ratio for meningococcal disease is similar to that for other diseases where susceptibility shows polygenic inheritance, and a number of host genetic factors have now been identified to affect either susceptibility to meningococcal disease or severity of disease. The molecules implicated include proteins on epithelial surfaces, the complement cascade, pattern recognition receptors, clotting factors, and inflammatory mediators. Deficiencies in the complement pathways are consistently associated with an increased risk of meningococcal disease, with specific polymorphisms in mannose-binding lectin and factor H found to be associated with disease susceptibility. A genome-wide association study of 7,522 individuals in Europe identified single nucleotide polymorphisms (SNPs) within the *CFH* and *CFHR3* genes that were associated with host susceptibility to meningococcal disease. Complement-mediated bacteriolysis is known to be extremely important in protection against meningococcal disease, giving these associations biologic plausibility. In particular, factor H attaches to various binding proteins expressed on the bacterial surface, downregulating complement activation and allowing the organism to evade host responses.

In terms of disease severity, a meta-analysis of data from smaller studies found that SNPs in genes encoding plasminogen activator inhibitor 1 *(SERPINE1)*, IL-1 receptor antagonist *(IL1RN),* and IL-1β *(IL1B)* are associated with increased mortality from meningococcal disease, as reflected in pathophysiologic changes that occur during invasive disease.

CLINICAL MANIFESTATIONS

The most common form of meningococcal infection is asymptomatic carriage of the organism in the nasopharynx. In the rare cases where invasive disease occurs, the clinical spectrum of meningococcal disease varies widely, but the highest proportion of cases present with meningococcal meningitis (30–50%). Other recognized presentations include bacteremia without sepsis, meningococcal septicemia with or without meningitis, pneumonia, chronic meningococcemia, and occult bacteremia. Focal infections in various sites (e.g., myocardium, joints, pericardium, bone, eye, peritoneum, sinuses, middle ear) are well recognized, and all may progress to disseminated disease. Urethritis, cervicitis, vulvovaginitis, orchitis, and proctitis may also occur.

Acute meningococcal septicemia cannot be distinguished from other viral or bacterial infections early after onset of symptoms (Table 237.1). Typical nonspecific early symptoms include fever, irritability, lethargy, respiratory symptoms, refusal to drink, and vomiting. Less

Table 237.1 Prevalence of Symptoms and Signs in Children and Young People with Meningococcal Septicemia, Meningococcal Disease, and Meningococcal Meningitis

	PREVALENCE RANGE (NUMBER OF STUDIES)		
SYMPTOM OR SIGN	**BACTERIAL MENINGITIS**	**MENINGOCOCCAL DISEASE**	**MENINGOCOCCAL SEPTICEMIA**
Fever	66–97% (10)	58–97% (7)	98% (1)
Vomiting or nausea	18–70% (10)	44–76% (6)	
Rash	9–62% (6)	59–100% (9)	70% (1)
Headache	3–59% (7)	16–49% (5)	40% (1)
Lethargy	13–87% (6)	36–65% (3)	59% (1)
Coughing	N/A (0)	15–27% (2)	33% (1)
Irritable or unsettled	21–79% (8)	36–67% (3)	32% (1)
Runny nose	N/A (0)	24% (1)	31% (1)
Muscle ache or joint pain	23% (1)	7–65% (3)	30% (1)
Refusing food or drink	26–76% (4)	13–60% (3)	27% (1)
Altered mental state*	26–93% (6)	45–81% (3)	N/A (0)
Stiff neck	13–74% (13)	5–71% (6)	N/A (0)
Impaired consciousness	60–87% (4)	10–72% (2)	N/A (0)
Unconsciousness	4–18% (4)	N/A (0)	N/A (0)
Chills or shivering	N/A (0)	39% (1)	N/A (0)
Photophobia	5–16% (2)	2–31% (5)	N/A (0)
Respiratory symptoms	25–49% (4)	16–23% (2)	N/A (0)
Breathing difficulty	13–34% (4)	11% (1)	N/A (0)
Cold hands or feet	N/A (0)	43% (1)	N/A (0)
Shock	8–16% (2)	27–29% (2)	N/A (0)
Seizures	14–38% (12)	7–17% (3)	N/A (0)
Diarrhea	21–29% (2)	7–9% (2)	N/A (0)
Abdominal pain or distention	17% (1)	4% (1)	N/A (0)
Leg pain	N/A (0)	11–37% (2)	N/A (0)
Thirst	N/A (0)	8% (1)	N/A (0)
Sore throat, coryza, or throat infection	18% (1)	24% (1)	N/A (0)
Ill appearance	N/A (0)	79% (1)	N/A (0)
Capillary refill time >2sec	N/A (0)	83% (1)	N/A (0)
Hypotension	N/A (0)	28% (1)	N/A (0)
Abnormal skin color	N/A (0)	19% (1)	N/A (0)
Bulging fontanel†	13–45% (4)	N/A (0)	N/A (0)
Ear infection or ear, nose, and throat infections‡	18–49% (5)	N/A (0)	N/A (0)
Chest infection	14% (1)	N/A (0)	N/A (0)
Brudzinski sign	11–66% (2)	N/A (0)	N/A (0)
Kernig sign	10–53% (3)	N/A (0)	N/A (0)
Abnormal pupils	10% (1)	N/A (0)	N/A (0)
Cranial nerve pair involvement	4% (1)	N/A (0)	N/A (0)

Table 237.1 Prevalence of Symptoms and Signs in Children and Young People with Meningococcal Septicemia, Meningococcal Disease, and Meningococcal Meningitis—cont'd

	PREVALENCE RANGE (NUMBER OF STUDIES)		
SYMPTOM OR SIGN	**BACTERIAL MENINGITIS**	**MENINGOCOCCAL DISEASE**	**MENINGOCOCCAL SEPTICEMIA**
Toxic or moribund state	3–49% (2)	N/A (0)	N/A (0)
Back rigidity	46% (1)	N/A (0)	N/A (0)
Paresis	6% (1)	N/A (0)	N/A (0)
Focal neurologic deficit	6–47% (3)	N/A (0)	N/A (0)

*This includes confusion, delirium, and drowsiness.
†The age ranges in the four studies are 0-14 yr, 0-2 yr, 0-12 mo, and 0-13 wk.
‡One study reported the number of children and young people with ear, nose, and throat infections; the four other studies reported the number of ear infections only.
Classification of conditions presented in the table reflects the terminology used in the evidence.
N/A, Not applicable.
Data from National Collaborating Center for Women's and Children's Health (UK). Bacterial meningitis and meningococcal septicaemia: management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care. *NICE Clinical Guidelines, No 102.* London: RCOG Press; 2010.

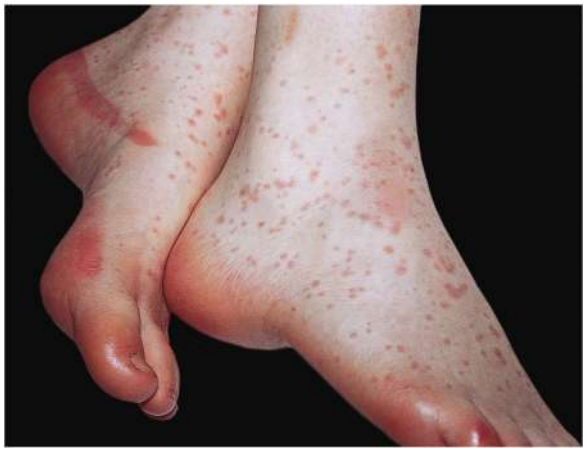

Fig. 237.2 Meningococcemia. A maculopapular, nonhemorrhagic rash that subsequently became petechial. *(From Habif TP, ed. Clinical Dermatology, 6th ed. Philadelphia: Mosby; 2016: Fig 9-59.)*

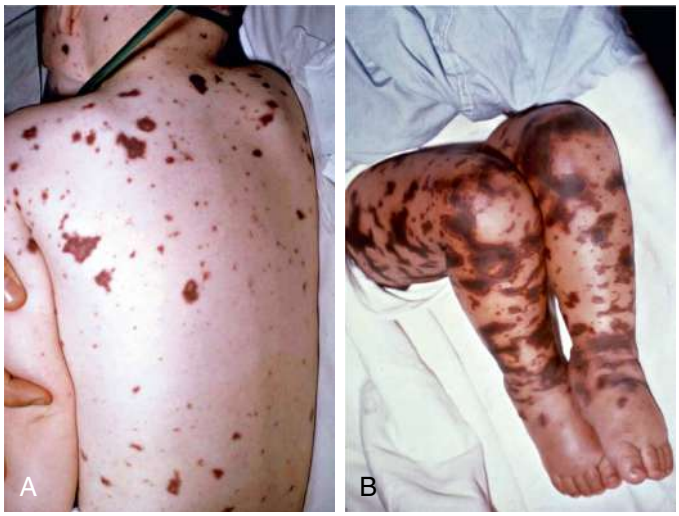

Fig. 237.3 A, Purpuric rash in 3-yr-old child with meningococcemia. B, Purpura fulminans in 11-mo-old child with meningococcemia. *(From Thompson ED, Herzog KD. Fever and rash. In: Zaoutis L, Chiang V, eds. Comprehensive Pediatric Hospital Medicine. Philadelphia: Mosby; 2007: Figs. 62-6 and 62-7.)*

frequently, diarrhea, sore throat, and chills/shivering are reported. A maculopapular rash, which is indistinguishable from rashes seen after viral infections, is evident in approximately 10% of cases early in the course of infection (Fig. 237.2). Limb pain, myalgia, or refusal to walk may occur as the primary complaint in 7% of otherwise clinically unsuspected cases. As the disease progresses, cold hands or feet and abnormal skin color may be important signs, capillary refill time becomes prolonged, and a nonblanching or petechial rash will develop in >80% of cases. In fulminant meningococcal septicemia, the disease progresses rapidly over several hours from fever with nonspecific signs to septic shock characterized by prominent petechiae and purpura **(purpura fulminans)** with poor peripheral perfusion, tachycardia (to compensate for reduced blood volume resulting from capillary leak), increased respiratory rate (to compensate for pulmonary edema), hypotension (a late sign of shock in young children), confusion, and coma (resulting from decreased cerebral perfusion). Coagulopathy, electrolyte disturbance (especially hypokalemia), acidosis, adrenal hemorrhage, renal failure, and myocardial failure may all develop (Fig. 237.3). Meningitis may be present.

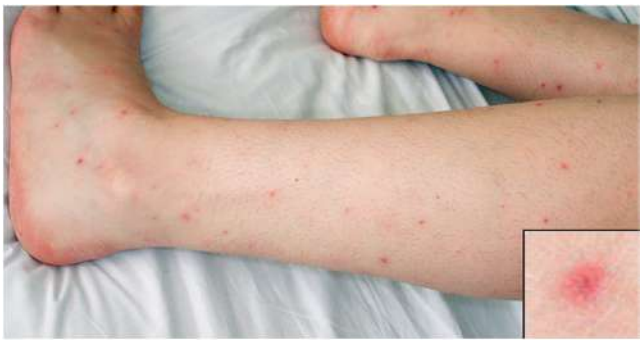

Fig. 237.4 Rash of chronic meningococcemia. *(From Persa OD, Jazmati N, Robinson N, et al. A pregnant woman with chronic meningococcaemia from Neisseria meningitidis with lpxL1-mutations. Lancet. 2014;384:1900.)*

Meningococcal meningitis is indistinguishable from meningitis caused by other bacteria. Nonspecific symptoms and signs (see Table 237.1), including fever and headache, predominate, especially in the young and early in the illness. Children <5 years old rarely report headache. More specific symptoms of photophobia, nuchal rigidity, bulging of the fontanel, and clinical signs of meningeal irritation may develop but are unusual in infants. Seizures and focal neurologic signs occur less frequently than in patients with meningitis caused by *Streptococcus pneumoniae* or *Haemophilus influenzae*. A meningoencephalitis-like picture can occur, associated with rapidly progressive cerebral edema and death from increased ICP, which may be more common with capsular group A infection.

Occult meningococcal bacteremia manifests as fever with or without associated symptoms that suggest a minor viral infection. Resolution of bacteremia may occur without antibiotics, but sustained bacteremia leads to meningitis in approximately 60% of cases and to distant infection of other tissues.

Chronic meningococcemia, which occurs rarely, is characterized by fever, nontoxic appearance, arthralgia, headache, splenomegaly, and a maculopapular or petechial rash (Fig. 237.4). Symptoms are intermittent, with a mean duration of illness of 6-8 weeks. Blood culture results are usually positive, but cultures may initially be sterile. Chronic meningococcemia may spontaneously resolve, but meningitis may develop in untreated cases. Some cases have been associated with complement deficiency and others with sulfonamide therapy. One report indicates that up to 47% of isolates from patients with chronic meningococcemia (vs <10% in acute cases) have a pathogenic variant in the *lpxl1* gene, leading to a reduced inflammatory response and a milder course of infection.

DIAGNOSIS

The initial diagnosis of meningococcal disease should be made on clinical assessment to avoid delay in implementation of appropriate therapy. Laboratory findings are variable but may include leukocytopenia or leukocytosis, often with increased percentages of neutrophils and band forms, and anemia, thrombocytopenia, proteinuria, and hematuria. Elevations of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may occur, but in patients with rapid onset of disease, these values may be within normal limits at presentation. Increased CRP in the presence of fever and petechiae makes the diagnosis likely. Hypoalbuminemia, hypocalcemia, hypokalemia, hypomagnesemia, hypophosphatemia, hypoglycemia, and metabolic acidosis, often with increased lactate levels, are common in patients with meningococcal septicemia. Patients with coagulopathy have decreased serum concentrations of prothrombin and fibrinogen and prolonged coagulation times.

A confirmed diagnosis of meningococcal disease is established by isolation of *N. meningitidis* from a normally sterile body fluid such as blood, CSF, or synovial fluid. Meningococci may be identified in a Gram stain preparation and/or culture of petechial or purpuric skin lesions, although this procedure is rarely undertaken, and occasionally are seen on Gram stain of the buffy coat layer of a centrifuged blood sample. Although blood culture may be positive in more than two thirds of cases before antibiotic use, culture results often are negative if the patient has been treated with antibiotics before collection of the culture specimen; data suggest that <50% are culture positive. Isolation of the organism from the nasopharynx is not diagnostic of invasive disease because the organism is a common commensal.

PCR using primers specific for meningococcal genes (e.g., *ctrA*) has high sensitivity and specificity for detection of meningococci using whole blood samples and has increased confirmation of suspected cases by >40% in the United Kingdom.

Lumbar puncture should be undertaken to establish a diagnosis of meningococcal meningitis in patients without contraindications, including presence of septic shock, coagulopathy, thrombocytopenia, respiratory distress, seizures, increased ICP, or local infection. In patients with meningococcal meningitis, the cellular and chemical characteristics of the CSF are those of acute bacterial meningitis, showing gram-negative diplococci in up to 75% of cases. CSF culture results may be positive in patients with meningococcemia in the absence of CSF pleocytosis or clinical evidence of meningitis; conversely, positive CSF specimens that are gram positive are sometimes culture negative. Overdecolorized pneumococci in Gram stain preparations can be mistaken for meningococci, and therefore empirical therapy should not be narrowed to *N. meningitidis* infection on the basis of Gram stain findings alone.

Detection of capsular polysaccharide antigens using rapid latex agglutination tests on CSF can support the diagnosis in cases clinically consistent with meningococcal disease, but the tests have not performed adequately in clinical practice (poor sensitivity and cross-reactivity of capsular group B test with *Escherichia coli* K1 antigen) and have been replaced by molecular diagnostic methods. Urine antigen testing is insensitive and should not be used. PCR-based assays for detection of meningococci in blood and CSF have been developed, and multiplex PCR assays that detect several bacterial species associated with meningitis, including the meningococcus, are used in some laboratories.

Differential Diagnosis

Meningococcal disease can appear similar to sepsis or meningitis caused by many other gram-negative bacteria, *S. pneumoniae, Staphylococcus aureus,* or group A streptococcus; to Rocky Mountain spotted fever, ehrlichiosis, or epidemic typhus; and to bacterial endocarditis. Viral and other infectious etiologies of meningoencephalitis should be considered in some cases.

Petechial **rashes** are common in viral infections (enteroviruses, influenza and other respiratory viruses, measles virus, Epstein-Barr virus, cytomegalovirus, parvovirus) and may be confused with meningococcal disease. Petechial or purpuric rashes are also associated with protein C or protein S deficiency, platelet disorders (including idiopathic thrombocytopenic purpura), Henoch-Schönlein purpura, connective tissue disorders, drug eruptions, and trauma, including nonaccidental injury. The nonpetechial, blanching maculopapular rash observed in some cases of meningococcal disease, especially early in the course, may initially be confused with a viral exanthem.

TREATMENT

Antibiotics

Empirical antimicrobial therapy should be initiated immediately after the diagnosis of invasive meningococcal infection is suspected and cultures are obtained, using a **third-generation cephalosporin** to cover the most likely bacterial pathogens until the diagnosis is confirmed. In regions with a high rate of β-lactam–resistant *S. pneumoniae,* empirical *addition* of intravenous (IV) **vancomycin** is recommended (see Chapter 643.1) while awaiting the outcome of bacterial identification and sensitivity, but this is unnecessary in other settings where cephalosporin resistance of pneumococci is very rare (in these settings a risk assessment of each case should be made). Once the diagnosis of β-lactam–sensitive meningococcal disease is confirmed in the laboratory, some authorities recommend a switch to penicillin. Even with no evidence that survival outcomes are different, however, limited evidence from one study indicates that in meningococcal purpura, necrotic skin lesions are less common among children treated with ceftriaxone than with penicillin. Furthermore, it may be cost-effective to use a once-daily dose of ceftriaxone for therapy in younger children, and this is the recommended practice in the United Kingdom (Table 237.2). No adequate studies have investigated the optimal duration of therapy for children, but the course is generally continued for 5-7 days.

Early treatment of meningococcal infections may prevent serious sequelae, but timely early diagnosis is often difficult in the absence of petechial or purpuric skin findings. Among children presenting with petechial rashes, 1–10% may have underlying meningococcal disease, and protocols have been established to ensure that these patients are identified without exposing the >90% of cases without meningococcal disease to unnecessary parenteral antibiotic therapy (Fig. 237.5).

Isolates of *N. meningitidis* with decreased susceptibility to penicillin (minimal inhibitory concentration of penicillin of 0.1-1.0 mg/mL) have been reported from Europe, Africa, Canada, and the United States (4% of isolates in 2006). Decreased susceptibility is caused at least in part by altered penicillin-binding protein 2 and does not appear to adversely affect the response to therapy. Isolates with reduced susceptibility to third-generation cephalosporins have been described in France, but the level of reduced susceptibility is not likely to affect therapeutic outcomes where these agents are used for treatment.

Supportive Care

Most children with meningococcal disease can be managed with antibiotics and simple supportive care and will improve rapidly. However, with an overall 5–10% case fatality rate, the priority in initiating management of children presenting with meningococcal disease is identification of the life-threatening features of the disease: shock and increased ICP. Delayed initiation of supportive therapy is associated with poor outcome, and protocols have therefore been established to aid clinicians in a step-by-step approach (http://www.meningitis.org). In all children presenting with meningococcal disease, assessment of the airway should be performed, because the airway could be compromised as a result of a depressed level of consciousness (elevated ICP in meningitis or poor cerebral perfusion in shock). In patients with meningococcal septicemia, supplementary oxygen should be used to treat hypoxia, which is caused by pulmonary edema (from capillary leak), and some patients will require endotracheal intubation. Hypovolemia requires both volume

Table 237.2 Treatment of *Neisseria meningitidis* Invasive Infections Beyond the Newborn Period

DRUG	ROUTE	DOSE	DOSING INTERVAL (hr)	MAXIMUM DAILY DOSE	NOTES
Penicillin G	IM or IV	300,000-400,000 units/kg/day	4-6 (4-hourly for meningitis)	12-24 million units	Does not clear carriage, and "prophylaxis" is required at the end of treatment
Ampicillin	IM or IV	200-400 mg/kg/day	4-6 (4-hourly for meningitis)	8 g	Does not clear carriage, and "prophylaxis" is required at the end of treatment
Cefotaxime‡	IM or IV	180-225 mg/kg/day	6-8 (6-hourly for meningitis)	8-12 g	Recommended in the neonate
Ceftriaxone	IM or IV	75-100 mg/kg/day	12-24	2-4 g	Preferred treatment as only once or twice daily, and may reduce skin complications
ALTERNATIVE THERAPY IN THE FACE OF LIFE-THREATENING β-LACTAM ALLERGY					
Chloramphenicol*	IV	50-100 mg/kg/day	6	2-4 g	Adjust based on target serum concentrations (15-25 mg/L)
Meropenem†	IV	60-120 mg/kg/day	8	3-6 g	

*Monitor blood levels to avoid toxicity.
†Rate of cross-reactivity in penicillin-allergic adults is 2–3%.
‡May not be available due to manufacturing issues.
IM, Intramuscular; IV, intravenous.

replacement and inotropic support to maintain cardiac output. Because ongoing fluid resuscitation may lead to pulmonary edema, endotracheal intubation and ventilation should be initiated in a patient who remains in compensated shock after 40 mL/kg of fluid resuscitation to improve oxygenation and reduce work of breathing. Aggressive fluid resuscitation with unbuffered electrolyte solutions in febrile African children led to increased mortality; similar studies in industrialized settings are required. Metabolic and hematologic abnormalities are common in meningococcal septicemia, and protocols recommend anticipation, assessment, and correction of glucose, potassium, calcium, magnesium, phosphate, clotting factors, and anemia.

Children with meningococcal meningitis should be cautiously managed with maintenance fluids (fluid restriction is not recommended and may be harmful), and those with increased ICP should be managed with close attention to maneuvers to maintain normal cerebral perfusion. If there is shock in the presence of elevated ICP, the shock should be carefully corrected to ensure that cerebral perfusion pressure is maintained.

Many adjunctive therapies have been attempted in patients with severe meningococcal septicemia, but few have been subjected to randomized controlled trials (RCTs). Data are insufficient to recommend the use of anticoagulant or fibrinolytic agents, extracorporeal membrane oxygenation, plasmapheresis, or hyperbaric oxygen. In well-designed clinical trials, an antibody directed against endotoxin (HA1A) did not confer any benefit in children with meningococcal disease, and although initially promising in adult sepsis, activated protein C was not useful in pediatric sepsis and was associated with an increased risk of bleeding. Recombinant bactericidal permeability increasing protein was studied in an underpowered (survival endpoint) trial and showed some potentially beneficial effects against secondary end-points (amputations, transfusions, functional outcome) and requires further investigation.

Although the benefits of **corticosteroids** for adjunctive therapy in pediatric *bacterial* meningitis caused by *H. influenzae* type b (Hib) are accepted, no pediatric data specifically demonstrate benefit in *meningococcal* meningitis. However, some authorities extrapolate from animal data, from experience with Hib, and from compelling data from adult meningitis and recommend corticosteroids as adjunctive therapy in pediatric meningococcal meningitis, given with or soon after the first dose of antibiotics. Therapeutic doses of corticosteroids should not be used routinely in meningococcal septicemia. Some intensivists recommend replacement doses of corticosteroids in patients with treatment-refractory septic shock, because severe sepsis caused by meningococcus is associated with adrenal insufficiency resulting from adrenal necrosis or hemorrhage (Waterhouse-Friderichsen syndrome).

COMPLICATIONS

Adrenal hemorrhage, endophthalmitis, arthritis, endocarditis, pericarditis, myocarditis, pneumonia, lung abscess, peritonitis, and renal infarcts can occur during acute infection. Renal insufficiency requiring dialysis may result from prerenal failure. Reactivation of latent herpes simplex virus infections is common during meningococcal infection.

A self-limiting immune complex vasculitis may occur, usually in the first 10 days after onset of the disease, resulting in various manifestations, including fever, rash, arthritis, and rarely, iritis, pericarditis, or carditis. The arthritis is monoarticular or oligoarticular, involves large joints, and is associated with sterile effusions that respond to nonsteroidal antiinflammatory drugs. Because most patients with meningococcal meningitis become afebrile by the seventh hospital day, persistence or recrudescence of fever after 5 days of antibiotics warrants evaluation for immune complex–mediated complications.

The most common complication of acute severe meningococcal septicemia is focal skin infarction, which typically affects the lower limbs and can lead to substantial scarring and require skin grafting. Distal tissue necrosis in purpura fulminans may require amputation (which should be delayed to allow demarcation) in approximately 2% of survivors. Avascular necrosis of epiphyses and epiphyseal-metaphyseal defects can result from the generalized DIC and may lead to growth disturbance and late skeletal deformities.

Deafness is the most frequent neurologic sequela of meningitis, occurring in 5–10% of children. Cerebral arterial or venous thrombosis with resultant cerebral infarction can occur in severe cases. Meningococcal meningitis is rarely complicated by subdural effusion or empyema or by brain abscess. Other rare neurologic sequelae include ataxia, seizures, blindness, cranial nerve palsies, hemiparesis or quadriparesis, and obstructive hydrocephalus (manifests 3-4 weeks after the onset of illness). Behavioral and psychosocial complications of the disease are frequently reported.

PROGNOSIS

The case fatality rate for invasive meningococcal disease is 5–10%, with clear differences related to age of the patient and meningococcal genotype. Most deaths occur within 48 hours of hospitalization in children with meningococcemia. Poor prognostic factors on presentation include hypothermia or extreme hyperpyrexia, hypotension or shock, purpura fulminans, seizures, leukopenia, thrombocytopenia (including DIC), acidosis, and high circulating levels of endotoxin and TNF-α. The presence of petechiae for <12 hours before admission, absence of meningitis, and low or normal ESR indicate rapid, fulminant progression and a poorer prognosis.

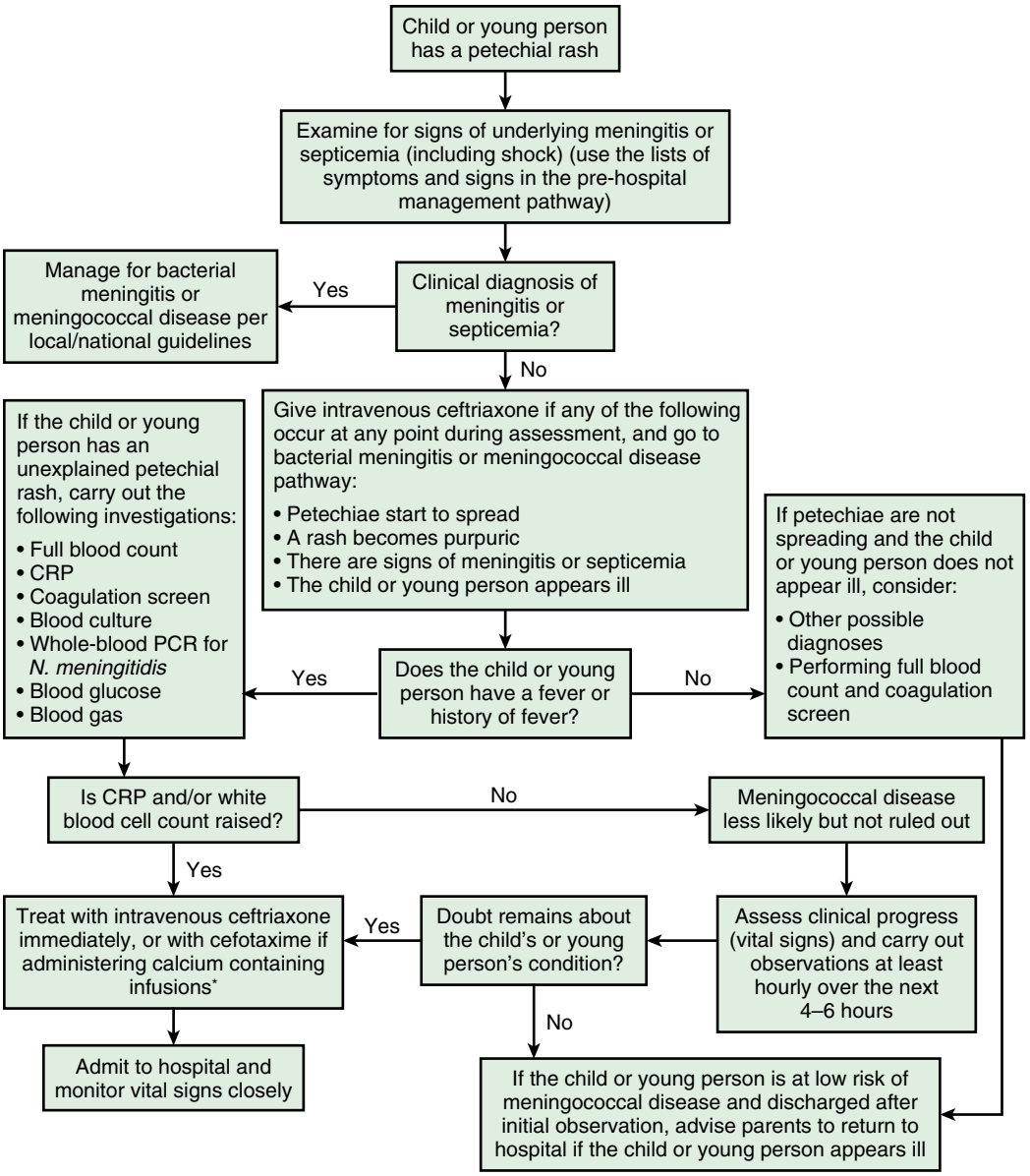

Fig. 237.5 Treatment algorithm for petechial rash. *See Medicines and Healthcare Products Regulatory Agency Drug Safety Update, 2009;3(3). Available from www.mhra.gov.uk. CRP, C-reactive protein; PCR, polymerase chain reaction. *(Data from National Collaborating Center for Women's and Children's Health (UK). Bacterial meningitis and meningococcal septicaemia: management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care. NICE Clinical Guidelines, No 102. London: RCOG Press; 2010.)*

Because complement deficiency is rare in patients with capsular group B infection, screening is unlikely to be useful in detecting cases caused by this group, but some authorities recommend routine screening in these cases. However, with one third or more of cases of disease caused by groups X, Y, and W apparently associated with complement deficiency, it is clearly appropriate to screen after infection with non-B capsular groups.

PREVENTION

Secondary Prevention

Close contacts of patients with meningococcal disease are at increased risk of infection because such individuals are likely to be colonized with the index case's (hyperinvasive) strain. Antibiotic prophylaxis should be offered as soon as possible to individuals who have been exposed directly to a patient's oral secretions, for whom the risk may be 1,000 times the background rate in the population. This includes household, kissing, and close family contacts of cases, as well as child-care and recent preschool contacts in the United States. Up to 30% of cases occur in the first week, but the risk persists for up to 1 year after presentation of the index case. Although prophylaxis is effective in preventing secondary cases, coprimary cases may occur in the days after presentation of the index case, and contacts should be carefully evaluated if they develop symptoms. Advice on management of nonclose contacts, such as those in daycare, nursery settings, or school and other institutions, varies in different countries because the risk of a secondary case in this situation is low and opinion on risk assessment varies. **Ceftriaxone**, **ciprofloxacin**, and **rifampin** are 90–95% effective in reducing nasopharyngeal carriage of *N. meningitidis* and are acceptable agents for prophylaxis, with ciprofloxacin the drug of choice in some countries (Table 237.3). **Azithromycin** should not be used as the first-line choice for prophylaxis but is recommended in the rare instance of ciprofloxacin resistance. Prophylaxis is not routinely recommended for medical personnel except those with exposure to aerosols of respiratory secretions, such as through mouth-to-mouth resuscitation, intubation, or suctioning before or in the 24 hours after antibiotic therapy is initiated in the index case.

Neither penicillin nor ampicillin treatment eradicates nasopharyngeal carriage and should not be routinely used for prophylaxis. Patients with meningococcal infection treated solely with penicillin or ampicillin are therefore at risk of relapse or transmission to a close contact and should receive antimicrobial prophylaxis with one of the agents listed in Table 237.3 before hospital discharge. The preference is to use ceftriaxone for *treatment* of the index case, in which case further prophylaxis is not required. Droplet infection control precautions should be observed for hospitalized patients for 24 hours after initiation of effective therapy. All confirmed or probable cases of meningococcal infection must be reported to the local public health department according to national or regional regulations.

Table 237.3 Antibiotic Prophylaxis to Prevent *Neisseria meningitidis* Infection*

AGE-GROUP	DOSE	DURATION	EFFICACY
RIFAMPIN†			
Infants <1 mo¶	5 mg/kg PO every 12 hr	2 days (4 doses)	
Children ≥1 mo and adults	15-20 mg/kg PO every 12 hr (max 600 mg)	2 days (4 doses)	90–95%
CEFTRIAXONE			
Children <15 yr	125 mg IM	1 dose	90–95%
Children ≥15 yr and adults	250 mg IM	1 dose	90–95%
CIPROFLOXACIN			
Children ≥1 mo and adults†,‡	20 mg/kg (max 500 mg) PO	1 dose	90–95%
AZITHROMYCIN (NOT RECOMMENDED ROUTINELY)			
All ages	10 mg/kg (max 500 g) PO	1 dose	90%

*Recommended for household and kissing contacts. In the United States, chemoprophylaxis is recommended for:
- Household contact, especially children <2 yr old
- Childcare or preschool contact at any time during 7 days before onset of illness
- Direct exposure to index patient's secretions through kissing, sharing toothbrushes, or eating utensils at any time during 7 days before onset of illness
- Mouth-to-mouth resuscitation, unprotected contact during endotracheal intubation during 7 days before onset of illness
- Frequently slept in same dwelling as index patient during 7 days before onset of illness
- Passengers seated directly next to the index case during airline flights lasting more than 8 hours (gate to gate), or passengers seated within one seat in any direction from an index case on a flight of any duration if the index case was coughing or vomiting during the flight
- Always check with current local public health guidance for full recommendations

†Not recommended for pregnant women (ceftriaxone is agent of choice in this setting).
‡Use only if fluoroquinolone-resistant strains of *N. meningitidis* have not been identified in the community.
¶Discussion with an expert is recommended for treatment in infants age <1 mo.
IM, Intramuscularly; PO, orally (by mouth).

Close contacts of cases could also be immunized to further reduce the risk of secondary infection, as described later.

Vaccination

Meningococcal plain *polysaccharide vaccines* containing capsular polysaccharides from capsular groups A + C or capsular groups A, C, W, and Y have been available since the 1960s and used in the control of outbreaks and epidemics and for high-risk groups. However, polysaccharide vaccines are poorly immunogenic in infants, do not induce immunologic memory, and are associated with *immunologic hyporesponsiveness* (reduced response to future doses of polysaccharide). Plain polysaccharide vaccines have been superseded by meningococcal protein-polysaccharide *conjugate vaccines,* which are generally more immunogenic than plain polysaccharides, are immunogenic from early infancy, induce immunologic memory, and are not associated with hyporesponsiveness. The conjugate vaccines contain meningococcal polysaccharides that are chemically conjugated to a carrier protein. Three carrier proteins are used in various meningococcal conjugate vaccines: tetanus toxoid, diphtheria toxoid, and the mutant diphtheria toxin CRM197. However, although plain polysaccharide vaccines should be considered redundant in most industrialized countries where the new-generation conjugates are available, they may still have a role in some regions where conjugates are not yet available.

The first meningococcal conjugate vaccine used was a monovalent capsular group C meningococcal conjugate vaccine **(MenC)**, introduced in the United Kingdom in 1999 and administered to all children and young people <19 years old in a mass catch-up campaign before establishment in the routine infant immunization schedule. The MenC vaccine has proved highly effective (>95%) in controlling disease through both direct protection of the vaccinated population and induction of herd immunity, protecting the wider population. *Herd immunity* is induced through the impact of conjugate vaccines on colonization, reducing carriage and blocking transmission of meningococci among adolescents and young adults. Monovalent MenC vaccines are used widely in the industrialized countries of Western Europe, Canada, and Australia, where disease caused by capsular group C meningococci has virtually disappeared. However, serologic surveys show that antibody levels wane, especially after infant immunization, and booster doses are now recommended during adolescence to sustain individual and population immunity.

Quadrivalent meningococcal A, C, Y, and W conjugate vaccines **(MenACWY)** have been available since 2005 and are routinely used for U.S. adolescents and as a single adolescent booster dose in some countries that had established MenC infant programs more than a decade ago. MenACWY was initially introduced as a single dose at 11 years of age in the United States, but concerns about waning immunity led to the adoption of a second dose. The initial reports on the effectiveness (>80%) of MenACWY in the U.S. program indicates that these vaccines are likely to provide control of disease caused by capsular groups C, W, and Y (capsular group A being unimportant currently), although the program has taken some time to become fully established. As the population of immunized adolescents and young adults in the United States grows, the effects of these vaccines on carriage of meningococci likely will reduce disease among other segments of the population through herd immunity, assuming the transmission dynamics of Y and W meningococci are the same as for capsular group C. Although MenACWY vaccines are not currently recommended in the United States for routine use in younger age-groups in view of the low rate of disease caused by these capsular groups in infancy, they may provide broader protection in countries that are already using MenC vaccines in infant programs. Other combination vaccines containing various conjugates, including Hib-MenC (used in the United Kingdom as a 12-month booster) and Hib-MenCY, may have a role in broadening protection beyond MenC in early life. Table 237.4 outlines the current U.S. programmatic recommendations.

Individuals of any age at high risk of meningococcal disease, such as those with complement deficiency, and travelers to regions where there is a risk of epidemic meningococcal disease caused by A or W should receive MenACWY (see Table 237.4). The risk of disease among close contacts of cases of disease caused by vaccine capsular groups may be further reduced if they are offered MenACWY in addition to antimicrobial prophylaxis. A possible association between MenACWY-diphtheria toxoid and Guillain-Barré syndrome, which caused concern early after the vaccine was first used in the United States, has not been substantiated.

A capsular group A meningococcal conjugate vaccine **(MenA)** has been developed for use in the sub-Saharan African meningitis belt, and implementation in 2010 through mass vaccination appears to have interrupted disease caused by this capsular group.

The majority of disease in infants and in most industrialized countries is caused by capsular *group B polysaccharide–bearing meningococci*. This polysaccharide capsule has chemical identity with glycosylated protein antigens in the human fetus and, as a "self" antigen, is therefore not immunogenic in humans and leads to the theoretical risk of induction of autoimmunity. Vaccine development has therefore focused on subcapsular protein antigens. Several countries (e.g., Cuba, Norway, New Zealand) successfully controlled capsular group B epidemics by immunizing with tailor-made outer membrane vesicle vaccines

Table 237.4 Recommendations for Meningococcal Vaccination (United States, 2021)

GENERAL POPULATION			
2-23 MO	**2-10 YR**	**11-23 YR**	**≥24 YR**
Not routinely recommended	Not routinely recommended	A single dose of MenACWY conjugate vaccine at age 11-12 yr with a booster dose at age 16 yr MenB series may be offered at age 16-23 yr on basis of shared clinical decision-making (2 doses of MenB-FHbp or 4CMenB)	Not routinely recommended

SPECIAL POPULATIONS AT INCREASED RISK OF MENINGOCOCCAL DISEASE			
RISK FACTOR	**2-23 MO**	**2-9 YR**	**≥10 YR**
Persistent complement deficiencies (including patients using a complement inhibitor), functional or anatomic asplenia	4 doses of MenACWY conjugate vaccine at 2, 4, 6, and 12 mo*; if commencing at age 7-23 mo, 2 doses of MenACWY conjugate vaccine, with second dose administered at age ≥12 mo and ≥12 wk after first dose	2 doses of MenACWY conjugate vaccine at least 8 wk apart*	2 doses of MenACWY conjugate vaccine at least 8 wk apart* *and* MenB vaccine (2 doses of 4CMenB or 3 doses of MenB-Hbp) †
At risk during a community outbreak with a vaccine capsular group covered by the relevant vaccine	4 doses of MenACWY conjugate vaccine at 2, 4, 6, and 12 mo*; if commencing at age 7-23 mo, 2 doses of MenACWY conjugate vaccine, with second dose administered at age ≥12 mo and ≥12 weeks after first dose	2 doses of MenACWY conjugate vaccine at least 8 wk apart*	2 doses of MenACWY conjugate vaccine at least 8 wk apart* *or* MenB vaccine (2 doses of 4CMenB or 3 doses of MenB-FHbp) † depending on the capsular group of the outbreak
Travel to or resident of countries where meningococcal disease is hyperendemic or epidemic‡	4 doses of MenACWY conjugate vaccine at 2, 4, 6, and 12 mo*; if commencing at age 7-23 mo, 2 doses of MenACWY conjugate vaccine, with second dose administered at age ≥12 mo and ≥12 weeks after first dose	2 doses of MenACWY conjugate vaccine at least 8 wk apart*	2 doses of MenACWY conjugate vaccine at least 8 wk apart*
Persons with HIV infection	4 doses of MenACWY conjugate vaccine at 2, 4, 6, and 12 mo*; if commencing at age 7-23 mo, 2 doses of MenACWY conjugate vaccine, with second dose administered at age ≥12 mo and ≥12 weeks after first dose	2 doses of MenACWY conjugate vaccine at least 8 wk apart*	2 doses of MenACWY conjugate vaccine at least 8 wk apart*

*Booster every 5 yr if ongoing risk (after 3 yr if <7 yr old).
†Boosters 1 yr after primary series and every 2-3 yr thereafter if remains at increased risk.
‡For example, visitors to the "meningitis belt" of sub-Saharan Africa. Vaccination also is required by the government of Saudi Arabia for all travelers to Mecca during the annual Hajj.
Note that different MenACWY conjugate vaccines are interchangeable, but different MenB vaccines (4CMenB and MenB-FHbp) are not interchangeable
Adapted from https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/mening.html

prepared from blebs of outer membrane harvested from the respective epidemic strains. The principal limitation of outer membrane vesicle vaccines is that the bactericidal antibody responses induced by immunization are limited to the vaccine strain, because the response is largely directed against the homologous PorA (serosubtype) protein, and they are therefore not considered for use in endemic settings, including the United States or most other industrialized countries.

Promising approaches for prevention of capsular group B disease have been developed over the past decade. One vaccine that was developed for adolescent immunization was licensed in the United States in 2014 and contains two variants of factor H–binding protein (**2FHbp**; Pfizer vaccines); it appears highly immunogenic in the target population, inducing bactericidal antibodies directed against a panel of strains bearing variants of fHbp. It is currently recommended for use in high-risk groups and during outbreaks (see Table 237.4). Factor H–binding protein appears to be an important virulence determinant, aiding survival of meningococci in blood, and is expressed by virtually all strains.

A four-component meningococcal vaccine, **4CMenB** (Bexsero, GSK Vaccines), is licensed in Europe and North America and available in various other regions. This vaccine contains outer membrane vesicles (derived from the New Zealand outbreak strain) and three recombinant proteins: a single variant of factor H–binding protein (FHbp), neisserial adhesin A (NadA), and neisserial heparin-binding antigen (NHBA). 4CMenB vaccine induced bactericidal antibodies against strains containing the vaccine antigens in infants, toddlers, and adolescents in clinical trials. The vaccine appears to have a generally favorable safety profile, although induction of fever in infants and pain at the injection site in other age-groups are common. This vaccine has been used to control university outbreaks of capsular group B meningococcal disease in the United States and Canada and hyperendemic disease in Quebec, Canada. Current recommendations for use in the United States are outlined in Table 237.4. It was recommended for routine use in the infant immunization program in the United Kingdom in 2014 and deployed from September 2015. Early data reported a 75% reduction in age-groups that were fully eligible for vaccination, with a high coverage rate of 95% (a nonsignificant vaccine effectiveness of 53% after two doses and 59% after a booster dose at 1 year of age). A large cluster randomized trial in Australia found no effect of 4CMenB on carriage of disease-causing meningococci, highlighting that the benefit of this vaccine is likely to be via direct protection.

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Chapter 238

Neisseria gonorrhoeae (Gonococcus)

Katherine Hsu, Sanjay Ram, and Toni Darville

Neisseria gonorrhoeae is the causative agent of **gonorrhea**, an infection of the genitourinary tract mucous membranes and of the mucosa of the rectum, oropharynx, and conjunctiva. Among sexually transmissible infections, gonorrhea transmitted by sexual contact or perinatally is second only to chlamydial infections in the number of cases reported to the U.S. Centers for Disease Control and Prevention (CDC). This high prevalence and the development of antibiotic-resistant strains have led to significant morbidity.

ETIOLOGY

N. gonorrhoeae is a nonmotile, aerobic, non–spore-forming, gram-negative diplococcus with flattened adjacent surfaces. Optimal growth occurs at 35–37°C (95–98.6°F) and at pH 7.2-7.6 in an atmosphere of 3–5% carbon dioxide. The specimen should be inoculated quickly onto fresh, moist, modified Thayer-Martin or specialized transport media, because gonococci do not tolerate drying. Thayer-Martin selective medium contains antimicrobial agents that inhibit the normal flora present in clinical specimens from mucosal sites that may otherwise overgrow gonococci. Presumptive identification may be based on colony appearance, Gram stain, and production of cytochrome oxidase. Gonococci are differentiated from other *Neisseria* spp. by the fermentation of glucose but not maltose, sucrose, or lactose. Gram-negative diplococci are seen in infected material, often within polymorphonuclear leukocytes (PMNs).

As with all gram-negative bacteria, *N. gonorrhoeae* possesses a cell envelope composed of an inner cytoplasmic membrane, a middle layer of peptidoglycan, and an outer membrane. The outer membrane contains **lipooligosaccharide** (**LOS**; also called **endotoxin**), phospholipid, and a variety of proteins that contribute to cell adherence, tissue invasion, and resistance to host defenses. Systems previously used to characterize gonococcal strains included auxotyping and serotyping. **Auxotyping** is based on genetically stable requirements of strains for specific nutrients or cofactors as defined by an isolate's ability to grow on chemically defined media. **Serotyping** systems were based on specific monoclonal antibodies directed against a porin protein called **PorB** (formerly *Protein I* or *PorI*), a trimeric outer membrane protein that makes up a substantial part of the gonococcal envelope structure. Changes in the PorB protein present in a community are believed to result, at least in part, from selective immune pressure. DNA-based typing methods have now supplanted auxotyping and serotyping. Older gel-based DNA-based typing methods that included restriction fragment length polymorphism (RFLP) analysis of genomic DNA or rRNA (ribotyping) or typing of genes encoding opacity protein *(opa)* were labor intensive and sometimes lacked the ability to accurately discriminate among strains. Methods currently used include the *N. gonorrhoeae* multiantigen sequence typing **(NG-MAST)**, which examines the sequences of the variable internal fragments of two highly polymorphic *N. gonorrhoeae* genes (*porB* encoding PorB and *tbpB* encoding subunit B of transferrin-binding protein), multilocus sequence typing (**MLST**), which analyzes the sequences of seven chromosomal housekeeping genes, and whole genome sequencing.

EPIDEMIOLOGY

Since gonorrhea became a nationally notifiable disease in 1944, U.S. rates have ranged between a historic high of 467.7 cases per 100,000 population in 1975 and a historic low of 98.1 per 100,000 in 2009. However, rates of gonorrhea have increased almost every year since 2009 (with an overall increase of 118% between 2009 and 2021), with a total of 710,151 cases and a rate of 214.0/100,000 reported in 2021. Rates of reported gonorrhea are also highest in the South (242.9/100,000); among young adults age 20-24 (860.5 cases per 100,000); among males (249.7/100,000 vs 177.9/100,000 among females); and among Blacks (652.9/100,000 vs 78.9/100,000 among Whites). The higher case rate among men and the magnitude of recent increases suggest either increased transmission, increased case ascertainment (e.g., through increased extragenital screening among men who have sex with men [MSM]), or both. The concurrent increase in cases reported among women suggests parallel increases in heterosexual transmission, increased screening among women, or both.

Molecular typing methods (e.g., NG-MAST, MLST) are used to analyze the spread of individual strains of *N. gonorrhoeae* within a community. Maintenance and subsequent spread of gonococcal infections in a community are sustained through continued transmission by asymptomatically infected people and also by a **hyperendemic**, **high-risk** core group such as commercial sex workers, MSM, or adolescents with multiple sexual partners. This latter observation reflects that most persons who have symptomatic gonorrhea cease sexual activity and seek care, unless economic need or other factors (e.g., drug addiction) drive persistent sexual activity. Thus many core transmitters belong to a subset of infected persons who lack or ignore symptoms and continue to be sexually active, underscoring the importance of seeking out and treating the sexual contacts of infected persons who present for treatment. **Oral sex** has a role in sustaining gonorrhea in MSM by providing a pool of untreated asymptomatic pharyngeal infections and may account for as much as one third of symptomatic gonococcal urethritis in MSM.

Gonococcal infection of neonates usually results from peripartum exposure to infected exudate from the cervix of the mother. An acute infection begins 2-5 days after birth. The incidence of neonatal infection depends on the prevalence of gonococcal infection among pregnant women, prenatal screening for gonorrhea, and neonatal ophthalmic prophylaxis.

PATHOGENESIS AND PATHOLOGY

N. gonorrhoeae infects primarily columnar epithelium because stratified squamous epithelium is relatively resistant to invasion. Mucosal invasion by gonococci results in a local inflammatory response that produces a purulent exudate consisting of PMNs, serum, and desquamated epithelium. The gonococcal LOS (endotoxin) exhibits direct cytotoxicity, causing ciliostasis and sloughing of ciliated epithelial cells. Tumor necrosis factor (TNF) and other cytokines are thought to mediate the cytotoxicity of gonococcal infections. Complement activation also contributes to the acute inflammatory response.

Gonococci may ascend the urogenital tract, causing urethritis or epididymitis in postpubertal males and acute endometritis, salpingitis, and peritonitis (collectively termed **acute pelvic inflammatory disease** or **PID)** in postpubertal females. Dissemination from the fallopian tubes through the peritoneum to the liver capsule results in **perihepatitis** (Fitz-Hugh–Curtis syndrome). Gonococci that invade the lymphatics and blood vessels may cause inguinal lymphadenopathy; perineal, perianal, ischiorectal, and periprostatic abscesses; and **disseminated gonococcal infection** (DGI).

A number of gonococcal virulence and host immune factors are involved in the penetration of the mucosal barrier and subsequent manifestations of local and systemic infection. Selective pressure from different mucosal environments probably leads to changes in the outer membrane of the organism, including expression of variants of pili, opacity (Opa) proteins (formerly called *protein II*), and LOS. These changes may enhance gonococcal attachment, invasion, replication, and evasion of the host's immune response.

For infection to occur, the gonococcus must first attach to host cells. Gonococci adhere to the microvilli of nonciliated epithelial cells by hairlike protein structures (pili) that extend from the cell wall. Pili undergo high-frequency antigenic variation that may aid in

the organism's escape from the host immune response and may provide specific ligands for different cell receptors. Opa proteins, most of which confer an opaque appearance to colonies, function as ligands for members of the carcinoembryonic antigen–related cell adhesion molecule **(CEACAM)** family of proteins or heparin sulfate proteoglycans (HSPGs) to facilitate binding to human cells. Interactions between complement receptor 3 (CR3) on cervical epithelial cells and complement iC3b (deposited on bacteria), pili, and PorB on the gonococcal surface facilitate cellular entry of gonococci in women. In contrast, the interaction between LOS and asialoglycoprotein receptor (ASGP-R) permits gonococcal entry into male urethral epithelial cells. Gonococci that express certain Opa proteins adhere to CEACAM3 and are phagocytosed by human neutrophils in the absence of serum. The interaction of Opa with CEACAM1 on $CD4^+$ T lymphocytes may suppress their activation and proliferation and contribute to the immunosuppression associated with gonorrhea. A gonococcal IgA protease inactivates IgA1 by cleaving the molecule in the hinge region and could contribute to colonization or invasion of host mucosal surfaces.

Other phenotypic changes that occur in response to environmental stresses allow gonococci to establish infection. Examples include iron-repressible proteins such as transferrin-binding proteins (TbpA and TbpB) and lactoferrin-binding proteins (LbpA and LbpB) for binding to and extracting iron from transferrin or lactoferrin, respectively, anaerobically expressed proteins, and proteins that are synthesized in response to contact with epithelial cells. Gonococci may grow in vivo under anaerobic conditions or in an environment with a relative lack of iron.

Approximately 24 hours after attachment, the epithelial cell surface invaginates and surrounds the gonococcus in a phagocytic vacuole. This phenomenon is thought to be mediated by the insertion of the gonococcal PorB protein into the host cell, causing alterations in membrane permeability. Subsequently, phagocytic vacuoles begin releasing gonococci into the subepithelial space by means of exocytosis. Viable organisms may then cause local disease (i.e., salpingitis) or disseminate through the bloodstream or lymphatics.

Serum IgG and IgM directed against gonococcal proteins and LOS activate complement on gonococci. Gonococci have evolved several mechanisms to dampen complement activation. Scavenging cytidine monophospho-*N*-acetyl neuraminic acid (CMP-Neu5Ac, the donor molecule for sialic acid) to sialylate its LOS is one such example, which reduces binding of bactericidal antibodies and simultaneously enhances binding of a complement inhibitor called **factor H** (FH). This property is often lost on subculturing gonococci on medium that lacks CMP-Neu5Ac and is thus termed *unstable serum resistance*. In contrast, *stable serum resistance* (complement resistance independent of LOS sialylation) is often seen in gonococci that express particular porin proteins (most PorB.1As and select PorB.1Bs), which enables them to bind to complement inhibitors such as FH and C4b-binding protein (C4BP). Such strains are often associated with disseminated disease. *N. gonorrhoeae* differentially subverts the effectiveness of complement and alters the inflammatory responses elicited in human infection. Stably serum-resistant DGI isolates show less C3b deposition on their surface, inactivate C3b more rapidly, generate less C5a, and result in less inflammation at local sites. PID isolates (grown in the absence of the donor molecule for sialic acid) are serum sensitive, deposit more C3b on their surface, generate more C5a, and result in more inflammation at local sites. IgG antibody directed against gonococcal reduction-modifiable protein **(Rmp)** blocks complement-mediated killing of *N. gonorrhoeae.* Anti-Rmp blocking antibodies may harbor specificity for outer membrane protein (e.g., OmpA) sequences shared with other *Neisseria* spp. or Enterobacteriaceae, may be directed against a unique Rmp sequence upstream of the OmpA-shared region that includes a cysteine loop, or both. Preexisting antibodies directed against Rmp facilitate transmission of gonococcal infection to exposed women; Rmp is highly conserved in *N. gonorrhoeae,* and the blocking of mucosal defenses may be one of its functions. Gonococcal adaptation also appears to be important in the evasion of killing by neutrophils. Examples include sialylation of LOS, increases in catalase production, and changes in the expression of surface proteins. Neutrophil phagosomes bearing gonococci show delayed fusion with primary granules, promoting gonococcal survival within neutrophils. Other strategies gonococci employ to evade killing by neutrophils include blocking lysozyme activity (mediated by the proteins SliC and adhesin complex protein [ACP]) and degrading neutrophil extracellular traps.

Host factors may influence the incidence and manifestations of gonococcal infection. Prepubertal girls are susceptible to vulvovaginitis and rarely experience salpingitis. *N. gonorrhoeae* infects noncornified epithelium, and the thin noncornified vaginal epithelium and alkaline pH of the vaginal mucin predispose this age-group to infection of the lower genital tract. Estrogen-induced cornification of the vaginal epithelium in neonates and mature females resists infection. Postpubertal females are more susceptible to salpingitis, especially during menses, when diminished bactericidal activity of the cervical mucus and reflux of blood from the uterine cavity into the fallopian tubes facilitate passage of gonococci into the upper reproductive tract.

Populations at risk for DGI include asymptomatic carriers; neonates; menstruating, pregnant, and postpartum women; MSM; and individuals with congenital or acquired (for example, via pharmacologic inhibition) defects in complement. The asymptomatic carrier state implies failure of the host immune system to recognize the gonococcus as a pathogen, the capacity of the gonococcus to avoid being killed, or both. **Pharyngeal colonization** has been proposed as a risk factor for DGI. The high rate of asymptomatic infection in pharyngeal gonorrhea may account for this phenomenon. Women are at greater risk for development of DGI during menstruation, pregnancy, and the postpartum period, presumably because of the maximal endocervical shedding and decreased peroxidase bactericidal activity of the cervical mucus during these periods. A lack of neonatal bactericidal IgM antibody is thought to account for the increased susceptibility of neonates to DGI. Persons with terminal complement component deficiencies (C5-C9) are at considerable risk for development of recurrent episodes of DGI.

CLINICAL MANIFESTATIONS

Gonorrhea is manifested by a spectrum of clinical presentations from asymptomatic carriage, to the characteristic localized mucosal infections, to disseminated systemic infection (see Chapter 163).

Asymptomatic Gonorrhea

The incidence of asymptomatic gonorrhea in children has not been ascertained. Gonococci have been isolated from the oropharynx of young children who have been abused sexually by male contacts; oropharyngeal symptoms are usually absent. Most genital tract infections produce symptoms in children. However, as many as 80% of sexually mature females with urogenital gonorrhea infections are asymptomatic in settings in which most infections are detected through screening or other case-finding efforts. This situation is in contrast to that in men, who are asymptomatic only 10% of the time. Asymptomatic rectal carriage of *N. gonorrhoeae* has been documented in 26–68% of females with urogenital infection. Most persons with positive rectal culture results are asymptomatic. Most pharyngeal gonococcal infections are asymptomatic, although rarely **acute tonsillopharyngitis** or **cervical lymphadenopathy** can occur. Pharyngeal gonorrhea is easily acquired through fellatio and may account for a significant proportion of urethral gonorrhea in MSM. Pharyngeal gonorrhea is increasingly prevalent, particularly among adolescents and young adults, associated with overall increasing prevalence of oral sex behaviors.

Uncomplicated, Localized Gonorrhea

Genital gonorrhea has an incubation period of 2-5 days in men and 5-10 days in women. Primary infection develops in the urethra of males, the vulva and vagina of prepubertal females, and the cervix of postpubertal females. Neonatal ophthalmitis (ophthalmia neonatorum) occurs in both genders.

Urethritis is usually characterized by a purulent discharge and by dysuria without urgency or frequency. Untreated urethritis in males resolves spontaneously in several weeks or may be complicated by epididymitis, penile edema, lymphangitis, prostatitis, or seminal vesiculitis. Gram-negative intracellular diplococci are found in the discharge.

In MSM, the rectal mucosa can become infected after receptive anal intercourse. Symptoms range from painless mucopurulent discharge and scant rectal bleeding to overt proctitis with associated rectal pain and tenesmus.

In prepubertal females, **vulvovaginitis** is usually characterized by a purulent vaginal discharge with a swollen, erythematous, tender, and excoriated vulva. Dysuria may occur. Gonococcal infection should be considered in any girl with vaginal discharge, even when sexual abuse is not suspected; sexual abuse must be considered strongly when gonococcal infection is diagnosed in prepubertal children beyond the neonatal period. In postpubertal females, symptomatic gonococcal **cervicitis** and urethritis are characterized by purulent discharge, suprapubic pain, dysuria, intermenstrual bleeding, and dyspareunia. The cervix may be inflamed and tender. In urogenital gonorrhea limited to the lower genital tract, pain is not enhanced by moving the cervix and the adnexa are not tender to palpation. Purulent material may be expressed from the urethra or ducts of the Bartholin gland. Rectal gonorrhea is often asymptomatic but may cause proctitis with symptoms of anal discharge, pruritus, bleeding, pain, tenesmus, and constipation. Asymptomatic rectal gonorrhea may not be from anal intercourse but may represent translocation of infected secretions from cervicovaginal infection.

Gonococcal **ophthalmitis** may be unilateral or bilateral and may occur in any age-group after inoculation of the eye with infected secretions. **Ophthalmia neonatorum** caused by *N. gonorrhoeae* usually appears from 2-5 days after birth (see Chapter 674). Ocular infection in older patients results from inoculation or autoinoculation from a genital site. The infection begins with mild inflammation and a serosanguineous discharge. Within 24 hours, the discharge becomes thick and purulent and tense edema of the eyelids with marked chemosis occurs. If the disease is not treated promptly, corneal ulceration, rupture, and blindness may follow.

Disseminated Gonococcal Infection

Hematogenous dissemination occurs in 1–3% of all gonococcal infections, more frequently after asymptomatic primary infections than symptomatic infections. Women previously accounted for the majority of cases, with symptoms beginning 7-30 days after infection and within 7 days of menstruation in about one half of cases, but more recent case series describe more male than female cases. The most common manifestations are asymmetric arthralgia, petechial or pustular acral skin lesions, tenosynovitis, suppurative arthritis, and rarely, carditis, meningitis, and osteomyelitis. The most common initial symptom is acute onset of **polyarthralgia with fever**. Only 25% of patients complain of skin lesions. Most deny genitourinary symptoms; however, primary mucosal infection is documented by genitourinary cultures. Results of approximately 80–90% of cervical cultures are positive in women with DGI. In males, urethral culture results are positive in 50–60%, pharyngeal culture results are positive in 10–20%, and rectal culture results are positive in 15% of cases.

DGI is classified into two clinical syndromes that have some overlapping features. The more common **tenosynovitis-dermatitis syndrome** is characterized by fever, chills, skin lesions, and polyarthralgia predominantly involving the wrists, hands, and fingers. Blood culture results are positive in approximately 30–40% of cases, and results of synovial fluid cultures are almost uniformly negative. In **suppurative arthritis syndrome**, systemic symptoms and signs are less prominent and monoarticular arthritis is more common, often involving the knee. A polyarthralgia phase may precede the monoarticular infection. In cases of monoarticular involvement, synovial fluid culture results are positive in approximately 45–55%, and synovial fluid findings are consistent with septic arthritis. Blood culture results are usually negative. DGI in neonates usually occurs as a polyarticular suppurative arthritis.

Dermatologic lesions usually begin as painful, discrete, 1- to 20-mm, pink or red macules that progress to maculopapular, vesicular, bullous, pustular, or petechial lesions. The typical necrotic pustule on an erythematous base is distributed unevenly over the extremities, including the palmar and plantar surfaces, usually sparing the face and scalp. The lesions number between 5 and 40, and 20–30% may contain gonococci. Although immune complexes may be present in DGI, complement levels are normal, and the role of the immune complexes in pathogenesis is uncertain.

Acute endocarditis is an uncommon (1–3%) but often fatal manifestation of DGI that usually leads to rapid destruction of the aortic valve. **Acute pericarditis** is a rarely described entity in patients with disseminated gonorrhea. **Meningitis** with *N. gonorrhoeae* has been documented, and signs and symptoms are similar to those of any acute bacterial meningitis.

DIAGNOSIS

Laboratory confirmation of gonococcal infection is essential, given the legal implications of potential sexual abuse in children and the need to refer sex partners of adolescents and adults for treatment. Given the advent of highly sensitive and specific nucleic acid amplification tests (NAATs), the use of less sensitive, nonamplified test technologies (nucleic acid hybridization/probe tests, nucleic acid genetic transformation tests, or enzyme immunoassays) is no longer justified. Culture and susceptibility testing capability still need to be maintained, because culture is necessary to evaluate suspected cases of gonorrhea treatment failure and to monitor developing resistance to current treatment regimens.

Gram Stain and Culture

Gram stains can be useful in the initial evaluation of patients with suspected gonococcal infection. In males with symptomatic urethritis, a presumptive diagnosis of gonorrhea can be made by identification of gram-negative intracellular diplococci (within PMNs) in the urethral discharge. A similar finding in females is not sufficient because *Mima polymorpha* and *Moraxella,* which are normal vaginal flora, have a similar appearance. The sensitivity of the Gram stain for diagnosing gonococcal cervicitis and asymptomatic infections is also low. The presence of commensal *Neisseria* spp. in the oropharynx prevents the use of the Gram stain for diagnosis of pharyngeal gonorrhea.

Culture can be performed of any site, including nongenital sites. Advantages of culture include the availability of an isolate for further studies, including antibiotic susceptibility testing. Disadvantages of culture include more stringent transport and growth requirements, lower sensitivity than NAATs, and a delay in availability of results. Material for cervical cultures is obtained as follows. After the exocervix is wiped, a swab is placed in the cervical os and rotated gently for several seconds. Male urethral specimens are obtained by placement of a small swab 2-3 cm into the urethra. Rectal swabs are best obtained by passing a swab 2-4 cm into the anal canal; specimens that are heavily contaminated by feces should be discarded. For optimal culture results, specimens should be obtained with noncotton swabs, inoculated directly onto culture plates containing selective media (see later), and incubated immediately. The choice of anatomic sites to culture depends on the sites exposed and the clinical manifestations. If symptoms are present, samples from the urethra and rectum can be cultured for men, and samples from the endocervix and rectum can be cultured for all females, regardless of a history of anal intercourse. A pharyngeal culture specimen should be obtained from both men and women if symptoms of pharyngitis are present with a history of recent oral exposure or oral exposure to a person known to have genital gonorrhea. In a suspected case of **child sexual abuse**, culture or FDA approved NAAT are recommended methods of detection for *N. gonorrhoeae* in genital and extragenital specimens. Culture of the endocervix should not be attempted until after puberty.

Specimens from sites that are normally colonized by other organisms (e.g., cervix, rectum, pharynx) should be inoculated on a selective culture medium, such as modified Thayer-Martin medium (fortified with vancomycin, colistin, nystatin, and trimethoprim to inhibit growth of indigenous flora). Specimens from sites that are normally sterile or minimally contaminated (i.e., synovial fluid, blood, cerebrospinal fluid) should be inoculated on a nonselective chocolate agar medium. If DGI is suspected, blood, pharynx, rectum, urethra, cervix, and synovial fluid (if involved) should be cultured. Cultured specimens should

be incubated promptly at 35–37°C (95–98.6°F) in 3–5% carbon dioxide. When specimens must be transported to a central laboratory for culture plating, a reduced, nonnutrient holding medium (i.e., Amies [modified Stuart] transport medium) preserves specimens with minimal loss of viability for up to 6 hours. When transport may delay culture plating by >6 hours, it is preferable to inoculate the sample directly onto a culture medium and transport it at an ambient temperature in a CO_2-enriched atmosphere. The Transgrow and John E. Martin Biological Environmental Chamber (JEMBEC) systems of modified Thayer-Martin medium are alternative transport systems.

Nucleic Acid Amplification Tests

The U.S. FDA has approved NAATs for use with genital (endocervical, vaginal, male urethral, and female and male first-catch urine) and extragenital (pharyngeal and rectal) specimens. Advantages of using NAATs include less stringent transport conditions, more rapid turnaround time, flexibility in sampling source (providing additional feasibility of testing in settings where a physical exam is not done), and patient preference for less invasive sampling. However, NAATs cannot provide antimicrobial susceptibility results, so in cases of persistent gonococcal infection after treatment, clinicians should perform both culture and antimicrobial susceptibility testing. Although urine specimens are acceptable for women, the sensitivity for screening appears to be lower than with vaginal or endocervical swab samples. In contrast, the sensitivity and specificity of urine and urethral swab specimens from men are similar, so first-catch urine is the recommended sample type for urethral screening in men. Product inserts for each NAAT vendor must be carefully examined to assess current indications and allowable specimens. Some NAAT platforms are now FDA cleared for use with specimens from the rectum and pharynx, facilitating their use for clinical management of extragenital infections (gonorrhea screening of rectal and pharyngeal sites with NAATs is recommended quarterly for some sexually active MSM, e.g., those taking HIV prophylaxis). NAATs have not yet been FDA cleared for specimens from the conjunctiva, joint fluid, blood, or cerebrospinal fluid. Rapid NAATs with shortened turnaround times of 30 minutes and waivers allowing use in point-of-care settings such as physician offices, community clinics, and other outpatient settings have now also been FDA cleared.

Although data regarding NAAT for children are more limited and performance is test-dependent, there is no evidence that performance of FDA-approved NAAT for detection of *N. gonorrhoeae* among children differs from that among adults. In a multicenter study of NAATs using strand displacement amplification or transcription-mediated amplification in children being evaluated for sexual abuse, urine from prepubertal girls was a reliable alternative to vaginal culture for detection for *N. gonorrhoeae*. Consultation with an expert is necessary before using NAAT in this context, both to minimize the possibility of cross-reaction with nongonococcal *Neisseria* species and other commensals (e.g., *N. meningitidis, N. sicca, N. lactamica, N. cinerea,* or *Moraxella catarrhalis*) and to ensure correct interpretation of results. Because of the implications of a diagnosis of *N. gonorrhoeae* infection in a child, only CLIA-validated, FDA-cleared NAATs should be used, and all positive specimens should be retained for additional confirmatory testing.

TREATMENT

All patients who are presumed or proven to have gonorrhea should be evaluated for concurrent syphilis, HIV, and *Chlamydia trachomatis* infection. The incidence of *Chlamydia* co-infection is 15–25% among males and 35–50% among females. Patients beyond the neonatal period should be treated presumptively for *C. trachomatis* infection unless a negative chlamydial NAAT result is documented at the time treatment is initiated for gonorrhea. However, if chlamydial test results are not available or if a non-NAAT result is negative for *Chlamydia,* patients should be treated for both gonorrhea and *Chlamydia* infection (see Chapter 272.2). Persons who receive a diagnosis of gonorrhea should be instructed to abstain from sexual activity for 7 days after treatment and until all sex partners are adequately treated (7 days after receiving treatment and resolution of symptoms, if present). Sexual partners exposed in the preceding 60 days should be examined, specimens collected, and presumptive treatment started.

N. gonorrhoeae has progressively developed resistance to the antibiotics used to treat it. Antimicrobial resistance in *N. gonorrhoeae* occurs as plasmid-mediated resistance to penicillin and tetracycline and chromosomally mediated resistance to penicillins, tetracyclines, spectinomycin, fluoroquinolones, cephalosporins, and azithromycin. Emergence of cephalosporin resistance worldwide has prompted designation of *N. gonorrhoeae* as antibiotic-resistance threat level "Urgent" by the CDC. Surveillance data from the CDC Gonococcal Isolate Surveillance Project reveal concerning fluctuations in minimum inhibitory concentration (MIC) for the oral cephalosporin **cefixime** and the injectable third-generation cephalosporin **ceftriaxone**, leading the CDC to revise its U.S. gonorrhea treatment guidelines in 2012 to dual therapy (usually a combination of ceftriaxone and azithromycin) in an attempt to preserve the last commercially available effective treatment. However, the CDC revised its recommendations in 2020; ceftriaxone is now the only first-line recommended treatment for gonorrhea at all sites. The change from dual therapy to monotherapy was based on (1) increasing concern for antimicrobial stewardship and the potential impact of dual therapy on commensal organisms and concurrent pathogens, (2) new pharmacokinetic and pharmacodynamic data regarding optimal dosing for gonorrhea, and (3) increasing azithromycin resistance (and therefore no optimal second drug to pair with a cephalosporin if dual therapy were the goal).

Table 238.1 summarizes first-line treatment regimens for neonate, child (weight ≤45 kg), adolescent, and adult gonococcal regimens. Mucosal, localized infections are treatable with single doses; disseminated infections are treated for a minimum of 1 week.

Alternative regimens exist for adolescents and adults but are extremely limited. For patients with cephalosporin allergy, the combination of gentamicin (240 mg intramuscularly [IM]) plus azithromycin (2 g orally [PO]) cured 100% of uncomplicated urogenital cases in a trial of U.S. patients age 15-60 years; the combination of gemifloxacin (320 mg PO) (not licensed for use in those <18 years old) plus azithromycin (2 g PO) cured >99% of uncomplicated urogenital cases in the same trial but was limited by 8% of patients vomiting within 1 hour of dual oral drug administration. For patients with azithromycin allergy, doxycycline (100 mg PO twice daily for 7 days) can be used in place of azithromycin as an alternative second antimicrobial. If ceftriaxone is not available, alternative cephalosporins include oral cefixime (800 mg PO), which has limited efficacy for pharyngeal gonorrhea, and other single-dose injectable cephalosporin regimens, such as ceftizoxime (500 mg IM) or cefoxitin (2 g IM) with probenecid (1 g PO), neither of which offers any advantage over ceftriaxone for urogenital infection, and their efficacy against pharyngeal infection is less certain.

Pregnant women with gonococcal infection should be treated with standard adult therapy. If allergy precludes standard treatment, consultation with an infectious disease specialist is recommended. HIV–co-infected patients with gonococcal infection are treated the same as HIV-negative patients.

Follow-up test of cure is not recommended for persons diagnosed with uncomplicated urogenital or rectal gonorrhea receiving recommended or alternative regimens. However, any person with pharyngeal gonorrhea should return 7-14 days after treatment for a test of cure using culture, NAAT, or both, because pharyngeal gonorrhea is more difficult to eradicate. Symptoms persisting after treatment should be evaluated by culture for *N. gonorrhoeae* (with or without simultaneous NAAT), and any gonococci isolated should be tested for antimicrobial susceptibility. **Treatment failure** should be considered in (1) persons whose symptoms do not resolve within 3-5 days after appropriate treatment and who report no sexual contact during posttreatment follow-up and (2) persons with a positive test of cure (i.e., positive culture >72 hours or positive NAAT ≥7 days after receiving recommended treatment) who report no sexual contact during posttreatment follow-up.

COMPLICATIONS

Prompt diagnosis and correct therapy ensure complete recovery from uncomplicated gonococcal disease. Complications of gonorrhea result

Table 238.1 Recommended Treatment of Gonococcal Infections

AGE GROUP	INFECTION	TREATMENT REGIMEN	LENGTH OF THERAPY
Neonates	Ophthalmia neonatorum	Ceftriaxone* 25-50 mg/kg IV or IM *OR* cefotaxime 100 mg/kg IV or IM	Once
	Disseminated infection Scalp abscess Septic arthritis	Ceftriaxone 25-50 mg/kg IV or IM every day *OR* cefotaxime 25-50 mg/kg IV or IM q8–12h†	7 days
	Meningitis	Ceftriaxone 25-50 mg/kg IV or IM every day *OR* cefotaxime 25-50 mg/kg IV or IM q8-12h	10-14 days
	Endocarditis	Ceftriaxone 25-50 mg/kg IV or IM every day *OR* cefotaxime 25-50 mg/kg IV or IM q8-12h	Minimum 28 days
Children ≤45 kg	Pharyngeal infection Anorectal infection Urogenital infection	Ceftriaxone 25-50 mg/kg IV or IM (max 500 mg)	Once
	Conjunctivitis	Ceftriaxone 50 mg/kg IM (max 1 g) plus consider lavage of infected eye with saline solution	Once
	Disseminated infection Septic arthritis	Ceftriaxone 50 mg/kg IV or IM every day (max 1 g daily)	7 days
	Meningitis	Ceftriaxone 50 mg/kg IV or IM q12-24h (max 4 g daily)	10-14 days
	Endocarditis	Ceftriaxone 50 mg/kg IV or IM q12-24h (max 4 g daily)	Minimum 28 days
Adults, adolescents, and children >45 kg	Pharyngeal infection Anorectal infection Urogenital infection	Ceftriaxone 500 mg IM (or 1 g IM for persons ≥150 kg)	Once
	Conjunctivitis	Ceftriaxone 1 g IM plus consider lavage of infected eye with saline solution	Once
	Disseminated infection Septic arthritis	Ceftriaxone 1 g IV or IM every day	7 days
	Meningitis	Ceftriaxone 1-2 g IV q12-24h	10-14 days
	Endocarditis	Ceftriaxone 1-2 g IV q12-24h	Minimum 28 days

*Ceftriaxone should be administered cautiously to neonates with hyperbilirubinemia, especially those born prematurely. Cefotaxime can be administered for those neonates unable to receive ceftriaxone because of simultaneous administration of IV calcium. Consult neonatal dosing references.
†Dose or dosing frequency changes after postnatal age >7 days of life: consult neonatal dosing references.
IM, Intramuscularly; IV, intravenously; max, maximum; PO, orally.
From Wangu Z, Hsu KK. *Neisseria gonorrhoeae.* In Long SS, Prober CG, Fischer M, Kimberlin D, eds. *Principles and Practice of Pediatric Infectious Diseases,* 6th ed. Philadelphia: Elsevier; 2023: Table 126.1.

from the spread of gonococci from a local site of invasion. Complications and permanent sequelae may be associated with delayed treatment, recurrent infection, metastatic sites of infection (meninges, aortic valve), and delayed or topical therapy of gonococcal ophthalmia.

The interval between primary infection and development of a complication is usually days to weeks. In postpubertal females, endometritis may occur, especially during menses, and may progress to salpingitis, tuboovarian abscess, and peritonitis (PID). Manifestations of PID include signs of lower genital tract infection (e.g., vaginal discharge, suprapubic pain, cervical tenderness) and upper genital tract infection (e.g., fever, leukocytosis, elevated erythrocyte sedimentation rate, and adnexal tenderness or mass). The differential diagnosis includes gynecologic diseases (ovarian cyst, ovarian tumor, ectopic pregnancy) and intraabdominal disorders (appendicitis, urinary tract infection, inflammatory bowel disease). Although *N. gonorrhoeae* and *C. trachomatis* are implicated in many cases of PID, this syndrome encompasses a spectrum of infectious diseases of the upper genital tract caused by *N. gonorrhoeae, C. trachomatis,* and endogenous flora (streptococci, anaerobes, gram-negative bacilli). Treatment must therefore be broad. For women with more severe symptoms (inability to exclude surgical emergency, presence of tuboovarian abscess, severe illness, nausea, vomiting, or high fever), pregnancy, or lack of response to outpatient therapy within 72 hours, parenteral therapy should be initiated in the hospital. The decision to hospitalize adolescents with acute PID should be based on the same criteria used for older women, because the clinical response to outpatient treatment is similar among younger and older women.

Recommended parenteral regimens are ceftriaxone (1 g intravenously [IV] every 24 hours [q24h]) and metronidazole (500 mg PO or IV q12h); or cefotetan (2 g IV q12h); or cefoxitin (2 g IV q6h). Each of these regimens (ceftriaxone and metronidazole; cefotetan; or cefoxitin) should be combined with doxycycline (100 mg PO or IV q12h). An alternative parenteral regimen is ampicillin-sulbactam (3 g IV q6h) plus doxycycline (100 mg PO or IV q12h) or clindamycin (900 mg IV q8h) plus a loading dose of gentamicin (2 mg/kg IV or IM) followed by maintenance gentamicin (1.5 mg/kg q8h). Clinical experience should guide the transition to oral therapy, which usually can be initiated within 24 hours of improvement. Thereafter doxycycline (100 mg PO twice daily [bid]) to complete 14 days of total therapy, with oral clindamycin (450 mg PO 4 times daily [qid]) or metronidazole (500 mg PO bid) added for more effective anaerobic coverage, is provided. Parenteral therapy and IM/PO therapy appear to be similar in terms of clinical efficacy for younger and older women with PID of mild to moderate severity. Recommended IM/PO therapy regimens are as follows: a single dose of ceftriaxone (500 mg IM); single doses of cefoxitin (2 g IM) and probenecid (1 g PO) plus doxycycline (100 mg PO bid); or another parenteral third-generation cephalosporin (e.g., ceftizoxime). Each of these regimens (ceftriaxone; cefoxitin and probenecid; other

parenteral third-generation cephalosporin) should be combined with doxycycline (100 mg PO bid) and metronidazole (500 mg PO bid) for 14 days.

Once inside the peritoneum, gonococci may seed the liver capsule, causing a perihepatitis with right upper quadrant pain **(Fitz-Hugh–Curtis syndrome)**, with or without signs of salpingitis. Perihepatitis may also be caused by *C. trachomatis*. Progression to PID occurs in approximately 20% of cases of gonococcal cervicitis, and *N. gonorrhoeae* is isolated in approximately 40% of cases of PID in the United States. Untreated cases may lead to hydrosalpinx, pyosalpinx, tubo-ovarian abscess, and eventual sterility. Even with adequate treatment of PID, the risk for sterility from bilateral tubal occlusion approaches 20% after one episode of salpingitis and exceeds 60% after three or more episodes. The risk for ectopic pregnancy is increased approximately sevenfold after one or more episodes of salpingitis. Additional sequelae of PID include chronic pain, dyspareunia, and increased risk for recurrent PID.

Urogenital gonococcal infection acquired during the first trimester of pregnancy carries a high risk for septic abortion. After 16 weeks of pregnancy, infection leads to **chorioamnionitis**, a major cause of premature rupture of the membranes and premature delivery.

In males, without treatment, gonococcal urethritis usually resolves spontaneously over several weeks to months. Epididymitis and acute or chronic prostatitis are uncommon complications; most men with gonococcal epididymitis also have overt urethritis. Even more unusual complications include penile edema associated with penile dorsal lymphangitis or thrombophlebitis, periurethral abscess or fistulas, seminal vesiculitis, and balanitis in uncircumcised men.

PREVENTION

Efforts to develop gonococcal vaccines that confer broad cross-protection have been unsuccessful thus far. A pilus vaccine elicited an antibody response and conferred protection against challenge with the homologous strain but did not protect against disease in a trial involving 3,250 volunteers. The high degree of interstrain and intrastrain antigenic variability of pili poses a formidable barrier to the development of a single effective pilus vaccine. An outer membrane vaccine that was enriched in PorB also elicited an antibody response but failed to protect male volunteers against challenge with the homologous strain, likely because small amounts of Rmp present in the vaccine preparation elicited subversive antibodies. A formalin-killed whole cell vaccine trial in 62 volunteers in an Inuvik population in Canada also failed to provide any protection. Gonococcal surface structures, such as the porin protein (isolated without contaminating Rmp), proteins expressed under various stress conditions that may be encountered in vivo and have been identified by proteomic and transcriptomic approaches, and lipooligosaccharides, may prove more promising as vaccine candidates.

A retrospective epidemiologic analysis showed that a meningococcal outer membrane vesicle vaccine (MeNZB) that was used to curb an epidemic of group B meningococcal disease in New Zealand was associated with a clinical efficacy of 31% against gonorrhea, which lends optimism for development of a gonococcal vaccine. However, efficacy was only 14% in persons co-infected with gonorrhea and chlamydia. Cross-reactive antigens shared by *N. gonorrhoeae* and *N. meningitidis* may have contributed to the efficacy of the group B outer membrane vesicle vaccine against gonorrhea.

In the absence of a vaccine, prevention of gonorrhea in adolescents and adults can be achieved through **education**, use of **barrier protection** (especially condoms), **frequent screening** of high-risk populations as recommended by the U.S. Preventive Services Task Force (PSTF) and CDC (e.g., sexually active women ≤24 years old, MSM, individuals previously infected with gonorrhea), and **early identification and treatment** of contacts—all sex partners within the 60 days preceding symptom onset or gonorrhea diagnosis or, if none, the most recent sex partner should be examined and treated presumptively. For heterosexual patients, expedited partner therapy (EPT) with cefixime (800 mg) can be delivered to partners by the patient, a public health worker, or a collaborating pharmacy, as permitted by law (https://www.cdc.gov/std/ept/legal/). EPT has been shown to be safe and effective in the prevention of reinfection with gonorrhea and is endorsed by the American Academy of Pediatrics, American Academy of Family Physicians, and Society of Adolescent Health and Medicine, along with other clinical organizations, for use when in-person evaluation and treatment of the partner is impractical or unsuccessful. (Because of limited data regarding the effectiveness of EPT in reducing persistent or recurrent gonorrhea among MSM and the high risk for coexisting undiagnosed sexually transmitted infections such as HIV, shared clinical decision-making regarding EPT for MSM is recommended.)

An infant born to a woman with cervical gonococcal infection has an approximately 30% risk of acquiring ophthalmic infection compared with a <5% risk if ocular prophylaxis is given. **Gonococcal ophthalmia neonatorum** can be prevented by instilling erythromycin (0.5%) ophthalmic ointment into each eye in a single application at birth (see Chapter 674). If erythromycin ointment is unavailable, infants at risk for *N. gonorrhoeae* (especially those born to a mother with untreated gonococcal infection or with no prenatal care) can be administered ceftriaxone 25-50 mg/kg IV or IM, not to exceed 500 mg, in a single dose.

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Chapter 239
Kingella kingae

Pablo Yagupsky

Kingella kingae is being increasingly recognized as the most common etiology of skeletal system infections in young children.

ETIOLOGY

K. kingae is a fastidious, facultative anaerobic, β-hemolytic member of the Neisseriaceae family that appears as pairs or short chains of gram-negative coccobacilli with tapered ends (Fig. 239.1).

EPIDEMIOLOGY

K. kingae is asymptomatically carried in the posterior pharynx, and the colonized mucosa is the source of bloodstream invasion of the bacterium and its dissemination to the skeletal system or the endocardium, sites for which the organism has a particular tropism. **Colonization** usually starts after 6 months of age, suggesting that maternally derived immunity, coupled with limited socialization, prevents the early acquisition of the bacterium. Colonization reaches a prevalence of 10% between 12 and 24 months and decreases in older children. Carried strains are replaced after weeks or months, suggesting that carriage induces a strain-specific immune response that eradicates the colonizing strain but does not prevent the acquisition of an antigenically different organism. The vast majority of colonized children remain healthy, and the annual risk of a carrier to develop an invasive infection is <1%.

Pharyngeal colonization plays a crucial role in the **transmission** of the organism through intimate contact between siblings and playmates. Daycare attendance increases the risk for colonization and transmission, and clusters of invasive infection have been reported in childcare facilities.

The species elaborates four different polysaccharide capsules (a-d), which appear to represent important virulence factors. Whereas capsules a and b characterize 95% of all invasive strains, capsules c and d are especially found in mere pharyngeal colonizers. Colonizing *K. kingae* strains differ in their invasive potential. Whereas certain clones are commonly found as respiratory colonizers but are seldom isolated from disease sites, other clones are responsible for most of the morbidity burden worldwide.

Invasive *K. kingae* disease is most frequently diagnosed in otherwise healthy children between the ages 6 months and 4 years, coinciding

with the peak prevalence of **pharyngeal carriage** (Fig. 239.2). In contrast, older children and adults with *K. kingae* infections often have underlying chronic diseases, immunosuppressing conditions, malignancy, or cardiac valve pathology. Because of the highly fastidious nature of the organism, *K. kingae* is rarely recovered using traditional culture methods. An annual incidence of 9.4 per 100,000 culture-proven invasive infections among Israeli children <5 years old has been calculated, but this figure can be considered only a minimal estimate because of the suboptimal culture detection of the organism. When sensitive species-specific nucleic acid amplification test (NAAT) methods are consistently used, *K. kingae* appears as the most frequent etiology of skeletal system infections in children 6 months to 4 years old. In a Swiss study in which sensitive NAATs were routinely employed, the organisms caused 88% of all joint and bone infections in this age-group.

PATHOGENESIS

The pathogenesis of *K. kingae* disease begins with adherence of the organism to the pharyngeal epithelium, mediated by pili and a non-pilus adhesin. *K. kingae* secretes a potent repeats-in-toxin (RTX) toxin that is cytotoxic to respiratory epithelial cells, macrophages, and synoviocytes, suggesting that it may play a role in disrupting the respiratory mucosa, promoting survival of the bacterium in the bloodstream, and facilitating invasion of skeletal system tissues. Children with *K. kingae* disease frequently present with symptoms of an upper respiratory infection, hand-foot-and-mouth disease, herpangina, herpetic stomatitis, or buccal aphthous ulcers, suggesting that viral-induced damage to the colonized mucosal surface facilitates invasion of the bloodstream.

CLINICAL DISEASE

Septic arthritis is the most common invasive *K. kingae* infection in children, followed by bacteremia, osteomyelitis, and endocarditis (Table 239.1). Except for patients with endocarditis, the presentation of invasive *K. kingae* infections is frequently mild, and a normal body temperature <38°C (100.4°F), a normal C-reactive protein (CRP) level, and a normal white blood cell (WBC) count are common, requiring a high index of clinical suspicion. Mild to moderate thrombocytosis has been described in more than one third of patients.

Septic Arthritis

K. kingae septic arthritis primarily affects the large, weight-bearing joints and the upper extremity joints. However, *K. kingae* infections of the small metacarpophalangeal, sternoclavicular, sacroiliac, and tarsal joints and the vertebral facets are also relatively common, in contrast to traditional bacterial pathogens associated with septic arthritis (see Chapter 726). The disease has an acute presentation, and children are brought to medical attention after a median of 3 days. The leukocyte count in the synovial fluid shows <50,000 WBCs/μL in almost 25% of the patients, and the Gram stain of synovial fluid is positive in only a small percentage of cases. Involvement of the hip joint resembles toxic synovitis, and the possibility of a *K. kingae* infection should always be suspected in children <4 years old presenting with hip pain or a limp.

Osteomyelitis

K. kingae osteomyelitis usually involves the long bones of the extremities (see Chapter 725). The calcaneus, talus, sternum, and clavicle are also frequently affected (and are rarely infected by other bacterial pathogens). In contrast to *K. kingae* arthritis, the onset of *K. kingae* bone infections is insidious, and the disease follows a subacute and indolent clinical course (Fig. 239.3). In >70% of patients *K. kingae* osteomyelitis is diagnosed after ≥1 week. MRI may show a distinct involvement of cartilages that are not yet ossified, which is only accompanied by a minor soft tissue reaction. Dissemination to the apophysis or epiphysis and contiguous joints is frequent. Despite the frequent diagnostic delay, chronic osteomyelitis and functional orthopedic disabilities are unusual.

SPONDYLODISCITIS

In industrialized countries, *K. kingae* is the most common bacterium detected in children <4 years old with spondylodiscitis. The organism presumably penetrates the rich network of blood vessels that traverse the cartilaginous vertebral end plates and enters the annulus in young children during a bacteremic episode. *K. kingae* spondylodiscitis usually involves the lumbar intervertebral spaces and, with decreasing frequency, thoracolumbar, thoracic, lumbosacral, and cervical disks. Involvement of multiple disks is uncommon. Patients present with limping, lumbar pain, back stiffness, refusal to sit or walk, neurologic symptoms, or abdominal complaints. Radiography or MRI studies demonstrate narrowing of the intervertebral space. Patients respond well to appropriate antibiotic treatment and recover without complications, although residual thinning of the intervertebral space may occur. Drainage of paraspinal abscesses is necessary when signs of cord compression appear.

Tenosynovitis

K. kingae is the etiology of most cases of hematogenous invasion of the tendon sheaths in children <4 years of age. The disease usually affects the extensor tendons of the hands and wrists and, more rarely, the ankles and the feet.

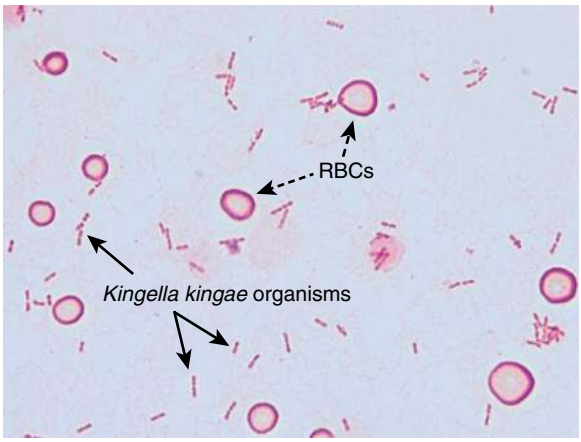

Fig. 239.1 Typical Gram stain of a positive blood culture vial from a child with *K. kingae* bacteremia showing pairs and short chains of plump gram-negative coccobacilli. RBCs, Red blood cells.

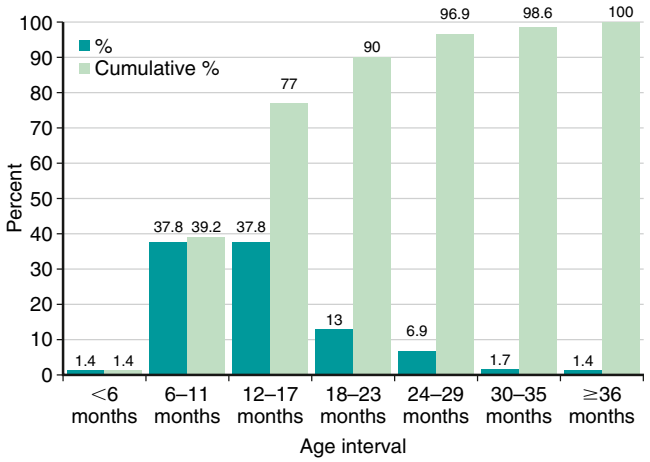

Fig. 239.2 Age distribution of 291 previously healthy children with invasive *K. kingae* infection. *(Data from Dubnov-Raz G, Ephros M, Garty BZ, et al. Invasive pediatric Kingella kingae infections: a nationwide collaborative study. Pediatr Infect Dis J. 2010;29:639–643.)*

Table 239.1 Clinical Spectrum and Relative Frequency of *K. kingae* Infections

CLINICAL DISEASE	FREQUENCY
Septic arthritis	+++
Osteomyelitis	++
Spondylodiscitis	+
Tenosynovitis	±
Bursitis	±
Bacteremia with no focus	+++
Endocarditis	+
Pericarditis	+
Laryngotracheobronchitis	±
Pneumonia	±
Pleural empyema	±
Keratitis	±
Corneal abscess	±
Endophthalmitis	±
Eyelid abscess	±

+++, Very common; ++, common; +, infrequent; ±, exceptional.

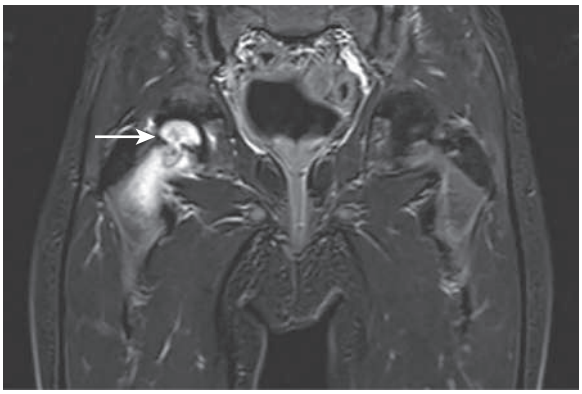

Fig. 239.3 *K. kingae* transphyseal osteomyelitis of the femur *(arrow)*. This 3-yr-old child limped for 3 weeks and was diagnosed with toxic synovitis. He was afebrile and had a leukocyte count of 9.8 × 10^9 cells/L, a C-reactive protein level of 12 mg/L, and an erythrocyte sedimentation rate of 42 mm/hr. *(Courtesy Prof. Dimitri Ceroni, Hôpitaux Universitaires de Genève.)*

Occult Bacteremia

Patients with *K. kingae* bacteremia and no focal infection (occult bacteremia) usually present with mild to moderate fever, symptoms suggestive of a viral upper respiratory infection, a mean CRP level of 2.2 mg/dL, and a mean WBC count of 12,700/μL. Children with *K. kingae* bacteremia respond favorably to a short course of antibiotics.

Endocarditis

In contrast to other *K. kingae* infections, *K. kingae* endocarditis is also diagnosed in school-age children, adolescents, and adult patients. The disease may affect native and prosthetic valves. Predisposing factors include congenital cardiac malformations or rheumatic valvular disease, but some patients have previously normal hearts. Typically, the left side of the heart is involved, usually the mitral valve. Fever and acute-phase reactants are elevated more in patients with endocarditis than in those with uncomplicated bacteremia; no particular cutoff value accurately distinguishes between the two conditions. Despite the exquisite susceptibility of *K. kingae* to antibiotics, cardiac failure, septic shock, cerebrovascular accident (stroke), and other life-threatening complications are common; the mortality rate is high (>10%); and many surviving patients later require valvular repair or replacement. Because of the potential severity of *K. kingae* endocarditis, routine echocardiographic evaluation of bacteremic children is recommended by some experts.

DIAGNOSIS

The diagnosis of *K. kingae* disease can be established by isolation of the bacterium from a normally sterile site such as blood, synovial fluid, or bone tissue. Although *K. kingae* grows on routine bacteriologic media, its recovery from exudates is frequently unsuccessful. Detection is enhanced by inoculating synovial fluid specimens into blood culture vials, suggesting that diluting samples in a large volume of nutrient broth reduces the concentration of detrimental factors. The bacteriologic diagnosis is significantly improved by the use of NAATs (polymerase chain reaction). The initial approach consisted of amplifying the 16S ribosomal RNA (rRNA) gene, which is present in all bacteria followed by sequencing the species-specific amplicon to identify the pathogen. The original molecular assays are being replaced by real-time polymerase chain reaction tests that target *K. kingae*–specific genes that can be completed in a few hours. Routine use of these assays results in a fourfold improvement in the detection of the organism compared with the blood culture vial method and reduces the fraction of culture-negative septic arthritis in young children. The three *K. kingae*–specific genes that are targeted by the current tests are the *rtx* operon that encodes the RtxA toxin; the *cpn*60 (chaperonin 60 gene), also known as *gro*EL; and the malate dehydrogenase *(mdh)* gene that combines excellent sensitivity and specificity and should be the preferred method.

Because the bacterium frequently invades joints and bones that are small or difficult to reach or intervertebral disks, exudate samples or tissues are often unavailable for analysis. An alternative noninvasive diagnostic approach has been proposed consisting of obtaining an oropharyngeal specimen and subjecting it to a sensitive *K. kingae*–specific NAAT. A compatible clinical picture, coupled with a positive test result, supports *K. kingae* as the probable cause of the disease. This strategy has the obvious limitation that the background carriage rate of the organism is around 10% in children of the relevant age and twice as high in those attending daycare centers, reducing the predictive value of a positive result. On the other hand, because the colonized oropharynx is the source of the bloodborne dissemination of the bacterium, the negative predictive value of the assay is high. For practical purposes, failure to detect *K. kingae* DNA sequences when using a sensitive molecular test virtually rules out the organism as the etiology of the infection.

Novel commercially available plasma metagenomic next-generation sequencing assays appear to be a promising tool for detecting the organism, especially in patients with endocarditis receiving antibiotics.

TREATMENT

K. kingae is usually highly susceptible to penicillin and cephalosporins but exhibits decreased susceptibility to oxacillin, precluding the use of isoxazolyl penicillins for confirmed *K. kingae* infections. Although β-lactamase production is frequently detected in colonizing *K. kingae* strains, its prevalence among invasive organisms is low and shows wide geographic variation. Testing for β-lactamase production should be routinely performed in all isolates derived from normally sterile body sites.

Because of the lack of specific guidelines for treating *K. kingae* disease, patients have been administered a variety of antibiotic regimens according to protocols developed for infections caused by traditional bacterial pathogens. The first-line therapy for skeletal infections in young children usually consists of intravenous (IV) administration of a second- or third-generation **cephalosporin**, pending culture or NAAT results. *K. kingae* is always *resistant* to glycopeptide antibiotics and clindamycin, a serious concern in areas where skeletal infections caused by community-associated methicillin-resistant *Staphylococcus aureus* are common, and **vancomycin** or **clindamycin** are initially

administered to children with presumptive septic arthritis or osteomyelitis. The initial antibiotic regimen is frequently changed to a cephalosporin (e.g., ceftriaxone) once *K. kingae* is identified or to ampicillin after β-lactamase production is excluded. A favorable clinical response and decreasing CRP levels to ≤20 μg/mL are used to guide switching to oral antibiotics and defining the duration of therapy. Antibiotic treatment has ranged from 2 to 3 weeks for *K. kingae* arthritis, from 3 to 6 weeks for *K. kingae* osteomyelitis, and from 3 to 12 weeks for *K. kingae* spondylodiscitis. Although some children with septic arthritis have been managed with repeat joint aspirations and lavage, most patients respond promptly to conservative treatment with appropriate antibiotics and do not require invasive surgical procedures.

Children with *K. kingae* bacteremia without focal infection are initially treated with an IV β-lactam antibiotic and are subsequently switched to an oral drug once the clinical condition has improved. In most cases, therapy is administered for 1-2 weeks.

Patients with *K. kingae* endocarditis are usually treated with an IV β-lactam antibiotic alone or in combination with an aminoglycoside for 4-7 weeks. Early surgical intervention is necessary for life-threatening complications unresponsive to medical therapy.

PREVENTION

Because the risk of asymptomatic pharyngeal carriers for developing an invasive *K. kingae* infection is low, in the absence of clinical disease, there is no indication to eradicate the organism from the colonized mucosal surfaces. Nonetheless, in 25 reported outbreaks of *K. kingae* infections in child daycare centers, 68 of 402 (17%) classmates developed a proven or presumptive infection, including fatal endocarditis, within 1 month, indicating that the causative strains combined unusual transmissibility and virulence. Under these circumstances, prophylactic antibiotic therapy to eradicate colonization in contacts and prevent further cases of the disease has been employed, consisting of either rifampin alone 10 mg/kg or 20 mg/kg twice daily for 2 days or rifampin in combination with amoxicillin (80 mg/kg/day) for 2 days or 4 days. The effectiveness of these regimens has ranged between 47% and 80%, indicating that eradication of *K. kingae* from colonized mucosae is difficult to achieve. However, after antibiotic prophylaxis administration, no further cases of the disease have been detected, suggesting that reduction of the bacterial density by antibiotics, extinction of the precipitating viral infection, and/or induction of an effective immune response by prolonged carriage is enough to decrease transmissibility and prevent additional cases.

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Chapter 240

Haemophilus influenzae

Nadia A. Kadry and Joseph W. St. Geme III

Effective vaccines to prevent ***Haemophilus influenzae* type b (Hib)** disease, introduced in the United States and most other countries, have resulted in a dramatic decrease in the incidence of infections caused by this organism. However, mortality and morbidity from Hib infection remain a problem worldwide, primarily in resource poor countries. Occasional cases of invasive disease caused by non–type b strains continue to occur but are infrequent. Nontypeable isolates of *H. influenzae* are an important cause of otitis media, sinusitis, and chronic bronchitis.

ETIOLOGY

H. influenzae is a fastidious, gram-negative, pleomorphic coccobacillus that requires factor X (hematin) and factor V (phosphopyridine nucleotide) for growth. Some *H. influenzae* isolates are surrounded by a polysaccharide capsule and can be segregated into one of six antigenically and biochemically distinct serotypes designated types a, b, c, d, e, and f. Isolates without a polysaccharide capsule are considered nontypeable. Isolates can also be categorized based on the production of indole and the presence of ornithine decarboxylase and urease and are sorted into biotypes I-VIII.

EPIDEMIOLOGY

Before the advent of an effective Hib conjugate vaccine in 1988, Hib was a major cause of serious disease among children. There was a striking age distribution of cases, with >90% in children <5 years old and the majority in children <2 years old. The annual attack rate of invasive disease was 64-129 cases per 100,000 children <5 years old. Invasive disease caused by strains producing a non–type b capsule has been much less frequent but continues to occur. The incidence of invasive disease caused by type b and non–type b serotypes has been estimated at approximately 0.08 and 1.02 cases, respectively, per 100,000 children <5 years old per year in the United States. Nontypeable (nonencapsulated) *H. influenzae* strains also occasionally cause invasive disease, especially in neonates, immunocompromised children, and children in resource poor countries. The estimated rate of invasive disease caused by nontypeable *H. influenzae* in the United States is 1.88 per 100,000 children <5 years old per year. Nontypeable isolates are common etiologic agents in otitis media, sinusitis, and chronic bronchitis. More recent evidence also implicates nasopharyngeal colonization with nontypeable *H. influenzae* in the development of asthma and allergic airway disease.

Humans are the only natural hosts for *H. influenzae,* which is part of the normal respiratory flora in 60–90% of healthy children. Most isolates are nontypeable. Before the advent of Hib conjugate vaccines, *H. influenzae* type b could be isolated from the pharynx of 2–5% of healthy preschool and school-age children, with lower rates among infants and adults. Asymptomatic colonization with Hib occurs at a much lower rate in immunized populations.

The continued circulation of type b strains despite current vaccine coverage levels suggests that elimination of Hib disease may be a formidable task. The few cases of Hib invasive disease in the United States now occur in both unvaccinated and fully vaccinated children. Approximately 50% of cases occur in infants who are too young to have received a complete primary vaccine series. Among the cases in patients who are old enough to have received a complete vaccine series, the majority are underimmunized. To highlight this point, during a shortage of Hib vaccine, invasive disease developed in five children in Minnesota, all of whom were incompletely immunized. Continued efforts are necessary to provide currently available Hib conjugate vaccines to children in resource poor countries, where affordability remains an important issue.

In the prevaccine era, certain groups and individuals had an increased incidence of invasive Hib disease, including Alaskan Natives, American Indians (Apache, Navajo), and African Americans. Persons with certain chronic medical conditions were also known to be at increased risk for invasive disease, including individuals with sickle cell disease, asplenia, congenital and acquired immunodeficiencies, and malignancies. Unvaccinated infants with invasive Hib infection are also at increased risk for recurrence, reflecting that they typically do not develop a protective immune response to *H. influenzae.*

Socioeconomic risk factors for invasive Hib disease include childcare outside the home, the presence of siblings of elementary school age or younger, short duration of breastfeeding, and parental smoking. A history of otitis media is associated with an increased risk for invasive disease. Much less is known about the epidemiology of invasive disease caused by non–type b strains, and it is not clear whether the epidemiologic features of Hib disease apply to disease caused by non-Hib strains.

Among age-susceptible household contacts who have been exposed to a case of invasive Hib disease, there is increased risk for secondary cases of invasive disease in the first 30 days after exposure, especially in susceptible children <24 months old. Whether a similar increased risk exists for contacts of individuals with non-Hib disease is unknown.

The mode of transmission is usually direct contact or inhalation of respiratory tract droplets containing *H. influenzae.* The incubation period for invasive disease is variable, and the exact period of communicability is unknown. Most children with invasive Hib disease are colonized in the nasopharynx before initiation of antimicrobial therapy; 25–40% may remain colonized during the first 24 hours of therapy.

With the decline of disease caused by type b organisms, disease caused by other serotypes (a, c-f) and by nontypeable strains has been recognized more clearly. There is no evidence that non–type b infections have increased in frequency. However, clusters of type a and, less often, type e and type f infections have occurred. Data from Israel suggest that nontypeable *H. influenzae* is the most common cause of invasive *H. influenzae* disease in that country.

PATHOGENESIS

The pathogenesis of Hib disease begins with adherence to respiratory epithelium and colonization of the nasopharynx, which is mediated by pilus and nonpilus adherence factors. The mechanism of entry into the intravascular compartment is unclear but appears to be influenced by cytotoxic factors. Once in the bloodstream, Hib, and perhaps other encapsulated strains, resist intravascular clearance mechanisms at least in part because of the polysaccharide capsule. In the case of Hib, the magnitude and duration of bacteremia influence the likelihood of dissemination of bacteria to sites such as the meninges and joints.

Noninvasive *H. influenzae* infections such as otitis media, sinusitis, and bronchitis are usually caused by nontypeable strains. These organisms gain access to sites such as the middle ear and sinus cavities by direct extension from the nasopharynx. Factors facilitating spread from the nasopharynx include eustachian tube dysfunction and antecedent viral infections of the upper respiratory tract.

Antibiotic Resistance

Ampicillin resistance is increasingly common among *H. influenzae* isolates. Resistance is typically driven by plasmid-mediated production of a β-lactamase. β-lactamase–negative ampicillin-resistant isolates have been identified and manifest resistance by production of a β-lactam–insensitive cell wall synthesis enzyme called *penicillin binding protein 3* (PBP 3).

Amoxicillin-clavulanate is uniformly active against *H. influenzae* clinical isolates except for the rare β-lactamase–negative ampicillin-resistant isolates. Among macrolides, azithromycin has in vitro activity against a high percentage of *H. influenzae* isolates; in contrast, the activity of erythromycin and clarithromycin against *H. influenzae* clinical isolates is poor. *H. influenzae* resistance to third-generation cephalosporins has not been documented. Resistance to quinolones is rare, and resistance to trimethoprim-sulfamethoxazole (TMP-SMX) is present in approximately 10% of isolates.

Immunity

In the prevaccine era, the most important known element of host defense was antibody directed against the type b capsular polysaccharide polyribosylribitol phosphate **(PRP)**. Anti-PRP antibody is acquired in an age-related fashion and facilitates clearance of Hib from blood, in part related to opsonic activity. Antibodies directed against antigens such as outer membrane proteins or lipopolysaccharide (LPS) may also have a role in opsonization. Both the classical and alternative complement pathways are important in defense against Hib.

Before the introduction of vaccination, protection from Hib infection was presumed to correlate with the concentration of circulating anti-PRP antibody at the time of exposure. A serum antibody concentration of >0.15 μg/mL was considered protective against invasive infection. Unimmunized infants >6 months old and young children usually lacked an anti-PRP antibody concentration of this magnitude and were susceptible to disease after encountering Hib. This lack of antibody in infants and young children may have reflected a maturational delay in the immunologic response to thymus-independent type 2 antigens such as unconjugated PRP, presumably explaining the high incidence of type b infections in infants and young children in the prevaccine era.

The conjugate vaccines act as thymus-dependent antigens and elicit serum antibody responses in infants and young children (Table 240.1). These vaccines are believed to prime memory antibody responses on subsequent encounters with PRP. The concentration of circulating anti-PRP antibody in a child primed by a conjugate vaccine may not correlate precisely with protection, presumably because a memory response may occur rapidly on exposure to PRP and provide protection. Conjugate vaccines have been shown to be highly effective against Hib disease and have been shown to reduce nasopharyngeal carriage rates.

Much less is known about immunity to other *H. influenzae* serotypes or to nontypeable isolates. For nontypeable isolates, evidence suggests that antibodies directed against one or more outer membrane proteins are bactericidal and protect against experimental challenge. A variety of antigens have been evaluated in an attempt to identify vaccine candidates for nontypeable *H. influenzae,* including outer membrane proteins (P1, P2, P4, P5, P6, D15, and Tbp A/B), LPS, various adhesins (e.g., Hap, HMW1, and HMW2), and lipoprotein D.

DIAGNOSIS

Presumptive identification of *H. influenzae* is established by direct examination of a clinical specimen after staining with Gram reagents. Because of its small size, pleomorphism, and occasional poor uptake of stain, as well as the tendency for proteinaceous fluids to have a red background, *H. influenzae* is sometimes difficult to visualize. Furthermore, given that identification of *H. influenzae* by microscopy requires at least 10^5 bacteria/mL in a clinical specimen (e.g., cerebrospinal fluid [CSF]), failure to visualize organisms does not preclude their presence.

Culture of *H. influenzae* requires prompt transport and processing of specimens because the organism is fastidious. Specimens should not be exposed to drying or temperature extremes. Primary isolation of *H. influenzae* can be accomplished on chocolate agar.

Serotyping of *H. influenzae* is accomplished by slide agglutination with type-specific antisera or through polymerase chain reaction (PCR) amplification of the capsule locus *(cap)*. Importantly, antigen-based detection methods are prone to false positives because of antigen cross-reactivity with other encapsulated organisms and are therefore not recommended as the primary diagnostic approach. Real-time PCR and nucleic acid amplification tests (NAATs) can be used to specifically detect *H. influenzae*. Accurate serotyping is essential to monitor progress toward elimination of type b invasive disease. Timely reporting of cases to public health authorities should be ensured.

CLINICAL MANIFESTATIONS AND TREATMENT

The initial antibiotic therapy for invasive infections possibly caused by *H. influenzae* should be a parenterally administered antibiotic effective

Table 240.1 *Haemophilus influenzae* Type b (Hib) Conjugate Vaccines Available in the United States

VACCINE	TRADE NAME	COMPONENTS	MANUFACTURER
PRP-T	ActHib	PRP conjugated to tetanus toxoid	Sanofi
PRP-T	Hibrix	PRP conjugated to tetanus toxoid	GlaxoSmithKline Biologicals
PRP-OMP	PedvaxHIB	PRP conjugated to OMP	Merck
PRP-T/DTaP-IPV	Pentacel	PRP-T + DTaP-IPV vaccines	Sanofi Pasteur
PRP-OMP/DTaP-IPV-HepB	Vaxelis	PRP-OMP + DTaP-IPV + HepB vaccines	Merck

DTaP, Diphtheria and tetanus toxoids and acellular pertussis vaccine; HepB, hepatitis B vaccine; IPV, trivalent inactivated polio vaccine; OMP, outer membrane protein complex from *Neisseria meningitidis*; PRP, polyribosylribitol phosphate.

in sterilizing all foci of infection and effective against ampicillin-resistant strains, usually an **extended-spectrum cephalosporin** such as ceftriaxone. After the antimicrobial susceptibility of the isolate has been determined, an appropriate agent can be selected to complete the therapy. **Ampicillin** remains the drug of choice for the therapy of infections caused by susceptible isolates. If the isolate is resistant to ampicillin, in selected circumstances **ceftriaxone** can be administered once daily for outpatient therapy.

Oral antimicrobial agents are sometimes used to complete a course of therapy initiated by the parenteral route and are typically initial therapy for noninvasive infections such as otitis media and sinusitis. If the organism is susceptible, **amoxicillin** is the drug of choice. An oral second- or third-generation cephalosporin or amoxicillin-clavulanate may be used when the isolate is resistant to ampicillin.

Meningitis

In the prevaccine era, meningitis accounted for more than half of all cases of invasive *H. influenzae* disease. Clinically, meningitis caused by Hib cannot be differentiated from meningitis caused by *Neisseria meningitidis* or *Streptococcus pneumoniae* (see Chapter 643.1). It may be complicated by other foci of infection such as the lungs, joints, bones, and pericardium.

Antimicrobial therapy should be administered intravenously for 7-14 days for uncomplicated cases. Ceftriaxone and ampicillin cross the blood-brain barrier during acute inflammation in concentrations adequate to treat *H. influenzae* meningitis. Intramuscular therapy with ceftriaxone may be an alternative in patients with normal organ perfusion.

The prognosis of Hib meningitis depends on the age at presentation, duration of illness before appropriate antimicrobial therapy, CSF capsular polysaccharide concentration, and rapidity with which organisms are cleared from CSF, blood, and urine. Clinically manifested inappropriate secretion of antidiuretic hormone and evidence of focal neurologic deficits at presentation are poor prognostic features. Approximately 6% of patients with Hib meningitis are left with some hearing impairment, probably because of inflammation of the cochlea and the labyrinth. **Dexamethasone** (0.6 mg/kg/day divided every 6 hours for 2 days), particularly when given shortly before or concurrent with the initiation of antimicrobial therapy, decreases the incidence of hearing loss. Major neurologic sequelae of Hib meningitis include behavior problems, language disorders, impaired vision, mental retardation, motor abnormalities, ataxia, seizures, and hydrocephalus.

Cellulitis

Children with Hib cellulitis often have an antecedent upper respiratory tract infection. They usually have no prior history of trauma, and the infection is thought to represent seeding of the organism to the involved soft tissues during bacteremia. The head and neck, particularly the cheek and preseptal region of the eye, are the most common sites of involvement. The involved region generally has indistinct margins and is tender and indurated. **Buccal cellulitis** is classically erythematous with a violaceous hue, although this sign may be absent. *H. influenzae* may often be recovered directly from an aspirate of the leading edge, although this procedure is seldom performed. A blood culture may also reveal the causative organism. Other foci of infection may be present concomitantly, particularly in children <18 months old. A diagnostic lumbar puncture should be considered at diagnosis in these children.

Parenteral antimicrobial therapy is indicated until patients become afebrile, after which an appropriate oral antimicrobial agent may be substituted. A 7- to 10-day course is customary.

Preseptal Cellulitis

Infection involving the superficial tissue layers anterior to the orbital septum is termed *preseptal cellulitis,* which may be caused by *H. influenzae.* Uncomplicated preseptal cellulitis does not imply a risk for visual impairment or direct central nervous system (CNS) extension. However, concurrent bacteremia may be associated with the development of meningitis. *H. influenzae* preseptal cellulitis is characterized by fever, edema, tenderness, warmth of the lid, and, occasionally, purple discoloration. Evidence of interruption of the integument is usually absent. Conjunctival drainage may be associated. *S. pneumoniae, Staphylococcus aureus,* and group A *Streptococcus* cause clinically indistinguishable preseptal cellulitis. The latter two pathogens are more likely when fever is absent and the integument is interrupted (e.g., because of an insect bite or trauma).

Children with preseptal cellulitis in whom *H. influenzae* and *S. pneumoniae* are etiologic considerations (young age, high fever, intact integument) should have a blood culture obtained. In addition, a diagnostic lumbar puncture should be considered.

Parenteral antibiotics are indicated for preseptal cellulitis. Because methicillin-susceptible and methicillin-resistant *S. aureus, S. pneumoniae,* and group A β-hemolytic streptococci are other causes, empirical therapy should include agents active against these pathogens. Patients with preseptal cellulitis without concurrent meningitis should receive **parenteral therapy for about 5 days, until fever and erythema have abated**. In uncomplicated cases, antimicrobial therapy should be given for 10 days.

Orbital Cellulitis

Infections of the orbit are infrequent and usually develop as complications of acute ethmoid or sphenoid sinusitis. Orbital cellulitis may manifest as lid edema but is distinguished by the presence of proptosis, chemosis, impaired vision, limitation of the extraocular movements, decreased mobility of the globe, or pain on movement of the globe. The distinction between preseptal and orbital cellulitis may be difficult and is best determined by CT scan.

Orbital infections are treated with **parenteral therapy for at least 14 days**. Underlying sinusitis or orbital abscess may require surgical drainage and more prolonged antimicrobial therapy.

Supraglottitis or Acute Epiglottitis

Supraglottitis is a cellulitis of the tissues of the laryngeal inlet (see Chapter 433). It has become exceedingly rare since the introduction of conjugate Hib vaccines. Direct bacterial invasion of the involved tissues is probably the initiating pathophysiologic event. This dramatic, potentially lethal condition can occur at any age. Because of the risk of sudden, unpredictable airway obstruction, supraglottitis is a medical emergency. Other foci of infection, such as meningitis, are rare. Antimicrobial therapy directed against *H. influenzae* and other etiologic agents should be administered parenterally, but only after the airway is secured, and therapy should be continued until patients are able to take fluids by mouth. The duration of antimicrobial therapy is typically 7 days.

Pneumonia

The true incidence of *H. influenzae* pneumonia in children is unknown because invasive procedures required to obtain culture specimens are seldom performed (see Chapter 449). In the prevaccine era, type b strains were believed to be the usual cause. The signs and symptoms of pneumonia caused by *H. influenzae* cannot be differentiated from those of pneumonia caused by many other microorganisms. Other foci of infection may be present concomitantly.

Children <12 months old in whom *H. influenzae* pneumonia is suspected should receive parenteral antimicrobial therapy initially because of their increased risk for bacteremia and its complications. Older children who do not appear severely ill may be managed with an oral antimicrobial. Therapy is continued for 7-10 days. Uncomplicated pleural effusion associated with *H. influenzae* pneumonia requires no special intervention. However, if empyema develops, chest tube or **surgical drainage** is generally indicated.

Suppurative Arthritis

Large joints, such as the knee, hip, ankle, and elbow, are affected most often (see Chapter 726). Other foci of infection may be present concomitantly. Although single-joint involvement is the rule, multijoint involvement occurs in approximately 6% of cases. The signs and symptoms of septic arthritis caused by *H. influenzae* are indistinguishable from those in arthritis caused by other bacteria.

Uncomplicated septic arthritis should generally be treated with an appropriate **parenteral antimicrobial for at least a few days**. If the clinical response is satisfactory, the remainder of the course of

antimicrobial treatment may be given orally. Therapy is typically given for 3 weeks for uncomplicated septic arthritis, but may be continued beyond 3 weeks, until the C-reactive protein concentration is normal and clinical symptoms are resolved.

Pericarditis

H. influenzae is a rare cause of pericarditis (see Chapter 489). Affected children often have had an antecedent upper respiratory tract infection. Fever, respiratory distress, and tachycardia are consistent findings. Other foci of infection may be present concomitantly.

The diagnosis may be established by recovery of the organism from blood or pericardial fluid. Gram stain or detection of PRP in pericardial fluid, blood, or urine (when type b organisms are the cause) may aid the diagnosis**.** Antimicrobials should be provided parenterally in a regimen similar to that used for meningitis (see Chapter 643.1). Pericardiectomy is useful for draining the purulent material effectively and preventing tamponade and constrictive pericarditis.

Bacteremia Without an Associated Focus

Bacteremia caused by *H. influenzae* may be associated with fever without any apparent focus of infection (see Chapter 220). In this situation, risk factors for occult bacteremia include the magnitude of fever (≥39°C [102.2°F]) and the presence of leukocytosis (≥15,000 cells/μL). In the prevaccine era, meningitis developed in approximately 25% of children with occult Hib bacteremia if left untreated. In the vaccine era, this *H. influenzae* infection has become exceedingly rare. When it does occur, the child should be reevaluated for a focus of infection and a second blood culture should be performed. The child should be hospitalized and given parenteral antimicrobial therapy after a diagnostic lumbar puncture and chest radiograph are obtained.

Miscellaneous Infections

Rarely, *H. influenzae* causes urinary tract infection, epididymoorchitis, cervical adenitis, acute glossitis, infected thyroglossal duct cysts, uvulitis, endocarditis, endophthalmitis, primary peritonitis, osteomyelitis, and periappendiceal abscess.

Invasive Disease in Neonates

Neonates occasionally have invasive *H. influenzae* infection. In the infant with illness within the first 24 hours of life, especially in association with maternal chorioamnionitis or prolonged rupture of membranes, transmission of the organism to the infant is likely to have occurred through the maternal genital tract (which is colonized with nontypeable *H. influenzae* in <1% of pregnant women). Manifestations of neonatal invasive infection include bacteremia with sepsis, pneumonia, respiratory distress syndrome with shock, conjunctivitis, scalp abscess or cellulitis, and meningitis. Less frequently, mastoiditis, septic arthritis, and congenital vesicular eruption may occur.

Otitis Media

Acute otitis media is one of the most common infectious diseases of childhood (see Chapter 680). It results from the spread of bacteria from the nasopharynx through the eustachian tube into the middle ear cavity. Usually, because of a preceding viral upper respiratory tract infection, the mucosa in the area becomes hyperemic and swollen, resulting in obstruction and an opportunity for bacterial multiplication in the middle ear.

The most common bacterial pathogens are *H. influenzae, S. pneumoniae,* and *Moraxella catarrhalis.* Most *H. influenzae* isolates causing otitis media are nontypeable. Ipsilateral conjunctivitis may also be present. **Amoxicillin (80-90 mg/kg/day)** is a suitable first-line oral antimicrobial agent, because the probability that the causative isolate is resistant to amoxicillin and the risk for invasive potential are sufficiently low to justify this approach. Alternatively, in certain cases, a single dose of ceftriaxone constitutes adequate therapy.

In the case of treatment failure or if a β-lactamase–producing isolate is obtained by tympanocentesis or from drainage fluid, amoxicillin-clavulanate (Augmentin) is a suitable alternative.

Conjunctivitis

Acute infection of the conjunctivae is common in childhood (see Chapter 666). In neonates, *H. influenzae* is an infrequent cause. However, it is an important pathogen in older children. Most *H. influenzae* isolates associated with conjunctivitis are nontypeable, although type b isolates and other serotypes are occasionally found. Empirical treatment of conjunctivitis beyond the neonatal period usually consists of topical antimicrobial therapy with **sulfacetamide**. Topical fluoroquinolone therapy is to be avoided because of its broad spectrum, high cost, and high rate of emerging resistance among many bacterial species. Ipsilateral otitis media caused by the same organism may be present and requires oral antibiotic therapy.

Sinusitis

H. influenzae is an important cause of acute sinusitis in children, likely the most common etiology since implementation of routine vaccination against *S. pneumoniae* (see Chapter 429). Chronic sinusitis lasting >1 year or severe sinusitis requiring hospitalization is often caused by *S. aureus* or anaerobes such as *Peptococcus, Peptostreptococcus,* and *Bacteroides.* Nontypeable *H. influenzae* and viridans group streptococci are also frequently recovered.

For uncomplicated sinusitis, **amoxicillin** is acceptable initial therapy. However, if clinical improvement does not occur, a broader-spectrum agent, such as amoxicillin-clavulanate, may be appropriate. A 10-day course is sufficient for uncomplicated sinusitis. Hospitalization for parenteral therapy is rarely required; the usual reason is suspicion of progression to orbital cellulitis.

PREVENTION

Immunization with a Hib conjugate vaccine is recommended for all infants. Prophylaxis is indicated if close contacts of an index patient with type b disease are unvaccinated. The contagiousness of non-Hib infections is not known, and prophylaxis is not recommended.

Vaccine

Several Hib conjugate vaccines are currently marketed in the United States, containing either PRP–outer membrane protein **(PRP-OMP)** or PRP–tetanus toxoid **(PRP-T)**, which differ in the carrier protein used and the method of conjugating the polysaccharide to the protein (see Table 240.1 and Chapter 215). Available combination vaccines include Pentacel (Sanofi Pasteur), which consists of PRP-T combined with DTaP vaccine (diphtheria and tetanus toxoids and acellular pertussis) and IPV vaccine (trivalent, inactivated polio vaccine), and Vaxelis (Merck), which consists of PRP-OMP combined with DTaP, IPV, and hepatitis B vaccine.

The Hib conjugate vaccines stimulate circulating anticapsular antibody and provide long-term immunity through B-cell memory.

Prophylaxis

Unvaccinated children <48 months old who are in close contact with an index case of invasive Hib infection are at increased risk for invasive infection. The risk for secondary disease for children >3 months old is inversely related to age. About half the secondary cases among susceptible household contacts occur in the first week after hospitalization of the index case. Because many children are now protected against Hib by prior immunization, the need for prophylaxis has greatly decreased. When prophylaxis is used, **rifampin** is indicated for all members of the household or close-contact group, including the index patient, if the group includes one or more children <48 months old who are not fully immunized.

Parents of children hospitalized for invasive Hib disease should be informed of the increased risk for secondary infection in other young children in the same household if they are not fully immunized. Parents of children exposed to a single case of invasive Hib disease in a childcare center or nursery school should be similarly informed, although there is disagreement about the need for rifampin prophylaxis for these children.

For prophylaxis, children should be given rifampin orally (0-1 months old, 10 mg/kg/dose; >1 month old, 20 mg/kg/dose, not to exceed 600 mg/dose) once daily for 4 consecutive days. The adult dose is 600 mg once daily. Rifampin prophylaxis is not recommended for pregnant women.

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Chapter 241

Chancroid *(Haemophilus ducreyi)*

H. Dele Davies and Shirley Delair

Chancroid is a sexually transmitted disease characterized by painful genital ulceration and inguinal lymphadenopathy.

ETIOLOGY AND EPIDEMIOLOGY

Chancroid is caused by *Haemophilus ducreyi,* a fastidious gram-negative bacillus. It is most common in many low- and middle-income countries but also occurs sporadically in high-income countries. Most cases in high-income countries occur in returning travelers (90% are male) from endemic areas or occasionally in localized urban outbreaks associated with commercial sex workers. Chancroid is a risk factor for transmission of HIV. Diagnosis of chancroid in infants and children is strong evidence of sexual abuse. Male circumcision lowers the risk for chancroid. The incidence of chancroid has declined significantly since 1981 and remains low in the United States.

CLINICAL MANIFESTATIONS

The incubation period is 4-7 days, with a small, inflammatory papule on the preputial orifice or frenulum in men and on the labia, fourchette, or perineal region in women. The lesion becomes pustular, eroded, and ulcerative within 2-3 days. The ulcer edge is classically ragged and undermined. Without treatment, the ulcers may persist for weeks to months. Painful, tender inguinal lymphadenitis occurs in >50% of cases, more often among men. The lymphadenopathy can become fluctuant to form **buboes**, which can spontaneously rupture.

DIAGNOSIS

Diagnosis is usually established by the clinical presentation and the exclusion of both syphilis *(Treponema pallidum)* and herpes simplex virus infections. The ulcer of chancroid is accompanied by concurrent **lymphadenopathy** that is usually unilateral, unlike lymphogranuloma venereum (see Chapter 272.4). Genital herpes is characterized by vesicular lesions with a history of recurrence (see Chapter 299). Gram stain of ulcer secretions may show gram-negative coccobacilli in parallel clusters ("school of fish"). Culture requires expensive, special media and has a sensitivity of only 80%. There are currently no U.S. Food and Drug Administration (FDA)–approved polymerase chain reaction (PCR) tests for *H. ducreyi*. PCR and indirect immunofluorescence using monoclonal antibodies are available as research tools and are performed by some clinical laboratories using their own in-house Clinical Laboratory Improvement Amendments (CLIA)–verified kits.

TREATMENT

Most *H. ducreyi* organisms are resistant to penicillin and ampicillin because of plasmid-mediated β-lactamase production. Spread of plasmid-mediated resistance among *H. ducreyi* has resulted in lack of efficacy of previously useful drugs such as sulfonamides and tetracyclines. Chancroid is easy to treat if recognized early. The current treatment recommendation is for **azithromycin** (1 g as a single dose orally [PO]) or **ceftriaxone** (250 mg as a single dose intramuscularly) or **ciprofloxacin** (500 mg twice daily PO for 3 days) or **erythromycin** (500 mg 3 times daily PO for 7 days), the latter most often used in low- and middle-income countries, Fluctuant nodes may require drainage. Symptoms usually resolve within 3-7 days. Relapses can usually be treated successfully with the original treatment regimen. Patients with HIV infection may require a longer duration of treatment. Persistence of the ulcer and the organism after therapy should raise suspicion of resistance to the prescribed antibiotic.

Patients with chancroid should be evaluated for other sexually transmitted infections, including syphilis, genital herpes, hepatitis B virus, HIV, chlamydia, and gonorrhea; an estimated 10% have concomitant syphilis or genital herpes. If initial HIV or syphilis testing is negative, patients should be tested again in 3 months because of the high rates of co-infections. In low- and middle-income countries, patients with a compatible genital ulcer are treated for both chancroid and syphilis. All sexual contacts of patients with chancroid should be evaluated and treated.

COMPLICATIONS

Complications include **phimosis** in men and secondary bacterial infection. **Bubo** formation may occur in untreated cases. Genital ulceration as a syndrome increases the risk for transmission of HIV.

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Chapter 242

Moraxella catarrhalis

Timothy F. Murphy and Oscar G. Gómez-Duarte

Moraxella catarrhalis is an unencapsulated, gram-negative diplococcus and is a **human-specific pathogen** that colonizes the respiratory tract beginning in infancy. Patterns of colonization and infection with *M. catarrhalis* are changing in countries where pneumococcal conjugate vaccines are used widely. The most important clinical manifestation of *M. catarrhalis* infection in children is **otitis media**.

ETIOLOGY

M. catarrhalis has long been considered to be an upper respiratory tract commensal. Substantial genetic heterogeneity exists among strains of *M. catarrhalis*. Several outer membrane proteins demonstrate sequence differences among strains, particularly in regions of the proteins that are exposed on the bacterial surface. *M. catarrhalis* endotoxin lacks repeating polysaccharide side chains and is thus a lipooligosaccharide (LOS). In contrast to other gram-negative respiratory pathogens, such as *Haemophilus influenzae* and *Neisseria meningitidis,* the LOS of *M. catarrhalis* is relatively conserved among strains; only three serotypes (A, B, and C), based on oligosaccharide structure, have been identified. Genetic and antigenic differences among strains account for the observation that resolving an infection by one strain does not induce protective immunity to other strains. *M. catarrhalis* causes recurrent infections, which generally represent reinfection by new strains.

EPIDEMIOLOGY

The ecologic niche of *M. catarrhalis* is the human respiratory tract. The bacterium has not been recovered from animals or environmental sources. **Age** is the most important determinant of the prevalence of upper respiratory tract colonization. Common throughout infancy, nasopharyngeal colonization is a dynamic process with active turnover as a result of acquisition and clearance of strains of *M. catarrhalis*. Some geographic variation in rates of colonization is observed. On the basis of monthly or bimonthly cultures, colonization during the first year of life may range from 33% to 100%. Several factors likely account for this variability among studies, including living conditions, daycare attendance, hygiene, environmental factors (e.g., household smoking), and genetics of the population. The prevalence of colonization steadily decreases with age. Understanding nasopharyngeal colonization patterns is important, because the pathogenesis of otitis media involves migration of the bacterium from the nasopharynx to the middle ear via the eustachian tube.

The widespread use of pneumococcal polysaccharide vaccines in many countries has resulted in alteration of patterns of nasopharyngeal colonization in the population. A relative decrease in colonization by vaccine pneumococcal serotypes and *M. catarrhalis* has resulted in a decreased number of new upper respiratory infection episodes **associated with** *Streptococcus pneumoniae* and *M. catarrhalis*.

PATHOGENESIS OF INFECTION

Strains of *M. catarrhalis* differ in their virulence properties. The species is composed of complement-resistant and complement-sensitive genetic lineages, with the **complement-resistant** strains being more strongly associated with virulence. Strains that cause infection in children differ in several phenotypic characteristics from strains that cause infection in adults, in whom the most common clinical manifestation is lower respiratory tract infection in the setting of chronic obstructive pulmonary disease.

The presence of several **adhesin** molecules with differing specificities for various host cell receptors reflects the importance of adherence to the human respiratory epithelial surface in the pathogenesis of infection. *M. catarrhalis* has long been viewed as an exclusively extracellular pathogen. However, the bacterium is now known to invade multiple cell types, including bronchial epithelial cells, small airway cells, and type 2 alveolar cells. In addition, *M. catarrhalis* resides intracellularly in lymphoid tissue, providing a reservoir for persistence in the human respiratory tract. As with many gram-negative bacteria, *M. catarrhalis* sheds vesicles from its surface during growth. These vesicles are internalized by respiratory epithelial cells and mediate several virulence mechanisms, including B-cell activation, induction of inflammation, and delivery of β-lactamases. Analysis of genomes reveals modest genetic heterogeneity among strains.

M. catarrhalis forms biofilms in vitro and in the middle ears of children with chronic and recurrent otitis media. It also promotes stable polymicrobial biofilms by enhancing the survival of other bacterial colonizing otopathogens. **Biofilms** are communities of bacteria encased in a matrix attached to a surface. Bacteria in biofilms are more resistant to antibiotics and to host immune responses than bacteria growing individually in planktonic form.

CLINICAL MANIFESTATIONS

M. catarrhalis causes predominantly mucosal infections in children. The mechanism of infection is **migration** of the infecting strains from the nasopharynx to the middle ear in the case of otitis media or to the sinuses in the case of sinusitis. The inciting event for both otitis media and sinusitis is often a preceding viral infection.

Acute Otitis Media

Approximately 80% of children have one or more episodes of otitis media by age 3 years. Otitis media is the most common reason that children receive antibiotics. On the basis of culture of middle ear fluid obtained by tympanocentesis, the predominant causes of acute otitis media are *S. pneumoniae, H. influenzae,* and *M. catarrhalis*. *M. catarrhalis* is cultured from the middle ear fluid in 15–20% of patients with acute otitis media. When more sensitive methods (e.g., polymerase chain reaction [PCR]) are used, the number of middle ear fluid samples from children with otitis media in which *M. catarrhalis* is detected is substantially greater than by culture alone. The distribution of the causative agents of otitis media is changing as a result of widespread administration of pneumococcal conjugate vaccines, with *M. catarrhalis* and *H. influenzae* proportionally more common than *S. pneumoniae*.

Acute otitis media caused by *M. catarrhalis* is clinically milder than otitis media caused by *H. influenzae* or *S. pneumoniae,* with less fever and lower prevalence of a red, bulging tympanic membrane. However, substantial overlap in symptoms is seen, making it impossible to predict etiology in an individual child on the basis of clinical features. Tympanocentesis is required to make an etiologic diagnosis but is not performed routinely, and thus treatment of otitis media is generally empirical.

Recurrent Otitis Media and Otitis Media with Effusion

Otitis media with effusion refers to the presence of fluid in the middle ear in the absence of signs and symptoms of acute infection. Children who experience four or more episodes of acute otitis media in a year or who have at least 8 months of middle ear effusion in a year are defined as **otitis prone**. These children have conductive hearing loss, which places them at risk for speech delays and altered language development. Analysis of middle ear fluid from children with otitis media with effusion using sensitive molecular techniques (e.g., PCR) indicates that bacterial DNA is present in up to 80% of samples from such children. Indeed, *M. catarrhalis* DNA is present, both alone and as a copathogen, in a larger proportion of cases of otitis media with effusion than of acute otitis media. Biofilms may account for these observations, although definitive evidence is lacking.

Sinusitis

A small proportion of viral upper respiratory tract infections are complicated by bacterial sinusitis. According to findings of studies that use sinus puncture, *M. catarrhalis* accounts for approximately 20% of cases of acute bacterial sinusitis in children and a smaller proportion in adults. Sinusitis caused by *M. catarrhalis* is clinically indistinguishable from that caused by *S. pneumoniae* or *H. influenzae*.

Bacteremia

M. catarrhalis rarely causes bacteremia or invasive infections in children. When bacteremia occurs, the usual source is the respiratory tract. Some children have underlying immunocompromising conditions, but no particular immunodeficiency is associated with invasive *M. catarrhalis* infections.

Pneumonia

M. catarrhalis is an uncommon cause of community-acquired pneumonia in children. Among older patients with chronic obstructive pulmonary disease, *M. catarrhalis* is associated with acute exacerbations.

DIAGNOSIS

The clinical diagnosis of otitis media is made by demonstration of erythema and bulging of the tympanic membrane and/or fluid in the middle ear by pneumatic otoscopy. A tympanocentesis is required to establish an etiologic diagnosis, but this procedure is not performed routinely. Thus the choice of antibiotic for otitis media is empirical and generally based on guidelines. Management of bacterial sinusitis is also empirical, because determining the etiology of sinusitis requires a **sinus puncture**, also a procedure that is not performed routinely.

The key to making a microbiologic diagnosis is distinguishing *M. catarrhalis* from commensal *Neisseria* organisms that are part of the normal upper respiratory tract flora. Indeed, the difficulty in distinguishing colonies of *M. catarrhalis* from *Neisseria* spp. explains in part why *M. catarrhalis* has been overlooked in the past as a respiratory tract pathogen. *M. catarrhalis* produces round, opaque colonies that can be slid across the agar surface without disruption—the "hockey puck sign." In addition, after 48 hours, *M. catarrhalis* colonies tend to be larger than *Neisseria* and take on a pink color. A variety of biochemical tests distinguish *M. catarrhalis* from *Neisseria* spp., and commercially available kits based on these tests are available.

Sensitive tests that employ PCR to detect respiratory tract bacterial pathogens in human respiratory tract secretions are in development. In addition, metagenomics next-generation sequencing is a noninvasive option to make a diagnosis of upper or lower respiratory infections associated with *M. catarrhalis* through evaluation of bacterial-derived DNA in blood samples. Their application will likely contribute new information about the epidemiology and disease patterns of *M. catarrhalis*.

TREATMENT

A high proportion of cases of *M. catarrhalis* otitis media resolve spontaneously. Treatment of otitis media is empirical, and clinicians are advised to follow guidelines of the American Academy of Pediatrics (see Chapter 680).

Strains of *M. catarrhalis* rapidly acquired β-lactamase worldwide in the 1970s and 1980s, rendering essentially all strains resistant to amoxicillin. When *M. catarrhalis* is present as a copathogen in otitis media, its β-lactamase reduces the susceptibility of nontypeable *H. influenzae* and *S. pneumoniae* to amoxicillin. Antimicrobial susceptibility patterns have remained relatively stable for decades. However, strains of *M. catarrhalis* that are resistant to macrolides and fluoroquinolones have been isolated in several centers in Asia. Careful surveillance will be important to track the potential emergence of resistant strains more widely. Most strains of *M. catarrhalis* are susceptible to amoxicillin/clavulanic acid, extended-spectrum cephalosporins, macrolides (azithromycin, clarithromycin), trimethoprim-sulfamethoxazole, and fluoroquinolones.

PREVENTION

Vaccines to prevent otitis media and other infections caused by *M. catarrhalis* are under development, but none is yet available.

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Chapter 243

Pertussis (*Bordetella pertussis* and *Bordetella parapertussis*)

Emily E. Souder and Sarah S. Long

Pertussis is an acute respiratory tract infection; the term *pertussis* means "intense cough" and is preferable to *whooping cough,* because most infected individuals do not "whoop."

ETIOLOGY

Bordetella pertussis is the cause of epidemic pertussis and the usual cause of sporadic pertussis. *Bordetella parapertussis* is an occasional cause of sporadic pertussis that contributes significantly to total cases of pertussis in Eastern and Western Europe and has been detected during occasional regional pertussis outbreaks in the United States. *B. pertussis* and *B. parapertussis* are exclusive pathogens of humans and some primates. *Bordetella holmesii,* first identified as a cause of bacteremia in immunocompromised hosts without cough illness, is increasingly reported to cause pertussis-like cough illness in small outbreaks in healthy persons. *Bordetella bronchiseptica* is a common animal pathogen. Occasional reports in humans describe a variety of body sites involved, and cases typically occur in immunocompromised persons or young children with intense exposure to animals. *Bordetella petrii,* frequently found in soil, has been reported in cases of osteomyelitis, mastoiditis, and chronic respiratory infection in patients with cystic fibrosis. *Bordetella hinzii* has been isolated from the respiratory tract of poultry and rodents and has rarely been associated with human disease, including endocarditis, bacteremia, and urinary tract infection. Protracted coughing (which in some cases can be paroxysmal) is attributable sporadically to *Mycoplasma,* parainfluenza viruses, influenza viruses, enteroviruses, respiratory syncytial virus (RSV), or adenoviruses.

EPIDEMIOLOGY

A recent modeling study estimated that in 2014, 24.1 million cases of pertussis and 160,700 deaths caused by pertussis occurred worldwide in children <5 years, reflecting significantly higher numbers than actual case counts. Before vaccination was available, pertussis was the leading cause of death from communicable disease among U.S. children <14 years, with 10,000 deaths annually. Widespread use of whole cell pertussis vaccine (DTP) led to a >99% decline in cases. After the low U.S. number of 1,010 cases reported in 1976, there was an increase in annual pertussis incidence to 1.2 cases per 100,000 population from 1980 through 1989, with epidemic pertussis in many states in 1989–1990, 1993, and 1996. Since then, pertussis has become increasingly endemic, with shifting burden of disease to young infants, adolescents, and adults. By 2004, the incidence of reported pertussis in the United States was 8.9 cases per 100,000 in the general population and approximately 150 per 100,000 in infants <2 months, with 25,827 total cases reported, the highest since 1959. A total of 40 pertussis-related deaths were reported in 2005, and 16 pertussis-related deaths were reported in 2006; >90% of these cases occurred in infants.

Prospective and serologic studies show that pertussis is underrecognized, especially among adolescents and adults, in whom the actual number of U.S. cases is estimated to be 600,000 annually. A number of studies have documented pertussis in 13–32% of adolescents and adults with cough illness for >7 days. Responding to these changes in epidemiology, vaccination containing tetanus toxoid, reduced-content diphtheria toxoid, and acellular pertussis antigens **(Tdap)** was recommended in 2006 for 11- to 12-year-olds and was aimed to enhance control. With >70% uptake of Tdap in adolescents, the burden of disease in young adolescents fell commensurately, but without evidence of protection of the community (herd) of young infants, older adolescents, and adults. An epidemiologic shift has occurred as a result of substantial and rapid waning of protection after both DTaP and Tdap in the aging cohort of children and adolescents who were not primed with DTP (whole cell) vaccine, which was no longer used in the United States after 1997. The >42,000 cases of pertussis and 20 deaths reported in 2012 were the highest numbers in >50 years. A shift in disease burden was observed among 7- to 10-year-olds in 2010, 13- to 14-year-olds in 2012, and 14- to 16-year-olds in 2014 as the cohort of solely DTaP-vaccinated persons aged.

Neither natural disease nor vaccination provides complete or lifelong immunity against pertussis reinfection or disease. Subclinical reinfection undoubtedly contributed significantly to immunity against disease ascribed previously to both vaccine and prior infection. The resurgence of pertussis can be attributed to a variety of factors, including partial control of pertussis leading to less continuous exposure and increased awareness and improved diagnostics. Rapidly waning vaccine-induced immunity and pathogen adaptation are the most important factors currently. Although the DTaP series is protective short-term, vaccine effectiveness wanes rapidly, with estimates of only 10% protection 8.5 years after the fifth dose. Tdap protection also is short-lived, with efficacy falling from >70% initially to 34% within 2-4 years. A retrospective cohort study of children born between 1999 and 2016 found that the risk of pertussis among immunized children was 5 times higher ≥3 years after vaccination compared with <1 year after vaccination. Divergence of circulating strains from vaccine strains began with the introduction of DTP, but with the exclusive use of acellular pertussis vaccines, **pertactin-deficient strains** emerged and have become dominant in countries where these vaccines are used. Pertactin-deficient *B. pertussis* was first reported in the United States from a Philadelphia infant case collection from 2008 to 2011. The Centers for Disease Control and Prevention (CDC) subsequently reported the earliest U.S. isolate from 1994 and rapid dominance of pertactin-deficient strains in the United States since 2010. Despite the role of pertactin as a bacterial virulence factor, illness severity in infants with pertactin-deficient *B. pertussis* is similar to that of pertactin-producing strains. Pending introduction of novel pertussis vaccine(s) that reduce colonization and transmission, pertussis will continue to be endemic, with cycling epidemics.

PATHOGENESIS

Bordetella organisms are small, fastidious, gram-negative coccobacilli that colonize only ciliated epithelium. The exact mechanism of disease symptomatology remains unknown. *Bordetella* species share a high degree of DNA homology among virulence genes. Only *B. pertussis* expresses **pertussis toxin (PT),** the major virulence protein. PT has numerous proven biologic activities (e.g., histamine sensitivity, insulin secretion, leukocyte dysfunction). Although injection of PT in experimental animals causes lymphocytosis immediately by rerouting lymphocytes to remain in the circulating blood pool, PT

does not cause cough. PT appears to have a central, but not a singular, role in pathogenesis. *B. pertussis* produces an array of other biologically active substances, many of which are postulated to have a role in disease and immunity. After aerosol acquisition, **filamentous hemagglutinin (FHA)**, some **agglutinogens** (especially fimbriae [Fim] types 2 and 3), and the 69-kDa **pertactin (Prn)** protein are important for attachment to ciliated respiratory epithelial cells. **Tracheal cytotoxin**, **adenylate cyclase**, and PT appear to inhibit clearance of organisms. Tracheal cytotoxin, **dermonecrotic factor**, and adenylate cyclase are postulated to be predominantly responsible for the local epithelial damage that produces respiratory symptoms and facilitates absorption of PT. Both antibody and cellular immune responses follow infection and immunization. Antibody to PT neutralizes toxin, and antibody to Prn enhances opsonophagocytosis. Both disease and DTP appear to drive a mixed cellular and antibody (Th1) immunologic response, whereas both DTaP and Tdap drive a narrow, antibody-dominant (Th2) response.

Pertussis is extremely contagious, with attack rates as high as 100% in susceptible individuals exposed to aerosol droplets at close range. High airborne transmission rates were shown in a baboon model of pertussis despite vaccination with the acellular vaccine. *B. pertussis* does not survive for prolonged periods in the environment. Chronic carriage by humans is not documented. After intense exposure, as in households, the rate of subclinical infection is as high as 80% in fully immunized or previously infected individuals. When carefully sought, a symptomatic source case can be found for most patients—usually a sibling or related adult.

CLINICAL MANIFESTATIONS

Classically, pertussis is a prolonged disease, divided into catarrhal, paroxysmal, and convalescent stages. The **catarrhal stage** (1-2 weeks) begins insidiously after an incubation period ranging from 3 to 12 days with nondistinctive symptoms of congestion and rhinorrhea variably accompanied by low-grade fever, sneezing, lacrimation, and conjunctival suffusion. As initial symptoms wane, coughing marks the onset of the **paroxysmal stage** (2-6 weeks). The cough begins as a dry, intermittent, irritative hack and evolves into the inexorable paroxysms that are the hallmark of pertussis. A well-appearing, playful toddler with insignificant provocation suddenly expresses an anxious aura and may clutch a parent or comforting adult before beginning a machine-gun burst of uninterrupted cough on a single exhalation, chin and chest held forward, tongue protruding maximally, eyes bulging and watering, face purple, until coughing ceases and a loud whoop follows as inspired air traverses the still partially closed airway. **Posttussive emesis** is common, and exhaustion is universal. The number and severity of paroxysms escalate over days to a week and remain at that plateau for days to weeks. At the peak of the paroxysmal stage, patients may have one or more episodes hourly. As the paroxysmal stage fades into the **convalescent stage** (≥2 weeks), the number, severity, and duration of episodes diminish.

Infants <3 months old do not display the classic stages. The catarrhal phase lasts only a few days or is unnoticed, and then, after the most insignificant startle from a draft, light, sound, sucking, or stretching, a well-appearing young infant begins to choke, gasp, gag, and flail the extremities, with face reddened. Cough may not be prominent, especially in the early phase, and whoop is infrequent. Apnea and cyanosis can follow a coughing paroxysm, or apnea can occur as the only symptom (without cough). Both are more common with pertussis than with neonatal viral infections. The paroxysmal and convalescent stages in young infants are lengthy. Paradoxically, in infants, cough and whooping may become louder and more classic in convalescence. "Exacerbations" of paroxysmal coughing can occur throughout the first year of life with subsequent respiratory illnesses; these are not a result of recurrent infection or reactivation of *B. pertussis*.

Adolescents and previously immunized children have foreshortening of all stages of pertussis. **Adults** have no distinct stages. Classically, adolescents and adults describe a sudden feeling of strangulation followed by uninterrupted coughs, feeling of suffocation, bursting headache, diminished awareness, and then a gasping breath, usually without a whoop. Posttussive emesis and intermittency of paroxysms separated by hours of well-being are specific clues to the diagnosis. At least 30% of adolescents and adults with pertussis have nonspecific cough illness, distinguished only by duration, which usually is >21 days.

Findings on physical examination generally are uninformative. Signs of lower respiratory tract disease are not expected unless complicating secondary bacterial pneumonia is present. Conjunctival hemorrhages and petechiae on the upper body are common.

DIAGNOSIS

Pertussis should be suspected in any individual who has a pure or predominant complaint of cough, especially if the following features are *absent*: fever, malaise or myalgia, exanthem or enanthem, sore throat, hoarseness, tachypnea, wheezes, and rales. For sporadic cases, a clinical case definition of cough of ≥14 days' duration with at least one associated symptom of paroxysms, whoop, or posttussive vomiting has a sensitivity of 81% and specificity of 58% for confirmation of pertussis. Pertussis should be suspected in older children whose cough illness is *escalating* at 7-10 days and whose coughing *is not* continuous, but rather comes in bursts. Pertussis should be suspected in infants <3 months old with gagging, gasping, apnea, cyanosis, or a brief resolved unexplained event (BRUE). Sudden infant death occasionally is caused by *B. pertussis*.

Adenoviral infections usually are distinguishable by associated features, such as fever, sore throat, and conjunctivitis. *Mycoplasma* causes protracted episodic coughing, but patients usually have a history of fever, headache, and systemic symptoms at the onset of disease as well as more continuous cough and the frequent finding of rales on auscultation of the chest. Epidemics of *Mycoplasma* and *B. pertussis* in young adults can be difficult to distinguish on clinical grounds. Although pertussis often is included in the differential diagnosis of young infants with afebrile pneumonia, *B. pertussis* is not associated with staccato cough (breath with every cough), purulent conjunctivitis, tachypnea, rales, or wheezes that typify infection by *Chlamydia trachomatis* or predominant lower respiratory tract signs that typify infection by RSV. Unless an infant with pertussis has secondary pneumonia and then appears ill, the findings on examination between paroxysms, including respiratory rate, are entirely normal. Foreign body aspiration should be considered in the differential diagnosis.

Leukocytosis (15,000-100,000 cells/μL) caused by *absolute lymphocytosis* is characteristic in the catarrhal stage. Lymphocytes are normal small cells, rather than the large, atypical lymphocytes seen with viral infections. Adults, partially immune children, and occasionally infants may have less impressive lymphocytosis. Absolute increase in neutrophils suggests a different diagnosis or secondary bacterial infection. Eosinophilia is not a manifestation of pertussis. A severe course and death are correlated with rapid-rise and extreme leukocytosis (median peak white blood cell count in fatal vs nonfatal cases: 94,000 vs 18,000/μL, respectively) and thrombocytosis (median peak platelet count in fatal vs nonfatal cases: 782,000 vs 556,000/μL, respectively). Chest radiographic findings are only mildly abnormal in the majority of hospitalized infants, showing perihilar infiltrate or edema (sometimes with a butterfly appearance) and variable atelectasis. Parenchymal consolidation suggests secondary bacterial infection. Pneumothorax, pneumomediastinum, and subcutaneous emphysema can be seen occasionally.

Methods for confirmation of infection by *B. pertussis* (culture, polymerase chain reaction [PCR], serology) have limitations in sensitivity, specificity, or practicality, and the relative value of tests depends on the setting, phase of disease, and purpose of use (e.g., as clinical diagnostic vs epidemiologic tools). **PCR** testing on nasopharyngeal wash specimens is the laboratory test of choice for *B. pertussis* identification. Both stand-alone and multiplex assays are U.S. Food and Drug Administration (FDA) cleared and available commercially. PCR assays using only single primers (IS*481*) cannot differentiate between some *Bordetella* spp. and do not detect *B. parapertussis*. Multiplex assays using multiple targets can distinguish species. All assays detect pertactin-deficient strains. For **culture**, a specimen is obtained by deep nasopharyngeal aspiration or with the use of a flexible swab

(Dacron or calcium alginate–tipped) held in the posterior nasopharynx for 15-30 seconds (or until the cough occurs). A 1% casamino acid liquid is acceptable for holding a specimen up to 2 hours; Stainer-Scholte broth or Regan-Lowe semisolid transport medium is used for longer transport periods, up to 4 days. The preferred isolation media are Regan-Lowe charcoal agar with 10% horse blood and 5-40 μg/mL cephalexin and Stainer-Scholte media with cyclodextrin resins. Cultures are incubated at 35–37°C in a humid environment and examined daily for 7 days for slow-growing, tiny, glistening colonies. Results of culture and PCR are expected to be positive in unimmunized, untreated children during the catarrhal and early paroxysmal stages of disease. *However, less than 20% of culture or PCR tests have positive results in partially or remotely immunized individuals tested in the paroxysmal stage.*

Serologic tests for detection of change in antibodies to *B. pertussis* antigens between acute and convalescent samples are the most sensitive diagnostic tests in immunized individuals and are useful epidemiologically. A single serum sample showing IgG antibody to PT >90 IU/mL (>2 standard deviations [SD] above the mean of the immunized population) indicates recent symptomatic infection and usually is positive in the mid-paroxysmal phase. Tests for IgA and IgM pertussis antibody, or antibody to antigens other than PT, are not reliable methods for serologic diagnosis of pertussis.

TREATMENT

Infants <3 months old with suspected pertussis usually are hospitalized, as are many 3- to 6-month-old patients (i.e., unless witnessed paroxysms are not severe) and patients of any age if significant complications occur. Prematurely born young infants have a high risk for severe, potentially fatal disease, and children with underlying cardiac, pulmonary, muscular, or neurologic disorders have increased risk of poor outcome beyond infancy. Table 243.1 lists caveats in the assessment and care of infants with pertussis. The specific, limited goals of hospitalization are to (1) assess progression of disease and likelihood of life-threatening events at peak of disease, (2) maximize nutrition, (3) prevent or treat complications, and (4) educate parents in the natural history of the disease and in care that will be given at home. Heart rate, respiratory rate, and pulse oximetry are monitored continuously with alarm settings so that paroxysms can be witnessed and recorded by healthcare personnel. Detailed cough records and documentation of feeding, vomiting, and weight change provide data to assess severity. Features of typical paroxysms that are not life threatening are duration <45 seconds; red, but not blue, color change; tachycardia or bradycardia (but not <60 beats/min in infants); oxygen desaturation that spontaneously resolves rapidly at the end of the paroxysm; whooping or strength for brisk self-rescue at the end of the paroxysm; self-expectorated mucus plug; and posttussive exhaustion but not unresponsiveness. Assessing the need to provide oxygen, stimulation, or suctioning requires skilled personnel who can watchfully observe an infant's ability for self-rescue but who will intervene rapidly and expertly when necessary. The benefit of a quiet, dimly lighted, undisturbed, comforting environment cannot be overestimated or forfeited in a desire to monitor and intervene. Feeding children with pertussis is challenging. The risk of precipitating cough by nipple feeding does not warrant nasogastric, nasojejunal, or parenteral alimentation in most infants. The composition or thickness of formula does not affect the quality of secretions, cough, or retention. Large-volume feedings are avoided.

Table 243.1 Considerations in the Assessment and Care of Infants with Pertussis

- Infants with potentially fatal pertussis may appear well between episodes.
- A paroxysm must be witnessed before a decision is made between hospital and home care.
- Only analysis of carefully compiled cough record permits assessment of severity and progression of illness.
- Suctioning of the nose, oropharynx, or trachea should not be performed on a "preventive" schedule.
- Feeding in the period after a paroxysm may be more successful than after napping.
- Family support begins at the time of hospitalization with empathy for the child's and family's experience to date, transfer of the burden of responsibility for the child's safety to the healthcare team, and delineation of assessments and treatments to be performed.
- Family education, recruitment as part of the team, and continued support after discharge are essential.

Within 48-72 hours, the direction and severity of disease are obvious from an analysis of the recorded information. Hospital discharge is appropriate if, over 48 hours, disease severity is unchanged or diminished, intervention is not required during paroxysms, nutrition is adequate, no complication has occurred, and parents are adequately prepared for care at home. Apnea and seizures occur in the incremental phase of illness and in patients with complicated disease. Portable oxygen, monitoring, or a suction apparatus should not be needed at home.

Infants who have apnea, paroxysms that lead to life-threatening events, or respiratory failure require escalating respiratory support and frequently require intubation and pharmaceutically induced paralysis.

Antibiotics

An antimicrobial agent always is given when pertussis is suspected or confirmed to decrease contagiousness and to afford possible clinical benefit. ***Azithromycin*** *is the drug of choice in all age-groups, either for treatment or postexposure prophylaxis* (Table 243.2). Macrolide resistance has been reported rarely in the United States, and recent isolates have retained susceptibility despite genetic strain adaptations. *Infantile hypertrophic pyloric stenosis (IHPS)* is associated with macrolide use in young infants, especially in those <14 days old, with higher risk in those receiving erythromycin vs azithromycin. The benefits of postexposure prophylaxis or treatment of infants far outweigh the risk of IHPS. Young infants should be managed expectantly if projectile vomiting occurs. The FDA also warns of the risk of fatal heart rhythms with the use of azithromycin in patients already at risk for cardiovascular events, especially those with prolongation of the QT interval. Trimethoprim-sulfamethoxazole (TMP-SMX) is an alternative to azithromycin for infants >2 months old and children unable to receive azithromycin. Because of its limited effectiveness, treatment of *B. parapertussis* is based on clinical judgment and is considered in high-risk populations. Agents are the same as for *B. pertussis*. Treatment of infections caused by other *Bordetella* spp. should be undertaken with consultation of a subspecialist.

Adjunct Therapies

No rigorous clinical trial has demonstrated a beneficial effect of β_2-adrenergic stimulants such as salbutamol and albuterol. Fussing associated with aerosol treatment triggers paroxysms. No randomized, blinded clinical trial of sufficient size has been performed to evaluate the usefulness of corticosteroids in the management of pertussis; their clinical use is not warranted. A randomized, double-blind, placebo-controlled trial of pertussis immunoglobulin (IGIV) was halted prematurely because of expiration/lack of additional supply of the study product; there was no indication of clinical benefit. Standard immunoglobulin has not been studied and should not be used for treatment or prophylaxis.

Isolation

Patients with suspected pertussis are placed in isolation with **droplet precautions** to reduce close respiratory or mucous membrane contact with respiratory secretions. All healthcare personnel should wear a mask on entering the room. Screening for cough should be performed on entrance of patients to emergency departments, offices, and clinics to begin isolation immediately and until 5 days after initiation of azithromycin therapy. Children and staff with pertussis in childcare facilities or schools should be excluded until therapy has been taken for 5 days.

Care of Household and Other Close Contacts

Azithromycin should be given promptly to all household contacts and other close contacts, such as those in daycare, regardless of age, history

Table 243.2 Recommended Antimicrobial Treatment and Postexposure Prophylaxis for Pertussis

	PRIMARY AGENTS		ALTERNATIVE AGENT*	
AGE GROUP	**AZITHROMYCIN**	**ERYTHROMYCIN**	**CLARITHROMYCIN**	**TMP-SMX**
<1 mo	Recommended agent 10 mg/kg/day in a single dose for 5 days	Not preferred Erythromycin is substantially associated with infantile hypertrophic pyloric stenosis Use if azithromycin is unavailable; 40-50 mg/kg/day in 4 divided doses for 14 days	Not recommended (safety data unavailable)	Contraindicated for infants <2 mo of age (risk for kernicterus)
1-5 mo	10 mg/kg/day in a single dose for 5 days	40-50 mg/kg/day in 4 divided doses for 14 days	15 mg/kg/day in 2 divided doses for 7 days	Contraindicated at age <2 mo For infants age ≥2 mo: TMP 8 mg/kg/day plus SMX 40 mg/kg/day in 2 divided doses for 14 days
Infants age ≥6 mo and children	10 mg/kg in a single dose on day 1 (max 500 mg), then 5 mg/kg/day (max 250 mg) on days 2-5	40-50 mg/kg/day (max 2 g/day) in 4 divided doses for 14 days	15 mg/kg/day in 2 divided doses (max 1 g/day) for 7 days	TMP 8 mg/kg/day plus SMX 40 mg/kg/day in 2 divided doses (max TMP: 320 mg/day) for 14 days
Adults	500 mg in a single dose on day 1, then 250 mg/day on days 2-5	2 g/day in 4 divided doses for 14 days	1 g/day in 2 divided doses for 7 days	TMP 320 mg/day to SMX 1600 mg/day in 2 divided doses for 14 days

*Trimethoprim-sulfamethoxazole (TMP-SMX) can be used as an alternative agent to macrolides in patients ≥2 mo old who are allergic to macrolides, who cannot tolerate macrolides, or who are infected with a rare macrolide-resistant strain of *Bordetella pertussis*.

Adapted from Centers for Disease Control and Prevention (CDC). Recommended antimicrobial agents for treatment and postexposure prophylaxis of pertussis: 2005 CDC guidelines. *MMWR*. 2005;54:1–16.

of immunization, or symptoms (see Table 243.2). The same drugs and age-related doses used for treatment are used for prophylaxis. Visitation and movement of coughing family members in the hospital must be assiduously controlled until therapy has been taken for 5 days. In close contacts <7 years old who have received fewer than four doses of DTaP, DTaP should be given to complete the recommended series. Children <7 years old who received a third DTaP dose >6 months before exposure, or a fourth dose ≥3 years before exposure, should be given a booster dose. Individuals ≥9 years old should be given Tdap. Unmasked healthcare personnel exposed to untreated cases should be evaluated for postexposure prophylaxis and follow-up. Coughing healthcare personnel with or without known exposure to pertussis should be evaluated promptly for pertussis.

COMPLICATIONS

Infants <2 months old have the highest reported rates of pertussis-associated hospitalization (82%), pneumonia (25%), seizures (4%), encephalopathy (1%), and death (1%). Infants <4 months old account for 90% of cases of fatal pertussis. Preterm birth and young maternal age are significantly associated with fatal pertussis. Neonates with pertussis have substantially longer hospitalizations, greater need for oxygen, and greater need for mechanical ventilation than neonates with viral respiratory tract infection. The strategy of preventing pertussis in newborns through the vaccination of women with Tdap during pregnancy from 27 through 36 weeks of gestation is 80–91% effective. One study found that among infants with pertussis, disease severity was reduced in those whose mothers were vaccinated during pregnancy, with maternal vaccination being 58% effective in preventing hospitalization.

The principal complications of pertussis are **apnea**, **secondary infections** (e.g., otitis media, pneumonia), and **physical sequelae** of forceful coughing. Fever, tachypnea or respiratory distress between paroxysms, and absolute neutrophilia are clues to pneumonia. Expected pathogens include *Staphylococcus aureus, Streptococcus pneumoniae,* and bacteria of oropharyngeal flora. Increased intrathoracic and intraabdominal pressure during coughing can result in conjunctival and scleral hemorrhage, petechiae on the upper body, epistaxis, pneumothorax and subcutaneous emphysema, umbilical or inguinal hernia, and rarely, hemorrhage in the central nervous system or retina. Laceration of the lingual frenulum occurs occasionally.

The need for intensive care and mechanical ventilation usually is limited to infants <3 months old and children with underlying conditions. Respiratory failure from apnea may mandate intubation and ventilation through the days when disease peaks; the prognosis is good. Progressive **pulmonary hypertension** in very young infants and secondary **bacterial pneumonia** are severe complications of pertussis and are the usual causes of death. Pulmonary hypertension and cardiogenic shock with fatal outcome are associated with extreme elevation of lymphocyte and platelet counts. Autopsies in fatal cases show luminal aggregates of leukocytes in the pulmonary vasculature. Extracorporeal membrane oxygenation of infants with pertussis in whom mechanical ventilation failed has been associated with >80% fatality (questioning the advisability of this procedure). Exchange transfusion or leukapheresis is associated with marked reduction in lymphocyte and platelet counts. Although recovery has been reported in several cases, the benefit is unproven. Echocardiography should be performed in critically ill infants with pertussis to detect the presence of pulmonary hypertension and to intervene expeditiously.

Acute neurologic events during pertussis almost always are the result of **hypoxemia** or **hemorrhage** associated with coughing or apnea in young infants. Apnea or bradycardia or both may result from apparent laryngospasm or vagal stimulation just before a coughing episode, from obstruction during an episode, or from hypoxemia after an episode. Seizures usually are a result of hypoxemia, but hyponatremia from excessive secretion of antidiuretic hormone during pneumonia can occur. The only neuropathology documented in pertussis is parenchymal hemorrhage and ischemic necrosis.

Bronchiectasis has been reported rarely after pertussis. Children who have pertussis before age 2 years may have abnormal pulmonary function into adulthood.

PREVENTION

Universal immunization of children with pertussis vaccine, beginning in infancy with reinforcing dose(s) through adolescence and adulthood, is central to the *control* of pertussis. *Prevention* of pertussis mortality in young infants depends on universal maternal immunization during each pregnancy and focused full immunization of contacts, both children and adults of all ages.

DTaP Vaccines

Several diphtheria and tetanus toxoids combined with acellular pertussis vaccines **(DTaP)** or combination products currently are licensed in the United States for children <7 years old. Acellular pertussis vaccines all contain inactivated PT and two or more additional antigens (FHA, Prn, and Fim 2 and 3). Clinical effectiveness immediately at completion of the five-dose series is approximately 80% for illness defined as "paroxysmal cough" for >21 days. Mild local and systemic adverse events are not uncommon, but more serious events (i.e., persistent crying for ≥3 hours or a hypotonic hyporesponsive episode) are rare after DTaP, are not specific to pertussis vaccine or associated with serious sequelae, and are not contraindications to subsequent doses.

Four doses of DTaP should be administered during the first 2 years of life, generally at ages 2, 4, 6, and 15-18 months. In high-risk settings, infants may be given DTaP as early as 6 weeks of age, with monthly doses through the third dose. The fourth dose may be administered as early as 12 months of age, provided that 6 months have elapsed since the third dose. When feasible, the same DTaP product is recommended for all doses of the primary vaccination series. The fifth dose of DTaP is recommended for children at 4-6 years of age; a fifth dose is not necessary if the fourth dose in the series is administered on or after the fourth birthday.

Local reactions increase modestly in rate and severity with successive doses of DTaP. Swelling of the entire thigh or upper arm, sometimes accompanied by pain, erythema, and fever, has been reported in 2–3% of vaccinees after the fourth or fifth dose of a variety of DTaP products. Limitation of activity is less than might be expected. Swelling subsides spontaneously without sequelae. The pathogenesis is unknown. Extensive limb swelling after the fourth dose of DTaP usually is not associated with a similar reaction to the fifth dose and is not a contraindication to subsequent dose(s) of pertussis vaccines.

Exempting children from pertussis immunization should be considered only within the narrow limits as recommended. Exemptors have significantly increased the risk for pertussis and play a role in outbreaks of pertussis among immunized populations. Although well-documented pertussis confers short-term protection, the duration of protection is unknown; immunization should be completed on schedule in children diagnosed with pertussis. Pertussis vaccine (DTaP or Tdap) can be administered concurrently with any vaccine on the immunization schedule.

Tdap Vaccines

Two tetanus toxoid, reduced-diphtheria toxoid, and acellular pertussis antigen vaccine (Tdap) products were licensed in 2005 and recommended universally in 2006 for adolescents. The preferred age for Tdap vaccination is 11-12 years. All adolescents and adults of any age (including ≥65 years) who have not received Tdap should receive a single dose of Tdap promptly, regardless of interval since Td, or at least in place of one Td booster at the 10-year interval, or when indicated during wound management.

Pregnant women should be given Tdap during *every* pregnancy to provide passive antibody protection to the infant until administration of DTaP. Although Tdap can be given at any time during pregnancy, optimal administration is early in the period between 27 through 36 weeks of gestation to maximize antibody concentration at birth. The safety of Tdap during pregnancy and effectiveness in reducing fatal pertussis in infants are proven. Special effort should be made to ensure that contacts of infants have received DTaP or Tdap as recommended.

Clinical trials support the safety and immunogenicity of a second dose of Tdap; however, antipertussis antibodies decline rapidly after the first year. The CDC performed a decision analysis model of repeating Tdap at either a 5- or 10-year interval for the general population and concluded that "booster(s)" would have limited impact on pertussis disease burden. There is not a recommendation for a routine second dose of Tdap in the general population. A single dose of Tdap should be given to children 7-10 years of age who lack DTaP dose(s). Since 2019, the updated CDC recommendations allow use of either Tdap or Td when Td alone is indicated for catch-up dose(s), or for decennial immunization, or for wound management in individuals who have received Tdap.

Vaccines Under Development

Several strategies are being tested to create pertussis vaccines that elicit a Th1 response, dampen the density of mucosal infection and transmission, provide sustained protection against disease, and have tolerable reactogenicity. These include use of live attenuated *B. pertussis,* a genetically (rather than a chemically) inactivated PT component, novel antigens, and adjuvants.

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Chapter 244

Salmonella

Jeffrey S. McKinney

Salmonellosis is one of the most widely distributed and common food-borne and fecal-oral diseases in humans, and ***Salmonellae*** live in the intestinal tracts of multiple species. *Salmonella* infections are a major public health problem, with disproportionate morbidity and mortality among infants and children and in certain immunocompromised individuals.

Clinically, *Salmonellae* have been most broadly classified as being either nontyphoidal or typhoidal, with the latter causing typhoid (also known as *enteric*) fever. The differences in the disease manifestations from these two groups of pathogens, one predominantly causing intestinal inflammation and the other leading to systemic disease, are increasingly understood to be related to specific genes and pathogenicity islands in the genomes of the respective organisms.

Most nontyphoidal serovars of *Salmonella* (widely distributed across multiple host species) are rarely able to overcome defense mechanisms in humans that limit bacterial dissemination from the intestine. Thus in immunocompetent humans, nontyphoidal serovars usually produce a self-limiting gastroenteritis. By contrast, *S.* Typhi and *S.* Paratyphi (i.e., the typhoidal strains of *Salmonella,* notably host-restricted to only humans) possess virulence traits that more readily allow them to overcome mucosal barrier functions and then cause severe systemic illness, even in immunocompetent patients.

However, a purely binary classification of *Salmonellae* as nontyphoidal vs typhoidal can be a problematic oversimplification. For example, reports from Africa have identified strains of nontyphoidal *Salmonellae* that are highly invasive and increasingly common. Like many gram-negative bacteria, mobile or differentially expressed genetic elements can radically alter phenotypes in *Salmonellae,* sometimes in direct response to selective pressures like antimicrobial exposures given to individual patients and/or in broader settings like agricultural antimicrobial use.

Although DNA hybridization studies result in enough similarities for all *Salmonellae* to currently be classified in the single species *Salmonella enterica,* serologic studies can resolve more than 2,000 serotypes. Serotype and DNA sequencing identification has helped clinical laboratories better trace disease outbreaks, and the Centers for Disease Control and Prevention (CDC) has published recent guidelines for a more consistent terminology to help both laboratory and clinical teams confront complex classification nomenclature.

Host differences are also profoundly relevant to the outcomes of *Salmonella* exposures, infections, and disease. Infants and children, patients with certain immunologic vulnerabilities, and the extent to which a given *Salmonella* infection can evade host defenses and/or antibacterial drugs can help predict, or at least better understand, the ultimate impact of *Salmonella* on both individual and public health.

244.1 Nontyphoidal Salmonellosis

Jeffrey S. McKinney

ETIOLOGY

Salmonellae are motile, nonsporulating, gram-negative rods that grow in aerobic and facultative anaerobic conditions. They remain viable at ambient or reduced temperatures for days and may survive for weeks in sewage, foods, pharmaceutical agents, and fecal material. They are resistant to many physical agents but can be killed by heat to 54.4°C (130°F) for 1 hour or 60°C (140°F) for 15 minutes.

Most serotypes of nontyphoidal *Salmonella* have a broad host spectrum, including both warm-blooded and cold-blooded vertebrates, and even insects like flies and cockroaches. Some serotypes have more limited host ranges, such as *S. dublin* in cattle (recovered in human infections associated with unpasteurized milk) and *S. choleraesuis* in pigs. In human infections, these two serotypes also have a notable propensity to cause more bacteremia and fewer gastrointestinal symptoms as compared with many other nontyphoidal *Salmonellae*. In sub-Saharan Africa, nontyphoidal *Salmonella* has become a leading cause of **bacteremia**. Up to 95% of the serovars associated with invasive *Salmonella* disease among children in this geographic region are *Salmonella* serovar Typhimurium (mostly of an unusual variant designated **multilocus sequence type 313**), a variant of sequence type 313 that does not express phase 2 flagella, or *Salmonella* serovar Enteritidis. This information represents a deviation from the historical assumption that nontyphoidal *Salmonella* is, by definition, relatively noninvasive.

In the United States, nontyphoidal *Salmonella* infections still generally cause **gastroenteritis** that is localized and self-limiting. In these uncomplicated cases, nontyphoidal *Salmonella* infection does not justify treatment with antibiotics. However, nontyphoidal infections can be severe in the young, the elderly, and patients with vulnerabilities in their immunity.

EPIDEMIOLOGY

Salmonellosis has a significant cost to society. Globally, estimates suggest there are more than 90 million cases of *Salmonella* gastroenteritis annually, causing more than 150,000 deaths. In the United States, CDC estimates suggest an annual burden of more than 1.3 million *Salmonella* infections, causing more than 26,000 hospitalizations, 420 deaths, and $400 million in direct medical costs, with approximately 30 people with unreported *Salmonella* illness for every one case confirmed by a laboratory test. Nearly half of culture-proven nontyphoidal *Salmonella* infections occur in children, with the highest incidence among infants. With the burden of HIV infections and malnutrition in Africa, nontyphoidal *Salmonella* bacteremia has emerged as a major cause of morbidity and mortality among both children and adults in Africa.

Nontyphoidal *Salmonella* has a worldwide distribution, with the incidence influenced by local standards of hygiene, sanitation, and availability of safe water and food. Modern practices of mass food production and distribution increase the potential for epidemics, which may be scattered so broadly as to only be fully appreciated via **robust national monitoring systems**, such as the CDC's **FoodNet** (https://www.cdc.gov/foodnet/foodnet-fast.html). FoodNet also helps build capacity for food-borne disease surveillance through close collaborations with PulseNet, EHS-Net, Global SalmSurv, and other partners.

Poultry meat and eggs are traditionally known to be a common source of salmonellosis, and even riding in a shopping cart next to poultry meat is a risk factor for infection of infants. However, consumption of a wide variety of foods has now been associated with outbreaks, including fruits, vegetables, and multiple factory-processed foods such as peanut butter, cookies, and infant formula.

Salmonella infections in many parts of the world may be related to **animal husbandry practices**, including drug-resistant strains that emerge in response to the widespread use of agricultural antimicrobials. Subtherapeutic antimicrobials are often added to animal feeds to promote animal growth. There is now strong evidence linking resistance to quinolones to the use of this group of antimicrobials in animal feeds. Resistance to ciprofloxacin approached 10% of all nontyphoidal *Salmonella* isolates assessed by the CDC in 2017.

In addition to the effect of antibiotic use in animal feeds, the relationship of *Salmonella* infections to prior antibiotic use in children in the month before the infection is well recognized. This association may be related to alterations in gut microbial ecology, which predisposes to colonization and infection with antibiotic-resistant *Salmonella* isolates. The CDC reports that nontyphoidal *Salmonella* isolates during the period 2015–2017 continue to manifest increasing rates of resistance, with 16% of isolates being resistant to at least one essential antibiotic (including ciprofloxacin, azithromycin, ceftriaxone, ampicillin, and trimethoprim-sulfamethoxazole). *Variation in resistance among different strains makes Salmonella culture and antibiotic susceptibility testing very important.*

It appears that some **multidrug-resistant (MDR)** strains of *Salmonella* are also more virulent than susceptible strains. Poor clinical outcomes with these infections do not relate solely to the initial empiric choice of ineffective antibiotics. Over the past 3 decades, ***S.* Typhimurium phage type DT104** has emerged as a globally disseminated MDR strain. Typically resistant to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline, DT104 also has the capacity to acquire resistance to other antibiotics. Many of the resistance genes in DT104 are harbored on genomic islands. Integrons can also encode and disseminate virulence genes.

Several risk factors are associated with outbreaks of *Salmonella* infection. Animals constitute the principal source of human disease from nontyphoidal *Salmonella*. **High-risk pets** include reptiles, amphibians, poultry and other birds, rodents, and other small mammals. The risk of *Salmonella* from turtles was so high that the U.S. Food and Drug Administration (FDA) banned the interstate sale and distribution of turtles with shell length of less than 4 inches. Exposures can also occur from contact with cages or tanks with pets, from touching some pet foods and treats, and even at zoos *without* direct contact with an infected animal.

Animals that carry *Salmonella* still appear healthy and clean and can readily transmit nontyphoidal *Salmonella,* including in **childcare centers and schools**. When nontyphoidal serovars are identified in a childcare attendee or staff member, adherence to hygiene practices is used to control infection. Return to school is allowed as long as stools are contained in a young child's diaper, toilet-trained children do not have accidents using the toilet, and stool frequency becomes no more than two stools above the child's normal stooling frequency per day. In notable contrast to infections with typhoidal strains, demonstration of clearance of nontyphoidal *Salmonella* from stool cultures is neither sought nor required.

Given the ubiquitous nature of the organism, **nosocomial infections** with nontyphoidal *Salmonella* strains can also occur via contaminated equipment and diagnostic or pharmacologic preparations. Patient-to-patient spread can also occur in hospital settings, particularly among vulnerable hosts like neonates. Nursery nosocomial infections from *Salmonella* can be very difficult to control, sometimes taking months to stop and/or serving as a source for further spread through a hospital.

PATHOGENESIS

The estimated number of bacteria that must be ingested to cause symptomatic disease in healthy adults is 10^6-10^8 *Salmonella* organisms. Normal gastric acidity inhibits *Salmonella* multiplication, with most organisms rapidly killed at gastric pH <2.0. Achlorhydria, buffering medications, and rapid gastric emptying after gastroenterostomy allow more viable organisms to reach the small intestine and thus lower the infectious dose. Neonates and infants have hypochlorhydria and rapid gastric emptying, which contribute to their increased vulnerability to infection, even at lower inoculum exposures.

The typical intestinal response to nontyphoidal *Salmonella* infection is **enterocolitis**, with diffuse mucosal inflammation and edema, sometimes with erosions and microabscesses. Intestinal inflammation with neutrophils and macrophages usually involves the lamina propria. Underlying intestinal lymphoid tissue and mesenteric lymph

nodes enlarge and may demonstrate small areas of necrosis. Lymphoid hypertrophy may interfere with blood supply to the gut mucosa and/or serve as a leading edge for intussusception. Hyperplasia of the reticuloendothelial system can also be found in the liver and spleen. If bacteremia develops, it may lead to localized infection and suppuration in almost any organ.

Central to *S.* Typhimurium pathogenesis are two **type III secretion systems**. These systems secrete and translocate bacterial proteins termed **effectors** into host cells. These effectors manipulate the host cell to allow bacterial invasion and assembly of an intracellular niche conducive to bacterial survival and replication. Two **genomic pathogenicity islands** encode these type III systems.

The *Salmonella* pathogenicity island 1 (SPI-1) is involved with epithelial cell adherence and invasion (Fig. 244.1), which involves host cell membrane ruffling caused by organized actin rearrangement (Fig. 244.2). This adherent and invasive phenotype of *Salmonella* is activated under conditions like those found in the human small intestine (high osmolarity, low oxygen).

The *Salmonella* pathogenicity island 2 (SPI-2) is involved with formation of the *Salmonella*-containing vacuole (Fig. 244.3), creating a replication-permissive intracellular space (Fig. 244.4). Intracellular *S.* Typhimurium is found within special vacuoles that have diverged from the normal endocytic pathway. An ability to survive within monocytes/macrophages is a key process for *S.* Typhimurium to establish a systemic infection. Survival within host cells also shields *Salmonella* from antimicrobials. For example, gentamicin is not considered effective in vivo against *Salmonella,* even for strains found susceptible to this drug in vitro, because gentamicin does not effectively reach intracellular bacteria.

Bacteremia and systemic disease are possible with any *Salmonella* serotype, especially in individuals with reduced host defenses. Inflammatory bowel disease or gut ischemia can cause intestinal mucosal barrier defects. Malnutrition, corticosteroid therapy, interleukin (IL)-12/interferon gamma axis defects, and posttransplant immunosuppressant agents can significantly compromise cell-mediated immunity. The reticuloendothelial system can be overloaded with hemoglobin or iron or have impaired function from lymphoma or leukemia. In addition, other underlying systemic conditions can predispose to serious *Salmonella* infections, including sickle cell disease, collagen vascular diseases, HIV/AIDS, defects in T_H1 or T_H17 immunity, and chronic granulomatous disease.

As stated earlier, neonates and infants less than 3 months of age are also at higher risk of bacteremia from nontyphoidal *Salmonella*. This risk influences empiric treatment with appropriate antibiotics, even in otherwise healthy patients in this young age-group.

Patients with sickle cell disease are at very high risk for *Salmonella* septicemia and osteomyelitis. This risk may be related to the presence of numerous infarcted areas in the gastrointestinal tract, bones, and reticuloendothelial organs, along with reduced phagocytic and opsonizing capacity of patients with sickle cell disease.

CLINICAL MANIFESTATIONS

Acute Enteritis

The most common clinical presentation of salmonellosis is acute enteritis. After an incubation period of 6-72 hours (mean 24 hours), there is often abrupt-onset nausea, vomiting, and crampy abdominal pain, located predominantly in the periumbilical area and the lower abdominal quadrants. These symptoms are usually followed by mild to severe watery diarrhea, sometimes containing blood, neutrophils, and mucus. Although fever is a classic feature, younger infants may exhibit a normal or subnormal temperature. Symptoms usually subside within 2-7 days in otherwise healthy children. However, some children experience a septicemia-like picture, with symptoms including high fever, drowsiness, confusion, abdominal distention, meningismus, and/or seizures.

Bacteremia

After *Salmonella* gastroenteritis, it is estimated that 1–5% of otherwise healthy children are thought to experience transient bacteremia after nontyphoidal *Salmonella* in U.S. settings. Bacteremia is usually accompanied by fever in older children but is often not associated with fever in infants. As described earlier, specific vulnerable hosts are far more likely to have systemic infection. Children with HIV can have recurrent nontyphoidal *Salmonella* septicemia, despite antibiotic therapy, even without positive stool cultures or any clear nidus of infection. Some nontyphoidal strains are more likely to result in bacteremia, even without obvious gastrointestinal symptoms, including *S. dublin* and *S. choleraesuis*. In Africa, nontyphoidal *Salmonella* is a much more common cause of pediatric bacteremia (see next).

Nontyphoidal *Salmonella* Bacteremia as Emerging Disease in Africa

In Africa, particularly sub-Saharan Africa, nontyphoidal *Salmonella* has been increasingly recognized among the most common causes of *all* bacteremia in febrile children. Children age 6-36 months are at greatest risk, and case fatality rates can reach 25%.

Clinical features among children with invasive nontyphoidal *Salmonella* infections can be confusing, as diarrhea is often *not* a prominent feature. Furthermore, 60% of these children have an apparent lower respiratory tract infection (perhaps from co-infection or comorbidity). Fever is present in 95% but may have no apparent focus. Figure 244.5 summarizes other clinical features. The lack of specificity of these features severely compromises the ability of current clinical algorithms to identify invasive nontyphoidal *Salmonella* infections. Accordingly, blood culture and clinical microbiology systems for bacterial growth, isolation, speciation, and antibiotic susceptibility testing are required for diagnosis and well-informed treatment decision-making.

It remains unclear exactly why invasive infections by nontyphoidal *Salmonella* seem so much more frequent in Africa compared with the dominance of typhoid *Salmonellae* in Asia. HIV is one identified host risk factor for nontyphoidal *Salmonella* infection. Indeed, recurrent nontyphoidal *Salmonella* infection was part of early CDC case definitions for AIDS. However, only 20% of African children with invasive nontyphoidal *Salmonella* disease are HIV positive. Other risks for invasive nontyphoidal *Salmonella* may include recent or severe malaria infections, anemia, and malnutrition.

The epidemic patterns thus far appreciated for invasive infections by nontyphoidal *Salmonella* in Africa suggest that epidemics may occur over several years, peaking in the rainy season. However, it remains unclear how relevant human diarrheal disease or gastrointestinal carriage, or even food or zoonotic sources are, for invasive nontyphoidal *Salmonella* infection in this setting. Thus optimal strategies for interrupting transmission are also not known. This is particularly problematic, given the emergence of extensive antibiotic resistance among nontyphoidal *Salmonella* isolates, including the lineage referred to as *sequence type 313* (ST313).

Recent studies have attempted to better understand the geographic spread and genetic features of ST313 lineage variants isolated internationally over time. Intriguingly, the antibiotic-resistance patterns of these lineages seem to correlate with some large-scale or sequential changes in empiric (e.g., chloramphenicol, third-generation cephalosporins, ciprofloxacin, and azithromycin) antibiotic use. ST313 lineage genomic analysis also reveals the accumulation of **pseudogenes**, in what may be crucial ***loss*-of-function genetic events** involved in ST313 stepwise evolution, perhaps as part of adaptation to a more restricted (human) host range and from an intestinal to a systemic lifestyle.

For invasive nontyphoidal *Salmonella* infections in Africa, evolving resistance patterns seem likely to force increasing reliance on more expensive treatment options. Local resistance patterns may help empirically, but given the rapid spread of various ST313 lineages, susceptibility testing of individual patient isolates will be needed to ensure appropriate antibiotic choices. Targeted resistance gene sequencing, especially for gyrase mutations related to quinolone resistance, may also be warranted as that drug class becomes more widely used.

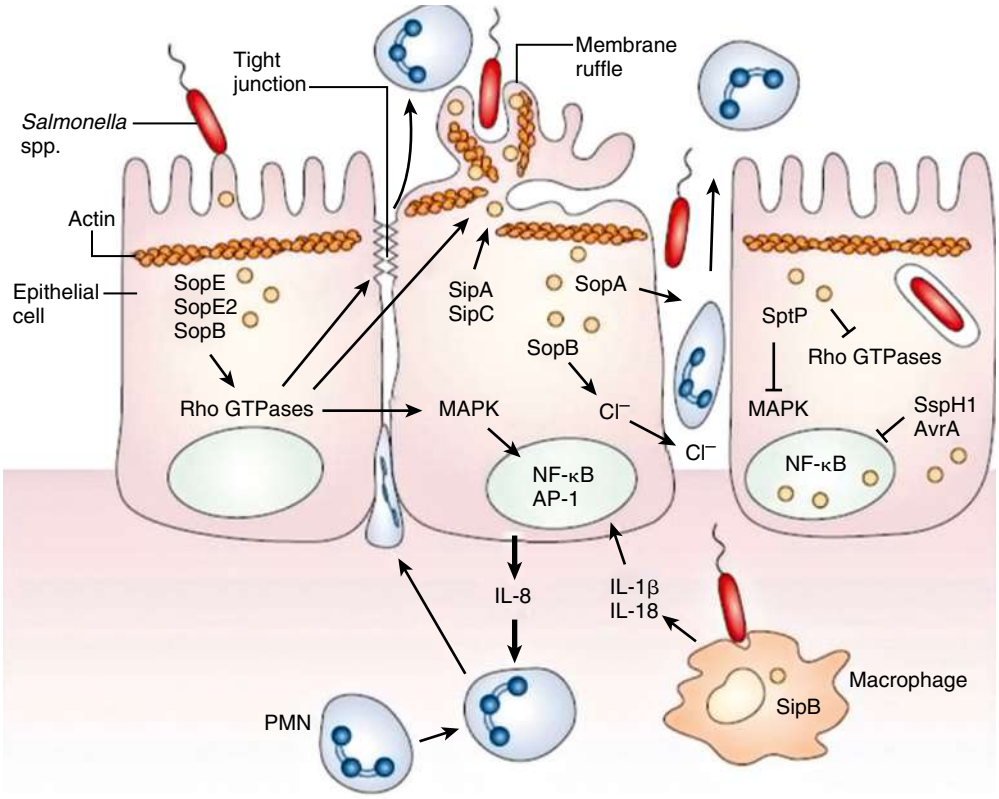

Fig. 244.1 On contact with the epithelial cell, *Salmonellae* assemble the *Salmonella* pathogenicity island 1–encoded type III secretion system (TTSS-1) and translocate effectors *(yellow spheres)* into the eukaryotic cytoplasm. Effectors such as SopE, SopE2, and SopB then activate host Rho guanosine triphosphatase (GTPase), resulting in the rearrangement of the actin cytoskeleton into membrane ruffles, induction of mitogen-activated protein kinase (MAPK) pathways, and destabilization of tight junctions. Changes in the actin cytoskeleton, which are further modulated by the actin-binding proteins SipA and SipC, lead to bacterial uptake. MAPK signaling activates the transcription factors activator protein-1 (AP-1) and nuclear factor-κB (NF-κB), which turn on production of the proinflammatory polymorphonuclear leukocyte (PMN) chemokine interleukin (IL)-8. SipB induces caspase-1 activation in macrophages, with the release of IL-1β and IL-18, augmenting the inflammatory response. In addition, SopB stimulates Cl^- secretion by its inositol phosphatase activity. The destabilization of tight junctions allows the transmigration of PMNs from the basolateral to the apical surface, paracellular fluid leakage, and access of bacteria to the basolateral surface. However, the transmigration of PMNs also occurs in the absence of tight-junction disruption and is further promoted by SopA. The actin cytoskeleton is restored, and MAPK signaling is turned off by the enzymatic activities of SptP. This also results in the downmodulation of inflammatory responses, to which SspH1 and AvrA also contribute by inhibiting activation of NF-κB. *(From Haraga A, Ohlson MB, Miller SI. Salmonellae interplay with host cells. Nat Rev Microbiol. 2008;6:53–66.)*

Nontyphoidal *Salmonella* Bacteremia in Other Geographic Regions

The emergence of invasive, high-mortality nontyphoidal *Salmonella* infections in Africa underscores that the traditional binary division of *Salmonella* infections into typhoidal vs nontyphoidal may be a problematic oversimplification. However, in settings outside of Africa, nontyphoidal *Salmonella* infections still tend to be self-limiting and noninvasive and are low-mortality events for most children who are immunocompetent.

Risk factors for systemic spread of nontyphoidal *Salmonella* include underlying sickle cell disease, HIV/AIDS, intestinal mucosal barrier defects, malnutrition, IL-12/interferon gamma axis defects, defects in T_H1 or T_H17 immunity, corticosteroid therapy or posttransplant immunosuppressants, reticuloendothelial system dysfunction (e.g., from overload with hemoglobin or iron), lymphoma or leukemia, collagen vascular diseases, and chronic granulomatous disease. Neonates and infants less than 3 months of age are also at higher risk of bacteremia from nontyphoidal *Salmonella*.

Extraintestinal Focal Infection

After bacteremia, *Salmonellae* have the propensity to cause focal suppurative infection of many organs. The most common focal infections involve the skeletal system, meninges, and intravascular sites. The peak incidence of *Salmonella* meningitis is in infancy, and the infection may be associated with a florid clinical course, high mortality, and neurologic sequelae in survivors.

Chronic *Salmonella* Carriage

Although traditionally considered a complication among *adults* with *Salmonella* infection, chronic *Salmonella* carriage has important medical and epidemiologic implications and may occasionally occur in children. Colonization of the gallbladder by *S.* Typhi and persistent shedding from the gallbladder have long been appreciated. Reports suggest some nontyphoidal *Salmonellae* (e.g., invasive nontyphoidal *Salmonella* currently in Africa) can also establish long-term carriage states.

Antibiotic treatments of *Salmonella* infections are paradoxical in that the prospect of becoming a chronic carrier is believed to be increased by exposure to antibiotics. Yet clearance of established chronic carrier status requires prolonged medical treatment using antibiotics to which the *Salmonella* is susceptible and sometimes requires gallstone or gallbladder removal.

DIAGNOSIS

Few clinical features are specific enough to *Salmonella* to allow differentiation from other infectious causes of gastroenteritis or diarrhea. Serologic tests also do not have diagnostic value. Definitive diagnosis requires identification of *Salmonella* via stool **nucleic acid amplification test** (NAAT) or **bacterial cultures**. Stool cultures have higher yields

than rectal swabs. Blood cultures are suggested for patients at higher risk of bacteremia or endovascular focus and when enteric fever is a concern. Additionally, cultures of bone marrow (particularly valuable if antimicrobial agents have been administered or if stringent criteria are met for **fever of unknown origin**), duodenal fluid, and urine may be beneficial to detect enteric fever. In patients with sites of local suppuration, aspirated specimens should be Gram-stained and cultured.

Salmonella organisms grow well on nonselective or enriched media, such as blood agar, chocolate agar, and nutrient broth, but stool specimens containing mixed bacterial flora require a selective medium, such as McConkey, xylose-lysine-deoxycholate, bismuth sulfate, or Salmonella-Shigella (SS) agar for isolation of *Salmonella*. Given *Salmonella* variation and evolution, it is important to pursue bacterial isolation, species identification, and ***antibiotic susceptibility testing*** *to best inform the choice of effective therapeutic agents.* State public health laboratories require *Salmonella* isolates as part of outbreak detection and investigation, increasingly via genomic characterization of strains.

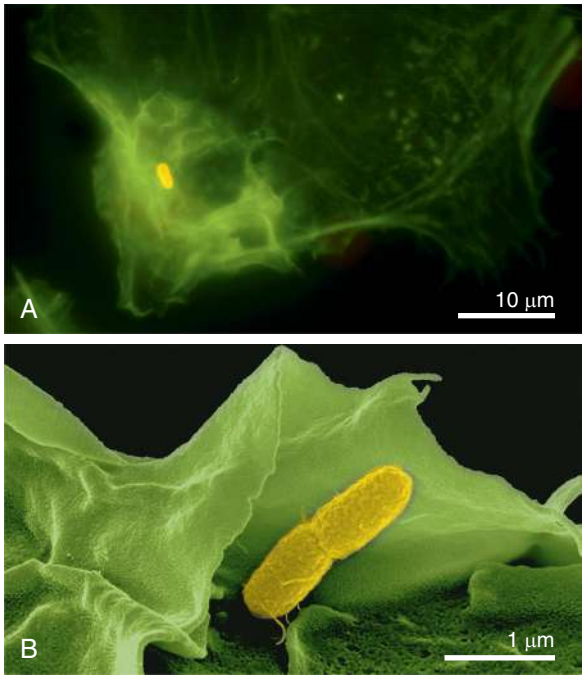

Fig. 244.2 *Salmonella* SPI-1–mediated effects include host cell actin cytoskeletal rearrangements and host cell membrane ruffling as part of *Salmonella* invasion. **A,** HeLa cell infected with *Salmonella* fixed and stained for the actin cytoskeleton with phalloidin *(green)* and for *Salmonella (yellow).* **B,** Cos cell infected with *Salmonella* and prepared for scanning electron microscopy. Cell surface extensions in the process of enveloping the bacterium are pseudocolored green, and the microbe is in yellow. *(From Rottner K, Stradal TEB, Wehland J. Bacteria-host-cell interactions at the plasma membrane: stories on actin cytoskeleton subversion. Dev Cell. 2005;9:3–17.)*

TREATMENT

Appropriate therapy depends on the specific clinical presentation of *Salmonella* infection. In children with gastroenteritis, rapid clinical assessment, correction of dehydration and electrolyte disturbances, and supportive care are key. Antimotility drugs (e.g., loperamide) should not be given to children less than 18 years of age with acute diarrhea, but antiemetic drugs (e.g., ondansetron) can be given to facilitate oral rehydration in children older than 4 years.

Antibiotics are generally *not* recommended for the treatment of isolated uncomplicated *Salmonella* gastroenteritis because they can disrupt normal intestinal flora and potentially prolong the fecal excretion of *Salmonella*.

However, empiric antibiotics are started for young infants (<3 months old) and for children with increased possibility of disseminated infection (e.g., children with HIV, malignancies, sickle cell disease, immunodeficiencies, or immunosuppression, as detailed earlier). In the United States, this empiric therapy includes a third-generation cephalosporin, with a blood culture obtained just before the initial dose. If a patient does not appear ill and does not have any evidence of disseminated infection, oral azithromycin can be started, pending blood culture results. Ampicillin, trimethoprim-sulfamethoxazole, or a fluoroquinolone may be considered as treatment options for susceptible strains.

In cases of bacteremia, blood cultures need to be repeated to confirm clearance of infection. Transition from parenteral third-generation

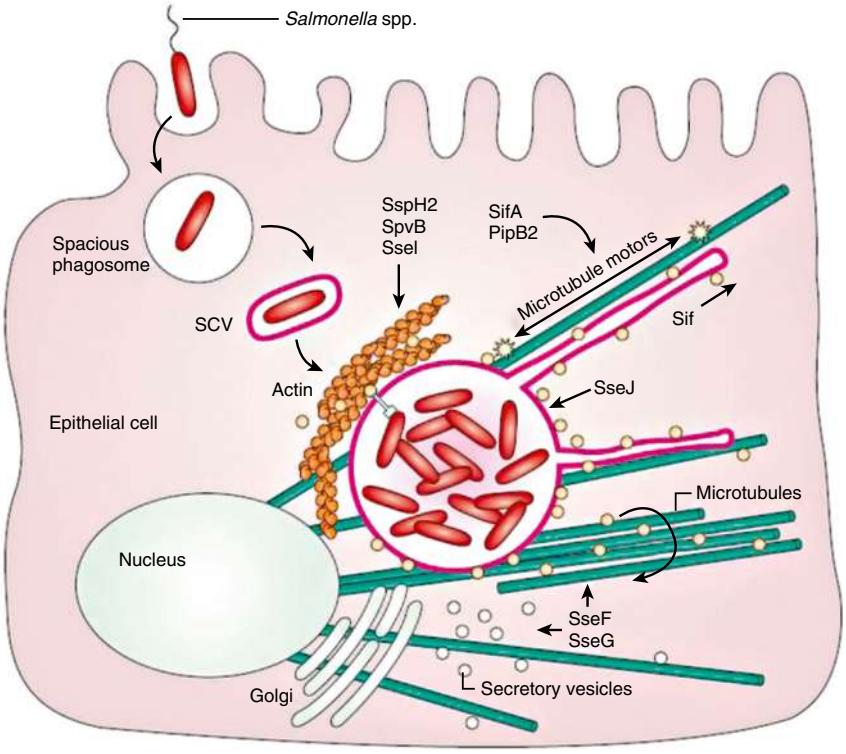

Fig. 244.3 Formation of the *Salmonella*-containing vacuole (SCV) and induction of the *Salmonella* pathogenicity island 2 (SPI-2) type III secretion system (TTSS) within the host cell. Shortly after internalization by macropinocytosis, *Salmonellae* are enclosed in a spacious phagosome that is formed by membrane ruffles. Later, the phagosome fuses with lysosomes, acidifies, and shrinks to become adherent around the bacterium and is called the SCV. It contains the endocytic marker lysosomal-associated membrane protein 1 (LAMP-1; *purple*). The *Salmonella* SPI-2 is induced within the SCV and translocates effector proteins *(yellow spheres)* across the phagosomal membrane several hours after phagocytosis. The SPI-2 effectors SifA and PipB2 contribute to formation of *Salmonella*-induced filament along microtubules *(green)* and regulate microtubule motor *(yellow star shape)* accumulation on the Sif and the SCV. SseJ is a deacylase that is active on the phagosome membrane. SseF and SseG cause microtubule bundling adjacent to the SCV and direct Golgi-derived vesicle traffic toward the SCV. Actin accumulates around the SCV in an SPI-2–dependent manner, in which SspH2, SpvB, and SseI are thought to have a role. *(From Haraga A, Ohlson MB, Miller SI. Salmonellae interplay with host cells. Nat Rev Microbiol. 2008;6:53–66.)*

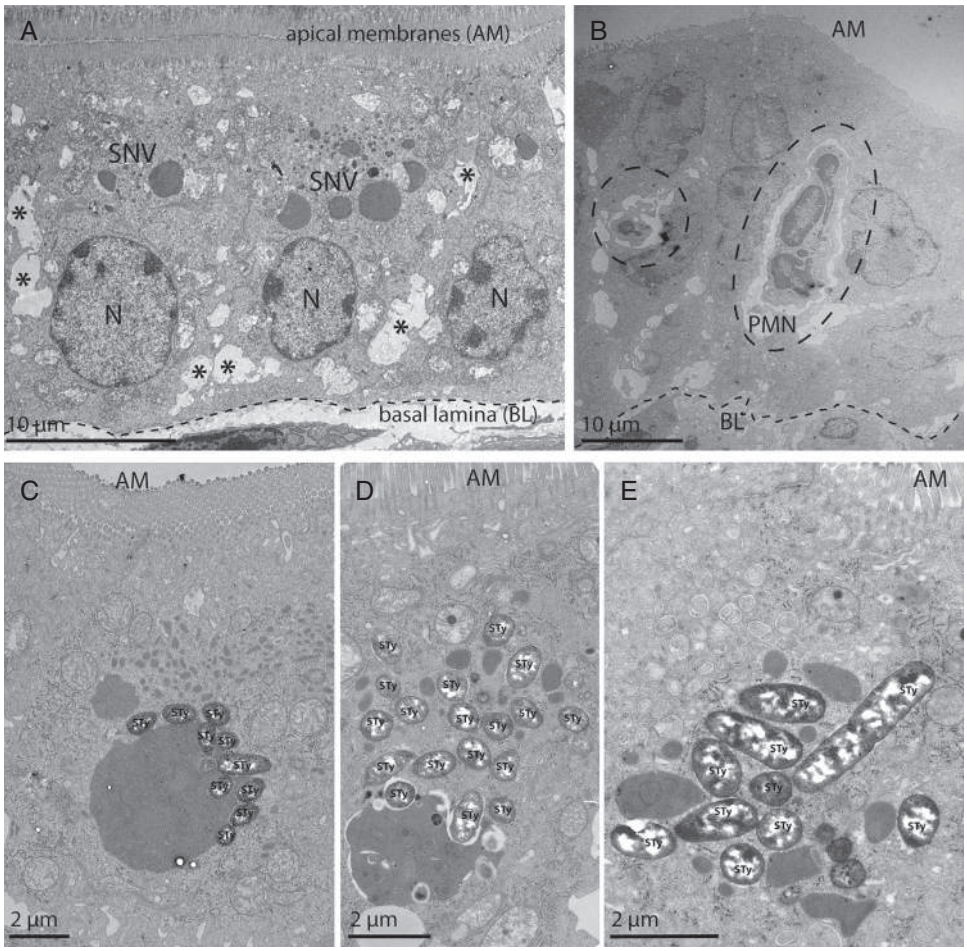

Fig. 244.4 Ultrastructural analysis of the distal small intestine with transmission electron microscopy. Distal small intestinal tissue was fixed with 1% glutaraldehyde. Short segments were cut open, post fixed with osmium tetroxide, contrasted with uranyl acetate, and dehydrated with a graded ethanol series before been embedded in epoxy resin. Thin sections were contrasted with lead citrate and analyzed in a JEM-1400 transmission electron microscope (JEOL). Images were taken with TemCam-F216 camera using EM MENU software (both TVIPS). **A,** Enterocytes in the distal intestine of healthy 5-day old neonates exhibit large supranuclear vacuoles (SNV) in their apical cytoplasm; the nuclei are situated at the basolateral site (N). SNV contain internalized milk proteins. Asterisks indicate intercellular spaces between enterocytes. **B,** 4 days after infection of 1-day-old mice with S. Typhimurium, the epithelium is infiltrated by polymorphonuclear cells (PMN). **C-E,** Intraepithelial Salmonella microcolonies are observed. Some bacteria reside in spherical vacuoles, which contain electron-dense material resembling the content of SNVs. Other bacteria appear to be localized in tight membrane-bound vesicles with few visible connections between them, or with vesicles filled with electron dense material. *(From Zhang K, Griffiths G, Repnik U, Hornef M. Seeing is understanding: Salmonella's way to penetrate the intestinal epithelium. Int J Med Microbiol. 2018 Jan;308:97-106. Fig. 2.)*

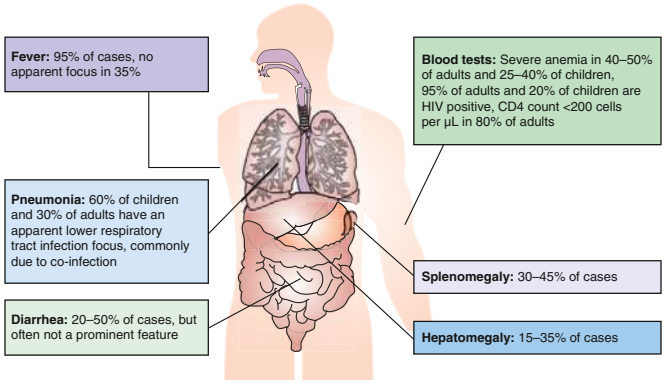

Fig. 244.5 Clinical features of invasive nontyphoidal Salmonella (NTS) disease in adults and children in Africa. *(From Feasey NA, Dougan G, Kingsley RA, et al. Invasive non-typhoidal Salmonella disease: an emerging and neglected tropical disease in Africa. Lancet. 2012;379: 2489–2499.)*

cephalosporin to oral azithromycin or a fluoroquinolone can be considered after documented clearance of blood cultures and exclusion of secondary sites, for a total 7- to 10-day course. Disseminated disease needs to be rigorously excluded, as therapy is more prolonged for meningitis (4 weeks) and osteomyelitis or other focal metastatic infections (4-6 weeks).

Given the heterogeneity, evolution, and rapid geographic spread of *Salmonella,* it is important to maintain awareness of resistance trends as related to local and national community isolate patterns, any relevant interstate outbreaks, and global patterns of emerging *Salmonella* resistance. Serially updated resources with this information include local microbiology laboratory data and open-access reporting systems like the U.S. National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS). In NARMS reports from 2018, the majority (81%) of nontyphoidal *Salmonella* from humans were still *not* resistant to any of the antimicrobials tested. However, approximately 3%, 10%, and 0.3% of nontyphoidal *Salmonella* isolated from humans were intrinsically resistant to ceftriaxone, ciprofloxacin, and azithromycin, respectively.

Some contemporary nontyphoidal *Salmonellae* are of particular interest, given their resistance to antimicrobials. *S.* Typhimurium DT104 spread globally in the 1990s, when it was resistant to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline. DT104 now sometimes also has reduced susceptibility to fluoroquinolones. Nontyphoidal *Salmonella* ST313 lineages (described earlier) continue

to show resistance pattern evolution in Africa. In the United States, *S.* Infantis has now supplanted other leading serotypes in poultry and not only exhibits deceased susceptibility to fluoroquinolones because of a gyrA pathogenic variant but also contains an MDR plasmid that carries up to 10 resistance genes, conferring resistance to cephalosporins, tetracycline, chloramphenicol, and sulfonamides. This MDR strain of serovar Infantis has been reported to account for up to 35% of the nontyphoidal Salmonella infections in Israel.

PROGNOSIS

Most otherwise healthy children with *Salmonella* gastroenteritis recover fully without antimicrobial treatment. Malnourished children and those who do not receive adequate supportive care can be at risk for prolonged diarrhea and complications. Young infants and immunocompromised patients often have systemic involvement, and children with HIV can have a florid and recurring course.

After infection, nontyphoidal *Salmonella* are excreted in feces for a median of 5 weeks, during which time the recovering patient can infect others via fecal-oral routes or by contaminating foods. A prolonged carrier state is rare in children but is more common among those with biliary tract disease and/or cholelithiasis.

PREVENTION

Control of transmission of *Salmonella* infections to humans requires control of the infection in animal reservoirs, judicious use of agricultural antimicrobials, prevention of contamination of foodstuffs, and appropriate standards of food processing and inspection. Parents should be advised about the risk of various pets (especially reptiles, amphibians, and rodents).

Large outbreaks are often related to mass food production, presenting among widely geographically distributed patients. In the United States, CDC outbreak investigations are reported, via this site: https://www.cdc.gov/Salmonella/outbreaks.html, which includes maps and epidemiologic, traceback, and laboratory data, including outbreaks linked to specific foods, animals, and other sources. Awareness of these events can potentially blunt the extent of a given outbreak and/or alert caregivers of vulnerable hosts.

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244.2 Enteric Fever (Typhoid and Paratyphoid Fever)

Jeffrey S. McKinney

Enteric fever *(typhoid or paratyphoid fever)* remains endemic in many developing countries. Given the ease of modern travel, cases regularly occur in developed countries as well, usually among returning travelers or from secondary transmission from an asymptomatic carrier.

ETIOLOGY

Typhoid fever is caused by *S. enterica* serovar Typhi (*S.* Typhi). A similar but often less severe disease is caused by *Salmonella* Paratyphi A, B, and C. All are classically referred to as typhoidal *Salmonellae*. Typhoidal *Salmonellae* share more than 90% of their genes with the classic nontyphoidal strain, *S.* Typhimurium, but several genetic clusters known as *pathogenicity islands* and other genes have been acquired during evolution. The inactivation of single genes and the acquisition or loss of genes may have contributed to host adaptation and restriction of typhoidal strains. Importantly, whereas nontyphoidal *Salmonella* are found in many hosts and can be transmitted among them, typhoidal *Salmonella* only infects humans.

In contrast to the diarrheal symptoms classically encountered in gastroenteritis caused by nontyphoidal *Salmonellae,* enteric fever caused by typhoid or paratyphoid *Salmonellae* may present as abdominal pain without diarrhea, a fever without focus, and/or with extraintestinal foci of infection. Indeed, although enteric fever clearly starts in the gastrointestinal tract, the systemic nature of its presentation and symptomatology (and even its initial hard-to-detect primary bacteremia) can delay diagnosis, in particular among patients returning from or living in endemic areas, where the differential diagnosis for fevers is broad.

EPIDEMIOLOGY

Recent large-scale data and modeling efforts estimate that 14.3 million cases of typhoid and paratyphoid fevers occurred globally in 2017, a decline from 25.9 million cases in 1990. Incidence rates peak in the 5- to 9-year-old age-group, with roughly 13% of cases occurring in children younger than 5 years and roughly 56% of cases among children younger than 15 years of age. South and Southeast Asia have notably high incidence rates, whereas moderate incidence rates are reported from Central and South America, Africa, Central and East Asia, and Oceania (Fig. 244.6).

Typhoid fever is notable for the ongoing emergence of heterogeneous new patterns of drug resistance. After early outbreaks of chloramphenicol-resistant *S.* Typhi infections, *S.* Typhi strains emerged that were **multidrug resistant (MDR)**, fully resistant to all *three* of the traditional primary treatment antimicrobials: ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol. There is also a considerable increase in fluoroquinolone-resistant and even ceftriaxone-resistant isolates of *S.* Typhi. In the United States, most travel-associated cases of typhoid fever are now fluoroquinolone resistant.

There are now *S.* Typhi strains that are **extensively drug resistant (XDR)** not only to ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol but also to ceftriaxone and with full or intermediate resistance to ciprofloxacin. It appears that the new XDR *S.* Typhi strains came from a large outbreak in 2016 linked to contaminated water in Pakistan's Sindh province. XDR Typhi infections were then reported globally among travelers to or from Pakistan. In 2019 U.S. residents with *no* history of international travel were also diagnosed with XDR typhoid fever. The optimal therapy for these XDR isolates is still being determined, with preliminary recommendations suggesting the empiric use of a carbapenem (e.g., meropenem), azithromycin, or both.

S. Typhi is highly adapted to infections of humans, and the discovery of a large number of **pseudogenes** in *S.* Typhi suggests that its genome may have undergone degeneration as part of a specialized association with the human host. *S.* Typhi has no apparent ability to cause transmissible disease in other animals. Thus direct or indirect contact with an infected human (either sick or a chronic carrier) is a prerequisite for infection. Ingestion of foods or water contaminated with human feces is the most common mode of transmission. So-called street vendor foods outside the home are one risk factor noted in one case control study from Pakistan; such risks are included in practical guidance for travelers about food and water precautions from the CDC Yellow Book (Health Information for International Travel). However, more general water-borne outbreaks related to poor sanitation or water system contamination have also been described. Other causes of infection include consuming oysters and other shellfish cultivated in water contaminated by human sewage and the use of night soil as fertilizer.

PATHOGENESIS

Human volunteer experiments have established an infecting dose of about 10^5–10^9 organisms, with an incubation period ranging from 4 to 14 days. After ingestion, *S.* Typhi invades the gut mucosa of the terminal ileum via specialized antigen sampling cells known as *M cells* that overlie gut-associated lymphatic tissues, through enterocytes, or via a paracellular route. In contrast to nontyphoidal *Salmonella, S.* Typhi expresses factors that notably downregulate the pathogen receptor–mediated host inflammatory response. It assembles type III secretion systems to inject bacterial effectors that modulate host cell biology in elegant ways, including but not limited to rearrangements of host cell actin, facilitating invasion across the outer cell membrane and a host cell membrane ruffling process that forms a phagosome containing the bacteria. This phagosome fuses with lysosomes, acidifies, and shrinks to become adherent around the bacterium, forming the *Salmonella*-containing vacuole (SCV). This intracellular niche offers *Salmonella* a physical barrier to some

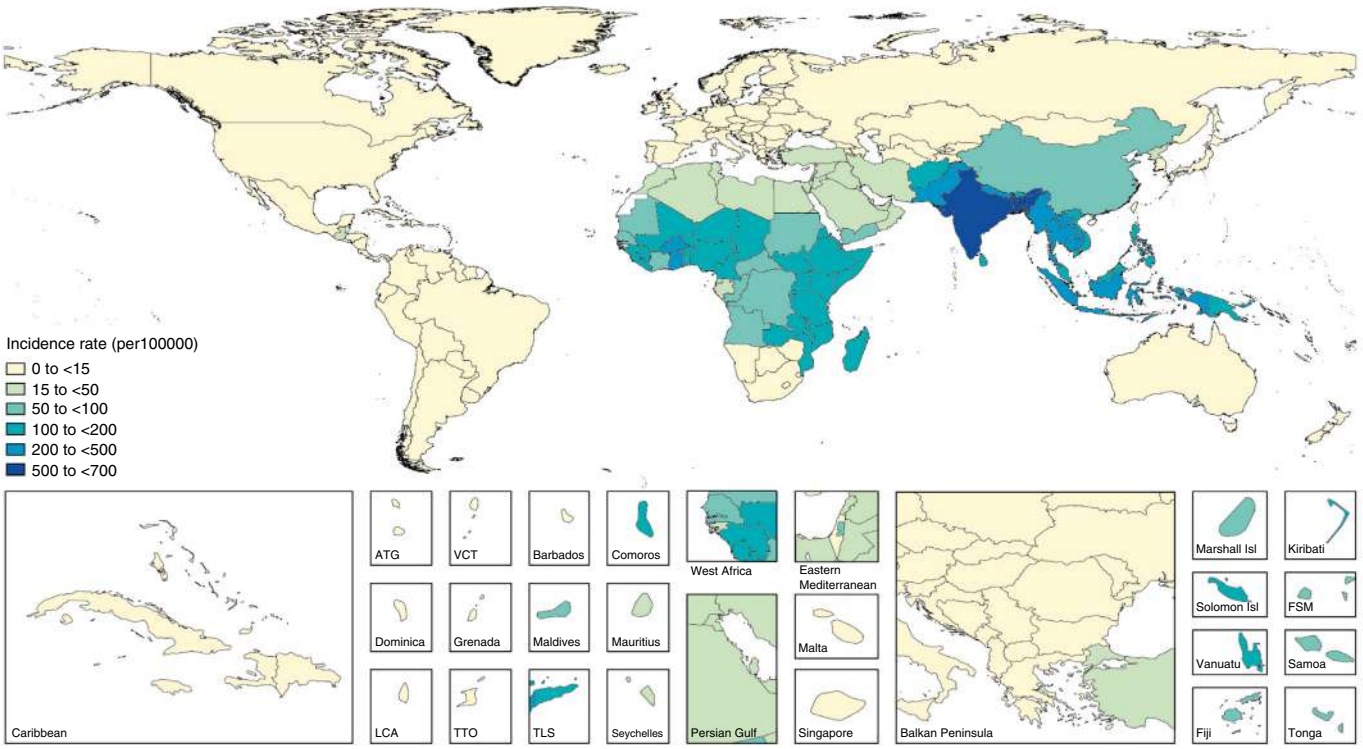

Fig. 244.6 Incidence rates (per 100,000) of typhoid and paratyphoid fevers, by country, in 2017. Inset maps detail smaller locations. ATG, Antigua and Barbuda; FSM, Federated States of Micronesia; Isl, Islands; LCA, Saint Lucia; TLS, Timor-Leste; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines. *(From GBD 2017 Typhoid and Paratyphoid Collaborators. The global burden of typhoid and paratyphoid fevers: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Infect Dis. 2019;19[4]:369–381.)*

drugs (e.g., gentamicin, which has very poor intracellular penetration) and an intracellular replication site and means of host cell–mediated systemic spread.

After passing through the intestinal mucosa, *S.* Typhi organisms enter the mesenteric lymphoid system and then pass into the bloodstream via the lymphatics. This primary bacteremia is usually asymptomatic, and blood culture results are frequently negative at this early stage. The blood-borne bacteria are disseminated through the body and are thought to colonize the organs of the reticuloendothelial system, where they replicate within macrophages. After a period of bacterial replication, *S.* Typhi organisms are shed back into the blood, causing a secondary bacteremia that coincides with the onset of clinical symptoms and marks the end of the incubation period (Fig. 244.7). During this secondary bacteremia, classically with fever, blood cultures are far more frequently positive, although culture of bone marrow can be even more sensitive.

Both typhoidal and nontyphoidal *Salmonellae* are members of the same species and share substantive commonalities, including more than 90% of their DNA sequences. Yet a deeper appreciation of how and why typhoidal and nontyphoidal species differ offers insights at multiple levels, ranging from genetics and ecology, to pathobiology, to more nuanced clinical recognition and care.

Despite typhoidal (and paratyphoidal, used interchangeably in this section, unless specified otherwise) fevers being synonymous with the clinical diagnosis of **enteric fever**, the initial enteric inflammation from *S.* Typhi is notably less than that caused from most nontyphoidal *Salmonellae*. Clinically, presenting symptoms of typhoid tend to include less diarrhea and far less gut mucosal inflammation. In host cell cultures, *S.* Typhi induces lower levels of IL-8 neutrophil chemoattractant and less of a toll-like receptor 5 (TLR5)–driven proinflammatory response than seen with nontyphoidal *Salmonella*. One potential implication of this is that nontyphoidal *Salmonella* may use inflammation-derived luminal substances such as electron acceptors like nitrate and tetrathionate, perhaps in competition with other fermenting gut microbes. Intriguingly, *S.* Typhi has genomic *decay* in a network of nontyphoidal *Salmonella* genes that are involved in anerobic metabolic pathways.

This is not to say that *S.* Typhi never results in intestinal lesions. In advanced stages of typhoid fever, life-threatening intestinal perforation can occur. However, the histopathology of typhoid perforation is distinct from the inflammation seen with nontyphoidal *Salmonella* gastroenteritis. With *S.* Typhi, inflammation that can finally penetrate the intestinal muscularis and serosa to cause perforation seems to originate from *deeper* sites, including underlying lymphoid tissue. In other tissues, including liver, spleen, lymph nodes, and bone marrow, **typhoid nodules** composed of macrophage aggregates can also form.

Gallbladder colonization is also a notable feature of *S.* Typhi and can result in years-long *Salmonella* carriage and shedding, with profound public health implications. The primary bacteremia of *S.* Typhi can seed the gallbladder, where exposure to bile upregulates *S.* Typhi (but seemingly *not* nontyphoidal *Salmonella*) type 3 secretion system genes that result in increased epithelial cell invasion.

S. Typhi expresses a surface **Vi (virulence) capsular polysaccharide** that is *not* present in nontyphoidal *Salmonella* or in *S.* Paratyphi A or B (which is relevant to the community-level impact of current Vi-based vaccines). Encoded as part of the *S.* Typhi pathogenicity island 7 (SPI-7), the Vi capsular polysaccharide interferes with the surface exposure of *S.* Typhi lipopolysaccharide and flagellin in ways that dampen host TLR-4 and -5 mediated **innate immune responses**. Vi also blocks complement C3 binding to the *S.* Typhi surface, interfering with **phagocytosis**.

Characterization of the **typhoid toxin** represents a major advance in understanding typhoid fever. Furthermore, in contrast to the Vi capsular polysaccharide, the typhoid toxin is expressed in both typhoidal *and* paratyphoidal *Salmonellae*. This toxin may prove important for new therapeutic or diagnostic innovations based on antitoxin

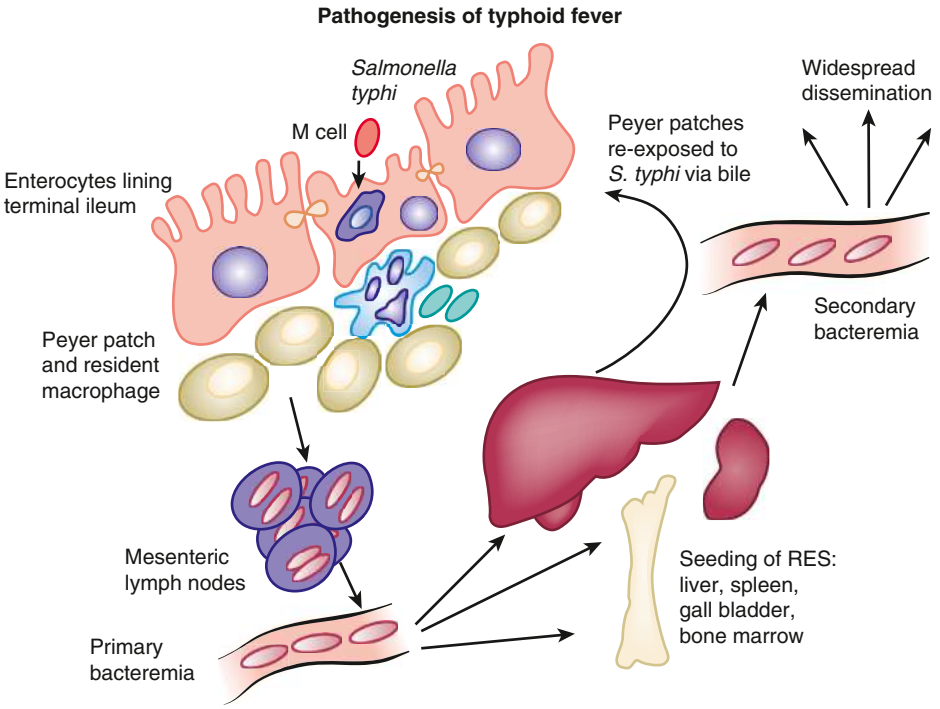

Fig. 244.7 Pathogenesis of typhoid fever, involving invasion of ileal enterocyte and Peyer patches and mesenteric lymph nodes, seeding the reticuloendothelial system (RES). Both primary and secondary bacteremia events can occur and relate to clinical stages of disease. *(Adapted from Richens J. Typhoid fever. In: Cohen J, Powderly WG, Opal SM, eds. Infectious Diseases, 2nd ed. London: Mosby; 2004:1561–1566.)*

approaches. Typhoid toxin has three subunits. Subunit CdtB has DNAse I–like nuclease activity that causes double-stranded breaks in host cell DNA, leading to host G2/M cell cycle arrest and/or cell death. Subunit PltA is a pertussis-like toxin with mono–adenosine diphosphate (ADP)–ribotransferase activity. Subunit PltB is a pertussis-like toxin with receptor binding activity to glycans, especially sialoglycans, terminated in Neu5Ac. The functional typhoid toxin is composed of one CdtB and one PltA subunit, plus five PltB subunits. Typhoid toxin genes are expressed by intracellular *S.* Typhi in the SCV of host cells. The trafficking of the toxin uses an elegant mechanism, in which PltB binding to Neu5Ac is involved in both toxin export and toxin endocytosis into target cells. The fact that Neu5Ac is the target for binding by PltB may help explain the cell tropism of typhoid toxin and also some of the human restriction of typhoidal infections and pathobiology at a molecular level.

The presence/gain/site-specific expression of certain virulence factors by typhoidal *Salmonellae* may help explain disease nuances involved in typhoid fever. Acquisition and spread of resistance genes are also a clear and present danger.

The overall quantity of **pseudogenes** in *S.* Typhi versus nontyphoidal *Salmonella* genomes is also noteworthy. Whereas *S.* Typhi's 200 pseudogenes account for roughly 4% of all its genes, the classic nontyphoidal *Salmonella* exemplar *S.* Typhimurium genome includes less than 1% pseudogenes. One broad conceptual model for this is that *S.* Typhimurium remains more of a "generalist," with a broad host range and more genes to facilitate survival in different hosts. By contrast, *S.* Typhi may have become a "specialist," evolving to infect only humans. Furthermore, *S.* Typhi may infect humans in specific ways that better evade/suppress early mucosal inflammatory events and cause more systemic spread, as well as sustained colonization and long-term shedding. This conceptual model may offer insights to understand the ongoing evolution or emergence of some new nontyphoidal *Salmonella* strains that (akin to typhoidal strains) tend to cause more systemic infections, as highlighted by the evolution of the nontyphoidal *Salmonella* ST313 strain in Africa.

In addition to the virulence of infecting organisms, host factors also influence predisposition to infection. Patients with HIV are at significantly higher risk for infection with *S.* Typhi and *S.* Paratyphi. Patients with *Helicobacter pylori* infection also have an increased risk of acquiring typhoid fever. Compared to most nontyphoidal *Salmonella* infections that are often more severe and systemic in hosts with immune abnormalities, outbreaks of typhoid fever with systemic spread often affect many hosts who do *not* have significant underlying immunocompromise.

CLINICAL MANIFESTATIONS

The incubation period of typhoid fever is usually 7-14 days but depends on the infecting dose and ranges between 3 and 30 days. The presentation varies, from mild illness with low-grade fever and malaise, to a severe clinical picture with profound abdominal discomfort and multiple complications.

Severity and clinical outcome are influenced by many factors. These include duration of illness, age, previous exposure or vaccination history, virulence of the infecting strain, and quantity of the inoculum ingested. Given the profound changes in antimicrobial susceptibility patterns, choice of appropriate antimicrobial therapy is increasingly challenging, both empirically (given multiple various patterns of resistance) and after antimicrobial susceptivity results are secured (given the increasing inadequacy of many previously effective drugs).

The presentation of typhoid fever may vary by patient age. Some reports from South Asia suggest typhoid fever may be more severe in children less than 5 years old in terms of rates of complications and hospitalization. In infancy, complications such as disseminated intravascular coagulation seem more common, with higher case fatality rates. By contrast, neurologic complications and intestinal bleeding or perforation seem less common among children.

Typhoid fever can start as a seemingly mild illness and then progress to a clinical picture that manifests as high-grade fever. It can include a wide variety of associated features, such as anorexia, vomiting, hepatomegaly or splenomegaly, abdominal pain, and/or headache (Table 244.1). In children, diarrhea may occur in earlier stages of the illness but may be followed by constipation, potentially interfering with ready access to stool for important microbial culture and susceptibility testing. In the absence of localizing signs, the early stages of the disease may be very difficult to differentiate from other endemic diseases, such as malaria and dengue fever. In some cases, a macular or maculopapular rash ("rose spots") may be visible around the seventh to tenth day of the illness. These lesions may be difficult to see in dark-skinned children and may occur in crops on the lower

chest and abdomen, typically lasting 2-3 days (Fig. 244.8). Although so-called pulse fever dissociation (relative bradycardia during fevers) has historically been invoked as a feature of typhoid fever, it has low positive predictive value, is nonspecific, and seems much less common in children than in adults.

It is recognized that MDR *S.* Typhi infection is a more severe clinical illness with higher rates of toxicity, complications, and case fatality rates. Depending on the specific infecting strain, this may be related to greater virulence and higher numbers of circulating bacteria.

If no complications occur, symptoms and physical findings gradually resolve within 2-4 weeks. However, illness may contribute to malnutrition. Although enteric fever caused by *S.* Paratyphi has traditionally been considered a more mild illness than that from *S.* Typhi, paratyphoid fever can also be severe, with significant drug resistance, morbidity, and complications.

COMPLICATIONS

Although altered liver function is found in many patients with enteric fever, clinically significant hepatitis, jaundice, and cholecystitis are relatively rare and may be associated with worse outcomes. Intestinal hemorrhage and perforation are infrequent among children. Intestinal perforation may be preceded by marked increase in abdominal pain (often in the right lower quadrant), tenderness, vomiting, and features of peritonitis. Peritoneal signs may be masked in patients receiving steroids.

Rare complications include toxic myocarditis, which may manifest as arrhythmias, sinoatrial block, or cardiogenic shock (Table 244.2). Neurologic complications are relatively uncommon among children; they include delirium, psychosis, increased intracranial pressure, acute cerebellar ataxia, chorea, deafness, and Guillain-Barré syndrome. Although case fatality rates can be higher among patients with neurologic complications, recovery usually occurs without sequelae. Other reported complications include fatal bone marrow necrosis, disseminated intravascular coagulation, hemolytic-uremic syndrome, pyelonephritis, nephrotic syndrome, meningitis, endocarditis, parotitis, orchitis, and suppurative lymphadenitis.

The propensity to become a carrier follows the epidemiology of gallbladder disease and cholelithiasis, generally increasing with patient age and antimicrobial resistance.

DIAGNOSIS

The mainstay of the diagnosis of typhoid fever is a positive culture of *S.* Typhi or *S.* Paratyphi from the blood or other anatomic site. Results of blood cultures are positive in 40–60% of patients seen early in the course of disease, but serial high-volume blood cultures may be required to identify *Salmonella* bacteremia. Stool and urine culture results may also become positive after the first week, and the stool culture may occasionally be positive even during the incubation period. NAATs for *Salmonella* can be part of diagnostic screening, but rectal swab samples are less sensitive than stool samples. In this era of increasing antibiotic resistance (not only common but also heterogeneous patterns), species identification without culture to check antibiotic susceptibilities is suboptimal. *Indeed, antibiotic susceptibility testing is now essential for determining optimal therapy.* Bone marrow culture is highly sensitive (around 90%) and remains positive in more than 50% of cases despite several days of antibiotic therapy. Bone marrow collection is relatively invasive, however, and tends to be employed as part of an extensive workup for patients meeting stringent criteria for a true fever of unknown origin. Punch biopsies from characteristic rose spots may be culture positive in up to 63% of cases, even with prior antibiotic treatment.

Results of other laboratory investigations are largely nonspecific for the diagnosis of typhoid fever. The Widal test has common false-negative and false-positive results, and as a serologic test is highly dependent on geographic area and endemicity. Tests such as coagulation studies, liver function studies, and abdominal imaging are examples of studies that may be of use in assessing for complications of typhoid fever.

Table 244.1 Common Clinical Features of Typhoid Fever in Children*

FEATURE	RATE (%)
High-grade fever	95
Coated tongue	76
Anorexia	70
Vomiting	39
Hepatomegaly	37
Diarrhea	36
Toxicity	29
Abdominal pain	21
Pallor	20
Splenomegaly	17
Constipation	7
Headache	4
Jaundice	2
Obtundation	2
Ileus	1
Intestinal perforation	0.5

*Data collected in Karachi, Pakistan, from 2,000 children.

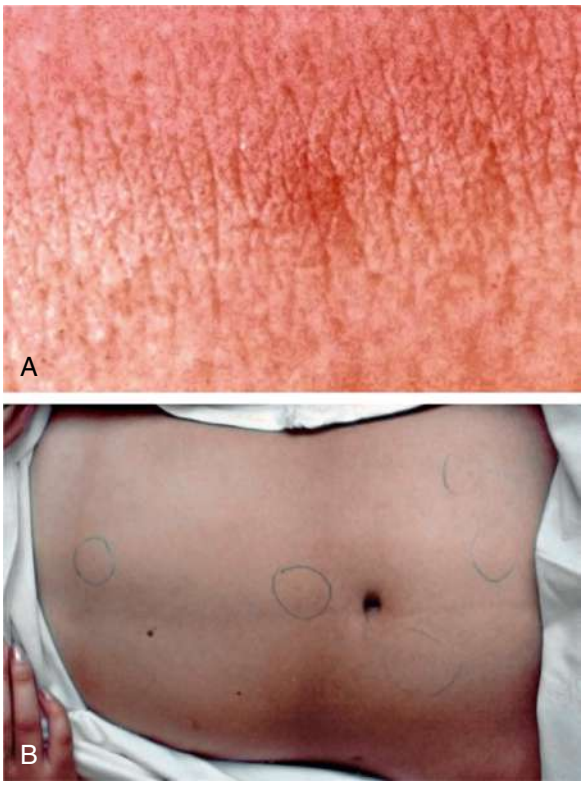

Fig. 244.8 A, "Rose spot" in volunteer with experimental typhoid fever. B, Small cluster of rose spots, usually located on lower abdomen. Lesions may be more difficult to identify in darker-skinned people. *(From Huang DB, DuPont HL. Problem pathogens: extra-intestinal complications of Salmonella enterica serotype Typhi infection. Lancet Infect Dis. 2005;5:341–348.)*

Table 244.2 Extraintestinal Infectious Complications of Typhoid Fever Caused by *Salmonella enterica* Serotype Typhi

ORGAN SYSTEM	PREVALENCE (%)	RISK FACTORS	COMPLICATIONS
Central nervous system	3–35	Residence in endemic region, malignancy, endocarditis, congenital heart disease, paranasal sinus infections, pulmonary infections, meningitis, trauma, surgery, osteomyelitis of skull	Encephalopathy, cerebral edema, subdural empyema, cerebral abscess, meningitis, ventriculitis, transient Parkinsonism, motor neuron disorders, ataxia, seizures, Guillain-Barré syndrome, psychosis
Cardiovascular system	1–5	Cardiac abnormalities (e.g., existing valvular abnormalities, rheumatic heart disease, congenital heart defects)	Endocarditis, myocarditis, pericarditis, arteritis, congestive heart failure
Pulmonary system	1–6	Residence in endemic region, past pulmonary infection, sickle cell anemia, alcohol abuse, diabetes, HIV infection	Pneumonia, empyema, bronchopleural fistula
Bone and joint	<1	Sickle cell anemia, diabetes, systemic lupus erythematosus, lymphoma, liver disease, previous surgery or trauma, extremes of age, corticosteroid use	Osteomyelitis, septic arthritis
Hepatobiliary system	1–26	Residence in endemic region, pyogenic infections, intravenous drug use, splenic trauma, HIV, hemoglobinopathy	Cholecystitis, hepatitis, hepatic abscesses, splenic abscess, peritonitis, paralytic ileus
Genitourinary system	<1	Urinary tract abnormalities, pelvic pathology, systemic abnormalities	Urinary tract infection, renal abscess, pelvic infections, testicular abscess, prostatitis, epididymitis
Soft tissue infections	At least 17 cases reported in English-language literature	Diabetes	Psoas abscess, gluteal abscess, cutaneous vasculitis
Hematologic	At least 5 cases reported in English-language literature		Hemophagocytosis syndrome

From Huang DB, DuPont HL. Problem pathogens: extra-intestinal complications of *Salmonella enterica* serotype Typhi infection. *Lancet Infect Dis.* 2005;5:341–348.

DIFFERENTIAL DIAGNOSIS

Typhoid fever may mimic many febrile illnesses without localizing signs. In early stages, it can be confused with alternative conditions, such as gastroenteritis, bronchitis, and bronchopneumonia. As the disease progresses, the differential diagnosis may include bacterial sepsis, malaria, dengue fever, infectious mononucleosis, acute hepatitis, tuberculosis, brucellosis, tularemia, leptospirosis, amebiasis, Q fever, toxoplasmosis, and rickettsial diseases. A classic cause of fevers among travelers returning from endemic areas, typhoid fever can also occur in those with direct, or even unappreciated, contact with other infected people.

TREATMENT

Antibiotic resistance among *S.* Typhi strains is now so heterogeneous and dynamic that the importance of obtaining **antibiotic susceptibility tests** on clinical isolates cannot be overemphasized. Although empiric antibiotics still may be started, final decision-making about optimal treatment should be based on antibiotic susceptibility results. Molecular testing of specific resistance genes can also help assess mechanisms and evolution of resistance.

For years, third-generation cephalosporins (e.g., ceftriaxone or cefotaxime) were a mainstay of empiric therapy. They were considered effective even for **MDR** *S.* Typhi and/or for the increasing number of *S.* Typhi that were quinolone resistant. Yet now, with the recent emergence of **XDR** *S.* Typhi, third-generation cephalosporins may no longer be sufficient.

In *S.* Typhi, MDR isolates are defined as resistant to all the first line of antibiotics previously suggested by the World Health Organization (WHO): ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol. XDR *S.* Typhi is not only resistant to ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol but also resistant to third-generation cephalosporins and quinolones. Gene sequencing, including one innovative study using clinical isolates from children with *S.* Typhi septicemia, found the phenotype of the XDR *S.* Typhi isolates matches with their genotypes, featured by the acquisitions of the genes bla_{TEM1}, dhfR7, sul1, catA1, qnrS, and $bla_{CTX\text{-}M\text{-}15}$ and a point mutation on gyrA.

XDR *S.* Typhi cases were first noted by Pakistani health authorities in 2016, originating in Hyderabad, Sindh. By 2018, international transmission of XDR *S.* Typhi cases had been noted. In 2019 and 2020, XDR *S.* Typhi was recovered from patients in the United States, both with and *without* a travel history. Patients without a travel history lived in six widely distributed states and did not appear to be linked or have a common source of infection. An unrelated cluster of ceftriaxone-resistant Typhi infections linked to Iraq has also been reported in the United States and the United Kingdom.

Taken together, this information led to an official CDC Health Advisory in 2021 suggesting the need for empiric carbapenem, azithromycin, or both for patients in the United States with suspected typhoid fever who traveled to Pakistan or Iraq, as well as those who had *not* traveled from the United States. Patients with severe or complicated illness should receive a carbapenem, such as meropenem. Case reports have suggested that patients who do not improve on a carbapenem alone may benefit from the addition of a second antibiotic such as azithromycin. Patients with uncomplicated illness may be treated with oral azithromycin alone. By contrast, for patients in the United States who traveled to countries other than Pakistan or Iraq, ceftriaxone *may* still be effective.

In the United States, resistance to meropenem (a carbapenem) or azithromycin was not reported during 2017–2021. By contrast, roughly 80% of Typhi strains isolated in the United States now are resistant or have decreased susceptibility to quinolones, including ciprofloxacin.

New MDR and XDR strains illustrate the profound importance of recognizing what antimicrobials will likely *not* work. Meanwhile, an encouraging relative reduction in the proportion of MDR strains in some areas of Asia means some patients with susceptible *S.* Typhi infections can be treated with agents recently considered ineffective. Namely, in some highly endemic regions of South and Southeast Asia,

strains susceptible to amoxicillin or trimethoprim-sulfamethoxazole are increasingly common.

The optimal duration of antimicrobial therapy is unclear, but most agents are suggested for at least 10-14 days, with longer courses for amoxicillin or trimethoprim-sulfamethoxazole, 21 days for chloramphenicol, and as little as 7 days for azithromycin. Relapse rates can occur in almost 20% of patients within 4 weeks, especially in immunocompromised patients.

In addition to antimicrobials, supportive treatment and maintenance of appropriate fluid and electrolyte balance are important. Although additional treatment with dexamethasone (3 mg/kg initial dose, followed by 1 mg/kg every 6 hours for 48 hours) is recommended by some for severely ill patients with shock, obtundation, stupor, or coma, corticosteroids should be administered only under strict supervision, because their use may mask signs of abdominal complications.

PROGNOSIS

The prognosis for a patient with enteric fever depends on the rapidity of diagnosis and institution of appropriate antibacterial therapy. Other factors are patient age, underlying health and nutrition, the causative *Salmonella* serotype, and the appearance of complications. Infants and children with underlying malnutrition and infections with resistant isolates are at higher risk of adverse outcomes.

Despite appropriate therapy, 2–4% of infected children may experience relapse. Individuals who excrete *S.* Typhi more than 3 months after infection are regarded as chronic carriers. A chronic urinary carrier state can develop in children with schistosomiasis.

PREVENTION

Of the major risk factors for outbreaks of typhoid fever, contamination of water supplies with sewage is most important. Other risk factors are contact with another acutely infected individual or a chronic carrier and lack of water or sanitation services. During outbreaks, central chlorination and domestic water purification are important. In endemic situations, consumption of street foods, especially ice cream and cut fruit, is recognized as an important risk factor. Human-to-human spread by chronic carriers is also important, and attempts should be made to target food handlers and high-risk groups for *S.* Typhi carriage screening. Chronic carriers can be counseled as to the risk for disease transmission and the importance of handwashing.

In the United States, two vaccines have been licensed by the FDA. Systematic review and meta-analysis of randomized controlled clinical trials estimate the cumulative efficacy of these two vaccines as only roughly 50%. The Ty21a **live attenuated vaccine** can be used in people 6 years and older. It is administered orally, every other day, for a total of four doses to be completed at least 1 week before potential exposure; booster frequency is every 5 years. The Ty21a vaccine induces both cell-mediated and humoral immune responses against *S.* Typhi. It also may provide some protection against *S.* Paratyphi B. The **unconjugated** Vi capsular polysaccharide vaccine can be used in people 2 years and older. It is administered intramuscularly in a single dose to be administered at least 2 weeks before potential exposure; booster frequency is every 2 years. This unconjugated vaccine induces a **T-cell–independent humoral immune response** with lack of prolonged protection.

Conjugated vaccines have been recommended, developed, and now deployed by the WHO. By covalently conjugating the Vi capsular polysaccharide to carrier proteins, conjugate vaccines can induce a **T-cell–dependent humoral immune response**, even in young children. Conjugated typhoid vaccines are under development, using a variety of carrier proteins, including tetanus toxoid, Exoprotein A from *Pseudomonas,* and diphtheria toxoid. The WHO has recommended the introduction of a single-dose typhoid conjugate vaccine for infants and children age 6 months and older. A large study of the Typbar-TCV conjugate vaccine in Hyderabad, Pakistan, found vaccine effectiveness was 55% against suspected typhoid fever and 95% against blood culture–confirmed *S.* Typhi. The vaccine was also 97% effective against XDR *S.* Typhi. In 2019, a historic milestone was successfully achieved in Pakistan with the vaccination in Sindh province of more than 9.4 million children age from 9 months to 15 years against typhoid fever, with a coverage rate of 95%. Pakistan is the first country in the world to introduce the WHO-recommended typhoid conjugate vaccine (TCV) into its routine immunization program.

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Chapter 245

Shigella

Patrick C. Seed

Shigellosis, infection by *Shigella* species, is acute invasive enteric infection clinically manifested by diarrhea that is often bloody. The term **dysentery** describes a syndrome of bloody diarrhea with fever, abdominal cramps, rectal pain, and mucoid stools. **Bacillary dysentery** is a term often used to distinguish dysentery caused by *Shigella* from amebic dysentery caused by *Entamoeba histolytica*.

ETIOLOGY

Four species of *Shigella* cause the disease shigellosis: *Shigella dysenteriae* (group A), *Shigella flexneri* (group B), *Shigella boydii* (group C), and *Shigella sonnei* (group D). Serotypes 15, 19, 19, and 1 in groups A-D, respectively, further distinguish the species. Species and group distributions vary geographically and by antimicrobial susceptibility.

EPIDEMIOLOGY

The World Health Organization (WHO) estimates that 80-165 million cases of shigellosis occur each year worldwide, resulting in 600,000 deaths annually. *Shigella* spp. are endemic to temperate and tropical climates and are most common in countries and regions with inadequate public health sanitation and hygiene. In the U.S. Foodborne Disease Active Surveillance Network **(FoodNet)**, *Shigella* remains the third most important pathogen. In 2020, the top three diarrheagenic pathogens, *Campylobacter, Salmonella,* and *Shigella,* had laboratory-confirmed incidence rates (cases per 100,000 population) of 14.35, 13.33, and 3.05, respectively. Although infection can occur at any age, children younger than 10 years, identified as Black and of Hispanic ethnicity, have the highest incidence rates. Males have an approximately 2.7-fold higher incidence than females. Upwards of 30% of children with shigellosis are hospitalized. Death resulting from shigellosis is rare among children (<0.1%). Infection in the first 6 months of life is rare. Breast milk from women living in endemic areas contains antibodies to both virulence plasmid-encoded antigens and lipopolysaccharides, and breastfeeding might partially explain the age-related incidence.

Asymptomatic infection of children and adults occurs frequently in endemic areas. In cases of *Shigella* dysentery, up to 75% of family member contacts may have asymptomatic infection. Infection with *Shigella* occurs most often during the warm months in temperate climates and during the rainy season in tropical climates. In industrialized societies, up to 50% of locally diagnosed cases are associated with international travel; the highest-risk travel designation is Africa, followed by Central America, South America, and parts of Asia. In recent years in the United States, travel to Haiti, the Dominican Republic, or India has been associated with acquisition of antibiotic-resistant (fluoroquinolone) *S. sonnei* infections. Additional risk factors include men who have sex with men (MSM), including recent U.S. outbreaks of azithromycin-resistant *S. sonnei* infections among affected individuals in the Midwest.

In developed countries, *S. sonnei* is the most common cause and *S. flexneri* is the second most common cause of bacillary dysentery; in preindustrial societies, *S. flexneri* is most common and *S. sonnei* second

in frequency. *S. boydii* is found primarily in India. *S. dysenteriae* serotype 1 tends to occur in massive epidemics but is also endemic in Asia and Africa, where it is associated with high mortality rates (5–15%). The epidemiologic transition has favored the emergence of *S. sonnei* as the dominant serogroup in some countries, although the reason for this epidemiologic shift is not clear.

Contaminated food (often a salad or other item requiring extensive handling of the ingredients) and water are important vectors. Exposure to both contaminated freshwater and contaminated salt water is a risk factor for infection. Rapid spread within families, custodial institutions, and childcare centers demonstrates the ability of *Shigella* to be transmitted from one individual to the next and the requirement for ingestion of very few organisms to cause illness. Human challenge studies have demonstrated the high infectivity and low infectious dose for *Shigella* spp. Ten bacteria of the species *S. sonnei* and *S. dysenteriae* can cause dysentery. In contrast, ingestion of 10^8-10^{10} *Vibrio cholerae* is necessary to cause cholera.

PATHOGENESIS

Shigella has specialized mechanisms to survive the low gastric pH. Shigella survives the acid environment in the stomach and moves through the gut to the colon, its target organ. *Shigella* spp. use a coordinated, temperature-controlled program to hijack and invade colonic epithelial cells. A large (220 kb) plasmid encodes a group of polypeptides involved in cell invasion and killing, and loss of the plasmid attenuates virulence. **Enteroinvasive** *Escherichia coli* (EIEC) that harbor a closely related plasmid containing these invasion genes behave clinically similar to *Shigellae* (see Chapter 246). The virulence plasmid encodes a type III secretion system required to trigger entry into epithelial cells and apoptosis in macrophages. This secretion system translocates effector molecules from the bacterial cytoplasm to the membrane and cytoplasm of target host cells through a needle-like appendage. The **type III secretion system** is composed of approximately 50 proteins, including the Mxi and Spa proteins involved in assembly and regulation of the type III secretion system, chaperones (IpgA, IpgC, IpgE, and Spa15), transcription activators (VirF, VirB, and MxiE), translocators (IpaB, IpaC, and IpaD), and approximately 30 effector proteins. In addition to the major plasmid-encoded virulence traits, chromosomally encoded factors are required for full virulence.

Shigellosis mostly affects the distal colon, although pancolitis can occur. *Shigella* spp. traverse the colonic epithelium through M cells in the follicle-associated epithelium overlying the Peyer patches. Localized or diffuse mucosal edema, ulcerations, friable mucosa, bleeding, and exudate may occur. Microscopically, ulcerations, pseudomembranes, epithelial cell death, infiltration extending from the mucosa to the muscularis mucosae by polymorphonuclear leukocytes (PMNs) and mononuclear cells, and submucosal edema occur.

After *Shigella* transcytosis through M cells, it encounters resident macrophages and subverts macrophage killing by activating the inflammasome and inducing pyroptosis, apoptosis, and proinflammatory signaling. Free bacteria invade the epithelial cells from the basolateral side, move into the cytoplasm by actin polymerization, and spread to adjacent cells. Proinflammatory signaling by macrophages and epithelial cells further activates the innate immune response involving natural killer cells and attracts PMNs. The influx of PMNs disintegrates the epithelial cell lining, which initially exacerbates the infection and tissue destruction by facilitating the invasion of more bacteria. Ultimately, PMNs phagocytose and kill *Shigella,* thus contributing to the resolution of the infection.

Some *Shigella* spp. produce toxins, including Shiga toxin and enterotoxins. **Shiga toxin** is a potent exotoxin that inhibits protein synthesis. It is produced in significant amounts by *S. dysenteriae* serotype 1, by a subset of *E. coli* known as **enterohemorrhagic** *E. coli* (EHEC) or Shiga toxin–producing *E. coli,* and occasionally by other *Shigella* spp. Shiga toxin inhibits protein synthesis to injure vascular endothelial cells and trigger the severe complication of hemolytic-uremic syndrome (see Chapter 246). Targeted deletion of the genes for other enterotoxins (*ShET1* and *ShET2*) decreases the incidence of fever and dysentery in human challenge studies. Lipopolysaccharides are virulence factors for all *Shigellae;* other traits are important for only a few serotypes (e.g., Shiga toxin synthesis by *S. dysenteriae* serotype 1 and *ShET1* by *S. flexneri* 2a).

IMMUNITY

In symptomatic infection, *Shigella* activates an intense innate immune response through triggering extracellular and intracellular pathogen recognition systems. The induction of acute inflammation with a massive recruitment of PMNs produces intensive local tissue destruction. In rectal biopsies of infected patients, acute-phase proinflammatory cytokines are induced, including interleukin (IL)-1β, IL-6, IL-8, tumor necrosis factor (TNF)-α, and TNF-β. Concurrently, antiinflammatory genes encoding IL-10 and transforming growth factor-β are also upregulated to mitigate uncontrolled inflammation. Furthermore, interferon-γ expression is induced during human infection and is required to limit *Shigella* invasion in intestinal epithelial cells and macrophages. *Shigella*-specific immunity elicited upon natural infection is characterized by the induction of a humoral response. Local secretory immunoglobulin A (IgA) and serum IgG are produced against lipopolysaccharide and some protein effectors (Ipas). Protection is thought to be serotype specific. Natural protective immunity arises only after several episodes of infection, is of short duration, and seems to be effective in limiting reinfection, particularly in young children. However, children have delayed and reduced antigen-specific antibody-secreting cells with late and reduced mucosa IgA production against *Shigella*. Less effective adaptive immunity may put children at more risk for increased disease severity, mortality, and recurrences.

CLINICAL MANIFESTATIONS AND COMPLICATIONS

Shigella spp. produce intraintestinal and extraintestinal symptoms. *Bacillary dysentery is clinically similar regardless of infecting serotype or species,* but different species produce illnesses with different severity and risk for mortality, with *S. dysenteriae* type 1 most likely to produce any single manifestation and with greater severity. Ingestion of *Shigellae* is followed by an incubation period of 12 hours to several days before symptoms ensue. Severe abdominal pain, emesis, anorexia, generalized toxicity, urgency, and painful defecation characteristically occur (Table 245.1). *The typically high **fever** with shigellosis distinguishes it from EHEC.* The **diarrhea** may be watery and large volume initially, evolving into frequent, small-volume, bloody, mucoid stools. Most children never progress to the stage of bloody diarrhea, but some have bloody stools from the outset. Significant dehydration is related to the fluid and electrolyte losses in stool and emesis. Untreated diarrhea can last 7-10 days; only approximately 10% of patients have diarrhea persisting for >10 days. Persistent diarrhea occurs in malnourished infants, children with AIDS, and occasionally previously normal children. Even nondysenteric disease can be complicated by persistent illness. Physical examination initially shows abdominal distention and tenderness, hyperactive bowel sounds, and a tender rectum on digital examination. **Rectal prolapse** may be present, particularly in malnourished children.

Neurologic findings are among the most common extraintestinal manifestations of bacillary dysentery, occurring in as many as 40% of hospitalized children. EIEC can cause similar neurologic toxicity. Convulsions, headache, lethargy, confusion, nuchal rigidity, or hallucinations may be present before or after the onset of diarrhea. Animal models suggest Shiga toxins activate brain endothelial cells and microglia and increase neurotransmitter levels. However, infections with Shiga toxin–positive and –negative strains can lead to neurologic features. **Seizures** sometimes occur when little fever is present, suggesting that simple febrile convulsions do not explain their appearance. Hypocalcemia or hyponatremia may be associated with seizures in a small number of patients. Although symptoms often suggest central nervous system infection, and cerebrospinal fluid pleocytosis with minimally elevated protein levels can occur, meningitis caused by *Shigellae* is rare. Based on animal studies, it has been suggested that proinflammatory mediators, including TNF-α and IL-1β, nitric oxide, and corticotropin-releasing hormone, play a role in the enhanced susceptibility to *Shigella*-mediated seizures and encephalopathy.

The most common complication of shigellosis is **dehydration** (Table 245.2). Inappropriate secretion of antidiuretic hormone with profound hyponatremia can complicate dysentery, particularly when *S. dysenteriae* is the etiologic agent. Hypoglycemia and protein-losing enteropathy are common and are decreased by early appropriate antibiotic therapy. Severe protein-losing enteropathy is associated with prolonged illness and linear growth shortfalls. **Bacteremia** is uncommon except in girls or women infected with HIV, malnourished children, young infants, and children with *S. dysenteriae* serotype 1 infection. When bacteremia occurs with dysentery (<5%), it is as likely to be caused by other enteric bacteria as by *Shigella* itself. The presence of *E. coli, Klebsiella,* and other enteric bacteria in blood cultures of children with shigellosis may reflect the loss of the barrier function during severe colitis. The mortality rate is high (approximately 20%) when sepsis occurs, with a greater likelihood of occurrence in HIV-infected persons. Other major complications include **disseminated intravascular coagulation** (DIC), particularly in very young, malnourished children. Despite the extent to which the intestinal epithelial barrier is lost, bacteremia and DIC are uncommon.

Neonatal shigellosis is rare, particularly among exclusively breastfed infants. Neonates may have only low-grade fever with mild, nonbloody diarrhea. However, complications occur more often in neonates than in older children and include septicemia, meningitis, dehydration, colonic perforation, and toxic megacolon.

Hemolysis, anemia, and **hemolytic-uremic syndrome** (HUS) frequently complicate *S. dysenteriae* serotype 1 infection. HUS is caused by Shiga toxin–mediated vascular endothelial injury. Shiga toxin–producing non-*dysenteriae Shigella* and *E. coli* that produce Shiga toxins (e.g., *E. coli* O157:H7, *E. coli* O111:NM, *E. coli* O26:H11, and less often, many other serotypes) also cause HUS (see Chapter 560.5).

Rectal prolapse, toxic megacolon or pseudomembranous colitis (usually associated with *S. dysenteriae*), cholestatic hepatitis, conjunctivitis, iritis, corneal ulcers, pneumonia, arthritis (usually 2-5 weeks after enteritis), reactive arthritis, cystitis, myocarditis, and vaginitis (typically with blood-tinged discharge associated with *S. flexneri*) are uncommon events. Although rare, surgical complications of shigellosis can be severe; the most common are intestinal obstruction and appendicitis with and without perforation.

On average, the severity of illness and risk of death are least with disease caused by *S. sonnei* and greatest with infection by *S. dysenteriae* type 1. Risk groups for severe illness and poor outcomes include infants; children who are not breastfed; children with HIV; children recovering from measles; malnourished children and adults; adults >50 years old; and patients with dehydration, unconsciousness, hypothermia or hyperthermia, hyponatremia, or lesser stool frequency who have a history of convulsions when first seen. Death is a rare outcome in well-nourished older children. Multiple factors contribute to death in malnourished children with shigellosis, including illness in the first year of life, altered consciousness, dehydration, hypothermia, thrombocytopenia, anemia, hyponatremia, renal failure, hyperkalemia, hypoglycemia, bronchopneumonia, and bacteremia.

The rare shigellosis-associated Ekiri syndrome, or "lethal toxic encephalopathy," constitutes severe toxicity, convulsions, extreme hyperpyrexia, and headache, followed by brain edema and a rapidly fatal outcome without sepsis or significant dehydration.

DIFFERENTIAL DIAGNOSIS

Although clinical features suggest shigellosis, they usually are insufficiently specific to allow confident diagnosis. Infection by *Campylobacter jejuni, Salmonella* spp., EIEC, Shiga toxin–producing *E. coli* (EHEC, e.g., *E. coli* O157:H7), *Yersinia enterocolitica, Clostridioides difficile,* and *Entamoeba histolytica,* as well as inflammatory bowel disease, produce overlapping features and may challenge the clinician.

DIAGNOSIS

Presumptive data supporting a diagnosis of bacillary dysentery include the finding of fecal leukocytes (usually >50 or 100 PMNs per high-power field, confirming the presence of colitis), fecal blood, and

Table 245.2 Clinical Complications of Shigellosis

INTESTINAL COMPLICATIONS
Rectal prolapse*
Toxic megacolon
Intestinal perforation
Intestinal obstruction
Appendicitis
Persistent diarrhea
EXTRAINTESTINAL COMPLICATIONS
Dehydration
Severe hyponatremia (serum sodium <126 mmol/L)*
Hypoglycemia
Focal infections (e.g., meningitis, osteomyelitis, arthritis, splenic abscesses, vaginitis)
Sepsis, usually in malnourished or immunocompromised persons
Seizure or encephalopathy
Leukemoid reaction (peripheral leukocytes >40000/μL)*
POSTINFECTIOUS MANIFESTATIONS
Hemolytic-uremic syndrome (HUS)*
Reactive arthritis†
Irritable bowel syndrome (IBS)‡
Malnutrition

*Significantly more common in episodes with *Shigella dysenteriae* type 1 than with all other *Shigella* spp. among Bangladeshi children younger than 15 yr during the 1990s (rectal prolapse [52% vs 15%], severe hyponatremia [58% vs 26%], leukemoid reaction [22% vs 2%], and HUS [8% vs 1%]).

†Typical acute symptoms include asymmetric oligoarthritis (usually lower limb), enthesitis, dactylitis, and back pain. Extraarticular manifestations include conjunctivitis and uveitis; urethritis and other genitourinary tract manifestations; oral, skin, and nail lesions; and rarely, cardiac abnormalities.

‡IBS follows approximately 4% of *Shigella* episodes in studies from high-resource settings.

Adapted from Kotloff KL, Riddle MS, Platts-Mills JA, et al. Shigellosis. *Lancet.* 2018;391:801–810.

Table 245.1 Acute Clinical Manifestations of Shigellosis in Children <5 Years Old

MANIFESTATION	DYSENTERY (*n* = 757)	WATERY DIARRHEA (*n* = 288)
Fever	607 (80%)	207 (72%)
Abdominal cramps	616 (81%)	137 (48%)
Vomiting	136 (18%)	89 (31%)
WHO-defined dehydration	95 (13%)	134 (47%)
Tenesmus	511 (68%)	32 (11%)
Rectal prolapse	19 (3%)	4 (1%)

From Kotloff KL, Riddle MS, Platts-Mills JA, et al. Shigellosis. *Lancet.* 2018;391:801–810.

demonstration in peripheral blood of leukocytosis with a dramatic left shift (often with more bands than mature segmented neutrophils). The total peripheral white blood cell count is usually 5,000-15,000 cells/μL, although leukopenia and leukemoid reactions occur.

Culture of both stool and rectal swab specimens optimizes the chance of diagnosing *Shigella* infection. Culture media should include MacConkey agar and selective media such as xylose-lysine-deoxycholate and *Salmonella-Shigella* agar. Transport media should be used if specimens cannot be cultured promptly. Appropriate media should be used to exclude *Campylobacter* and *Salmonella* spp. and other agents. Studies of outbreaks and illness in volunteers show that the laboratory is often not able to confirm the clinical suspicion of shigellosis even when the pathogen is present. Multiple fecal cultures improve the yield of *Shigella*.

Culture-based diagnosis of *Shigella* infection, as with other enteric infections, is being displaced by molecular methods, often multiplexed, allowing testing for a panel of potential agents in a single rapid assay. Studies using molecular methods such as polymerase chain reaction (PCR) suggest that culture significantly underestimates the true frequency of infection. Quantitative PCR improves the ascertainment of *Shigella* burden in children with moderate to severe diarrhea in low-income countries. The generally **high negative predictive value** (NPV) of many molecular tests for *Shigella* (generally >95–97%) make the tests useful for decisions regarding antibiotic use and discontinuation and the necessity to test for additional etiologies of diarrhea. Molecular testing provides no information about antibiotic susceptibility. Stool cultures should be considered where antibiotic-resistant organisms are prevalent. In children who appear toxic, blood cultures should be obtained, especially in very young or malnourished infants, because of their increased risk of bacteremia.

TREATMENT

As with gastroenteritis from other causes, the first concern in a child with suspected shigellosis should be for fluid and electrolyte correction and maintenance (see Chapter 387). Drugs that impair intestinal motility (e.g., diphenoxylate hydrochloride with atropine [Lomotil] or loperamide [Imodium]) should not be used because of the risk of more severe and prolonged illness.

Nutrition is a key concern in areas where malnutrition is common. A high-protein and high-caloric diet during convalescence enhances growth in 6 months after infection. Controlled studies show that cooked green bananas, a food rich in amylase-resistant starches, significantly improves outcome in severe disease. A single large dose of **vitamin A** (200,000 IU) lessens the severity of shigellosis in settings where vitamin A deficiency is common. **Zinc** supplementation (20 mg elemental zinc for 14 days) significantly decreases the duration of diarrhea, improves weight gain during recovery, enhances adaptive immunity to *Shigellae,* and decreases diarrheal disease in malnourished children.

The decision to use **antibiotics** remains challenging (Fig. 245.1). Many experts recommend withholding antibacterial therapy because of the self-limited nature of the infection, the cost of drugs, the risk of emergence of resistant organisms, the risk of prolonging carriage (if *Salmonella* is present), or increasing the risk for HUS (EHEC). When a rapid multiplexed molecular stool pathogen detection test is available, waiting for a definitive diagnosis before administrating antibiotics should be considered. However, a counter-argument of empirical treatment for all children with suspected shigellosis has validity. Untreated illness can cause a child to have prolonged illness; chronic or recurrent diarrhea can ensue. Malnutrition can develop or worsen during prolonged illness, particularly in children in developing countries. The risk of continued excretion and subsequent infection of family contacts further argues against the strategy of withholding antibiotics.

Shigella antimicrobial susceptibility varies by species and geography. In the United States, strains are frequently resistant to ampicillin (74%) and trimethoprim-sulfamethoxazole (TMP-SMX) (36%). In general, the proportion of antibiotic-resistant isolates is lower in North America and Europe than in Asia or Africa. Previously, *Shigella* was widely regarded as susceptible in vitro to azithromycin, ceftriaxone, cefotaxime, cefixime, nalidixic acid, and quinolones. However, the Centers for Disease Control and Prevention (CDC) reports that 87% of *S. sonnei*–related U.S. cases are ciprofloxacin nonsusceptible, of which only approximately half followed international travel. Among MSM, clusters of shigellosis caused by *S. sonnei* and, to a lesser extent, *S. flexneri* were reported with up to 87% azithromycin resistance. International travel increases the risk for antibiotic-resistant infection. For example, Chinese isolates of *S. sonnei* are often resistant to TMP-SMX (94.5%), ampicillin (40.3%), piperacillin (36.5%), and ceftriaxone (12.8%).

Currently, in most developed and resource-poor countries, *Shigella* strains are often resistant to ampicillin and TMP-SMX. Therefore these drugs should not be used for empirical treatment of suspected shigellosis; they should be instituted only if the strain is known to be susceptible (e.g., in an outbreak caused by a defined strain). Empirical therapy in children with dysentery should be given based on considerations of regional infection cluster data and international travel history. **Ceftriaxone** (50-100 mg/kg/24 hr as a single daily dose intravenously or intramuscularly) can be used for empirical therapy, especially for small infants. The oral third-generation cephalosporin **cefixime** (8 mg/kg/24 hr divided every 12-24 hours) may be considered, although treatment failures for *S. sonnei* infections have been reported in adults; oral first- and second-generation cephalosporins are inadequate as alternative drugs despite in vitro susceptibility. **Azithromycin** (12 mg/kg/24 hr orally for the first day, followed by 6 mg/kg/24 hr for the next 4 days) has proved to be an effective alternative drug for shigellosis. **Ciprofloxacin** (20-30 mg/kg/24 hr divided into two doses) is the drug of choice recommended by the WHO for all patients with bloody diarrhea, regardless of age. Note that since 2015, the CDC has tracked increasing resistance and reduced susceptibility to ciprofloxacin and azithromycin in the United States. Concurrent zinc supplementation is recommended with antibiotic therapy.

Although **quinolones** are reported to cause arthropathy in immature animals and are associated with neuropathy, these risks are low in children and are outweighed by the value of these drugs for the treatment of this potentially life-threatening disease. However, some experts recommend that the quinolones be reserved for seriously ill children with bacillary dysentery caused by an organism suspected or known to be resistant to other agents, because overuse of quinolones promotes the development of resistance to these drugs.

Treatment of patients in whom *Shigella* infection is suspected on clinical grounds should be initiated when these patients are first evaluated. Molecular stool testing or culture is obtained to exclude other pathogens and, in the case of culture, to assist in antibiotic changes should a child fail to respond to empirical therapy. A child who has typical dysentery and who responds to initial empirical antibiotic treatment should be continued on that drug for a full 5-day course even if the stool culture is negative, because of the method's low NPV. The logic of this recommendation is based on the proven difficulty of culturing *Shigella* from stools of ill patients during adult volunteer infection studies. In a child who fails to respond to therapy of a dysenteric syndrome in the presence of initially negative stool culture results, additional cultures should be obtained, or molecular testing, where available and cost-permissive, should be performed, and the child should be reevaluated for other possible diagnoses. In the child with negative molecular stool testing for *Shigellae,* the high NPV makes the diagnosis less likely, and alternative diagnoses should be considered.

PREVENTION

Numerous measures have been recommended to decrease the risk of *Shigella* transmission to children. Mothers should be encouraged to *prolong breastfeeding* of infants. Families and daycare personnel

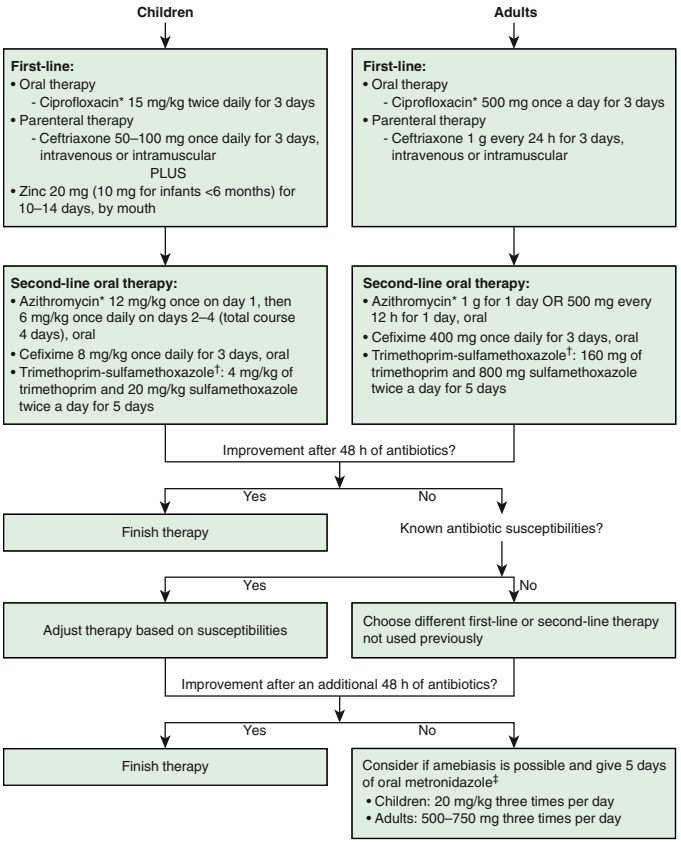

Fig. 245.1 Management algorithm: guidelines for treatment of shigellosis. Empirical therapy should be directed by hospital, clinical laboratory, or public health antibiograms whenever possible. Minimal inhibitory concentrations of 0.12-1.0 μg/mL for ciprofloxacin might be considered susceptible by laboratory standards but could harbor resistance genes known to confer decreased susceptibility. *Fluoroquinolones and azithromycin should be used with caution in patients taking the antimalarial artemether, because these drugs can prolong the QT interval on the electrocardiogram and trigger arrhythmias. †Trimethoprim-sulfamethoxazole should be used if susceptibility is known or expected based on local data. ‡Per WHO recommendations. Another acceptable regimen is a 7- to 10-day course of metronidazole followed by a luminal agent such as paromomycin or diiodohydroxyquinoline. *(Data from The selection and use of essential medicines: report of the WHO Expert Committee, 2017. Geneva: World Health Organization; 2017. WHO technical report series; no. 1006.)*

should be educated in *proper handwashing* techniques and encouraged to wash hands after using the toilet, changing diapers, or engaging in preparation of foods. They should be taught how to manage potentially contaminated materials such as raw vegetables, soiled diapers, and diaper-changing areas. Children with diarrhea should be excluded from childcare facilities. Children should be supervised when handwashing after they use the toilet. Caretakers should be informed of the risk of transmission if they prepare food when they are ill with diarrhea. Families should be educated regarding the danger of swallowing contaminated water from ponds, lakes, or untreated pools. In developing countries, a safe water supply and appropriate sanitation systems are important measures for reducing the risk for shigellosis. There is not yet a vaccine that is effective for preventing infection by *Shigella*. **Measles immunization** can substantially reduce the incidence and severity of diarrheal diseases, including shigellosis. Every infant should be immunized against measles at the recommended age.

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Chapter 246

Escherichia coli

Patrick C. Seed

Escherichia coli is an important cause of intraintestinal and extraintestinal infections. **Intraintestinal infections** present as diarrheal illnesses. **Extraintestinal infections** include disease of the urinary tract (see Chapter 575), bloodstream (Chapters 148, 220, and 221), and central nervous system (Chapter 643). *E. coli* causing extraintestinal and intraintestinal infections carry unique genetic attributes that encode different sets of virulence factors and genetic programs. Extraintestinal pathogenic *E. coli* increasingly harbor multidrug resistances, including transferrable plasmids resulting in extended-spectrum β-lactamase (ESBL) production and resistance to penicillins, cephalosporins, and aztreonam. Carbapenemase-bearing *E. coli* have also emerged, often in combination with multi–antibiotic class resistance, resulting in highly drug-resistant strains.

E. coli are members of the Enterobacteriaceae family and are facultative anaerobic, gram-negative bacilli that usually ferment lactose. Most fecal *E. coli* organisms are commensal, are ubiquitous among the human gut microbiota starting in the first month of life, and do not cause diarrhea. Six major groups of **diarrheagenic** *E. coli* pathotypes have been characterized based on clinical, biochemical, and molecular-genetic features: enterotoxigenic *E. coli* (ETEC); enteroinvasive *E. coli* (EIEC); enteropathogenic *E. coli* (EPEC); *Shiga* toxin–producing *E. coli* (STEC), also known as enterohemorrhagic *E. coli* (EHEC) or verotoxin-producing *E. coli* (VTEC); enteroaggregative *E. coli* (EAEC or EggEC); and diffusely adherent *E. coli* (DAEC).

E. coli strains can also be categorized by their serogroup, where *O* refers to the lipopolysaccharide (LPS) O-antigen or serotype and *H* refers to the flagellar antigen, for example, *E. coli* O157:H7. However, because each pathotype contains many serotypes (e.g., 117 ETEC serotypes have been identified) and some serotypes can belong to more than one pathotype (e.g., O26:H11 can be either EPEC or EHEC depending on which specific virulence genes are present), serotyping usually does not provide definitive identification of pathotypes.

Virulence characteristics and the association of those traits with illness define **enteric** *E. coli* pathogenicity (Table 246.1). The mechanism by which *E. coli* produces **diarrhea** typically involves specific adherence to a glycoprotein or glycolipid receptor on a target intestinal cell, followed by production of a factor that injures or disturbs the function of intestinal cells. The genes for virulence properties and antibiotic resistance are often carried on transferable plasmids, pathogenicity islands, or bacteriophages.

In the developing world, diarrheagenic *E. coli* cause frequent infections in the first years of life and are responsible for 30–40% of all diarrhea cases in children worldwide. Cases peak during the warm months in temperate climates and during rainy season months in tropical climates. Most diarrheagenic *E. coli* strains (except STEC) require a large inoculum of organisms to induce disease, thus necessitating exposure to grossly contaminated ingestible materials. Infection is most likely when food-handling or sewage-disposal practices are suboptimal. The diarrheagenic *E. coli* pathotypes are also important in North America and Europe, although their epidemiology is less well defined in these areas than in the developing world. In North America, the various diarrheagenic *E. coli* strains may cause as much as 30% of infectious diarrhea in children <5 years old.

A significant proportion of asymptomatic healthy children living in developing countries carry diarrheagenic *E. coli* pathotypes. **Fecal contamination** (human and animal), which is common in the low-resource environments, facilitates the transmission of pathogens. Modern, highly sensitive microbiologic methods enhance the sensitivity

Table 246.1 Clinical Characteristics, Pathogenesis, and Diagnosis of Diarrheagenic *E. coli*

PATHOGEN	POPULATIONS AT RISK	CHARACTERISTICS OF DIARRHEA			MAIN VIRULENCE FACTORS		DIAGNOSIS
		WATERY	BLOODY	DURATION	ADHERENCE FACTORS	TOXINS	
ETEC	>1 yr old and travelers	+++	–	Acute	Colonization factor antigens (CFs or CFAs); ECP	Heat-labile enterotoxin (LT) Heat-stable enterotoxin (ST)	Detection of enterotoxins (LT and ST) by enzyme immunoassays or PCR *(lt, st)*
EIEC	>1 yr old	+	++	Acute	Invasion plasmid antigen (IpaA-D)		Detection of invasion plasmid antigen of *Shigella (ipaH)* by PCR
EPEC	<2 yr old	+++	+	Acute, prolonged or persistent	A/E lesion, intimin/Tir, EspABD, Bfp	EspF, Map, EAST1, SPATEs *(EspC)*	Detection of intimin gene *(eae)* ± bundle-forming pili (*bfp*A) by PCR and absence of *Shiga* toxins; HEp-2 cells adherence assay (LA, LLA)
STEC (EHEC/ VTEC)	6 mo to 10 yr and elderly persons	+	+++	Acute	A/E lesion, intimin/Tir, EspABD	*Shiga* toxins (Stx1, Stx2, and variants of Stx2)	Detection of *Shiga* toxins by enzyme immunoassays or PCR *(Stx1, Stx2)*; stool culture on MacConkey-sorbitol media to detect *E. coli* O157. Simultaneous culture for O157 and nonculture assays to detect *Shiga* toxins
EAEC	<2 yr old, HIV-infected patients, and travelers	+++	+	Acute, prolonged, or persistent	Aggregative adherence fimbriae (AAF)	SPATEs (Pic, Pet), ShET1, EAST1	Detection of *AggR*, AA plasmid, and other virulence genes: *aap, aatA, astA, set1A* by PCR; HEp-2 cells adherence assay (AA)
DAEC	>1 yr old and travelers	++	–	Acute	Afa/Dr, AIDA-I	SPATEs (Sat)	Detection of Dr adhesins (daaC or daaD) and Dr-associated genes by PCR; HEp-2 cells adherence assay (DA)

–, Not present; +, present; ++, common; +++, very common; A/E lesion, attaching and effacing lesion; AA, aggregative adherence; Bfp, bundle-forming pili; DA, diffuse adherence; DAEC, diffusely adherent *E. coli;* EAEC, enteroaggregative *E. coli;* EAST1, enteroaggregative heat-stable toxin; ECP, *E. coli* common pilus; EHEC, enterohemorrhagic *E. coli;* EIEC, enteroinvasive *E. coli;* EPEC, enteropathogenic *E. coli*; EspABD, *E. coli*–secreted proteins A, B, and D; ETEC, enterotoxigenic *E. coli;* LA, localized adherence; LLA, localized-like adherence; PCR, polymerase chain reaction; ShET1, *Shigella* enterotoxin 1; SPATEs, serine-protease autotransporter of Enterobacteriaceae; STEC, *Shiga* toxin–producing *E. coli*; Tir, translocated intimin receptor; VTEC, verotoxin-producing *E. coli*.

of detection in stool samples, and small numbers of bacteria can be detected in stool samples. Therefore the prevalence of various enteropathogens in children with and without diarrhea must be considered. Excretion of enteropathogens by children without diarrhea may be explained by characteristics of the pathogens (virulence heterogeneity), the host (host susceptibility, age, nutritional status, breastfeeding, immunity), and environmental factors (inoculum size).

ENTEROTOXIGENIC *ESCHERICHIA COLI*

ETEC accounts for a sizable fraction of dehydrating infantile diarrhea in the developing world (10–30%) and of **traveler's diarrhea** (20–60% of cases); ETEC is the most common cause of traveler's diarrhea. The Global Enteric Multicenter Study (GEMS) found heat-*stable* enterotoxin (ST)–expressing ETEC (with or without coexpression of *heat-labile* enterotoxin [LT]) to be a leading cause of diarrhea and increased risk for death in young children in developing countries of Asia and Africa. The typical signs and symptoms include explosive watery, nonmucoid, nonbloody diarrhea; abdominal pain; nausea; vomiting; and little or no fever. The illness is usually self-limited and resolves in 3-5 days but occasionally lasts >1 week.

Diarrhea follows ETEC colonization of the small intestine and elaboration of enterotoxin; however, ETEC causes few to no structural alterations in the gut mucosa. ETEC strains secrete one or two enterotoxins. LT, a large molecule consisting of five receptor-binding subunits

and one enzymatically active subunit, is structurally, functionally, and neutralizing antibody cross-reactive with cholera toxin produced by *Vibrio cholerae*. LT stimulates adenylate cyclase, resulting in increased cyclic adenosine monophosphate. ST is not related to cholera toxin and stimulates guanylate cyclase, resulting in increased cyclic guanosine monophosphate. Each toxin induces ion and water secretion into the intestinal lumen, resulting in profuse watery diarrhea. The toxin genes are carried on plasmids.

Colonization of the intestine requires fimbria **colonization factor antigens (CFAs)**, which promote adhesion to the intestinal epithelium. Over 25 CFA types exist and can be expressed alone or in combination. Roughly 30–50% of ETEC isolates lack a characterized CFA. However, novel CFAs continue to be identified.

CFAs are highly immunogenic, but their multiplicity and allelic variation elude vaccine development. Many strains produce a type IV pilus involved in colonization and shared among other gram-negative bacterial pathogens. ETEC express type 1 pili (the "common pilus"), produced by commensal and pathogenic *E. coli* strains. TibA, a nonfimbrial adherence factor, mediates potent bacterial attachment and invasion of cells. For many years, the O serogroup was used to distinguish pathogenic from commensal *E. coli*. Molecular classification of pathogenic *E. coli* based on specific virulence genes and whole genome phylogeny has largely replaced classic O serogroup typing.

ENTEROINVASIVE *ESCHERICHIA COLI*

EIEC infections produce watery diarrhea or dysentery with blood, mucus, and leukocytes in the stools, as well as fever, systemic toxicity, crampy abdominal pain, tenesmus, and urgency. The illness resembles **bacillary dysentery** because EIEC shares virulence genes with *Shigella* spp. Sequencing of multiple housekeeping genes indicates that EIEC is more related to *Shigella* than to noninvasive *E. coli*. EIEC diarrhea occurs mostly in outbreaks; however, endemic disease occurs in developing countries. In some areas of the developing world, as many as 5% of sporadic diarrhea episodes and 20% of bloody diarrhea cases are caused by EIEC (see Chapter 245).

EIEC behave like *Shigella* in their capacity to invade gut epithelium and cause colonic lesions with ulcerations, hemorrhage, mucosal and submucosal edema, and infiltration by polymorphonuclear leukocytes (PMNs). The invasive process involves initial entry into cells, intracellular multiplication, intracellular and intercellular spread, and host cell death. All bacterial genes necessary for entry into the host cell are clustered within a 30-kb region of a large virulence plasmid; these genes are closely related to those found on the invasion plasmid of *Shigella* spp. This region carries genes encoding the entry-mediating proteins, including proteins that form a needle-like injection apparatus called *type III secretion,* required for secreting the invasins (IpaA-D and IpgD). The Ipas are the primary effector proteins of epithelial cell invasion. EIEC contact with host cells triggers the syringe-like type III secretion apparatus and injection of Ipas into the host cell cytoplasm.

Like *Shigella* spp., EIEC are nonmotile (they lack H or flagellar antigens) and are usually non–lactose fermenting. The serogroups of EIEC share LPS antigens related to *Shigella* LPS.

ENTEROPATHOGENIC *ESCHERICHIA COLI*

EPEC causes acute, prolonged, and persistent diarrhea, primarily in children <2 years old in resource-poor countries, where the organism may account for 20% of infant diarrhea. In developed countries, EPEC causes occasional daycare center and pediatric ward outbreaks. Profuse watery, nonbloody diarrhea with mucus, vomiting, and low-grade fever are common symptoms. Prolonged diarrhea (>7 days) and persistent diarrhea (>14 days) can lead to **malnutrition**, a potentially mortality-associated outcome of EPEC infection in infants in the developing world. Studies show that breastfeeding is protective against diarrhea caused by EPEC.

EPEC colonization causes blunting of intestinal villi, local inflammatory changes, and sloughing of superficial mucosal cells; EPEC-induced lesions extend from the duodenum through the colon. EPEC induces a characteristic attaching and effacing histopathologic lesion, which is defined by the intimate attachment of bacteria to the epithelial surface and effacement of host cell microvilli. Factors responsible for the attaching and effacing lesion formation are encoded by the *locus of enterocyte effacement* (LEE), a pathogenicity island with genes for a type III secretion system, the translocated intimin receptor (Tir) and intimin, and multiple effector proteins such as the *E. coli*–secreted proteins (EspA-B-D). Some strains adhere to the host intestinal epithelium in a pattern known as *localized adherence,* a trait that is mediated in part by the type IV bundle-forming pilus (Bfp) encoded by a plasmid (the EAF plasmid). After initial contact, proteins are translocated through filamentous appendages, forming a physical bridge between the bacteria and the host cell; bacterial effectors (EspB, EspD, Tir) are translocated through these conduits. Tir moves to the surface of host cells, where it is bound by a bacterial outer membrane protein intimin (encoded by the *eae* gene). Intimin-Tir binding triggers polymerization of actin and other cytoskeletal components at the site of attachment. These cytoskeletal changes result in intimate bacterial attachment to the host cell, enterocyte effacement, and pedestal formation.

Other LEE-encoded effectors include Map, EspF, EspG, EspH, and SepZ. Various other effector proteins are encoded outside the LEE and secreted by the type III secretion system (the non–LEE-encoded proteins, or Nle). The contribution of these putative effectors (e.g., NleA/EspI, NleB, NleC, NleD) to virulence is still under investigation. The presence and expression of virulence genes vary among EPEC strains.

The *eae* (intimin) and *bfp*A genes serve as molecular markers of EPEC and genetically subdivide EPEC into typical and atypical strains. *E. coli* strains that are *eae*$^+$/*bfp*A$^+$ are classified as "typical" EPEC; most of these strains belong to common O:H serotypes. *E. coli* strains that are *eae*$^+$/*bfp*A$^-$ are classified as "atypical" EPEC. Current data suggest that atypical EPEC are more prevalent than typical EPEC in both developed and developing countries, even in persistent diarrhea cases. In the GEMS study, typical EPEC was most associated with increased risk of mortality, particularly in infants in Africa.

ENTEROAGGREGATIVE *ESCHERICHIA COLI*

EAEC infection produces (1) acute, prolonged, and persistent pediatric diarrhea in developing countries, most prominently in children <2 years old and in malnourished children; (2) acute and persistent diarrhea in HIV-infected adults and children; and (3) acute traveler's diarrhea; EAEC is the second most common cause of traveler's diarrhea after ETEC. Typical EAEC illness is manifested by watery, mucoid, secretory diarrhea with low-grade fever and little or no vomiting. The watery diarrhea can persist for ≥14 days. Patients with EAEC may have grossly bloody stools, and EAEC cannot be excluded on stool characteristics. EAEC colonization and infection lead to growth retardation and malnutrition in infants in the developing world.

EAEC organisms form a characteristic biofilm on the intestinal mucosa and induce shortening of the villi, hemorrhagic necrosis, and inflammatory responses. The proposed model of pathogenesis of EAEC infection involves three phases: adherence to the intestinal mucosa by way of the aggregative adherence fimbriae or related adhesins, stimulation of enhanced mucus production, and toxin-mediated inflammation that results in damage to the mucosa and intestinal secretion. Diarrhea caused by EAEC is predominantly secretory. The intestinal inflammatory response (elevated fecal lactoferrin, interleukin [IL]-8 and IL-1β) may be related to growth impairment and malnutrition.

EAEC strains adhere in an aggregative, stacked-brick pattern, called *aggregative adherence* (AA), mediated by the AA fimbriae (AAF-I, -II, and -III). Some strains produce toxins, including the plasmid-encoded enterotoxin EAST1 (encoded by *ast*A), a homolog of the ETEC ST; an autotransporter toxin called Pet; other STATE toxins; and the chromosomally encoded enterotoxin ShET1 (encoded by *setA* and *setB*). Other virulence factors include outer membrane and secreted proteins, such as dispersin *(aap),* and the dispersin transport complex (aatPABCD). EAEC is a heterogeneous group of *E. coli*. A transcriptional activator called **AggR** controls the expression of plasmid-borne and chromosomal virulence factors. Identification of AggR appears to reliably identify illness-associated pathogenic EAEC strains ("typical" EAEC). EAEC *agg*R-positive strains carrying one to three of the genes *aap, ast*A, and *set1A* are significantly associated with diarrhea compared

with EAEC isolates lacking these genes. Other than the AAF and AggR factors, EAEC strains are genetically diverse, display variable virulence, and belong to multiple serogroups.

SHIGA TOXIN–PRODUCING *ESCHERICHIA COLI*

The STEC, which include EHEC, produce a range of clinical syndromes from asymptomatic colonization, to mild diarrhea, to severe hemorrhagic colitis. Watery diarrhea that becomes bloody over several days characterizes STEC illness. STEC infrequently causes fever, a distinguishing difference with shigellosis or EIEC disease. Most people with STEC recover from the infection without further complication. However, 5–10% of children with STEC hemorrhagic colitis go on within a few days to develop systemic complications such as **hemolytic-uremic syndrome** (HUS), characterized by acute kidney failure, thrombocytopenia, and microangiopathic hemolytic anemia (see Chapter 560). Severe illnesses occur most often among children 6 months to 10 years old. Young children with STEC-associated bloody diarrhea and neutrophilic leukocytosis in the early course of their diarrhea are at risk for HUS progression. Older individuals can also develop HUS or thrombotic thrombocytopenic purpura.

STEC transmits person to person (e.g., in families and daycare centers) and in contaminated food and water; a small inoculum can lead to infection. STEC food-borne outbreaks have arisen from undercooked hamburger, apple cider, lettuce, spinach, mayonnaise, salami, dry fermented sausage, and unpasteurized dairy products.

STEC primarily affects the colon, where organisms adhere to intestinal cells and produce attaching-effacing lesions such as those seen with EPEC and contain related genes (e.g., *intimin, Tir, EspA-D*). Unlike EPEC, STEC produces two major **Shiga toxins** (Stx1 and Stx2; previously called *verotoxins* and *Shiga-like*). STEC may produce one or both toxins and their closely related variants. **Stx1** is essentially identical to Shiga toxin, the protein synthesis–inhibiting exotoxin of *Shigella dysenteriae* serotype 1. **Stx2** and variants of Stx2 are more distantly related to Shiga toxin, although they share conserved sequences.

STEC Shiga toxins are composed of a single A subunit noncovalently associated with a pentamer composed of identical B subunits. The B subunits bind to globotriaosylceramide (Gb_3), a glycosphingolipid receptor on host cells. The A subunit is taken up by endocytosis. The toxin target is the 28S ribosomal RNA (rRNA), which is depurated by the toxin at a specific adenine residue, causing protein synthesis to cease and affected cells to die. These toxins are carried on bacteriophages that are normally inactive (lysogenic) in the bacterial chromosome; when the phages are induced to replicate (e.g., by the stress induced by many antibiotics), they cause lysis of the bacteria and release of large amounts of toxin. Toxin translocation across the intestinal epithelium into the systemic circulation can lead to damage of vascular endothelial cells, resulting in activation of the coagulation cascade, formation of microthrombi, intravascular hemolysis, and ischemia.

The clinical outcome of an STEC infection depends on a strain-specific combination of epithelial attachment and the toxin factors. The Stx2 toxins are associated with a higher risk of causing HUS. Strains producing only Stx1 often cause only watery diarrhea and, infrequently, HUS.

The most common STEC serotypes are *E. coli* O157:H7, *E. coli* O111:NM, and *E. coli* O26:H11, although several hundred other STEC serotypes have also been described. *E. coli* **O157:H7** is the most virulent serotype and the serotype most frequently associated with HUS; however, other non-O157 serotypes also cause this illness.

ENTEROAGGREGATIVE HEMORRHAGIC *ESCHERICHIA COLI*

In 2011, a massive outbreak of an unusual O104:H4 strain of diarrheagenic *E. coli* began in Germany. Eventually, >4,000 individuals were sickened with hemorrhagic colitis; the outbreak involved primarily adults (<100 children were reported affected). More than 800 people developed HUS, and >50 of these individuals died. Genomic analysis suggested the outbreak strain was most closely related to EAEC and had acquired a lambdoid bacteriophage with genes for Shiga toxin Stx2a. It was thus a **hybrid** pathogen with colonization mechanisms similar to a typical EAEC strain and toxin production typical of an STEC strain. This outbreak strain carries Pic on the chromosome and a pAA-like plasmid encoding AAF, AggR, Pet, ShET1, and dispersin. A second virulence plasmid encodes multiple antibiotic resistances. The high morbidity and mortality associated with this strain may reflect the stronger adherence of EAEC compared with STEC, delivering more Stx to target cells. Alternative terminology for this strain includes **enteroaggregative hemorrhagic *E. coli*** and **Shiga toxin–producing EAEC**. Whether Shiga toxin production in an EAEC background merits separate classification is unclear. Organisms with Shiga toxin genes in an atypical EPEC background were designated as a separate group (referred to as **STEC**, **EHEC**, or **verotoxin-producing *E. coli***) before the relative importance of the various genes was clear. EPEC strains are a heterogeneous group themselves. The important issue is not the nomenclature, but rather the concept that virulence genes can move between *E. coli,* resulting in new variants.

DIFFUSELY ADHERENT *ESCHERICHIA COLI*

Multiple studies in both developed and developing countries find DAEC associated with diarrhea, particularly in children after the first 1-2 years of life. DAEC strains isolated from children and adults seem to represent two different bacterial populations. **Age-dependent susceptibility** or the use of inappropriate detection methods may explain discrepancies among epidemiologic studies. Data suggest that these organisms also cause traveler's diarrhea in adults. DAEC produces prolonged watery diarrhea that is usually not dysenteric.

DAEC strains produce **diffuse adherence** on intestinal epithelial cells using the Afa/Dr-like surface fimbriae (designated F1845). The outer membrane protein AIDA-I also associates with **diffuse adherence**. DAEC secrete the serine-protease autotransporters of Enterobacteriaceae (SPATE) cytotoxin Sat. Bacteria expressing Afa/Dr adhesins interact with membrane-bound receptors, including decay-accelerating factor (DAF). The structural and functional lesions induced by DAEC include loss of microvilli and a decrease in the expression and enzyme activities of functional brush border–associated proteins. Afa/Dr DAEC isolates produce a secreted autotransporter toxin that induces marked fluid accumulation in the intestine. DAEC strains typically induce IL-8 production in vitro.

DIAGNOSIS

The features of suspected *E. coli* diarrheal illness are seldom distinctive enough to allow confident diagnosis strictly on clinical observations and routine laboratory studies such as blood counts. Practical, non–DNA-dependent methods for routine diagnosis of diarrheagenic *E. coli* have been developed primarily for STEC. Serotype O157:H7 is suggested by isolation of an *E. coli* that fails to ferment sorbitol on MacConkey sorbitol medium; latex agglutination confirms that the organism contains O157 LPS. Commercially available enzyme immunoassay or latex agglutination assays detect Shiga toxins in the routine hospital laboratory, although their variable sensitivity may limit their value.

Commercial assays such as the FilmArray Gastrointestinal Panel and Eurofins Diatherix Panel rapidly detect genetic markers for EPEC, EAEC, ETEC, STEC, and EIEC, among other pathogen genes, directly from a fecal sample in several hours and have been shown to reduce hospitalizations and treatment costs. Although some STEC (O157:H7 strains) can be detected in routine microbiology laboratories using selective media and appropriate antisera, the diagnosis of other diarrheagenic *E. coli* infection is traditionally made based on tissue culture assays (e.g., HEp-2-cells assay for EPEC, EAEC, and DAEC) or identification of specific virulence factors of the bacteria by phenotype (e.g., toxins) or genotype. Multiplex, real-time, or conventional polymerase chain reaction (PCR) can be used for presumptive diagnosis of isolated *E. coli* colonies. The genes commonly used for diagnostic PCR are *lt* and *st* for ETEC; *IpaH* or *iaL* for EIEC; *eae* and *bfp*A for EPEC; *eae, Stx1,* and *Stx2* for STEC; *AggR* or the AA plasmid for EAEC; and *daaC* or *daaD* for DAEC.

Serotyping does not provide definitive identification of pathotypes (except for selected cases such as O157:H7) because each pathotype

contains many serotypes and some serotypes can belong to more than one pathotype. Consequently, serotyping should not be used routinely for diarrheagenic *E. coli* identification in clinical laboratories (e.g., to diagnose EPEC in infantile diarrhea), except during an outbreak investigation.

Other laboratory data are, at best, *nonspecific* indicators of etiology. Fecal leukocyte examination of the stool is often positive with EIEC or occasionally positive with other diarrheagenic *E. coli*. With EIEC and STEC there may be an elevated peripheral blood PMN count with a left shift. Determination of *Stx2* blood levels in the early, post-bloody diarrhea period may be useful to identify children at risk of HUS; however, a validated clinical test is not readily available. Fecal lactoferrin, IL-8, and IL-1β can be used as inflammatory markers. Electrolyte changes are nonspecific, reflecting only fluid loss.

TREATMENT

The cornerstone of management is appropriate fluid and electrolyte therapy (Fig. 246.1). In general, this therapy should include oral replacement and maintenance with rehydration solutions such as those specified by the World Health Organization (WHO). Early volume expansion during STEC infection may reduce renal injury and improve patient outcomes. Upon refeeding, continued supplementation with oral rehydration fluids is appropriate to prevent recurrence of dehydration. Early refeeding (within 6-8 hours of initiating rehydration) with breast milk or infant formula or solid foods should be encouraged. Prolonged withholding of feeding can lead to chronic diarrhea and malnutrition. If the child is malnourished, oral zinc should be given to speed recovery and decrease the risk of future diarrheal episodes.

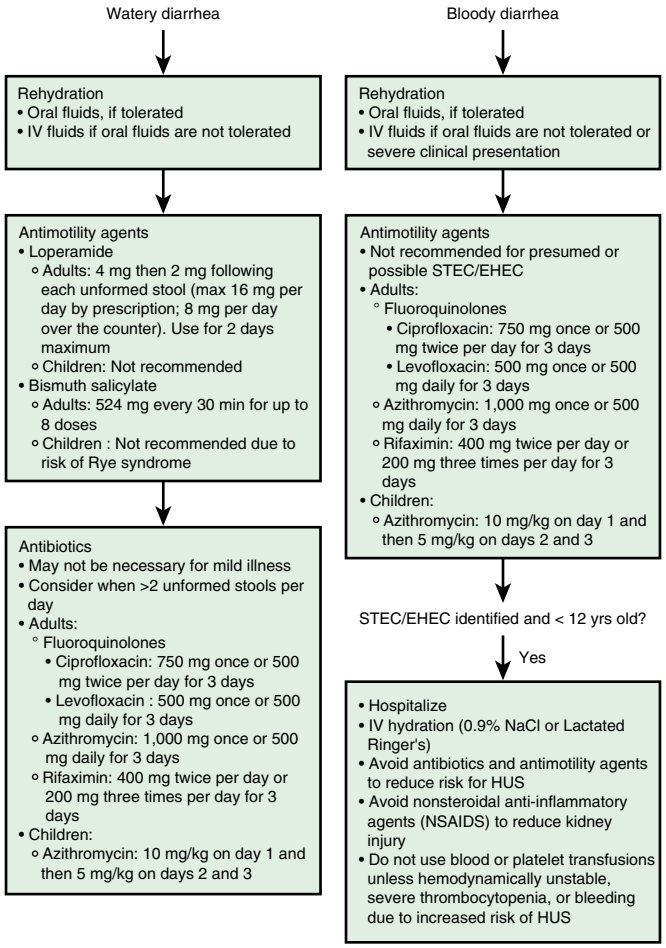

Fig. 246.1 Algorithmic treatment summary for presumed and possible *E. coli* diarrheal illness.

In children, validated criteria for antimicrobial therapy of diarrheal disease do not exist. The routine use of antimicrobials to treat childhood diarrhea is not recommended by the WHO except in severe cases. Nonbloody diarrhea rarely requires antimicrobial therapy. Antimicrobials should be reserved for dysenteric presentations, when host immunity is compromised by specific disorders, malnutrition, and chronic disease (Table 246.2). Antimicrobials should also be considered for severe traveler's diarrhea and diarrhea accompanied by fever and bloody stools. In settings of good healthcare resources, rapid molecular testing for STEC should be performed before initiating antibiotics, which can increase the risk for HUS.

Emerging antimicrobial resistance among diarrheal *E. coli* and other bacterial pathogens complicates treatment. Multiple studies in developing countries have found that diarrheagenic *E. coli* strains typically are resistant to antibiotics such as trimethoprim-sulfamethoxazole (TMP-SMX) and ampicillin (60–70%). Most data come from case series or clinical trials in adults with traveler's diarrhea. ETEC responds to antimicrobial agents such as TMP-SMX when the *E. coli* strains are susceptible. ETEC cases from traveler's diarrhea trials respond to ciprofloxacin, azithromycin, and rifaximin. However, other than for a child recently returning from travel in the developing world, empirical treatment of severe *watery diarrhea* with antibiotics is seldom appropriate.

In resource-poor settings where rapid molecular panel tests are not available, EIEC infections may be treated before culture results are finalized because the clinician suspects shigellosis and has begun empirical therapy. If the organisms prove to be susceptible, TMP-SMX is an appropriate choice. Although treatment of EPEC infection with TMP-SMX intravenously or orally for 5 days may be effective in speeding resolution, the lack of a rapid diagnostic test in the resource-poor setting makes treatment decisions difficult. Ciprofloxacin or rifaximin is useful for EAEC traveler's diarrhea, but pediatric data are sparse. Specific therapy for DAEC has not been defined.

The STEC strains represent a particularly difficult therapeutic dilemma; many antibiotics can induce bacterial stress, toxin production, and phage-mediated bacterial lysis with toxin release. Antibiotics should not be given for STEC infection because they can increase the risk of HUS (see Chapter 560). In settings with rapid molecular diagnostics, a delay in providing antibiotics is rarely consequential and can allow the clinician to more confidently recommend or exclude antibiotics from the therapeutic plan.

PREVENTION OF ILLNESS

In the developing world, prevention of disease caused by pediatric diarrheagenic *E. coli* is probably best done by maintaining prolonged breastfeeding, paying careful attention to personal hygiene, and following proper food- and water-handling procedures. People traveling

Table 246.2 Risk Factors Favoring Antibiotic Therapy in Children with Acute Diarrhea

RISK FACTOR	EVIDENCE
CHILD FACTORS	
Age <3 mo	Poor evidence in general; strong indication for neonates
Severe clinical presentation	Poor evidence but strong indications
Malnutrition	Strong evidence
Chronic disease and immune deficiency	Strong evidence (IBD and HIV); otherwise poor evidence; strong indications
SETTING FACTORS	
Daycare centers, closed institutions, hospitals	Strong evidence if bacteria spread is a potential
Traveler's diarrhea	Evidence for adult is strong; poor evidence in children

to these places can be best protected by handwashing and consuming only processed water, bottled beverages, breads, fruit juices, fruits that can be peeled, or foods that are served steaming hot.

Prophylactic antibiotic therapy is effective in adult travelers but has not been studied in children and is not recommended. Public health measures, including sewage disposal and food-handling practices, have made pathogens that require a large inoculum to produce illness relatively uncommon in industrialized countries where food screening and public health measures are robust. Food-borne outbreaks of STEC are a problem for which no adequate solution has been found. During the occasional hospital outbreak of EPEC disease, attention to enteric isolation precautions and cohorting may be critical.

Protective immunity against diarrheagenic *E. coli* remains an active area of research, and no vaccines are available for clinical use in children. Multiple vaccine candidates based on bacterial toxins and colonization factors have shown promise for prevention of ETEC in adult travelers, but long-term protection with these vaccines has not been optimal, particularly in children.

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Chapter 247

Cholera

James P. Nataro

Cholera is a dehydrating diarrheal disease that rapidly leads to death in the absence of immediate initiation of appropriate treatment. Worldwide, 1.3 billion people are at risk for cholera, resulting in an estimated 1-4 million cases and 95,000 deaths annually. Cholera is highly prone to producing outbreaks, and the ongoing outbreaks in Yemen and Haiti emphasize how cholera and potentially other infectious diseases can easily reemerge in areas that have long been considered free of the disease after a natural disaster or war-related conflicts.

ETIOLOGY

Cholera is caused by *Vibrio cholerae,* a gram-negative, comma-shaped bacillus, subdivided into serogroups by its somatic O antigen. Of the >200 serogroups, only serogroups O1 and O139 have been associated with epidemics, although some non-O1, non-O139 *V. cholerae* strains (e.g., O75, O141) are pathogenic and can cause small outbreaks. A flagellar H antigen is present but is not used for species identification. The O1 serogroup is further divided into classical and El Tor biotypes based on its biochemical characteristics. Since the turn of the 21st century, only **O1 El Tor** has been reported; hybrids and variants of *V. cholerae* O1 El Tor possessing classical genes have been reported worldwide. These hybrid and variant strains have been associated with more severe disease.

Each biotype of *V. cholerae* can be further subdivided into Inaba, Ogawa, and Hikojima serotypes based on the antigenic determinants on the O antigen. **Inaba** strains have A and C antigenic determinants, whereas **Ogawa** strains have A and B antigenic determinants. **Hikojima** strains produce all three antigenic determinants but are unstable and rare. Recent studies reveal that serotype switching results from a selection process as yet unidentified.

EPIDEMIOLOGY

The first six cholera pandemics originated in the Indian subcontinent and were caused by classical O1 *V. cholerae*. The seventh pandemic is the most extensive of all and is caused by *V. cholerae* O1 El Tor. This pandemic began in 1961 in Sulawesi, Indonesia, and has spread to the Indian subcontinent, Southeast Asia, Africa, Oceania, Southern Europe, and the Americas. In 1991, *V. cholerae* O1 El Tor first appeared in Peru before rapidly spreading in the Americas. Cholera becomes **endemic** in areas after outbreaks when a large segment of the population develops immunity to the disease after recurrent exposure. Although the Ganges River valley is the historical home of cholera, it is estimated that >90% of global cases now occur in Africa, where the disease remains highly endemic.

In 1992 the first non-O1 *V. cholerae* that resulted in epidemics was identified in India and Bangladesh and was designated *V. cholerae* **O139**. From 1992 to 1994, this organism replaced O1 as the predominant cause of cholera in South Asia but has since been an uncommon etiologic agent.

The hybrid El Tor strains were first identified sporadically in Bangladesh. In 2004, during routine surveillance in Mozambique, isolates of *V. cholerae* O1 El Tor carrying classical genes were identified. Since then, hybrid and variant El Tor strains have been reported in other parts of Asia and Africa and have caused outbreaks in India and Vietnam. Although the classical biotype has virtually disappeared, its genes remain within the El Tor biotype. The current circulating strain in Haiti is closely related to the South Asian strain.

Humans are the only known hosts for *V. cholerae,* but free-living and plankton-associated *V. cholerae* exist in the marine environment. The organism thrives best in moderately salty water but can survive in rivers and freshwater if nutrient levels are high, as occurs when there is organic pollution such as human feces. The formation of a biofilm on abiotic surfaces and the ability to enter a viable but nonculturable state have been hypothesized as factors that allow *V. cholerae* to persist in the environment during interepidemic periods. Surface sea temperature, pH, chlorophyll content, the presence of iron compounds and chitin, and climatic conditions such as amount of rainfall and sea level rise are all important environmental factors that influence the survival of *V. cholerae* in the environment.

Consumption of **contaminated water** and ingestion of **undercooked shellfish** are the main modes of transmission, but additional food sources are becoming increasingly common. In cholera-endemic areas, the incidence is highest among children <2 years old, probably driven by the lack of previous exposure in young children. However, during cholera epidemics, all age-groups are usually affected, particularly in areas with no previous *V. cholerae* transmission. Persons with blood group O, decreased gastric acidity, malnutrition, immunocompromised states, and absence of local intestinal immunity (i.e., prior exposure) are at increased risk for developing severe disease. Household contacts of cholera-infected patients are at high risk of infection, because the stools of infected patients contain high concentrations of the pathogen. Moreover, upon repeated cycles of passage through humans, the organism becomes more virulent, demonstrating an increased number of copies of the cholera toxin-encoding genes.

PATHOGENESIS

Large inocula of bacteria (>10^8 colony-forming units [CFUs]) are required for severe cholera to occur; however, for persons whose gastric barrier is disrupted, a much lower dose (10^5 CFUs) is required, and the infectious dose may be lower after serial propagation of the pathogen through humans. After ingestion of *V. cholerae* from the environment, several changes occur in the microorganisms as they traverse the human intestine: increased expression of genes required for nutrient acquisition, downregulation of chemotactic responses, and expression of motility factors. Freshly excreted organisms (5-24 hours after shedding) are maximally infectious and may represent the predominant pathway for person-to-person transmission during epidemics.

The principal virulence factors of *V. cholerae* O1 are the cholera toxin and the toxin-coregulated pilus, a colonization factor that confers adherence to the epithelium of the small intestine (Fig. 247.1). The cholera toxin consists of five binding B subunits and one active A subunit. The B subunits are responsible for binding to the GM_1 ganglioside receptors located in the small intestinal epithelial cells. After binding, the A subunit is translocated into the cell, where it catalyzes adenosine diphosphate (ADP) ribosylation of the *alpha* subunit of the G_s signaling protein, which becomes constitutively active. G_s stimulates adenylate cyclase, leading to accumulation of cyclic adenosine

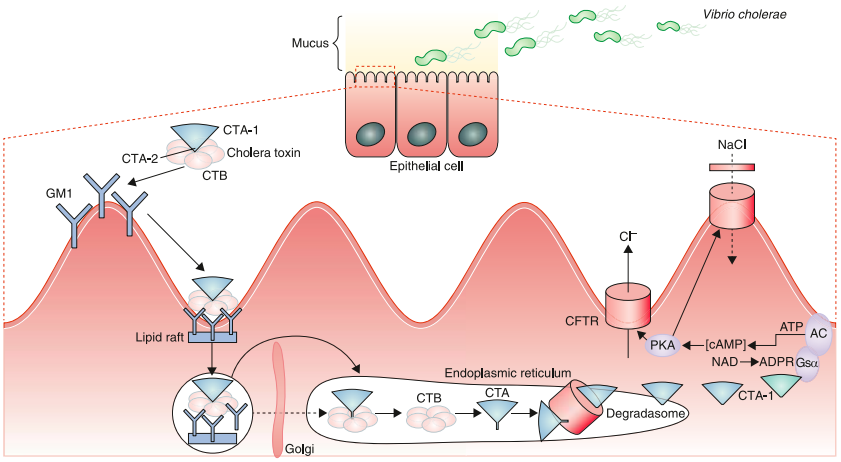

Fig. 247.1 Cholera pathogenesis and cholera toxin action. After ingestion, *Vibrio cholerae* colonize the small intestine and secrete cholera toxin, which has a doughnut-like structure with a central enzymatic toxic-active A (CTA-1 + CTA-2) subunit associated with a pentameric B subunit (CTB). After binding to GM_1 ganglioside receptors on small intestinal epithelial cells, which are mainly localized in lipid rafts on the cell surface, the cholera toxin is endocytosed and transported to the degradosome via the endoplasmic reticulum (ER) by a retrograde pathway, which, dependent on cell type, may or may not involve passage through the Golgi apparatus. In the ER, CTA dissociates from CTB, allowing CTA-1 to reach the cytosol by being translocated through the degradosome pathway. In the cytosol, CTA-1 subunits rapidly refold and bind to the Gsα subunit of adenylate cyclase (AC) in the cell membrane; on binding, CTA-1 adenosine diphosphate (ADP)-ribosylates the Gsα subunit, which stimulates AC activity, leading to an increase in intracellular concentration of cyclic adenosine monophosphate (cAMP), activation of protein kinase A (PKA), phosphorylation of the cystic fibrosis transmembrane conductance regulator (CFTR), a major chloride channel, and extracellular secretion of chloride ions (Cl^-) and water. Cholera toxin–induced Cl^- (and bicarbonate ion) secretion is particularly pronounced in intestinal crypt cells, whereas the increased intracellular cAMP concentrations in villus cells mainly inhibit the uptake of sodium chloride (NaCl) and water. *(Adapted from Clemens J, Shin S, Sur D, et al. New-generation vaccines against cholera. Nat Rev Gastroenterol Hepatol. 2011;8:701–710; by permission of Nature Publishing Group.)*

monophosphate and subsequent hyperactivation of the cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel. Increased chloride and bicarbonate secretion by CFTR is accompanied by sodium and water loss into the small bowel, greatly exceeding the ability of the colon to reabsorb the fluid. These events eventually lead to massive purging of electrolyte-rich stool, potentially resulting in rapid dehydration and depletion of electrolytes, including sodium, chloride, bicarbonate, and potassium. Metabolic acidosis and hypokalemia then ensue.

CLINICAL MANIFESTATIONS

Most cases of cholera are mild or inapparent. Among symptomatic individuals, approximately 20% develop severe **dehydration** that can rapidly lead to death. After a typical incubation period of 1-2 days (range: several hours to 5 days), acute watery **diarrhea** and **vomiting** ensue. The onset may be sudden, with profuse watery diarrhea, but some patients have a prodrome of anorexia and abdominal discomfort and the stool may initially be brown. Diarrhea can progress to painless purging of profuse *rice-water stools* (suspended flecks of mucus) with a fishy smell, which is the hallmark of the disease (Figs. 247.2 and 247.3). Fever is infrequent and suggests a different diagnosis. Vomiting with clear watery fluid is usually present at the onset of the disease. Stool from cholera patients typically contains more sodium (along with potassium and bicarbonate) compared with stool from diarrhea caused by other pathogens; the high stool volume, coupled with the presence of electrolytes, challenges clinicians to avoid dehydration and electrolyte imbalance. Muscle cramping and weakness commonly occur as a result of potassium and calcium imbalance.

The term **cholera gravis** refers to the most severe form of the disease, characterized by rice water stools and fecal purging at rates of up to 500-1,000 mL/hr. This condition inevitably leads to dehydration, manifested by decreased urine output, a sunken fontanel (in infants), sunken eyes, absence of tears, dry oral mucosa, shriveled hands and feet ("washerwoman's hands"), poor skin turgor, thready pulse, and tachycardia. If left untreated, hypotension and vascular collapse are inevitable (see Fig. 247.3). Patients with metabolic acidosis can present with typical Kussmaul breathing. Although patients may be initially thirsty and awake, they rapidly progress to obtundation and coma. If fluid losses are not rapidly corrected, death can occur within hours.

Cholera sicca is an unusual manifestation of severe cholera in which very rapid fluid loss is confined to the intestinal lumen; such patients may succumb to dehydration without frank diarrhea.

LABORATORY FINDINGS

Findings associated with dehydration such as elevated urine specific gravity and hemoconcentration are evident. **Hypoglycemia** is a common finding that is caused by decreased food intake during the acute illness. Serum potassium may be initially normal or even high in the presence of metabolic acidosis; however, as the acidosis is corrected, hypokalemia may become evident. **Metabolic acidosis** caused by bicarbonate loss and tissue hypoperfusion is a prominent finding in severe cholera. Serum sodium and chloride levels may be normal or decreased, depending on the severity of the disease. Serum calcium may be elevated because of hemoconcentration.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

In children who have acute watery diarrhea with severe dehydration residing in a cholera-endemic area or who have recently traveled to an area known to have cholera, the disease may be suspected pending laboratory confirmation. Cholera differs from other diarrheal diseases in that it often occurs in large outbreaks affecting both adults and children. Treatment of dehydration should begin as soon as possible. Diarrhea caused by other etiologies (e.g., enterotoxigenic *Escherichia coli* or rotavirus) may be difficult to distinguish from cholera clinically. Microbiologic isolation of *V. cholerae* remains the gold standard for diagnosis. Although definitive diagnosis is not required for treatment to be initiated, laboratory confirmation is necessary for epidemiologic surveillance. *V. cholerae* may be isolated from stools, vomitus, or rectal swabs. Specimens may be transported on Cary-Blair media if they cannot be processed immediately. Selective media, such as thiosulfate-citrate–bile salts sucrose (TCBS) agar, should be used; *V. cholerae* exhibits a distinctive morphology on this medium, with confirmation made by serotyping. Because most laboratories in industrialized countries do not routinely culture for *V. cholerae,* clinicians should request appropriate cultures for clinically suspected cases.

Rapid diagnostic tests are currently available and show high sensitivity and specificity. These tests may be especially useful in areas with limited laboratory capacity, allowing early identification of cases at the

Fig. 247.2 Rice-water stool in a patient with cholera. *(Modified from Harris JB, LaRocque RC, Qadri F. Cholera. Lancet. 2012;379:2466–2474.)*

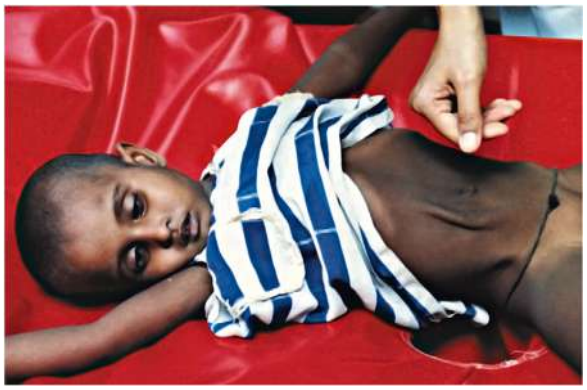

Fig. 247.3 A child lying on a cholera cot showing typical signs of severe dehydration from cholera. The patient has sunken eyes, lethargic appearance, and poor skin turgor, but within 2 hours was sitting up, alert, and eating normally. *(From Sack DA, Sack RB, Nair GB, et al. Cholera. Lancet. 2004;363:223–233.)*

onset of an outbreak and facilitating a timely response. Molecular identification with the use of polymerase chain reaction and DNA probes is available but often not feasible in areas where cholera exists. Stool examination reveals few fecal leukocytes and erythrocytes because cholera does not cause inflammation. Dark-field microscopy may be used for rapid identification of typical *darting motility* in wet mounts of rice-water stools, a finding that disappears once specific antibodies against *V. cholerae* O1 or O139 are added.

COMPLICATIONS

When optimally treated, patients with cholera typically recover fully without complications. Most adverse outcomes occur as a result of delayed or inadequate rehydration therapy. **Renal failure** from prolonged hypotension can occur. Unless potassium supplementation is provided, **hypokalemia** can lead to nephropathy and focal myocardial necrosis. Hypoglycemia is common among children and can lead to seizures unless it is appropriately corrected. Pneumonia is a frequent complication in young children and may be the result of aspiration during vomiting.

TREATMENT

Rehydration is the mainstay of therapy (see Chapter 74). Appropriate case management substantially decreases case fatalities to <1%. Application of World Health Organization (WHO) recommendations for diarrheal rehydration is recommended for all patients with diarrhea, but particularly when cholera is in the differential diagnosis. Children with mild or moderate dehydration may be treated with oral rehydration solution (ORS) unless the patient is in shock, is obtunded, or has intestinal ileus. Careful monitoring should occur during ORS, with attention to progression to more severe dehydration. Vomiting is not a contraindication to ORS. Severely dehydrated patients (>10% body weight) require intravenous fluid, ideally with lactated Ringer solution. When available, rice-based ORS should be used when oral rehydration is attempted, because this fluid has been shown to be superior to standard ORS in children and adults with cholera. The aim of rehydration should be replacement of the entire fluid deficit within 4 hours, if possible. Careful monitoring of ongoing losses is essential. If stool volumes cannot be measured, losses may be roughly estimated at 10-20 mL/kg of body weight for each episode of diarrhea or vomiting. After initial rehydration, patients should be reassessed every 1-2 hours, or more frequently if profuse diarrhea is ongoing; diarrhea typically begins to remit after 24 hours. Feeding should not be withheld during diarrhea. Frequent, small feedings are better tolerated than less frequent, large feedings.

Antibiotics should only be given in patients with moderately severe to severe dehydration. As soon as vomiting stops (usually within 4-6 hours after initiation of rehydration therapy), an antibiotic to which local *V. cholerae* strains are sensitive must be administered. Antibiotics shorten the duration of illness, decrease fecal excretion of *Vibrio*, decrease the volume of diarrhea, and reduce the fluid requirement during rehydration. Single-dose antibiotics increase compliance and are generally recommended; **doxycycline**, **ciprofloxacin**, and **azithromycin** are effective against cholera. The most clinical evidence for efficacy exists for tetracycline antibiotics (especially a single 300-mg dose of doxycycline). However, there are increasing reports of resistance to tetracyclines and to trimethoprim-sulfamethoxazole and other drugs. Because of these multidrug-resistant strains, antibiotic treatment must be tailored based on available susceptibility results from the area. **Recommendations for single-dose therapy for children include** doxycycline 2-4 mg/kg PO as a single dose up to 300 mg; 300 mg PO should be given to children 12 years of age and older. Alternative single dose regimens include azithromycin 20 mg/kg (max 1 g) PO, or ciprofloxacin 20 mg/kg (max 1 g) PO. Children >12 years of age should receive the adult doses. Cephalosporins and aminoglycosides are not clinically effective against cholera and therefore should not be used, even if in vitro tests show strains to be sensitive.

Zinc should be given as soon as vomiting stops. Zinc deficiency is common among children in many developing countries. Zinc supplementation in children <5 years old shortens the duration of diarrhea and reduces subsequent diarrhea episodes when given daily for 14 days at the time of the illness. Children <6 months old should receive 10 mg of oral zinc daily for 2 weeks, and children >6 months should receive 20 mg of oral zinc daily for 2 weeks.

PREVENTION

Improved personal hygiene, access to clean water, and sanitation are the mainstays of cholera control. Travelers from developed countries often have no prior exposure to cholera and are therefore at risk of developing the disease. Children traveling to cholera-affected areas should avoid drinking potentially contaminated water and eating high-risk

Table 247.1 Available Oral Cholera Vaccines*

VACCINE TRADE NAME	CONTENTS	DOSING SCHEDULE
Dukoral (Crucell)	1 mg of recombinant B subunit of cholera toxin plus 2.5×10^{10} colony-forming units of the following strains of *V. cholerae*: Formalin-killed El Tor Inaba (Phil 6973) Heat-killed classical Inaba (Cairo 48) Heat-killed classical Ogawa (Cairo 50) Formalin-killed classical Ogawa (Cairo 50)	Children 2-6 yr old: 3 doses, 1-6 wk apart Adults and children >6 yr old: 2 doses, 1-6 wk apart
Shanchol (Shantha Biotech) Euvichol (Eubiologics)	*V. cholerae* O1: 600 EU Formalin-killed El Tor Inaba (Phil 6973) 300 EU Heat-killed classical Inaba (Cairo 48) 300 EU Heat-killed classical Ogawa (Cairo 50) 300 EU Formalin-killed classical Ogawa (Cairo 50) *V. cholerae* O139-600 EU of formalin-killed strain 4260B	Adults and children ≥1 yr old: 2 doses, 2 wk apart

*WHO-prequalified vaccines.

foods such as raw or undercooked fish and shellfish. No country or territory requires vaccination against cholera as a condition for entry.

Alarmed by the increasing prevalence of cholera, in 2011 the World Health Assembly recommended the use of oral cholera vaccines to complement existing water, sanitation, and hygiene initiatives for cholera control. In 2016, a live oral cholera vaccine, CVD 103-Hg-R (Vaxchora, PaxVax), was licensed in the United States for use in adults age 18-64 years traveling to cholera-affected areas.

Older-generation parenteral cholera vaccines have not been recommended by the WHO because of the limited protection they confer and their high reactogenicity. Oral cholera vaccines are safe, are protective for approximately 2-5 years and confer moderate herd protection. Three oral cholera vaccines are currently available internationally and recognized by the WHO (Table 247.1). An internationally licensed killed whole cell oral cholera vaccine with recombinant B subunit (Dukoral, Crucell) has been available in >60 countries, including the European Union, and provides protection against cholera in endemic areas as well as cross-protection against certain strains of enterotoxigenic *E. coli*. The two other vaccines (Shanchol, Shantha Biotech; and Euvichol, Eubiologics) are variants of the first vaccine and contain the *V. cholerae* O1 and O139 antigens but do not contain the B subunit. Without the B subunit, these vaccines do not require buffer for administration, thereby reducing administration costs and resources, making them easier to deploy.

Several countries are now using oral cholera vaccines in mass vaccination campaigns where cholera remains a substantial problem. A cholera vaccine stockpile, established by the WHO, is now available and can be accessed by countries at risk for cholera, supplementing efforts to lessen the impact of this ongoing cholera scourge.

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Chapter 248

Campylobacter

Ericka V. Hayes

Campylobacter, typically *Campylobacter jejuni* and *Campylobacter coli,* are found globally and are among the most common causes of human intestinal infections. Clinical presentation varies by age and underlying conditions.

ETIOLOGY

More than 20 species of *Campylobacter* are recognized. Most of these have been isolated from humans, and many are considered pathogenic. The most significant of these are *C. jejuni* and *C. coli,* which are believed to cause the majority of human enteritis. More than 100 serotypes of *C. jejuni* have been identified. *C. jejuni* has been subspeciated into *C. jejuni* subsp. *jejuni* and *C. jejuni* subsp. *doylei.* Although *C. jejuni* subsp. *doylei* has been isolated from humans, it is much less common, less hardy, and more difficult to isolate. Other species, including *Campylobacter fetus, Campylobacter lari,* and *Campylobacter upsaliensis,* have been isolated from patients with diarrhea, although much less frequently (Table 248.1). Emerging *Campylobacter* spp. have been implicated in acute gastroenteritis, inflammatory bowel disease, and peritonitis, including *C. concisus* and *C. ureolyticus*. Additional *Campylobacter* spp. have been isolated from clinical specimens, but their roles as pathogens have not been established.

Campylobacter organisms are gram-negative, curved, thin (0.2-0.8 μm wide), non–spore-forming rods (0.5-5 μm long) that usually have tapered ends. They are smaller than most other enteric bacterial pathogens and have variable morphology, including short, comma-shaped or S-shaped organisms and long, multispiraled, filamentous, seagull-shaped organisms. Individual organisms are usually motile with a flagellum at one or both poles depending on the species. Such morphology enables these bacteria to colonize the mucosal surfaces of both the gastrointestinal (GI) and respiratory tracts and move through them in a spiraling motion. Most *Campylobacter* organisms are microaerophilic, occasionally partially anaerobic, and oxidase positive. Most can transform into coccoid forms under adverse conditions, especially oxidation.

EPIDEMIOLOGY

Worldwide, *Campylobacter* enteritis is a leading cause of acute diarrhea. Efforts to reduce *Campylobacter* contamination and use of safe handling practices have led to decreased incidence. *Campylobacter* infections can be both food-borne and water-borne and most frequently result from ingestion of contaminated **poultry** (chicken, turkey) or **raw milk**. Less often, the bacteria come from drinking water, household pets (cats, dogs, hamsters), and farm animals. Infections are more common in resource-limited settings, are prevalent year-round in tropical areas, and can exhibit seasonal peaks in temperate regions (late spring with a peak midsummer in most of the United States, with a smaller secondary peak in late fall). In industrialized countries, *Campylobacter* infections peak in early childhood and again in young adulthood (15-44 years). This second peak is not seen with *Salmonella* and *Shigella* infections. In resource-limited countries, repeated infections are common in childhood, leading to increased immunity and rare disease in adulthood. Each year in the United States, there are an estimated 1.5 million cases of *Campylobacter* infection; in 2022 the incidence of infections with *Campylobacter* was 19.2 infections per 100,000 population. Of these, death is rare, with 50-150 reports annually. In The Netherlands, medical record review shows that, on average, each resident acquires asymptomatic *Campylobacter* colonization every 2 years, progressing to symptomatic infection in approximately 1% of colonized people.

Table 248.1 *Campylobacter* Species Associated with Human Disease

SPECIES	DISEASES IN HUMANS	COMMON SOURCES
C. jejuni	Gastroenteritis, bacteremia, Guillain-Barré syndrome	Poultry, raw milk, cats, dogs, cattle, swine, monkeys, water
C. coli	Gastroenteritis, bacteremia	Poultry, raw milk, cats, dogs, cattle, swine, monkeys, oysters, water
C. fetus	Bacteremia, meningitis, endocarditis, mycotic aneurysm, diarrhea	Sheep, cattle, birds, dogs
C. hyointestinalis	Diarrhea, bacteremia, proctitis	Swine, cattle, deer, hamsters, raw milk, oysters
C. lari	Diarrhea, colitis, appendicitis, bacteremia, UTI	Seagulls, water, poultry, cattle, dogs, cats, monkeys, oysters, mussels
C. upsaliensis	Diarrhea, bacteremia, abscesses, enteritis, colitis, hemolytic-uremic syndrome	Cats, dogs, other domestic pets
C. concisus	Diarrhea, gastritis, enteritis, periodontitis	Human oral cavity, dogs
C. sputorum	Diarrhea, bedsores, abscesses, periodontitis	Human oral cavity, cattle, swine, dogs
C. rectus	Periodontitis	
C. mucosalis	Enteritis	Swine, dogs
C. jejuni subsp. doylei	Diarrhea, colitis, appendicitis, bacteremia, UTI	Swine
C. curvus	Gingivitis, alveolar abscess	Poultry, raw milk, cats, dogs, cattle, swine, monkeys, water, human oral cavity
C. gracilis	Head and neck abscesses, abdominal abscesses, empyema	Dogs
C. cryaerophila	Diarrhea	Swine

Food-borne infection is most common and can be seen with the consumption of raw or undercooked meat and by cross-contamination of other foods. Although **chickens** are the classic source of *Campylobacter,* many animal sources of human food can also harbor *Campylobacter,* including seafood. *C. coli* has been linked to swine. Poultry is more likely to be heavily contaminated, whereas red meats often have fewer organisms. Unpasteurized milk products are also a documented source. Additionally, many pets can carry *Campylobacter,* and flies inhabiting contaminated environments can acquire the organism. Shedding from animals can contaminate water sources. Humans can acquire infection from water, although much less frequently than from contaminated food. **Airborne** (droplet) **transmission** of *Campylobacter* has occurred in poultry workers. Use of antimicrobials in animal foods may increase the prevalence of antibiotic-resistant *Campylobacter* isolated from humans.

Human infection can result from exposure to as few as 500 bacteria, although a higher dose (>9,000 bacteria) is often needed to cause illness reproducibly. Inoculum effectiveness is dependent on host factors, including immune status and stomach acidification. *C. jejuni* and *C. coli* spread person to person, perinatally, and at childcare centers where diapered toddlers are present. People infected with *C. jejuni* usually shed the organism for weeks, but some can shed for months, with children tending toward longer shedding. **Handwashing** is critical to preventing spread in these environments.

PATHOGENESIS

Most *Campylobacter* isolates are acid sensitive and should, in theory, be eradicated in the stomach. Therefore models for the pathogenesis of *C. jejuni* enteritis include mechanisms to transit the stomach, adhere to intestinal mucosal cells, and initiate intestinal lumen fluid accumulation. Host conditions associated with reduced gastric acidity, such as proton pump inhibitor use, and foods capable of shielding organisms in transit through the stomach may help allow *Campylobacter* to reach the intestine. Once there, *Campylobacter* is able to adhere to and invade intestinal mucosal cells through motility, including use of flagellae, and by the use of surface proteins (e.g., PEB1, CadF), large plasmids (e.g., pVir), surface adhesins (e.g., JIpA), and chemotactic factors. Lumen fluid accumulation is associated with direct damage to mucosal cells resulting from bacterial invasion and potentially from an enterotoxin and other cytotoxins. Additionally, *C. jejuni* has mechanisms that enable transit away from the mucosal surface. The factors used depend on the species involved.

Campylobacter spp. differ from other enteric bacterial pathogens in that they have both *N*- and *O*-linked glycosylation capacities. *N*-linked glycosylation is associated with molecules expressed on the bacterial surface, and *O*-linked glycosylation appears limited to flagellae. Slipped-strand mispairing in glycosylation loci results in modified, antigenically distinct surface structures. It is hypothesized that antigenic variation provides a mechanism for immune evasion.

C. fetus possesses a high molecular weight S-layer protein that mediates high-level resistance to serum-mediated killing and phagocytosis and is therefore thought to be responsible for the propensity to produce bacteremia. *C. jejuni* and *C. coli* are generally sensitive to serum-mediated killing, but serum-resistant variants exist. Some suggest these serum-resistant variants may be more capable of systemic dissemination.

Campylobacter infections can be followed by **Guillain-Barré syndrome** (GBS), **reactive arthritis**, and **erythema nodosum**. Such complications are thought to be from molecular mimicry between nerve, joint, and dermal tissue and *Campylobacter* surface antigens. Most *Campylobacter* infections are not followed by immunoreactive complications, indicating that host conditions along with other factors, in addition to molecular mimicry, are required for these complications. It is proposed that low-grade inflammation caused by *Campylobacter,* below the threshold that can be detected by endoscopy, results in cross-talk with gut nerves, leading to symptoms.

CLINICAL MANIFESTATIONS

There are a variety of clinical presentations of *Campylobacter* infections, depending on host factors such as age, immune competence, and underlying conditions. Infection presents most often as gastroenteritis, but also as bacteremia, neonatal infections, and, less often, extraintestinal infections.

Acute Gastroenteritis

Acute gastroenteritis with diarrhea is usually caused by *C. jejuni* (90–95%) or *C. coli* and, rarely, by *C. lari, C. hyointestinalis,* or *C. upsaliensis.* Infections with *C. jejuni* and *C. coli* are indistinguishable by clinical presentation. The average incubation period is 3 days (range: 1-7 days). One third of symptomatic patients can have a prodrome with fever, headache, dizziness, and myalgias; 1-3 days later, they develop cramping abdominal pain and loose, watery stools or, less frequently, mucus-containing bloody stools. In severe cases (approximately 15%), blood appears in the stools 2-4 days after the onset of symptoms. In younger children, >50% may develop blood in their stools. Some patients do not develop diarrhea at all, most often children who are 6-15 years old. Fever may be the only manifestation initially and is most pronounced in patients >1 year old. A reported 60–90% of older children also complain of abdominal pain. The abdominal pain is most frequently periumbilical and sometimes persists after the stools return to normal. The abdominal pain can mimic appendicitis, colitis, or intussusception. Nausea is common, with up to 25% of adults developing vomiting. Vomiting tends to be more common the younger the patient and is most frequent in infants. Infection with species other than *C. jejuni* and *C. coli* may have milder symptoms.

Diarrhea lasts approximately 7 days and will resolve spontaneously. More mild disease can last 1-2 days; 20–30% of patients will have symptoms for 2 weeks, and 5–10% are symptomatic for >2 weeks. Relapse can occur in 5–10% of patients. Persistent or recurrent *Campylobacter* gastroenteritis has been reported in immunocompetent patients, in patients with hypogammaglobulinemia (both congenital and acquired), and in patients with AIDS. Persistent infection can mimic chronic **inflammatory bowel disease** (IBD); therefore *Campylobacter* infection should also be considered when evaluating for IBD. Some evidence supports that *Campylobacter* infection may also be the trigger for development of IBD. Fecal shedding of the organisms in untreated patients usually lasts for 2-3 weeks, with a range from a few days to several months. Shedding tends to occur longer in young children. Acute appendicitis, mesenteric lymphadenitis, and ileocolitis have been reported in patients who have had appendectomy during *C. jejuni* infection.

Bacteremia

Transient bacteremia has been shown in early acute infection in 0.1–1% of patients. With the exception of bacteremia caused by *C. fetus,* bacteremia with *Campylobacter* occurs most often among patients with chronic illnesses or immunodeficiency (e.g., HIV), severe malnutrition, and in extremes of age. However, bacteremia is also well described in patients without underlying disease. The majority of cases of bacteremia are asymptomatic. *C. fetus* causes bacteremia in adults with or without identifiable focal infection, usually in the setting of underlying conditions such as malignancy, immunodeficiency, or diabetes mellitus. When symptomatic, *C. jejuni* bacteremia is associated with fever, headache, malaise, and abdominal pain. Relapsing or intermittent fever is associated with night sweats, chills, and weight loss when the illness is prolonged. Lethargy and confusion can occur, but focal neurologic signs are unusual without cerebrovascular disease or meningitis. Moderate leukocytosis with left shift may be found. Variable presentations have been described, including transient asymptomatic bacteremia, rapidly fatal septicemia, and prolonged bacteremia of 8-13 weeks.

Focal Extraintestinal Infections

Focal infections caused by *C. jejuni* are rare and occur mainly among neonates and immunocompromised patients. Multiple sites have been reported, including meningitis, pneumonia, thrombophlebitis, pancreatitis, cholecystitis, ileocecitis, urinary tract infection, arthritis, peritonitis, pericarditis, and endocarditis. *C. fetus* shows a predilection for vascular endothelium, leading to endocarditis, pericarditis, thrombophlebitis, and mycotic aneurysms. *C. hyointestinalis* has been associated with proctitis, *C. upsaliensis* with breast abscesses, and *C. rectus* with periodontitis.

Perinatal Infections

Perinatal infections are most often acquired at birth from a mother infected with or shedding *Campylobacter.* Maternal *C. fetus* and *C. jejuni* infections may be asymptomatic and can result in abortion, stillbirth, premature delivery, or neonatal infection with sepsis and meningitis. Severe perinatal infections are uncommon and are caused most often by *C. fetus* and, rarely, by *C. jejuni*. Neonatal infection with *C. jejuni* is associated with diarrhea that may be bloody. Nosocomial infections in nurseries have also been described.

DIAGNOSIS

The clinical presentation of *Campylobacter* enteritis can be similar to that of enteritis caused by other bacterial pathogens. The differential diagnosis includes *Shigella, Salmonella, Escherichia coli, Yersinia enterocolitica, Aeromonas, Vibrio parahaemolyticus,* and amebiasis. Fecal leukocytes are found in as many as 75% of cases, and fecal blood is present in 50% of cases (higher in pediatric patients). *Campylobacter* should be considered in patients with bloody stools, fever, and abdominal pain.

The diagnosis of *Campylobacter* enteritis is usually confirmed by identification of the organism in cultures of stool or rectal swabs. Isolation is most likely from selective media such as CAMPY-agar grown in microaerophilic conditions (5–10% oxygen), 1–10% carbon dioxide, with some hydrogen. Some *C. jejuni* grow best at 42°C (107.6°F). Growth on solid media results in small (0.5-1.0 mm), slightly raised, smooth colonies. Organisms can be identified from stool microscopically in approximately 50% of known *Campylobacter* cases. Gram stain is even less sensitive. Stool culture is >90% sensitive and is the standard method of diagnosis. Visible growth on stool culture is most often present in 1-2 days. Visible growth in blood cultures is often not apparent until 5-14 days after inoculation.

Routine culture may be adequate for isolation of *C. jejuni* because of the large numbers of bacteria that are often present. However, because *Campylobacter* organisms grow more slowly under routine conditions than do other enteric bacteria, routine culture can result in failure because of overgrowth of other enteric bacteria. *Campylobacter* culture can be enhanced, when necessary, with selective media. However, selective culture media developed to enhance isolation of *C. jejuni* may inhibit the growth of other *Campylobacter* spp. Filtration methods are available and can preferentially enrich for *Campylobacter* by selecting for their small size. These methods allow subsequent culture of the enriched sample on antibiotic-free media, enhancing rates of isolation of *Campylobacter* organisms inhibited by the antibiotics included in standard selective media. Isolation of *Campylobacter* from normally sterile sites does not require enhancement procedures. Clinically, it is not necessary to speciate *Campylobacter* because the disease is the same. Speciation can be done, when needed, and specialized laboratories can perform strain typing when required for epidemiologic purposes.

For rapid diagnosis of *Campylobacter* enteritis, direct carbolfuchsin stain of fecal smear, indirect fluorescence antibody test, dark-field microscopy, or latex agglutination were used historically. Polymerase chain reaction testing is more specific and sensitive and has become more widely available for rapid testing, often grouped with testing for other bacterial, viral, and parasitic stool pathogens in a multiplex assay. At this time, the recommendation remains to confirm all positive rapid tests with culture, which also allows for susceptibility testing and epidemiologic investigations. Antigen tests are also available, although false-positive results have been reported. Serologic diagnosis is also possible and is most helpful in patients with late-onset reactive arthritis or GBS, because these patients may have negative stool cultures by the time of presentation with these late complications.

COMPLICATIONS

Severe, prolonged *C. jejuni* infection can occur in patients with immunodeficiencies, including hypogammaglobulinemia, malnutrition, and AIDS. In patients with AIDS, increased frequency and severity of *C. jejuni* infection occurs; severity correlates inversely with CD4 count. Complications can include acute complications, as described earlier, and late-onset complications that may present after the acute infection has resolved. The most common late-onset complications include reactive arthritis and GBS.

Reactive Arthritis

Reactive arthritis can accompany *Campylobacter* enteritis in adolescents and adults, especially in patients who are positive for HLA-B27 (see Chapter 198). Reactive arthritis occurs in up to 3% of patients, although up to 13% may have joint symptoms. This manifestation usually appears 1-2 weeks after the onset of diarrhea (range 5-40 days). It involves mainly large joints and resolves without sequelae. The arthritis is typically migratory and occurs without fever. Synovial fluid lacks bacteria. The arthritis responds well to nonsteroidal antiinflammatory drugs and typically resolves after 1 week, though cases are reported with symptoms lasting for several months. Reactive arthritis with conjunctivitis, urethritis, and rash (including erythema nodosum) also occurs but is less common.

Guillain-Barré Syndrome

GBS is an acute demyelinating disease of the peripheral nervous system characterized clinically by acute flaccid paralysis and is the most common cause of neuromuscular paralysis worldwide (see Chapter 656). GBS carries a mortality rate of approximately 2%, and approximately 20% of patients develop major neurologic sequelae. *C. jejuni* has been identified as the trigger in up to 40% of patients with GBS and is most closely linked to the serotypes Penner O19 and O41. It has been reported 1-12 weeks after *C. jejuni* gastroenteritis in 1 of every 1,000 *C. jejuni* infections. Stool cultures obtained from patients with GBS at the onset of neurologic symptoms have yielded *C. jejuni* in >25% of the cases. Serologic studies suggest that 20–45% of patients with GBS have evidence of recent *C. jejuni* infection. Molecular mimicry between nerve tissue GM_1 ganglioside and *Campylobacter* surface antigens may be the triggering factor in *Campylobacter*-associated GBS. The Miller Fisher variant, which more often affects cranial nerves, is characterized by ataxia, areflexia, and ophthalmoplegia and is linked to cross-reacting antibodies to the GQ1b ganglioside found in cranial nerve myelin; the most common serotype for this variant is Penner O2. When associated with *Campylobacter,* GBS is more likely to be the axonal form and has a worse prognosis with slower recovery and more neurologic disability. The management of GBS includes supportive care, intravenous immunoglobulin, and plasma exchange.

Other Complications

Immunoglobulin A nephropathy and immune complex glomerulonephritis with *C. jejuni* antigens in the kidneys have been reported. *Campylobacter* infection has also been associated with hemolytic anemia and hemolytic-uremic syndrome.

Treatment

Fluid replacement, correction of electrolyte imbalance, and supportive care are the mainstays of treatment of children with *Campylobacter* gastroenteritis. Antimotility agents are contraindicated because they can cause prolonged or fatal disease. The need for antibiotic therapy in healthy patients with uncomplicated gastroenteritis is controversial. Most healthy children do not require antibiotic therapy. Data suggest a shortened duration of symptoms (by an average of 1.3 days) and intestinal shedding of organisms if antibiotics are initiated early in the disease. Antibiotics are recommended for patients with bloody stools, high fever, or a severe course and for children who are immunosuppressed or have underlying diseases and individuals at high risk of developing severe disease (e.g., pregnancy). Extraintestinal infections (e.g., bacteremia) should also be treated with antibiotics.

Most *Campylobacter* isolates are susceptible to macrolides, fluoroquinolones, aminoglycosides, chloramphenicol, tetracyclines, and clindamycin (though there is no clinical efficacy data for these last three agents, only in vitro data) and are resistant to cephalosporins, penicillins, and trimethoprim. Resistance to tetracyclines, macrolides, and more often, fluoroquinolones has been increasingly reported. **Antibiotic resistance** among *C. jejuni* has become a serious worldwide problem. Macrolide resistance is increased in areas such as Thailand and Ireland, whereas fluoroquinolone resistance has been reported in Spain, Hungary, and multiple low and middle income countries in >50% of cultured *Campylobacter*. Fluoroquinolone resistance continues to increase in the United States and is related to the use of quinolones in veterinary medicine and food products along with acquisition from travelers and antibiotic overuse. Erythromycin-resistant *Campylobacter* isolates are less common in the United States; therefore **azithromycin** is the drug of choice if therapy is required, particularly in pediatric patients. For treatment of gastroenteritis, the duration is 3-5 days. Drug sensitivities should be determined for patients who do not respond to therapy or any patient with invasive or extraintestinal infection. Sepsis is treated with parenteral antibiotics such as meropenem or imipenem, with or without an aminoglycoside. For extraintestinal infection caused by *C. fetus,* prolonged therapy is advised. *C. fetus* isolates resistant to erythromycin and fluoroquinolones have been reported; therefore empirical therapy for serious *C. fetus* infection should avoid these agents pending susceptibilities.

PROGNOSIS

Although *Campylobacter* gastroenteritis is usually self-limited, immunosuppressed children (including children with AIDS) can experience a protracted or severe course. Septicemia in newborns and immunocompromised hosts has a poor prognosis, with an estimated mortality rate of 30–40%. Additional prognosis is based on the secondary sequelae that may develop.

PREVENTION

Most human *Campylobacter* infections are sporadic and are acquired from infected animals or contaminated foods or water. Interventions to minimize transmission include good hand hygiene; cooking meats thoroughly; preventing recontamination after cooking by not using the same surfaces, utensils, or containers for both uncooked and cooked food; and avoiding unpasteurized dairy products. Also, it is important to ensure that water sources are not contaminated and that water is kept in clean containers. Persons infected with *Campylobacter* should avoid recreational water for at least 1 week after resolution of symptoms or as guided by local public health authorities. Contact with infected animals should be avoided. No specific isolation is required; **standard precautions** are sufficient, although in a hospital or clinic setting with an incontinent child, **contact precautions** are indicated. Outbreaks can occur in childcare settings. Infants and children should be excluded from childcare centers until stools are able to be contained in the diaper or for continent children when they no longer have fecal accidents and stool frequency is no more than two stools above that child's baseline (stools may remain loose). Breastfeeding appears to decrease symptomatic *Campylobacter* disease but does not reduce colonization. All cases of *Campylopbacter* should be reported to local health departments, as it is a nationally notifiable condition.

Several approaches at immunization have been studied, including the use of live-attenuated organisms, subunit vaccines, and killed–whole cell vaccines. No vaccine is currently available.

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Chapter 249

Yersinia

Ericka V. Hayes

The genus *Yersinia* is a member of the order Enterobacterales, family Yersiniaceae and comprises more than 14 named species, 3 of which are established as human pathogens. *Yersinia enterocolitica* is by far the most common *Yersinia* species causing human disease and produces fever, abdominal pain that can mimic appendicitis, and diarrhea. *Y. pseudotuberculosis* is most often associated with mesenteric lymphadenitis. *Y. pestis* is the agent of **plague** and typically causes an acute febrile lymphadenitis (bubonic plague) and less often occurs as septicemic, pneumonic, pharyngeal, or meningeal plague. Other *Yersinia* species are uncommon causes of infections in humans, and their identification is often an indicator of immunodeficiency.

Yersinia is enzootic and can colonize pets. Infections in humans are incidental and most often result from contact with infected animals or their tissues; ingestion of contaminated water, milk, or meat; or for *Y. pestis,* the bite of infected fleas or inhalation of respiratory droplets (human, dog, cat). Association with human disease is less clear for *Y. frederiksenii, Y. intermedia, Y. kristensenii*, *Y. aldovae, Y. bercovieri, Y. mollaretii, Y. rohdei,* and *Y. ruckeri*. Some *Yersinia* isolates replicate at low temperatures (1–4°C [33.8–39.2°F]) or survive at high temperatures (50–60°C [122–140°F]). Thus common food preparation and storage and common pasteurization methods might not limit the number of bacteria. Most are sensitive to oxidizing agents.

249.1 *Yersinia enterocolitica*

Ericka V. Hayes

ETIOLOGY

Yersinia enterocolitica is a large, gram-negative coccobacillus that exhibits little or no bipolarity when stained with methylene blue and carbolfuchsin. It ferments glucose and sucrose but not lactose, is oxidase negative, and reduces nitrate to nitrite. These facultative anaerobes grow well on common culture media and are motile at 22°C (71.6°F) but not 37°C (98.6°F). Optimal growth temperature is 25–28°C (77–82.4°F); however, the organism can grow at refrigerator temperature. *Y. enterocolitica* includes pathogenic and nonpathogenic members. It has six different biotypes (1A, 1B, and 2-5). *Y. enterocolitica* relies on other bacteria for iron uptake, and conditions associated with **iron overload** increase the risk of infection.

EPIDEMIOLOGY

Y. enterocolitica is transmitted to humans through food, water, animal contact, and contaminated blood products. Transmission can occur from mother to newborn. *Y. enterocolitica* appears to have a global distribution but is seldom a cause of tropical diarrhea. In 2022, the Centers for Disease Control and Prevention (CDC) Foodborne Diseases Active Surveillance Network (FoodNet) reported an incidence of culture-confirmed *Y. enterocolitica* infection in the United States of 1.97 per 100,000 population (635% increase compared to 2015, and an increase of 216% since 2020). Infection may be more common in Northern Europe. Most infections occur among children <5 years old (incidence: 1.6-1.9 per 100,000 population), with the majority among children <1 year old. It is estimated that *Y. enterocolitica* accounts for 5% of illnesses secondary to major bacterial enteric pathogens in children <5 years old in the United States. Cases are more common in colder months and among males.

Natural reservoirs of *Y. enterocolitica* include pigs, rodents, rabbits, sheep, cattle, horses, dogs, and cats, with **pigs** being the major animal reservoir. Direct or indirect contact with animals, including pets, other domesticated animals, and wild animals, may be responsible for <1% of cases of enteric illnesses caused by *Y. enterocolitica*. Culture and molecular techniques have found the organism in a variety of foods and beverages, including vegetable juice, pasteurized milk, carrots, and water. Consumption of contaminated water or food, particularly undercooked pork, is the most common form of transmission to humans. A source of sporadic *Y. enterocolitica* infections is **chitterlings** (pig intestines, "chitlins"), a traditional dish in the southeastern United States and in Latin America, often in celebration of winter holidays. The infection is often seen in young infants in the household because of contamination of bottle and food preparation when chitterlings are prepared. In one study, 71% of human isolates were indistinguishable from the strains isolated from pigs. *Y. enterocolitica* is an occupational threat to butchers.

In part because of its capacity to multiply at refrigerator temperatures, *Y. enterocolitica* can be transmitted by intravenous injection of contaminated fluids, including blood products.

Patients with conditions leading to iron overload are at higher risk of developing *Yersinia* infections.

PATHOGENESIS

The *Yersinia* organisms most often enter by the gastrointestinal tract and cause mucosal ulcerations in the ileum. Necrotic lesions of Peyer patches and **mesenteric lymphadenitis** occur. If septicemia develops, suppurative lesions can be found in infected organs. Infection can trigger **reactive arthritis** and **erythema nodosum**, particularly in HLA-B27–positive individuals.

Virulence traits of pathogenic biotypes (1B and 2-5) are encoded by chromosomal genes and a highly conserved 70-kb virulence plasmid (pYV/pCD). The chromosomal genes control the production of heat-stable enterotoxins, and the plasmid allows penetration through the intestinal wall. Adherence, invasion, and toxin production are the essential mechanisms of pathogenesis. The bacteria mainly invade the intestinal epithelium in the Peyer patches of the ileum. After invasion, plasmid-encoded type III secretion of three antiphagocytic proteins protects *Yersinia* against the immunologic response of local macrophages. From Peyer patches, bacteria can disseminate to cause local or systemic disease. Motility appears to be required for *Y. enterocolitica* pathogenesis. Bioserotypes most associated with clinical illness in humans are 1B/O:8, 2/O:5,27, 2/O:9, 3/O:3, and 4/O:3, with bioserotype 4/O:3 being the most common type in the United States. *Yersinia* does not produce siderophores and uses analogous siderophores from other bacteria or host-chelated iron stores to thrive, placing patients with iron overload, as in hemochromatosis, thalassemia, and sickle cell disease, at higher risk for infection.

CLINICAL MANIFESTATIONS

Disease occurs most often as enterocolitis with diarrhea, fever, and abdominal pain. Acute enteritis is more common among younger children, and mesenteric lymphadenitis that can mimic appendicitis may be found in older children and adolescents. The incubation period is usually 4-6 days after exposure (range: 1-14 days). Stools may be watery and contain leukocytes and, less often, frank blood and mucus. Duration of diarrhea is often longer for *Y. enterocolitica* than for other causes of acute gastroenteritis, ranging from 12 to 22 days in several studies. Fever is common. Notably, prominent **pharyngitis** may be seen in 20% of patients at presentation, which may help distinguish it from other causes of gastroenteritis. *Y. enterocolitica* is excreted in stool for 1-4 weeks. Family contacts of a patient are often found to be asymptomatically colonized with *Y. enterocolitica. Y. enterocolitica* septicemia is less common and is most often found in very young children (<3 months old) and immunocompromised persons. Systemic infection can be associated with splenic and hepatic abscesses, osteomyelitis, septic arthritis, meningitis, endocarditis, and mycotic aneurysms. Exudative pharyngitis, pneumonia, empyema, lung abscess, and acute respiratory distress syndrome occur infrequently.

Reactive complications include **erythema nodosum**, **reactive arthritis**, and rarely uveitis. These manifestations may be more

common in select populations (Northern Europeans), in association with HLA-B27, and in females.

DIAGNOSIS

Diagnosis is made typically through isolation of the organism, usually from the stool. *Y. enterocolitica* is easily cultured from normally sterile sites but requires special procedures for isolation from stool, where other bacteria can outgrow it. *Yersinia* should be cultured on selective agar (cefsulodin-irgasan-novobiocin [CIN]) at 25–28°C (77–82.4°F) to increase yield. If O:3 serogroup is suspected, MacConkey agar should be used at 25–28°C (77–82.4°F). Multiplex polymerase chain reaction (PCR) testing for *Y. enterocolitica* is also available, including on commercially available multiplex stool panels. Many laboratories do not routinely perform the tests required to detect *Y. enterocolitica;* procedures targeted to this organism must be specifically requested. A history indicating contact with environmental sources of *Yersinia* and detection of fecal leukocytes are helpful indicators of a need to test for *Y. enterocolitica.* The isolation of *Yersinia* from stool should be followed by tests to confirm that the isolate is a pathogen. Serodiagnosis is not readily available, and utility is limited by cross-reactivity.

Differential Diagnosis

The clinical presentation is similar to other forms of bacterial enterocolitis. The most common considerations include *Shigella, Salmonella, Campylobacter, Clostridioides difficile,* enteroinvasive *Escherichia coli, Y. pseudotuberculosis*, and occasionally *Vibrio*-related diarrheal disease. Amebiasis, appendicitis, Crohn disease, ulcerative colitis, diverticulitis, and pseudomembranous colitis should also be considered.

TREATMENT

Enterocolitis in an immunocompetent patient is a self-limited disease, and no benefit from antibiotic therapy is established. Patients with systemic infection and very young children (in whom septicemia is common) should be treated. *Y. enterocolitica* organisms are typically susceptible to trimethoprim-sulfamethoxazole (TMP-SMX), aminoglycosides, third-generation cephalosporins, and quinolones, although strains resistant to quinolones have been reported. *Y. enterocolitica* produces β-lactamases, which are responsible for resistance to penicillins and first-generation cephalosporins. **TMP-SMX is the recommended empirical treatment for enterocolitis in children (generally a 5-day course) because it has activity against most strains and is well tolerated. In severe infections such as bacteremia, third-generation cephalosporins, with or without aminoglycosides, are effective, and usually a 3-week course of therapy is administered, with possible transition to oral therapy.** Patients on deferoxamine should discontinue iron chelation therapy during treatment for *Y. enterocolitica,* especially if they have complicated gastrointestinal (GI) infection or extraintestinal infection.

COMPLICATIONS

Reactive arthritis, erythema nodosum, erythema multiforme, hemolytic anemia, thrombocytopenia, and systemic dissemination of bacteria have been reported in association with *Y. enterocolitica* infection. Septicemia is more common in younger children, and reactive arthritis is more common in older patients. Arthritis appears to be mediated by immune complexes, which form as a result of antigenic mimicry, and viable organisms are not present in involved joints.

PREVENTION

Prevention centers on reducing contact with environmental sources of *Yersinia.* Families should be warned of the high risk of chitterling preparation, especially with young infants and children in the household. The CDC has developed guidance for the public regarding safe practices for chitterling preparation found here: https://www.cdc.gov/yersinia/chitlins.html. Breaking the chain of transmission from animal reservoirs to humans holds the greatest potential to reduce infections, and the techniques applied must be tailored to the reservoirs in each geographic area. There is no licensed vaccine.

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249.2 *Yersinia pseudotuberculosis*

Ericka V. Hayes

Yersinia pseudotuberculosis has a worldwide distribution; *Y. pseudotuberculosis* disease is less common than *Y. enterocolitica* disease. The most common form of disease is a **mesenteric lymphadenitis** that produces an appendicitis-like syndrome. *Y. pseudotuberculosis* is associated with a Kawasaki syndrome–like illness in approximately 8% of cases.

ETIOLOGY

Y. pseudotuberculosis is a small, gram-negative, aerobic, and facultative anaerobic coccobacillus. As with *Y. enterocolitica,* it ferments glucose and does not ferment lactose, is oxidase negative, catalase producing, urea splitting, and shares a number of morphologic and culture characteristics. It is differentiated biochemically from *Y. enterocolitica* on the basis of ornithine decarboxylase activity; fermentation of sucrose, sorbitol, and cellobiose; and other tests, although some overlap between species occurs. Antisera to somatic O antigens and sensitivity to *Yersinia* phages can also be used to differentiate the two species. Subspecies-specific DNA sequences that allow direct probe- and primer-specific differentiation of *Y. pestis, Y. pseudotuberculosis,* and *Y. enterocolitica* have been described. *Y. pseudotuberculosis* is more closely related phylogenetically to *Y. pestis* than to *Y. enterocolitica.*

EPIDEMIOLOGY

Y. pseudotuberculosis is zoonotic, with reservoirs in wild rodents, rabbits, deer, farm animals, various birds, and domestic animals, including cats and canaries. Transmission to humans is by consumption of or contact with contaminated animals or contact with an environmental source contaminated by animals, often water. Direct evidence of transmission of *Y. pseudotuberculosis* to humans by consumption of lettuce and raw carrots has been reported. The organism has a worldwide distribution; however, infections are more commonly reported in Europe, in boys, and in the winter. During 1996–2014, FoodNet reported 224 cases of infections secondary to *Y. pseudotuberculosis* in the United States, with an annual average incidence of 0.03 per 100,000 persons. Compared with *Y. enterocolitica* infections, those caused by *Y. pseudotuberculosis* are more likely to be invasive and occur in adolescents and adults. Iron-overloading conditions, AIDS, other immunodeficiencies, and other debilitating diseases (including liver cirrhosis) may predispose to invasive *Y. pseudotuberculosis* infection.

PATHOGENESIS

Ileal and colonic mucosal ulceration and mesenteric lymphadenitis are hallmarks of the infection. Necrotizing epithelioid granulomas may be seen in the mesenteric lymph nodes, but the appendix is often grossly and microscopically normal. The mesenteric nodes are often the only source of isolation of the organism. *Y. pseudotuberculosis* antigens bind directly to human leukocyte antigen (HLA) class II molecules and can function as **superantigens**, which might account for the clinical illness resembling **Kawasaki syndrome**.

CLINICAL MANIFESTATIONS

Pseudoappendicitis and **mesenteric lymphadenitis** with **abdominal pain** (often right lower quadrant tenderness), fever, and leukocytosis constitute the most common clinical presentation. Enterocolitis and extraintestinal spread are uncommon. Iron overload, diabetes mellitus, and chronic liver disease are often found concomitantly with extraintestinal *Y. pseudotuberculosis* infection. Renal involvement with tubulointerstitial nephritis, azotemia, pyuria, and glucosuria can occur. *Y. pseudotuberculosis* can present as a Kawasaki syndrome–like illness with fever of 1-6 days' duration, strawberry tongue, pharyngeal erythema, scarlatiniform rash, cracked, red, and swollen lips, conjunctivitis, sterile pyuria, periungual desquamation, and thrombocytosis.

Some of these children have had coronary changes. Other uncommon manifestations include septic arthritis, massive lower GI bleeding, postaneurysmal prosthetic vascular infection, and acute encephalopathy.

DIAGNOSIS

PCR of involved tissue can be used to identify *Y. pseudotuberculosis;* isolation by culture can require an extended interval. Involved mesenteric lymph nodes removed at appendectomy can yield the organism by culture. Abdominal CT scan or ultrasound examination of children with unexplained fever and abdominal pain can reveal a characteristic picture of enlarged mesenteric lymph nodes and thickening of the terminal ileum with or without peritoneal findings, including appendiceal inflammation and periappendiceal fluid. *Y. pseudotuberculosis* is rarely recovered from stool. Serologic testing is available in specialized labs.

Differential Diagnosis

Appendicitis (most common), inflammatory bowel disease, and other intraabdominal infections should be considered. Kawasaki syndrome, staphylococcal or streptococcal disease, leptospirosis, Stevens-Johnson syndrome, and collagen vascular diseases, including acute-onset juvenile idiopathic arthritis, can mimic the syndrome with prolonged fever and rash. *C. difficile* colitis, meningitis, encephalitis, enteropathic arthropathies, acute pancreatitis, sarcoidosis, toxic shock syndrome, typhoid fever, and ulcerative colitis may also be considered.

TREATMENT

Uncomplicated mesenteric lymphadenitis caused by *Y. pseudotuberculosis* is a self-limited disease, and antimicrobial therapy is not required. Few data exist on optimal treatment and duration of therapy. Infections with *Y. pseudotuberculosis* can generally be managed the same as those caused by *Y. enterocolitica*. Culture-confirmed bacteremia should be treated with a third-generation cephalosporin with or without an aminoglycoside, TMP-SMX, fluoroquinolones, or chloramphenicol.

COMPLICATIONS

Erythema nodosum and reactive arthritis can follow infection. Coronary aneurysm formation has been described with disease presenting as Kawasaki syndrome–like illness. Rare local complications of GI disease include perforation, obstruction, and intussusception.

PREVENTION

Avoiding exposure to potentially infected animals and good food-handling practices can prevent infection. The sporadic nature of the disease makes application of targeted prevention measures difficult.

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249.3 Plague (*Yersinia pestis*)

Ericka V. Hayes

ETIOLOGY

Y. pestis is a gram-negative, facultative anaerobe that is a pleomorphic, nonmotile, non–spore-forming coccobacillus and a potential agent of bioterrorism. It evolved from *Y. pseudotuberculosis* through acquisition of chromosomal changes and plasmid-associated factors that are essential to its virulence and survival in mammalian hosts and fleas. *Y. pestis* shares bipolar staining appearance with *Y. pseudotuberculosis* and can be differentiated by biochemical reactions, serology, phage sensitivity, and molecular techniques. *Y. pestis* exists in four biovars: Antigua (Africa), Medievalis (Central Asia), Orientalis (widespread), and Microtus (Asia). Of note, Microtus, while highly virulent in mice, does not cause disease in humans.

EPIDEMIOLOGY

Plague is endemic in at least 24 countries, with Democratic Republic of the Congo, Madagascar, and Peru accounting for the highest numbers of cases. Approximately 3,000 cases are reported worldwide per year, with 100-200 deaths. Plague is uncommon in the United States (0-40 reported cases/yr); most of these cases occur west of a line from east Texas to east Montana, with 80% of cases in California, New Mexico, Arizona, and Colorado. In 2015, there was a cluster of 11 cases (with 3 deaths) in 4 months related to exposure at Yosemite National Park in California's Sierra Nevada Mountains. The epidemic form of disease killed approximately 25% of the population of Europe in the Middle Ages in a series of several epidemics and pandemics. The epidemiology of **epidemic** plague involves extension of infection from the zoonotic reservoirs to urban rats, *Rattus rattus* and *Rattus norvegicus,* and from fleas of urban rats to humans. Epidemics are no longer seen. Selective pressure exerted by plague pandemics in medieval Europe is hypothesized for enrichment of a pathogenic deletion variant in the gene encoding CCR5 (CCR5-Δ32). The enhanced frequency of this mutation in European populations endows approximately 10% of European descendants with relative resistance to acquiring HIV-1.

The most common mode of transmission of *Y. pestis* to humans is through **flea bites**. Historically, most human infections are thought to have resulted from bites of fleas that acquired infection from feeding on infected urban rats. Less frequently, infection is caused by contact with infectious body fluids or tissues or inhalation of respiratory secretions of infected animals. Currently, most cases of plague secondary to direct animal contact or inhalation of animal secretions are related to domestic **cats** or **dogs**. Direct transmission from human to human through droplet inhalation is possible but extremely rare. Laboratory transmission of *Y. pestis* has been described as well. Sylvatic plague can exist as a stable enzootic infection or as an epizootic disease with high host mortality. Ground squirrels, rock squirrels, prairie dogs, rats, mice, bobcats, cats, rabbits, and chipmunks may be infected. Transmission among animals is usually by flea bite or by ingestion of contaminated tissue. *Xenopsylla cheopis* is the flea usually associated with transmission to humans, but >30 species of fleas have been demonstrated as vector competent, and *Pulex irritans,* the human flea, can transmit plague and might have been an important vector in some historical epidemics. Both sexes are similarly affected by plague, and transmission is more common in colder regions and seasons, possibly because of temperature effects on *Y. pestis* infections in vector fleas.

PATHOGENESIS

In the most common form of plague, infected fleas regurgitate organisms into a patient's skin during feeding. The bacteria translocate via lymphatics to regional lymph nodes, where *Y. pestis* replicates, resulting in **bubonic plague**. In the absence of rapidly implemented specific therapy, **bacteremia** can occur, resulting in purulent, necrotic, and hemorrhagic lesions in many organs. Both plasmid and chromosomal genes are required for full virulence. Pneumonic plague can be secondary to bacteremia or primary when infected material is inhaled. The organism is highly transmissible from persons with pneumonic plague and from domestic cats with pneumonic infection. This high transmissibility and high morbidity and mortality have provided an impetus for attempts to use *Y. pestis* as a biologic weapon.

CLINICAL MANIFESTATIONS

Y. pestis infection can manifest as several clinical syndromes; infection can also be subclinical. The three principal clinical presentations of plague are bubonic plague, septicemic plague, and pneumonic plague. **Bubonic plague** is the most common form and accounts for 80–90% of cases in the United States. From 2 to 8 days after a flea bite, lymphadenitis develops in lymph nodes closest to the inoculation site, including the inguinal (most common), axillary, or cervical regions. These buboes are very tender. Fever, chills, weakness, prostration, headache, and the development of septicemia are common. The skin might show insect bites or scratch marks. Purpura and gangrene of the extremities can

develop as a result of disseminated intravascular coagulation (DIC). These lesions may be the origin of the name Black Death. Untreated plague results in death in >50% of symptomatic patients. Death can occur within 2-4 days after onset of symptoms.

Occasionally, *Y. pestis* establishes systemic infection and induces the systemic symptoms seen with bubonic plague without causing a bubo **(primary septicemic plague)**. Because of the delay in diagnosis linked to the lack of the bubo, septicemic plague carries an even higher case fatality rate than bubonic plague. In some regions, bubo-free septicemic plague accounts for 25% of cases.

Pneumonic plague is the least common but most dangerous and lethal form of the disease. Incubation for primary pneumonic plague is 1-6 days. Pneumonic plague can result from hematogenous dissemination or, rarely, as primary pneumonic plague after inhalation of the organism from a human or animal with plague pneumonia or potentially from a biologic attack. Signs of pneumonic plague include severe pneumonia with high fever, dyspnea, and hemoptysis.

Meningitis, tonsillitis, and gastroenteritis can occur. Meningitis tends to be a late complication after inadequate treatment. Tonsillitis and gastroenteritis can occur with or without apparent bubo formation or lymphadenopathy.

DIAGNOSIS

Plague should be suspected in patients with fever and history of exposure to small animals in endemic areas. Bubonic plague should be suspected in a patient with a painful swollen lymph node, fever, and prostration who has been potentially exposed to fleas or rodents in the western United States. A history of camping or the presence of flea bites increases the index of suspicion.

Y. pestis is readily transmitted to humans by some routine laboratory manipulations. **Thus it is imperative to clearly notify a laboratory when submitting a sample suspected of containing *Y. pestis*.** Laboratory diagnosis is based on bacteriologic culture or direct visualization using Gram, Giemsa, or Wayson stain of lymph node aspirates, blood, sputum, or exudates. *Y. pestis* grows slowly under routine culture conditions and best at temperatures that differ from those used for routine cultures in many clinical laboratories. Colonies are described as having a classic "fried egg appearance" and grow on sheep blood and chocolate agars, typically growing after 48-72 hours of incubation. Note some automated biochemical bacteria identification systems may misidentify *Y. pestis*. Suspected isolates of *Y. pestis* should be forwarded to a reference laboratory for confirmation. Special containment shipping precautions are required. A rapid antigen test detecting *Y. pestis* F1 antigen in sputum and serum samples exists. PCR testing and immunohistochemical staining for rapid identification are available in some reference and public health laboratories. Cases of plague should be reported to local and state health departments and the CDC. Serologic testing is also available. A single positive serologic test confirms the diagnosis, but in early illness seroconversion may not yet have occurred; negative tests should be interpreted with caution, particularly if there is high clinical suspicion for the diagnosis, and patients should continue to be treated.

Differential Diagnosis

The Gram stain of *Y. pestis* may be confused with *Enterobacter agglomerans*. Mild and subacute forms of bubonic plague may be confused with other disorders causing localized lymphadenitis and lymphadenopathy, including bacterial lymphadenitis, tularemia, and *Bartonella henselae* (cat scratch) lymphadenitis. Septicemic plague may be indistinguishable from other forms of overwhelming bacterial sepsis.

Pulmonary manifestations of plague are similar to those of anthrax, Q fever, and tularemia, all agents with **bioterrorism** and **biologic warfare** potential. Thus the presentation of a suspected case, and especially any cluster of cases, requires immediate reporting. Additional information on this aspect of plague and procedures can be found at https://emergency.cdc.gov/agent/plague/index.asp.

TREATMENT

Patients with suspected plague should be placed on **droplet isolation** until pneumonia is ruled out, sputum cultures are negative, and antibiotic treatment has been administered for 48 hours. The treatment of choice for bubonic plague historically has been **streptomycin** (30 mg/kg/day, maximum 2 g/day, divided every 12 hours intramuscularly [IM] for 10 days). Intramuscular streptomycin is inappropriate for septicemia because absorption may be erratic when perfusion is poor. The poor central nervous system penetration of streptomycin also makes this an inappropriate drug for meningitis. Furthermore, streptomycin might not be widely and immediately available**. Gentamicin (children, 7.5 mg/kg IM or intravenously [IV] every 24 hours; adults, 5 mg/kg IM or IV every 24 hours) has been shown to be as efficacious as streptomycin; in patients with abscesses, an additional agent may be needed in addition to an aminoglycoside because of poor abscess penetration (typically a fluoroquinolone). Dual therapy is recommended for moderate to severe septicemic or pneumonic plague as well as bubonic plague with large buboes or any suspected case of bioterrorism-related plague. Ciprofloxacin** 10 mg/kg every 8 or 12 hr IV or 15 mg/kg every 8 or 12 hr PO (maximum 400 mg/dose IV, 500 mg/dose every 8 hr PO or 750 mg/dose every 12 hr PO) and **levofloxacin** are also effective. Meningitis is usually treated with chloramphenicol or a fluoroquinolone. Resistance to these agents and relapses are rare. *Y. pestis* is susceptible in vitro to **fluoroquinolones**, which are effective in treating experimental plague in animals. *Y. pestis* is susceptible in vitro to penicillin, but penicillin is ineffective in treatment of human disease. Mild bubonic disease may be treated with oral chloramphenicol or doxycycline in children >8 years old. Clinical improvement is usually noted within 48 hours of initiating treatment. Recommended duration of therapy is 10-14 days, with a switch to oral therapy 2 days after defervescence and clinical improvement. Drainage of suppurative buboes may be needed; material is infectious, and appropriate precautions should be taken intraoperatively.

Postexposure prophylaxis should be given to close contacts of patients with pneumonic plague. Antimicrobial prophylaxis is recommended within 7 days of exposure for persons with direct, close contact with a patient with pneumonic plague or those exposed to an accidental or bioterrorist aerosol. Recommended regimens for postexposure prophylaxis for children regardless of age include doxycycline, ciprofloxacin, or levofloxacin for a 7-day course at the treatment doses. Contacts of cases of uncomplicated bubonic plague do not require prophylaxis. *Y. pestis* is a potential agent of bioterrorism that can require mass casualty prophylaxis.

PREVENTION

Avoidance of exposure to infected animals and fleas is the best method of prevention of infection. In the United States, special care is required in environments inhabited by rodent reservoirs of *Y. pestis* and their ectoparasites. Patients with plague should be isolated if they have pulmonary symptoms, and infected materials should be handled with extreme care. There is currently no available licensed vaccine for *Y. pestis* in the United States. Several vaccine development trials are underway, and recombinant subunit vaccines based on rF1 and rV antigens seem to be the most promising. Using baits containing live vaccines for oral immunization of wild animals may be a helpful alternative for control of epidemics.

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Chapter 250

Aeromonas and *Plesiomonas*

Ameneh Khatami and Adam J. Ratner

Aeromonas and *Plesiomonas* are gram-negative bacilli that include species capable of causing enteritis and, less frequently, skin and soft tissue infections and invasive disease. They are common in freshwater and brackish water and colonize animals and plants in these environments.

250.1 *Aeromonas*

Ameneh Khatami and Adam J. Ratner

ETIOLOGY

Aeromonas is a member of the Aeromonadaceae family and includes two major groups of isolates: the nonmotile *psychrophilic* organisms that infect cold-blooded animals, most often fish, and the motile *mesophilic* organisms that infect humans and other warm-blooded animals. *Aeromonas* species are oxidase- and catalase-positive, facultatively anaerobic, gram-negative bacilli that ferment glucose. *Aeromonas* is a diverse genus with difficult taxonomy and species differentiation because of high nucleotide variability and has undergone multiple reclassifications of species and taxa in recent years. Sixteen species are recognized as clinically significant human pathogens, with *Aeromonas hydrophila, Aeromonas veronii* biotype sobria, and *Aeromonas caviae* most frequently associated with human infection. *Aeromonas dhakensis,* which was first isolated from children with diarrhea in Dhaka, Bangladesh, and was initially classified as a subspecies of *A. hydrophila,* has been recognized as a distinct species and an important cause of human infection.

EPIDEMIOLOGY

Aeromonas organisms are found in fresh and brackish aquatic environments, including rivers and streams, well water, both treated and bottled drinking water, and sewage. These organisms are most often detected in aquatic environments during warm-weather months, when they reach greater population densities. Rates of human infection may also exhibit seasonality depending on local conditions. For example, *Aeromonas* is isolated with increased frequency from May to October in the Northern Hemisphere. Some species resist chlorination of water and exhibit tolerance to high salt concentrations. *Aeromonas* has been isolated from meats, milk, seafood, seaweed, and vegetables consumed by humans. Asymptomatic colonization occurs in humans and is more common in inhabitants of tropical regions. Most human infections with *Aeromonas* are associated with exposure to contaminated water but may also be contracted via other routes, including ingestion of contaminated food. A systematic review of cases of traveler's diarrhea worldwide implicated *Aeromonas* in 0.8–3.3% of infections, with highest frequencies in travelers to Southeast Asia and Africa. A study in Bangladesh of >56,000 stool samples from patients with diarrhea found that approximately 25% had a bacterial etiology detected, 13% of which were *Aeromonas*. *Aeromonas* infections have also been acquired at various sites of natural disasters. For example, after the 2004 Thailand tsunami, *Aeromonas* was the leading cause of skin and soft tissue infection among survivors.

PATHOGENESIS

Clinical and epidemiologic data seem to support that *Aeromonas* organisms are **enteric** pathogens, although this point is not universally accepted. Reasons for uncertainty include a lack of outbreaks with clonally distinct isolates, infrequent person-to-person transmission, absence of a robust animal model, and overlapping prevalence in symptomatic and asymptomatic individuals. In addition, there are conflicting data when comparing the human challenge model with characteristics of suspected outbreaks of *Aeromonas* enteritis, further complicating interpretation.

Aeromonas isolates possess a variety of potential virulence factors, including constitutive *polar* and inducible *lateral* flagella, fimbriae, outer membrane proteins, endotoxin (lipopolysaccharide), and capsule. The mechanistic role of many of these factors in human pathogenicity remains unclear. Polar flagella provide motility in liquid media, and lateral flagella may act as adhesins. There are numerous hemolysins, proteases, and heat-labile and heat-stable enterotoxins. *Aeromonas* cytotoxic enterotoxin **(Act/aerolysin)** is secreted by a type II secretion system and is able to lyse erythrocytes, inhibit phagocytosis, and induce cytotoxicity in eukaryotic cells. *Aeromonas* also has a type III secretion system with an effector protein that causes actin reorganization and eventual apoptosis in vitro. A type VI secretion system has been described and functions analogously to a phage tail, with antimicrobial activity.

Aeromonas sobria is the most enterotoxic among clinical isolates, and cytotoxic activity with cytopathic and intracellular effects is found in 89% of isolates. A few strains produce Shiga toxin. Some clinically important species have also been shown to harbor a cholera-like toxin (**Asao toxin**). *Aeromonas* has serine proteases that can cause a cascade of inflammatory mediators, leading to vascular leakage, and in vitro studies show induction of apoptosis in murine macrophages by human isolates of *Aeromonas*. There are limited data on *quorum-sensing* molecules, which coordinate gene expression according to local density and may be involved in biofilm production or population control.

CLINICAL MANIFESTATIONS

Aeromonas may colonize humans asymptomatically or cause illness, including enteritis, focal invasive infections, and septicemia. Although apparently immunologically normal individuals may present with any of these manifestations, invasive disease is more common among immunocompromised persons.

Enteritis

The most common clinical manifestation of infection with *Aeromonas* is enteritis, which occurs primarily among children <3 years old. *Aeromonas* is the third or fourth most common cause of childhood **bacterial diarrhea** and has been isolated from 2% to 10% of patients with diarrhea and 1–5% of asymptomatic controls. One study demonstrated isolation from hospitalized neonates with diarrhea at rates of 0–19% depending on the season. Isolation from human feces also varies geographically based on food habits, level of sanitation, population demographics, aquaculture and farming practices, and laboratory isolation methods used. *Aeromonas* diarrhea is often watery and self-limited, although a dysentery-like syndrome with blood and mucus in the stool has also been described. Fever, abdominal pain, and vomiting are common in children. Choleric diarrhea with "rice-water" stools can also occur. Enteritis caused by *A. hydrophila* and *A. sobria* tends to be acute and self-limited, whereas 30% of patients with *A. caviae* enteritis have chronic or intermittent diarrhea that may last 4-6 weeks. *A. sobria* and *A. caviae* are most frequently associated with **traveler's diarrhea**. Complications of *Aeromonas* enteritis include intussusception, failure to thrive, hemolytic-uremic syndrome, bacteremia, and postinfectious chronic colitis. *Aeromonas* infection may also present as acute segmental colitis, mimicking inflammatory bowel disease or ischemic colitis.

Skin and Soft Tissue Infections

Skin and soft tissue infections are the second most common presentation of *Aeromonas,* most commonly associated with *A. hydrophila, A. veronii,* and *A. schubertii*. Predisposing factors include local trauma and exposure to contaminated fresh water. *Aeromonas* soft tissue infections have been reported after bites from a number of animal species, including alligators, tigers, bears, and snakes, and from tick

bites. These infections have also been reported after sports injuries and medicinal leech therapy. Antibiotic prophylaxis is generally used in conjunction with leech therapy because of the presence of *A. hydrophila* in the gastrointestinal (GI) tract of leeches, where they aid in the breakdown of ingested red blood cells. However, emerging reports of ciprofloxacin-resistant strains of *Aeromonas* isolated from leeches may affect this practice. The spectrum of skin and soft tissue infections is broad, ranging from a localized skin nodule to life-threatening necrotizing fasciitis, myonecrosis, and gas gangrene. Soft tissue infections are most frequently found on the extremities, are often polymicrobial, and are 3 times more likely in men than in women. *Aeromonas* **cellulitis**, the most common skin manifestation, clinically presents similar to other forms of bacterial cellulitis but should be suspected in wounds after contact with a water source, especially during the summer.

Septicemia

Aeromonas septicemia, strongly associated with *A. veronii* biovar sobria and *A. dhakensis* infection, is the third most common presentation of infection and is associated with a mortality rate of 27–73%. Higher incidence occurs during summer months or during the wet season in the tropics. Patients present with the classic signs and symptoms of gram-negative sepsis and may have GI symptoms, including abdominal pain, nausea, vomiting, and diarrhea. From 2% to 4% of patients may present with ecthyma gangrenosum–like lesions. *Aeromonas* may be the only organism isolated or may be part of a polymicrobial bacteremic illness. Most cases (approximately 80%) occur in immunocompromised adults or those with hepatobiliary disease and in young children in whom the source of infection is probably *Aeromonas* in the GI tract. Less frequently, bacteremia can be secondary to trauma-related myonecrosis or infected burns. In such patients, mortality is often higher than in those with primary bacteremia because of the underlying trauma. Rarely, *Aeromonas* bacteremia occurs in otherwise healthy adults exposed to fresh water.

Other Infections

Aeromonas is a rare cause of GI infections such as necrotizing gastroenteritis, peritonitis, cholecystitis, appendicitis, and liver and pancreas abscess formation; cardiovascular infections, including endocarditis and septic embolism; and pulmonary infections, including tracheobronchitis, pneumonia, empyema, and lung abscess formation. *Aeromonas* is also associated with musculoskeletal infections, including osteomyelitis, pyogenic arthritis, pyomyositis, and necrotizing fasciitis, as well as ocular and ear, nose, and throat infections, including endophthalmitis, keratitis, orbital cellulitis, otitis media, and epiglottitis. Other rare infections include meningitis, urinary tract infection, pelvic inflammatory disease, lymphadenitis, hot tub folliculitis, and surgical wound infections. *Aeromonas* is associated with tracheobronchitis and aspiration pneumonia after near-drowning.

DIAGNOSIS

Diagnosis is established by isolation of *Aeromonas* in culture. The organism is generally grown on standard media when the source material is normally sterile. Often, *Aeromonas* is not identified by typical laboratory protocols for examining stool specimens. If *Aeromonas* is suspected, the yield may increase if the laboratory is notified before testing, because overnight enrichment in alkaline peptone water and culture on selective agars may be useful. Most strains (approximately 90%) produce β-hemolysis on blood agar. Lactose-fermenting strains of *Aeromonas* like *A. caviae* may not be identified if the clinical laboratory does not routinely perform oxidase tests on lactose fermenters isolated on MacConkey agar. Aeromonads are resistant to vibriostatic agent O129; however, differentiation of *Aeromonas* from *Vibrio* spp. and identification of *Aeromonas* spp. and subspp. is not reliable using biochemical testing. Similarly, classification of *Aeromonas* strains at the species and subspecies level is difficult to achieve by sequencing regions of the 16S rRNA gene. Sequencing of housekeeping genes, such as *gyrB* and *rpoD,* and multilocus sequence typing are accurate for species identification but are time-, cost- and labor-intensive. Increasingly, laboratories use matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectrometry to rapidly identify organisms because this method is accurate for *Aeromonas* as a genus and for many of the clinically important species. Because stool culture–based diagnosis is time-consuming, labor-intensive, and costly on per positive culture basis, molecular tests for various enteric bacterial pathogens, including multiplex polymerase chain reaction (PCR) assays that include targets for detection of *Aeromonas,* have been developed and are commercially available in some areas.

TREATMENT

Aeromonas **enteritis** is usually self-limited, and antimicrobial therapy may not be indicated, although some studies suggest that **antimicrobial therapy** may shorten the course of the illness. Antimicrobial therapy is reasonable to consider in patients with protracted diarrhea, dysentery-like illness, or underlying conditions such as hepatobiliary disease or an immunocompromised state. Antibiotic sensitivity varies among species and also by geography; therefore it is important to perform **susceptibility testing**. Chromosomally mediated class B, C, and D β-lactamases are found in most species and can be difficult to identify because many are inducible. These include metallo- and AmpC β-lactamases, which can lead to clinical failure if carbapenems or third-generation cephalosporins are used as monotherapy in high-organism-load infections. There is near-uniform resistance to penicillins. Surgical intervention is the primary therapeutic modality in cases of **necrotizing fasciitis**, with most patients requiring more than one **debridement** in the first 48 hours. **Septicemia** can be treated with a **fourth-generation cephalosporin** (e.g., cefepime) or **ciprofloxacin**, with or without an aminoglycoside, although specific therapy should be guided by susceptibility data. Another option for less severe infections includes trimethoprim-sulfamethoxazole (TMP-SMX). Evidence-based recommendations for duration of treatment are lacking, and thus treatment is typically guided by clinical response. In general, diarrhea is treated for 3 days, wound infections for 7-10 days, and bacteremia for 14-21 days, depending on clinical response and host characteristics.

PREVENTION

Reducing contact with contaminated environmental fresh and brackish water and contaminated foods should reduce the risk for *Aeromonas* infections. Some *Aeromonas* outer membrane proteins are immunogenic and are candidate antigens for preclinical vaccine development.

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250.2 *Plesiomonas shigelloides*

Ameneh Khatami and Adam J. Ratner

ETIOLOGY

Plesiomonas shigelloides is a facultatively anaerobic, gram-negative, non–spore-forming bacillus that ferments glucose. It is a catalase-, oxidase-, and indole-positive motile organism with polar flagella. A high level of genetic diversity has been recognized among *P. shigelloides* strains, reflecting frequent homologous recombination.

EPIDEMIOLOGY

P. shigelloides is ubiquitous in freshwater and, because it can tolerate salinity of up to 4%, can be found in estuarine or brackish water, as well as animal inhabitants of these ecosystems, including fish, shellfish, crustaceans, water mammals, amphibians, reptiles, and other vertebrates. *P. shigelloides* has been recovered from healthy (colonized)

and diseased animals, including cats. It can cause both sporadic infections and outbreaks in a range of animals. As a mesophile with optimal growth temperature of 35–39°C (95–102.2°F), *P. shigelloides* has been found most often in tropical waters or during warmer months, although there are increasing reports of isolation from surface water in colder climates. Similarly, most cases of infection occur during the warmer months of the year. *P. shigelloides* is not a usual commensal organism in the human GI tract, and infection of humans is thought to be the result of consumption of contaminated water or raw seafood or possibly through contact with colonized animals. The frequency of isolation of *P. shigelloides* from diarrheal stools in these circumstances has been reported to range from 2% to >10%. Mixed infection with *Salmonella, Aeromonas,* rotavirus, or other enteric pathogens may occur in almost one third of patients. The majority of symptomatic patients in North America have a known exposure to potentially contaminated water or seafood (notably oysters) or have traveled abroad. *Plesiomonas* has been reported to be associated with 1.3–5.4% of episodes of **traveler's diarrhea**, with the highest rates associated with travel to South and Southeast Asia. Other risk factors include immune compromise (in particular HIV infection), blood dyscrasias (including sickle cell disease), and young age. The highest rates of *Plesiomonas* **enteritis** occur in children <2 years old. Although *P. shigelloides* has a worldwide distribution, there is unexplained geographic variability in the incidence of enteritis that may be related to water temperatures and a lack of hygiene and sanitation.

PATHOGENESIS

Epidemiologic and microbiologic evidence in the form of a series of food-borne outbreaks attributable to *P. shigelloides* indicates that this organism is an **enteropathogen**. However, the pathogenic capacity of *P. shigelloides* has not been confirmed through oral challenge studies, and these organisms have been isolated from the stools of healthy individuals at a low rate. The mechanism of enteritis is not known, but putative virulence factors have been described, including cholera-like toxin, heat-labile and heat-stable enterotoxins, and lipopolysaccharide. Most strains of *P. shigelloides* also secrete a β-hemolysin, which is thought to be a major virulence factor. In vitro studies show that isolates of *P. shigelloides* can invade and induce apoptosis in cells of enteric origin, as well as exhibiting evidence of modulation of host defenses through inhibition of cathepsins involved in antigen processing and presentation.

CLINICAL MANIFESTATIONS

Clinical disease in humans generally begins 24-48 hours after exposure to the organism, although incubation periods in excess of 4 days have been reported. Diarrhea can occur in all age-groups, including neonates, is typically secretory, and less often presents as invasive dysentery. Secretory **enteritis** usually presents as a mild self-limiting disease with watery diarrhea and abdominal pain, but in 13% of cases diarrhea can persist for >2 weeks. Dehydration, hypokalemia, and peritonitis are uncommon complications; however, there have been several reports of a cholera-like presentation with severe secretory diarrhea. The frequency of secretory vs dysenteric presentation seems to cluster by individual outbreak, suggesting that either the human populations or the bacterial populations involved are associated with each particular presentation. **Dysentery** presents with macroscopic blood and/or mucus in the stool, significant abdominal pain, and vomiting, with more severe cases also associated with fever. Fatal outcomes have been reported with severe cases of *Plesiomonas* dysentery, although in most of these cases the exact role of *P. shigelloides* is unclear.

Extraintestinal infections, usually bacteremia, are rare and usually occur in patients with underlying immunodeficiency. About 90% of these cases are monomicrobial, and in almost half, *P. shigelloides* is also isolated from a site other than blood. Rarely, bacteremia accompanying enteritis has been documented in apparently otherwise normal children. Septicemia also appears to result from ingestion of contaminated water or seafood and has a high mortality rate in adults. Other extraintestinal diseases include pneumonia, meningitis, osteomyelitis, septic arthritis, reactive arthritis, abscesses, and focal infections of the GI or reproductive tracts. Almost one third of all bacteremias occur in neonates who present with early-onset sepsis and meningitis, and although rare, these make up most of the reported cases of *P. shigelloides* meningitis and have a very high mortality rate (80%). In several cases of neonatal disease, *Plesiomonas* has also been isolated from maternal feces, suggesting intrapartum vertical transmission. Compared with *Aeromonas* and *Vibrio* spp., traumatic wounds sustained in aquatic environments less often contain *P. shigelloides*.

DIAGNOSIS

P. shigelloides is a non–lactose-fermenting organism and grows well on traditional enteric media with optimal growth at 30°C (86°F), although selective techniques may be required to isolate the organism from mixed cultures and to differentiate *P. shigelloides* from *Shigella* spp. If enrichment is necessary, alkaline peptone water or bile peptone broth may be used. Colonies are nonhemolytic on 5% blood agar. Many strains cross-react with *Shigella* on serologic testing but can be differentiated easily as oxidase-positive organisms. *P. shigelloides* has a unique biochemical profile and can generally be identified using commercial kits. Rapid identification systems, including MALDI-TOF, can also be used to identify *P. shigelloides*. *P. shigelloides* is included in at least one U.S. Food and Drug Administration (FDA)–approved commercial panel that detects a range of enteropathogens directly from diarrheal stools (culture independent) by PCR.

TREATMENT

Enteritis caused by *P. shigelloides* is usually mild and self-limited. In cases associated with dehydration or with a cholera-like disease, patients usually respond favorably to **oral rehydration solution**. Consideration of **antimicrobial therapy** is reserved for patients with prolonged or bloody diarrhea, those who are immunocompromised, the elderly, and the very young. Data from uncontrolled studies suggest that antimicrobial therapy may decrease the duration of symptoms, although no difference was found in an exclusively pediatric study.

P. shigelloides produces a chromosomally encoded, noninducible β-lactamase, which generally renders strains resistant to the penicillins, including broad-spectrum penicillins. *P. shigelloides* is also usually resistant to aminoglycosides and tetracyclines. Most strains of *P. shigelloides* are susceptible to β-lactam/β-lactamase inhibitor combinations and to TMP-SMX, some cephalosporins, carbapenems, and fluoroquinolones; however, therapy should be guided by **antimicrobial susceptibility testing** because resistance to TMP-SMX, fluoroquinolones, and other agents has been reported.

Severe cases of *P. shigelloides* dysentery should be treated similarly to shigellosis (with empirical **azithromycin** or a **third-generation cephalosporin** for children and ciprofloxacin or azithromycin for adults). Antibiotics are essential for therapy of extraintestinal disease. Empirical therapy with a third-generation cephalosporin is often first-line management, because most isolates are susceptible in vitro. Alternatives include carbapenems, aztreonam, β-lactam/β-lactamase inhibitor combinations, and quinolones. Definitive therapy should be guided by the susceptibility of the individual isolate. Duration of therapy ranges from 1 to 2 weeks but may be extended depending on underlying chronic conditions and clinical response.

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Chapter 251

Pseudomonas, Burkholderia, and *Stenotrophomonas*

251.1 *Pseudomonas aeruginosa*

Thomas S. Murray and Ashley C. Howard

ETIOLOGY

Pseudomonas aeruginosa is an aerobic, gram-negative rod. It can multiply in a great variety of environments that contain minimal amounts of organic compounds. Strains from clinical specimens do not ferment lactose, are oxidase positive, and may produce β-hemolysis on blood agar. Many strains produce pigments, including pyocyanin, pyoverdine, and pyorubrin, that diffuse into and color the surrounding medium. Strains of *P. aeruginosa* are differentiated for epidemiologic purposes by a variety of genotyping methods, including restriction fragment length polymorphisms using pulsed-field gel electrophoresis, multilocus sequence typing, and more recently, whole genome sequencing.

EPIDEMIOLOGY

P. aeruginosa is a classic "opportunist." It rarely causes disease in people who do not have a predisposing risk factor. Compromised host defense mechanisms resulting from trauma, neutropenia, mucositis, immunosuppression, or impaired mucociliary transport explain the predominant role of this organism in producing opportunistic infections. In pediatric settings, it is frequently seen in the respiratory secretions of children with **cystic fibrosis** (CF). In a pediatric review of 2,545 facilities from 2015 to 2017 by the National Healthcare Safety Network (NHSN), *P. aeruginosa* ranked among the top 10 organisms to cause **central line–associated bloodstream infections** in all units: 2.8% neonatal intensive care unit (NICU), 5% pediatric intensive care unit (PICU), 5% pediatric oncology units, and 3.1% pediatric wards. *P. aeruginosa* was also the second most common cause of **catheter-associated urinary tract infections** (UTIs) (18.4%) and **ventilator-associated pneumonia** (16.1%) and the third most common cause of postoperative surgical site infections (8.3%). In a multicenter U.S. prospective study of 33 sites from 2014 to 2018, *P. aeruginosa* was isolated in 2.7% of bacteremic episodes in children ≤1 year old and 3.7 % in children ≤17 years of age.

P. aeruginosa and other pseudomonads frequently enter the hospital environment on the clothes, skin, or shoes of patients or hospital personnel, with plants or vegetables brought into the hospital, and in the gastrointestinal (GI) tract of patients. Colonization of any moist or liquid substance may ensue; the organisms may be found growing in any water reservoir, including distilled water, and in hospital kitchen sinks and laundries, some antiseptic solutions, and equipment used for respiratory therapy and urinary procedures. Colonization of skin, throat, stool, and nasal mucosa of patients is low at admission to the hospital but increases to as high as 50–70% with prolonged hospitalization and with the use of broad-spectrum antibiotics, chemotherapy, mechanical ventilation, and urinary catheters. Patients' intestinal microbial flora may be altered by the broad-spectrum antibiotics, reducing resistance to colonization and permitting *P. aeruginosa* in the environment to populate the GI tract. Intestinal mucosal breakdown associated with medications, especially cytotoxic agents, and nosocomial enteritis may provide a pathway by which *P. aeruginosa* spreads to the lymphatics or bloodstream.

PATHOLOGY

The pathologic manifestations of *P. aeruginosa* infections depend on the site and type of infection. Because of its elaboration of toxins and invasive factors, the organism can often be seen invading blood vessels and causing vascular necrosis. In some infections there is spread through tissues with necrosis and microabscess formation. In patients with CF, focal and diffuse bronchitis/bronchiolitis leading to bronchiolitis obliterans has been reported.

Pathogenesis

Invasiveness of *P. aeruginosa* is mediated by a host of virulence factors. Bacterial attachment is facilitated by pili that adhere to epithelium damaged by prior injury or infection. Extracellular proteins, proteases, elastases, and cytotoxins disrupt cell membranes, and in response, host-produced cytokines cause capillary vascular permeability and induce an inflammatory response. Dissemination and bloodstream invasion follow extension of local tissue damage and are facilitated by the antiphagocytic properties of endotoxin, the exopolysaccharide, and protease cleavage of immunoglobulin G. *P. aeruginosa* also produces numerous exotoxins, including exotoxin A, which causes local necrosis and facilitates systemic bacterial invasion. *P. aeruginosa* possesses a type III secretion system composed of a needle structure that inserts into host cell membranes and allows secretion of exotoxins directly into host cells. The host responds to infection with a robust inflammatory response, recruiting neutrophils to the infection site and producing antibodies to *P. aeruginosa* proteins. There is a lack of convincing data that these antibodies are protective against the establishment of infection.

In addition to acute infection, *P. aeruginosa* is also capable of chronic persistence because of the formation of **biofilms**, organized communities of bacteria encased in an extracellular matrix. Biofilm formation requires attachment to a surface, proliferation of the organism, and production of exopolysaccharide as the main bacterial component of the extracellular matrix. A mature biofilm can persist despite an intense host immune response and is resistant to many antimicrobials.

CLINICAL MANIFESTATIONS

Most clinical patterns are related to opportunistic infections in immunocompromised hosts (see Chapter 223) or are associated with shunts and indwelling catheters (see Chapter 224). *P. aeruginosa* may be introduced into a minor wound of a healthy person as a secondary invader, and cellulitis and a localized abscess that exudes green or blue pus may follow. The characteristic skin lesions of *P. aeruginosa,* **ecthyma gangrenosum**, whether caused by direct inoculation or a metastatic focus secondary to septicemia, begin as pink macules and progress to hemorrhagic nodules and eventually to ulcers with ecchymotic and gangrenous centers with eschar formation, surrounded by an intense red areola (Table 251.1 and Fig. 251.1).

Outbreaks of dermatitis and UTIs caused by *P. aeruginosa* have been reported in healthy persons after use of pools or hot tubs. Skin lesions of folliculitis develop several hours to 2 days after contact with these water sources. Skin lesions may be erythematous, macular, papular, or pustular. Illness may vary from a few scattered lesions to extensive truncal involvement. In some children, malaise, fever, vomiting, sore throat, conjunctivitis, rhinitis, and swollen breasts may be associated with dermal lesions. UTIs caused by *P. aeruginosa* are most often nosocomial and are often associated with the presence of an indwelling urinary catheter, urinary tract malformations, and previous antibiotic use. UTIs may be minimized or prevented by prompt removal of the catheter and by early identification and corrective surgery of obstructive lesions when present.

Burns and Wound Infection

The surfaces of burns or wounds are frequently populated by *P. aeruginosa* and other gram-negative organisms; this initial colonization with a low number of adherent organisms is a prerequisite to invasive disease. *P. aeruginosa* colonization of a burn site may develop into **burn wound sepsis**, which has a high mortality rate when the density of organisms reaches a critical concentration. Administration of antibiotics may

Table 251.1 *Pseudomonas aeruginosa* Infections

INFECTION	COMMON CLINICAL CHARACTERISTICS
Endocarditis	Native right-sided (tricuspid) valve disease with intravenous drug abuse
Pneumonia	Compromised local (lung) or systemic host defense mechanisms; nosocomial (respiratory), bacteremic (malignancy), or abnormal mucociliary clearance (cystic fibrosis) may be pathogenetic; cystic fibrosis is associated with mucoid *P. aeruginosa* organisms producing capsular slime
Central nervous system infection	Meningitis, brain abscess; contiguous spread (mastoiditis, dermal sinus tracts, sinusitis); bacteremia or direct inoculation (trauma, surgery)
External otitis	Swimmer's ear; humid warm climates, swimming pool contamination
Malignant otitis externa	Invasive, indolent, febrile, toxic, destructive, necrotizing lesion in young infants, immunosuppressed neutropenic patients, or diabetic patients; associated with seventh nerve palsy and mastoiditis
Chronic mastoiditis	Ear drainage, swelling, erythema; perforated tympanic membrane
Keratitis	Corneal ulceration; contact lens keratitis
Endophthalmitis	Penetrating trauma, surgery, penetrating corneal ulceration; fulminant progression
Osteomyelitis/septic arthritis	Puncture wounds of foot and osteochondritis; intravenous drug abuse; fibrocartilaginous joints, sternum, vertebrae, pelvis; open fracture osteomyelitis; indolent pyelonephritis and vertebral osteomyelitis
Urinary tract infection	Iatrogenic, nosocomial; recurrent UTIs in children, instrumented patients, and those with obstruction or stones
Intestinal tract infection	Immunocompromised, neutropenia, typhlitis, rectal abscess, ulceration, rarely diarrhea; peritonitis in peritoneal dialysis
Ecthyma gangrenosum	Metastatic dissemination; hemorrhage, necrosis, erythema, eschar, discrete lesions with bacterial invasion of blood vessels; also subcutaneous nodules, cellulitis, pustules, deep abscesses
Primary and secondary skin infections	Local infection; burns, trauma, decubitus ulcers, toe web infection, green nail (paronychia); whirlpool dermatitis; diffuse, pruritic folliculitis; vesiculopustular or maculopapular, erythematous lesions

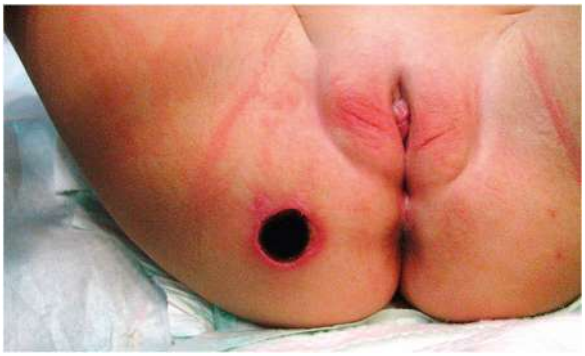

Fig. 251.1 Round, nontender skin lesion on 2-yr-old female's buttock. Note the black ulcerated center of the lesion and its red margin. *(From Ghanaiem H, Engelhard D. A healthy 2-year-old child with a round black skin lesion. J Pediatr. 2013;163:1225.)*

diminish the susceptible microbiologic flora, permitting strains of relatively resistant *P. aeruginosa* to flourish. Multiplication of organisms in devitalized tissues or associated with prolonged use of intravenous or urinary catheters increases the risk for septicemia with *P. aeruginosa*, a major problem in burned patients (see Chapter 89).

Cystic Fibrosis

P. aeruginosa is common in patients with CF, with increasing prevalence as children get older (see Chapter 454). Initial infection is caused by **nonmucoid environmental strains** of *P. aeruginosa*, but after a variable period, **mucoid strains** of *P. aeruginosa* that produce the antiphagocytic exopolysaccharide alginate, which are rarely encountered in other conditions, predominate. Repeated isolation of mucoid *P. aeruginosa* from the sputum is associated with increased morbidity and mortality. The infection begins insidiously or even asymptomatically, and the progression has a highly variable pace. In children with CF, antibody does not eradicate the organism, and antibiotics are only partially effective; thus after infection becomes chronic, it cannot be completely eradicated. Repeated courses of antibiotics select for *P. aeruginosa* strains that are resistant to multiple antibiotics.

Immunocompromised Persons

Children with leukemia or other malignancies, particularly those who are receiving immunosuppressive therapy and who are neutropenic, typically with intravascular catheters, are extremely susceptible to septicemia caused by invasion of the bloodstream by *P. aeruginosa* that is colonizing the respiratory or GI tract. Signs of sepsis are often accompanied by a generalized vasculitis, and hemorrhagic necrotic lesions may be found in all organs, including the skin (ecthyma gangrenosum) (see Fig. 251.1). Hemorrhagic or gangrenous perirectal cellulitis or abscesses may occur, associated with ileus and profound hypotension.

Nosocomial Pneumonia

Although not a frequent cause of community-acquired pneumonia in children, *P. aeruginosa* does cause nosocomial pneumonia, especially ventilator-associated pneumonia, in patients of all ages. *P. aeruginosa* has historically been found to contaminate ventilators, tubing, and humidifiers. Such contamination is uncommon now because of disinfection practices and routine changing of equipment. Nevertheless, colonization of the upper respiratory tract and the GI tract may be followed by aspiration of *P. aeruginosa*–contaminated secretions, resulting in severe pneumonia. Prior use of broad-spectrum antibiotics is a risk factor for colonization with antibiotic-resistant strains of *P. aeruginosa*. One of the most challenging situations is distinguishing between colonization and pneumonia in intubated patients. This distinction can

often only be definitively resolved by using invasive culture techniques such as quantitative bronchoalveolar lavage.

Infants

P. aeruginosa is an occasional cause of **nosocomial bacteremia** in newborns and accounts for 2–5% of positive blood culture results in NICUs. A frequent focus preceding bacteremia is **conjunctivitis**. Older infants rarely present with community-acquired sepsis caused by *P. aeruginosa.* In the few reports describing community-acquired sepsis, preceding conditions included ecthyma-like skin lesions, virus-associated transient neutropenia, and prolonged contact with contaminated bath water or a hot tub.

DIAGNOSIS

P. aeruginosa infection is rarely clinically distinctive. Diagnosis depends on recovery of the organism from the blood, cerebrospinal fluid (CSF), urine, or needle aspirate of the lung or from purulent material obtained by aspiration of subcutaneous abscesses or areas of cellulitis. In the appropriate clinical setting, recovery of *P. aeruginosa* from a coughed or suctioned sputum may represent infection; but it also may only represent colonization, and clinical judgment is required. Rarely, skin lesions that resemble *P. aeruginosa* infection may follow septicemia caused by *Aeromonas hydrophila,* other gram-negative bacilli, and *Aspergillus.* When *P. aeruginosa* is recovered from nonsterile sites such as skin, mucous membranes, or voided urine, quantitative cultures may be useful to differentiate colonization from invasive infection. In general, ≥100,000 colony-forming units/mL of fluid or gram of tissue is evidence suggestive of invasive infection. Quantitative cultures of tissue and skin are not routine and require consultation with the clinical microbiology laboratory.

TREATMENT

Systemic infections with *P. aeruginosa* should be treated promptly with an antibiotic to which the organism is susceptible in vitro. Response to treatment may be limited, and prolonged treatment may be necessary for systemic infection in immunocompromised hosts.

Septicemia and other aggressive infections should be treated with either one or two bactericidal agents. Although the number of agents required is controversial, the evidence continues to suggest that the benefit of adding a second agent is questionable, even when studies have included immunosuppressed patients. *Appropriate antibiotics for single-agent therapy include ceftazidime, cefepime, ticarcillin-clavulanate, and piperacillin-tazobactam. Gentamicin or another aminoglycoside may be used concomitantly for synergistic effect.*

Ceftazidime has proved to be extremely effective in patients with CF, at 150-400 mg/kg/day divided every 6-8 hours intravenously (IV) to a maximum of 6 g/day. Piperacillin or piperacillin-tazobactam 240-400 mg/kg/day divided every 6-8 hours IV to a maximum of 12 g/day also has proved to be effective therapy for susceptible strains of *P. aeruginosa.* Continuous infusions of β-lactam antibiotics are more effective than the same daily dose given as pulse infusions.

Additional effective antibiotics include imipenem-cilastatin, meropenem, and aztreonam. Ciprofloxacin (20-30 mg/kg/day orally every 8-12 hours up to 500 mg/dose) is the only available effective oral *P. aeruginosa* therapy, and although commonly used in children with CF, it is not approved in the United States for persons <18 years old, except for oral treatment of UTIs or when treating multidrug-resistant (MDR) *P. aeruginosa*. Inhaled therapy with either tobramycin or aztreonam is also used for chronic pulmonary infection, with inhaled colistin reserved for the treatment of resistant pseudomonads. Macrolide therapy decreases pulmonary exacerbations in patients with chronic lung disease and *P. aeruginosa* infection. The mechanism relates to altering the virulence properties of *P. aeruginosa* rather than direct bacterial killing.

It is important to base continued treatment on antimicrobial susceptibility tests because **antibiotic resistance** of *P. aeruginosa* is increasing. *P. aeruginosa* has many mechanisms for resistance to multiple classes of antibiotics, including but not limited to pathogenic variants, production of β-lactamases, and drug efflux pumps. Throughout the United States there has been an alarming increase in MDR *P. aeruginosa* isolates resistant to at least three antibiotic classes recovered from children. NHSN data from 2015 to 2017 show 2.8% NICU, 12% PICU, 6% pediatric oncology, and 5.5% pediatric ward *P. aeruginosa* isolates were MDR, with increasing rates of carbapenem and piperacillin/tazobactam resistance as well.

Several newer agents demonstrate efficacy against MDR *P. aeruginosa*. Ceftazidime-avibactam and ceftolozane-tazobactam combine cephalosporins with a β-lactamase inhibitor. Ceftolozane-tazobactam inhibits AmpC and other extended-spectrum β-lactamases but lacks activity against carbapenemases. Ceftazidime-avibactam inhibits class A carbapenemases but not metallo-β-lactamases. Cefiderocol, a siderophore cephalosporin, has enhanced stability to β-lactamases, including metallo-β-lactamases, Amp C, and carbapenemases.

Meningitis can occur by spread from a contiguous focus, as a secondary focus when there is bacteremia, or after invasive procedures. *P. aeruginosa* meningitis is best treated with ceftazidime or meropenem in combination with an aminoglycoside such as gentamicin, both given IV. Concomitant intraventricular or intrathecal treatment with gentamicin may be required when IV therapy fails but is not recommended for routine use.

SUPPORTIVE CARE

P. aeruginosa infections vary in severity from *superficial* to *intense* septic presentations. With severe infections there is often multisystem involvement and a systemic inflammatory response. Supportive care is similar to care for severe sepsis caused by other gram-negative bacilli and requires support of blood pressure, oxygenation, and appropriate fluid management.

PROGNOSIS

The prognosis is dependent primarily on the nature of the underlying factors that predisposed the patient to *P. aeruginosa* infection. In severely immunocompromised patients, the prognosis for patients with *P. aeruginosa* sepsis is poor unless susceptibility factors such as neutropenia or hypogammaglobulinemia can be reversed. The overall mortality rate was 12.3% in one series of 232 children with *P. aeruginosa* bacteremia, with 3% dying within 48 hours of admission. Resistance of the organism to first-line antibiotics also decreases the chance of survival. The outcome may be improved when there is a urinary tract portal of entry, absence of neutropenia or recovery from neutropenia, and drainage of local sites of infection.

P. aeruginosa is recovered from the lungs of most children who die of CF and adds to the slow deterioration of these patients. The prognosis for normal development is poor in the few infants who survive *P. aeruginosa* meningitis.

PREVENTION

Prevention of infections is dependent on limiting contamination of the healthcare environment and preventing transmission to patients. Effective hospital infection control programs are necessary to identify and eradicate sources of the organism as quickly as possible. In hospitals, infection can be transmitted to children by the hands of personnel, from washbasin surfaces, from catheters and other hospital equipment, and from solutions used to rinse suction catheters.

Strict attention to hand hygiene before and between contacts with patients may prevent or interdict epidemic disease. Meticulous care and sterile procedures in the suctioning of endotracheal tubes, insertion and maintenance of indwelling catheters, and removal of catheters as soon as medically reasonable greatly reduce the hazard of extrinsic contamination by *P. aeruginosa* and other gram-negative organisms. Prevention of follicular dermatitis caused by *P. aeruginosa* contamination of whirlpools or hot tubs is possible by maintaining pool water at a pH of 7.2-7.8. Antimicrobial stewardship programs that promote the appropriate use of antibiotics in the hospital setting are critical for reducing the rates of MDR *P. aeruginosa*.

Infections in burned patients may be minimized by protective isolation, debridement of devitalized tissue, and topical applications of bactericidal cream. Administration of intravenous immunoglobulin

may be used. Approaches under investigation to prevent infection include development of a *P. aeruginosa* vaccine. No vaccine is currently licensed in the United States.

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251.2 *Burkholderia cepacia* Complex

Ashley C. Howard and Thomas S. Murray

Burkholderia cepacia is a filamentous gram-negative rod now recognized to be a group of related species or **genomovars** *(B. cepacia, B. cenocepacia, B. multivorans)*. It is ubiquitous in the environment but may be difficult to isolate from respiratory specimens in the laboratory, requiring an enriched, selective media oxidation-fermentation base supplemented with polymyxin B–bacitracin-lactose agar (OFPBL) and as long as 3 days of incubation.

B. cepacia is a classic opportunist that rarely infects normal tissue but can be a pathogen for individuals with preexisting damage to respiratory epithelium, especially persons with CF or with immune dysfunction such as chronic granulomatous disease. *B. cepacia* has multiple virulence factors, including lipopolysaccharide, flagella, and a type III secretion system that promotes invasion of respiratory epithelial cells. Resistance to many antibiotics and disinfectants appears to be a factor in the emergence of *B. cepacia* as a nosocomial pathogen. In critical care units it may colonize the tubing used to ventilate patients with respiratory failure. In some patients this colonization may lead to invasive pneumonia and septic shock. Although *B. cepacia* is found throughout the environment, human-to-human spread among CF patients occurs either directly by inhalation of aerosols or indirectly from contaminated equipment or surfaces, accounting for the strict infection control measures for children with CF who are colonized with *B. cepacia*. For example, CF patients colonized with *B. cepacia* are asked not to attend events where other persons with CF will be present. *B. cepacia* infections in persons with CF may represent chronic infection in some patients, but others, especially those with *Burkholderia cenocepacia*, genomovar III, can develop an acute respiratory syndrome of fever, leukocytosis, and progressive respiratory failure, with more rapid decline in pulmonary function and lower survival rate. In 2016-2017, two healthcare-associated *B. cepacia* outbreaks among non-CF patients occurred as a result of contaminated liquid docusate that infected 63 persons from 12 states and prefilled saline flushes that infected 163 persons with 7 deaths. In August 2021, a healthcare-associated outbreak of *B. stabilis* was linked to ultrasound gel used in 59 persons in six states, with 48 cases of bloodstream infection.

Treatment in hospitals should include standard precautions and avoidance of placing colonized and uncolonized patients in the same room. The use of antibiotics is guided by susceptibility studies of a patient's isolates, because the susceptibility pattern of this species is quite variable and resistant strains are common. *Trimethoprim-sulfamethoxazole (TMP-SMX) and doxycycline or minocycline are potential oral therapies for B. cepacia complex. For IV therapy without meningitis, meropenem (20-40 mg/kg/dose every 8 hours with a maximum dose of 6 g/day) with a second agent such as TMP-SMX, doxycycline, minocycline, ceftazidime, or amikacin is recommended.* Extended infusions should be considered for difficult-to-treat infections. Even though there is primary resistance to aminoglycosides, these agents may be useful in combination with other antibiotics. Treatment with two or more agents may be necessary to control the infection and avoid the development of resistance. Cefiderocol, because of its increased stability against β-lactamases, has activity against some MDR *B. cepacia complex.*

BURKHOLDERIA MALLEI (GLANDERS)

Glanders is a severe infectious disease of horses and other domestic and farm animals that is caused by *Burkholderia mallei,* a nonmotile, gram-negative bacillus that is occasionally transmitted to humans. It is acquired by inoculation into the skin, usually at the site of a previous abrasion, or by inhalation of aerosols. Laboratory workers may acquire it from clinical specimens. The disease is relatively common in Asia, Africa, and the Middle East. The clinical manifestations include septicemia, acute or chronic pneumonitis, and hemorrhagic necrotic lesions of the skin, nasal mucous membranes, and lymph nodes. The diagnosis is usually made by recovery of the organism in cultures of affected tissue. Glanders is treated with sulfadiazine, tetracyclines, or chloramphenicol and streptomycin over many months. The disease has been eliminated from the United States, but interest in this organism has increased because of the possibility of its use as a bioterrorism agent (see Chapter 763). Although standard precautions are appropriate when caring for hospitalized infected patients, biosafety level 3 precautions are required for laboratory staff working with *B. mallei.* No vaccine is available.

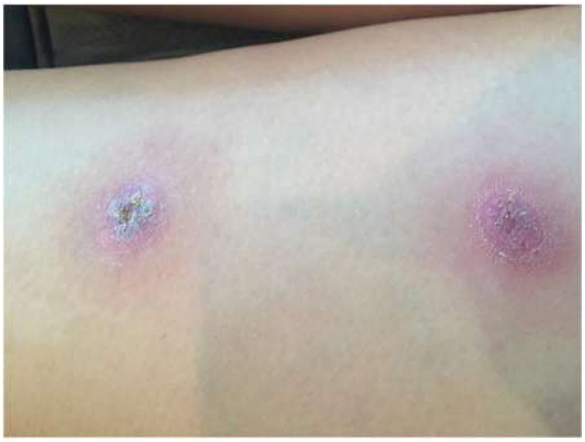

Fig. 251.2 Thigh abscesses at the sites of mosquito bites in a 15-yr-old Pennsylvania resident who had recently returned from Thailand, July 2016. Photo was taken 7 wk after onset. *(From Mitchell PK, Campbell C, Montgomery MP, et al. Notes from the field: travel–associated melioidosis and resulting laboratory exposures—United States, 2016. MMWR. 2017;66[37]:1001–1002.)*

BURKHOLDERIA PSEUDOMALLEI (MELIOIDOSIS)

Melioidosis is an important disease of Southeast Asia and northern Australia and occurs in the United States mainly in persons returning from endemic areas. The causative agent is *Burkholderia pseudomallei,* an inhabitant of soil and water in the tropics. It is ubiquitous in endemic areas, and infection follows inhalation of dust, ingestion, or direct contamination of abrasions or wounds. Human-to-human transmission has only rarely been reported. Serologic surveys demonstrate that asymptomatic infection occurs in endemic areas. The disease may remain latent and appear when host resistance is reduced, sometimes years after the initial exposure. Diabetes mellitus is a risk factor for severe melioidosis. In 2021, four cases of melioidosis with two deaths occurred in Kansas, Minnesota, Texas, and Georgia in persons, including children, with no known travel. The exposure is unknown but thought to be from a single source, such as a contaminated imported product or animal.

Melioidosis may present as a **primary skin lesion** (vesicle, bulla, or urticaria) (Fig. 251.2). Pulmonary infection may be subacute and mimic tuberculosis or may present as an acute necrotizing pneumonia. Occasionally, septicemia occurs and numerous abscesses are noted in various organs of the body. Myocarditis, pericarditis, endocarditis, intestinal abscess, cholecystitis, acute gastroenteritis, UTIs, septic arthritis, paraspinal abscess, osteomyelitis, mycotic aneurysm, and generalized lymphadenopathy all have been observed. Melioidosis may also present as an encephalitic illness with fever and seizures. It is also an agent of severe wound infections after contact with contaminated water after a tsunami. Diagnosis is based on visualization of characteristic small, gram-negative rods in exudates or growth on laboratory media such as eosin–methylene blue or MacConkey agar. Serologic

tests are available, and diagnosis can be established by a fourfold or greater increase in antibody titer in an individual with an appropriate syndrome. It is recognized as a possible agent of bioterrorism, and if suspected, the clinical microbiology laboratory should be notified immediately (see Chapter 763).

B. pseudomallei is susceptible to many antimicrobial agents, and the U.S. Centers for Disease Control and Prevention (CDC) recommends meropenem or ceftazidime as IV therapies and TMP-SMX or doxycycline as oral therapy. Other choices include aminoglycosides, tetracycline, chloramphenicol, and amoxicillin-clavulanate. Therapy should be guided by antimicrobial susceptibility tests; two or three agents such as ceftazidime or meropenem plus TMP-SMX, sulfisoxazole, or an aminoglycoside are usually chosen for severe or septicemic disease. For severe disease, prolonged treatment for 2-6 months is recommended to prevent relapses. Appropriate antibiotic therapy generally results in recovery.

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251.3 *Stenotrophomonas*

Ashley C. Howard and Thomas S. Murray

Stenotrophomonas maltophilia (formerly *Xanthomonas maltophilia* or *Pseudomonas maltophilia*) is a short to medium-sized, straight, gram-negative bacillus. It is ubiquitous in nature and can be found in the hospital environment, especially in tap water or standing water, and may contaminate sinks and hospital equipment such as nebulizers. Strains isolated in the laboratory may be contaminants, may be a commensal from the colonized surface of a patient, or may represent an invasive pathogen. The species is an opportunist and is often recovered from immunosuppressed patients and patients with CF after multiple courses of antimicrobial therapy. Serious infections usually occur among those requiring intensive care, including neonatal intensive care, typically patients with ventilator-associated pneumonia or catheter-associated infections. Prolonged antibiotic exposure appears to be a frequent factor in nosocomial *S. maltophilia* infections, probably because of its endogenous antibiotic-resistance pattern. Common types of infection include pneumonia after airway colonization and aspiration, bacteremia, soft tissue infections, endocarditis, and osteomyelitis. *S. maltophilia* bacteremia is a **nosocomial infection** associated with the presence of a central venous catheter.

Strains vary as to antibiotic susceptibility, and the treatment of *S. maltophilia* can be difficult because of inherent antimicrobial resistance. Data are lacking on whether there is clinical benefit to treat *S. maltophilia* recovered from the respiratory tract of a patient with CF. For invasive infections, ***TMP-SMX*** *(20 mg/kg/day TMP component every 6-8 hours) is the treatment of choice and is the only antimicrobial for which susceptibility is routinely reported.* ***Minocycline*** *monotherapy has recently been shown to be a viable alternative to TMP-SMX* and is reported for TMP-SMX resistance strains with fewer adverse effects and similar clinical outcomes. Mean inhibitory concentration testing is available for other antibiotics, such as ticarcillin-clavulanate, and also reserved for TMP-SMX–resistant isolates. *For resistant organisms or for patients who cannot tolerate sulfa drugs, other options based on clinical outcome include ciprofloxacin and ceftazidime alone or in combination with other agents such as aminoglycosides.*

ACKNOWLEDGMENTS

We would like to acknowledge Dr. Robert S. Baltimore for his contribution to this chapter and Dr. Michelle R. Rychalsky for antibiotic dosing regimens.

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Chapter 252

Tularemia (*Francisella tularensis*)

Kevin J. Downes

Tularemia is a **zoonosis** caused by the gram-negative bacterium *Francisella tularensis.* Tularemia is primarily a disease of wild animals; human disease is incidental and usually results from **tick** or **deer fly** bites or from contact with infected live or dead wild animals. The illness caused by *F. tularensis* is manifest by multiple clinical syndromes, the most common consisting of an ulcerative lesion at the site of inoculation with regional **lymphadenopathy** or **lymphadenitis**. *F. tularensis* is also a potential agent of **bioterrorism** (see Chapter 763).

ETIOLOGY

Francisella tularensis is a small, nonmotile, pleomorphic, catalase-positive, gram-negative coccobacillus. It can be classified into four main subspecies: *F. tularensis* subsp. *tularensis* (type A), *F. tularensis* subsp. *holarctica* (type B), *F. tularensis* subsp. *mediasiatica*, and *F. tularensis* subsp. *novicida*. Type A can be further subdivided into four distinct genotypes designated A1a, A1b, A2a, and A2b, with A1b appearing to produce more serious disease in humans. Although all subspecies of *F. tularensis* can cause human infections, types A and B are most common, and type A is the most virulent. *F. tularensis* is an intracellular organism than can infect various host cell types, including macrophages, hepatocytes, and epithelial cells. It is one of the most virulent bacterial pathogens known, with as few as 10 microorganisms causing infections in humans and animals.

EPIDEMIOLOGY

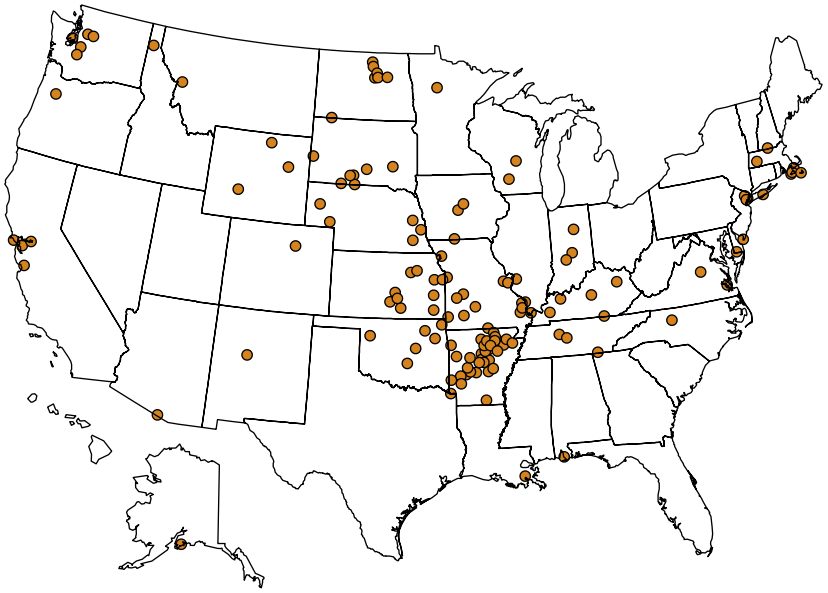
Tularemia is primarily found in the Northern Hemisphere. Type A is found predominantly in North America, whereas type B is found throughout North America, Europe, and Asia. Human infections with type B are usually milder and have lower mortality rates compared to infections with type A. *F. tularensis* subsp. *mediasiatica* appears to be restricted to Central Asia, whereas *F. tularensis* subsp. *novicida* has been isolated in North America, Australia, and Southeast Asia.

According to the Centers for Disease Control and Prevention (CDC), the number of annual reported cases of tularemia in the United States from 2010 to 2019 ranged from 124 to 314 per year. In 2015 the number of cases reported in the United States was the highest it had been over the previous 50 years. Tularemia occurs all over the Unites States, with the majority of cases reported from central states (Fig. 252.1). The U.S. incidence of tularemia from 2010 to 2019 was 0.10 per 100,000 residents; Arkansas (3.1/100,000), South Dakota (1.9/100,000), and Nebraska (0.9/100,000) were the states with the highest incidence.

Although cases of tularemia occur all year, most cases and outbreaks occur in warm summer months (May-September). Tularemia is more common in males, although this is less true in children compared with adults. There is a bimodal distribution based on age with peaks in childhood (5-9 years) and later adulthood (50-69 years), potentially because of greater opportunities for environmental and animal exposures at these ages (Fig. 252.2).

PATHOGENESIS

Of all the zoonotic diseases, tularemia is unusual because of the different modes of transmission of disease. A large number of animals serve as a reservoir for this organism. In the United States, rabbits and ticks are the principal reservoirs. Dogs may be an intermediate vector. In the United States, *Amblyomma americanum* (lone star tick), *Dermacentor variabilis* (dog tick), and *Dermacentor andersoni* (wood tick) are the most common tick vectors. These ticks usually feed on infected small



* One dot is placed randomly within county of residence for each reported case.

Fig. 252.1 Map of reported cases of tularemia—United States, 2020. *(From Centers for Disease Control and Prevention: Tularemia—Statistics, https://www.cdc.gov/tularemia/statistics/index.html, Accessed: August 25, 2021.)*

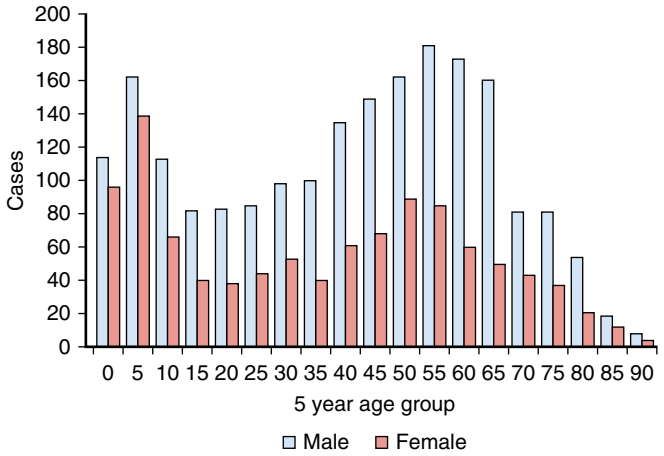


Fig. 252.2 Incidence of reported cases of tularemia by age and sex—United States, 2001–2020. *(From Centers for Disease Control and Prevention: Tularemia—Statistics, https://www.cdc.gov/tularemia/statistics/index.html, Accessed: August 25, 2021.)*

rodents and later feed on humans. Deer flies (*Chrysops* spp.) can also transmit tularemia and are present in the western United States. *F. tularensis* subsp. *tularensis* is carried by rabbits, ticks, and tabanid flies (e.g., deer flies), whereas subsp. *holarctica* is associated with aquatic habitats and transmitted primarily by mosquitoes, but also aquatic rodents (beavers, muskrats), hares, voles, ticks, tabanid flies, and ingestion of contaminated water (e.g., ponds, rivers).

The organism can penetrate both intact skin and mucous membranes (eyes, mouth, gastrointestinal [GI] tract, or lungs), which are the most common portals of entry. Transmission can occur through the bite of infected ticks or other biting insects, by contact with infected animals or their carcasses, by consumption of contaminated foods or water, or through inhalation, as might occur in a laboratory setting or if a machine (e.g., lawn mower) runs over an infected animal carcass. Hunting or skinning infected wild rodents, such as rabbits or prairie dogs, has been the source of infection in numerous reports. Domesticated animals such as cats and hamsters can also transmit tularemia. Importantly, this organism is not transmitted from person to person.

Usually >10^8 organisms are required to produce infection if *F. tularensis* bacteria are ingested, but as few as 10 organisms may cause disease if they are inhaled or injected into the skin (i.e., via an insect bite). Infection with *F. tularensis* stimulates the host to produce antibodies, which have been recognized as important in the immune response to this organism. The *F. tularensis* envelope is largely responsible for virulence and plays major roles in the ability of the organism to evade the immune system, attach to and invade cells, and cause severe disease. The body is most dependent on cell-mediated immunity to contain and eradicate *F. tularensis*. Tularemia is usually followed by specific protection; chronic infection or reinfection is therefore unlikely.

CLINICAL MANIFESTATIONS

Symptoms of tularemia vary based on the mode of transmission. The average incubation period from infection until clinical symptoms is 3 days (range: 1-21 days). Early symptoms of infection are generally nonspecific: fever, chills, myalgias, arthralgias, headache, and fatigue. Bacteremia may be common in the early stages of infection. Acute infections often present with sudden onset of fever, and a pulse-temperature dissociation may be present. Findings on physical examination may include lymphadenopathy, hepatosplenomegaly, or skin lesions. Table 252.1 shows the frequency of various symptoms and examination findings.

The clinical manifestations of tularemia have been divided into six major clinical syndromes (Table 252.2). **Ulceroglandular** and **glandular** disease are the two most common forms of tularemia in children. Infections after the bites of ticks or deer flies take these forms. Within 48-72 hours after inoculation of the skin, an erythematous, tender, or pruritic papule may appear at the portal of entry. This papule may enlarge and form an ulcer with a black base. Ulcers are generally erythematous and painful with raised borders and may last several weeks, especially if untreated. Various other skin lesions have been described, including erythema multiforme and erythema nodosum. Approximately 20% of patients may develop a generalized maculopapular rash that occasionally becomes pustular. The unifying manifestation of glandular and ulceroglandular forms of tularemia is **painful regional lymphadenopathy**. Adenopathy may develop before, concurrent with, or

Table 252.1 Common Clinical Manifestations of Tularemia in Children

SIGN OR SYMPTOM	APPROXIMATE FREQUENCY (%)
Lymphadenopathy	90
Fever (>38.3°C [100.9°F])	85
Ulcer/eschar/papule	45
Pharyngitis	40
Myalgias/arthralgias	40
Nausea/vomiting	35
Hepatosplenomegaly	35

Table 252.2 Clinical Syndromes of Tularemia in Children

CLINICAL SYNDROME	CHARACTERISTICS OF SYNDROME
Ulceroglandular	Skin ulcer/eschar at site of inoculation; painful regional adenopathy
Glandular	Painful regional adenopathy without detectable skin ulceration
Pneumonia	Nonproductive cough, dyspnea, pleuritic chest pain; multilobar/diffuse infiltrates > lobar infiltrates on chest radiography
Oropharyngeal	Pharyngitis, mucosal ulcers, cervical adenopathy
Oculoglandular	Unilateral, painful, and often purulent conjunctivitis; chemosis; conjunctival ulcers; preauricular adenopathy
Typhoidal	Severe systemic disease (sepsis-like syndrome): high fever, headaches, myalgias, arthralgias, neurologic symptoms

after skin ulceration in ulceroglandular disease. Cervical or posterior auricular nodes are involved after bites on the head or neck, whereas enlarged axillary or epitrochlear nodes signal exposure on the arms. Nodes may vary in size from 0.5 to 10 cm and appear singly or in clusters. These affected nodes may become fluctuant and drain spontaneously and are often associated with overlying skin changes. Late suppuration of the involved nodes has been described in 25–30% of patients despite effective therapy. Examination of this material from such lymph nodes usually reveals sterile necrotic material. Mortality with these forms of tularemia is rare, especially with implementation of effective treatment.

Oropharyngeal tularemia results from consumption of poorly cooked meats or contaminated water. This syndrome is characterized by acute pharyngitis, with or without tonsillitis, and cervical lymphadenitis. Infected tonsils may become large and develop a yellowish-white membrane that may resemble the membranes associated with diphtheria. GI disease may also occur and usually presents with mild, unexplained diarrhea or emesis but may progress to rapidly fulminant and fatal disease. GI bleeding can develop in more severe forms associated with intestinal ulcers.

Oculoglandular disease is uncommon, but when it does occur, the portal of entry is the conjunctiva. Contact with contaminated fingers or debris is the most common mechanism of this form of tularemia. Disease is generally unilateral. The conjunctiva is painful and inflamed with yellowish nodules and pinpoint ulcerations. Purulent conjunctivitis with ipsilateral preauricular or submandibular lymphadenopathy can develop and is referred to as **Parinaud oculoglandular syndrome**, although this term is not specific to tularemia. Corneal ulceration and perforation are uncommon but serious complications of this form of disease.

The **typhoidal** form is usually associated with a large inoculum of organisms and is a term used to describe nonlocalizing disease, regardless of the mode of transmission or portal of entry. Patients are often critically ill and bacteremic, and symptoms mimic those with other forms of sepsis: high fevers, confusion, rigors, myalgias, vomiting, and diarrhea. Clinicians practicing in tularemia-endemic regions must always consider this diagnosis in critically ill children. Complications of bacteremia with *F. tularensis* can include the development of meningitis, pericarditis, hepatitis, peritonitis, endocarditis, skin/soft tissue abscesses, and osteomyelitis. Because of its increased virulence, *F. tularensis* subsp. *tularensis* (type A disease) is more often associated with typhoidal tularemia. Patients with tularemia meningitis usually develop a marked cerebrospinal fluid (CSF) pleocytosis with a monocytic predominance. As with other causes of bacterial meningitis, CSF glucose is low and protein is high.

Pneumonia caused by *F. tularensis* **(pneumonic form)** can develop after inhalation (primary pulmonary infection) or secondary to hematogenous spread. Inhalation-related infection has been described in laboratory workers who are working with the organism and results in a relatively high mortality rate. Aerosols from farming activities involving rodent contamination (haying, threshing) or animal carcass destruction with lawn mowers have been reported to cause pneumonia as well. Patients generally complain of a nonproductive cough, dyspnea, or pleuritic chest pain. Chest radiographs of patients with pneumonic tularemia most often reveal diffuse, patchy infiltrates rather than focal areas of consolidation. Pleural effusions can also be present. In pulmonary infections, hilar or mediastinal adenopathy can develop, and in severe forms, necrotizing or hemorrhagic pneumonitis can occur. Mortality with pneumonic tularemia is high if untreated.

DIAGNOSIS

The diagnosis can be delayed because symptoms are often similar to other, more common infections. The history and physical examination of the patient may suggest the diagnosis, especially if the patient has a history of animal or tick exposure. Routine hematologic blood tests are nondiagnostic. **Definitive diagnosis is made by growth of *F. tularensis* in culture.** *F. tularensis* can be isolated in culture of lymph node biopsies or aspirates, blood, wounds, pharyngeal swabs, pleural fluid, or sputum specimens, although cultures are positive in only approximately 10% of cases. The organism can be identified on culture from skin lesions and lymph nodes for as long as a month after onset of disease. Polymerase chain reaction of tissue specimens may be more sensitive than culture but is currently used to make a presumptive diagnosis only.

F. tularensis can be cultured in the microbiology laboratory on cysteine–glucose–blood agar, but care should be taken to alert the personnel in the laboratory if this is attempted so that they can take the proper precautions to protect themselves from acquiring infection; biosafety level 3 containment is necessary to avoid occupational exposure. Histopathologic findings of involved lymph nodes demonstrate granulomas with central necrosis (early) and caseation (late). Unfortunately, these findings cannot distinguish tularemia from other causes of granulomatous lymphadenitis, such as tuberculosis, cat-scratch disease (*Bartonella henselae* infection), or sarcoidosis.

The diagnosis of tularemia is most often established via serology. In the standard tube agglutination (TA) test, a single titer of ≥1:160 in a patient with a compatible history and physical findings can establish the diagnosis. A microagglutination (MA) test is also available, and ≥1:128 is considered positive. Patients often do not produce detectable antibodies until the second week of illness, so negative testing in the acute phase does not rule out infection. A fourfold increase in titer from paired serum samples collected >2 weeks apart (i.e., acute and convalescent titers) can also be considered diagnostic. False-negative serologic responses can be obtained early in the infection or if paired sera are collected too close together. False-positive serologic tests can also result from cross-reactivity with other gram-negative organisms, such as *Brucella* or *Legionella* species, particularly at low titers. Once infected, patients may have a positive agglutination test result (1:20-1:80) that persists for life. Other testing techniques available include enzyme-linked immunosorbent assay (ELISA), analysis of urine for tularemia antigen, indirect immunofluorescent assay, and immunohistochemical staining; these studies have less well-established roles in the diagnosis of tularemia.

Differential Diagnosis

The differential diagnosis of **ulceroglandular** or **glandular** tularemia is broad and includes infection with pathogens that cause acute or subacute lymphadenitis: cat-scratch disease *(B. henselae)*, infectious mononucleosis, typical bacterial pathogens (*Staphylococcus aureus,* group A streptococcus), *Mycobacterium tuberculosis,* nontuberculous mycobacteria, *Toxoplasma gondii, Sporothrix schenckii,* plague *(Yersinia pestis)*, anthrax *(Bacillus anthracis)*, melioidosis *(Burkholderia pseudomallei)*, and rat-bite fever *(Streptobacillus moniliformis, Spirillum minus)*. Noninfectious processes such as sarcoidosis and Kawasaki disease can also present similarly. **Oculoglandular** disease may also occur with other infectious agents, such as *B. henselae, Treponema pallidum, Coccidioides immitis,* herpes simplex virus (HSV), adenoviruses, and the bacterial agents responsible for purulent conjunctivitis. **Oropharyngeal** tularemia must be differentiated from the same diseases that cause ulceroglandular/glandular disease and from cytomegalovirus, HSV, adenovirus, and other viral or bacterial etiologies. **Pneumonic** tularemia must be differentiated from the other atypical pathogens that cause community-acquired pneumonia, such as *Mycoplasma* and *Chlamydophila,* as well as mycobacteria, fungi, and rickettsiae. Inhalation plague, anthrax, and Q fever could also present similarly. **Typhoidal** tularemia must be differentiated from other forms of sepsis and from enteric fever (typhoid and paratyphoid fever) and brucellosis.

TREATMENT

Aminoglycosides are the mainstay of treatment of tularemia: **gentamicin is the drug of choice for the treatment of tularemia in children**, and streptomycin is the drug of choice in adults. Table 252.3 displays therapeutic options for treatment of tularemia and for postexposure prophylaxis. **Ciprofloxacin is often used for mild (localized) cases**, especially those caused by subsp. *holarctica,* but is less commonly prescribed in children. Doxycycline has been used successfully, but the relapse rate is higher than with aminoglycosides, and so it is not generally recommended. Ciprofloxacin and doxycycline are often used as adjunctive therapy for treatment of tularemia meningitis because of the poor penetration of aminoglycosides in the CSF. Ciprofloxacin can also be considered in cases of moderate/severe disease after initial treatment with an aminoglycoside, if an IV-to-PO switch is warranted based on clinical improvement. β-lactam agents demonstrate poor activity against *F. tularensis* and should not be used.

Therapy with aminoglycosides is typically continued for 7-10 days, but a longer course is needed in more severe disease; 5-7 days may be sufficient for mild cases. Ciprofloxacin treatment is typically 10-14 days, although there is no FDA-approved regimen for tularemia specifically. Treatment with doxycycline should be continued for 14-21 days because of an increased risk of relapse, likely because of its bacteriostatic nature.

PROGNOSIS

Poor outcomes are associated with a delay in appropriate treatment, but with rapid recognition and treatment, fatalities are exceedingly rare. The mortality rate for severe untreated disease (e.g., pneumonia, typhoidal disease) can be as high as 30%. Otherwise, the overall mortality rate is <1%. Subspecies *tularensis* is associated with more aggressive disease and worse outcomes than subsp. *holarctica*.

Relapses are uncommon if aminoglycoside therapy is used. Patients typically defervesce within 24-48 hours after starting therapy, although lymphadenopathy can take several weeks to resolve fully. Late suppuration of involved lymph nodes may occur despite adequate therapy. Patients who have not started on appropriate therapy early may respond more slowly to antimicrobial therapy.

PREVENTION

Prevention of tularemia is based on avoiding exposure. Children living in tick-endemic regions should be taught to avoid tick-infested areas. Families should have a tick control plan for their immediate environment and for their pets. Protective clothing should be worn when entering a tick-infested area. Insect repellents can be used safely

Table 252.3 Recommended Treatment for Children with Tularemia

INDICATION	DRUG AND DOSAGE	DURATION
Moderate-severe disease	Gentamicin 5-7.5 mg/kg/day IV or IM divided every 8-12 hr* *or* Streptomycin 30-40 mg/kg/day IM divided every 12 hr (max 1 g/dose)	≥10 days
Mild disease	Gentamicin 5-7.5 mg/kg/day IV or IM divided every 8-12 hr* *or* Ciprofloxacin 20-40 mg/kg/day PO divided every 12 hr (max 500 mg/dose)	5-7 days 10-14 days
Meningitis	Streptomycin or gentamicin (in doses given for moderate-severe disease) *PLUS* Ciprofloxacin (20-40 mg/kg/day IV divided every 12 hr) *or* Doxycycline 4.4 mg/kg/day IV divided every 12 hr (max 100 mg/dose)	≥10 days
Postexposure prophylaxis	Doxycycline 4.4 mg/kg/day PO divided twice daily (max 100 mg/dose) *or* Ciprofloxacin 20-40 mg/kg/day PO divided twice daily (max 500 mg/dose)	14 days

*Once-daily dosing of gentamicin could be considered, although it has not specifically been studied for this indication.
IM, Intramuscularly; IV, intravenously; PO, per os (i.e., by mouth).

in infants and children. Children should undergo frequent tick checks during and after their time in tick-infested areas. If ticks are found on the child, forceps should be used to pull the tick straight out. The skin should be cleansed before and after this procedure. Children should also be taught to avoid sick and dead animals. Children should be encouraged to wear gloves, masks, and eye protection while cleaning wild game. Further, families should cook wild game thoroughly before eating.

Prophylactic antimicrobial agents are generally not effective in preventing tularemia and should not be used after exposure, with the exception of laboratory or bioterrorism exposures. No tularemia vaccine is currently available to the general public (one is available for high-risk laboratory workers through the Department of Defense). Standard precautions are adequate for hospitalized children with tularemia because no cases of person-to-person transmission have been identified.

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Chapter 253

Brucella

Kevin J. Downes

Human **brucellosis** is caused by organisms of the genus *Brucella* and continues to be a major public health problem worldwide. Humans are accidental hosts and acquire this **zoonosis** from direct contact with an infected animal (cattle, sheep, camels, goats, and swine) or consumption of products of an infected animal. Although brucellosis is widely recognized as an occupational risk among adults working with livestock, much of the brucellosis in children is food-borne and is associated with consumption of unpasteurized dairy products. *Brucella* spp. are also potential agents of bioterrorism (see Chapter 763).

ETIOLOGY

Brucella abortus (cattle), *Brucella melitensis* (goats and sheep), *Brucella suis* (swine), and *Brucella canis* (dogs) are the most common organisms responsible for human disease. These organisms are small, aerobic, non–spore-forming, nonmotile, gram-negative coccobacillary bacteria. *Brucella* spp. are fastidious in their growth but can be grown on various laboratory media, including blood and chocolate agars.

EPIDEMIOLOGY

Brucellosis is endemic in many parts of the world and is especially prevalent in the Mediterranean basin, Persian Gulf, Indian subcontinent, and parts of Mexico and Central and South America. There are approximately 500,000 new cases annually worldwide, although accurate estimates of the prevalence of disease are lacking because of underreporting and underdiagnosis. Childhood brucellosis accounts for 10–30% of cases.

B. melitensis is the most prevalent species causing human brucellosis and is most often carried by sheep, goats, camels, and buffalo. Elk, caribou, bison, deer, moose, and swine can also be infected. Because of improved sanitation and animal vaccination, brucellosis has become rarer in countries with effective public health and domestic animal health programs, although recreational or occupational exposures continue to occur. **Consumption of raw or unpasteurized dairy products** in a child who has lived in or traveled to an endemic area is the key risk factor for pediatric brucellosis because most childhood cases are acquired via ingestion. In the United States in 2010, >50% of cases occurred in California, Arizona, Florida, and Texas. All age-groups can be infected by *Brucella,* and infections are more common in males, likely because of more frequent occupational and recreational exposures.

B. abortus cattle vaccine strain RB51 is a live, attenuated vaccine that has been used to vaccinate cattle in the United States since 1996. Very rare cases of human infection with this vaccine strain have been reported secondary to consumption of unpasteurized milk from vaccinated cows. These strains are resistant to rifampin, a primary agent used in the treatment of brucellosis, so clinicians should consider RB51 in a patient with the correct exposure history.

PATHOGENESIS

Modes of transmission for these organisms include inoculation through cuts or abrasions in the skin, inoculation of the conjunctiva, inhalation of infectious aerosols, or ingestion of contaminated meat or dairy products. **Infected livestock are the most common source of human infection.** In children the primary means of infection is through eating or drinking unpasteurized or raw dairy products. Individuals in endemic areas with occupational exposures to animals, such as farmers, veterinarians, and slaughterhouse workers, are at highest risk; exposure to an infected animal's abortion products or feces are notable risk factors in such occupations. Laboratory workers are more often exposed to infected aerosols. The risk for infection depends on the nutritional and immune status of the host, the route of inoculation, and the species of *Brucella.* For reasons that remain unclear, it has been suggested that *B. melitensis* and *B. suis* are more virulent than *B. abortus* or *B. canis.*

The major virulence factor for *Brucella* spp. appears to be its cell wall lipopolysaccharide (LPS). Strains containing smooth LPS have been demonstrated to have greater virulence and are more resistant to killing by polymorphonuclear leukocytes. These organisms are facultative intracellular pathogens that can survive and replicate within the mononuclear phagocytic cells (monocytes, macrophages) of the reticuloendothelial system. Even though *Brucella* spp. are chemotactic for entry of leukocytes into the body, the leukocytes are less efficient at killing these organisms than other bacteria despite the assistance of serum factors such as complement. *Brucella* spp. possess multiple strategies to evade immune responses and establish and maintain chronic infection. Specifically, during chronic stages of infection, organisms persist within the liver, spleen, lymph nodes, and bone marrow and result in granuloma formation.

Antibodies are produced against the LPS and other cell wall antigens, providing a means of diagnosis and likely playing a role in long-term immunity. The major factor in recovery from infection appears to be development of a cell-mediated immune response, resulting in macrophage activation and enhanced intracellular killing. Specifically, sensitized T lymphocytes release cytokines (e.g., interferon-γ, tumor necrosis factor-α), which activate the macrophages and enhance their intracellular killing capacity.

CLINICAL MANIFESTATIONS

Brucellosis is a systemic illness that can be quite difficult to diagnose in children. Symptoms can be acute or insidious in nature and are usually nonspecific. The incubation period is generally 2-4 weeks but may be shorter with *B. melitensis*. Fever is present in >75% of cases, and the fever pattern can vary widely. The most common physical complaints are arthralgia, myalgia, and back pain. Systemic symptoms, such as fatigue, sweats, chills, anorexia, headache, weight loss, and malaise, are reported in the majority of adult cases but are less frequent in children. Other associated symptoms include abdominal pain, diarrhea, rash, vomiting, cough, and pharyngitis.

The most common physical manifestation of brucellosis is hepatic and splenic enlargement, which is present in approximately half of cases. Whereas arthralgia is common, arthritis occurs in a minority of cases. Arthritis is typically monoarticular and most

often involves the knee or hip in children and the sacroiliac joint in adolescents and adults. Several types of skin lesions have been described with brucellosis, but there is no typical rash for this infection. Epididymo-orchitis also can occur and is more common in adolescents and adults.

In endemic countries, *Brucella* spp. are an important cause of occult bacteremia in young children. Because of the organism's ability to establish chronic infection, hepatic and splenic abscesses may develop. High-grade fever and elevations in liver enzymes are common among children with primary bacteremia. Children with positive blood cultures typically have more acute presentations with increased markers of inflammation (leukocyte count, CRP, ferritin) compared with culture-negative cases. Recurrent episodes of bacteremia can also occur (<10% of cases), especially with inadequate primary treatment. These recurrent episodes are less often associated with fever (40% of cases), potentially indicating the indolent nature of chronic *Brucella* infections in children.

Serious manifestations of brucellosis include endocarditis, meningitis, osteomyelitis, and **spondylitis**. Although headache and malaise may be demonstrated in patients with uncomplicated brucellosis, invasion of the nervous system occurs in only 1–4% of cases. Death from brucellosis is rare, occurring in less than 1% of cases. Neonatal and congenital infections with these organisms have also been described, resulting from transplacental transmission, breast milk, and blood transfusions. The signs and symptoms associated with congenital/neonatal brucellosis are nonspecific.

Hematologic abnormalities are common with brucellosis but occur in less than half of cases; leukopenia is the most common cytopenia to develop. Hemolytic complications can include microangiopathic hemolytic anemia, thrombotic microangiopathy, and autoimmune hemolytic anemia. Secondary cases of hemophagocytic lymphohistiocytosis have also been described after brucellosis in children. Elevations of liver enzymes occur in approximately half of all cases of brucellosis and are more common when bacteremia is present.

DIAGNOSIS

A definitive diagnosis of brucellosis is established by isolating and identifying the organisms from cultures of the blood (most common), bone marrow, or other fluids and tissues. Unfortunately, cultures are insensitive and positive in only a minority of pediatric cases. In a study of 436 children with brucellosis in Israel from 2005 to 2014, 76% had positive blood cultures. However, the prevalence of bacteremia in this cohort, 64% of whom were hospitalized, was much higher than most prior reports, in which less than half of cases have had positive blood cultures. Isolation of the organism from a blood culture sample may require as long as 4 weeks unless the laboratory is using an automated culture system such as the lysis-centrifugation method, where the organism can be recovered in 5-7 days. Therefore it is prudent to alert the clinical microbiology laboratory that brucellosis is suspected, so that cultures can be held longer. Bone marrow cultures may be superior to blood cultures when evaluating patients who have received previous antimicrobial therapy.

In addition to bacterial isolation, various serologic tests have been applied to the diagnosis of brucellosis. Microagglutination or serum (tube) agglutination tests are the most widely used and detect antibodies against *B. abortus, B. melitensis,* and *B. suis*. These methods do not detect antibodies against *B. canis* or *B. abortus* vaccine strain RB51, which lack the smooth LPS; *B. canis*–specific antigen is required to diagnose this species. Antibodies can also be detected by other tests such as enzyme-linked immunosorbent assay (ELISA). The Rose Bengal plate test (RBT) is a rapid agglutination test that is used as a screening test in many endemic regions. It has good sensitivity (>95%) and low cost, but confirmation of RBT results with microbiologic or other serologic tests is advised.

For a diagnosis to be made via serology alone, acute and convalescent samples taken 2-4 weeks apart are recommended; a fourfold or greater rise in titers is diagnostic of an acute infection. No single titer is ever diagnostic, but most patients with acute infections have titers of ≥1:160; lower titers may be present early in the disease course. Immunoglobulin M (IgM) antibodies can generally be detected within a week of illness onset, whereas IgG is detectable 2-4 weeks after infection.

Because patients with active infection have both an IgM and an IgG response and the serum agglutination test measures the total quantity of agglutinating antibodies, the total quantity of IgG is measured by treatment of the serum with 2-mercaptoethanol. This fractionation is important in determining the significance of the antibody titer because low levels of IgM can remain in the serum for weeks to months after the infection has been treated. IgG titers decrease with effective therapy, and a negative 2-mercaptoethanol test after treatment indicates a favorable response.

It is important to remember that all serologic results must be interpreted in light of a patient's history and physical examination. False-positive results from cross-reacting antibodies to other gram-negative organisms, such as *Yersinia enterocolitica, Francisella tularensis,* and *Vibrio cholerae,* can occur. In addition, the prozone effect can give false-negative results in the presence of high titers of antibody. To avoid this issue, serum that is being tested should be diluted to ≥1:320.

The enzyme immunoassay should only be used for suspected cases with negative serum agglutination tests or for the evaluation of patients in the following situations: (1) complicated cases, (2) suspected chronic brucellosis, or (3) reinfection. Polymerase chain reaction assays have been developed but are not available in most clinical laboratories.

Differential Diagnosis

Brucellosis should be considered in the differential diagnosis of fever of unknown origin in endemic areas. It may present similar to other infections such as tularemia, cat scratch disease, malaria, typhoid fever, histoplasmosis, blastomycosis, and coccidioidomycosis. Infections caused by *Mycobacterium tuberculosis,* atypical mycobacteria, rickettsiae, and *Yersinia* can also present similar to brucellosis.

TREATMENT

Many antimicrobial agents are active in vitro against *Brucella* spp., but clinical effectiveness does not always correlate with these results. Agents that provide good intracellular killing are required for elimination of *Brucella* infections. Because of the risk of relapse with monotherapy, combination therapy is generally recommended. Additionally, prolonged therapy (6 weeks or longer) is necessary to ensure an adequate and sustained response.

For uncomplicated infections in children 8 years of age or older, ≥6 weeks of doxycycline in combination with rifampin is recommended (Table 253.1). For children younger than age 8 years, trimethoprim-sulfamethoxazole (TMP-SMX) plus rifampin is advised because of concerns about prolonged tetracycline use in young children. Although data support that the combination of doxycycline plus an aminoglycoside (streptomycin, gentamicin) is superior to the other oral combination therapies, with fewer treatment failures and relapses, the inconvenience of parenteral therapy may limit this approach in uncomplicated cases, particularly in resource-limited settings. Fluoroquinolones may be a viable alternative to doxycycline or TMP-SMX but have not been studied in children.

In more serious infections (e.g., endocarditis, meningitis, osteoarticular infections), three-drug therapy is advised. An aminoglycoside (streptomycin, gentamicin) should be administered for the first 7-14

Table 253.1 Recommended Therapy for Treatment of Brucellosis

AGE/CONDITION	TREATMENT REGIMEN	DURATION
≥8 yr, uncomplicated infection	Doxycycline (PO; 4.4 mg/kg/day, max 200 mg/day) in 2 divided doses	≥6 wk
	plus	
	Rifampin (PO; 15-20 mg/kg/day, max 600-900 mg/day) in 1-2 divided doses	≥6 wk
	Alternative:	
	Doxycycline (PO; 4.4 mg/kg/day, max 200 mg/day) in 2 divided doses	≥6 wk
	plus	
	Streptomycin (IM/IV; 20-40 mg/kg/day, max 1 g/day) in 2-4 divided doses	2-3 wk
	or	
	Gentamicin (IM/IV; 5-7.5 mg/kg/day) once daily*	1-2 wk
<8 yr, uncomplicated infection	Trimethoprim-sulfamethoxazole (PO; trimethoprim: 10 mg/kg/day, max 480 mg/day; sulfamethoxazole: 50 mg/kg/day, max 2.4 g/day) in 2 divided doses	≥6 wk
	plus	
	Rifampin (PO; 15-20 mg/kg/day, max 600-900 mg/day) in 1-2 divided doses	≥6 wk
Complicated infection (meningitis, endocarditis, osteomyelitis, spondylitis)	Streptomycin (IM/IV; 20-40 mg/kg/day, max 1 g/day) in 2-4 divided doses	1-2 wk
	or	
	Gentamicin (IM/IV; 5-7.5 mg/kg/day) once daily*	1-2 wk
	plus	
	Doxycycline (IV/PO; 4.4 mg/kg/day, max 200 mg/day) in 2 divided doses	≥6 wk†
	(Trimethoprim-sulfamethoxazole should be used for children <8 yr of age)	
	plus	
	Rifampin (IV/PO; 15-20 mg/kg/day, max 600-900 mg/day) in 1-2 divided doses	≥6 wk†

*Gentamicin can be given in divided doses if indicated based on age.
†4-6 mo for meningitis or endocarditis.
Note: Because of resistance of *B. abortus* strain RB51 to rifampin, treatment with doxycycline plus trimethoprim-sulfamethoxazole should be used if this isolate is identified.

days of therapy, along with doxycycline (or TMP-SMX) plus rifampin, which are continued for at least 6 weeks. For meningitis and endocarditis, therapy is often continued for 4-6 months. Surgical intervention should be pursued when appropriate, such as when deep tissue abscesses have developed.

If *B. abortus* RB51 (cattle vaccine strain) is identified (or suspected) as the cause of infection, the use of rifampin should be avoided. This is because the strain was derived by selection in rifampin-enriched media and is thus inherently resistant to rifampin. As a result, a combination of doxycycline and TMP-SMX should be used as treatment.

Although relapse occurs in approximately 5–15% of cases, antimicrobial resistance is rare. Relapse is confirmed by isolation of *Brucella* within weeks to months after therapy has ended. Prolonged treatment is the key to preventing disease relapse, and steps should be taken to assure compliance with the long courses of therapy needed to achieve eradication.

PROGNOSIS

The primary indication of clinical response is resolution of symptoms, which may be slow; the average time to defervescence is 4-5 days. The prognosis after therapy is excellent if patients are compliant with the prolonged therapy. Patients should be followed clinically and serologically for 1-2 years. Before the use of antimicrobial agents, the course of brucellosis was often prolonged and associated with death. Since the institution of specific therapy, most deaths are a result of specific organ system involvement (e.g., endocarditis) in complicated cases. Initiation of antimicrobial therapy may precipitate a Jarisch-Herxheimer–like reaction, presumably because of a large antigen load, but these reactions are rarely associated with serious complications.

PREVENTION

Prevention of brucellosis depends on effective eradication of the organism from livestock. Pasteurization of milk and dairy products for human consumption remains an important aspect of prevention. It should be noted that certification of raw milk does not eliminate the risk of brucellosis acquisition. No vaccine currently exists for use in children, and therefore education of the public continues to have a prominent role in the prevention of brucellosis.

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Chapter 254

Legionella

Jeffrey S. Gerber

Legionellosis comprises **Legionnaires' disease** (*Legionella* pneumonia), other invasive extrapulmonary *Legionella* infections, and an acute flulike illness known as **Pontiac fever**. In contrast to the syndromes associated with invasive disease, Pontiac fever is a self-limited illness that develops after aerosol exposure and may represent a toxic or hypersensitivity response to *Legionella.*

ETIOLOGY

Legionellaceae are aerobic, non–spore-forming, nonencapsulated, gram-negative bacilli that stain poorly with Gram stain when performed on smears from clinical specimens. Stained smears of *Legionella pneumophila* taken from colonial growth resemble *Pseudomonas.* Unlike other *Legionella* species, *Legionella micdadei* stains acid fast. Although more than 60 species of the genus have now been identified, the majority (90%) of clinical infections are caused by *L. pneumophila,* and most of the remainder are caused by *L. micdadei, L. bozemanii, L. dumoffii,* and *L. longbeachae.*

The organisms are fastidious and require L-cysteine, ferric ion, and α-keto acids for growth. Colonies develop within 3-5 days on buffered charcoal yeast extract agar, which may contain selected antibiotics to inhibit overgrowth by other microorganisms; *Legionella* rarely grows on routine laboratory media.

EPIDEMIOLOGY

The environmental reservoir of *Legionella* in nature is freshwater (lakes, streams, thermally polluted waters, potable water), and invasive pneumonia (Legionnaires' disease) is related to exposure to human-made water systems (plumbing, showerheads, cooling towers, certain medical devices, decorative fountains, hot tubs) via aerosols containing the bacteria. Growth of *Legionella* occurs more readily in warm water, and exposure to warm-water sources is an important risk factor for disease. Epidemic and sporadic cases (most common) of community-acquired Legionnaires' disease can be attributed to potable water in the local environment of the patient. Risk factors for acquisition of sporadic community-acquired pneumonia include exposure to cooling towers, nonmunicipal water supply, residential plumbing repairs, and lower water heater temperatures, which facilitate growth of bacteria or lead to release of a bolus of biofilm containing *Legionella* into potable water. The mode of transmission may be by inhalation of aerosols or by microaspiration. Outbreaks of Legionnaires' disease have been associated with protozoa in the implicated water source; replication within these eukaryotic cells presumably amplifies and maintains *Legionella* within the potable-water distribution system or in cooling towers. Outbreaks of community-acquired pneumonia and some nosocomial outbreaks have been linked to common sources, including hot water heaters, evaporative condensers, cooling towers, whirlpool baths, water births, humidifiers, and nebulizers. Travel-associated Legionnaires' disease and Pontiac fever are increasingly recognized in major outbreaks. Although person-to-person transmission has been reported, if it does occur, it is extremely rare.

Hospital-acquired infections are most often linked to potable water. Exposure may occur through three general mechanisms: (1) inhalation of contaminated water vapor through artificial ventilation; (2) aspiration of ingested microorganisms, including those in gastric feedings that are mixed with contaminated tap water; and (3) inhalation of aerosols from showers, sinks, and fountains. Extrapulmonary legionellosis may occur through topical application of contaminated tap water into surgical or traumatic wounds. In contrast to Legionnaires' disease, Pontiac fever outbreaks have occurred through exposure to aerosols from whirlpool baths and ventilation systems.

The incidence of legionellosis in the United States continues to rise, and nearly 10,000 cases were reported to the Centers for Disease Control and Prevention (CDC) through the National Notifiable Disease Surveillance System in 2018. Because this is a passive reporting system, these are likely underestimates of the incidence of disease, which is estimated to occur at least twice as often as reported. An active laboratory-based and population-based surveillance system for tracking *Legionella* infections was recently launched by CDC, which will help to better assess its true incidence and epidemiology. (For up-to-date information, see https://www.cdc.gov/legionella/.)

Legionellosis demonstrates geographic differences, and the vast majority of cases are classified as Legionnaires' disease (99.5%), with a small fraction as Pontiac fever (0.5%). *Legionella* infections are reported most frequently in fall and summer, and recent studies show an association with total monthly rainfall and humidity. Approximately 0.5–5.0% of those exposed to a common source develop pneumonia, whereas the attack rate in Pontiac fever outbreaks is very high (85–100%). Although *Legionella* is associated with 0.5–10% of pneumonia cases in adults, it is a rare cause of pneumonia in children, accounting for <1% of cases; however, infrequent testing for *Legionella* might underestimate its prevalence. Acquisition of antibodies to *L. pneumophila* in healthy children occurs progressively over time, although these antibodies presumably reflect subclinical infection, mild respiratory disease, or antibodies that cross-react with other bacterial species. Community-acquired Legionnaires' disease in children is increasingly reported (1.7% of reported cases), and most cases occur in children 15-19 years old, followed by infants. The incidence in infants is reported to be 0.11 per 100,000. Legionnaires' disease is particularly severe in neonates. The epidemiology of hospital-acquired Legionnaires' disease in children is derived almost exclusively from case reports, so the true incidence of this entity is unknown.

PATHOGENESIS

Although *Legionella* can be grown on artificial media, the intracellular environment of eukaryotic cells provides the definitive site of growth. *Legionella* organisms are facultative intracellular parasites of eukaryotic cells. In nature, *Legionella* replicate within protozoa found in freshwater. In humans, the main target cell for *Legionella* is the alveolar macrophage, although other cell types may also be invaded. After entry, virulent strains of *L. pneumophila* stimulate the formation of a special phagosome that permits bacterial replication to proceed. The phagosome consists of components of the endoplasmic reticulum and escapes the degradative lysosomal pathway. Growth in macrophages occurs to the point of cell death, followed by reinfection of new cells, until these cells are activated and can subsequently kill intracellular microorganisms. Acute, severe infection of the lung provokes an acute inflammatory response and necrosis. Early on, more bacteria are found in extracellular spaces as a result of intracellular replication, lysis, and release of bacteria. Subsequently, macrophage activation and other immune responses produce intense infiltration of tissue by macrophages that contain intracellular bacteria, ultimately leading to control of bacterial replication and killing.

Corticosteroid therapy poses a high risk for infection by interfering with T-cell and macrophage function. Although community-acquired Legionnaires' disease may occur in healthy, immunocompetent patients without other comorbid conditions, those who have defects in cellular-mediated immunity are at higher risk for infection. As in other diseases caused by facultative intracellular microorganisms, the outcome is critically dependent on the specific and nonspecific immune responses of the host, particularly macrophage and T-cell responses.

Risk factors for Legionnaires' disease in adults include chronic diseases of the lung (smoking, bronchitis), older age, diabetes, renal failure, immunosuppression associated with organ transplantation, corticosteroid therapy, and episodes of aspiration. In surveys of community-acquired infection, a significant number of adults have no identified risk factors. The number of reported cases of community-acquired Legionnaires' disease in children is small. Among these cases, immunocompromised status, especially corticosteroid treatment, coupled with exposure to contaminated potable water, is the major risk factor.

Infection in a few children with chronic pulmonary disease without immune deficiency has also been reported, but infection in children lacking any risk factors is uncommon. The modes of transmission of community-acquired disease in children include exposure to mists, freshwater, water coolers, and other aerosol-generating apparatuses. Nosocomial *Legionella* infection has been reported more frequently than community-acquired disease in children and usually occurs in those who are immunocompromised (e.g., stem cell transplants, solid organ transplants), those with structural lung disease, or neonates receiving mechanical ventilation. The modes of acquisition include **microaspiration**, frequently associated with nasogastric tubes, and **aerosol inhalation**. Bronchopulmonary *Legionella* infections are reported in patients with cystic fibrosis and have been associated with aerosol therapy or mist tents. Legionnaire's disease is also reported in children with asthma and tracheal stenosis. Chronic corticosteroid therapy for asthma is a reported risk factor for *Legionella* infections in children.

CLINICAL MANIFESTATIONS

Legionnaires' disease was originally believed to cause atypical pneumonia associated with extrapulmonary symptoms and laboratory abnormalities, including diarrhea, confusion, hyponatremia, hypophosphatemia, abnormal liver function studies, and evidence of renal dysfunction. Although a subset of patients may exhibit these classic manifestations, *Legionella* infection typically causes pneumonia that is indistinguishable from pneumonia produced by other infectious agents. The incubation period for Legionnaires' disease is typically between 2 and 10 days, though it occasionally can be 3-4 weeks. Fever, cough, and chest pain are common presenting symptoms; the cough may be productive of purulent sputum or may be nonproductive. Although the classic chest radiographic appearance demonstrates rapidly progressive alveolar filling infiltrates, the chest radiographic appearance is widely variable, with tumor-like shadows, evidence of nodular infiltrates, unilateral or bilateral infiltrates, or cavitation, although cavitation is rarely seen in immunocompetent patients. This picture overlaps substantially with disease caused by *Streptococcus pneumoniae.* Although pleural effusion is less often associated with Legionnaires' disease, its frequency varies so widely that neither the presence nor absence of effusion is helpful in the differential diagnosis.

Most reports of nosocomial *Legionella* pneumonia in children demonstrate the following clinical features: rapid onset, temperature >38.5°C (101.3°F), cough, pleuritic chest pain, tachypnea, and dyspnea. Abdominal pain, headache, and diarrhea are also common. Chest radiographs reveal lobar consolidations or diffuse bilateral infiltrates, and pleural effusions may be noted. Usually there is no clinical response to broad-spectrum β-lactam (penicillins and cephalosporins) or aminoglycoside antibiotics. Concomitant infection with other pathogens, including *Mycoplasma pneumoniae* and *Chlamydia pneumoniae,* occurs in 5–10% of cases of Legionnaires' disease; therefore, detection of another potential pulmonary pathogen does not preclude the diagnosis of legionellosis.

Pontiac Fever

Pontiac fever in adults and children is characterized by a shorter incubation period (1-3 days) followed by high fever, myalgia, headache, and extreme debilitation, lasting for 3-5 days. Cough, breathlessness, diarrhea, confusion, and chest pain may occur, but there is no evidence for invasive infection. The disease is self-limited without sequelae. Virtually all exposed individuals seroconvert to *Legionella* antigens. A very large outbreak in Scotland that affected 35 children was attributed to *L. micdadei,* which was isolated from a whirlpool spa. The onset of illness was 1-7 days (median: 3 days), and all exposed children developed significant titers of specific antibodies to *L. micdadei.* The pathogenesis of Pontiac fever is not known. In the absence of evidence of true infection, the most likely hypothesis is that this syndrome is caused by a toxic or hypersensitivity reaction to microbial antigens.

DIAGNOSIS

Culture of *Legionella* from sputum, other respiratory tract specimens, blood, or tissue is the gold standard against which indirect methods of detection should be compared. If present, pleural fluid should be obtained for culture. Specimens obtained from the respiratory tract that are contaminated with oral flora must be treated and processed to reduce contaminants and plated onto selective media. Because these are costly and time-consuming methods, many laboratories do not process specimens for culture.

The urinary antigen assay that detects *L. pneumophila* serogroup I has revolutionized the diagnosis of *Legionella* infection and has 80% sensitivity and 99% specificity. The assay is a useful method in the prompt diagnosis of Legionnaires' disease caused by this serogroup, which accounts for the majority of symptomatic infections. In the United States, this test is frequently used because it is widely available in reference laboratories. Where available, polymerase chain reaction (PCR) is used to identify *L. pneumophila* from bronchoscopic lavage and other clinical specimens to the exclusion of other respiratory pathogens. Other methods, including direct immunofluorescence, have low sensitivity and are generally not employed. Serological testing is of little clinical utility, as seroconversion may not occur for several weeks after the onset of infection, the available serologic assays do not detect all strains of *L. pneumophila* or all species, and cross reactivity occurs with several other gram-negative organisms.

In view of the low sensitivity of direct detection and the slow growth of the microorganism in culture, multiple diagnostics (culture, urine antigen, PCR if available) should be sent simultaneously and empiric antibiotic therapy considered when there is suggestive clinical evidence, including the lack of response to usual antibiotics.

TREATMENT

In community-acquired pneumonia in adults who are hospitalized, guidelines recommend empiric treatment with a β-lactam plus a macrolide or quinolone for treatment of atypical microorganisms *(Legionella, C. pneumoniae, M. pneumoniae).* Evidence-based guidelines for management of community-acquired pneumonia in children typically do not include *Legionella* in the differential diagnosis or empiric treatment recommendations. Effective treatment of Legionnaires' disease is based in part on the intracellular concentration of antibiotics. **Azithromycin** or the **quinolones** (ciprofloxacin and levofloxacin) have generally replaced erythromycin as therapy for patients with diagnosed *Legionella* infection. **Doxycycline** is an acceptable alternative. In serious infections or in high-risk patients, parenteral therapy is recommended initially, although oral conversion is favored when tolerated, particularly because of the generally high bioavailability of oral macrolides, quinolones, and tetracyclines. The duration of antibiotic therapy for Legionnaires' disease in adults is typically for a minimum of 5 days, although therapy may be continued for 10-14 days in more seriously ill or immunocompromised patients. Treatment of extrapulmonary infections, including prosthetic valve endocarditis and sternal wound infections, may require prolonged therapy. In vitro data and case reports suggest that trimethoprim-sulfamethoxazole may also be effective. A large, retrospective study of hospitalized adults with *Legionella* pneumonia found no difference in mortality between those treated with azithromycin and with quinolones. The role of combination therapy is unknown. Antibiotic treatment for Pontiac fever is not recommended.

PROGNOSIS

The mortality rate for community-acquired Legionnaires' disease in adults who are hospitalized is approximately 15% but may exceed 50% in immunocompromised patients, although reporting bias might inflate these estimates. Precise estimates for children are unknown. The prognosis depends on underlying host factors and possibly on the duration of illness before initiation of appropriate therapy. Despite appropriate antibiotic therapy, patients may succumb to respiratory complications, such as acute respiratory distress syndrome. A high mortality rate is noted in case reports of premature infants and children, virtually all of whom have been immunocompromised. Delay in diagnosis is also associated with increased mortality. Consequently, *Legionella* should be considered in the differential diagnosis of both community-acquired and nosocomial pneumonia in children, especially in cases refractory to empirical therapy or with epidemiologic risk factors for legionellosis.

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Chapter 255

Bartonella

Rachel C. Orscheln

The spectrum of disease resulting from human infection with *Bartonella* species includes the association of **bacillary angiomatosis** and **cat scratch disease** with *Bartonella henselae.* There are more than 30 validated species of *Bartonella,* but six major species are responsible for most human disease: *B. henselae, B. quintana, B. bacilliformis, B. elizabethae, B. vinsonii,* and *B. clarridgeiae* (Table 255.1). The remaining *Bartonella* spp. have been found primarily in animals, particularly rodents and moles. However, zoonotic infections from animal-associated strains of *Bartonella* spp. have been reported. In 2013 a novel *Bartonella* agent with the proposed name *Candidatus* Bartonella ancashi *(Bartonella ancashensis)* was described as a cause of **verruga peruana**.

Members of the genus *Bartonella* are gram-negative, oxidase-negative, fastidious, aerobic rods that ferment no carbohydrates. *B. bacilliformis* is the only species that is motile, achieving motility by means of polar flagella. Optimal growth is obtained on fresh media containing ≥5% sheep or horse blood in the presence of 5% carbon dioxide. The use of lysis centrifugation for specimens from blood followed by cultivation on chocolate agar for extended periods (2-6 weeks) enhances recovery.

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255.1 Cat Scratch Disease *(Bartonella henselae)*

Rachel C. Orscheln

The most common presentation of *Bartonella* infection is cat scratch disease (**CSD**), which is a subacute, regional lymphadenitis caused most frequently by *B. henselae*. CSD is the most common cause of chronic lymphadenitis that persists for >3 weeks.

ETIOLOGY

B. henselae can be cultured from the blood of healthy cats. *B. henselae* organisms are the small, pleomorphic, gram-negative bacilli visualized with Warthin-Starry stain in affected lymph nodes from patients with CSD. Development of serologic tests that showed prevalence of antibodies in 84–100% of cases of CSD, culturing of *B. henselae* from CSD nodes, and detection of *B. henselae* by polymerase chain reaction (PCR) in the majority of lymph node samples and pus from patients with CSD confirmed the organism as the cause. Occasional cases of CSD may be caused by other organisms, including *B. clarridgeiae, B. grahamii*, *B. alsatica,* and *B. quintana*.

EPIDEMIOLOGY

CSD is common, with >24,000 estimated cases per year in the United States. *B. henselae* is transmitted most frequently by cutaneous inoculation through the bite or scratch of a cat. However, transmission may occur through other routes, such as flea bites. Most patients (87–99%) with CSD have had contact with cats, many of which are kittens <6 months old, and >50% of patients have a definite history of a cat scratch or bite. Cats have high-level bacteremia with *Bartonella* spp. for months without any clinical symptoms; kittens are more frequently bacteremic than adult cats. Transmission between cats occurs through the cat flea, *Ctenocephalides felis.* In temperate zones, most cases occur between September and March, perhaps in relation to the seasonal breeding of domestic cats or to the close proximity of family pets in the fall and winter. In tropical zones, there is no seasonal prevalence. Distribution is worldwide, and infection occurs in all races.

Cat scratches appear to be more common among children, and males are affected more often than females. CSD is a sporadic illness; usually only one family member is affected, even though many siblings play with the same kitten. However, clusters do occur, with family cases within weeks of one another. Anecdotal reports have implicated other sources, such as dog scratches, wood splinters, fishhooks, cactus spines, and porcupine quills.

PATHOGENESIS

The pathologic findings in the primary inoculation **papule** and affected lymph nodes are similar. Both show a central avascular, necrotic area with surrounding lymphocytes, giant cells, and histiocytes. Three stages of involvement occur in affected nodes, sometimes simultaneously in the same node. The first stage consists of generalized enlargement with thickening of the cortex and hypertrophy of the germinal center and with a predominance of lymphocytes. Epithelioid granulomas with Langerhans giant cells are scattered throughout the node. The second stage is characterized by granulomas that increase in density, fuse, and become infiltrated with polymorphonuclear leukocytes, with beginning central necrosis. In the third stage, necrosis progresses with formation of large, pus-filled sinuses. This purulent material may rupture into surrounding tissue. Similar granulomas have been found in the liver, spleen, and osteolytic lesions of bone when those organs are involved.

Table 255.1 *Bartonella* Species Causing the Majority of Human Disease

DISEASE	ORGANISM	VECTOR	PRIMARY RISK FACTOR
Bartonellosis (Carrión disease)	*B. bacilliformis*	Sandfly *(Lutzomyia verrucarum)*	Living in endemic areas (Andes Mountains)
Cat scratch disease	*B. henselae* *B. clarridgeiae*	Cat	Cat scratch or bite
Trench fever	*B. quintana*	Human body louse	Body louse infestation during outbreak
Bacteremia, endocarditis	*B. henselae* *B. elizabethae* *B. vinsonii* *B. quintana*	Cat for *B. henselae* Rat for *B. elizabethae* Vole for *B. vinsonii* Human body louse for *B. quintana*	Severe immunosuppression
Bacillary angiomatosis	*B. henselae* *B. quintana*	Cat for *B. henselae* Human body louse for *B. quintana*	Severe immunosuppression
Peliosis hepatis	*B. henselae* *B. quintana*	Cat for *B. henselae* Human body louse for *B. quintana*	Severe immunosuppression

CLINICAL MANIFESTATIONS

After an incubation period of 7-12 days (range: 3-30 days), one or more 3- to 5-mm red papules develop at the site of cutaneous inoculation, often reflecting a linear cat scratch. These lesions are often overlooked because of their small size but are found in at least 65% of patients when careful examination is performed (Fig. 255.1). Lymphadenopathy is generally evident within 1-4 weeks (Fig. 255.2). **Chronic regional lymphadenitis** is the hallmark, affecting the first or second set of nodes draining the entry site. Affected lymph nodes in order of frequency include the axillary, cervical, submandibular, preauricular, epitrochlear, femoral, and inguinal nodes. Involvement of one or more groups of nodes occurs in 10–20% of patients, although at a given site, half the cases involve several nodes.

Nodes involved are usually tender and have overlying erythema but without cellulitis. They usually range between 1 and 5 cm in size, although they can become much larger. From 10% to 40% eventually suppurate. The duration of enlargement is usually 1-2 months, with persistence up to 1 year in rare cases. Fever occurs in approximately 30% of patients, usually 38–39°C (100.4–102.2°F). Other nonspecific symptoms, including malaise, anorexia, fatigue, and headache, affect less than one third of patients. Transient rashes, which may occur in approximately 5% of patients, are mainly truncal maculopapular rashes. Erythema nodosum, erythema multiforme, and erythema annulare have also been reported.

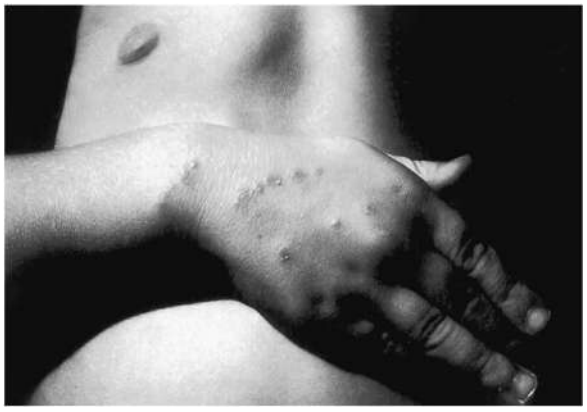

Fig. 255.1 A child with typical cat scratch disease demonstrating the original scratch injuries and the primary papule that soon thereafter developed proximal to the middle finger. *(Courtesy Dr. V.H. San Joaquin, University of Oklahoma Health Sciences Center, Oklahoma City.)*

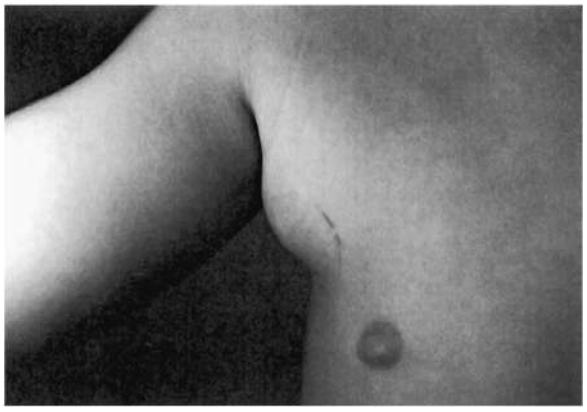

Fig. 255.2 Right axillary lymphadenopathy followed the scratches and development of a primary papule in this child with typical cat scratch disease. *(From Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases, 6th ed. Philadelphia: Elsevier; 2006:2737.)*

CSD is usually a self-limited infection that spontaneously resolves within a few weeks to months. The most common ocular presentation of CSD is **Parinaud oculoglandular syndrome**, which is unilateral conjunctivitis followed by preauricular lymphadenopathy and occurs in 5% of patients with CSD (Fig. 255.3). Direct eye inoculation as a result of rubbing with the hands after cat contact is the presumed mode of spread. A conjunctival granuloma may be found at the inoculation site. The involved eye is usually not painful and has little or no discharge but may be quite red and swollen. Submandibular or cervical lymphadenopathy may also occur.

More severe, disseminated illness occurs up to 14% of patients and is characterized by presentation with high fever, often persisting for several weeks. Other prominent symptoms include significant abdominal pain and weight loss. **Hepatosplenomegaly** may occur, although hepatic dysfunction is rare (Fig. 255.4). Granulomatous changes may be seen in the liver and spleen. Another common site of dissemination is bone, with the development of multifocal **granulomatous osteolytic lesions** associated with localized pain but without erythema,

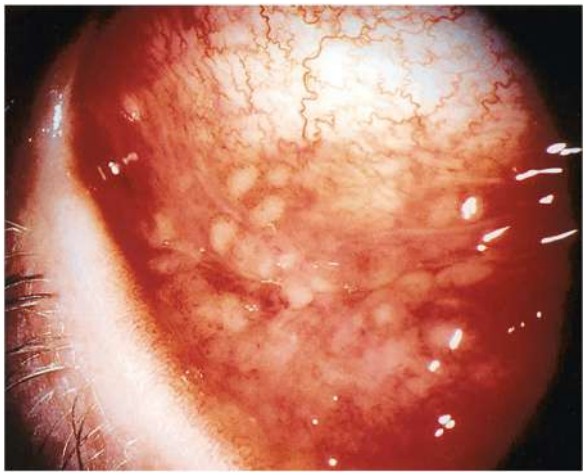

Fig. 255.3 The granulomatous conjunctivitis of Parinaud oculoglandular syndrome is associated with ipsilateral local lymphadenopathy, usually preauricular and, less often, submandibular. *(From Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases, 6th ed. Philadelphia: Elsevier; 2006:2739.)*

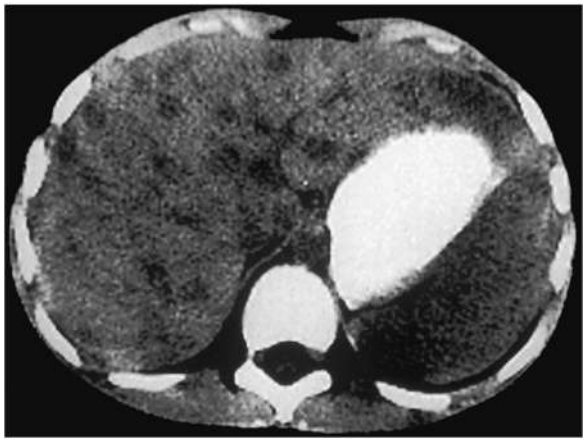

Fig. 255.4 In this CT scan of a patient with hepatic involvement of cat scratch disease, the absence of enhancement of the multiple lesions after contrast infusion is consistent with the granulomatous inflammation of this entity. Treated empirically with various antibiotics without improvement before establishment of this diagnosis, the patient subsequently recovered fully with no further antimicrobial therapy. *(Courtesy Dr. V.H. San Joaquin, University of Oklahoma Health Sciences Center, Oklahoma City.)*

tenderness, or swelling. Other uncommon manifestations are neuroretinitis with papilledema and stellate macular exudates, encephalitis, endocarditis, and atypical pneumonia.

DIAGNOSIS

In most cases the diagnosis can be strongly suspected on clinical grounds in a patient with history of exposure to a cat. Serologic testing can be used to confirm the diagnosis. Most patients have elevated IgG antibody titers at presentation. However, the IgM response to *B. henselae* has frequently resolved by the time testing is considered. There is cross reactivity among *Bartonella* spp., particularly *B. henselae* and *B. quintana*.

If tissue specimens are obtained, bacilli may be visualized with Warthin-Starry and Brown-Hopps tissue stains. *Bartonella* DNA can be identified through PCR analysis of tissue specimens. Culturing of the organism is not generally practical for clinical diagnosis. Next-generation sequencing and 16S rRNA sequencing have been used to identify *Bartonella* species on tissue that is fresh or formalin-fixed, as well as on body fluids other than blood.

Differential Diagnosis

The differential diagnosis of CSD includes virtually all causes of lymphadenopathy (see Chapter 539). The more common entities include pyogenic (suppurative) lymphadenitis, primarily from staphylococcal or streptococcal infections, atypical mycobacterial infections, and malignancy. Less common entities are tularemia, brucellosis, and sporotrichosis. Epstein-Barr virus, cytomegalovirus, and *Toxoplasma gondii* infections usually cause more generalized lymphadenopathy.

LABORATORY FINDINGS

Routine laboratory tests are not helpful. The erythrocyte sedimentation rate is often elevated. The white blood cell count may be normal or mildly elevated. Hepatic transaminases are often normal but may be elevated in systemic disease. Ultrasonography or CT may reveal many granulomatous nodules in the liver and spleen; the nodules appear as hypodense, round, irregular lesions and are usually multiple. However, CSD presenting as a solitary splenic lesion has been reported.

TREATMENT

Antibiotic treatment of CSD is not always needed and is not clearly beneficial. For most patients, treatment consists of conservative symptomatic care and observation. Studies show a significant discordance between in vitro activity of antibiotics and clinical effectiveness. For many patients, diagnosis is considered in the context of failure to respond to β-lactam antibiotic treatment of presumed staphylococcal lymphadenitis.

A small prospective study of oral azithromycin (500 mg on day 1, then 250 mg on days 2-5; for smaller children, 10 mg/kg/24 hr on day 1 and 5 mg/kg/24 hr on days 2-5) showed a decrease in initial lymph node volume in 50% of patients during the first 30 days, but after 30 days there was no difference in lymph node volume. No other clinical benefit was found. For the majority of patients, CSD is self-limited, and resolution occurs over weeks to months without antibiotic treatment. Azithromycin, clarithromycin, trimethoprim-sulfamethoxazole (TMP-SMX), rifampin, ciprofloxacin, and gentamicin appear to be the best agents if treatment is considered.

Suppurative lymph nodes that become tense and extremely painful may require surgical drainage for both therapeutic and diagnostic purposes.

Children with hepatosplenic CSD appear to respond well to treatment with azithromycin with or without the addition of rifampin.

COMPLICATIONS

Encephalopathy can occur in as many as 5% of patients with CSD and typically manifests 1-3 week after the onset of lymphadenitis as the sudden onset of neurologic symptoms, which often include seizures, combative or bizarre behavior, and altered level of consciousness. Imaging studies are generally normal. The cerebrospinal fluid is normal or shows minimal pleocytosis and protein elevation. Recovery occurs without sequelae in almost all patients but may take place slowly over many months.

Other neurologic manifestations include peripheral facial nerve paralysis, myelitis, radiculitis, compression neuropathy, and cerebellar ataxia. One patient has been reported to have encephalopathy with persistent cognitive impairment and memory loss.

Stellate macular retinopathy is associated with several infections, including CSD. Children and young adults present with unilateral or, rarely, bilateral loss of vision with central scotoma, optic disc swelling, and macular star formation from exudates radiating out from the macula. The findings usually resolve completely, with recovery of vision, generally within 2-3 months. The optimal treatment for the neuroretinitis is unknown, although treatment of adults with doxycycline and rifampin for 4-6 weeks has had good results.

Hematologic manifestations include hemolytic anemia, thrombocytopenic purpura, nonthrombocytopenic purpura, and eosinophilia. **Leukocytoclastic vasculitis**, similar to Henoch-Schönlein purpura, has been reported in association with CSD in one child. A systemic presentation of CSD with pleurisy, arthralgia or arthritis, mediastinal masses, enlarged nodes at the head of the pancreas, and atypical pneumonia also has been reported.

PROGNOSIS

The prognosis for CSD in a normal host is generally excellent, with resolution of clinical findings over weeks to months. Recovery is occasionally slower and may take as long as 1 year.

PREVENTION

Person-to-person spread of *Bartonella* infections is not known. Isolation of the affected patient is not necessary. Prevention would require elimination of cats from households, which is not practical or necessarily desirable. Awareness of the risk of cat (and particularly kitten) scratches should be emphasized to parents. Cat scratches or bites should be washed immediately. Cat flea control is helpful.

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255.2 Bartonellosis (*Bartonella bacilliformis*)

Rachel C. Orscheln

The first human *Bartonella* infection described was **bartonellosis**, a geographically distinct disease caused by *B. bacilliformis*. There are two predominant forms of illness caused by *B. bacilliformis*: **Oroya fever**, a severe, febrile hemolytic anemia, and **verruca peruana** (verruga peruana), an eruption of hemangioma-like lesions. *B. bacilliformis* also causes asymptomatic infection. Bartonellosis is also called **Carrión disease**.

ETIOLOGY

B. bacilliformis is a small, motile, gram-negative organism with a brush of ≥10 unipolar flagella, which appear to be important components for invasiveness. An obligate aerobe, it grows best at 28°C (82.4°F) in semisolid nutrient agar containing rabbit serum and hemoglobin.

EPIDEMIOLOGY

Bartonellosis is a zoonosis found only in mountain valleys of the Andes Mountains in Peru, Ecuador, Colombia, Chile, and Bolivia at altitudes and environmental conditions favorable for the vector, which is the **sandfly**, *Lutzomyia verrucarum*.

PATHOGENESIS

After the sandfly bite, *Bartonella* organisms enter the endothelial cells of blood vessels, where they proliferate. Found throughout the reticuloendothelial system, they then reenter the bloodstream and parasitize erythrocytes. They bind on the cells, deform the membranes, and then enter intracellular vacuoles. The resultant hemolytic anemia may involve as many as 90% of circulating erythrocytes. Patients who survive this acute phase may or may not experience the cutaneous manifestations, which are nodular hemangiomatous lesions or verrucae ranging in size from a few millimeters to several centimeters.

CLINICAL MANIFESTATIONS

The incubation period is 2-14 weeks. Patients may be totally asymptomatic or may have nonspecific symptoms such as headache and malaise without anemia.

Oroya fever is characterized by fever with rapid development of anemia. Clouding of the sensorium and delirium are common symptoms and may progress to overt psychosis. Physical examination demonstrates signs of severe hemolytic anemia, including icterus and pallor, sometimes in association with generalized lymphadenopathy.

In the preeruptive stage of **verruca peruana** (Fig. 255.5), patients may complain of arthralgias, myalgias, and paresthesias. Inflammatory reactions such as phlebitis, pleuritis, erythema nodosum, and encephalitis may develop. The appearance of verrucae is pathognomonic of the eruptive phase. Lesions vary greatly in size and number.

DIAGNOSIS

The diagnosis of bartonellosis is established on clinical grounds in conjunction with a blood smear demonstrating organisms or with blood culture. The anemia is macrocytic and hypochromic, with reticulocyte counts as high as 50%. *B. bacilliformis* may be seen on Giemsa stain preparation as red-violet rods in the erythrocytes. In the recovery phase, organisms change to a more coccoid form and disappear from the blood. In the absence of anemia, the diagnosis depends on blood cultures. In the eruptive phase, the typical verruca confirms the diagnosis. Antibody testing has been used to document infection.

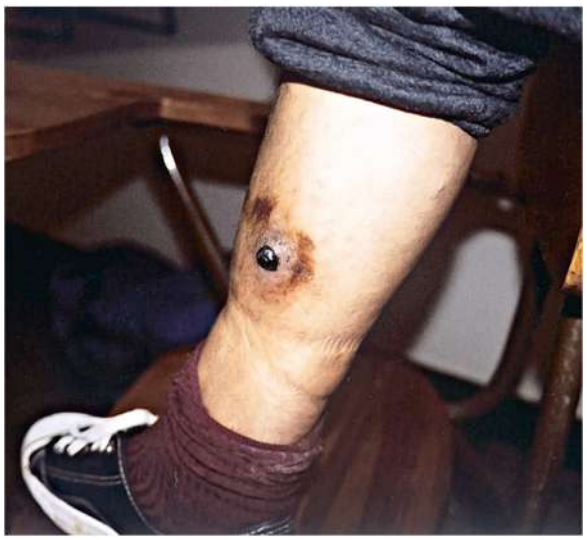

Fig. 255.5 A single large lesion of verruca peruana on the leg of an inhabitant of the Peruvian Andes. Such lesions are prone to superficial ulceration, and their vascular nature may lead to copious bleeding. Ecchymosis of the skin surrounding the lesion is also evident. *(Courtesy Dr. J.M. Crutcher, Oklahoma State Department of Health, Oklahoma City.)*

TREATMENT

B. bacilliformis is sensitive to many antibiotics, including rifampin, tetracycline, and chloramphenicol. Treatment is highly effective in rapidly diminishing fever and eradicating the organism from the blood. **Chloramphenicol** (50-75 mg/kg/day) is considered the drug of choice because it is also useful in the treatment of concomitant infections such as *Salmonella.* Fluoroquinolones are used successfully as well. Blood transfusions and supportive care are critical in patients with severe anemia. Antimicrobial treatment for verruca peruana is considered when there are >10 cutaneous lesions, if the lesions are erythematous or violaceous, or if the onset of the lesions was <1 month before presentation. Oral rifampin is effective in the healing of lesions. Surgical excision may be needed for lesions that are large and disfiguring or that interfere with function.

PREVENTION

Prevention depends on avoidance of the vector, particularly at night, by the use of protective clothing and insect repellents (see Chapter 218).

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255.3 Trench Fever *(Bartonella quintana)*

Rachel C. Orscheln

ETIOLOGY

The causative agent of trench fever was first designated *Rickettsia quintana,* was then assigned to the genus *Rochalimaea,* and now has been reassigned as *Bartonella quintana.*

EPIDEMIOLOGY

Trench fever was first recognized as a distinct clinical entity during World War I, when more than a million troops in the trenches were infected. Infection with *B. quintana* is currently rare in the United States and primarily occurs in the setting of conditions favorable to body lice infestations, such as homelessness, crowding, and poor sanitation. When pooled samples of head and body lice have been collected from homeless populations, up to 33% of individuals have lice pools that test positive for *B. quintana.*

Humans are the only known reservoir. No other animal is naturally infected, and usual laboratory animals are not susceptible. The **human body louse**, *Pediculus humanus* var. *corporis,* is the vector and is capable of transmission to a new host 5-6 days after feeding on an infected person. Lice excrete the organism for life; transovarian passage does not occur. Humans may have prolonged asymptomatic bacteremia for years.

CLINICAL MANIFESTATIONS

The incubation period for trench fever averages about 22 days (range: 4-35 days). The clinical presentation is highly variable. Symptoms can be very mild and brief. About half of infected persons have a single febrile illness with abrupt onset lasting 3-6 days. In other patients, prolonged, sustained fever may occur. More commonly, patients have periodic febrile illness with three to eight episodes lasting 4-5 days each, sometimes occurring over 1 year or more. This form is reminiscent of malaria or **relapsing fever** *(Borrelia recurrentis).* Afebrile bacteremia can occur.

Clinical findings usually consist of fever (typically with a temperature of 38.5–40°C [101.3–104°F]), malaise, chills, sweats, anorexia, and severe headache. Common findings include marked conjunctival injection, tachycardia, myalgias, arthralgias, and severe pain in the neck, back, and legs. Crops of erythematous macules or papules may occur on the trunk on as many as 80% of patients. Splenomegaly and mild liver enlargement may be noted.

DIAGNOSIS

In nonepidemic situations, it is impossible to establish a diagnosis of trench fever on clinical grounds because the findings are not distinctive. A history of body louse infection or having been in an area of epidemic disease should heighten suspicions. *B. quintana* can be cultured from the blood with modification to include culture on epithelial cells. Serologic tests for *B. quintana* are available, but there is cross-reaction with *B. henselae*.

TREATMENT

There are no controlled trials of treatment, but bacteremia with *Bartonella* treated with a combination of gentamicin and doxycycline increases the rate of cure compared with other regimens, such as doxycycline or β-lactam antibiotics alone.

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255.4 Bacillary Angiomatosis and Bacillary Peliosis Hepatis (*Bartonella henselae* and *Bartonella quintana*)

Rachel C. Orscheln

Both *B.henselae* and *B.quintana* cause vascular proliferative disease in severely immunocompromised persons, primarily adult patients with acquired immune deficiency syndrome (AIDS), persons receiving cancer chemotherapy, and organ transplant recipients. The subcutaneous and lytic bone lesions of bacillary angiomatosis can be caused by infection with either *B. henselae* or *B. quintana*. The lesions of peliosis hepatis are almost exclusively associated with *B. henselae*.

BACILLARY ANGIOMATOSIS

Lesions of cutaneous bacillary angiomatosis, also known as **epithelioid angiomatosis**, are the most easily identified and recognized form of *Bartonella* infection in immunocompromised hosts. They are found primarily in patients with AIDS who have very low CD4 counts. The clinical appearance can be quite diverse. The vasoproliferative lesions of bacillary angiomatosis may be cutaneous or subcutaneous and may resemble the vascular lesions (verruca peruana) of *B. bacilliformis* in immunocompetent persons, characterized by erythematous papules on an erythematous base with a collarette of scale. They may enlarge to form large, pedunculated lesions and may ulcerate. Trauma may result in profuse bleeding.

Bacillary angiomatosis may be clinically indistinguishable from Kaposi sarcoma. Other considerations in the differential diagnosis are pyogenic granuloma and verruca peruana *(B. bacilliformis)*. Deep soft tissue masses caused by bacillary angiomatosis may mimic a malignancy.

Osseous bacillary angiomatosis lesions typically involve the long bones. These lytic lesions are very painful and highly vascular and are occasionally associated with an overlying erythematous plaque. The high degree of vascularity produces a positive result on a technetium-99m methylene diphosphonate bone scan, resembling that of a malignant lesion.

Lesions can be found in virtually any organ, producing similar vascular proliferative lesions. They may appear raised, nodular, or ulcerative when seen on endoscopy or bronchoscopy. They may be associated with enlarged lymph nodes with or without an obvious local cutaneous lesion. Brain parenchymal lesions have been described.

BACILLARY PELIOSIS

Bacillary peliosis affects the reticuloendothelial system, primarily the liver **(peliosis hepatis)** and, less frequently, the spleen and lymph nodes. It is a vasoproliferative disorder characterized by random proliferation of venous lakes surrounded by fibromyxoid stroma harboring numerous bacillary organisms. Clinical findings include fever and abdominal pain in association with abnormal liver function test results, particularly a greatly increased alkaline phosphatase level. Cutaneous bacillary angiomatosis with splenomegaly may be associated with thrombocytopenia or pancytopenia. The vascular proliferative lesions in the liver and spleen appear on CT scan as hypodense lesions scattered throughout the parenchyma. The differential diagnosis includes hepatic Kaposi sarcoma, lymphoma, and disseminated infection with *Pneumocystis jirovecii* or *Mycobacterium avium* complex.

BACTEREMIA AND ENDOCARDITIS

B. henselae, B. quintana, B. vinsonii, and *B. elizabethae* all are reported to cause bacteremia or endocarditis. They are associated with symptoms such as prolonged fevers, night sweats, and profound weight loss. A cluster of cases in Seattle in 1993 occurred in a homeless population with chronic alcoholism. These patients with high fever or hypothermia were thought to represent *urban trench fever,* but no body louse infestation was associated. Some cases of culture-negative endocarditis may represent *Bartonella* endocarditis. One report described central nervous system involvement with *B. quintana* infection in two children.

DIAGNOSIS

The diagnosis of bacillary angiomatosis is made initially by biopsy. The characteristic small-vessel proliferation with mixed inflammatory response and the staining of bacilli by Warthin-Starry silver distinguish bacillary angiomatosis from pyogenic granuloma or Kaposi sarcoma (see Chapter 304). Travel history can usually preclude verruca peruana.

Culture is impractical for CSD but is the diagnostic procedure for suspected bacteremia or endocarditis. Lysis centrifugation technique or fresh chocolate or heart infusion agar with 5% rabbit blood and prolonged incubation may increase the yield of culture. PCR on tissue can also be a useful tool, and positive serologic testing can provide support for the diagnosis.

TREATMENT

Bartonella infections in immunocompromised hosts caused by both *B. henselae* and *B. quintana* have been treated successfully with antimicrobial agents. Bacillary angiomatosis responds rapidly to erythromycin, azithromycin, and clarithromycin, which are the drugs of choice. Alternative choices are doxycycline or tetracycline. Severely ill patients with peliosis hepatis or patients with osteomyelitis may be treated initially with a macrolide or doxycycline and the addition of rifampin or gentamicin. The use of doxycycline for 6 weeks with the addition of an aminoglycoside for a minimum of 2 weeks is associated with improved prognosis in endocarditis. A Jarisch-Herxheimer reaction may occur. Relapses may follow, and prolonged treatment for several months may be necessary.

PREVENTION

Immunocompromised persons should consider the potential risks of cat ownership because of the risks for *Bartonella* infections as well as toxoplasmosis and enteric infections. Those who elect to obtain a cat should adopt or purchase a cat >1 year old and in good health. Prompt washing of any wounds from cat bites or scratches is essential.

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Section 6

Anaerobic Bacterial Infections

Chapter 256

Botulism (*Clostridium botulinum*)

Mark R. Schleiss

There are three naturally occurring forms of human botulism, characterized by mode of acquisition: **infant botulism** (intestinal toxemia), **food-borne botulism**, and **wound botulism**. Infant botulism is the most common form in the United States. Under rare circumstances of altered intestinal anatomy, physiology, and microflora, older children and adults may contract infant-type botulism **(adult intestinal toxemia)**. Two other forms, both human-made, also occur: **inhalational botulism**, from inhaling accidently aerosolized toxin, and **iatrogenic botulism**, from overdosage of botulinum toxin used for therapeutic or cosmetic purposes.

ETIOLOGY

Botulism is the acute, flaccid paralysis caused by the neurotoxin produced by *Clostridium botulinum* or, infrequently, an equivalent neurotoxin produced by the related species *Clostridium butyricum* and *Clostridium baratii. C. botulinum* is a gram-positive, spore-forming, obligate anaerobe whose natural habitat worldwide is soil, dust, and marine sediments. The organism is found in a wide variety of fresh and cooked agricultural products. Remarkably, the spores of some *C. botulinum* strains endure boiling for several hours, enabling the organism to survive efforts at food preservation. In contrast, botulinum toxin is heat labile and easily destroyed by heating at ≥85°C (185°F) for 5 minutes. Neurotoxigenic *C. butyricum* has been isolated from soils near Lake Weishan in China, the site of food-borne botulism outbreaks associated with this organism, and from vegetables, soured milk, and cheeses. Although first recognized in China, cases of infant botulism caused by *C. butyricum* have now been identified in Japan, Europe, and the United States. Little is known about the ecology of neurotoxigenic *C. baratii*.

Botulinum toxin is synthesized as a 150-kDa precursor protein that enters the circulation and is transported to the neuromuscular junction. The toxin is only released by actively replicating (vegetative) bacteria and not the spore form. At the neuromuscular junction, toxin binds to the neuronal membrane on the presynaptic side of the neural synapse. It undergoes proteolysis to a 100-kDa heavy chain and a 50-kDa light chain. These chains are joined via disulfide bond formation. The heavy chain contains the neuronal attachment sites that mediate binding to presynaptic nerve terminals. It also mediates translocation of the light chain into the cell cytoplasm after binding. The light chain, a key component of the toxin, is a member of the zinc metalloprotease family and mediates cleavage of the fusogenic SNARE (Soluble NSF Attachment REceptor) protein family member, SNAP-25. Cleavage of this protein precludes release of acetylcholine from axons at the presynaptic terminal, abrogating nerve signaling and producing paralysis. Botulinum toxin is among the most potent poisons known to humankind; indeed, the parenteral human lethal dose is estimated to be on the order of 10^{-6} mg/kg. The toxin blocks neuromuscular transmission and causes death through airway and respiratory muscle paralysis. At least nine antigenic toxin types, designated by letters A-H and X, are distinguished serologically by demonstration of the inability of neutralizing antibody against one toxin type to protect against a different type. Toxin types are further differentiated into subtypes by differences in the nucleotide sequences of their toxin genes. The gene for botulinum toxin for some toxin types and subtypes resides on a plasmid. Some toxins are fully activated by the bacteria that produce them (proteolytic strains of types A, B, and F), and some require exogenous proteolytic activation (types E and nonproteolytic types B and F).

The toxin types serve as convenient clinical and epidemiologic markers. Toxin types A, B, E, and F are well-established causes of human botulism, whereas types C and D cause illness in other animals. Toxin types A and B cause the majority of cases of infant botulism in the United States. Neurotoxigenic *C. butyricum* strains produce a type E toxin, whereas neurotoxigenic *C. baratii* strains produce a type F toxin. Type G toxin has not been established as a cause of either human or animal disease. Some strains produce two toxins such as B and A or B and F; rare strains may produce three toxins. Dual (bivalent) toxin mediated disease tends to be more severe than single toxin production.

EPIDEMIOLOGY

Infant botulism has been reported from all inhabited continents except Africa. Notably, in a typical case the infant is the only family member who is ill. The most striking epidemiologic feature of infant botulism is its age distribution: approximately 90% of cases involving infants 3 weeks to 6 months of age, with a broad peak spanning 2-4 months of age. Cases have been recognized in infants as young as 1.5 days or as old as 382 days at onset. Identified risk factors for the illness include breastfeeding, the ingestion of honey, a slow intestinal transit time (<1 stool/day), and ingestion of untreated well water (Fig. 256.1). Although breastfeeding appears to provide protection against fulminant sudden death from infant botulism, cases can occur in breastfed infants at the time of introduction of nonhuman milk for feeding.

Although infant botulism is an uncommon and often unrecognized illness, it is the most common form of human botulism in the United States, with approximately 80-140 hospitalized cases diagnosed annually. The Council of State and Territorial Epidemiologists (CSTE) maintains a **National Botulism Surveillance System** for intensive surveillance for cases of botulism in the United States (https://www.cdc.gov/botulism/surveillance.html). In 2017, 182 laboratory-confirmed botulism cases were reported to Centers for Disease Control and Prevention (CDC). Botulism was predominately observed in infants, with 141 such cases reported. A total of 19 (10%) food-borne cases and 19 (10%) wound cases were reported. Infant botulism cases were reported from 26 states and the District of Columbia, with California reporting the

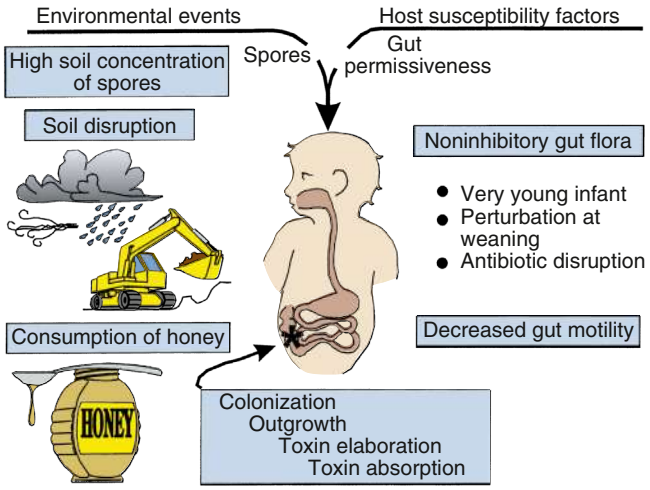

Fig. 256.1 Environmental, host, and pathophysiologic events in infant botulism. *(From Arnon SS, Long SS. Clostridium botulinum [Botulism]. In Long SS, Prober CG, Fischer M, Kimberlin DW, eds. Principles and Practice of Pediatric Infectious Diseases, 6th ed. Philadelphia: Elsevier; 2023: Fig. 189.3, p. 1019.)*

most (n = 48, 34%). Toxin type B (n = 88) predominated. The median age of infants was 4 months (range: 0-12 months), and no deaths were reported.

Food-borne botulism results from the ingestion of a food in which *C. botulinum* has multiplied and produced toxin. Although the traditional view of food-borne botulism has been thought of as resulting chiefly from ingestion of home-canned foods, in fact, outbreaks in North America have been more often associated with restaurant-prepared foods, including nacho cheese in convenience stores, sautéed onions, chopped garlic, and seal blubber (in Alaska). Other outbreaks in the United States have occurred from commercial foods sealed in plastic pouches that relied solely on refrigeration to prevent outgrowth of *C. botulinum* spores. Uncanned foods responsible for food-borne botulism cases include peyote tea, hazelnut flavoring added to yogurt, sweet cream cheese, sautéed onions in patty melt sandwiches, potato salad, and fresh and dried fish, including botulism type E that has been acquired by eating an Egyptian salt-cured fish dish called fesikh. For food-borne botulism cases reported to the 2017 National Botulism Surveillance System, the median age of patients was 42 years (range: 14-85 years), and three deaths were reported. Most of the continental U.S. outbreaks resulted from proteolytic type A or type B strains, whereas in Alaska and Canada, most food-borne outbreaks have resulted from nonproteolytic type E strains. A further hazard of type E strains is their ability to grow at the temperatures maintained by household refrigerators (5°C [41°F]).

Wound botulism is an exceptionally rare disease, with <400 cases reported worldwide, but it is important to pediatrics because adolescents and children may be affected. Although many cases have occurred in young, physically active males who are at the greatest risk for traumatic injury, wound botulism also occurs with crush injuries in which no break in the skin is evident. In recent years, wound botulism from injection has become increasingly common in adult heroin abusers in the western United States and in Europe, not always with concomitant evidence of abscess formation or cellulitis.

A single outbreak of **inhalational botulism** was reported in 1962 in which three laboratory workers in Germany were exposed unintentionally to aerosolized botulinum toxin. Some patients in the United States have been hospitalized by accidental overdose of therapeutic or cosmetic botulinum toxin.

PATHOGENESIS

All forms of botulism produce disease through a final common pathway. Botulinum toxin is carried by the bloodstream to peripheral cholinergic synapses, where it binds irreversibly, blocking acetylcholine release and causing impaired neuromuscular and autonomic transmission. **Infant botulism** results from ingesting the spores of botulinum toxin–producing strains, with subsequent spore germination, multiplication, and production of botulinum toxin in the large intestine. This sequence is distinct from **food-borne botulism**, which is an intoxication that results when preformed botulinum toxin contained in an improperly preserved or inadequately cooked food is swallowed. **Wound botulism** results from spore germination and colonization of traumatized tissue by *C. botulinum;* the pathogenesis of this form of botulism is similar in this respect to that of tetanus. **Inhalational botulism** occurs when aerosolized botulinum toxin is inhaled and could conceivably be a route of exposure generated by a bioterrorist attack.

Because botulinum toxin is not a *cytotoxin,* it does not cause overt macroscopic or microscopic pathology. Pathologic changes (pneumonia, petechiae on intrathoracic organs) may be found at autopsy, but these are secondary changes and not primarily attributable to botulinum toxin. No diagnostic technique is available to identify botulinum toxin binding at the neuromuscular junction. Nerve conduction velocity studies are typically normal. Electromyography (EMG) findings are often nonspecific and nondiagnostic (see later). The healing process in botulism consists of sprouting new terminal unmyelinated motor neurons. Movement resumes when these new nerve terminals locate noncontracting muscle fibers and reinnervate them by inducing formation of a new motor end plate. In experimental animals, this process takes about 4 weeks.

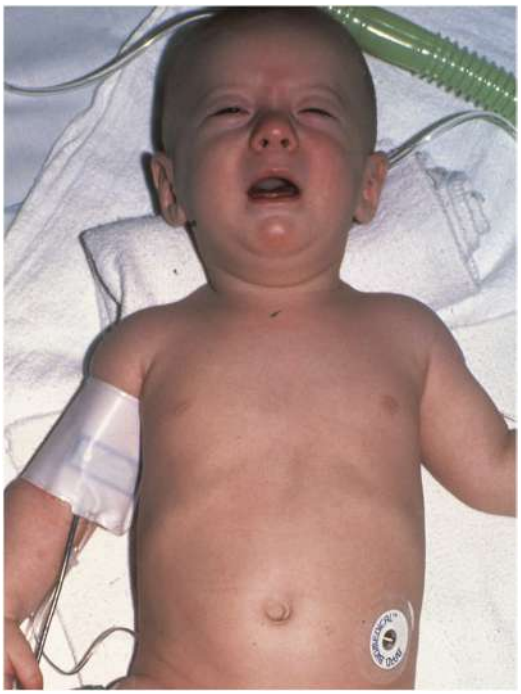

Fig. 256.2 A 3-mo-old infant with botulism just before intubation. Note bilateral ptosis and facial palsy and the absence of tears. *(From Arnon SS, Long SS. Clostridium botulinum [Botulism]. In: Long SS, Prober CG, Fischer M, Kimberlin DW, eds. Principles and Practice of Pediatric Infectious Diseases, 6th ed. Philadelphia: Elsevier; 2023: Fig. 189.4, p. 1020.)*

CLINICAL MANIFESTATIONS

The full clinical spectrum of **infant botulism** ranges from mild to fulminant sudden death. Botulinum toxin is distributed hematogenously. Because relative blood flow and density of innervation are greatest in the bulbar musculature, all forms of botulism manifest neurologically as a symmetric, *descending,* flaccid paralysis beginning with the cranial nerve musculature and progressing over hours to days. **Bulbar palsies** may manifest with such symptoms as poor feeding, weak suck, feeble cry, drooling, and even obstructive apnea. These clinical clues unfortunately may not be recognized as bulbar in origin (Fig. 256.2). Patients with evolving illness may already have generalized weakness and hypotonia in addition to bulbar palsies when first examined. The brain itself is spared in infant botulism, because botulinum toxin does not cross the blood-brain barrier.

In contrast to botulism caused by *C. botulinum,* a majority of the rare cases caused by intestinal colonization with *C. butyricum* are associated with a Meckel diverticulum accompanying abdominal distention, often leading to misdiagnosis as an acute abdomen. The also rare *C. baratii* type F infant botulism cases have been characterized by very young age at onset, rapidity of onset, and greater severity but shorter duration of paralysis.

In older children with **food-borne** or **wound botulism**, the onset of neurologic symptoms follows a characteristic pattern of diplopia, ptosis, dry mouth, dysphagia, dysphonia, and dysarthria, with decreased gag and corneal reflexes. Importantly, because the toxin acts only on motor nerves, paresthesias are not seen in botulism, except when a patient hyperventilates from anxiety. The sensorium remains clear, but this fact may be difficult to ascertain because of the slurred speech.

Food-borne botulism begins with gastrointestinal (GI) symptoms of nausea, vomiting, or diarrhea in approximately 30% of cases. These symptoms are thought to result from metabolic by-products of growth of *C. botulinum* or from the presence of other toxic contaminants in the food, because GI distress is rarely observed in wound botulism. Constipation may occur in food-borne botulism once flaccid paralysis becomes evident. Illness usually begins 12-36 hours after ingestion of

the contaminated food but can range from as short as 2 hours to as long as 8 days. The incubation period in **wound botulism** is 4-14 days. Fever may be present in wound botulism but is absent in food-borne botulism unless a secondary infection (often pneumonia) is present. All forms of botulism display a wide spectrum of clinical severity, from the very mild, with minimal ptosis, flattened facial expression, minor dysphagia, and dysphonia, to the fulminant, with rapid onset of extensive paralysis, frank apnea, and fixed, dilated pupils. *Fatigability with repetitive muscle activity* is the clinical hallmark of botulism.

Infant botulism differs in apparent initial symptoms of illness only because the infant cannot verbalize them. Clinical progression can be more rapid and more severe in very young infants. The incubation period in infant botulism is estimated to be 3-30 days. Usually, the first indication of illness is a decreased frequency or even absence of defecation, and indeed, constipation may be the chief complaint (although this sign is also frequently overlooked). Parents typically notice inability to feed, lethargy, weak cry, and diminished spontaneous movement. Dysphagia may be evident, and an increase in secretions drooling from the mouth may be noted. Gag, suck, and corneal reflexes all diminish as the paralysis advances. Oculomotor palsies may be evident. Paradoxically, the pupillary light reflex may be unaffected until the child is severely paralyzed, or it may be initially sluggish. Loss of head control is typically a prominent sign. Opisthotonos may be observed. Respiratory arrest may occur suddenly from airway occlusion by unswallowed secretions or from obstructive flaccid pharyngeal musculature. Death from botulism results either from airway obstruction or paralysis of the respiratory muscles. Occasionally, the diagnosis of infant botulism is suggested by a respiratory arrest that occurs after the infant is curled into position for lumbar puncture or after the administration of an aminoglycoside antibiotic administered for suspected sepsis (see later).

In mild cases or in the early stages of illness, the physical signs of infant botulism may be subtle and easily missed. Eliciting cranial nerve palsies and fatigability of muscular function requires careful examination. Ptosis may not be seen unless the head of the child is kept erect.

DIAGNOSIS

Definitive diagnosis of botulism is made by specialized laboratory testing that requires hours to days to complete. Therefore clinical diagnosis is the foundation for early recognition of and response to all forms of botulism. Routine laboratory studies, including those of the cerebrospinal fluid (CSF), are normal in botulism unless dehydration, undernourishment (metabolic acidosis and ketosis), or secondary infection is present.

The **classic triad** of botulism is the acute onset of a symmetric, flaccid descending paralysis with clear sensorium, no fever, and no paresthesias. Suspected botulism represents a medical and public health emergency that is immediately reportable by telephone in most U.S. health jurisdictions. State health departments (first call) and the CDC (770-488-7100 at any time) can arrange for diagnostic testing, epidemiologic investigation, and provision of equine antitoxin.

The diagnosis of botulism is unequivocally established by demonstration of the presence of botulinum toxin in serum or of *C. botulinum* toxin or organisms in wound material, enema fluid, or feces. *C. botulinum* is not part of the normal resident intestinal flora of humans, and its presence in the setting of acute flaccid paralysis is diagnostic. An epidemiologic diagnosis of food-borne botulism can be established when *C. botulinum* organisms and toxin are found in food eaten by patients.

Electromyography can sometimes distinguish between causes of acute flaccid paralysis, although results may be variable, including normal, in patients with botulism. The distinctive EMG finding in botulism is facilitation (potentiation) of the evoked muscle action potential at high-frequency (50 Hz) stimulation. In infant botulism, a characteristic pattern known as **BSAP** (Brief, Small, Abundant motor unit action Potentials) is present only in clinically weak muscles. Nerve conduction velocity and sensory nerve function are normal in botulism.

Infant botulism requires a high index of suspicion for early diagnosis (Table 256.1). "Rule-out sepsis" remains the most common admission diagnosis. If a previously healthy infant (usually 2-4 months of age) demonstrates weakness with difficulty in sucking, swallowing, crying, or breathing, infant botulism should be considered a likely diagnosis. A careful cranial nerve examination is then quite helpful. Rare instances of co-infection with *Clostridioides difficile,* respiratory syncytial virus, or influenza virus have occurred.

Table 256.1 Mimics of Initial Diagnosis of Infant Botulism

NEUROMUSCULAR
Spinal muscular atrophy (type 1)
Congenital myasthenia gravis
Guillain-Barré syndrome and its variants
Poliomyelitis
Acute flaccid paralysis
Transverse myelitis
ADEM
Congenital myopathy
Encephalitis (viral, autoimmune)
Global developmental delay
Leukodystrophy
METABOLIC
Medium chain acetyl-coenzyme A deficiency
Carnitine deficiency
Congenital disorders of glycosylation
Urea cycle defects
Mitochondrial disorders
Glutaric aciduria type 1
Maple syrup urine disease
INFECTIOUS
Enteroviral and parechovirus encephalitis
Sepsis
OTHERS
Hypothyroidism
Drug ingestion
Organophosphate poisoning
Heavy metal poisoning (lead, arsenic)

Differential Diagnosis

Botulism is frequently misdiagnosed, most often as a **polyradiculoneuropathy** (Guillain-Barré or Miller Fisher syndrome), myasthenia gravis, or a central nervous system (CNS) disease (Table 256.2). In the United States, botulism is more likely than **Guillain-Barré syndrome**, intoxication, or poliomyelitis to cause a *cluster of cases* of acute flaccid paralysis. Botulism differs from other flaccid paralyses in its initial and prominent cranial nerve palsies that are disproportionate to milder weakness and hypotonia below the neck, in its symmetry, and in its absence of sensory nerve damage. Spinal muscular atrophy may closely mimic infant botulism at presentation.

Additional diagnostic procedures may be useful in rapidly excluding botulism as the cause of paralysis. The CSF is unchanged in botulism but is abnormal in many CNS diseases. Although the CSF protein concentration is eventually elevated in Guillain-Barré syndrome, it may be normal early in the illness. Imaging of the brain, spine, and chest may reveal hemorrhage, inflammation, or neoplasm. A test dose of edrophonium chloride briefly reverses paralytic symptoms in many patients with myasthenia gravis and, reportedly, in some with botulism, although this is rarely performed in infants. A close inspection of the skin, especially the scalp, may reveal an attached tick that is causing paralysis. Possible organophosphate intoxication should be pursued aggressively, because specific antidotes (oximes) are available and because the patient may be part of a commonly exposed group, some of whom have yet to demonstrate illness. Other tests that require days for results include stool culture for *Campylobacter jejuni* as a precipitant of Guillain-Barré syndrome, spinal muscular atrophy and other genetic (including mitochondrial) disorders, and assays for the autoantibodies that cause myasthenia gravis, Lambert-Eaton syndrome, and Guillain-Barré syndrome.

Table 256.2 Conditions Considered in the Differential Diagnosis of Food-Borne Botulism and Wound Botulism

Acute gastroenteritis
Myasthenia gravis
Guillain-Barré syndrome
Organophosphate poisoning
Meningitis
Encephalitis
Transverse myelitis
Psychiatric illness
Cerebrovascular accident
Poliomyelitis
Hypothyroidism
Genetic disorder
Aminoglycoside-associated paralysis
Tick paralysis
Hypocalcemia
Hypermagnesemia
Carbon monoxide poisoning
Hyperemesis gravidarum
Laryngeal trauma
Diabetic complications
Inflammatory myopathy
Overexertion

TREATMENT

Human botulism immune globulin, given intravenously (BIG-IV, also referred to as *BabyBIG*), is licensed for the treatment of infant botulism caused by type A or B botulinum toxin. The purified immunoglobulin is derived from pooled adult plasma from individuals immunized with pentavalent botulinum toxoid who were selected for their high titers of neutralizing antibody against botulinum neurotoxins type A and B. Treatment with BIG-IV consists of a single intravenous infusion of 50 mg/kg (see package insert) that should be given as soon as possible after infant botulism is suspected so as to immediately end the toxemia that is the cause of the illness and arrest progression of paralysis. *When the diagnosis of infant botulism is suspected, treatment should not be delayed for laboratory confirmation.* In the United States, for clinical consultation for a patient with suspected infant botulism, the patient's physician should contact the Infant Botulism Treatment and Prevention Program (IBTPP) on-call physician at (510) 231-7600 (24/7/365). To obtain BabyBIG for a patient with suspect infant botulism, the physician must contact the IBTPP on-call physicians (https://www.infantbotulism.org/physician/obtain.php). The use of BIG-IV shortens mean hospital stay from approximately 6 weeks to 2 weeks. Most of the decrease in hospital stay results from shorter duration of mechanical ventilation and reduced days in intensive care.

Older patients with suspected food, wound, or inhalational botulism may be treated with one vial of licensed equine heptavalent (A-G) botulinum antitoxin (HBAT). (https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5910a4.htm), which is available in the United States through the CDC by way of state and local health departments.

Antibiotic therapy is not part of the treatment of uncomplicated infant or food-borne botulism, because the toxin is primarily an intracellular molecule that is released into the intestinal lumen with vegetative bacterial cell death and lysis. Indeed, there is a theoretical concern that antibiotics with clostridiocidal activity may increase the amount of free toxin in the large bowel and actually worsen an infant's clinical status. Antibiotic use in infant botulism patients is indicated only for the treatment of secondary infections. In these patients, aminoglycosides in particular should be avoided, because this class of antibiotics can potentiate the action of botulinum toxin at the neuromuscular junction. Wound botulism requires aggressive treatment with antibiotics and antitoxin in a manner analogous to that for tetanus (see Chapter 257) and may require wound debridement to remove the source of the toxin.

SUPPORTIVE CARE

Management of botulism rests on the following three principles: (1) fatigability with repetitive muscle activity is the clinical hallmark of the disease, (2) complications are best avoided by anticipating them, and (3) meticulous supportive care is a necessity. The first principle applies mainly to feeding and breathing. Correct positioning is imperative to protect the airway and improve respiratory mechanics. The patient should be positioned face-up on a rigid-bottomed crib (or bed), the head of which is tilted at 30 degrees. A small cloth roll is placed under the cervical vertebrae to tilt the head back so that secretions drain to the posterior pharynx and away from the airway. In this tilted position, the abdominal viscera pull the diaphragm down, thereby improving respiratory mechanics. The patient's head and torso should not be elevated by bending the middle of the bed; in such a position, the hypotonic thorax would slump into the abdomen, and breathing would be compromised.

About half of patients with infant botulism require endotracheal intubation, which is best done prophylactically. The indications include diminished gag and cough reflexes and progressive airway obstruction by secretions. Enteral nutrition should be undertaken using a nasogastric or nasojejunal tube until sufficient oropharyngeal strength and coordination enable oral feeding by breast or bottle. Expressed breast milk is the most desirable food for infants, in part because of its immunologic components (e.g., secretory IgA, lactoferrin, leukocytes). Tube feeding also assists in the restoration of peristalsis, a nonspecific but probably essential part of eliminating *C. botulinum* from the intestinal flora. Intravenous feeding (hyperalimentation) is discouraged because of the potential for infection and the advantages of tube feeding.

Because sensation and cognitive function remain fully intact, providing auditory, tactile, and visual stimuli is beneficial. Maintaining strong central respiratory drive is essential, so sedatives and CNS depressants should be avoided. Full hydration and stool softeners such as lactulose may mitigate the protracted constipation. Cathartics are not recommended. Patients with food-borne and infant botulism excrete *C. botulinum* toxin and organisms in their feces, often for many weeks, and care should be taken in handling their excreta, with full engagement of hospital infection control staff. When bladder palsy occurs in severe cases, gentle suprapubic pressure with the patient in the sitting position with the head supported may help attain complete voiding and reduce the risk for urinary tract infection (UTI). Families of affected patients may require emotional and financial support, especially when the paralysis of botulism is prolonged.

COMPLICATIONS

Almost all the complications of botulism are *nosocomial,* and a few are iatrogenic (Table 256.3). Some critically ill, toxin-paralyzed patients who must spend weeks or months on ventilators in intensive care units inevitably experience some of these complications. Suspected "relapses" of infant botulism usually reflect premature hospital discharge or an inapparent underlying complication such as pneumonia, UTI, or otitis media.

PROGNOSIS

When the regenerating nerve endings have induced formation of a new motor end plate, neuromuscular transmission is restored. In the absence of complications, particularly those related to hypoxia, the prognosis in infant botulism is for full and complete recovery. Hospital stay in untreated infant botulism averages 5.7 weeks but differs significantly by toxin type, with patients with untreated type B disease being hospitalized a mean of 4.2 weeks and those with untreated type A disease being hospitalized a mean of 6.7 weeks.

In the United States, the case fatality ratio for hospitalized cases of infant botulism is <1%. After recovery, patients with untreated infant botulism appear to have an increased incidence of strabismus that requires timely screening and treatment. The case fatality ratio in food-borne and wound botulism varies by age, with younger patients having the best prognosis. Some adults with botulism have reported chronic weakness and fatigue for >1 year as sequelae of the illness.

Table 256.3 Complications of Infant Botulism

Acute respiratory distress syndrome
Aspiration
Clostridioides difficile enterocolitis
Hypotension
Inappropriate antidiuretic hormone secretion
Long bone fractures
Misplaced or plugged endotracheal tube
Nosocomial anemia
Otitis media
Pneumonia
Pneumothorax
Recurrent atelectasis
Seizures secondary to hyponatremia
Sepsis
Subglottic stenosis
Tracheal granuloma
Tracheitis
Transfusion reaction
Urinary tract infection

PREVENTION

Food-borne botulism is best prevented by adherence to safe methods of home canning (pressure cooker and acidification), by avoiding suspicious foods, and by heating all home-canned foods to 85°C (185°F) for ≥5 minutes. Wound botulism is best prevented by not using illicit drugs and by treating contaminated wounds with thorough cleansing, surgical debridement, and provision of appropriate antibiotics.

Many patients with infant botulism are presumed to have inhaled and then swallowed airborne clostridial spores; these cases cannot be prevented. However, a clearly identified and avoidable source of botulinum spores for infants is honey. *Honey is an unsafe food for any child <1 year old.* Corn syrups were once thought to be a possible source of botulinum spores, but evidence indicates otherwise. Breastfeeding appears to slow the onset of infant botulism and to diminish the risk for sudden death in infants in whom the disease develops.

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Chapter 257

Tetanus (*Clostridium tetani*)

Mark R. Schleiss

ETIOLOGY

The clinical syndrome of **tetanus** involves an acute, spastic paralytic illness caused by a neurotoxin produced by *Clostridium tetani*. Thus tetanus can be considered a toxin-mediated process more than an acute infectious process per se, because there are few, if any, symptoms elicited either by the presence of replicating microorganisms or through elicitation of the host inflammatory response. Unlike other pathogenic clostridia species, *C. tetani* is not a tissue-invasive organism. Instead, it causes illness through the toxin, **tetanospasmin**, more commonly referred to as *tetanus toxin*. Tetanospasmin is the second most poisonous substance known, surpassed in potency only by botulinum toxin. The human lethal dose of tetanus toxin is estimated to be 10^{-5} mg/kg. *C. tetani* is a motile, gram-positive, spore-forming obligate anaerobe. The organism's natural habitat worldwide is soil, dust, and the alimentary tracts of various animals.

C. tetani forms spores terminally, with a classic morphologic appearance resembling a drumstick or tennis racket when viewed microscopically. The formation of spores is a critical aspect of the organism's persistence in the environment. Spores can survive boiling but not autoclaving, whereas the vegetative cells are killed by antibiotics, heat, and standard disinfectants.

EPIDEMIOLOGY

Tetanus occurs worldwide and is endemic in many developing countries, although its incidence varies considerably. Public health efforts in recent years have had an impressive impact on tetanus-associated mortality, but many challenges remain. In 1990, 314,000 people died because of tetanus, whereas in 2017 there were just slightly over 38,000 deaths. Over half of these deaths (approximately 18,000) were in children under 5 years of age (Fig. 257.1A). Individuals age 15-49 years represent the second most common group to suffer tetanus-related mortality. Global mortality in adults is largely driven by **maternal tetanus**, which results from postpartum, postabortal, or postsurgical wound infection with *C. tetani*. Most mortality related to **neonatal tetanus** (also referred to as **umbilical tetanus**) occurs in South Asia and sub-Saharan Africa. The mortality of neonatal tetanus has been substantially reduced globally, driven by increased rates of maternal tetanus vaccination, although the disease remains endemic in a number of countries (see Fig. 257.1B). Reported tetanus cases in the United States have declined more than 95% since 1947, and deaths caused by tetanus have declined by more than 99% in that same period. From 2009 to 2017, a total of 264 cases and 19 deaths from tetanus were reported in the United States. Sixty (23%) cases were in persons 65 years of age or older, 168 (64%) were in persons 20 through 64 years of age, and 36 (13%) were in persons younger than 20 years, including 3 cases of neonatal tetanus. The majority of childhood cases of tetanus in the United States have occurred in unimmunized children whose parents objected to vaccination.

Most nonneonatal cases of tetanus are associated with a traumatic injury, often a penetrating wound inflicted by a dirty object such as a nail, splinter, fragment of glass, or unsterile injection. Tetanus may also occur in the setting of illicit drug injection. The disease has been associated with the use of contaminated suture material and after intramuscular injection of medicines, most notably quinine for chloroquine-resistant falciparum malaria. The disease may also occur in association with animal bites, abscesses (including dental abscesses), ear and other body piercing, chronic skin ulceration, burns, compound fractures, frostbite, gangrene, intestinal surgery, ritual scarification, infected insect bites, and female circumcision. Rarely, cases may present to clinical attention without an antecedent history of trauma. Tetanus is not transmitted person to person.

PATHOGENESIS

Tetanus typically occurs after spores (introduced by traumatic injury) germinate, multiply, and produce tetanus toxin. A plasmid carries the toxin gene. Toxin is produced only by the vegetative cell, not the spore. It is released after the vegetative phase of replication, with replication occurring under anaerobic conditions. The low oxidation-reduction potential of an infected injury site therefore provides an ideal environment for transition from the spore to the vegetative stage of growth. After bacterial cell death and lysis, **tetanospasmin** is produced. The toxin has no known function for clostridia in the soil environment where they normally reside. Tetanus toxin is a 150-kDa simple protein consisting of a heavy chain (100 kDa) and a light (50 kDa) chain joined by a single disulfide bond. Tetanus toxin binds at the neuromuscular junction and enters the motor nerve by endocytosis, after which it undergoes retrograde axonal transport, facilitated by dyneins, to the cytoplasm of the α-motoneuron. In the sciatic nerve, the transport rate was found to be 3.4 mm/hr. The toxin exits the motoneuron in the spinal cord and next enters adjacent spinal inhibitory interneurons, where it prevents release of the neurotransmitters glycine and γ-aminobutyric acid (GABA). Tetanus toxin thus blocks the normal inhibition of antagonistic muscles on which voluntary coordinated movement depends; as a consequence, affected muscles sustain maximal contraction and cannot relax. This aspect of pathogenesis lead to

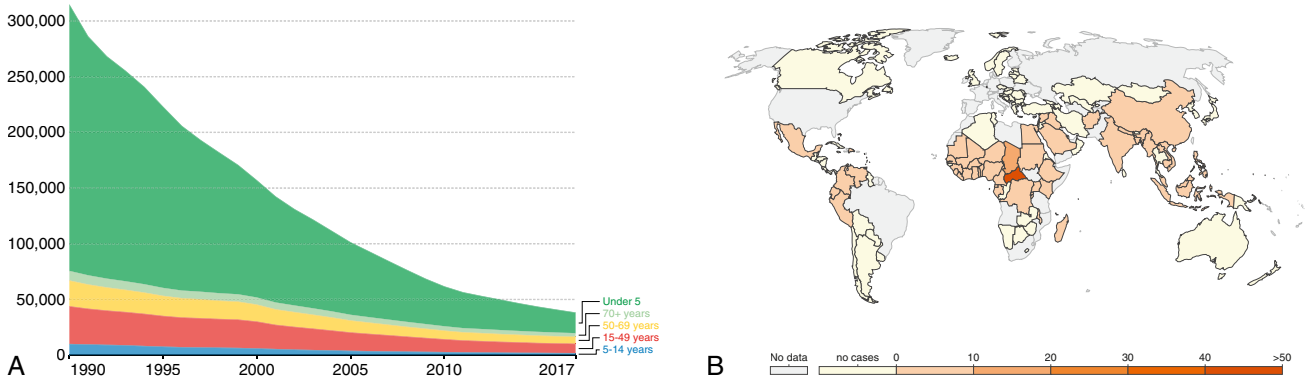

Fig. 257.1 Evolving epidemiology of tetanus. **A,** Deaths from tetanus, by age, globally from 1990 to 2017. Most cases of tetanus occur in children under the age of 5, and this group accounts for ~50% of the global mortality attributable to this infection. (Source: Institute for Health Metrics and Evaluation, Global Burden of Disease). **B,** Global distribution of neonatal tetanus. Number of new cases of neonatal tetanus per million, 2016. Sources: World Health Organization and UN Population Prospects, 2017. *(From Behrens H, Ochmann S, Dadonaite B, Roser M. Tetanus. Published online at OurWorldInData.org, 2019. Retrieved from https://ourworldindata.org/tetanus.)*

the term *lockjaw,* classically applied to the clinical manifestations of tetanus in the affected individual. Neurotransmission at neuromuscular junctions in the autonomic nervous system are also rendered unstable in tetanus, producing "autonomic storm" (described later).

The phenomenal potency of tetanus toxin is enzymatic. The 50-kDa light chain (A-chain) of tetanus toxin is a zinc-containing endoprotease whose substrate is synaptobrevin, a constituent protein of the docking complex that enables the synaptic vesicle to fuse with the terminal neuronal cell membrane. The cleavage of synaptobrevin is the final target of tetanus toxin, and even in low doses the neurotoxin will inhibit neurotransmitter exocytosis in the inhibitory interneurons. The blockage of GABA and glycine causes the physiologic effects of tetanus toxin. The 100-kDa heavy chain (B-chain) of the toxin contains its binding and internalization domains. It binds to disialogangliosides (GD2 and GD1b) on the neuronal membrane. The translocation domain aids the movement of the protein across that membrane and into the neuron.

Because *C. tetani* is not an invasive organism, its toxin-producing vegetative cells remain where introduced into the wound, which may display local inflammatory changes and a mixed bacterial flora.

CLINICAL MANIFESTATIONS

Tetanus is most often generalized but may also be localized. The incubation period typically is 2-14 days but may be as long as months after the injury. In **generalized tetanus**, the presenting symptom in about half of cases is **trismus** (masseter muscle spasm, or lockjaw). Headache, restlessness, and irritability are early symptoms, often followed by stiffness, difficulty chewing, dysphagia, and neck muscle spasm. The so-called **sardonic smile of tetanus *(risus sardonicus)*** results from intractable spasms of facial and buccal muscles. When the paralysis extends to abdominal, lumbar, hip, and thigh muscles, the patient may assume an arched posture of extreme hyperextension of the body, or **opisthotonos**, with the head and the heels bent backward and the body bowed forward. In severe cases, only the back of the head and the heels of the patient are noted to be touching the supporting surface. Opisthotonos is an equilibrium position that results from unrelenting total contraction of opposing muscles, all of which display the typical boardlike rigidity of tetanus. Laryngeal and respiratory muscle spasm can lead to airway obstruction and asphyxiation. Because tetanus toxin does not affect sensory nerves or cortical function, the patient unfortunately remains conscious, in extreme pain, and in fearful anticipation of the next tetanic seizure. The seizures are characterized by sudden, severe tonic contractions of the muscles, with fist clenching, flexion, and adduction of the arms and hyperextension of the legs. Without treatment, the duration of these seizures may range from a few seconds to a few minutes in length with intervening respite periods. As the illness progresses, the spasms become sustained and exhausting. The smallest disturbance by sight, sound, or touch may trigger a tetanic spasm. Dysuria and urinary retention result from bladder sphincter spasm; forced defecation may occur. Fever, occasionally as high as 40°C (104°F), is common and is caused by the substantial metabolic energy consumed by spastic muscles. Notable autonomic effects include tachycardia, dysrhythmias, labile hypertension, diaphoresis, and cutaneous vasoconstriction. The tetanic paralysis usually becomes more severe in the first week after onset, stabilizes in the second week, and ameliorates gradually over the ensuing 1-4 weeks.

Neonatal tetanus, the infantile form of generalized tetanus, typically manifests within 3-12 days of birth. It presents as progressive difficulty in feeding (sucking and swallowing), associated hunger, and crying. Paralysis or diminished movement, stiffness and rigidity to the touch, and spasms, with or without opisthotonos, are characteristic. The umbilical stump, which is typically the portal of entry for the microorganism, may retain remnants of dirt, dung, clotted blood, or serum, or it may appear relatively benign.

Localized tetanus results in painful spasms of the muscles adjacent to the wound site and may precede generalized tetanus. **Cephalic tetanus** is a rare form of localized tetanus involving the bulbar musculature and cranial nerves (particularly cranial nerve VII) that occurs with wounds or foreign bodies in the head, nostrils, or face. It also occurs in association with chronic otitis media. Cephalic tetanus is characterized by retracted eyelids, deviated gaze, trismus, *risus sardonicus,* and spastic paralysis of the tongue and pharyngeal musculature and may mimic a cerebrovascular accident.

DIAGNOSIS

The picture of tetanus is one of the most dramatic in medicine, and the diagnosis may be established clinically. The typical setting is an unimmunized patient (and/or mother) who was injured or born within the preceding 2 weeks, who presents with trismus, dysphagia, generalized muscle rigidity and spasm, and a clear sensorium.

Results of routine laboratory studies are usually normal. A peripheral leukocytosis may result from a secondary bacterial infection of the wound or may be stress-induced from the sustained tetanic spasms. The cerebrospinal fluid analysis is normal, although the intense muscle contractions may raise intracranial pressure. Serum muscle enzymes (creatine kinase, aldolase) may be elevated. Neither the electroencephalogram nor the electromyogram (EMG) shows a characteristic pattern, although EMG may show a continuous discharge of motor subunits and shortening or absence of the silent interval normally observed after an action potential. An assay for antitoxin levels is not readily available, although a serum antitoxin level of 0.01 IU/mL or higher is generally considered protective and makes the diagnosis of tetanus less likely. *C. tetani* is not always visible on Gram stain of wound material and is isolated by culture in only approximately 30% of cases. The **spatula test** is a simple diagnostic

bedside test that involves touching the oropharynx with a spatula or tongue blade. Normally this maneuver will elicit a gag reflex, as the patient tries to expel the spatula (negative test). If tetanus is present, patients develop a reflex spasm of the masseters and bite the spatula (positive test). This bedside diagnostic maneuver is said to have a high sensitivity and specificity.

Differential Diagnosis

Florid and generalized tetanus is typically not mistaken for any other disease. However, trismus may result from parapharyngeal, retropharyngeal, or dental abscesses or, rarely, from acute encephalitis involving the brainstem. Either rabies or tetanus may follow an animal bite, and rabies may manifest as trismus with seizures. Rabies may be distinguished from tetanus by hydrophobia, marked dysphagia, predominantly clonic seizures, and pleocytosis (see Chapter 320). Although strychnine poisoning may result in tonic muscle spasms and generalized seizure activity, it seldom produces trismus, and unlike in tetanus, general relaxation usually occurs between spasms. Hypocalcemia may produce tetany that is characterized by laryngeal and carpopedal spasms, but trismus is absent. Occasionally, epileptic seizures, narcotic withdrawal, or other drug reactions may suggest tetanus.

TREATMENT

Management of tetanus requires eradication of *C. tetani,* correction of wound environment conditions conducive to its anaerobic replication, neutralization of all accessible tetanus toxin, control of seizures and respiration, palliation, provision of meticulous supportive care, and, finally, prevention of recurrences.

Surgical wound excision and debridement are often needed to remove the foreign body or devitalized tissue that created the anaerobic growth conditions necessary for vegetative replication. Surgery should be performed promptly after administration of **human tetanus immunoglobulin (TIG)** and antibiotics. Excision of the umbilical stump in the neonate with tetanus is no longer recommended.

Tetanus toxin cannot be neutralized by TIG after it has begun its axonal ascent to the spinal cord. However, TIG should be given as soon as possible, with the goal of neutralizing toxin that diffuses from the wound into the circulation before the toxin can bind at distant muscle groups. The optimal dose of TIG has not been determined. Most experts recommend that a **single intramuscular (IM) injection of 500 units of TIG** is sufficient to neutralize systemic tetanus toxin; although doses as high as 3,000-6,000 have been recommended by some experts, they do not seem to confer better outcomes. Infiltration of part of the dose of TIG into the wound is no longer recommended by the Red Book Committee of the American Academy of Pediatrics, and the entire dose can be administered IM. If TIG is unavailable, use of human intravenous immunoglobulin (at a dose of 200-400 mg/kg) can be considered. Intravenous immunoglobulin contains 4-90 units/mL of TIG; the optimal dosage of intravenous immunoglobulin for treating tetanus is not known, and its use is not approved for this indication. In parts of the world where it is available, another alternative may be equine-derived tetanus antitoxin (TAT). This product is no longer available in the United States. A dose of 1,500-3,000 U is recommended and should be administered after appropriate testing for sensitivity and desensitization, because up to 15% of patients given the usual dose of TAT will experience serum sickness. The human-derived immunoglobulins are much preferred because of their longer half-lives (30 days) and the virtual absence of allergic and serum sickness adverse effects. Results of studies examining the potential benefit of intrathecal administration of TIG are conflicting. The TIG preparation available for use in the United States is neither licensed nor formulated for intrathecal or intravenous use.

Oral (or intravenous) **metronidazole** (30 mg/kg per day, given at 6-hour intervals; maximum dose, 4 g/day) decreases the number of vegetative forms of *C. tetani* and is currently considered the antibiotic of choice. **Parenteral penicillin G** (100,000 U/kg per day, administered at 4- to 6-hour intervals, with a daily maximum of 12 million U) is an alternative treatment. Antimicrobial therapy for a total duration of 7-10 days is recommended (https://publications.aap.org/redbook/book/347/chapter-abstract/5757094/Tetanus-Lockjaw).

Supportive care and pharmacologic interventions targeted at control of tetanic spasms are of critical importance in the management of tetanus. In light of this goal, all patients with generalized tetanus should receive muscle relaxants. **Diazepam** provides both relaxation and seizure control. For neonatal tetanus, an initial dose of 0.1-0.2 mg/kg every 3-6 hours given intravenously is subsequently titrated to control the tetanic spasms (continuous IV infusion doses of 15-40 mg/kg/day have been recommended, titrated to control the spasm). After 5-7 days, the dosage can be decreased by 5-10 mg/day, with the drug given orally or by the nasogastric route, after which the effective dose is sustained for 2-6 weeks before a tapered withdrawal. **Magnesium sulfate** may be useful in controlling autonomic dysfunction: a loading dose of 40 mg/kg IV over 30 minutes has been recommended in a study in tetanus patients >15 years of age, in which the loading dose was followed by 2 g/hr continuously for patients weighing >45 kg, or 1.5 g/hr continuously for patients weighing <45 kg. For neonatal tetanus, a loading dose of 50 mg/kg of magnesium sulfate, followed by a maintenance infusion of 30-50 mg/kg/hr (titrated against clinical effect) has been recommended. Monitoring of serum magnesium levels at least every 6 hours is recommended. In addition to diazepam, other benzodiazepines **(midazolam)**, **chlorpromazine**, **dantrolene**, and **baclofen** are also used. Intrathecal baclofen produces such complete muscle relaxation that apnea often ensues; like most other agents listed, baclofen should be used only in an intensive care unit setting. Favorable survival rates in generalized tetanus have been described with the use of neuromuscular blocking agents such as vecuronium and pancuronium, which produce a general flaccid paralysis that is then managed by mechanical ventilation. Autonomic instability is regulated with standard α- or β- (or both) blocking agents; morphine has also proved useful.

SUPPORTIVE CARE

Meticulous supportive care in a quiet, dark, secluded setting is most desirable. Because tetanic spasms may be triggered by minor stimuli, the patient should be sedated and protected from all unnecessary sounds, sights, and touch, and all therapeutic and other manipulations must be carefully scheduled and coordinated. Endotracheal intubation may not be required, but it should be done to prevent aspiration of secretions before laryngospasm develops. A tracheostomy kit should be immediately at hand for unintubated patients. Endotracheal intubation and suctioning easily provoke reflex tetanic seizures and spasms, so early tracheostomy should be considered in severe cases not managed by pharmacologically induced flaccid paralysis. Therapeutic botulinum toxin has been used for this purpose (i.e., to overcome trismus). Cardiorespiratory monitoring, frequent suctioning, and maintenance of the patient's substantial fluid, electrolyte, and caloric needs are fundamental. Careful nursing attention to mouth, skin, bladder, and bowel function is needed to avoid ulceration, infection, and obstipation. Prophylactic subcutaneous heparin has been suggested to be of value, but it must be balanced with the risk for hemorrhage. Enoxaparin would be an alternative for the patient for whom deep venous thrombosis (DVT) prophylaxis is warranted.

COMPLICATIONS

The seizures and the severe, sustained rigid paralysis of tetanus predispose the patient to many complications. Aspiration of secretions with attendant pneumonia is an important complication to consider and may be present at the time of the initial diagnosis. Maintaining airway patency often mandates endotracheal intubation and mechanical ventilation with their attendant hazards, including pneumothorax and mediastinal emphysema. The seizures may result in lacerations of the mouth or tongue, in intramuscular hematomas or **rhabdomyolysis** with myoglobinuria and renal failure, or in long bone or spinal fractures. Venous thrombosis, pulmonary embolism, gastric ulceration with or without hemorrhage, paralytic ileus, and decubitus ulceration are described as complications. Excessive use of muscle relaxants, which are an integral part of care, may produce iatrogenic apnea. Cardiac arrhythmias, including asystole, unstable blood pressure, and labile temperature regulation, reflect disordered autonomic nervous system control that may be aggravated by inattention to maintenance of intravascular volume needs.

Table 257.1 Tetanus Vaccination and Immune Globulin Use in Wound Management

HISTORY OF ABSORBED TETANUS TOXOID	CLEAN, MINOR WOUNDS		ALL OTHER WOUNDS*	
	DTaP, Tdap, OR Td†	TIG‡	DTaP, Tdap, Or TD†	TIG‡
Uncertain or <3 doses	Yes	No	Yes	Yes
3 or more doses	No, if <10 yr since last dose of tetanus-containing vaccine	No	No, if <5 yr since last tetanus-containing vaccine‖	No
	Yes, if ≥10 yr since last dose of tetanus-containing vaccine	No	Yes, if ≥5 yr since last tetanus-containing vaccine dose	No

*Including but not limited to wounds contaminated with dirt, feces, and saliva; puncture wounds; avulsions; wounds resulting from missiles, crushing, burns, and frostbite.
†DTaP is used for children younger than 7 yr. Tdap is preferred over Td for underimmunized children 7 yr and older who have not received Tdap previously.
‡Intravenous immune globulin should be used when TIG is unavailable.
‖More frequent boosters are not needed and can accentuate adverse events.
DT, Diphtheria and tetanus toxoid vaccine; DTaP, combined diphtheria toxoid–tetanus toxoid–acellular pertussis vaccine; Td, tetanus toxoid and reduced diphtheria toxoid vaccine; Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine; TIG, tetanus immune globulin.
Data from American Academy of Pediatrics. Tetanus (lockjaw). In Kiberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2021–2024 Report of the Committee on Infectious Diseases*, 32nd ed. Itasca, IL: American Academy of Pediatrics, 2021;750–755.

PROGNOSIS

Recovery in tetanus occurs through regeneration of synapses within the spinal cord that results in restoration of muscle relaxation. Interestingly, an episode of tetanus does not result in the production of toxin-neutralizing antibodies, presumably because the infinitesimally small amounts of toxin required to cause disease are not sufficient to elicit an immune response. Therefore active immunization with tetanus toxoid during convalescence and/or at discharge, with provision for completion of the primary vaccine series, is mandatory.

The most important factor that influences outcome is the quality of supportive care. Mortality is highest in the very young and the very old. A favorable prognosis is associated with a long incubation period, absence of fever, and localized disease. An unfavorable prognosis is associated with onset of trismus <7 days after injury and with onset of generalized tetanic spasms <3 days after onset of trismus. Sequelae of hypoxic brain injury, especially in infants, include cerebral palsy, diminished mental abilities, and behavioral difficulties. Most fatalities occur within the first week of illness. Reported case fatality rates for generalized tetanus are 5–35%, and for neonatal tetanus they extend from <10% with intensive care treatment to >75% without it. Cephalic tetanus has an especially poor prognosis because of breathing and feeding difficulties.

PREVENTION

Tetanus is an entirely and easily preventable disease. A serum antibody titer of ≥0.01 units/mL is considered protective. Active immunization should begin in early infancy with combined diphtheria toxoid–tetanus toxoid–acellular pertussis (DTaP) vaccine at 2, 4, 6, and 15-18 months of age, with boosters at 4-6 years (DTaP) and 11-12 years (Tdap) of age, and at 10-year intervals thereafter throughout adult life with tetanus and reduced diphtheria toxoid (Td). Recovery from tetanus does not confer permanent protective immunity, so immunization is recommended in those who have survived documented infection. Immunization of women with tetanus toxoid prevents neonatal tetanus, and pregnant women should receive one dose of reduced diphtheria and pertussis toxoids (Tdap) during each pregnancy, preferably at 27-36 weeks of gestation. Recommended immunization schedules are regularly updated; the most current versions may be found at http://www.cdc.gov/vaccines/schedules.

Arthus reactions (type III hypersensitivity reactions), a localized vasculitis associated with deposition of immune complexes and activation of complement, are reported rarely after tetanus vaccination. Mass immunization campaigns in developing countries have occasionally provoked a widespread hysterical reaction.

Wound Management

Tetanus prevention measures after trauma consist of inducing active immunity to tetanus toxin and of passively providing antitoxic antibody (Table 257.1). Tetanus prophylaxis is an essential part of all wound management, but specific measures depend on the nature of the injury and the immunization status of the patient. Prevention of tetanus must be included in planning for the consequences of bombings, natural disasters, and other possible civilian mass-casualty events.

Tetanus toxoid should always be given after a dog or other animal bite, even though *C. tetani* is infrequently found in canine mouth flora. **Nonminor wounds require human TIG** except those in a fully immunized patient (i.e., ≥3 doses of adsorbed tetanus toxoid). In any other circumstance (e.g., patients with an unknown or incomplete immunization history; crush, puncture, or projectile wounds; wounds contaminated with saliva, soil, or feces; avulsion injuries; compound fractures; or frostbite), TIG 250 units should be administered intramuscularly, regardless of the patient's age or weight. If TIG is unavailable, use of human intravenous immunoglobulin may be considered. If neither of these products is available, then 3,000-5,000 units of equine-derived TAT (in regions of the world where it is available) may be given intramuscularly after testing for hypersensitivity. Serum sickness may occur with this agent. Human monoclonal antibodies against the tetanus neurotoxin have recently been generated and characterized, but these are not yet available for clinical use.

The wound should undergo immediate, thorough surgical cleansing and debridement to remove foreign bodies and any necrotic tissue in which anaerobic conditions might develop. Tetanus toxoid should be given to stimulate active immunity and may be administered concurrently with **TIG** (or TAT); if a tetanus toxoid-containing vaccine and TIG are administered at the same time, then separate syringes and sites should be used. A tetanus toxoid booster (preferably Tdap) is administered to all persons with any wound if the tetanus immunization status is unknown or incomplete. A booster is administered to injured persons who have completed the primary immunization series if (1) the wound is clean and minor, but 10 or more years have passed since the last booster, or (2) the wound is more serious, and 5 or more years have passed since the last booster (see Table 257.1). Persons who experienced an Arthus reaction after a dose of tetanus toxoid–containing vaccine should not receive Td more frequently than every 10 years, even for tetanus prophylaxis as part of wound management. In a situation of delayed wound care, active immunization should be started at once.

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Chapter 258

Clostridioides difficile Infection

David P. Galloway and Mitchell B. Cohen

Clostridioides difficile (formerly *Clostridium difficile*) infection **(CDI)**, also known as **pseudomembranous colitis** or *C. difficile*–associated diarrhea, refers to gastrointestinal (GI) colonization with *C. difficile* resulting in a diarrheal illness. It is a common cause of **antibiotic-associated diarrhea** and the most common cause of healthcare-associated infections in the United States, accounting for 12% of these infections. An increase in inpatient and outpatient (community) acquisition of **CDI** has been observed, and additional risk factors have been identified.

ETIOLOGY

C. difficile is a gram-positive, spore-forming, anaerobic bacillus that is resistant to killing by alcohol. It is acquired from the environment or by the fecal-oral route. Organisms causing symptomatic intestinal disease produce **toxin A** and/or **toxin B**. These toxins affect intracellular signaling pathways, resulting in inflammation and cell death. The cytotoxic **binary toxin**, which belongs to the AB toxin family, is not present in the majority of strains but has been detected in epidemic strains.

EPIDEMIOLOGY

The incidence of **CDI** is increasing in pediatric patients, and the setting of acquisition is changing. There is both high incidence in hospitalized children and an emergence of community-onset infection. National data from the Centers for Disease Control and Prevention (CDC) estimate three cases of community-acquired **CDI** in children for every healthcare-acquired case. In addition to an overall increase in all strains, a *hypervirulent strain,* denoted **NAP1/BI/027** (also called **BI**), has emerged and is estimated to cause 10–20% of pediatric infections. This strain produces **binary toxin** and exhibits 16- and 23-fold increases in the production of toxins A and B, respectively.

Asymptomatic carriage occurs with potentially pathogenic strains and is common in neonates and infants ≤1 year old. A carrier frequency rate of 50% may occur in children <1 year old. Colonization rates decrease to less than 5% in healthy children >5 years old. Asymptomatic colonization with *C. difficile* is common in recently hospitalized patients, with rates of 20%. Carriers can infect other susceptible individuals.

Risk factors for **CDI** include the use of broad-spectrum antibiotics, hospitalization, exposure to a household member with diarrhea or an asymptomatic carrier, GI surgery, inflammatory bowel disease (IBD), Hirschsprung disease, chemotherapy, enteral tube feeding, proton pump inhibitor (PPI) or H_2-receptor antagonist use, malnutrition, and chronic illness.

PATHOGENESIS

Disease is caused by GI infection with a toxin-producing strain. Any process that disrupts normal flora, impairs the acid barrier defense, alters the normal GI immune response (e.g., IBD), or inhibits intestinal motility may lead to infection. Normal bowel flora appears to be protective, conferring *colonization resistance*.

By affecting intracellular signaling pathways and cytoskeletal organization, toxins induce an inflammatory response and cell death, leading to diarrhea and pseudomembrane formation. Antibodies against **toxin A** have been shown to confer protection against symptomatic disease, and failure of antibody production occurs in patients with recurrent disease.

CLINICAL MANIFESTATIONS

Infection with toxin-producing strains of *C. difficile* leads to a spectrum of disease ranging from mild, self-limited diarrhea, to explosive, watery diarrhea with occult blood or mucus, to **pseudomembranous colitis**, and even death. **Pseudomembranous colitis** is characterized by bloody diarrhea with accompanying fever, abdominal pain/cramps, nausea, and vomiting. Rarely, small-gut involvement, **toxic megacolon**, bacteremia, abscess formation, intestinal perforation, and death can occur.

Symptoms of **CDI** generally begin less than a week after colonization and may develop during or weeks after antibiotic exposure. Symptoms are generally more severe in certain populations, including patients receiving chemotherapy, patients with chronic GI disease (e.g., IBD), and some patients with cystic fibrosis (CF). **CDI**-associated **reactive arthritis** is an occasional complication, occurring in approximately 1.4% of children with **CDI**. Reactive arthritis begins a median of 10 days after initial GI symptoms, often accompanied by fever or rash. Joint involvement may be migratory or polyarticular and may resemble septic arthritis.

DIAGNOSIS

Evaluation for **CDI** should be reserved for children with **diarrhea**, defined as the passage of at least three loose stools within a 24-hour period or bloody diarrhea (Fig. 258.1 and Table 258.1). **CDI** is diagnosed by the detection of a *C. difficile* toxin in the stool of a symptomatic patient. Most patients present with a history of recent antibiotic

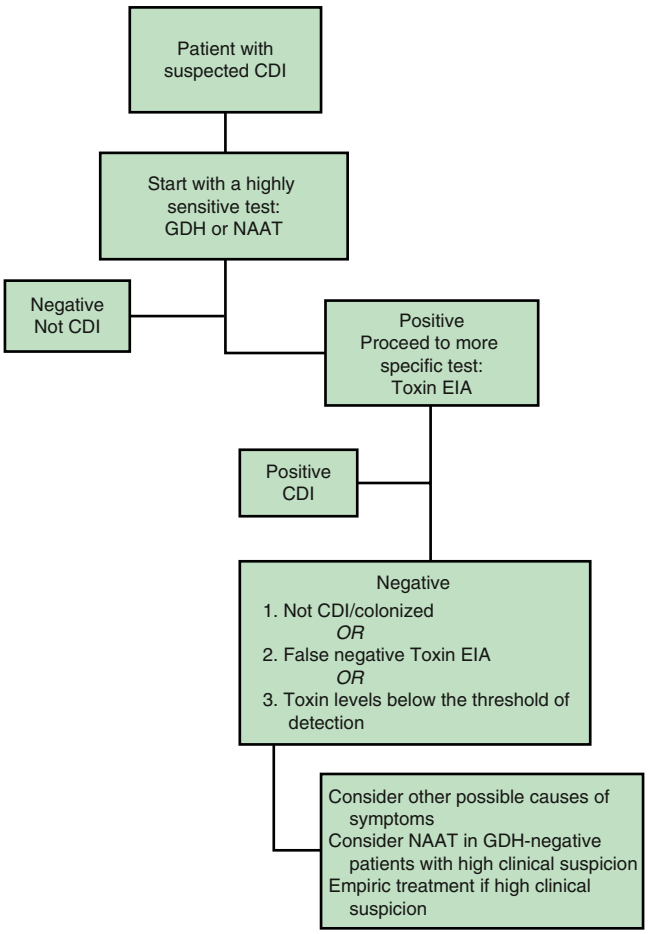

Fig. 258.1 Proposed algorithm for testing of *Clostridioides difficile* infection (CDI). EIA, Enzyme immunoassay; GDH, glutamate dehydrogenase; NAAT, nucleic acid amplification testing. *(From Kelly CR, Fischer M, Allegretti JR, et al. ACG clinical guidelines: prevention, diagnosis, and treatment of Clostridioides difficile in infections. Am J Gastroenterol. 2021;116:1124–1147, Fig. 1.)*

Table 258.1 Diagnosis of *C. difficile* Disease

- *Clostridium difficile* (renamed *Clostridioides difficile*) infection is diagnosed by a combination of clinical and laboratory findings.
- Diagnosis requires a positive test for the presence of *C. difficile* toxins.
- Glutamate dehydrogenase (GDH), produced by *C. difficile*, can be detected in stool. However, it is not specific and can be produced by nontoxigenic *C. difficile*.
- Enzyme immunoassay testing for toxin A and/or B has a variable sensitivity and specificity, a turnaround time of about 24 hours and correlates well with disease activity.
- Polymerase chain reaction testing has a high sensitivity and specificity, a turnaround time of less than 4 hours, and correlates less with disease activity, thus identifying patients with colonization and active infection. Increasingly, combination testing is being employed to improve diagnostic accuracy.
- Laboratory testing for *C. difficile* toxins should only be performed on patients with at least three unformed stools per 24 hours, who are not on laxatives, and is not useful as a test of cure.
- Pathologic findings can help to confirm the diagnosis.

From Semel JD. *Clostridioides difficile* colitis. In: Kellerman RD, Rakel DP, Heidelbaugh JJ, Lee EM, eds. *Conn's Current Therapy 2023.* Philadelphia: Elsevier; 2023:561.

use, but the absence of antibiotic exposure should not dissuade the clinician from considering this diagnosis and ordering the appropriate test. Conversely, high carriage rates without illness among infants should prompt careful consideration when testing and treating children <3 years old.

The standard test for toxin is the **enzyme immunoassay** (EIA), a same-day test for **toxin A** and/or **toxin B** with sufficient specificity (94–100%) but less-than-ideal sensitivity (88–93%). Many laboratories use **nucleic acid amplification tests** (NAATs) to supplement or supplant **EIA** with the goal of improving sensitivity. The sensitivities of the real-time polymerase chain reaction (PCR) assay for **toxin A/B** are superior compared with **EIA** for **toxin A/B** (95% vs 35%, respectively), and the specificity is equal (100%). However, some have questioned the clinical significance of low copy number–positive tests. For example, positive *C. difficile* PCR results occur with similar frequency in patients with IBD with and without an IBD exacerbation. A positive result in a highly sensitive PCR assay that detects low copy numbers of a toxin gene in *C. difficile* may reflect colonization in a subset of patients (e.g., with IBD), confounding clinical decision-making in managing disease exacerbations. To address this, **NAAT**-positive tests may be "confirmed" by toxin assays. In addition, eliminating certain high carrier populations from testing (e.g., children under 1 year of age) will increase the positive predictive value of laboratory testing. Because sensitivity is so high with molecular tests, if the first test is negative, repeat testing during the same episode of diarrhea is discouraged, as repeat testing in this setting is more likely to result in another negative or a false-positive test than a true positive test. Because shedding of *C. difficile* in stool can persist for several months after symptom resolution, tests of cure are impractical and are not performed.

Culture for organism isolation is a sensitive test but is labor intensive, taking several days. Culture alone is not specific because it does not differentiate between toxin-producing and non–toxin-producing strains.

Pseudomembranous nodules and characteristic plaques may be seen in colonoscopy or sigmoidoscopy, but endoscopy is usually not performed to make the diagnosis.

TREATMENT

Initial treatment of **CDI** involves discontinuation of any nonvital antibiotic therapy and administration of fluid and electrolyte replacement. For mild cases, this treatment may be curative. Drugs that decrease intestinal motility should be avoided. Asymptomatic patients should not be treated. Persistent symptoms or moderate to severe disease warrant antimicrobial therapy directed against *C. difficile*.

Oral metronidazole or vancomycin is the first-line therapy for mild to moderate **CDI** in children (Table 258.2). In adults, vancomycin or fidaxomicin are the preferred first-line therapies. For more severe infection, oral vancomycin is approved by the U.S. Food and Drug Administration (FDA) for CDI. Vancomycin exhibits ideal pharmacologic properties for treatment of this enteric pathogen because it is not absorbed in the gut. Vancomycin is suggested as a first-line agent for severe disease, as manifested by hypotension, peripheral leukocytosis, or severe pseudomembranous colitis. Fidaxomicin is approved for use in children at least 6 months of age and is a narrow-spectrum macrolide antibiotic with noninferior efficacy to vancomycin but superior recurrence prevention. Because treatment of CDI continues to evolve, adult-based protocols (Table 258.3) may be relevant to older children and adolescents.

Table 258.2 Treatment Recommendations for *Clostridioides difficile* Infection in Children

CDI CLASSIFICATION	ANTIBIOTIC REGIMEN
First episode or first recurrence,* nonsevere	Metronidazole 7.5 mg/kg/dose (max 500 mg/dose) PO tid × 10 days; *OR* Vancomycin 10 mg/kg/dose (max 125 mg/dose) PO qid × 10 days
Second or subsequent† recurrence, nonsevere	Vancomycin in a tapered and pulsed regimen‡; *OR* Vancomycin (dosing and duration as above) followed by rifaximin 10 mg/kg/dose (max 400 mg/dose) PO tid × 20 days§; *OR* Fidaxomicin 16 mg/kg/dose (max 200 mg/dose) PO bid × 10 days; *OR* Fecal microbiota transplantation
Severe/fulminant‖ (first or recurrent¶ episode)	Vancomycin 10 mg/kg/dose (max 500 mg/dose) PO qid × 10 days If critically ill, consider adding metronidazole 7.5 mg/kg/dose (max 500 mg/dose) IV tid × 10 days

*For first recurrence, consider vancomycin if metronidazole was used to treat initial episode.
†Recommend tapered and pulsed regimen if vancomycin was used for the initial infection.
‡Tapered and pulsed regimen: vancomycin 10 mg/kg/dose (max 125 mg/dose) qid × 10-14 days, then 10 mg/kg/dose (max 125 mg/dose) bid × 1 wk, then 10 mg/kg/dose (max 125 mg/dose) qd × 1 wk, and then 10 mg/kg/dose (max 125 mg/dose) every 2-3 days for 2-8 wk.
§Pediatric rifaximin dosing is not available and not FDA-approved for children younger than 12 yr.
‖Definitions for severe and fulminant CDI are based on expert consensus for adult patients and have not been validated. Severe: leukocytosis with a white blood cell count of ≥15,000 cells/μL or a serum creatinine level >1.5 mg/dL. Fulminant: hypotension or shock, ileus, megacolon.
¶If treating a recurrent episode that is severe/fulminant, consider extending vancomycin in a pulsed, tapering fashion as indicated above§ or fecal microbiota transplantation when clinically improved.
Data from McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis.* 2018; 66(7):e1–e48.

PROGNOSIS AND RECURRENCE

The response rate to initial treatment of CDI can reach >95%. Studies have demonstrated a variation in response rates based on the severity of CDI and the treatment agent. Treatment failure and recurrence have been increasing; the risk of subsequent reappearance increases with each recurrence.

Recurrences occur in 5–20% of patients, are diagnosed clinically, and generally occur within 4 weeks of treatment. Some recurrences result from incomplete eradication of the original strain, and others are caused by reinfection with a different strain. Treatment for the initial recurrence involves retreatment with the original antibiotic course.

Table 258.3 Recommendations for the Treatment of *C. difficile* Infection in Adults

CLINICAL DEFINITION		SUPPORTIVE CLINICAL DATA	RECOMMENDED TREATMENT*	STRENGTH OF RECOMMENDATION/QUALITY OF EVIDENCE
Initial infection		Leukocytosis with white blood cell count of ≤15,000 cells/mL and serum creatinine level <1.5 mg/dL	Fidaxomicin 200 mg bid × 10 days	Strong/high
			Vancomycin 125 mg qid × 10 days	Strong/high
			Alternate if previous agents are unavailable: metronidazole 500 mg tid PO × 10-14 days	Weak/high
	Fulminant	Hypotension or shock, ileus, megacolon	Vancomycin 500 mg qid PO or by nasogastric tube	Strong/moderate (oral vancomycin), weak/low (rectal vancomycin), strong/moderate (intravenous metronidazole)
			If ileus, consider adding rectal instillation of vancomycin; intravenous metronidazole (500 mg every 8 hr) should be administered with oral or rectal vancomycin, particularly if ileus is present	
Recurrence	First recurrence, nonsevere		Fidaxomicin 200 mg bid × 10 days, or bid × 5 days, then qod for 20 days *or*	Weak/low
			Use prolonged tapered and pulsed vancomycin regimen (if standard regimen was used for initial episode) 125 mg qid for 10-14 days, bid for 1 wk, qd for 1 wk, and then every 2 or 3 days for 2-8 wk, *or*	Weak/low
			Vancomycin 125 mg qid × 10 days (if metronidazole was used for the initial episode)	Weak/moderate
	Second or subsequent recurrence		Fidaxomicin 200 mg bid × 10 days, *or* bid × 5 days, then qod for 20 days	Weak/low
			Vancomycin in a tapered or pulsed regimen *or*	Weak/low
			Vancomycin 125 mg qid × 10 days, followed by rifaximin 400 mg tid × 20 days, *or*	Weak/low
			Fecal microbiota transplantation†	Strong/moderate

*All randomized trials have compared 10-day treatment courses, but some patients (particularly those treated with metronidazole) may have delayed response to treatment, and clinicians should consider extending treatment duration to 14 days in those circumstances.

†The opinion of the panel is that appropriate antibiotic treatments for at least two recurrences (i.e., three CDI episodes) should be tried before offering fecal microbiota transplantation. For adult patients with a recurrent CDI episode within the last 6 months, current guidelines suggest using bezlotoxumab in addition to appropriate antibiotics as the first approach.

PO, Orally (by mouth); qd, once daily; bid, twice daily; tid, 3 times daily; qid, 4 times daily; qod, every other day.

Adapted from McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis*. 2018;66(7):e1–e48, Table 1; and Johnson S, Lavergne V, Skinner AM, et al. Clinical practice guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 focused update guidelines on management of *Clostridioides difficile* infection in adults. *Clin Infect Dis*. 2021;73(5):e1029–e1044, Table 1.

Recurrences of CDI may be caused by a suboptimal immune response, failure to kill organisms that have sporulated, or failure of delivery of antibiotic to the site of infection in the case of ileus or toxic megacolon. Subsequent treatment with pulsed or tapered vancomycin decreases recurrence rates. In addition to this approach, other antibiotics (rifaximin or nitazoxanide), toxin-binding polymers (Tolevamer), and probiotics (*Saccharomyces boulardii* or *Lactobacillus* GG) have been used as adjunctive therapy. For adult patients with a recurrent CDI episode within the last 6 months, guidelines suggest using bezlotoxumab, a humanized monoclonal antibody against *C. difficile* toxin B, as a co-intervention. Because treatment of CDI continues to evolve, adult-based protocols (see Table 258.3) may be applicable for treatment of older children and adolescents.

Because failure to manifest an adequate antitoxin immune response is associated with a higher frequency of recurrent CDI, intravenous immune globulin has been used to treat recurrent disease. In the case of ileus or toxic megacolon, an enema of vancomycin may be used to place the antibiotic directly at the site of infection, although most often intravenous therapy is first attempted in this circumstance.

Fecal microbiota transplantation (FMT) has been used to address the disruption in normal gut flora thought to allow colonization with *C. difficile* (see Table 258.3). FMT involves the instillation of fecal material from a healthy donor into the patient's GI tract by nasoenteric tube, enema, capsules, or colonoscopy. Published FMT results in children with recurrent CDI are limited to case reports and small case series. There are few data to guide clinicians on the indications, route, efficacy, and safety of FMT in children. Initial reports indicate an overall success rate of approximately 90% in patients with recurrent CDI. Current approaches to FMT are not specific and involve complete reconstitution of the gut microbiome. The gut microbiota has been shown to influence susceptibility to genetic and environmentally acquired conditions. Transplantation of healthy donor fecal material to patients with CDI may reestablish the "normal" composition of the gut microbiota but has the theoretical concern of adding new, microbiome-based susceptibilities derived from the donor microbiome.

The FDA has approved an orally administered commercially available fecal microbiotic product for patients ≥18 years old, following antibiotic therapy for recurrent CDI. The goal is to prevent recurrence of CDI. Fecal-derived live bacteria from screened donors is administered once daily for 3 days.

It is important to recognize that postinfectious diarrhea may result from other causes, such as postinfectious irritable bowel syndrome, microscopic colitis, and IBD.

PREVENTION

The strategies for prevention of CDI include recognition of common sites of acquisition (hospitals, childcare settings, extended-care facilities); effective environmental cleaning (i.e., use of chlorinated cleaning solutions); appropriate antibiotic (antibiotic stewardship) and PPI prescription practices; cohorting of infected patients; contact precautions; and proper handwashing with soap and water. Probiotics may possibly reduce the incidence of *C. difficile*–associated diarrhea.

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Chapter 259

Other Anaerobic Infections

Michael E. Russo

Anaerobic bacteria are among the most numerous organisms colonizing humans and are also present widely in the soil. **Obligate anaerobes** are markedly or entirely intolerant of exposure to oxygen. **Facultative anaerobes** can survive in the presence of environmental oxygen but grow better in settings of reduced oxygen tension. This chapter concentrates on obligate anaerobes and associated infections.

Infections with endogenous anaerobes usually occur adjacent to mucosal surfaces, often as polymicrobial infections with aerobes. In many of these polymicrobial infections, it is unclear how direct a role anaerobes are playing in illness versus just being present by virtue of breached mucosal barriers. Traumatized areas that have been devascularized with resultant low oxygen tension provide ideal sites for anaerobic infection. Abscess formation can evolve over days to weeks and generally involves both aerobes and anaerobes. An example of such an infection is ruptured appendicitis leading to secondary peritonitis and intrabdominal abscesses. Pure anaerobic infections from endogenous bacteria are much less common (although certain relevant clinical syndromes such as Lemierre syndrome are discussed later).

The most common and clinically relevant anaerobic bacteria in pediatrics are listed in Table 259.1 and discussed further later in the chapter. The taxonomy has undergone significant changes over the years, and many species that would not have been easily identifiable may now be identified in clinical specimens with the widespread use of matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS). Our understanding of anaerobic bacteria in infections is largely limited to easily culturable species. As many anaerobes of the human microbiota remain unculturable, our understanding of anaerobic infections will continue to evolve with culture-independent methods such as metagenomic sequencing.

Bacteroides fragilis and related species are the predominant anaerobes of the large intestine and thus are involved in complicated intraabdominal infections. *Prevotella* spp., *Porphyromonas* spp., and *Fusobacterium* spp. reside in the upper respiratory tract and intestine and are most frequently involved in complications of pharyngitis and sinusitis or in aspiration pneumonia. The gram-positive anaerobic cocci (GPAC) have undergone significant taxonomic changes in recent years, with most prior *Peptostreptococcus* spp. being reclassified into the genera of *Finegoldia, Parvimonas, Anaerococcus,* and *Peptoniphilus*. It is not clear yet how clinically relevant this reclassification is Collectively, the GPAC are normal flora of the skin and upper respiratory, intestinal, and genital mucosa. They may be involved in complications of infections of any of these areas, but they are relatively less virulent than other anaerobic bacteria, and their recovery in culture may or may not be clinically relevant. The gram-positive anaerobic bacilli can be divided into spore forming (*Clostridium* spp.) and non–spore-forming (*Cutibacterium acnes* [formerly *Propionibacterium acnes*] and *Actinomyces* spp.). *C. acnes* lives within hair follicles and sebaceous glands and is an important cause of prosthetic infections, particularly related to ventricular shunts. Some *Actinomyces* spp. are obligate or facultative anaerobes and are discussed in Chapter 235. *Clostridium* spp. cause disease by proliferation and often by production of toxins. Of the >60 species that have been identified, only a few cause infections in humans. The most frequently implicated *Clostridium* spp. are *C. difficile* (see Chapter 258), *C. perfringens* (discussed further later), *C. botulinum* (see Chapter 256), and *C. tetani* (see Chapter 257).

CLINICAL MANIFESTATIONS

Anaerobic infections occur in a variety of sites throughout the body, with examples including complications of pharyngitis such as peritonsillar abscess and Lemierre syndrome (see Chapter 432), dental abscesses (see Chapter 358), complications of sinusitis such as orbital cellulitis (see Chapter 674) and brain abscess (see Chapter 644), aspiration pneumonia (see Chapter 447) and lung abscess (see Chapter 453), secondary peritonitis (see Chapter 419), appendicitis (see Chapter 391), necrotizing enterocolitis (see Chapter 136), and pelvic inflammatory disease and tubo-ovarian abscesses (see Chapter 163).

Table 259.1 Clinically Relevant Anaerobic Bacteria in Common Pediatric Infections

Gram-positive cocci	*Peptostreptococcus, Finegoldia, Parvimonas, Anaerococcus,* and *Peptoniphilus* spp.
Gram-positive, spore-forming rods	*Clostridium* spp.
Gram-positive, non–spore-forming rods	*Cutibacterium acnes* Some *Actinomyces* spp.
Gram-negative bacilli	*Bacteroides fragilis* *Prevotella, Porphyromonas,* and *Fusobacterium* spp.

Anaerobic Bacteremia

Anaerobic bacteremia is relatively rare in children, and the yield of routine anaerobic blood cultures in various settings and patient populations continues to be debated. There is wide practice variation on the routine collection of anaerobic blood culture bottles, and multiple studies have failed to consistently identify predictive risk factors for anaerobic bacteremia in children. *B. fragilis* bacteremia has been seen most frequently (albeit uncommonly) in two settings: early-onset sepsis in premature infants and sepsis in those with compromised lower gastrointestinal tract mucosa (perforation, surgery, or chemotherapy-induced mucositis). *Fusobacterium* spp. bacteremia is typically seen in the setting of Lemierre syndrome: **septic thrombophlebitis** of the internal jugular vein as a complication of pharyngitis.

Myonecrosis (Gas Gangrene)

C. perfringens is the major etiologic cause of myonecrosis, a rapidly progressive anaerobic soft tissue infection. Gas gangrene usually affects muscles compromised by surgical or trauma sites that become contaminated with *C. perfringens* spores from soil or other foreign material. Infection progresses rapidly (within 24 hours) with swelling, edema, crepitus, and myonecrosis. Severe shock and multiorgan dysfunction are common. A clue to the diagnosis of gas gangrene is pain out of proportion to the clinical appearance of the wound. Exudate from surgical specimens reveals gram-positive bacilli but few leukocytes. Early and complete debridement with excision of necrotic tissue is key to controlling the infection. Repeated, frequent assessment of tissue viability in the operating room is required; however, the prognosis is poor, and morbidity and mortality are high. The role of adjunctive hyperbaric oxygen therapy is uncertain.

Food Poisoning

C. perfringens can also produce an enterotoxin that causes **food poisoning**. This intoxication results in the acute onset of watery diarrhea and crampy abdominal pain. Therapy is mainly supportive and consists of rehydration and electrolyte replacement if necessary. The illness resolves spontaneously within 24 hours of onset, and thus specific etiologic diagnosis is rarely made unless a large outbreak is investigated by public health authorities. Frequent sources of infection include meat and other animal products served in group settings during which food is allowed to sit for hours at temperatures warm enough to promote growth of *C. perfringens*.

DIAGNOSIS

The diagnosis of anaerobic infection requires a high index of suspicion and the collection of appropriate and adequate specimens for anaerobic culture (Table 259.2). Culture specimens should be obtained in a manner that protects them from contamination with mucosal bacteria. Aspirates of infected sites, abscess material, and biopsy specimens are appropriate for anaerobic culturing. Specimens should be protected from atmospheric oxygen and transported to the laboratory immediately. Anaerobic transport medium increases the likelihood of recovery of obligate anaerobes. Gram staining is useful, because even if the organisms do not grow in culture, they can be seen on the smear. Once growth has occurred, many clinically relevant anaerobes may now be identified by MALDI-TOF MS. 16S ribosomal RNA (rRNA) gene sequencing at a reference laboratory can identify less common bacteria.

Table 259.2 Clues to the Presumptive Diagnosis of Anaerobic Infections*

Infection contiguous to or near a mucosal surface colonized with anaerobic bacteria (oropharynx, intestinal-genitourinary tract)
Severe tissue necrosis, abscesses, gangrene, or fasciitis
Gas formation in tissues (crepitus on exam or gas visible on imaging)
Failure to culture organisms using conventional aerobic microbiologic methods, despite the presence of visible organisms on Gram stain
Toxin-mediated syndromes: botulism, tetanus, gas gangrene, food poisoning, pseudomembranous colitis

*Suspicion of anaerobic infection is critical before specimens are sampled for culture to ensure optimal microbiologic techniques.

Antimicrobial resistance among anaerobes has increased over time, and the susceptibility of anaerobes to certain antibiotics has become less predictable. A rapid and simple screening test for β-lactamase production and presumptive penicillin resistance can be performed on some anaerobic gram-negative bacilli. More detailed susceptibility testing is usually only available at reference laboratories and may be recommended for isolates recovered from sterile body sites that are deemed clinically important and are known to have variable or unique susceptibilities. Because anaerobic bacteria are less routinely submitted for susceptibility testing, local antibiogram data are frequently limited and extrapolated from larger national case series.

TREATMENT

Treatment of anaerobic infections usually requires adequate drainage and appropriate antimicrobial therapy. Anaerobes can be generally lumped into groups of predicted susceptibility, but because most anaerobic infections are polymicrobial, the choice of agents is frequently driven by the aerobic bacteria suspected or proven to be involved. The specific dose, frequency, and duration vary widely by the specific clinical syndrome.

ANAEROBIC GRAM-NEGATIVE BACILLI

Most *B. fragilis* produces a β-lactamase that hydrolyzes penicillins but is inhibited by most β-lactamase inhibitors (clavulanate, sulbactam, and tazobactam but not avibactam). They also produce a cephalosporinase that hydrolyzes most cephalosporins but not cephamycins. Neither of the enzymes hydrolyzes carbapenems. Hence, most isolates are susceptible to ampicillin-sulbactam, amoxicillin-clavulanate, piperacillin-tazobactam, cefoxitin, and carbapenems (imipenem, meropenem, doripenem, and ertapenem). Notably, ceftazidime-avibactam is the exception to the reliability of β-lactamase inhibitors and does not have reliable *B. fragilis* activity. *Prevotella, Porphyromonas,* and *Fusobacterium* spp. are all generally less resistant than *Bacteroides*. They less frequently produce a β-lactamase, and many remain susceptible to penicillin. *Fusobacterium* spp. are usually susceptible to cephalosporins such as ceftriaxone, but *Prevotella* and *Porphyromonas* have more variable susceptibility.

Metronidazole is reliably active against nearly all anaerobic gram-negative bacilli. Clindamycin resistance in *B. fragilis* has increased over the years, and thus clindamycin is no longer recommended for empiric treatment, leading to the admonition against using clindamycin for infections "below the diaphragm." The other anaerobic gram-negative bacilli are usually still susceptible to clindamycin. Because of increasing resistance, moxifloxacin is no longer recommended as first-line therapy for infections involving anaerobic gram-negative bacilli.

ANAEROBIC GRAM-POSITIVE ORGANISMS

Most non–spore-forming, positive bacilli and some GPAC are resistant to metronidazole. Most are highly susceptible to penicillin but variably susceptible to clindamycin. Treatment of clostridial infections varies widely by the specific clinical syndrome and may or may not involve antibiotics and/or specific antitoxins.

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Section 7

Mycobacterial Infections

Chapter 260

Principles of Antimycobacterial Therapy

Stacene R. Maroushek

The treatment of mycobacterial infection and disease can be challenging. Patients require therapy with multiple agents, the offending pathogens commonly exhibit complex drug resistance patterns, and patients often have underlying conditions that affect drug choice and monitoring. Several of the drugs have not been well studied in children, and current recommendations are extrapolated from the experience in adults.

Single-drug therapy of *Mycobacterium tuberculosis* and nontuberculous mycobacteria is not recommended because of the high likelihood of developing antimicrobial resistance. Susceptibility testing of mycobacterial isolates often can aid in therapeutic decision-making.

AGENTS USED AGAINST MYCOBACTERIUM TUBERCULOSIS

Commonly Used Agents

Isoniazid

Isoniazid **(INH)** is a hydrazide form of isonicotinic acid and is bactericidal for rapidly growing *M. tuberculosis.* The primary target of INH involves the *INHA* gene, which encodes the enoyl acyl carrier protein (ACP) reductase needed for the last step of the mycolic acid biosynthesis pathway of cell wall production. Resistance to INH occurs after pathogenic variants in the *INHA* gene or in other genes encoding enzymes that activate INH, such as *katG*.

INH is indicated for the treatment of *M. tuberculosis, M. kansasii,* and *M. bovis.* The pediatric dosage is 10-15 mg/kg/day orally (PO) in a single dose, not to exceed 300 mg/day. The adult dosage is 5 mg/kg/day PO in a single dose, not to exceed 300 mg/day. Alternative pediatric dosing is 20-30 mg/kg PO in a single dose, not to exceed 900 mg/dose, given twice weekly under **directly observed therapy (DOT)**, in which patients are observed to ingest each dose of antituberculosis medication to maximize the likelihood of completing therapy. The duration of treatment depends on the disease being treated (Table 260.1). INH needs to be taken 1 hour before or 2 hours after meals because food decreases absorption. It is available in liquid, tablet, intravenous (IV; not approved by the U.S. Food and Drug Administration [FDA]), and intramuscular (IM) preparations.

Major **adverse effects** include hepatotoxicity in 1% of children and approximately 3% of adults (increasing with age) and dose-related peripheral neuropathy. Pyridoxine can prevent the peripheral neuropathy and is indicated for breastfeeding infants and their mothers, children and youth on milk- or meat-deficient diets, pregnant adolescents, and symptomatic HIV-infected children. Minor adverse events include rash, worsening of acne, epigastric pain with occasional nausea and vomiting, decreased vitamin D levels, and dizziness. The liquid formulation of INH contains sorbitol, which often causes diarrhea and stomach upset.

INH is accompanied by significant drug-drug interactions (Table 260.2). The metabolism of INH is by acetylation. Acetylation rates have minimal effect on efficacy, but **slow acetylators** have an increased risk for hepatotoxicity, especially when INH is used in combination with rifampin. Routine baseline liver function testing or monthly monitoring is only indicated for persons with underlying hepatic disease or those receiving concomitant hepatotoxic drugs, including other antimycobacterial agents, acetaminophen, or alcohol. Monthly clinic visits while taking INH alone are encouraged to monitor adherence, adverse effects, and worsening of infection.

Rifamycins

The rifamycins (rifampin, rifabutin, rifapentine) are a class of macrolide antibiotics developed from *Streptomyces mediterranei.* Rifampin is a synthetic derivative of rifamycin B, and rifabutin is a derivative of rifamycin S. Rifapentine is a cyclopentyl derivative. The rifamycins inhibit the DNA-dependent RNA polymerase of mycobacteria, resulting in decreased RNA synthesis. These agents are generally bactericidal at treatment doses, but they may be bacteriostatic at lower doses. Resistance is from a pathogenic variant in the DNA-dependent RNA polymerase gene *(rpoB)* that is often induced by previous incomplete therapy. Cross-resistance between rifampin and rifabutin has been demonstrated.

Rifampin is active against *M. tuberculosis, M. leprae, M. kansasii,* and *M. avium* complex. Rifampin is an integral drug in standard combination treatment of active *M. tuberculosis* disease and can be used as an alternative to INH in the treatment of latent tuberculosis infection in children who cannot tolerate INH. **Rifabutin** has a similar spectrum, with increased activity against *M. avium* complex. **Rifapentine** is undergoing pediatric clinical trials and appears to have activity similar to the activity of rifampin. The pediatric dosage of rifampin is 10-15 mg/kg/day PO in a single dose, not to exceed 600 mg/day. The adult dosage of rifampin is 5-10 mg/kg/day PO in a single dose, not to exceed 600 mg/day. Commonly used rifampin preparations include 150- and 300-mg capsules and a suspension that is usually formulated at a concentration of 10 mg/mL. The shelf life of rifampin suspension is short (approximately 4 weeks), so it should not be compounded with other antimycobacterial agents. An IV form of rifampin is also available for initial treatment of patients who cannot take oral preparations. Dosage adjustment is needed for patients with liver failure. Other rifamycins (rifabutin and rifapentine) have been poorly studied in children and are not recommended for pediatric use.

Rifampin can be associated with **adverse effects** such as transient elevations of liver enzymes; gastrointestinal (GI) upset with cramps, nausea, vomiting, and anorexia; headache; dizziness; and immunologically mediated fever and flulike symptoms. Thrombocytopenia and hemolytic anemias can also occur. Rifabutin has a similar spectrum of toxicities, except for an increased incidence of rash (4%) and neutropenia (2%). Rifapentine has fewer adverse effects but is associated with hyperuricemia and cytopenias, especially lymphopenia and neutropenia. All rifamycins can turn urine and other secretions (tears, saliva, stool, sputum) *orange,* which can stain contact lenses. Patients and families should be warned about this common but otherwise innocuous adverse effect.

Rifamycins induce the hepatic cytochrome P450 (CYP) isoenzyme system and are associated with the increased metabolism and decreased level of several drugs when administered concomitantly. These drugs include digoxin, corticosteroids such as prednisone and dexamethasone, dapsone, fluconazole, phenytoin, oral contraceptives, warfarin, and many antiretroviral agents, especially protease inhibitors and nonnucleoside reverse transcriptase inhibitors. Rifabutin has less of an effect on lowering protease inhibitor levels.

The use of pyrazinamide in combination with rifampin for short-course latent tuberculosis therapy has been associated with serious liver dysfunction and death. This combination has never been well studied or recommended for pediatric patients and should not be used.

Table 260.1 Recommended Usual Treatment Regimens for Drug-Susceptible Tuberculosis in Infants, Children, and Adolescents

INFECTION/DISEASE CATEGORY	REGIMEN	COMMENTS
LATENT *MYCOBACTERIUM TUBERCULOSIS* INFECTION*		
Isoniazid susceptible	12 wk of isoniazid plus rifapentine once a wk *or*	
	4 mo of rifampin once a day *or*	Continuous daily therapy is required. Intermittent therapy even by DOT is not recommended.
	9 mo of isoniazid once a day	If daily therapy is not possible, DOT twice a week can be used for 9 mo.
Isoniazid resistant	4 mo of rifampin once a day	Continuous daily therapy is required. Intermittent therapy even by DOT is not recommended.
Isoniazid-rifampin resistant	Consult a tuberculosis specialist.	Moxifloxacin or levofloxacin with or without ethambutol or pyrazinamide.
PULMONARY AND EXTRAPULMONARY INFECTION		
Except meningitis†	2 mo of isoniazid, rifampin, pyrazinamide, and ethambutol daily or twice weekly, followed by 4 mo of isoniazid and rifampin‡ by DOT§ for drug-susceptible *M. tuberculosis*	Some experts recommend a three-drug initial regimen (isoniazid, rifampin, and pyrazinamide) if the risk of drug resistance is low. DOT is highly desirable. If hilar adenopathy only and the risk of drug resistance is low, 6-mo course of isoniazid and rifampin is sufficient. Drugs can be given 2 or 3 times/wk under DOT.
	9-12 mo of isoniazid and rifampin for drug-susceptible *Mycobacterium bovis*	
Meningitis	2 mo of isoniazid, rifampin, pyrazinamide and an aminoglycoside‖ or ethionamide once daily, followed by 7-10 mo of isoniazid and rifampin once daily or twice weekly (9-12 mo total) for drug-susceptible *M. tuberculosis* At least 12 mo of therapy without pyrazinamide for drug-susceptible *M. bovis*	For patients who may have acquired tuberculosis in geographic areas where resistance to streptomycin is common, kanamycin, amikacin, or capreomycin can be used instead of streptomycin.

*Positive TST or IGRA result, no disease. See text for comments and additional acceptable/alternative regimens.
†Duration of therapy may be longer for human immunodeficiency virus (HIV)–infected people, and additional drugs and dosing intervals may be indicated
‡Medications should be administered daily for the first 2 wk to 2 mo of treatment and then can be administered 2-3 times/wk by DOT. (Twice-weekly therapy is not recommended for HIV-infected people.)
§If initial chest radiograph shows pulmonary cavities and sputum culture after 2 mo of therapy remains positive, the continuation phase is extended to 7 mo, for a total treatment duration of 9 mo.
‖Streptomycin, kanamycin, amikacin, or capreomycin.
DOT, Directly observed therapy; IGRA, interferon-γ release assay; TST, tuberculin skin test.
Adapted from American Academy of Pediatrics: *Red Book: 2018–2021 report of the Committee on Infectious Diseases*, 31st ed. Elk Grove Village, IL: AAP, 2018: Table 3.85.

Table 260.2 Isoniazid Drug-Drug Interactions

DRUG USED WITH ISONIAZID	EFFECTS
Acetaminophen, alcohol, rifampin	Increased hepatotoxicity of isoniazid or listed drugs
Aluminum salts (antacids)	Decreased absorption of isoniazid
Carbamazepine, phenytoin, theophylline, diazepam, warfarin	Increased level, effect, or toxicity of listed drugs due to decreased metabolism
Itraconazole, ketoconazole, oral hypoglycemic agents	Decreased level or effect of listed drugs due to increased metabolism
Cycloserine, ethionamide	Increased central nervous system adverse effects of cycloserine and ethionamide
Prednisolone	Increased isoniazid metabolism

No routine laboratory monitoring for rifamycins is indicated unless the patient is symptomatic. In patients with signs of toxicity, complete blood count (CBC) and kidney and liver function tests are indicated.

Pyrazinamide

Pyrazinamide **(PZA)** is a synthetic pyrazine analog of nicotinamide that is bactericidal against intracellular *M. tuberculosis* organisms in acidic environments, such as within macrophages or inflammatory lesions. A bacteria-specific enzyme (pyrazinamidase) converts PZA to pyrazinoic acid, which leads to low pH levels not tolerated by *M. tuberculosis*. Resistance is poorly understood but can arise from bacterial pyrazinamidase alterations.

PZA is indicated for the initial treatment phase of active tuberculosis in combination with other antimycobacterial agents. The pediatric dosage is 30-40 mg/kg/day PO in a single dose, not to exceed 2,000 mg/day. Twice-weekly dosing with DOT only is with 50 mg/kg/day PO in a single dose, not to exceed 4,000 mg/day. It is available in a 500-mg tablet and can be made into a suspension of 100 mg/mL.

Adverse effects include GI upset (e.g., nausea, vomiting, poor appetite) in approximately 4% of children, dosage-dependent hepatotoxicity, and elevated serum uric acid levels that can precipitate gout in susceptible adults. Approximately 10% of pediatric patients have elevated uric acid levels but with no associated clinical sequelae. Minor reactions include arthralgias, fatigue, and, rarely, fever.

Use of PZA in combination with rifampin for short-course treatment of latent tuberculosis is associated with serious liver dysfunction and death, and this combination should be avoided.

No routine laboratory monitoring for PZA is required, but monthly visits to reinforce the importance of therapy are desirable.

Ethambutol

Ethambutol is a synthetic form of ethylenedi-imino-di-1-butanol dihydrochloride that inhibits RNA synthesis needed for cell wall formation. At standard dosages, ethambutol is bacteriostatic, but at dosages >25 mg/kg, it has bactericidal activity. The mechanism of resistance to ethambutol is unknown, but resistance develops rapidly when ethambutol is used as a single agent against *M. tuberculosis.*

Ethambutol is indicated for the treatment of infections caused by *M. tuberculosis, M. kansasii, M. bovis,* and *M. avium* complex. Ethambutol should only be used as part of a combination treatment regimen for *M. tuberculosis.* Daily dosing is 15-25 mg/kg PO in a single dose, not to exceed 2,500 mg/day. Twice-weekly dosing is with 50 mg/kg PO in a single dose, not to exceed 2,500 mg/day. Dosage adjustment is needed in renal insufficiency. Ethambutol is available in 100- and 400-mg tablets.

The major adverse effect with ethambutol is **optic neuritis**, and thus ethambutol should generally be reserved for children old enough to have visual acuity and color discrimination reliably monitored. Visual changes are usually dosage dependent and reversible. Other adverse events include headache, dizziness, confusion, hyperuricemia, GI upset, peripheral neuropathy, hepatotoxicity, and cytopenias, especially neutropenia and thrombocytopenia.

Routine laboratory monitoring includes baseline and periodic visual acuity and color discrimination testing, CBC, serum uric acid levels, and kidney and liver function tests.

Less Commonly Used Agents

Aminoglycosides

The aminoglycosides used for mycobacterial infections include streptomycin, amikacin, kanamycin, and capreomycin. **Streptomycin** is isolated from *Streptomyces griseus* and was the first drug used to treat *M. tuberculosis.* **Capreomycin**, a cyclic polypeptide from *Streptomyces capreolus,* and **amikacin**, a semisynthetic derivative of kanamycin, are newer agents that are recommended when streptomycin is unavailable. Aminoglycosides act by binding irreversibly to the 30S subunit of ribosomes and inhibiting subsequent protein synthesis. Streptomycin exhibits concentration-dependent bactericidal activity, and capreomycin is bacteriostatic. Resistance results from a pathogenic variant in the binding site of the 30S ribosome, by decreased transport into cells, or by inactivation by bacterial enzymes. Cross-resistance between aminoglycosides has been demonstrated.

The aminoglycosides are indicated for the treatment of *M. tuberculosis* and *M. avium* complex. All are considered second-line drugs in the treatment of *M. tuberculosis* and should be used only when resistance patterns are known. Aminoglycosides are poorly absorbed orally and are administered by IM injection. Pediatric dosing ranges for streptomycin are 20 mg/kg/day if given daily and 20-40 mg/kg/day if given twice weekly; dosing is IM in a single daily dose. Capreomycin, amikacin, and kanamycin dosages are 15-30 mg/kg/day IM in a single dose, not to exceed 1 g/day. Dosage adjustment is necessary in renal insufficiency.

Aminoglycosides have **adverse effects** on proximal renal tubules, the cochlea, and the vestibular apparatus of the ear. Nephrotoxicity and ototoxicity account for most of the significant adverse events. Rarely, patients exhibit fever or rash with administration of aminoglycosides. Concomitant use of other nephrotoxic or ototoxic agents should be avoided, because adverse effects may be additive. An infrequent but serious synergistic, dosage-dependent aminoglycoside effect with nondepolarizing neuromuscular blockade agents can result in respiratory depression or paralysis.

Hearing and kidney function should be monitored at baseline and periodically. Early signs of ototoxicity include tinnitus, vertigo, and hearing loss. Ototoxicity appears to be irreversible, but early kidney damage may be reversible. As with other aminoglycosides, peak and trough drug levels are helpful in dosing and managing early toxicities.

Cycloserine

Cycloserine, derived from *Streptomyces orchidaceous* or *Streptomyces garyphalus,* is a synthetic analog of the amino acid D-alanine that interferes with bacterial cell wall synthesis through competitive inhibition of D-alanine components to be incorporated into the cell wall. It is bacteriostatic, and the mechanism of resistance is unknown.

Cycloserine is used to treat *M. tuberculosis* and *M. bovis*. The dosage is 10-20 mg/kg/day PO divided into two doses, not to exceed 1 g/day. It is available in a 250-mg capsule.

The major adverse effect is **neurotoxicity** with significant psychologic disturbance, including seizures, acute psychosis, headache, confusion, depression, and personality changes. The neurotoxic effects are additive with ethionamide and INH. Cycloserine has also been associated with megaloblastic anemia. It must be dosage-adjusted in patients with kidney impairment and should be used with caution in patients with underlying psychiatric illness.

Routine laboratory monitoring includes kidney and hepatic function, CBC, and cycloserine levels. Psychiatric symptoms are less common at blood levels <30 μg/mL.

Ethionamide

Ethionamide is structurally related to INH and is an ethyl derivative of thioisonicotinamide that inhibits peptide synthesis by an unclear mechanism thought to involve nicotinamide adenine dinucleotide (NAD) and NAD phosphate dehydrogenase disruptions. Ethionamide is bacteriostatic at most therapeutic levels. Resistance develops quickly if ethionamide is used as a single-agent therapy, although the mechanism is unknown.

Ethionamide is used as an alternative to streptomycin or ethambutol in the treatment of *M. tuberculosis* and has some activity against *M. kansasii* and *M. avium* complex. A metabolite, ethionamide sulfoxide, is bactericidal against *M. leprae.* Ethionamide has been shown to have good central nervous system (CNS) penetration and has been used as a fourth drug in combination with rifampin, INH, and PZA. The pediatric dosing is 15-20 mg/kg/day PO in two divided doses, not to exceed 1 g/day. It is available as a 250-mg tablet.

GI upset is common, and other **adverse effects** include neurologic disturbances (anxiety, dizziness, peripheral neuropathy, seizures, acute psychosis), hepatic enzyme elevations, hypothyroidism, hypoglycemia, and hypersensitivity reaction with rash and fever. Ethionamide should be used with caution in patients with underlying psychiatric or thyroid disease. The psychiatric adverse effects can be potentiated with concomitant use of cycloserine.

In addition to close assessment of mood, routine monitoring includes thyroid and liver function tests. In diabetic patients taking ethionamide, blood glucose levels should be monitored.

Fluoroquinolones

The fluoroquinolones are fluorinated derivatives of the quinolone class of antibiotics. Ciprofloxacin is a first-generation fluoroquinolone, and levofloxacin is the more active l-isomer of ofloxacin. **Moxifloxacin** and **gatifloxacin** are agents with emerging use in pediatric mycobacterial disease. Fluoroquinolones are not indicated for use in children <18 years old, but studies of their use in pediatric patients continue to indicate that they may be used in special circumstances. Fluoroquinolones are bactericidal and exert their effect by inhibition of DNA gyrase. The alterations in DNA gyrase result in relaxation of supercoiled DNA and breaks in double-stranded DNA. The mechanism of resistance is not well defined but likely involves pathogenic variants in the DNA gyrase.

Levofloxacin is an important second-line drug in the treatment of multidrug-resistant (MDR) *M. tuberculosis.* **Ciprofloxacin** has activity against *M. fortuitum* complex and against *M. tuberculosis.* The pediatric dosage of ciprofloxacin is 20-30 mg/kg/day PO or IV, not to exceed 1.5 mg/day PO or 800 mg/day IV. The adult dosage of ciprofloxacin is 500-750 mg/dose PO in two divided doses or 200-400 mg/dose IV every 12 hours. Ciprofloxacin is available in 100-, 250-, 500-, and 750-mg tablets and can be made in 5% (50 mg/mL) or 10% (100 mg/mL) suspensions. The dosage of levofloxacin for children is 5-10 mg/kg/day

given once daily either PO or IV, not to exceed 1,000 mg/day, and for adults, 500-1,000 mg/day PO or IV, not to exceed 1,000 mg/day. Levofloxacin is available in 250-, 500-, and 750-mg tablets, and a 50 mg/mL suspension can be extemporaneously compounded. The suspension has a shelf life of only 8 weeks.

The most common adverse effect of fluoroquinolones is **GI upset**, with nausea, vomiting, abdominal pain, and diarrhea, including pseudomembranous colitis. Other less common adverse effects include bone marrow depression, CNS effects (e.g., lowered seizure threshold, confusion, tremor, dizziness, headache), elevated liver transaminases, photosensitivity, and arthropathies. The potential for arthropathies (e.g., tendon ruptures, arthralgias, tendinitis) is the predominant reason that fluoroquinolones are not recommended for pediatric use. The mechanism of injury appears to involve the disruption of extracellular matrix of cartilage and depletion of collagen, a particular concern related to the bone and joint development of children.

Fluoroquinolones induce the CYP isoenzymes that can increase the concentrations of dually administered theophylline and warfarin. Nonsteroidal antiinflammatory drugs (NSAIDs) can potentiate the CNS effects of fluoroquinolones and should be avoided while taking a fluoroquinolone. Both ciprofloxacin and levofloxacin should be dosage-adjusted in patients with significant renal dysfunction.

While taking fluoroquinolones, patients should be monitored for hepatic and renal dysfunction, arthropathies, and hematologic abnormalities.

Linezolid

Linezolid is a synthetic oxazolidinone derivative. This drug is not currently approved for use against mycobacterial infection in pediatric or adult patients but has activity against some mycobacterial species. Studies on efficacy of treatment of mycobacterial infections are under way. Linezolid inhibits translation by binding to the 23S ribosomal component of the 50S ribosome subunit, preventing coupling with the 70S subunit. Resistance is thought to be from a point a pathogenic variant at the binding site but is poorly studied because only a few cases of resistance have been reported.

The approved indications for linezolid are for bacterial infections other than mycobacteria, but studies reveal in vitro activity against rapidly growing mycobacteria (*M. fortuitum* complex, *M. chelonae, M. abscessus*), *M. tuberculosis,* and *M. avium* complex. The dosage for 0- to 11-year-old children is 10 mg/kg/day PO or IV in divided doses every 8-12 hours. For persons >12 years old, the dosage is 600 mg PO or IV every 12 hours. Linezolid is available in 400- and 600-mg tablets and as a 20-mg/mL suspension.

Adverse effects of linezolid include GI upset (e.g., nausea, vomiting, diarrhea), CNS disturbances (e.g., dizziness, headache, insomnia, peripheral neuropathy), lactic acidosis, fever, myelosuppression, and pseudomembranous colitis. Linezolid is a weak inhibitor of monoamine oxidase A, and patients are advised to avoid foods with high tyramine content. Linezolid should be used cautiously in patients with preexisting myelosuppression.

In addition to monitoring for GI upset and CNS perturbations, routine laboratory monitoring includes CBC at least weekly.

Paraaminosalicylic Acid

Paraaminosalicylic acid **(PAS)** is a structural analog of paraaminobenzoic acid (PABA). It is bacteriostatic and acts by competitively inhibiting the synthesis of folic acid, similar to the action of sulfonamides. Resistance mechanisms are poorly understood.

PAS acts against *M. tuberculosis.* The dosage is 150 mg/kg/day PO in two or three divided doses. PAS is dispensed in 4-g packets, and the granules should be mixed with liquid and swallowed whole.

Common **adverse effects** include GI upset, and less common events include hypokalemia, hematuria, albuminuria, crystalluria, and elevations of hepatic transaminases. PAS can decrease the absorption of rifampin, and co-administration with ethionamide potentiates the adverse effects of PAS.

In addition to monitoring for weight loss, routine laboratory monitoring includes liver and kidney function tests.

Bedaquiline Fumarate

This oral diarylquinoline has been recommended for the treatment of MDR tuberculosis. Bedaquiline fumarate should be used as part of combination therapy and administered by direct observation. Although approved for patients ≥18 years old, bedaquiline may be considered for children on a case-by-case basis.

Serious **adverse effects** include hepatotoxicity and a prolonged QT interval.

Delamanid

Delamanid is a dihydro-nitroimidazooxazole derivative recently approved for use in the treatment of MDR tuberculosis. It acts by inhibiting the synthesis of mycobacterial cell wall compounds such as methoxymycolic acid and ketomycolic acid. Limited studies are available in the pediatric population, and delamanid should be used only in conjunction with a tuberculosis specialist.

Adverse effects include nausea, vomiting, dizziness, anxiety, shaking, and QT prolongation.

AGENTS USED AGAINST *MYCOBACTERIUM LEPRAE*

Dapsone

Dapsone is a sulfone antibiotic with characteristics similar to sulfonamides. Similar to other sulfonamides, dapsone acts as a competitive antagonist of PABA, which is needed for the bacterial synthesis of folic acid. Dapsone is bacteriostatic against *M. leprae.* Resistance is not well understood but is thought to occur after alterations at the PABA-binding site.

Dapsone is used in the treatment of *M. leprae* in combination with other antileprosy agents (rifampin, clofazimine, ethionamide). The pediatric dosage is 1-2 mg/kg/day PO as a single dose, not to exceed 100 mg/day, for a duration of 3-10 years. The adult dosage is 100 mg/day PO as a single dose. Dapsone is available in 25- and 100-mg scored tablets and as an oral suspension of 2 mg/mL. The dosage should be adjusted in renal insufficiency.

Dapsone has many reported **adverse effects**, including dosage-related hemolytic anemia, especially in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, pancreatitis, renal complications (acute tubular necrosis, acute renal failure, albuminuria), increased liver enzymes, psychosis, tinnitus, peripheral neuropathy, photosensitivity, and a hypersensitivity syndrome with fever, rash, hepatic damage, and malaise. Treatment may produce a *lepra reaction,* which is a nontoxic, paradoxical worsening of lepromatous leprosy with the initiation of therapy. This hypersensitivity reaction is not an indication to discontinue therapy. Dapsone should be used with caution in patients with G6PD deficiency or taking other folic acid antagonists. Dapsone levels can decrease with concomitant rifampin use and can increase with concomitant clotrimazole use.

Routine laboratory monitoring includes CBC weekly during the first month of therapy, weekly through 6 months of therapy, and then every 6 months thereafter. Other periodic assessments include kidney function with creatine levels, urinalysis, and liver function tests.

Clofazimine

Clofazimine is a synthetic phendimetrazine tartrate derivative that acts by binding to the mycobacterial DNA at guanine sites. It has slow bactericidal activity against *M. leprae.* Mechanisms of resistance are not well studied. No cross-resistance between clofazimine and dapsone or rifampin has been shown.

Clofazimine is indicated as part of a combination therapy for the treatment of *M. leprae.* It appears there may be some activity against other mycobacteria such as *M. avium* complex, although treatment failures are common. The safety and efficacy of clofazimine are poorly studied in children. The pediatric dosage is 1 mg/kg/day PO as a single dose, not to exceed 100 mg/day, in combination with dapsone and rifampin for 2 years and then additionally as a single agent for >1 year. The adult dosage is 100 mg/day PO. Clofazimine should be taken with food to increase absorption.

The most common adverse effect is a dosage-related, reversible, pink to tan-brown discoloration of the skin and conjunctiva. Other **adverse**

effects include a dry, itchy skin rash, headache, dizziness, abdominal pain, diarrhea, vomiting, peripheral neuropathy, and elevated hepatic transaminases.

Routine laboratory monitoring includes periodic liver function tests.

AGENTS USED AGAINST NONTUBERCULOUS MYCOBACTERIA

Cefoxitin

Cefoxitin, a cephamycin derivative, is a second-generation cephalosporin that, like other cephalosporins, inhibits cell wall synthesis by linking with penicillin-binding proteins to create an unstable bacterial cell wall. Resistance develops by alterations in penicillin-binding proteins.

Cefoxitin is often used in combination therapy for mycobacterial disease (Table 260.3). Pediatric dosing is based on disease severity, with a range of 80-160 mg/kg/day divided every 4-8 hours, not to exceed 12 g/day. Adult dosages are 1-2 g/dose, not to exceed 12 g/day. Cefoxitin is available in IV and IM formulations. Increased dosing intervals are needed with renal insufficiency.

Adverse effects are primarily hematologic (eosinophilia, granulocytopenia, thrombocytopenia, hemolytic anemia), GI (nausea, vomiting,

Table 260.3 Treatment of Nontuberculous Mycobacteria Infections in Children

ORGANISM	DISEASE	INITIAL TREATMENT
SLOWLY GROWING SPECIES		
Mycobacterium avium complex (MAC); *Mycobacterium haemophilum; Mycobacterium lentiflavum*	Lymphadenitis	Complete excision of lymph nodes; if excision incomplete or disease recurs, clarithromycin or azithromycin plus ethambutol and/or rifampin (or rifabutin).
	Pulmonary infection	Clarithromycin or azithromycin plus ethambutol with rifampin or rifabutin (pulmonary resection in some patients who fail to respond to drug therapy). For severe disease, an initial course of amikacin or streptomycin often is included. Clinical data in adults with mild to moderate disease support that 3-times-weekly therapy is as effective as daily therapy, with less toxicity. For patients with advanced or cavitary disease, drugs should be given daily.
Mycobacterium chimaera	Prosthetic valve endocarditis	Valve removal, prolonged antimicrobial therapy based on susceptibility testing.
	Disseminated	See text.
Mycobacterium kansasii	Pulmonary infection	Rifampin plus ethambutol with isoniazid daily. If rifampin resistance is detected, a three-drug regimen based on drug susceptibility testing should be used.
	Osteomyelitis	Surgical debridement and prolonged antimicrobial therapy using rifampin plus ethambutol with isoniazid.
Mycobacterium marinum	Cutaneous infection	None, if minor; rifampin, TMP-SMX, clarithromycin, or doxycycline* for moderate disease; extensive lesions may require surgical debridement. Susceptibility testing not routinely required.
Mycobacterium ulcerans	Cutaneous and bone infections	Daily intramuscular streptomycin and oral rifampin for 8 wk; excision to remove necrotic tissue, if present; potential response to thermotherapy.
RAPIDLY GROWING SPECIES		
Mycobacterium fortuitum group	Cutaneous infection	Initial therapy for serious disease is amikacin plus meropenem IV, followed by clarithromycin, doxycycline,* TMP-SMX, or ciprofloxacin PO on the basis of in vitro susceptibility testing; may require surgical excision. Up to 50% of isolates are resistant to cefoxitin.
	Catheter infection	Catheter removal and amikacin plus meropenem IV; clarithromycin, TMP-SMX, or ciprofloxacin orally on the basis of in vitro susceptibility testing.
Mycobacterium abscessus	Otitis media; cutaneous infection	There is no reliable antimicrobial regimen because of variability in drug susceptibility. Clarithromycin plus an initial course of amikacin plus cefoxitin or imipenem/meropenem; may require surgical debridement on the basis of in vitro susceptibility testing (50% are amikacin resistant).
	Pulmonary infection (in cystic fibrosis)	Serious disease; clarithromycin, amikacin, and cefoxitin or imipenem/meropenem on the basis of susceptibility testing; most isolates have very low MIC to tigecycline; may require surgical resection.
Mycobacterium chelonae	Catheter infection, prosthetic valve endocarditis	Catheter removal; debridement, removal of foreign material; valve replacement; and tobramycin (initially) plus clarithromycin, meropenem, and linezolid.
	Disseminated cutaneous infection	Tobramycin and meropenem or linezolid (initially) plus clarithromycin.

*Doxycycline can be used for short durations (i.e., ≤21 days) without regard to patient age but is not recommended for longer treatment durations in children <8 yr old. Only 50% of isolates of *M. marinum* are susceptible to doxycycline.

IV, Intravenously; MIC, minimum inhibitory concentration; PO, orally (by mouth); TMP-SMX, trimethoprim-sulfamethoxazole.

From Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2021–2024 Report of the Committee on Infectious Diseases*, 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021.

diarrhea with possible pseudomembranous colitis), and CNS related (dizziness, vertigo). Potential additive adverse effects can occur when cefoxitin is used with aminoglycosides.

Routine laboratory monitoring with long-term use includes CBC and liver and renal function tests.

Doxycycline

Doxycycline is in the tetracycline family of antibiotics and has limited use in pediatrics. As with other tetracyclines, doxycycline acts to decrease protein synthesis by binding to the 30S ribosome and to transfer RNA. It can also cause alterations to the cytoplasmic membrane of susceptible bacteria.

Doxycycline is used to treat *M. fortuitum* (see Table 260.3). Although it can be used to treat *M. marinum,* adult treatment failures have occurred. Pediatric dosing is based on age and weight. For children >8 years old who weigh <45 kg, the dosage is 4.4 mg/kg/day divided twice daily. Dosing for larger children and adults is 100 mg twice daily. Doxycycline is available as 50- and 100-mg capsules or tablets and in 25-mg/5 mL and 50-mg/5 mL suspensions.

Doxycycline use in children is limited by a **permanent tooth discoloration**, which becomes worse with long-term use. Other **adverse effects** include photosensitivity, liver and kidney dysfunction, and esophagitis, which can be minimized by dosing with large volumes of liquid. Doxycycline can decrease the effectiveness of oral contraceptives. Rifampin, carbamazepine, and phenytoin can decrease the concentration of doxycycline.

Routine laboratory monitoring with long-term use includes kidney and liver function tests as well as CBC.

Macrolides

Clarithromycin and azithromycin belong to the macrolide family of antibiotics. Clarithromycin is a methoxy derivative of erythromycin. Macrolides act by binding the 50S subunit of ribosomes, subsequently inhibiting protein synthesis. Resistance mechanisms for mycobacteria are not well understood but might involve binding site alterations. Clarithromycin appears to have synergistic antimycobacterial activity when combined with rifamycins, ethambutol, or clofazimine.

Clarithromycin is widely used for the prophylaxis and treatment of *M. avium* complex disease and also has activity against *M. abscessus, M. fortuitum,* and *M. marinum.* Azithromycin has significantly different pharmacokinetics compared with other macrolide agents and has not been studied and is not indicated for mycobacterial infections. The pediatric dosage of clarithromycin for primary prophylaxis of *M. avium* complex infections is 7.5 mg/kg/dose PO given twice daily, not to exceed 500 mg/day. This dosage is used for recurrent *M. avium* complex disease in combination with ethambutol and rifampin. The adult dosage is 500 mg PO twice daily to be used as a single agent for primary prophylaxis or as part of combination therapy with ethambutol and rifampin. Dosage adjustment is needed for renal insufficiency but not liver failure. Clarithromycin is available in 250- and 500-mg tablets and suspensions of 125 mg/5 mL and 250 mg/5 mL.

The primary adverse effect of clarithromycin is **GI upset**, including vomiting (6%), diarrhea (6%), and abdominal pain (3%). Other **adverse effects** include taste disturbances, headache, and QT prolongation if used with inhaled anesthetics, clotrimazole, antiarrhythmic agents, or azoles. Clarithromycin should be used cautiously in patients with renal insufficiency or liver failure.

Routine laboratory monitoring with prolonged use of clarithromycin includes periodic liver enzyme tests. Diarrhea is an early sign of pseudomembranous colitis.

Trimethoprim-Sulfamethoxazole

Trimethoprim-sulfamethoxazole (TMP-SMX) is formulated in a fixed ratio of one part TMP to five parts SMX. SMX is a sulfonamide that inhibits synthesis of dihydrofolic acid by competitively inhibiting PABA, similar to dapsone. TMP blocks production of tetrahydrofolic acid and downstream biosynthesis of nucleic acids and protein by reversibly binding to dihydrofolate reductase. The combination of the two agents is synergistic and often bactericidal.

TMP-SMX is often used in combination therapy for mycobacterial disease (see Table 260.3). Oral or IV pediatric dosage for serious infections is TMP 15-20 mg/kg/day divided every 6-8 hours, and for mild infections, TMP 6-12 mg/kg/day divided every 12 hours. The adult dosage is 160 mg TMP and 800 mg SMX every 12 hours. Dosage reduction may be needed in renal insufficiency. TMP-SMX is available in single-strength tablets (80/400 mg TMP-SMX) and double-strength tablets (160/800 mg TMP-SMX) and in a suspension of 40 mg TMP and 200 mg SMX per 5 mL.

The most common adverse effect with TMP-SMX is **myelosuppression**. It must be used with caution in patients with G6PD deficiency. Other **adverse effects** include renal abnormalities, rash, aseptic meningitis, GI disturbances (e.g., pancreatitis, diarrhea), and prolonged QT interval if co-administered with inhaled anesthetics, azoles, or macrolides.

Routine laboratory monitoring includes monthly CBC and periodic electrolytes and creatinine to monitor renal function.

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Chapter 261

Tuberculosis (*Mycobacterium tuberculosis*)

Lindsay H. Cameron and Jeffrey R. Starke

Mycobacterium tuberculosis has caused human disease for more than 4,000 years and is one of the most important infectious diseases worldwide. There are five closely related mycobacteria in the *Mycobacterium tuberculosis* complex: *M. tuberculosis, M. bovis, M. africanum, M. microti,* and *M. canetti. M. tuberculosis* is the most important cause of tuberculosis (TB) disease in humans. The tubercle bacilli are non–spore-forming, nonmotile, pleomorphic, weakly gram-positive curved rods 1-5 µm long, typically slender, and slightly bent. They can appear beaded or clumped under microscopy. They are obligate aerobes that grow in synthetic media containing glycerol as the carbon source and ammonium salts as the nitrogen source (Löwenstein-Jensen culture media). These mycobacteria grow best at 37–41°C (98.6–105.8°F), produce niacin, and lack pigmentation. A lipid-rich cell wall accounts for resistance to the bactericidal actions of antibody and complement. A hallmark of all mycobacteria is **acid fastness**—the capacity to form stable mycolate complexes with arylmethane dyes (crystal violet, carbolfuchsin, auramine, and rhodamine). They resist decoloration with ethanol and hydrochloric or other acids.

M. tuberculosis grows slowly, with a generation time of 12-24 hours. Isolation from clinical specimens on solid synthetic media usually takes 3-6 weeks, and drug susceptibility testing requires an additional 2-4 weeks. Growth can be detected in 1-3 weeks in selective liquid medium using radiolabeled nutrients (e.g., BACTEC radiometric system), and drug susceptibilities can be determined in an additional 3-5 days. Once mycobacterial growth is detected, the species of mycobacteria present can be determined within hours using high-pressure liquid chromatography analysis (identifying the mycolic acid fingerprint of each species) or DNA probes/nucleic amplification tests (NAATs).

NAATs are used to identify genes associated with *M. tuberculosis* drug resistance and complement phenotypic drug susceptibility testing. Results are available in hours, which expedites management decisions. Phenotypic drug susceptibility testing is necessary to confirm susceptibility to each drug. Restriction fragment length polymorphism genetic profiling of mycobacteria is a helpful tool to study the epidemiology of TB strain relatedness in both outbreaks and routine epidemiology of TB in a community.

CLINICAL STAGES

There are three major clinical stages of TB: exposure, infection, and disease. **Exposure** means a child has had recent significant contact (shared the air) with an adult or adolescent with infectious TB but lacks proof of infection. In this stage, the tuberculin skin test (TST) or interferon-γ release assay (IGRA) result is negative, the chest radiograph is normal, the physical examination is normal, and the child lacks signs or symptoms of disease. However, the child may be infected and develop TB disease rapidly, because there may not have been enough time for the TST or IGRA to turn positive. **Tuberculosis infection (TBI)** occurs when the individual inhales droplet nuclei containing *M. tuberculosis,* which survive intracellularly within the lung and associated lymphoid tissue. The hallmark of TBI is a positive TST or IGRA result. In this stage the child has no signs or symptoms and has a normal physical examination, and the chest radiograph is either normal or reveals only granuloma or calcifications in the lung parenchyma. **Disease** occurs when signs or symptoms or radiographic manifestations caused by *M. tuberculosis* become apparent. Not all infected individuals have the same risk of developing disease. An immunocompetent adult with untreated TBI has approximately a 5–10% lifetime risk of developing disease. In contrast, an infected child <1 year old has a 40% chance of developing TB disease within 9 months.

EPIDEMIOLOGY

TB remains a leading cause of death from an infectious disease worldwide. The global burden of TB is influenced by several factors, including the HIV pandemic; the development of **multidrug-resistant (MDR) tuberculosis**; the disproportionately low access of populations in low-resource settings worldwide to both diagnostic tests and effective medical therapy; and the COVID-19 pandemic.

The World Health Organization (WHO) 2020 Global Tuberculosis Report estimates that the COVID-19 pandemic could have a significant impact on access to essential TB services (human capital, financial), which may increase the rates of TB-associated morbidity and mortality. Many countries have had to allocate public health resources from TB prevention efforts toward COVID-19 prevention, including contact tracing and using GeneXpert machines for COVID-19 testing. The WHO predicts that this resource diversion from TB case-finding, testing, treatment, and prevention may result in an increase of global TB-associated deaths by 0.2-0.4 million per year.

Approximately 95% of TB cases occur in the developing world. In 2019, the 30 high-TB-burden countries accounted for 87% of incident cases (Fig. 261.1). Two thirds of cases occurred in eight countries, including India, Indonesia, China, the Philippines, Pakistan, Nigeria, Bangladesh, and South Africa. An estimated 10 million incident cases and 1.4 million TB-associated deaths occurred worldwide in 2019. The WHO 2020 Global Tuberculosis Report estimates that in 2019 there were 1.2 million childhood incident cases and 230,000 TB-associated deaths among children, including 32,000 TB-associated deaths among children living with HIV.

The incidence of drug-resistant TB has increased in some areas of the world in both adults and children. In 2019, the WHO reported a global total of 206,030 cases of multidrug- or rifampicin-resistant TB, a 10% increase from 2018 (Fig. 261.2). Isoniazid (INH)–monoresistant TB is resistance to INH alone, rifampicin-resistant TB (RR-TB) is resistance to at least rifampin, MDR-TB is defined as resistance to at least isoniazid and rifampin, and extensively drug-resistant tuberculosis TB (XDR-TB) includes MDR-TB plus resistance to any fluoroquinolone and at least one of three injectable drugs (kanamycin, capreomycin, or amikacin). In 2014, the worldwide estimate for MDR-TB in children was 2.9% of all cases and 0.1% for XDR-TB. The highest incidence of MDR-TB in children occurs in the Southeast Asian, African, and Western Pacific regions; however, the proportion of drug-resistant cases is highest in countries belonging to the Russian Federation, where over 30% of children with TB have a drug-resistant organism.

In the United States, TB case rates decreased steadily during the first half of the 20th century, long before the advent of antituberculosis drugs, as a result of improved living conditions and likely genetic selection favoring persons resistant to developing disease. A resurgence of TB in the late 1980s was associated primarily with the HIV epidemic, transmission of the organism in congregate settings including healthcare institutions, disease occurring in recent immigrants, and poor conduct of community TB control. Since 1992, the TB incidence in the

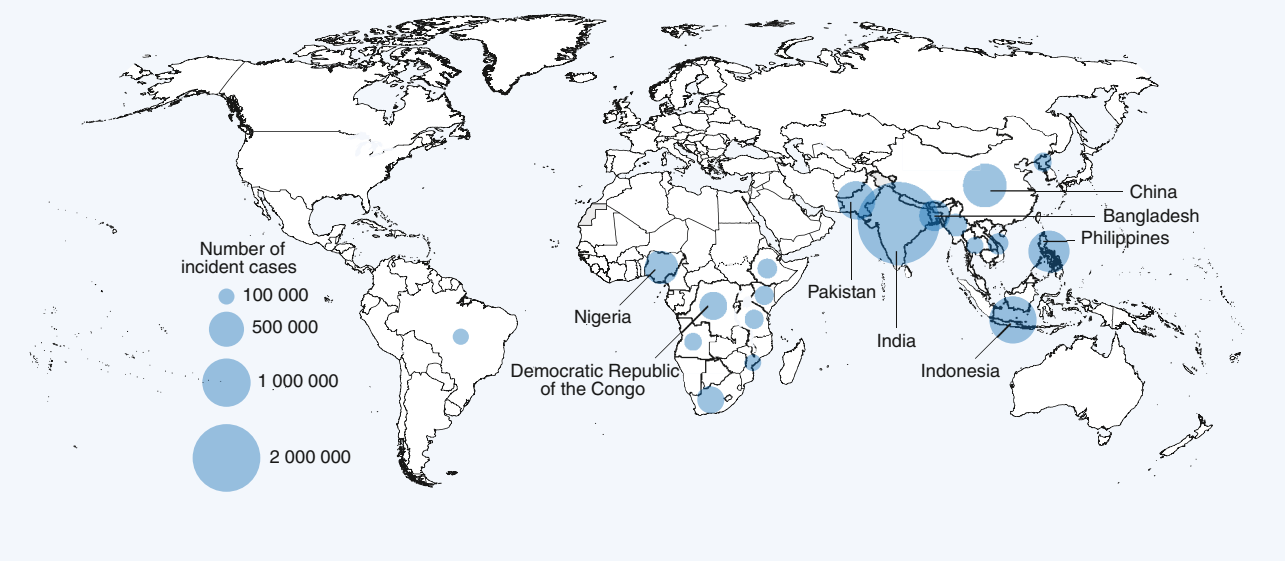

Fig. 261.1 Countries that had at least 100,000 incident cases of TB in 2021. The countries that rank first to eighth in terms of numbers of cases and that accounted for about two thirds of global cases in 2021 are labeled. *(From the World Health Organization: Global Tuberculosis Report 2022. Geneva: World Health Organization; 2022, Fig 12. License: CC BY-NC-SA 3.0 IGO.)*

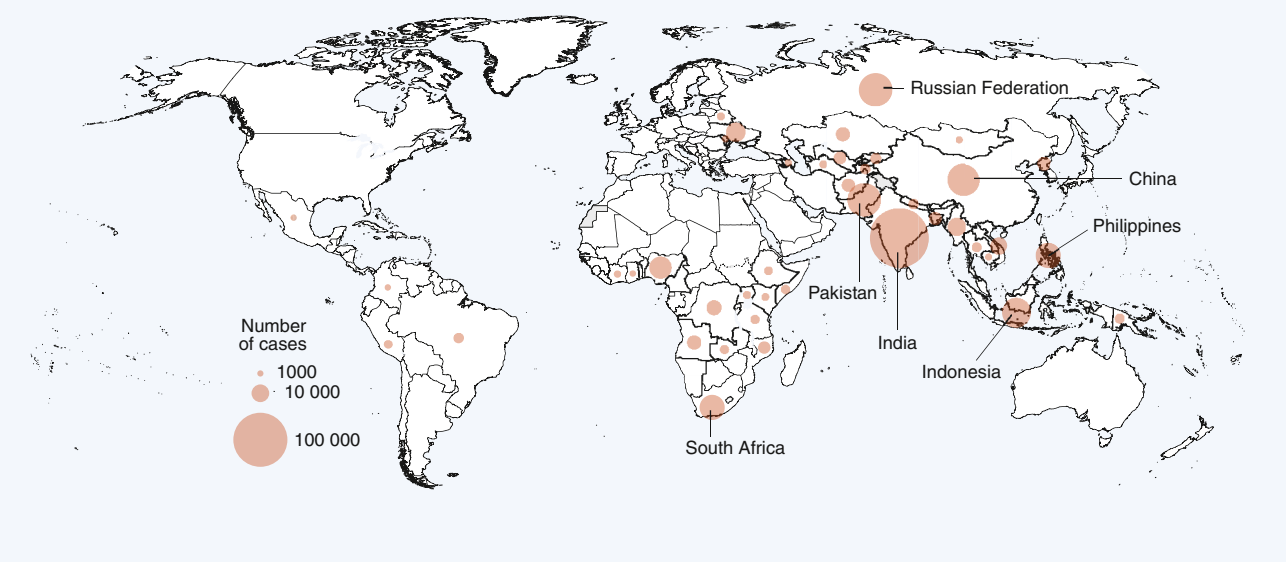

Fig. 261.2 Percentage of new TB cases with MDR-/RR-TB. The seven countries with the highest burden in terms of numbers of MDR/RR -TB cases and that accounted for two thirds of global MDR-/RR-TB cases in 2021 are labeled. *(From the World Health Organization: Global Tuberculosis Report 2022. Geneva: World Health Organization; 2022, Fig 17. License: CC BY-NC-SA 3.0 IGO.)*

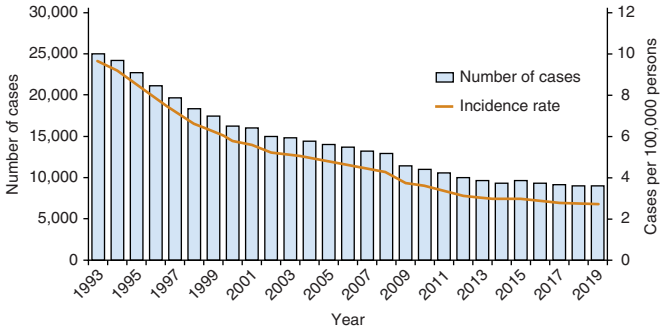

Fig. 261.3 Reported tuberculosis cases in the United States for 1993–2019 (as of October 29, 2020). *(From Centers for Disease Control and Prevention. Trends in Tuberculosis, 2019. Atlanta: U.S. Department of Health and Human Services; 2020.)*

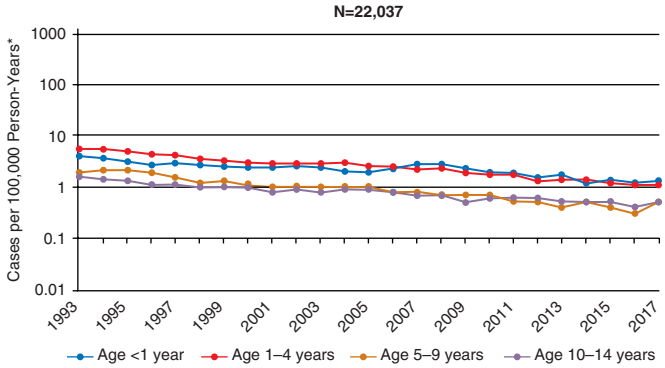

Fig. 261.4 Reported pediatric tuberculosis (TB) cases in the United States by age-group for the years 1993-2017. *Rates are presented on a logarithmic scale. *(From Centers for Disease Control and Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention. Pediatric Tuberculosis in United States, 1993–2017. Atlanta: U.S. Department of Health and Human Services; 2018.)*

United States has decreased over time. In 2020, the case rate was at the all-time low of 2.2 per 100,000 persons (Fig. 261.3).

In 2017, the incidence rate of TB among children <15 years was 0.7 cases per 100,000 person-years, a decline of 41% from 1993. The TB incidence rates were highest in children less than 12 months of age (1.3 per 100,000 person-years), followed by children age 1-4 years (1.1 per 100,000 person-years), and were lowest among children age 5-14 years (0.5 per 100,000 person-years) (Fig. 261.4).

From 1993 to 2017, non-United States–born children, children born to non-United States–born parents, and children of racial or ethnic minority status were disproportionately affected by TB. Non-United States–born children accounted for approximately 25% of the total number of childhood TB cases, the majority being from Mexico, followed by the Philippines, Somalia, Vietnam, Ethiopia, and Haiti (Fig. 261.5).

According to data reported to the National TB Surveillance System from 2007 to 2017, among United States–born children, the incidence rates of TB if both parents were non-United States–born and if one parent was non-United States–born were eight and three times higher, respectively, compared to United States–born children with both parents being United States–born. This is supported by prior research that found that 75% of United States–born children with TB had some international connection through a family member or previous travel or residence in a TB-endemic country. Similar to adults in the United

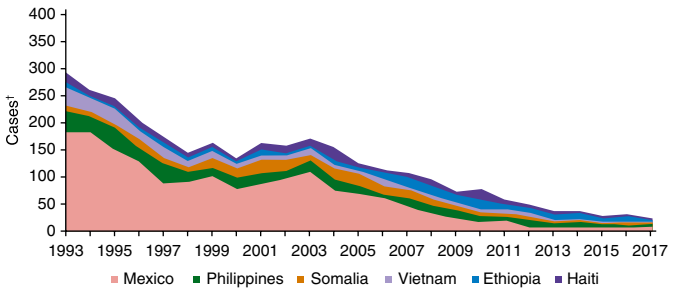

Fig. 261.5 Top six countries of birth for non–United States–born* pediatric TB cases for the years 1993-2017. *Non-United States–born refers to persons born outside the United States or its territories or not born to a US citizen. †Cases in United States–born children of non-United States–born parents are included in United States–born counts and thus not displayed in this figure. *(From Centers for Disease Control and Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention. Pediatric Tuberculosis in United States, 1993–2017. Atlanta: U.S. Department of Health and Human Services; 2018.)*

States, TB among children of racial-ethnic minority status occurs disproportionately. The incidence rates of TB among children of Native Hawaiian or Pacific Islander, Asian, Native American or Native Alaskan, Black, and Hispanic children were 144, 44, 22, 19, and 18 times higher, respectively, than among non-Hispanic White children.

The rates of drug-resistant TB in children in the United States remain low. A total of 89 childhood cases of MDR-TB were reported in the United States in 2015; of those, 70.8% were non-United States–born. Among children with culture-confirmed TB in the United States in 2015, 15.2% had organisms with resistance to at least one first-line drug and 0.9% had MDR organisms.

Most children are infected with *M. tuberculosis* in their home by someone close to them, but outbreaks of childhood TB also have occurred in elementary and high schools, nursery schools, daycare centers and homes, churches, school buses, and sports teams. Adults living with HIV who have pulmonary TB can transmit *M. tuberculosis* to children, and children living with HIV are at increased risk for developing TB after infection. Other specific groups are at high risk for acquiring TBI and progressing to tuberculosis disease (Table 261.1).

Table 261.1 Groups at High Risk for Acquiring Tuberculosis Infection and Developing Disease in Countries with Low Incidence

RISK FACTORS FOR TUBERCULOSIS INFECTION
Children exposed to high-risk adults
Foreign-born persons from high-prevalence countries
Homeless persons
Persons who inject drugs
Present and former residents or employees of correctional institutions, homeless shelters, and nursing homes
Healthcare workers caring for high-risk patients (if infection control is not adequate)
RISK FACTORS FOR PROGRESSION OF TUBERCULOSIS INFECTION TO TUBERCULOSIS DISEASE
Infants and children ≤4 yr old, especially those <2 yr old
Adolescents and young adults
Persons co-infected with human immunodeficiency virus
Persons with skin test conversion in the past 1-2 yr
Persons who are immunocompromised, especially in cases of malignancy and solid organ transplantation, immunosuppressive medical treatments including anti–tumor necrosis factor therapies, diabetes mellitus, chronic renal failure, silicosis, and malnutrition
RISK FACTORS FOR DRUG-RESISTANT TUBERCULOSIS
Personal or contact history of treatment for tuberculosis
Contacts of patients with drug-resistant tuberculosis
Birth or residence in a country with a high rate of drug resistance
Poor response to standard therapy
Positive sputum smears (acid-fast bacilli) or culture ≥2 mo after initiating appropriate therapy

TRANSMISSION

Transmission of *M. tuberculosis* is usually by inhalation of airborne mucus droplet nuclei, particles 1-5 μm in diameter that contain *M. tuberculosis.* Transmission rarely occurs by direct contact with an infected discharge or a contaminated fomite. The chance of transmission increases when the patient has a positive acid-fast smear of sputum, an extensive upper lobe infiltrate or cavity, copious production of thin sputum, and severe and forceful cough (although the absence of cough does not eliminate the risk of TBI). Environmental factors such as poor air circulation enhance transmission. Within several days to 2 weeks after beginning adequate chemotherapy, most adults no longer transmit the organism, but some patients remain infectious for many weeks. Young children with TB rarely infect other children or adults; tubercle bacilli are sparse in their endobronchial secretions, and cough is often absent or lacks the tussive force required to suspend infectious particles of the correct size. However, adolescents often present with adult-type cavity or endobronchial TB and can easily transmit the organism.

Airborne transmission of *M. bovis* and *M. africanum* also occurs rarely. *M. bovis* can penetrate the gastrointestinal (GI) mucosa or invade the lymphatic tissue of the oropharynx when large numbers of the organism are ingested. Human infection with *M. bovis* is rare in developed countries as a result of the pasteurization of milk and effective TB control programs for cattle. Approximately 46% of culture-proven childhood TB cases from the San Diego, California, region since 1994 were caused by *M. bovis,* likely acquired by children when visiting Mexico or another country or consuming dairy products from countries with suboptimal veterinary TB control programs.

Zoonotic transmission is an uncommon source of *M. tuberculosis* that has been reported in adults exposed to elephants and potentially cattle.

PATHOGENESIS

The **primary complex** (or **Ghon complex**) of TB includes local infection at the portal of entry and the regional lymph nodes that drain the area. The lung is the portal of entry in >98% of cases. The tubercle bacilli multiply initially within alveoli and alveolar ducts. Most of the bacilli are killed, but some survive within nonactivated macrophages, which carry them through lymphatic vessels to the regional lymph nodes. When the primary infection is in the lung, the hilar lymph nodes usually are involved, although an upper lobe focus can drain into paratracheal nodes. The tissue reaction in the lung parenchyma and lymph nodes intensifies over the next 2-12 weeks as the organisms grow in number and **tissue hypersensitivity** develops. The parenchymal portion of the primary complex often heals completely by fibrosis or calcification after undergoing caseous necrosis and encapsulation (Fig. 261.6). Occasionally, this portion continues to enlarge, resulting in focal pneumonitis and pleuritis. If caseation is intense, the center of the lesion liquefies and empties into the associated bronchus, leaving a residual cavity.

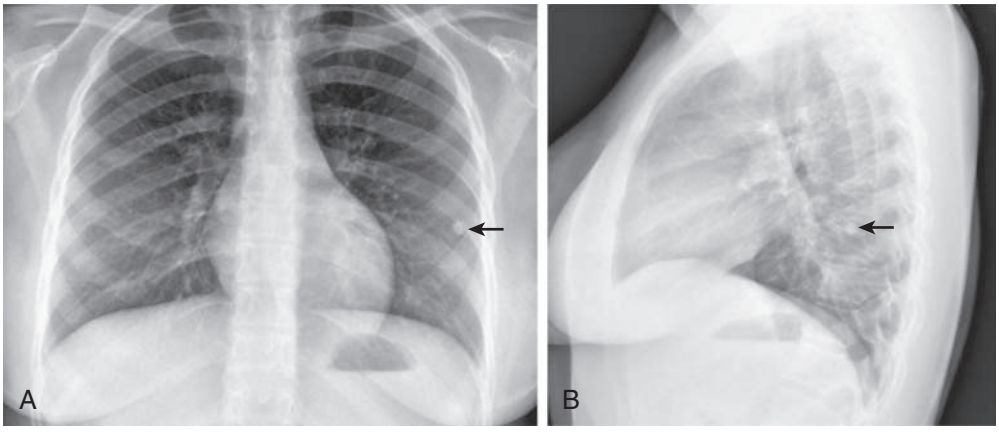

Fig. 261.6 Posteroanterior (A) and lateral (B) chest radiographs of an adolescent showing a 7-mm calcified granuloma in the left lower lobe *(arrows). (From Lighter J, Rigaud M. Diagnosing childhood tuberculosis: traditional and innovative modalities. Curr Probl Pediatr Adolesc Health Care. 2009;39:55–88.)*

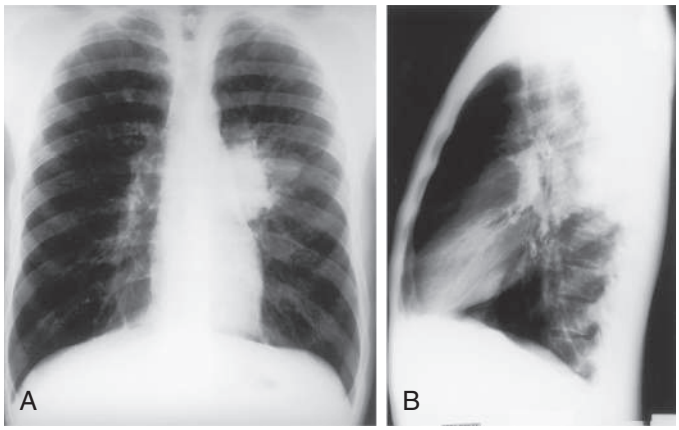

Fig. 261.7 A 14-yr-old child with proven primary tuberculosis. Frontal (**A**) and lateral (**B**) views of the chest show hyperinflation, prominent left hilar lymphadenopathy, and alveolar consolidation involving the posterior segment of the left upper lobe and the superior segment of the left lower lobe. *(From Hilton SVW, Edwards DK, eds. Practical Pediatric Radiology, 3rd ed. Philadelphia: Saunders; 2003:334.)*

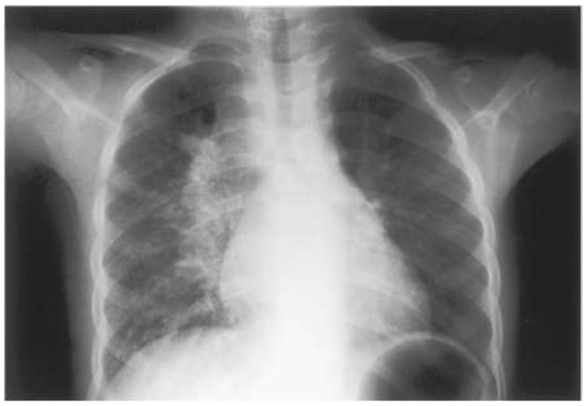

Fig. 261.8 An 8-yr-old child with a history of cough. A single frontal view of the chest shows marked right hilar and paratracheal lymphadenopathy with alveolar disease involving the right middle and lower lung fields. This was also a case of primary tuberculosis. *(From Hilton SVW, Edwards DK, eds. Practical Pediatric Radiology, 3rd ed. Philadelphia: Saunders; 2003:335.)*

The foci of infection in the regional lymph nodes develop some fibrosis and encapsulation, but healing is usually less complete than in the parenchymal lesion. Viable *M. tuberculosis* can persist for decades within these foci. In most cases of initial TBI, the lymph nodes remain normal in size. However, hilar and paratracheal lymph nodes that enlarge significantly as part of the host inflammatory reaction can encroach on a regional bronchus (Figs. 261.7 and 261.8). Partial obstruction of the bronchus caused by external compression can cause hyperinflation in the distal lung segment. Complete obstruction results in atelectasis. Inflamed caseous nodes can attach to the bronchial wall and erode through it, causing endobronchial TB or a fistula tract. The caseum causes complete obstruction of the bronchus. The resulting lesion is a combination of pneumonitis and atelectasis and has been called a **collapse-consolidation lesion** or **segmental lesion** (Fig. 261.9).

During the development of the primary complex, tubercle bacilli are carried to most tissues of the body through the blood and lymphatic vessels. Although seeding of the organs of the reticuloendothelial system is common, bacterial replication is more likely to occur in organs with conditions that favor their growth, such as the lung apices, brain, kidneys, and bones. **Disseminated tuberculosis** occurs if the number of circulating bacilli is large and the host's cellular immune response is inadequate. More often, the number of bacilli is small, leading to

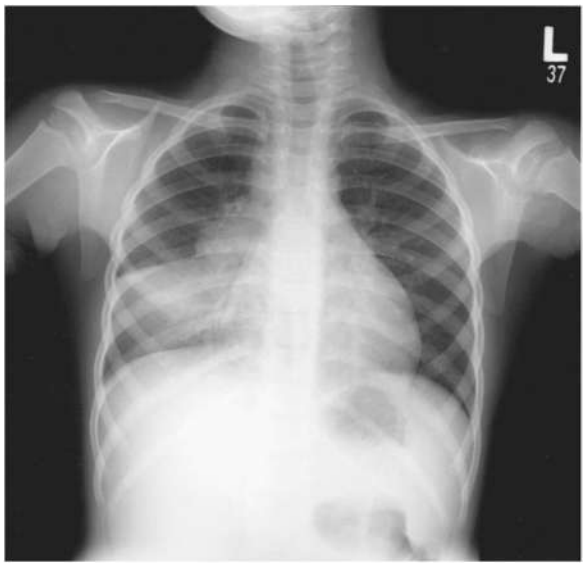

Fig. 261.9 Right-sided hilar lymphadenopathy and collapse-consolidation lesions of primary tuberculosis in a 4-yr-old child. *(From Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH (eds). Red Book: 2021-2024 Report of the Committee on Infectious Diseases, 32nd ed. Itasca, IL: American Academy of Pediatrics, 2021. p 805-806; with data from Furin J, Seddon J, Becerra M, et al. Management of Multi-drug-Resistant Tuberculosis Children: A Field Guide, 4th ed. Boston: The Sentinel Project for Pediatric Drug-Resistant Tuberculosis, 2019. Available at:* http://sentinel-project.org/wp-content/uploads/2019/02/Updated_DRTB-Field-Guide-2019-V3.pdf*)*

clinically inapparent metastatic foci in many organs. These remote foci usually become encapsulated, but they may be the origin of both **extrapulmonary tuberculosis** and **reactivation pulmonary tuberculosis**.

The time between initial infection and clinically apparent TB disease is variable. Disseminated and meningeal TB are early manifestations, often occurring within 2-6 months of acquisition. Significant lymph node or endobronchial TB usually appears within 3-9 months. Lesions of the bones and joints take several years to develop, whereas renal lesions become evident decades after infection. Extrapulmonary manifestations are more common in children than in adults and develop in 25–35% of children with TB vs approximately 10% of immunocompetent adults.

Pulmonary TB that occurs >1 year after the primary infection is usually caused by endogenous regrowth of bacilli persisting in partially encapsulated lesions. This **reactivation TB** is rare in young children but is common among adolescents and young adults. The most common form is an infiltrate or cavity in the apex of the upper lobes, where oxygen tension and blood flow are highest.

The risk for dissemination of *M. tuberculosis* is very high in persons living with HIV. Reinfection also can occur in persons with advanced HIV or AIDS. In immunocompetent persons, the response to the initial infection with *M. tuberculosis* usually provides protection against reinfection when a new exposure occurs. However, exogenous reinfection has been reported to occur in adults and children without immune compromise in highly endemic areas.

Immunity

Conditions that adversely affect cell-mediated immunity predispose to progression from TBI to disease. Rare specific genetic defects (Mendelian susceptibility to mycobacterial disease [MSMD]) associated with deficient cell-mediated immunity in response to mycobacteria include interleukin (IL)-12 receptor B1 deficiency *TYK2* pathogenic gene variants; ~15 other genes associated with primary immunodeficiencies such as *NEMO, STAT1, JAK1,* and *RORC;* and complete and partial interferon (IFN)-γ receptor 1 chain deficiencies. TBI is associated with a humoral antibody response, which plays a little known role in host defense. Shortly after infection, tubercle bacilli replicate in both free alveolar spaces and inactivated alveolar macrophages. Sulfatides in the

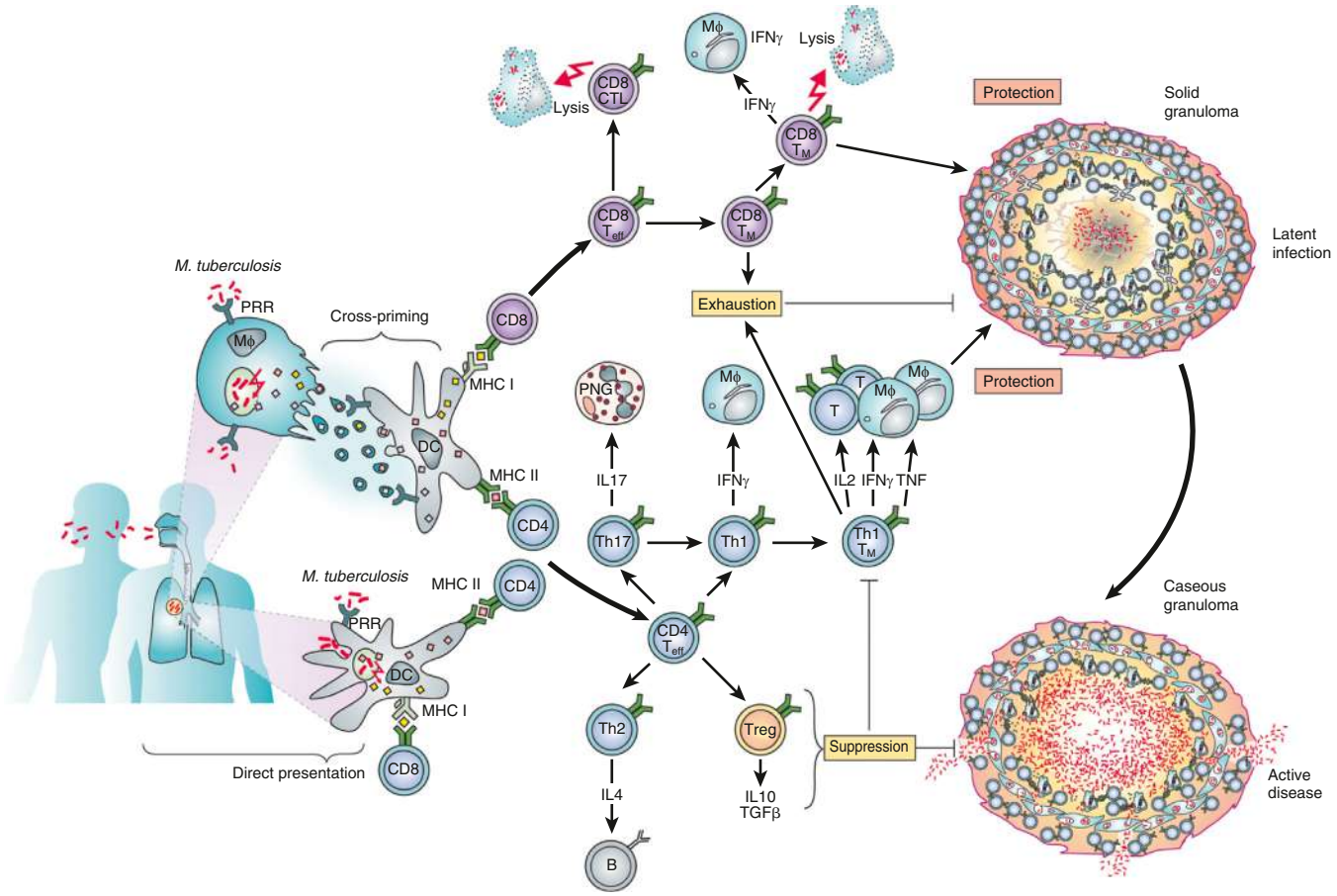

Fig. 261.10 Overview of the immune response in tuberculosis. Control of *Mycobacterium tuberculosis* is mainly the result of productive teamwork between T-cell populations and macrophages (Mø). *M. tuberculosis* survives within macrophages and dendritic cells (DCs) inside the phagosomal compartment. Gene products of major histocompatibility complex (MHC) class II are loaded with mycobacterial peptides that are presented to CD4 T cells. CD8 T-cell stimulation requires loading of MHC I molecules by mycobacterial peptides in the cytosol, either by egression of mycobacterial antigens into the cytosol or cross-priming, by which macrophages release apoptotic bodies carrying mycobacterial peptides. These vesicles are taken up by DCs and peptides presented. The CD4 T-helper (Th) cells polarize into different subsets. DCs and macrophages express pattern recognition receptors (PRRs), which sense molecular patterns on pathogens. Th1 cells produce interleukin (IL)-2 for T-cell activation, interferon-γ (IFN-γ), or tumor necrosis factor (TNF) for macrophage activation. Th17 cells, which activate polymorphonuclear granulocytes (PNGs), contribute to the early formation of protective immunity in the lung after vaccination. Th2 cells and regulatory T cells (Treg) counterregulate Th1-mediated protection via IL-4, transforming growth factor-β (TGF-β), or IL-10. CD8 T cells produce IFN-γ and TNF, which activate macrophages. They also act as cytolytic T lymphocytes (CTLs) by secreting perforin and granulysin, which lyse host cells and directly attack *M. tuberculosis*. These effector T cells (Teff) are succeeded by memory T cells (T_M). T_M cells produce multiple cytokines, notably IL2, IFN-γ, and TNF. During active containment in solid granuloma, *M. tuberculosis* recesses into a dormant stage and is immune to attack. Exhaustion of T cells is mediated by interactions between T cells and DCs through members of the programmed death 1 system. Treg cells secrete IL-10 and TGF-β, which suppress Th1. This process allows resuscitation of *M. tuberculosis,* which leads to granuloma caseation and active disease. B, B cell. *(From Kaufman SHE, Hussey G, Lambert PH. New vaccines for tuberculosis. Lancet. 2010;375:2110–2118.)*

mycobacterial cell wall inhibit fusion of the macrophage phagosome and lysosomes, allowing the organisms to escape destruction by intracellular enzymes. **Cell-mediated immunity** develops 2-12 weeks after infection, along with tissue hypersensitivity (Fig. 261.10). After bacilli enter macrophages, lymphocytes that recognize mycobacterial antigens proliferate and secrete lymphokines and other mediators that attract other lymphocytes and macrophages to the area. Certain lymphokines activate macrophages, causing them to develop high concentrations of lytic enzymes that enhance their mycobactericidal capacity. A discrete subset of regulator helper and suppressor lymphocytes modulates the immune response. Development of specific cellular immunity prevents progression of the initial infection in most persons.

The pathologic events in the initial TBI seem to depend on the balance among the mycobacterial antigen load; cell-mediated immunity (which enhances intracellular killing); and tissue hypersensitivity, which promotes extracellular killing. When the antigen load is small and the degree of tissue sensitivity is high, granuloma formation results from the organization of lymphocytes, macrophages, and fibroblasts. When both antigen load and degree of sensitivity are high, granuloma formation is less organized. Tissue necrosis is incomplete, resulting in formation of caseous material. When the degree of tissue sensitivity is low, as often occurs in infants or immunocompromised persons, the reaction is diffuse and the infection is not well contained, leading to dissemination and local tissue destruction. Tumor necrosis factor (TNF) and other cytokines released by specific lymphocytes promote cellular destruction and tissue damage in susceptible persons.

CLINICAL MANIFESTATIONS

Primary Pulmonary Disease

The **primary complex** includes the parenchymal pulmonary focus and the regional lymph nodes. Approximately 70% of lung foci are subpleural, and localized pleurisy is common. The initial parenchymal inflammation usually is not visible on chest radiograph, but a localized, nonspecific infiltrate may be seen before the development of tissue hypersensitivity. All lobar segments of the lung are at equal risk for initial infection. Two or more primary foci are present in 25% of cases. The hallmark of primary TB in the lung is the relatively large size of the regional lymphadenitis compared with the relatively small size

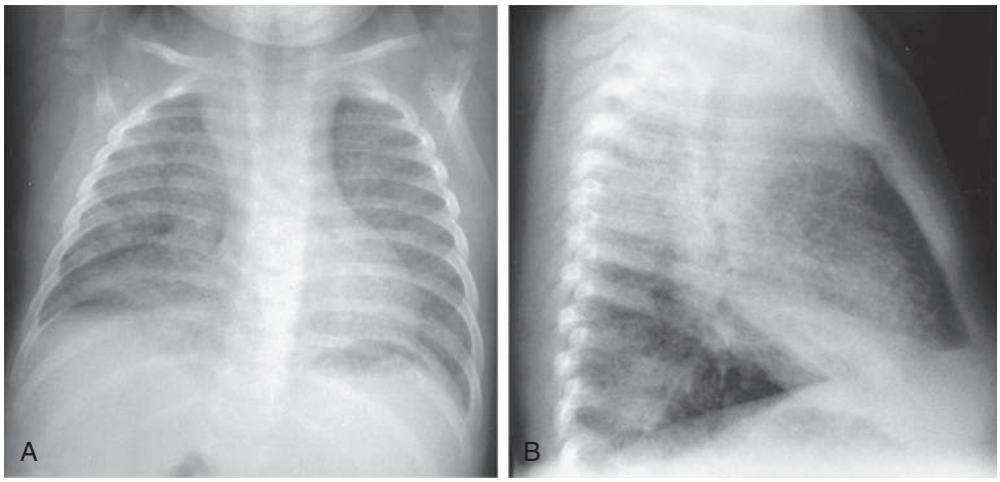

Fig. 261.11 Posteroanterior (A) and lateral (B) chest radiographs of an infant with miliary tuberculosis. The child's mother had failed to complete treatment for pulmonary tuberculosis twice within 3 years of this child's birth.

of the initial lung focus (see Figs. 261.7 and 261.8). As delayed-type hypersensitivity develops, the hilar lymph nodes continue to enlarge in some children, especially infants, compressing the regional bronchus and causing obstruction. The usual sequence is *hilar lymphadenopathy, focal hyperinflation,* and then *atelectasis.* The resulting radiographic shadows have been called **collapse-consolidation** or *segmental* TB (see Fig. 261.9). Rarely, inflamed caseous nodes attach to the endobronchial wall and erode through it, causing endobronchial TB or a fistula tract. The caseum causes complete obstruction of the bronchus, resulting in extensive infiltrate and collapse. Enlargement of the subcarinal lymph nodes can cause compression of the esophagus and, rarely, a bronchoesophageal fistula.

Most cases of tuberculous bronchial obstruction in children resolve fully with appropriate treatment. Occasionally, there is residual calcification of the primary focus or regional lymph nodes. The appearance of calcification implies that the lesion has been present for at least 6-12 months. Healing of the segment can be complicated by scarring or contraction associated with cylindrical bronchiectasis, but this is rare.

Children can have lobar TB pneumonia without impressive hilar lymphadenopathy. If the primary infection is progressively destructive, liquefaction of the lung parenchyma can lead to formation of a thin-walled primary TB cavity. Rarely, bullous tuberculous lesions occur in the lungs and lead to pneumothorax if they rupture. Erosion of a parenchymal focus of TB into a blood or lymphatic vessel can result in dissemination of the bacilli and a **miliary** pattern, with small nodules evenly distributed on the chest radiograph (Fig. 261.11).

The symptoms and physical signs of primary pulmonary TB in children are surprisingly meager considering the degree of radiographic changes often present. When active case finding is performed, up to 50% of infants and children with radiographically moderate to severe pulmonary TB have no physical findings. Infants are more likely to experience signs and symptoms. Nonproductive cough and mild dyspnea are the most common symptoms. Systemic complaints such as fever, night sweats, anorexia, and decreased activity occur less often. Some infants have difficulty gaining weight or develop a true failure-to-thrive syndrome that often does not improve significantly until several months of effective treatment have been taken. Pulmonary signs are even less common. Some infants and young children with bronchial obstruction have localized wheezing or decreased breath sounds that may be accompanied by tachypnea or, rarely, respiratory distress. These pulmonary symptoms and signs are occasionally alleviated by antibiotics, suggesting bacterial superinfection.

Progressive Primary Pulmonary Disease

A rare but serious complication of TB in a child occurs when the primary focus enlarges steadily and develops a large caseous center. Liquefaction can cause formation of a primary cavity associated with large numbers of tubercle bacilli. The enlarging focus can slough necrotic debris into the adjacent bronchus, leading to further intrapulmonary dissemination. Significant signs or symptoms are common in locally progressive disease in children. High fever, severe cough with sputum production, weight loss, and night sweats are common. Physical signs include diminished breath sounds, rales, and dullness or egophony over the cavity. The prognosis for full recovery is excellent with appropriate therapy.

Reactivation Tuberculosis

Pulmonary TB in adults usually represents endogenous reactivation of a site of TBI established previously in the body. This form of TB is rare in childhood but can occur in adolescence. Children with a healed TBI acquired when they were <2 years old rarely develop chronic reactivation pulmonary disease, which is more common in those who acquire the initial infection when they are >7 years old. The most common pulmonary sites are the original parenchymal focus, lymph nodes, and the apical seedings **(Simon foci)** established during the hematogenous phase of the early infection. This form of TB disease usually remains localized in the lungs, because the established immune response prevents further extrapulmonary spread. The most common radiographic findings are extensive infiltrates and thick-walled cavities in the upper lobes.

Older children and adolescents with reactivation TB are more likely to experience fever, anorexia, malaise, weight loss, night sweats, productive cough, hemoptysis, and chest pain than children with primary pulmonary TB. However, physical examination findings usually are minor or absent, even when cavities or large infiltrates are present. Most signs and symptoms improve within several weeks of starting effective treatment, although the cough can last for several months. This form of TB may be highly contagious if there is significant sputum production and cough. The prognosis for full recovery is excellent with appropriate therapy.

Pleural Effusion

Tuberculous pleural effusions, which can be local or general, originate in the discharge of bacilli into the pleural space from a subpleural pulmonary focus or caseated lymph node. Asymptomatic local pleural effusion is so common in primary TB that it is considered part of the primary complex. Larger and clinically significant effusions occur months to years after the primary infection. Tuberculous pleural effusion is uncommon in children <6 years old and rare in children <2 years old. Effusions are usually unilateral but can be bilateral. They are rarely associated with a segmental pulmonary lesion and are uncommon in disseminated TB. Often the radiographic abnormality is more extensive than would be suggested by physical findings or symptoms (Fig. 261.12).

Clinical onset of tuberculous pleurisy is often sudden and characterized by low to high fever, shortness of breath, chest pain on deep inspiration, and diminished breath sounds. The fever and other symptoms can last for several weeks after the start of antituberculosis chemotherapy. The TST is positive in 70–80% of cases. The prognosis is

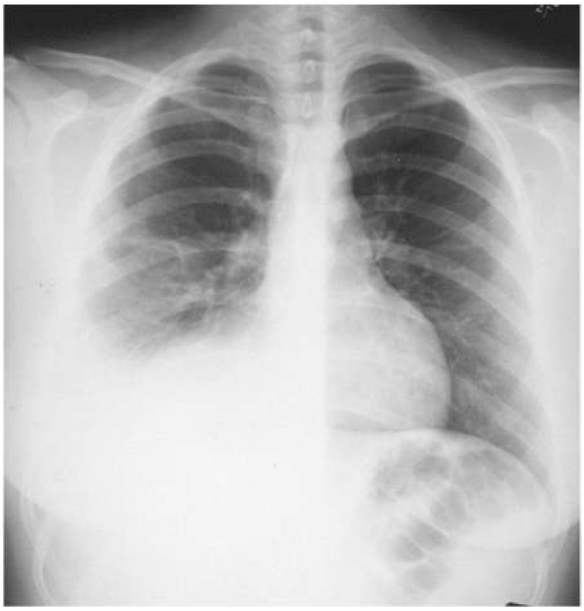

Fig. 261.12 Pleural tuberculosis in 16-yr-old female.

excellent, but radiographic resolution often takes months. Scoliosis is a rare complication from a long-standing effusion.

Examination of pleural fluid and the pleural membrane is important to establish the diagnosis of tuberculous **pleurisy**. The pleural fluid is usually yellow and only occasionally tinged with blood. The specific gravity is usually 1.012-1.025, the protein level is usually 2-4 g/dL, and the glucose concentration may be low, although it is usually in the low-normal range (20-40 mg/dL). Typically, there are several hundred to several thousand white blood cells per microliter (WBCs/μL), with an early predominance of polymorphonuclear leukocytes (PMNs) followed by a high percentage of lymphocytes. Acid-fast smears of the pleural fluid are rarely positive. Cultures of the fluid are positive in <30% of cases. Measurement of adenosine deaminase (ADA) levels may enhance the diagnosis of pleural TB. Biopsy of the pleural membrane is more likely to yield a positive acid-fast stain or culture, and granuloma formation can be demonstrated.

Pericardial Disease

The most common form of cardiac TB is pericarditis. It is rare, occurring in 0.5–4% of TB cases in children. Pericarditis usually arises from direct invasion or lymphatic drainage from subcarinal lymph nodes. The presenting symptoms are nonspecific, including low-grade fever, malaise, and weight loss. Chest pain is unusual in children. A pericardial friction rub or distant heart sounds with pulsus paradoxus may be present. The pericardial fluid is typically serofibrinous or hemorrhagic. Acid-fast smear of the fluid rarely reveals the organism, but cultures are positive in 30–70% of cases. ADA levels are elevated in TB pericarditis. The culture yield from pericardial biopsy may be higher, and the presence of granulomas often suggests the diagnosis. Partial or complete pericardiectomy may be required when constrictive pericarditis develops.

Lymphohematogenous (Disseminated) Disease

Tubercle bacilli are disseminated to distant sites, including the liver, spleen, skin, and lung apices, in all cases of TBI. Lymphohematogenous spread is usually asymptomatic. Rare patients experience protracted hematogenous TB caused by the intermittent release of tubercle bacilli as a caseous focus erodes through the wall of a blood vessel in the lung. The clinical picture subsequent to lymphohematogenous dissemination depends on the burden of organisms released from the primary focus to distant sites and the adequacy of the host's immune response. Although the clinical picture may be acute, more often it is indolent and prolonged, with spiking fever accompanying the release of organisms into the bloodstream. Multiple organ involvement is common, leading to hepatomegaly, splenomegaly, lymphadenitis in superficial or deep nodes, and papulonecrotic tuberculids appearing on the skin. Bones and joints or kidneys also can become involved. Meningitis occurs only late in the course of the disease. Early pulmonary involvement is surprisingly mild, but diffuse involvement becomes apparent with prolonged infection.

The most clinically significant form of disseminated TB is miliary disease, which occurs when massive numbers of tubercle bacilli are released into the bloodstream, causing disease in two or more organs. **Miliary tuberculosis** usually complicates the primary infection, occurring within 2-6 months of the initial infection. Although this form of disease is most common in infants and young children, it is also found in adolescents and older adults, resulting from the breakdown of a previously healed primary pulmonary lesion. The clinical manifestations of miliary TB are protean, depending on the number of organisms that disseminate and where they lodge. Lesions are often larger and more numerous in the lungs, spleen, liver, and bone marrow than in other tissues. Because this form of TB is most common in infants and malnourished or immunosuppressed patients, the host's immune incompetence likely plays a role in pathogenesis.

Rarely, the onset of miliary TB is explosive, and the patient can become gravely ill in several days. More often, the onset is insidious, with early systemic signs, including anorexia, weight loss, and low-grade fever. At this time, abnormal physical signs are usually absent. Generalized lymphadenopathy and hepatosplenomegaly develop within several weeks in approximately 50% of cases. The fever can then become higher and more sustained, although the chest radiograph usually is normal and respiratory symptoms are minor or absent. Within several more weeks, the lungs can become filled with tubercles, and dyspnea, cough, rales, or wheezing occur. The lesions of miliary TB are usually <2-3 mm in diameter when first visible on chest radiograph (see Fig. 261.11). The smaller lesions coalesce to form larger lesions and sometimes extensive infiltrates. As the pulmonary disease progresses, an alveolar air block syndrome can result in frank respiratory distress, hypoxia, and pneumothorax or pneumomediastinum. Signs or symptoms of meningitis or peritonitis are found in 20–40% of patients with advanced disease. Chronic or recurrent headache in a patient with miliary TB usually indicates the presence of meningitis, whereas the onset of abdominal pain or tenderness is a sign of tuberculous peritonitis. **Cutaneous lesions** include papulonecrotic tuberculids, nodules, or purpura. Choroid tubercles occur in 13–87% of patients and are highly specific for the diagnosis of miliary TB. Unfortunately, the TST is nonreactive in up to 40% of patients with disseminated TB.

Diagnosis of disseminated TB can be difficult, and a high index of suspicion by the clinician is required. Often the patient presents with fever of unknown origin (FUO). Early sputum or gastric aspirate cultures have a low sensitivity. Biopsy of the liver or bone marrow with appropriate bacteriologic and histologic examinations more often yields an early diagnosis. The most important clue is usually a history of recent exposure to an adult with infectious TB.

The resolution of miliary TB is slow, even with proper therapy. Fever usually declines within 2-3 weeks of starting chemotherapy, but the chest radiographic abnormalities might not resolve for many months. Occasionally, corticosteroids hasten symptomatic relief, especially when air block, peritonitis, or meningitis is present. The prognosis is excellent with early diagnosis and adequate chemotherapy.

Upper Respiratory Tract Disease

TB of the upper respiratory tract is rare in developed countries but is still observed in developing countries. Children with laryngeal TB have a crouplike cough, sore throat, hoarseness, and dysphagia. Most children with laryngeal TB have extensive upper lobe pulmonary disease, but occasional patients have primary laryngeal disease with a normal chest radiograph. TB of the middle ear results from aspiration of infected pulmonary secretions into the middle ear or from hematogenous dissemination in older children. The most common signs and symptoms are painless unilateral otorrhea, tinnitus, decreased hearing, facial paralysis, and a perforated tympanic membrane. Enlargement of

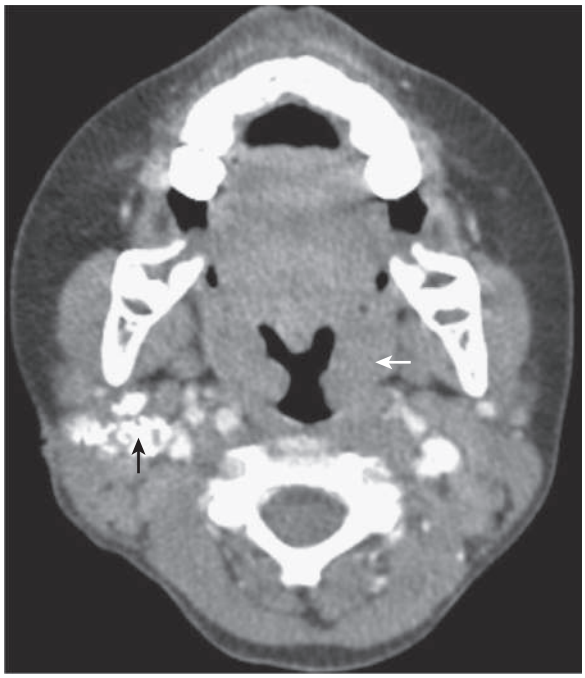

Fig. 261.13 Scrofula. Axial CT image of the neck in 8-yr-old male shows calcified right cervical lymphadenopathy *(black arrow)* and tonsillar swelling *(white arrow). (From Lighter J, Rigaud M. Diagnosing childhood tuberculosis: traditional and innovative modalities. Curr Probl Pediatr Adolesc Health Care. 2009;39:55–88.)*

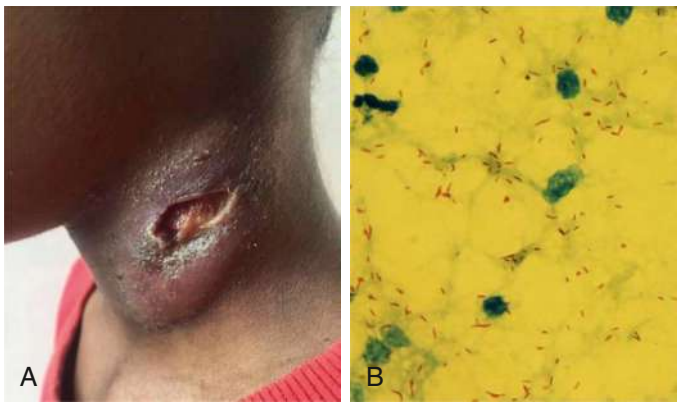

Fig. 261.14 Scrofula. A, Ulcerative lesion 3.2 × 2.1 cm with undermined edges and necrotic base with surrounding induration. B, Acid-fast bacilli. *(From Sharawat IK. Scrofula. J Pediatr. 2017;189:236.)*

lymph nodes in the preauricular or anterior cervical chains can accompany this infection. Diagnosis is difficult, because stains and cultures of ear fluid are often negative, and histology of the affected tissue often shows a nonspecific acute and chronic inflammation without granuloma formation.

Lymph Node Disease

TB of the superficial lymph nodes, often referred to as **scrofula**, is the most common form of extrapulmonary TB in children (Figs. 261.13-261.15). Historically, scrofula was usually caused by drinking unpasteurized cow's milk laden with *M. bovis*. Most current cases occur within 6-9 months of initial infection by *M. tuberculosis,* although some cases appear years later. The tonsillar, anterior cervical, submandibular, and supraclavicular nodes become involved secondary to extension of a primary lesion of the upper lung fields or abdomen. Infected nodes in the inguinal, epitrochlear, or axillary regions result from regional

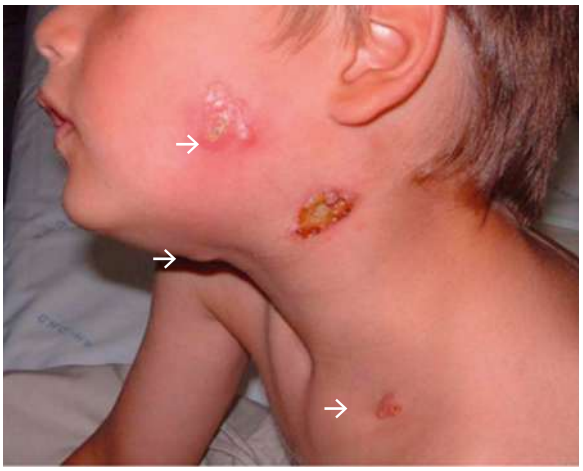

Fig. 261.15 Scrofula. Tuberculous lymphadenitis with fistula in 4-yr-old male associated with scrofuloderma *(arrows). (From Pereira C, Cascais M, Felix M, Salgado M. Scrofula in a child. J Pediatr. 2017;189:235.)*

lymphadenitis associated with TB of the skin or skeletal system. The nodes usually enlarge gradually in the early stages of lymph node disease. They are discrete, nontender, and firm but not hard. The nodes often feel fixed to underlying or overlying tissue. Disease is most often **unilateral**, but bilateral involvement can occur because of the crossover drainage patterns of lymphatic vessels in the chest and lower neck. As infection progresses, multiple nodes are infected, resulting in a mass of matted nodes. Systemic signs and symptoms other than a low-grade fever are usually absent. The TST is usually reactive. The chest radiograph is often normal (in 70% of cases). The onset of illness is occasionally more acute, with rapid enlargement, tenderness, and fluctuance of lymph nodes and with high fever. The initial presentation is rarely a fluctuant mass with overlying cellulitis or skin discoloration.

Lymph node TB can resolve if left untreated but more often progresses to caseation and necrosis. The capsule of the node breaks down, resulting in the spread of infection to adjacent nodes. Rupture of the node usually results in a draining sinus tract that can require surgical removal. **Tuberculous lymphadenitis** can usually be diagnosed by fine-needle aspiration (FNA) of the node and responds well to antituberculosis therapy, although the lymph nodes do not return to normal size for months or even years. Surgical removal is not usually necessary and must be combined with antituberculosis medication, because the lymph node disease is only one part of a systemic infection.

A definitive diagnosis of tuberculous adenitis usually requires histologic, bacteriologic, or molecular confirmation, which is best accomplished by FNA for culture, molecular testing, stain, and histology. If FNA is not successful in establishing a diagnosis, excisional biopsy of the involved node is indicated. Culture of lymph node tissue yields the organism in only approximately 50% of cases. Many other conditions can be confused with tuberculous adenitis, including infection caused by **nontuberculous mycobacteria (NTM)**, cat scratch disease *(Bartonella henselae),* tularemia, brucellosis, toxoplasmosis, pyogenic infection, or noninfectious causes, including tumor, branchial cleft cyst, and cystic hygroma. The most common problem is distinguishing infection caused by *M. tuberculosis* from lymphadenitis caused by NTM in geographic areas where NTM are common. Both conditions are usually associated with a normal chest radiograph and a reactive TST. An important clue to the diagnosis of tuberculous adenitis is an epidemiologic link to an adult with infectious TB. In areas where both diseases are common, culture or PCR testing of the involved tissue may be necessary to establish the exact cause of the disease.

Central Nervous System Disease

TB of the central nervous system (CNS) is the most serious complication in children and is fatal without prompt and appropriate treatment. **Tuberculous meningitis** usually arises from the formation of a metastatic caseous lesion in the cerebral cortex or meninges that develops

during the lymphohematogenous dissemination of the primary infection. This initial lesion increases in size and discharges small numbers of tubercle bacilli into the subarachnoid space. The resulting gelatinous exudate infiltrates the corticomeningeal blood vessels, producing inflammation, obstruction, and subsequent infarction of the cerebral cortex. The brainstem is often the site of greatest involvement, which accounts for the commonly associated dysfunction of cranial nerves III, VI, and VII. The exudate also interferes with the normal flow of cerebrospinal fluid (CSF) in and out of the ventricular system at the level of the basilar cisterns, leading to a communicating hydrocephalus. The combination of vasculitis, infarction, cerebral edema, and hydrocephalus results in the severe damage that can occur gradually or rapidly. Profound abnormalities in electrolyte metabolism from salt wasting or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) also contribute to the pathophysiology of tuberculous meningitis.

Tuberculous meningitis complicates approximately 0.3% of untreated TBIs in children. It is most common in children 6 months to 4 years old. Occasionally, tuberculous meningitis occurs many years after the infection, when rupture of one or more of the subependymal tubercles discharges tubercle bacilli into the subarachnoid space. The clinical progression of tuberculous meningitis may be rapid or gradual. Rapid progression tends to occur more often in infants and young children, who can experience symptoms for only several days before the onset of acute hydrocephalus, seizures, and cerebral edema. More often, the signs and symptoms progress slowly over weeks and are divided into three stages.

The **first stage** typically lasts 1-2 weeks and is characterized by nonspecific symptoms such as fever, headache, irritability, drowsiness, and malaise. Focal neurologic signs are absent, but infants can experience a stagnation or loss of developmental milestones. The **second stage** usually begins more abruptly. The most common features are lethargy, nuchal rigidity, seizures, positive Kernig and Brudzinski signs, hypertonia, vomiting, cranial nerve palsies, and other focal neurologic signs. The accelerating clinical illness usually correlates with the development of hydrocephalus, increased intracranial pressure, and vasculitis. Some children have no evidence of meningeal irritation but can have signs of encephalitis, such as disorientation, movement disorders, or speech impairment. The **third stage** is marked by coma, hemiplegia or paraplegia, hypertension, decerebrate posturing, deterioration of vital signs, and eventually death.

The prognosis of tuberculous meningitis correlates most closely with the clinical stage of illness at the time treatment is initiated. The majority of patients in the first stage have an excellent outcome, whereas most patients in the third stage who survive have permanent disabilities, including blindness, deafness, paraplegia, diabetes insipidus, or mental retardation. The prognosis for young infants is generally worse than for older children. It is imperative that antituberculosis treatment be considered for any child who develops basilar meningitis and hydrocephalus, cranial nerve palsy, or stroke with no other apparent etiology. Often the key to the correct diagnosis is identifying an adult who has infectious TB and is in contact with the child. Because of the short incubation period of tuberculous meningitis, the illness has not yet been diagnosed in the adult in many cases.

The diagnosis of tuberculous meningitis can be difficult early in its course, requiring a high degree of suspicion on the part of the clinician. The TST is nonreactive in up to 50% of cases, and 20–50% of children have a normal chest radiograph. The most important laboratory test for the diagnosis of tuberculous meningitis is examination and culture of the lumbar CSF. The CSF leukocyte count usually ranges from 10 to 500 cells/μL. PMNs may be present initially, but lymphocytes predominate in the majority of cases. The CSF glucose is typically <40 mg/dL but rarely <20 mg/dL. The protein level is elevated and may be extremely high (400-5,000 mg/dL) secondary to hydrocephalus and spinal block. Although the lumbar CSF is grossly abnormal, ventricular CSF can have normal chemistries and cell counts because this fluid is obtained from a site proximal to the inflammation and obstruction. During early stage one, the CSF can resemble that of viral aseptic meningitis, only to progress to the more severe CSF profile over several weeks. The success of the microscopic examination of acid-fast–stained CSF and mycobacterial culture is related directly to the volume of the CSF sample. Examinations or culture of small amounts of CSF are unlikely to demonstrate *M. tuberculosis.* It is recommended that serial collections of large-volume lumbar CSF (up to 15 mL) be obtained for acid-fast stain and culture. When 5-10 mL of lumbar CSF can be obtained, the acid-fast stain of the CSF sediment is positive in up to 30% of cases and the culture is positive in 50–70% of cases. Polymerase chain reaction (PCR) testing of the CSF and ADA levels can improve the diagnosis. Cultures of other body fluids can help confirm the diagnosis.

Radiographic studies can aid in the diagnosis of tuberculous meningitis. CT or MRI of the brain of patients with tuberculous meningitis may be normal during early stages of the disease. As the disease progresses, basilar enhancement and communicating hydrocephalus with signs of cerebral edema or early focal ischemia are the most common findings (Fig. 261.16). Some young children with tuberculous meningitis have one or several clinically silent tuberculomas, occurring most often in the cerebral cortex or thalamic regions.

Another manifestation of CNS TB is the **tuberculoma,** a tumor-like mass resulting from aggregation of caseous tubercles that usually manifests clinically as a brain tumor. Tuberculomas account for up to 30% of brain tumors in some areas of the world but are rare in North America. In adults, tuberculomas are most often supratentorial, but in children, they are often infratentorial, located at the base of the brain near the cerebellum (Fig. 261.17). Lesions are most often singular but may be multiple. The most common symptoms are headache, fever, focal neurologic findings, and convulsions. The TST is usually reactive, but the chest radiograph is usually normal. Surgical excision is sometimes necessary to distinguish tuberculoma from other causes of brain tumor. However, surgical removal is not necessary because most tuberculomas resolve with medical management. Corticosteroids are administered during the first few weeks of treatment or in the immediate postoperative period to decrease cerebral edema. On CT or MRI of the brain, tuberculomas usually appear as discrete lesions with a significant amount of surrounding edema. Contrast medium enhancement is often impressive and can result in a ringlike lesion. Since the advent of CT, the paradoxical development of tuberculomas in patients with tuberculous meningitis who are receiving ultimately effective chemotherapy has been recognized. The cause and nature of these tuberculomas are poorly understood, but they do not represent failure of antimicrobial treatment. This phenomenon should be considered whenever a child with tuberculous meningitis deteriorates or develops focal neurologic findings during treatment. Corticosteroids

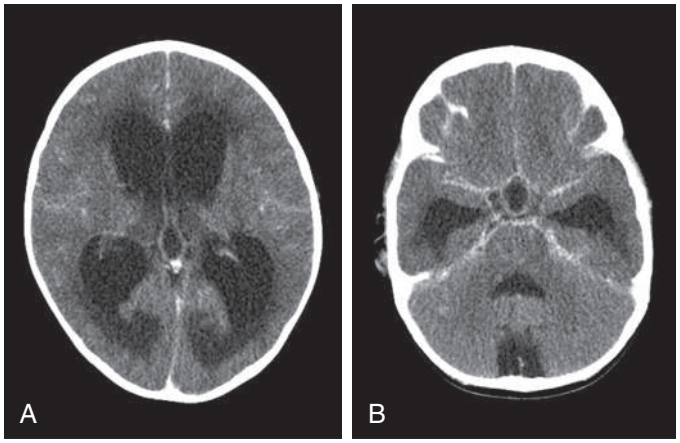

Fig. 261.16 Tuberculous meningitis in a child. **A** and **B**, Postcontrast CT images demonstrate intense enhancement in the suprasellar cistern, sylvian cistern, and prepontine cistern. Dilation of the ventricular system is seen, consistent with associated hydrocephalus. *(From Lerner A, Rajamohan A, Shiroishi MS, et al. Cerebral infections and inflammation. In Haaga JR, Boll DT, eds. CT and MRI of the Whole Body, 6th ed. Philadelphia: Elsevier; 2017: Fig 10-20.)*

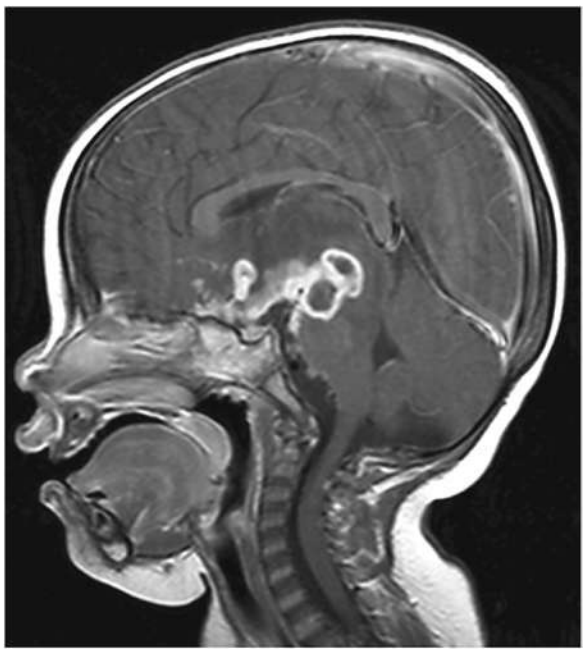

Fig. 261.17 MRI of brain of 3-yr-old child showing multiple pontine tuberculomas.

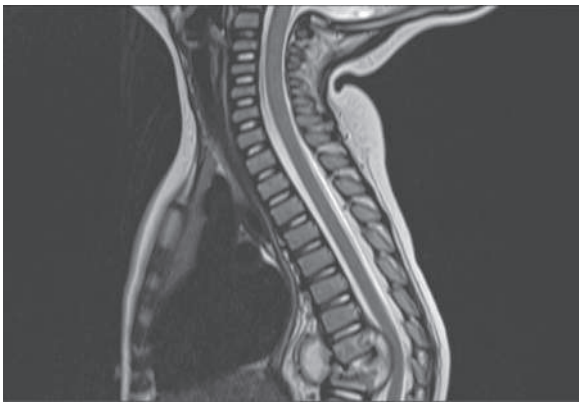

Fig. 261.18 Tuberculosis of the spine in a toddler. *(From Feder HM Jr, Rigos L, Teti K. Pott's disease in a Connecticut toddler. Lancet. 2016;388:504–505.)*

can alleviate the occasionally severe clinical signs and symptoms that occur. These lesions can persist for months or years.

Cutaneous Disease

Cutaneous TB is rare in the United States but occurs worldwide and accounts for 1–2% of tuberculosis (see Chapter 706).

Bone and Joint Disease

TB involving bone or joints is most likely to involve the vertebrae. The classic manifestation of **tuberculous spondylitis** is progression to **Pott disease**, in which destruction of the vertebral bodies leads to gibbus deformity and kyphosis (Fig. 261.18) (see Chapter 720.4). **Skeletal tuberculosis** is a late complication of TB and has become a rare entity since the availability of antituberculosis therapy but is more likely to occur in children than in adults. Tuberculous bone lesions can resemble pyogenic and fungal infections or bone tumors. *Multifocal bone involvement can occur.* A bone biopsy is essential to confirm the diagnosis. Surgical intervention is generally not necessary for cure, and the prognosis is excellent with adequate medical treatment. A sterile polyarticular (large joint) arthritis may also be noted in patients with active TB at another site.

Abdominal and Gastrointestinal Disease

TB of the oral cavity or pharynx is quite unusual. The most common lesion is a painless ulcer on the mucosa, palate, or tonsil with enlargement of the regional lymph nodes. TB of the parotid gland has been reported rarely in endemic countries. TB of the esophagus is rare in children but may be associated with a tracheoesophageal fistula in infants. These forms of TB are usually associated with extensive pulmonary disease and swallowing of infectious respiratory secretions. They can occur in the absence of pulmonary disease, by spread from mediastinal or peritoneal lymph nodes.

Tuberculous peritonitis occurs most often in young males and is uncommon in adolescents and rare in children. Generalized peritonitis can arise from subclinical or miliary hematogenous dissemination. Localized peritonitis is caused by direct extension from an abdominal lymph node, intestinal focus, or genitourinary TB. Rarely, the lymph nodes, omentum, and peritoneum become matted and can be palpated as a doughy, irregular, nontender mass. Abdominal pain or tenderness, ascites, anorexia, and low-grade fever are typical manifestations. The TST is usually reactive. The diagnosis can be confirmed by paracentesis with appropriate stains and cultures, but this procedure must be performed carefully to avoid entering a bowel that is adherent to the omentum.

Tuberculous enteritis is caused by hematogenous dissemination or by swallowing tubercle bacilli discharged from the patient's own lungs. The jejunum and ileum near Peyer patches and the appendix are the most common sites of involvement. The typical findings are shallow ulcers that cause pain, diarrhea or constipation, weight loss, and low-grade fever. Mesenteric adenitis usually complicates the infection. The enlarged nodes can cause intestinal obstruction or erode through the omentum to cause generalized peritonitis. The clinical presentation of tuberculous enteritis is nonspecific, mimicking other infections and conditions that cause diarrhea. The disease should be suspected in any child with chronic GI complaints and a reactive TST or positive IGRA. Biopsy, acid-fast stain, and culture of the lesions are usually necessary to confirm the diagnosis.

Genitourinary Disease

Renal TB is rare in children because the incubation period is several years or longer. Tubercle bacilli usually reach the kidney during lymphohematogenous dissemination. The organisms often can be recovered from the urine in cases of miliary TB and in some patients with pulmonary TB in the absence of renal parenchymal disease. In true renal TB, small caseous foci develop in the renal parenchyma and release *M. tuberculosis* into the tubules. A large mass develops near the renal cortex that discharges bacteria through a fistula into the renal pelvis. Infection then spreads locally to the ureters, prostate, or epididymis. Renal TB is often clinically silent in its early stages, marked only by sterile pyuria and microscopic hematuria. Dysuria, flank or abdominal pain, and gross hematuria develop as the disease progresses. Superinfection by other bacteria is common and can delay recognition of the underlying TB. Hydronephrosis or ureteral strictures can complicate the disease. Urine cultures for *M. tuberculosis* are positive in 80–90% of cases, and acid-fast stains of large volumes of urine sediment are positive in 50–70% of cases. The TST is nonreactive in up to 20% of patients. A pyelogram or CT scan often reveals mass lesions, dilation of the proximal ureters, multiple small filling defects, and hydronephrosis if ureteral stricture is present. Disease is most often unilateral.

Genital tract TB is uncommon in prepubescent males and females. This condition usually originates from lymphohematogenous spread, although it can be caused by direct spread from the intestinal tract or bone. Adolescent females can develop genital tract TB during the primary infection. The fallopian tubes are most often involved (90–100% of cases), followed by the endometrium (50%), ovaries (25%), and cervix (5%). The most common symptoms are lower abdominal pain and dysmenorrhea or amenorrhea. Systemic manifestations are usually absent, and the chest radiograph is normal in the majority of cases. The TST is usually reactive. Genital TB in adolescent males causes epididymitis or orchitis. The condition usually manifests as a painless, unilateral nodular swelling of the scrotum. Involvement of the glans

penis is extremely rare. Genital abnormalities and a positive TST in an adolescent male or female suggest genital tract TB.

Pregnancy and the Newborn

Pulmonary and particularly extrapulmonary TB other than lymphadenitis in a pregnant woman is associated with increased risk for prematurity, fetal growth retardation, low birthweight, and perinatal mortality. **Congenital TB** is rare because the most common result of female genital tract TB is infertility. Primary infection in the mother just before or during pregnancy is more likely to cause congenital infection than is reactivation of a previous infection. Congenital transmission usually occurs from a lesion in the placenta through the umbilical vein, when tubercle bacilli infect the fetal liver, where a primary focus with periportal lymph node involvement can occur. Organisms pass through the liver into the main fetal circulation and infect many organs. The bacilli in the lung usually remain dormant until after birth, when oxygenation and pulmonary circulation increase significantly. Congenital TB can also be caused by aspiration or ingestion of infected amniotic fluid. However, the most common route of infection for the neonate is postnatal airborne transmission from an adult with infectious pulmonary TB.

Perinatal Disease

Symptoms of congenital TB may be present at birth but usually begin by the second or third week of life. The most common signs and symptoms are respiratory distress, fever, hepatic or splenic enlargement, poor feeding, lethargy or irritability, lymphadenopathy, abdominal distention, failure to thrive, ear drainage, and skin lesions. The clinical manifestations vary in relation to the site and size of the caseous lesions. Many infants have an abnormal chest radiograph, most often with a miliary pattern. Some infants with no pulmonary findings early in the course of the disease later develop profound radiographic and clinical abnormalities. Hilar and mediastinal lymphadenopathy and lung infiltrates are common. Generalized lymphadenopathy and meningitis occur in 30–50% of infants.

The clinical presentation of TB in newborns is similar to that caused by bacterial sepsis and other congenital infections, such as syphilis, toxoplasmosis, and cytomegalovirus. The diagnosis should be suspected in an infant with signs and symptoms of bacterial or congenital infection whose response to antibiotic and supportive therapy is poor and in whom evaluation for other infections is unrevealing. The most important clue for rapid diagnosis of congenital TB is a maternal or family history of TB. Often, the mother's disease is discovered only after the neonate's diagnosis is suspected. The infant's TST is negative initially but can become positive in 1-3 months. A positive acid-fast stain of an early morning gastric aspirate from a newborn usually indicates TB. Direct acid-fast stains on middle ear discharge, bone marrow, tracheal aspirate, or tissue biopsy (especially liver) can be useful. The CSF should be examined, cultured, and sent for PCR testing. The mortality rate of congenital TB remains very high because of delayed diagnosis. Many children have a complete recovery if the diagnosis is made promptly and adequate chemotherapy is started.

Tuberculosis Disease in Children Living with HIV

In the United States, the rate of TB disease in children living with untreated HIV is 30 times higher than in children without HIV. Establishing the diagnosis of TB in a child living with HIV may be difficult because TST reactivity can be absent (also with a negative IGRA), culture confirmation is difficult, and the clinical features of TB are similar to many other HIV-related opportunistic infections and conditions. TB in children living with HIV is often more severe, progressive, and likely to occur in extrapulmonary sites. Radiographic findings are similar to those in children with normal immune systems, but lobar disease and lung cavitation are more common. Nonspecific respiratory symptoms, fever, and weight loss are the most common complaints. Rates of drug-resistant TB tend to be higher in adults living with HIV and probably are also higher in children living with HIV. Recurrent TB disease and relapsed TB occur more frequently in children living with HIV. The prognosis generally is good if TB disease is not far advanced at diagnosis and appropriate antituberculosis drugs are available.

The mortality rate of children living with HIV with TB is high, especially as the CD4 lymphocyte numbers decrease. In adults, the host immune response to TBI appears to enhance HIV replication and accelerate the immune suppression caused by HIV. Increased mortality rates are attributed to progressive HIV infection rather than TB. Therefore children living with HIV with potential TB exposures and/or recent TBI should be promptly evaluated and treated for TB. Conversely, all children with TB disease should be tested for HIV infection.

Children living with HIV who are given highly active antiretroviral therapy (HAART) are at high risk of developing **immune reconstitution inflammatory syndrome (IRIS)**. IRIS should be suspected in patients who experience a worsening of TB symptoms while receiving antituberculosis therapy (*paradoxical* IRIS) or who develop new-onset TB symptoms and radiographic findings after initiation of HAART (*unmasking* IRIS). Factors suggesting IRIS are temporal association (within 3 months of starting HAART), unusual clinical manifestations, unexpected clinical course, exclusion of alternative explanations, evidence of preceding immune restoration (rise in CD4 lymphocyte count), and decrease in HIV viral load. The most common clinical manifestations of IRIS in children are fever, cough, new skin lesions, enlarging lymph nodes in the thorax or neck, and appearance or enlargement of tuberculomas in the brain, with or without accompanying meningitis. The treatment of TB-associated IRIS in children living with HIV often included steroids but should be undertaken by a clinician with specific expertise in TB treatment.

IMMUNE-BASED TESTING ("TESTS OF TUBERCULOSIS INFECTION")

Tuberculin Skin Testing

The development of delayed-type hypersensitivity in most persons infected with the *M. tuberculosis* complex organisms makes the TST a useful diagnostic tool. The **Mantoux TST** is the intradermal injection of 0.1 mL purified protein derivative stabilized with Tween 80. T cells sensitized by prior infection are recruited to the skin, where they release lymphokines that induce induration through local vasodilation, edema, fibrin deposition, and recruitment of other inflammatory cells to the area. The amount of induration in response to the test should be measured by a trained person 48-72 hours after administration. In some patients, the onset of induration is >72 hours after placement; this is also a positive result. Immediate hypersensitivity reactions to tuberculin or other constituents of the preparation are short-lived (<24 hours) and not considered a positive result. Tuberculin sensitivity develops 3 weeks to 3 months (most often in 4-8 weeks) after inhalation of organisms.

Host-related factors, including very young age, malnutrition, immunosuppression by disease or drugs, viral infections (measles, mumps, varicella, influenza), vaccination with live-virus vaccines, and overwhelming TB, can depress the skin test reaction in a child infected with *M. tuberculosis*. Corticosteroid therapy can decrease the reaction to tuberculin, but the effect is variable; TST done at the time of initiating corticosteroid therapy is usually reliable. Approximately 10% of immunocompetent children with TB disease (up to 50% of those with meningitis or disseminated disease) do not react initially to purified protein derivative; most become reactive after several months of antituberculosis therapy. False-positive reactions to tuberculin can be caused by cross-sensitization to antigens of NTM, which generally are more prevalent in the geographic environment as one approaches the equator. These cross-reactions are usually transient over months to years and produce <10-12 mm of induration, but larger areas of induration can occur. Previous vaccination with bacille Calmette-Guérin (BCG) also can cause a reaction to a TST, especially if a person has received two or more BCG vaccinations. Approximately 50% of the infants who receive a BCG vaccine never develop a reactive TST, and the reactivity usually wanes in 2-3 years in those with initially positive skin test results. Older children and adults who receive a BCG vaccine are more likely to develop tuberculin reactivity, but most lose the reactivity by 5-10 years after vaccination. However,

Table 261.2 Tuberculin Skin Test (TST) or Interferon-γ Release Assay (IGRA): Recommendations for Infants, Children, and Adolescents*

CHILDREN FOR WHOM IMMEDIATE TST OR IGRA IS INDICATED†
Contacts of people with confirmed or suspected contagious tuberculosis (contact investigation)
Children with radiographic or clinical findings suggesting tuberculosis disease
Children immigrating from countries with endemic infection (e.g., Asia, Middle East, Africa, Latin America, countries from former Soviet Union), including international adoptees
Children with travel histories to countries with endemic infection and substantial contact with indigenous people from such countries‡
Children who should have annual TST or IGRA: Children infected with human immunodeficiency virus
CHILDREN AT INCREASED RISK FOR PROGRESSION OF TUBERCULOSIS INFECTION TO TUBERCULOSIS DISEASE
Children with other medical conditions, including diabetes mellitus, chronic renal failure, malnutrition, and congenital or acquired immunodeficiencies, and children receiving tumor necrosis factor (TNF) antagonists deserve special consideration. Without recent exposure, these children are not at increased risk of acquiring tuberculosis infection. Underlying immune deficiencies associated with these conditions theoretically would enhance the possibility for progression to severe disease.
Initial histories of potential exposure to tuberculosis should be included for all of these patients. If these histories or local epidemiologic factors suggest a possibility of exposure, immediate and periodic TST or IGRA should be considered.
An initial TST or IGRA should be performed before initiation of immunosuppressive therapy, including prolonged corticosteroid administration, organ transplantation, or use of TNF-α antagonists or blockers, or immunosuppressive therapy in any child requiring these treatments.

*Bacille Calmette-Guérin immunization is not a contraindication to a TST.
†Beginning as early as 3 mo of age.
‡If the child is well and has no history of exposure, the TST or IGRA should be delayed up to 10 wk after return.
From Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2021–2024 Report of the Committee on Infectious Diseases*, 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021:789.

Table 261.3 Definitions of Positive Tuberculin Skin Test (TST) Results in Infants, Children, and Adolescents*

INDURATION ≥5 MM
Children in close contact with known or suspected contagious people with tuberculosis disease
Children suspected to have tuberculosis disease: • Findings on chest radiograph consistent with active or previously tuberculosis disease • Clinical evidence of tuberculosis disease†
Children receiving immunosuppressive therapy‡ or with immunosuppressive conditions, including HIV infection
INDURATION ≥10 MM
Children at increased risk of disseminated tuberculosis disease: • Children <4 yr old • Children with other medical conditions, including Hodgkin disease, lymphoma, diabetes mellitus, chronic renal failure, or malnutrition (see Table 261.2)
Children with increased exposure to tuberculosis disease: • Children born in high-prevalence regions of the world • Children often exposed to adults with HIV infection, homeless, users of illicit drugs, residents of nursing homes, incarcerated or institutionalized, or migrant farm workers • Children who travel to high-prevalence regions of the world
INDURATION ≥15 MM
Children ≥4 yr old without any risk factors

*These definitions apply regardless of previous BCG immunization; erythema at TST site does not indicate a positive test result. Tests should be read at 48-72 hr after placement.
†Evidence by physical examination or laboratory assessment that would include tuberculosis in the working differential diagnosis (e.g., meningitis).
‡Including immunosuppressive doses of corticosteroids or tumor necrosis factor-α antagonists.
BCG, Bacille Calmette-Guérin; HIV, human immunodeficiency virus.
From Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2021–2024 Report of the Committee on Infectious Diseases*, 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021:788.

some individuals maintain tuberculin reactivity from BCG vaccine for many years. When present, skin test reactivity usually causes <10 mm of induration, although larger reactions occur in some persons.

The appropriate size of induration indicating a positive Mantoux TST result varies with related epidemiologic and risk factors. In children with no TB risk factors, skin test reactions are usually false-positive results. The American Academy of Pediatrics (AAP) and Centers for Disease Control and Prevention (CDC) discourage routine testing of all children and recommend targeted tuberculin testing of children at risk identified through periodic screening questionnaires (Table 261.2). Possible exposure to an adult with or at high risk for infectious pulmonary TB is the most crucial risk factor for children. Reaction size limits for determining a positive TST result vary with the person's risk for infection (Table 261.3). In those at highest risk of progression to TB disease, TST sensitivity is most important, whereas specificity is more important for persons at low risk of progression.

Interferon-γ Release Assay

Two blood tests—T-SPOT.*TB* (Oxford Immunotec; Marlborough, MA) and QuantiFERON-TB Gold/Gold Plus (QFT, Qiagen; Germantown, MD) detect IFN-γ generation by the patient's T cells in response to specific *M. tuberculosis* antigens (ESAT-6, CFP-10, and TB7.7). The QFT test measures whole blood concentrations of IFN-γ, and the T-SPOT.*TB* test measures the number of lymphocytes/monocytes producing IFN-γ. The test antigens are not present on *M. bovis*–BCG (vaccine) and *M. avium* complex, the major group of environmental mycobacteria, so one would expect higher specificity compared with the TST and fewer false-positive results. Both IGRAs have internal positive and negative controls. Internal positive controls allow for detection of an anergic test response, which is useful in children who are young and immunocompromised. Indeterminate (QFT)/invalid (T-SPOT.*TB*) responses occur when the test sample is negative but the positive control has insufficient activity or if the negative control has high background activity. Indeterminate/invalid results are also caused by technical factors (e.g., insufficient shaking of QFT tubes, delayed processing time). Most studies report indeterminate or invalid rates in children of 0–10%, which is influenced by a child's age and immune status. In children <2 years old, indeterminate rates can be as high as 8.1% vs 2.7% in older children, although more recent studies generally report much lower rates. *An indeterminate or invalid IGRA result is neither negative nor positive and cannot be used to guide treatment decisions.*

Some IGRAs cannot differentiate between TBI and TB disease. If available, certain IGRA tests will test CD4 and CD8 T-cell reactivity, which may help differentiate latent from active disease. Two clear advantages of the IGRAs are the need for only one patient encounter (vs two with TST) and the lack of cross-reaction with BCG vaccination and most other mycobacteria, thereby increasing test specificity for TBI. Studies comparing IGRA and TST performance in children have shown comparable sensitivity (85% in culture-confirmed children) between the two tests and superior IGRA specificity (95% vs 49%) in BCG-immunized, low-risk children.

Neither the TST nor the IGRAs perform well in infants and young children who are malnourished, severely immunocompromised, or have disseminated TB disease. It is now standard to use an IGRA in the evaluation of healthy young children ≥2 years of age, and most experts use IGRAs in younger children who are at low risk of TB infection, especially in those who have received a BCG vaccine. Both TST and

Table 261.4 Recommendations for Use of Tuberculin Skin Test (TST) and Interferon-γ Release Assay (IGRA) in Children

TST preferred, IGRA acceptable:
- Children <2 yr of age*

IGRA preferred, TST acceptable:
- Children ≥2 yr of age who have received BCG vaccine
- Children ≥2 yr of age who are unlikely to return for TST reading

TST and IGRA should be considered when:
- The initial and repeat IGRAs are indeterminate or invalid
- The initial test (TST or IGRA) is negative and:
  - Clinical suspicion for TB disease is moderate to high†
  - The child has a TB risk factor and is at high risk of progression and poor outcome (especially therapy with an immunomodulating biologic agent, e.g., TNF-α antagonist)†
- The initial TST is *positive* and:
  - ≥2 yr old and history of BCG vaccination
  - Additional evidence needed to increase adherence with therapy

*Some experts do not use an IGRA for children younger than 2 yr because of a relative lack of data for this age-group and the high risk of progression to disease.
†Positive result of either test is considered significant in these groups.
BCG, Bacille Calmette-Guérin; TB, tuberculosis, TNF, tumor necrosis factor.
Adapted from Starke JR, AAP Committee of Infectious Diseases. Interferon-γ release assays for diagnosis of tuberculosis infection and disease in children. *Pediatrics.* 2014;134(6):e1763–1773.

IGRA testing should be considered in children whose initial TST or IGRA result is negative for whom the risk of TB is high (to enhance the sensitivity of the combination of the two tests).

Technical advantages of the IGRAs over the TST include the need for a single patient encounter (vs two spaced in time with the TST), the lack of cross-reaction with BCG vaccination and most environmental mycobacteria, and eliminating the need for experience in correctly interpreting the TST. IGRAs are also useful for those who are unlikely to return for TST interpretation, those whose family is reluctant to treat a child with TBI based on a TST result alone, and those with a positive TST result in whom NTM disease is suspected (Table 261.4).

Most studies have shown no consistent, significant difference between the two commercially available IGRAs, and the CDC recommends no preference. Because of cost constraints, the WHO does not endorse IGRA use in low- and middle-income countries, even in those with a high prevalence of tuberculosis.

MYCOBACTERIAL SAMPLING, SUSCEPTIBILITY, AND CULTURE

The most specific confirmation of pulmonary TB is isolation of *M. tuberculosis* from a clinical sample. Sputum specimens for culture should be collected from adolescents and older children who are able to expectorate. Induced sputum with a jet nebulizer, inhaled saline, and chest percussion followed by nasopharyngeal suctioning is effective in children as young as 1 year. Sputum induction provides samples for both culture and acid-fast bacilli (AFB) staining. The traditional culture specimen in young children is the early morning gastric acid obtained before the child has arisen and peristalsis has emptied the stomach of the pooled respiratory secretions that have been swallowed overnight. However, even under optimal conditions, three consecutive morning gastric aspirates yield the organisms in <50% of cases. The culture yield from bronchoscopy is even lower, but this procedure can demonstrate the presence of endobronchial disease or a fistula. To improve the sensitivity of a diagnosis of TB in children, in high-burden TB settings, there is an increasing trend to collect nontraditional specimens, including stool, nasopharyngeal, and urine specimens. These specimens are easier to obtain than respiratory specimens but less sensitive in diagnosing TB in children compared to sputum or serial gastric aspirate specimens. Their diagnostic utility is increased when multiple specimens are collected in conjunction with traditional respiratory specimens. *Negative cultures never exclude the diagnosis of TB in a child.* The presence of a positive TST or IGRA, an abnormal chest radiograph consistent with TB, and history of recent exposure to an adult with infectious TB is highly suggestive of the clinical diagnosis of TB disease. If a likely adult source case has been identified, drug susceptibility test results of the isolate from the adult source usually can be used to determine the best therapeutic regimen for the child, except in very high-incidence areas, where the apparent source case might not be the actual one. Cultures should be always obtained from the child whenever the source case is unknown, there are multiple possible source cases, or the source case has possible or confirmed drug-resistant TB.

Confirmation of extrapulmonary TB is best achieved with a positive culture or PCR testing. However, for many forms of TB, the culture yield is only 25–50%, and probable diagnosis is by a combination of clinical signs and symptoms, analysis of body fluids when possible, radiographic or histopathologic evidence of TB, PCR testing, and elimination of other possible diagnoses.

Nucleic Acid Amplification Tests

The main NAAT studied in children with TB is PCR, which uses specific DNA sequences as markers for microorganisms. Compared with a clinical diagnosis of pulmonary TB in children, the sensitivity of PCR has varied from 25% to 83%, and specificity has varied from 80% to 100%. A negative PCR result never eliminates the diagnosis of TB, and the diagnosis is not confirmed by a positive PCR result.

NAAT identifies genes associated with drug resistance and is used to supplement culture-based (phenotypic) methods for drug susceptibility testing. It also decreases the time to identification of drug resistance from weeks to hours, which expedites the initiation of optimal therapy. Culture-based, phenotypic, drug susceptibility testing is necessary to confirm susceptibility to each drug; the absence of resistance genes is not always predictive of drug susceptibility. The interpretation of molecular-based drug susceptibility testing is constantly evolving, and an expert in the management of pediatric TB should be involved when drug resistance is suspected.

Gene Xpert MTB/RIF cartridge and Xpert MTB Ultra cartridge (Xpert; Cepheid, Sunnyvale, CA) are real-time PCR assays for *M. tuberculosis* that simultaneously detect **rifampin resistance**, which is often used as a proxy for MDR-TB. These assays use a self-contained cartridge system, which yields results from direct specimens in 2 hours and is less operator dependent than traditional PCR detection methods. Sensitivity and specificity of Xpert MTB/RIF have averaged 72–77% and 99% in AFB sputum smear–negative adults and 98–99% and 99–100% in AFB sputum smear–positive adults, respectively. Pediatric studies reveal that, compared to culture, the sensitivity and specificity of Xpert MTB/RIF is 62% and 98% on induced or expectorated sputa and 66% and 98% on gastric aspirates, respectively. For other specimen types (nasopharyngeal aspirate and stool), Xpert MTB/RIF pooled sensitivity for pulmonary TB ranges between 46% and 73% with a pooled specificity of 98% and 100%. Compared with smear microscopy, Xpert improved the sensitivity of detecting pediatric TB cases by 36–44%. For lymph node aspirates or biopsies, Xpert MTB/RIF compared with culture had a sensitivity and specificity of 90%. Compared to culture, Xpert MTB/RIF's sensitivity and specificity to detect rifampin resistance in respiratory specimens collected from children with suspected pulmonary TB are 86% and 98%, respectively.

Xpert Ultra is a next-generation assay that has enhanced performance in children who often have paucibacillary or smear-negative TB. The pooled sensitivity of Ultra for detection of *M. tuberculosis* was 73% in sputum samples, 64% in gastric aspirate samples, 53% in stool specimens, and 46% in nasopharyngeal samples. The pooled specificity was 98% in sputum samples, 98% in nasopharyngeal aspirate specimens, 98% in stool samples, and 95% in gastric aspirate samples. The WHO recommends use of Xpert Ultra in sputum and nasopharyngeal specimens collected from children for the diagnosis of TB and rifampin resistance, in addition to the use of Xpert MTB/RIF in sputum, gastric aspirate, nasopharyngeal aspirate, and stool specimens. Although cartridges for the Xpert systems are expensive, they offer advantages in rapid detection of MDR-TB and are especially useful in settings lacking

laboratory infrastructure. In many low-resource settings, Xpert has replaced smear microscopy; however, it has not replaced mycobacterial cultures and drug susceptibility studies.

TREATMENT

The basic principles of management of TB disease in children and adolescents are the same as in adults. Several drugs are used to effect a relatively rapid cure and prevent the emergence of secondary drug resistance during therapy (Tables 261.5 to 261.8). The choice of regimen depends on the extent of TB disease, the host, and the likelihood of drug resistance (see Chapter 260, Table 260.1). As recommended by the WHO and AAP, *the standard therapy of intrathoracic, presumed or confirmed drug-susceptible TB (pulmonary disease and/or hilar lymphadenopathy) in children is a 4- to 6-month regimen of multidrug therapy. The initial treatment regimen includes isoniazid, rifampin, pyrazinamide, and ethambutol.* The ethambutol can be discontinued once the organism is known to be susceptible to the other first-line drugs. Pyrazinamide is discontinued after 2 months, and isoniazid and rifampin are continued for an additional 2-4 months. Several clinical trials have shown that a 6-month regimen yields a success rate approaching 100%, with an incidence of clinically significant adverse reactions of <2%. Data from the SHINE trial (Shorter Treatment for Minimal Tuberculosis in Children) found that a 4-month treatment regimen in children age 0-16 years (≥3 kg) with nonsevere, smear negative, presumed drug-susceptible TB was noninferior to a 6-month course. Based on the results of this trial, the WHO supports the use of a 4-month treatment regimen in eligible children. Most experts recommend that all drug administration be either directly observed or electronically observed, meaning that a healthcare worker watches when the medications are administered to/or taken by the patients. When in-person **directly observed therapy (DOT)** or video directly observed therapy (VDOT) is used, intermittent (twice or thrice weekly) administration of drugs after an initial period as short as 2 weeks of daily therapy is as effective for drug-susceptible TB in children as daily therapy for the entire course.

Table 261.5 Dosage Recommendations for the Treatment of TB in Adults and Children[1]

			DOSE IN MG/KG (MAXIMUM DOSAGE IN PARENTHESES)			
DRUG	**ADULTS/CHILDREN[2]**		**DAILY**	**1 TIME/WK[3]**	**2 TIMES/WK[3]**	**3 TIMES/WK[3]**
Isoniazid	Adults		5 mg/kg (300 mg)	15 mg/kg (900 mg)	15 mg/kg (900 mg)	15 mg/kg (900 mg)
	Children		10– 15 mg/kg (300 mg)	—	20– 30 mg/kg (900 mg)	—
Rifampin	Adults		10 mg/kg (600 mg)	—	10 mg/kg (600 mg)	10 mg/kg (600 mg)
	Children		10– 20 mg/kg (600 mg)	—		10– 20 mg/kg (600 mg)
Rifabutin	Adults		5 mg/kg (300 mg)	—	5 mg/kg (300 mg)	5 mg/kg (300 mg)
	Children ≥12 yr		Appropriate dosing for children unknown			
Rifapentine	Adults		—	10 mg/kg (600 mg; continuation phase)	—	—
	Children					
Pyrazinamide	Adults (weight)	40– 55 kg	18.2– 25 mg/kg (1000 mg)	—	36.4– 50 mg/kg (2000 mg)	27.3– 37.5 mg/kg (1500 mg)
		56– 75 kg	20– 26.8 mg/kg (1500 mg)	—	40– 53.6 mg/kg (3000 mg)	33.3– 44.6 (2500 mg)
		76– 90 kg	22.2– 26.3 mg/kg (2000 mg)	—	44.4– 52.6 mg/kg (4000 mg)	33.3– 39.5 mg/kg (3000 mg)
	Children <40 kg		30– 40 mg/kg (2000 mg)	—		50 mg/kg (2000 kg)
Ethambutol[4]	Adults (weight)	40– 55 kg	14.5– 20 mg/kg (800 mg)	—	36.4– 50 mg/kg (2000 mg)	21.8– 30 mg/kg (1200 mg)
		56– 75 kg	16– 21.4 mg/kg (1200 mg)	—	37.3– 50 mg/kg (2800 mg)	26.7– 35.7 mg/kg (2000 mg)
		76– 90 kg	17.8– 21.1 mg/kg (1600 mg)	—	44.4– 52.6 mg/kg (4000 mg)	26.7– 31.6 mg/kg (2400 mg)
	Children		15– 20 mg/kg (1000 mg)	—	50 mg/kg (2500 mg)	—

[1]Although these regimens are broadly applicable, modifications may be needed for certain circumstances (patients on antiretroviral therapy [ART]). For more information, refer to treatment of tuberculosis guidelines. *MMWR* 2003; 52 (No.RR-11).
[2]For purposes of this document, adult dosing begins at age 15 years. Children weighing more than 40 kg should be dosed as adults. Adjust doses as the patient's weight changes.
[3]All patients prescribed an intermittent regimen should be given DOT.
[4]Ethambutol should be used with caution in young children since it is difficult to monitor their vision. However, if they have TB that is resistant to INH or RIF, a dose of 15 mg/kg per day can be used.
From Centers for Disease Control and Prevention. *Core Curriculum on Tuberculosis: What the Clinician Should Know*, 7th ed. Atlanta: CDC, 2021. Table 6.4. https://www.cdc.gov/tb/education/corecurr/pdf/chapter6.pdf

Table 261.6 Common Adverse Reactions to TB Drugs

CAUSED BY	ADVERSE REACTION	SIGNS AND SYMPTOMS	SIGNIFICANCE OF REACTION*
Any drug	Allergic	• Skin rash	May be serious or minor
Ethambutol	Eye damage	• Blurred or changed vision • Changed color vision	Serious
Isoniazid Pyrazinamide Rifampin	Hepatic toxicity	• Abdominal pain • Abnormal liver function test results • Dark urine • Fatigue • Fever for 3 or more days • Flulike symptoms • Lack of appetite • Nausea • Vomiting • Yellowish skin or eyes	Serious
Isoniazid	Nervous system damage	• Dizziness; tingling or numbness around the mouth	Serious
	Peripheral neuropathy	• Tingling sensation in hands and feet	Serious
Pyrazinamide	Stomach upset	• Stomach upset • Vomiting • Lack of appetite	May be serious or minor
	Gout	• Abnormal uric acid level** • Joint aches	Serious
Rifampin	Bleeding problems	• Easy bruising • Slow blood clotting	Serious
	Discoloration of body fluids	• Orange urine, sweat, or tears • Permanently stained soft contact lenses	Minor
	Drug interactions	• Interferes with certain medications such as birth control pills, birth control implants, and methadone treatment	May be serious or minor
	Sensitivity to the sun	• Frequent sunburn	Minor

*Patients should stop medication for serious adverse reactions and consult a clinician immediately. Patients can continue taking medication if they have minor adverse reactions.
**Asymptomatic elevated uric acid levels are expected with PZA treatment. Acute gouty arthritis, which is rare without preexisting gout, is a contraindication to PZA use.
EMB, ethambutol; INH, isoniazid; PZA, pyrazinamide; RIF,.
From Centers for Disease Control and Prevention. *Core Curriculum on Tuberculosis: What the Clinician Should Know*, 7th ed. Atlanta: CDC, 2021. Table 6.11. https://www.cdc.gov/tb/education/corecurr/pdf/chapter6.pdf

Table 261.7 Commonly Used Drug Regimens and Dosages for Treatment in Pediatric Patients with TB Infection (TBI)

DRUGS	DOSAGE FORMS AND AGE GROUP	ADMINISTRATION	DURATION (MO)	AGE RESTRICTION	COMMENTS
Isoniazid + Rifapentine (3HP)	Age ≥12 yr INH: 15 mg/kg rounded up to the nearest 50 or 100 mg (max 900 mg) Rifapentine (by weight): 10-14 kg: 300 mg 14.1-25 kg: 450 mg 25.1-32 kg: 600 mg 32.1-49.9 kg: 750 mg ≥50 kg: 900 mg Age 2-11 yr INH: 25 mg/kg, rounded up to the nearest 50 or 100 mg (max 900 mg) Rifapentine (see above)	Weekly (DOT)	3	Not for children <2 yr	Take with food, containing fat if possible, pyridoxine for selected patients RFP has drug-drug interactions
Rifampin (4R)	Adult: 10 mg/kg (max 600 mg) Child: 15-20 mg/kg (max 600 mg)	Daily (SAT)	4	None	Drug-drug interactions
INH + Rifampin	Same daily doses as when the drugs are used individually	Daily (SAT)	3	None	RIF has drug-drug interactions
INH	Adult: 5 mg/kg (max 300 mg) Child 10-15 mg/kg (max 300 mg) Adult: 15 mg/kg (max 900 mg) Child: 20-30 mg/kg (max 900 mg)	Daily (SAT) Twice weekly (DOT)	6 or 9	None	Seizures with overdose; pyridoxine for selected patients*

*Exclusively breastfed infants and for children and adolescents on meat- and milk-deficient diets; children with nutritional deficiencies, including all asymptomatic children living with HIV infection; and pregnant adolescents and women.
From Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2021–2024 Report of the Committee on Infectious Diseases*, 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021:805–806; and Nolt D, Starke JR. Tuberculosis infection in children and adolescents: testing and treatment. *Pediatrics*. 2021;148(6):e2021054663.

Table 261.8 Drug Grouping for the Treatment of MDR-TB

GROUP	INSTRUCTIONS	DRUG
Group A	Include all three drugs (unless they cannot be used), add delamanid if age >3 yr	Levofloxacin OR moxifloxacin Bedaquiline Linezolid
Group B	Add both drugs (unless they cannot be used)	Clofazimine Cycloserine or terizidone
Group C	Add to complete regimen (of four to five agents) Add when drugs from groups A or B cannot be used	Ethambutol Delamanid Pyrazinamide Imipenem-cilastatin Meropenem Amikacin OR streptomycin Ethionamide OR prothionamide *p*-Aminosalicylic acid

Extrapulmonary tuberculosis is usually caused by small numbers of mycobacteria. In general, the treatment for most forms of extrapulmonary TB in children, including cervical lymphadenopathy, is the same as for pulmonary TB. *Exceptions are bone and joint, disseminated, and CNS TB, for which there are inadequate data to recommend 6 months of therapy; these conditions are usually treated for 9-12 months.* Surgical debridement in bone and joint disease and ventriculoperitoneal shunting in CNS disease may be necessary adjuncts to medical therapy.

The optimal treatment of TB in children living with HIV has not been established. Adults living with HIV with TB disease can be treated successfully with standard regimens that include isoniazid, rifampin, pyrazinamide, and ethambutol. The total duration of therapy should be 6-9 months or 6 months after culture of sputum becomes sterile, whichever is longer. Data for children are limited to relatively small series. *Most experts believe that children living with inadequately controlled HIV who have drug-susceptible TB should receive the standard four-drug regimen for the first 2 months followed by isoniazid and rifampin for a total duration of at least 9 months. However, all treatment should be daily, not intermittent.* Children living with HIV appear to have more frequent adverse reactions to antituberculosis drugs and must be monitored closely during therapy. Co-administration of rifampin and some antiretroviral agents results in subtherapeutic blood levels of protease inhibitors and nonnucleoside reverse transcriptase inhibitors and toxic levels of rifampin. Concomitant administration of these drugs is not recommended. Treatment of children living with HIV with TB is often empirically based on epidemiologic and radiographic information because the radiographic appearance of other pulmonary complications of HIV in children, such as lymphoid interstitial pneumonitis and bacterial pneumonia, may be similar to that of TB. Therapy should be considered when TB cannot be excluded.

Drug-Resistant Tuberculosis

The incidence of drug-resistant TB is increasing in many areas of the world, including North America. There are two major types of drug resistance. **Primary resistance** occurs when a person is infected with *M. tuberculosis* that is already resistant to a particular drug. **Secondary resistance** occurs when drug-resistant organisms emerge as the dominant population during treatment. The major causes of secondary drug resistance are poor adherence to the medication by the patient or inadequate treatment regimens prescribed by the physician. Nonadherence to one drug is more likely to lead to secondary resistance than is failure to take all drugs. Secondary resistance is rare in children because of the small size of their mycobacterial population. Consequently, most drug resistance in children is primary, and patterns of drug resistance among children tend to mirror those found among adults in the same population. The main predictors of drug-resistant TB among adults are history of previous antituberculosis treatment, co-infection with HIV, and exposure to another adult with infectious drug-resistant TB.

Treatment of drug-resistant TB is successful only when at least two bactericidal drugs are given to which the infecting strain of M. tuberculosis is susceptible. When a child has possible drug-resistant TB, usually at least four or five drugs should be administered initially until the susceptibility pattern is determined and a more specific regimen can be designed. The specific treatment plan must be individualized for each patient according to the results of susceptibility testing on the isolates from the child or the adult source case. Treatment duration of 9 months with rifampin, pyrazinamide, and ethambutol is usually adequate for isoniazid-resistant TB in children. High-dose isoniazid is often added in those with low-level isoniazid-resistant TB. The recommendations for the treatment of MDR-TB have rapidly evolved in recent years. In 2019, the WHO advocated for the use of all-oral (injectable-free) regimens and reprioritized the order of the available oral drugs (Tables 261.8 and 261.9). Treatment regimens should prioritize administering group A and B drugs in addition to delamanid for children older than 3 years of age. Bedaquiline can be used in those older than 6 years of age. First-line treatment includes an all-oral regimen using three group A drugs and at least one group B drug. If only one or two group A medications are used, then group B drugs should be added to make a regimen of four drugs. Group C drugs are only used if the isolate is susceptible and when drugs from groups A and B cannot be used. The WHO recommends treatment of those with severe MDR-TB disease for 12-18 months; however, in children younger than 15 years with less severe MDR-TB disease, the treatment duration can be shortened to 9-12 months. The WHO defines severe MDR-TB disease as children with cavities or bilateral parenchymal disease on chest radiography or extrapulmonary forms of disease other than lymphadenopathy. Those with severe malnutrition; advanced immunosuppression; or positive smear, NAAT, or culture are also often treated with a longer course of therapy.

The second-line drugs require close monitoring for adverse effects and toxicity (see Table 261.9). The prognosis of single-drug–resistant or MDR-TB in children with nonsevere disease is good if the drug resistance is identified early in the treatment, if appropriate drugs are administered under DOT, if adverse reactions from the drugs are minor, and if the child and family are in a supportive environment. The treatment of drug-resistant TB in children always should be undertaken by a clinician with specific expertise in TB treatment.

Corticosteroids

Corticosteroids are useful in treating some children with TB disease. They are most beneficial when the host inflammatory reaction contributes significantly to tissue damage or impairment of organ function. There is convincing evidence that corticosteroids decrease mortality rates and long-term neurologic sequelae in some patients with **tuberculous meningitis** by reducing vasculitis, inflammation, and ultimately intracranial pressure. Lowering the intracranial pressure limits tissue damage and favors circulation of antituberculosis drugs through

Table 261.9 Drugs Used for Treating Drug-Resistant Tuberculosis in Infants, Children, and Adolescents*

DRUGS	DOSAGE, FORMS	DAILY DOSAGE (mg/kg)	MAXIMUM DOSE	ADVERSE REACTIONS
Amikacin†	Vials: 500 mg, 1 g	15-20 (IV or IM administration)	1 g	Auditory and vestibular toxic effects, nephrotoxic effects
Amoxicllin-clavulanate	(Strength expressed in terms of amoxicillin component) Syrup: 50 mg/mL 80 mg/mL 120 mg/mL (ES 600) Tablets: 500 mg 875 mg 1000 mg (XR tablet)	40 (amoxicillin component), twice daily	4 g (amoxicillin) 500 mg (clavulanate)	Abdominal pain, diarrhea, rash
Bedaquiline	Tablets: 20 mg, 100 mg	Adults and children ≥5 yr, 15 to <30 kg weeks 1-2: 200 mg/day; weeks 3-24: 100 mg 3x/week > 30 kg weeks 1-2: 400 mg/day; weeks 3-24: 200 mg 3x/week	600 mg/week	QTc prolongation, reduced levels with efavirenz co-administration
Clofazimine	Gelcaps: 50 mg 100 mg	2-5 per day	100 mg	QTc prolongation, reversible skin pigmentation
Cycloserine or terizidone	Capsules: 250 mg	10-20, given in 2 divided doses	1 g	Psychosis, personality changes, seizures, rash
Delamanid	Tablets: 50 mg 100 mg	6–11 years: 50 mg 2x/day 12–17 years: 100 mg 2x/day	100 mg/dose	QTc prolongation, adverse events with hypoalbuminemia, avoid if metronidazole allergic
Ethambutol	Tablets: 100 mg 400 mg	Children <40 kg: 15–25 Children ≥40 kg: 40-55 kg: 800 mg/ day PO 56-75 kg: 1200 mg/ day PO 76-90 kg: 1600 mg/ day PO	2.5 g	Optic neuritis (usually reversible), decreased red-green color discrimination, gastrointestinal tract disturbances, hypersensitivity
Ethionamide	Tablets: 125 mg 250 mg	15-20, given in 1–2 divided doses	1 g	GI tract disturbances, hepatotoxic effects, hypersensitivity reactions, hypothyroidism
Imipenem-cilastatin		60-100 per day, divided in 4 doses	4 g	Anemia, thrombocytopenia, eosinophilia, elevated liver enzymes
Levofloxacin	Tablets: 250 mg 500 mg 750 mg Oral solution: 25/mL Vials: 25 mg/mL	Adults: 750-1000 mg (daily) Children: 15-20 mg/kg daily	1 g	Theoretic effect on growing cartilage, joint pain, GI tract disturbances, rash, headache, restlessness, confusion
Linezolid	Tablets: 400 mg 600 mg Syrup: 20 mg/mL	Children <16 kg: 15 mg/kg once daily Children >16 kg: 10-12 mg/kg/day once daily	600 mg if ≥12 yr 300 mg if <12 yr	Bone marrow suppression, peripheral neuropathy, lactic acidosis, potential overlapping toxicity with nucleoside reverse transcriptase inhibitors
Moxifloxacin	Tablets: 400 mg IV solution: 400 mg/250 mL in 0.8% saline	Adults/adolescents: 400 mg Children: 10-15 mg/kg daily	400 mg; maximum doses of 600-800 mg per day are used for higher MIC or in malabsorption	Arthropathy, arthritis
p-Aminosalicylic acid (PAS)	Packets: 3 g	200-300 (2-4 times a day)	10 g	GI tract disturbances, hypersensitivity, hepatotoxic effects
Prothionamide	Tablets: 250 mg 500 mg	15-20 (divided twice daily)	1 g	GI tract disturbances, hepatotoxic effects, hypersensitivity reactions, hypothyroidism

Table 261.9 Drugs Used for Treating Drug-Resistant Tuberculosis in Infants, Children, and Adolescents*—cont'd

DRUGS	DOSAGE, FORMS	DAILY DOSAGE (mg/kg)	MAXIMUM DOSE	ADVERSE REACTIONS
Pyrazinamide	Scored tablets: 500 mg	30-40	2 g	Hepatotoxic effects, hyperuricemia, arthralgias, gastrointestinal tract upset
Streptomycin†	Vials: 1 g 4 g	20-40 (IM administration)	1 g	Auditory and vestibular toxic effects, nephrotoxic effects, rash

*These drugs should be used in consultation with a specialist in tuberculosis.
†Dose adjustment in renal insufficiency.
GI, Gastrointestinal; IM, intramuscular; IV, intravenous.
From Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2021–2024 Report of the Committee on Infectious Diseases*, 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021:805–806; and Furin J, Seddon J, Becerra M, et al. *Management of Multi-drug-Resistant Tuberculosis Children: A Field Guide*, 4th ed. Boston: The Sentinel Project for Pediatric Drug-Resistant Tuberculosis; 2019. Available at: http://sentinel-project.org/wp-content/uploads/2019/02/Updated_DRTB-Field-Guide-2019-V3.pdf

the brain and meninges. Short courses of corticosteroids also may be effective for children with **endobronchial tuberculosis** that causes respiratory distress, localized emphysema, or segmental pulmonary lesions. Several randomized clinical trials have shown that corticosteroids can help relieve symptoms and constriction associated with acute tuberculous **pericardial effusion**. Corticosteroids can cause dramatic improvement in symptoms in some patients with tuberculous pleural effusion and shift of the mediastinum. However, the long-term course of the disease is probably unaffected. Some children with severe **miliary tuberculosis** have dramatic improvement with corticosteroid therapy if the inflammatory reaction is so severe that alveolocapillary block is present. There is no convincing evidence to support a specific corticosteroid preparation. The most common regimen is **prednisone** 1-2 mg/kg/day in one to two divided doses orally for 4-6 weeks followed by a taper.

Supportive Care

Children receiving TB treatment should be followed carefully to promote **adherence** to therapy, to monitor for toxic reactions to medications, and to ensure that the TB is being adequately treated. Adequate **nutrition** is important. Patients should be seen at monthly intervals and should be given just enough medication to last until the next visit. **Anticipatory guidance** with regard to the administration of medications to children is crucial. The physician should foresee difficulties that the family might have in introducing several new medications in inconvenient dosage forms to a young child. The clinician must report all cases of suspected TB in a child to the local health department to be sure that the child and family receive appropriate care and evaluation.

Nonadherence to TB treatment is the major problem. The patient and family must know what is expected of them through verbal and written instructions in their primary language. Approximately 30–50% of patients taking long-term treatment are significantly nonadherent with self-administered medications, and clinicians are usually not able to determine in advance which patients will be nonadherent. Preferably, DOT should be instituted by the local health department.

Mycobacterium tuberculosis Infection

The following aspects of the natural history and treatment of TBI, often referred to as *latent TB infection,* in children must be considered in the formulation of recommendations about therapy:

1. Infants and children <5 years old with TBI who have been infected recently.
2. The risk for progression to disease is high.
3. Untreated infants with TBI have up to a 40% chance of development of TB disease.
4. The risk for progression decreases gradually through childhood until adolescence, when the risk increases.
5. Infants and young children are more likely to have life-threatening forms of TB, including meningitis and disseminated disease.
6. Children with TBI have more years at risk for development of disease than adults.

Because of these factors and the excellent safety profile of isoniazid, rifampin, and rifapentine in children, there is a tendency to err on the side of overtreatment in infants, young children, and adolescents.

The main TBI treatment regimens used in children are summarized in Table 261.7. The regimens include 6-9 months of **isoniazid** (daily or twice weekly by DOT), 3 months of daily **rifampin** and isoniazid, 4 months of daily rifampin, and once-weekly isoniazid and **rifapentine** (3HP) for 12 total doses. Because of improved treatment completion rates and noninferiority, the rifamycin-based, shorter treatment regimens are often favored over isoniazid monotherapy. The main indication for the use of isoniazid is if the child is at risk of drug-drug interactions with rifamycins.

Isoniazid therapy for TBI appears to be more effective for children than for adults, with several large clinical trials demonstrating a risk reduction of 70–90%. The risk of isoniazid-related hepatitis is minimal in infants, children, and adolescents, who tolerate the drug better than adults. Analysis of data from several studies demonstrates that the efficacy decreased significantly if isoniazid was taken for <9 months. However, the international standard is 6 months of treatment with isoniazid because of resource considerations. Isoniazid given twice weekly has been used extensively to treat TBI in children, especially schoolchildren and close contacts of case patients. DOT or VDOT should be considered when it is unlikely that the child and family will adhere to daily self-administration or if the child is at increased risk for rapid development of disease (newborns and infants, recent contacts, immunocompromised children). For healthy children taking isoniazid but no other potentially hepatotoxic drugs, routine biochemical monitoring and supplementation with pyridoxine are not necessary. Rifampin alone for 4 months is now frequently used for the treatment of TBI in infants, children, and adolescents. This regimen is most often used when a shorter, self-administered treatment regimen is preferred, when isoniazid cannot be tolerated, or the child has had contact with a source case infected with an isoniazid-resistant but rifamycin-susceptible organism. If a child is identified with TBI during a contact investigation or if the cost of rifampin is prohibitive for families, administration of the medication through VDOT programs offered by health departments should be considered. Rifapentine is a rifamycin with a very long half-life, allowing for weekly administration in conjunction with high-dose isoniazid. Studies have demonstrated that 12 doses of once-weekly isoniazid and rifapentine (3HP) are as effective for treating TBI and as safe as 9 months of daily isoniazid in children as young as 2 years. This is becoming the preferred regimen for the treatment of TBI in age-eligible children who are exposed to a contact with presumed pan-susceptible TB. Given the risk of selecting for drug-resistant isolates by missing intermittent doses of rifamycins, this treatment regimen currently is recommended only with DOT under the supervision of local health departments. The main reason children or adolescents are unable to complete this regimen is the inability to crush the tablets and the high pill burden. In these situations, the children are often transitioned to an alternative treatment regimen. A 3-month daily regimen of rifampin and isoniazid has been used throughout

Europe. Although this regimen has not been used regularly in the United States, experts believe it is favorable in children less than 5 years of age in whom the pill burden of 3HP is difficult. Studies have revealed that the shorter treatment regimens for TBI in children are equally efficacious as 9 months of isoniazid and are associated with superior treatment completion rates.

For children with MDR-TB, the regimen will depend on the drug-susceptibility profile of the contract case's organism; an expert in TB should be consulted. There are data that support the use of levofloxacin or moxifloxacin for treatment of MDR-TBI.

Few controlled studies have been published regarding the efficacy of any form of treatment for TBI in children living with HIV. A 9-month course of daily isoniazid is recommended. Most experts recommend that routine monitoring of serum hepatic enzyme concentrations be performed and pyridoxine be given when children living with HIV are treated with isoniazid. The optimal duration of rifampin therapy in children living with HIV with TBI is not known, but many experts recommend at least a 6-month course.

Isoniazid or rifampin should be given to children <5 years old who have a negative TST or IGRA result but who have a known recent exposure to an adult with potentially contagious TB disease. This practice is often referred to as **window prophylaxis**. By the time delayed hypersensitivity develops (2-3 months), an untreated child already may have developed severe TB. For these children, TST or IGRA is repeated 8-10 weeks after contact with the source case for TB has been broken (*broken contact* is defined as physical separation or adequate initial treatment of the source case). If the second test result is positive, the child should complete a treatment course for TBI (either 9 months of isoniazid or 4 months of rifampin). There is a benefit to using rifampin over isoniazid for window prophylaxis (unless contraindicated because of drug-drug interactions or prohibitive because of cost). By the time of the second test result (8-10 weeks later), if positive, the child receiving rifampin has approximately 2 months of therapy to complete compared to 7 months of isoniazid. Alternatively, if a new, shorter TBI treatment course is started after the second test result becomes positive (either 4 months of rifampin [if isoniazid was given as window prophylaxis], 12 weekly doses of isoniazid and rifapentine, or 3 months of isoniazid and rifampin), the treatment start date is day 1 of the new regimen. If the second test result is negative, TBI treatment can be stopped.

PREVENTION

The highest priority of any TB control program should be case finding and treatment, which interrupt transmission of infection between close contacts. All children and adults with symptoms suggestive of TB disease and those in close contact with an adult with suspected infectious pulmonary TB should be tested for TBI (by TST or IGRA) and examined as soon as possible. On average, 30–50% of household contacts to infectious cases are also infected, and 1% of contacts already have overt disease. This scheme relies on effective and adequate public health response and resources. Children, particularly young infants, should receive high priority during contact investigations because their risk for infection is high and they are more likely to rapidly develop severe forms of TB.

Mass testing of large groups of children for TBI is an inefficient process. When large groups of children at low risk for TB are tested, the vast majority of TST reactions are actually false-positive reactions because of biologic variability or cross-sensitization with NTM. However, testing of high-risk groups of adults or children should be encouraged because most of these persons with positive TST or IGRA results have TBI. Testing should take place only if effective mechanisms are in place to ensure adequate evaluation, follow-up, and treatment of the persons who test positive.

Bacille Calmette-Guérin Vaccination

The only available vaccine against TB is the BCG vaccine. The original vaccine organism was a strain of *M. bovis* attenuated by subculture every 3 weeks for 13 years. This strain was distributed to dozens of laboratories that continued to subculture the organism on different media under various conditions. The result has been production of many BCG vaccines that differ widely in morphology, growth characteristics, sensitizing potency, and animal virulence.

The administration route and dosing schedule for the BCG vaccines are important variables for efficacy. The preferred route of administration is intradermal injection with a syringe and needle because it is the only method that permits accurate measurement of an individual dose.

The BCG vaccines are extremely safe in immunocompetent hosts. Local ulceration and regional suppurative adenitis occur in 0.1–1% of vaccine recipients. Local lesions do not suggest underlying host immune defects and do not affect the level of protection afforded by the vaccine. Most reactions are mild and usually resolve spontaneously, but chemotherapy is needed occasionally. Surgical excision of a suppurative draining node is rarely necessary and should be avoided if possible. **Osteitis** is a rare complication of BCG vaccination that appears to be related to certain strains of the vaccine that are no longer in wide use. Systemic complaints such as fever, convulsions, loss of appetite, and irritability are extraordinarily rare after BCG vaccination. Profoundly immunocompromised patients can develop disseminated BCG infection after vaccination. Children living with HIV appear to have rates of local adverse reactions to BCG vaccines that are comparable with rates in immunocompetent children. However, the incidence in these children of disseminated infection months to years after vaccination is currently unknown.

Recommended vaccine schedules vary widely among countries. The official WHO recommendation is a single dose administered during infancy in populations where the risk for TB is high. However, *infants with known or suspected HIV infection should not receive a BCG vaccination.* In some countries, repeat vaccination is universal, although no clinical trials support this practice. In others, it is based on either TST or the absence of a typical scar. The optimal age for BCG administration and dosing schedule are unknown because adequate comparative trials have not been performed.

Although dozens of BCG trials have been reported in various human populations, the most useful data have come from several controlled trials. The results of these studies have been disparate. Some demonstrated substantial protection from BCG vaccines, but others showed no efficacy at all. A meta-analysis of published BCG vaccination trials suggested that BCG is 50% effective in preventing pulmonary TB in adults and children. The protective effect for disseminated and meningeal TB appears to be slightly higher, with BCG preventing 50–80% of cases. A variety of explanations for the varied responses to BCG vaccines have been proposed, including methodologic and statistical variations within the trials, interaction with NTM that either enhances or decreases the protection afforded by BCG, different potencies among the various BCG vaccines, and genetic factors for BCG response within the study populations. BCG vaccination administered during infancy has little effect on the ultimate incidence of TB in adults, suggesting waning protection with time.

BCG vaccination has worked well in some situations but poorly in others. Clearly, BCG vaccination has had little effect on the ultimate control of TB throughout the world, because >5 billion doses have been administered, but TB remains epidemic in most regions. BCG vaccination does not substantially influence the chain of transmission, because cases of contagious pulmonary TB in adults that can be prevented by BCG vaccination constitute a small fraction of the sources of infection in a population. The best use of BCG vaccination is to prevent life-threatening forms of TB in infants and young children.

BCG vaccination has never been adopted as part of the strategy for TB control in the United States. Widespread use of the vaccine would render subsequent TSTs less useful. However, BCG vaccination can contribute to TB control in select population groups. BCG is recommended for TST-negative, HIV-negative infants and children who are at high risk for intimate and prolonged exposure to persistently untreated or ineffectively treated adults with infectious

pulmonary TB and who cannot be removed from the source of infection or placed on long-term preventive therapy. It also is recommended for those who are continuously exposed to persons with TB who have bacilli that are resistant to isoniazid and rifampin. Any child receiving BCG vaccination should have a documented negative TST before receiving the vaccine. After receiving the vaccine, the child should be separated from the possible sources of infection until it can be demonstrated that the child has had a vaccine response, as evidenced by tuberculin reactivity, which usually develops within 1-3 months.

Prevention of Perinatal Tuberculosis

The most effective way of preventing TB infection and disease in the neonate or young infant is through appropriate testing and treatment of the mother and other family members. High-risk pregnant women should be tested with TST or IGRA, and those with a positive test result should receive a chest radiograph with appropriate abdominal shielding. If the mother has a negative chest radiograph and is clinically well, no separation of the infant and mother is needed after delivery. The child needs no special evaluation or treatment if the child remains asymptomatic. Other household members should undergo testing for TBI and further evaluation as indicated.

If the mother has suspected TB at the time of delivery, the newborn should be separated from the mother until the chest radiograph is obtained. If the mother's chest radiograph is abnormal, separation should be maintained until the mother has been evaluated thoroughly, including examination of the sputum. If the mother's chest radiograph is abnormal but the history, physical examination, sputum examination, and evaluation of the radiograph show no evidence of current active TB, it is reasonable to assume that the infant is at low risk for infection. The mother should receive appropriate TB treatment, and she and her infant should receive careful follow-up care.

If the mother's chest radiograph or AFB sputum smear shows evidence of current TB disease, additional steps are necessary to protect the infant. Isoniazid therapy for newborns has been so effective that separation of the mother and infant is no longer considered mandatory. Separation should occur only if the mother is ill enough to require hospitalization, has been or is expected to become nonadherent to treatment, or has suspected drug-resistant TB. Isoniazid treatment for the infant should be continued until the mother is sputum culture negative for ≥3 months. At that time, a TST should be placed on the child. If the test is positive, isoniazid is continued for a total duration of 9-12 months; if the TST is negative, isoniazid can be discontinued. Once the mother and child are taking adequate therapy, it is usually safe for the mother to breastfeed, because the medications, although found in milk, are present in low concentrations. If isoniazid resistance is suspected or the mother's adherence to medication is in question, continued separation of the infant from the mother should be considered. The duration of separation must be at least as long as is necessary to render the mother noninfectious. A TB expert should be consulted if the young infant has potential exposure to the mother or another adult with TB disease caused by an isoniazid-resistant strain of *M. tuberculosis*.

Although isoniazid is not thought to be teratogenic, the treatment of pregnant women who have asymptomatic TBI is often deferred until after delivery. However, symptomatic pregnant women or those with radiographic evidence of TB disease should be appropriately evaluated. Because pulmonary TB is harmful to both the mother and the fetus and represents a great danger to the infant after delivery, TB in pregnant women always should be treated. The most common regimen for drug-susceptible TB is isoniazid, rifampin, and ethambutol. The aminoglycosides and ethionamide should be avoided because of their teratogenic effect. The safety of pyrazinamide in pregnancy has not been established.

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Chapter 262

Hansen Disease (*Mycobacterium leprae*)

Cristina Tomatis Souverbielle and Asuncion Mejias

Leprosy (Hansen disease [**HD**]) is a heterogeneous, curable infection caused by *Mycobacterium leprae* that primarily affects the upper airway, skin, and peripheral nerves. Disease manifestations are mainly determined by the host's immunologic response to infection, resulting in a wide clinical spectrum. The majority of exposed individuals never develop clinical disease. HD is currently the accepted designation of leprosy, and contrary to popular folklore, HD is *not* highly transmissible and *is* treatable. In addition, the associated morbidity and disability can be prevented with early diagnosis and appropriate treatment.

MICROBIOLOGY

M. leprae is an obligate, intracellular, acid-fast, gram-positive bacillus of the family Mycobacteriaceae measuring 1-8 μm in length. It grows optimally at 27–33°C (80.6–91.4°F) yet cannot be cultured in vitro. The bacillus multiplies slowly, with a doubling time of 11-13 days. It is the only bacterium known to infect **Schwann cells** of peripheral nerves. Identification of acid-fast bacilli (AFB) in peripheral nerves is pathognomonic of leprosy.

EPIDEMIOLOGY

The prevalence of leprosy is variable, with most cases being identified in tropical and subtropical areas. The World Health Organization (WHO) goal to eliminate leprosy as a public health problem, defined as a reduction in its prevalence to less than 1 case per 10,000 population, was achieved at the global level in 2000. Despite an overall decline in reported prevalence, HD continues to afflict more than 2 million people worldwide. In 2022, 174,059 new cases were reported globally, with most cases occurring in Southeast Asia (mostly India), Africa, and South America (mostly Brazil). Of those, 5.92% occurred in children <15 years. In 2018, the WHO reviewed the available evidence on key issues related to the elimination of leprosy and developed a guidance WHO Guidelines for the Diagnosis, Treatment and Prevention of Leprosy. More recently, the WHO released Towards Zero Leprosy – Global Leprosy (Hansen's Disease) Strategy 2021-2030, which was aligned with the 2021-2030 road map for neglected tropical diseases during the same period.

Since 1984, HD has been a *notifiable disease* in the United States, with about 14,000 cases recorded since then. Since the 1990s, an average of 175 new cases are reported annually. Of the 159 new U.S. cases reported in 2020, 69% were identified in Texas, Louisiana, Hawaii, California, Florida, and New York. Most new cases (~75%) in the United States were identified among immigrants from HD-endemic countries or in citizens who have worked abroad in endemic areas. However, over one third of U.S. cases are **autochthonous** and do not report contact with foreign countries or people with leprosy.

The likelihood of developing HD is determined by several variables: age (with two incidence peaks: 10-14 years and 30 years), gender (male/female ratio 2:1, with no differences observed in children), genetics, immune status, type of leprosy (with higher risk in those exposed to patients with multibacillary disease), and possibly through exposure to **armadillos**. Whole genome sequencing has allowed identification of genes and polymorphisms associated with increased susceptibility to leprosy and found that approximately 5% of people are genetically susceptible to *M. leprae* infection. HD in immunocompromised

hosts has been reported in solid organ and bone marrow transplant recipients and patients receiving tumor necrosis factor (TNF)–blocking monoclonal antibodies. Patients with HIV infection do not appear to be at increased risk of acquiring leprosy, increased disease severity, or poor response to treatment. However, clinicians should be aware that concomitant HIV infection and leprosy can result in worsening of symptoms of leprosy during HIV treatment as a result of an immune reconstitution inflammatory syndrome.

The exact mechanism of transmission is not fully understood but is thought to occur primarily by the respiratory route. Natural infection occurs in humans and armadillos, which are the only recognized nonhuman reservoir. The risk of transmission from armadillos to humans seems low, and again, the mechanism is not fully understood. The incubation period between natural infection and overt clinical disease in humans ranges from 3 months to 20 years, with a mean of 4 years for **tuberculoid** leprosy and 10 years for **lepromatous** leprosy. Up to 10^7 viable bacilli per day can be shed in respiratory secretions of patients with **multibacillary** leprosy. The relative risk for developing disease in household contacts is 8- to 10-fold for lepromatous disease and 2- to 4-fold for the tuberculoid form. Transmissions by breast milk, the transplacental route, and through broken skin have been reported. Environmental factors and subclinically infected humans may also play a role in disease transmission. The infectivity of patients with HD becomes negligible within 24 hours of the first administration of effective therapy.

PATHOGENESIS

In the skin, *M. leprae* shows affinity for keratinocytes, macrophages, and histiocytes, and in peripheral nerves, the organism can be found in the Schwann cells. The mechanism of mycobacterial dissemination from the respiratory tract to the skin and nerves is thought to occur hematogenously but has not been completely elucidated. *M. leprae* induces demyelination and binds to the laminin-2 glycoprotein present in the basal lamina of Schwann cells in peripheral nerves, where it replicates slowly over several years. Infection stimulates the dedifferentiation of Schwann cells to immature cells through the activation of the Erk1/2 pathway. This reprogramming of Schwann cells seems to be linked to disease dissemination. In addition to the direct nerve invasion, the immune response to infection also contributes to nerve damage. Schwann cells express human leukocyte antigen (HLA) class II molecules and present mycobacterial peptides to the HLA class II restricted $CD4^+$ T cells, which initiate an inflammatory response. These events explain the nerve damage seen in paucibacillary disease and in reversal reactions. Swelling within the perineurium leads to ischemia, further nerve damage, and eventually fibrosis and axonal death.

DISEASE CLASSIFICATION

Disease classification is important to determine potentially infectious cases and prognosis. Based on the cellular immune response and disease dissemination, two classification schemes for leprosy are frequently used: the Ridley-Jopling scale and the WHO classification:

A. The **Ridley-Jopling scale** is used in the United States and describes the five types of leprosy, according to clinical spectrum of disease, bacillary load, and findings on histopathology.
   1. *Tuberculoid form*: Patients usually have a vigorous and specific cellular immune response to *M. leprae* antigens and have a small number of skin lesions, generally one to three well-demarcated macules or plaques with elevated borders (Fig. 262.1) and reduced or absent sensation. The lesions are infiltrated by T-helper 1 (Th1) cells producing abundant interferon (IFN)-γ and TNF-α, forming well-demarcated granulomas, with few, if any, bacilli found within the lesions.
   2. *Borderline tuberculoid form*
   3. *Borderline form*
   4. *Borderline lepromatous*
   5. *Lepromatous form*: Patients have an absence of specific cellular immunity to *M. leprae* (but intact immunity to *Mycobacterium tuberculosis*) and present the most severe form of disease. They manifest clinically apparent infiltration of peripheral nerves and skin lesions (usually many lesions and not all hypoesthetic or anesthetic), with a high load of bacilli in the absence of an effective cell-mediated immune response. Skin biopsies reveal extensive infiltration of the skin and nerves, containing messenger RNA for Th2 cytokines such as interleukin (IL)-4 and IL-10, poorly formed granulomas, and uncontrolled proliferation of bacilli within foamy macrophages. A large amount of circulating antibody to *M. leprae* is present but does not confer protective immunity. Over time, patients with the lepromatous form develop a systemic disease with symmetric peripheral nerve involvement and a diffuse infiltrative dermopathy that includes thickening of the facial skin and hair loss of the eyelashes and eyebrows (madarosis), leading to the classic presentation of the *leonine facies*. They also have involvement of the nasal mucosa causing nasal congestion and epistaxis.
   6. The majority of patients will present with a borderline form. From borderline tuberculoid to borderline lepromatous forms, there is a progressive reduction in cellular immune responses, an increase in bacillary load, more frequent hypopigmented skin lesions and nerve involvement, and higher antibody titers (Fig. 262.2). Patients with the extreme forms of the disease (tuberculoid and lepromatous) are considered to have stable cell-mediated immunity, because their disease manifestations do not change much over time. In contrast, patients with borderline disease have unstable cell-mediated immunity and demonstrate changes in their clinical manifestations over time toward the polar forms (downgrade) or present sudden reversal reactions (upgrade). *Indeterminate leprosy* is the earliest form of the disease and is seen most frequently in young children. Patients usually have a single hypopigmented macule with poorly defined borders, without erythema or induration. Anesthesia is minimal or absent, especially if the lesion is on the face. The diagnosis is

Fig. 262.1 Tuberculous leprosy in a patient who has a single skin lesion with a raised border and flattened center.

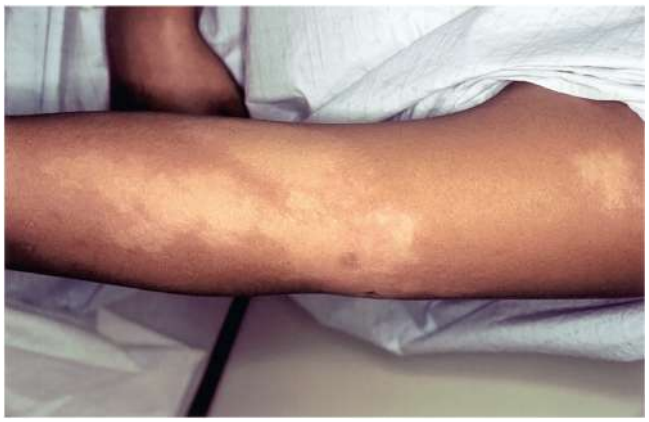

Fig. 262.2 Borderline leprosy in a patient who has numerous hypopigmented lesions with poorly defined borders.

usually one of exclusion in the setting of a contact investigation. Tissue biopsies show diagnostic evidence of leprosy but do not meet sufficient criteria for classification. Up to 50–75% of these lesions will heal spontaneously, and the rest will progress to another form of leprosy.

B. The **WHO classification** can be used when histologic evaluation and confirmatory diagnosis is unavailable, a common scenario in the field. This simplified scheme is based on the number of skin lesions:
   1. Paucibacillary (1-5 patches)
   2. Multibacillary (>5 patches)

CLINICAL MANIFESTATIONS

The host immune response determines the clinical spectrum of leprosy. Skin and serologic studies suggest that up to 90% of infected people develop immunity after exposure, without manifesting clinical disease. In genetically susceptible individuals with sufficient exposure to become infected, the cellular host's immunologic response to infection and unique tropism for peripheral nerves determine the wide spectrum of clinical (and histologic) manifestations. Regardless of the disease subtype, HD affects the skin and peripheral nerves. Leprosy lesions usually do not itch or hurt. Polymorphisms in vitamin D and its receptor have been proposed to play a role in the manifestations of leprosy.

Skin Involvement

The most common skin lesions are **macules** or **plaques** with unclear outer limits, with or without neurologic symptoms. Diffuse infiltrative lesions and subcutaneous nodules are less common. Initial lesions are insidious hypopigmented macules, although they may appear erythematous on pale skin. Lesions may involve any area of the body, are more pronounced in cooler areas (e.g., earlobes, nose), and occur less frequently in the scalp, axillae, or perineum. Approximately 70% of skin lesions have reduced sensation; the degree of hypoesthesia depends on the location and size of the lesion and the degree of Th1 immune response. Examination of the skin should ideally be performed in natural sunlight and include testing for hypoesthesia to light touch, pinprick, temperature, and anhidrosis. Studies in endemic areas in children <15 years old have shown a predominance of **paucibacillary** forms, with a predominance of single lesions.

Nerve Involvement

Peripheral nerves are most frequently affected early in the disease and should be palpated for thickness and tenderness (Fig. 262.3), as well as evaluated for both motor and sensory function, particularly temperature and light touch. The posterior tibial nerve (medial malleolus) is the most common nerve affected, followed by the ulnar (elbow), median (wrist), lateral popliteal (fibular neck), and facial nerves. The skin lesions overlying a nerve trunk distribution predict the involvement of nerves in the vicinity. There is a pure **neuritic** form of leprosy, usually occurring in India and Nepal, in which patients present with asymmetric neuropathy but lack skin lesions.

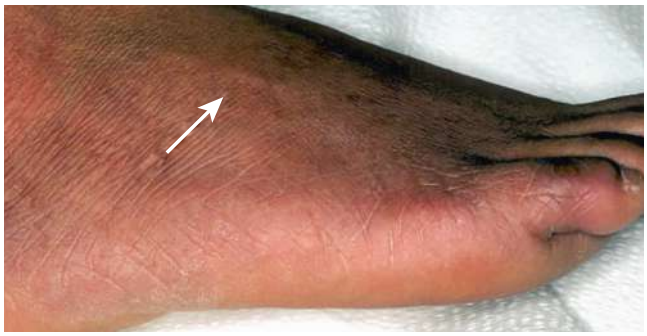

Fig. 262.3 Thickened, superficial peroneal nerve of leprosy.

Other Organ Involvement

Ocular involvement leading to vision loss results from both direct bacillary invasion of the eye and optic nerve damage. **Lagophthalmos** occurs when there is destruction of the facial nerve (cranial nerve VII), and trigeminal nerve (cranial nerve V) destruction causes anesthesia of the cornea and conjunctiva, leading to abrasions. Facial skin lesions are associated with a 10-fold higher risk of facial nerve damage. Systemic involvement of other organs is seen mainly in patients with lepromatous leprosy, where a high bacillary burden leads to infiltration of the nasal mucosa, bones, and testes. Renal involvement and amyloidosis are rare findings.

Immunologic Reactions

Leprosy reactions are acute clinical exacerbations reflecting disturbances of the immunologic balance to *M. leprae* infection and occurring in 30–50% of all leprosy patients. These sudden changes occur in patients with borderline and lepromatous leprosy, typically during the initial years after infection (sometimes as the initial presentation), but can occur before, during, or after completion of treatment. There are two main types of leprosy reactions, which require immediate treatment to prevent long-term complications. In children <15 years old, leprosy reactions range from 1% to 30% and are mainly type 1 reactions.

Type 1 reactions (also known as **reversal reactions**) occur in one third of patients with borderline disease. These reactions are characterized by acute edema and increased erythema, warmth, and painful inflammation of preexisting cutaneous plaques or nodules, with acute swelling and tenderness of peripheral nerves that can quickly progress to cause nerve abscesses and necrosis. There may be a peripheral lymphocytosis and an increased cytokine response, but systemic symptoms are uncommon and appear to be associated with an increase in Th1-mediated reactivity to mycobacterial antigens. Increased serum concentrations of CXCL10 have been found in type 1 reactions. Rapid and sustained reversal of the inflammatory process using corticosteroids is essential to prevent continued nerve damage.

Type 2 reactions, or **erythema nodosum leprosum (ENL)**, occur in borderline lepromatous and lepromatous forms, as these patients have the highest levels of *M. leprae* antigens and antibodies, most often in the first 2 years after starting therapy. ENL is distinguished from reversal reactions by the development of new painful, erythematous subcutaneous nodules with an accompanying systemic inflammatory response. ENL is accompanied by high circulating concentrations of TNF-α. Patients develop high fever and signs

of systemic toxicity, and in severe cases, ENL can be life threatening, presenting with features similar to septic shock. Deposition of extravascular immune complexes leads to neutrophil infiltration and activation of complement in the skin and other organs. Tender, erythematous dermal papules or nodules (resembling erythema nodosum) occur in clusters, typically on extensor surfaces of the lower extremities and face. Immune complex deposition also contributes to migrating polyarthralgias, painful swelling of lymph nodes and spleen, iridocyclitis, vasculitis, orchitis, and, rarely, nephritis. Patients may present with a single acute episode, a relapsing form comprising multiple acute episodes, or a chronic continuous form. Management of type 2 reactions is usually more complicated because of recurrence and systemic involvement.

Lucio phenomenon (erythema necroticans) is an uncommon but potentially fatal reaction distinct from type 1 or 2 reactions and occurs in patients with untreated lepromatous leprosy and in patients whose ancestry is from Mexico. It is a necrotizing vasculitis caused by *M. leprae* directly invading the endothelium. Clinically, patients develop violaceous or hemorrhagic plaques, followed by ulcerations in the absence of systemic complaints. Secondary bacterial infections are common.

DIAGNOSIS

The diagnosis of HD requires high clinical suspicion and should be considered in any patient with a **hypoesthetic or anesthetic skin lesion that does not respond to standard treatment**, especially if there is a history of travel or residence in an endemic region or a history of contact with leprosy patients or armadillos. There are no reliable tests to diagnose subclinical leprosy. Full-thickness skin biopsy and polymerase chain reaction (PCR) are the main laboratory tests to aid in the diagnosis. Patients are considered to have HD if they have **one or more of the three cardinal signs**: loss of sensation in a localized skin lesion (pale or erythematous), thickened peripheral nerve with loss of sensation and/or weakness of muscles enervated by that nerve, or the presence of AFB on biopsy. The positive predictive value for the diagnosis of leprosy in patients meeting all three criteria is 98%.

To confirm the diagnosis and determine the extent of nerve involvement and the type of infiltrate, a full-thickness skin biopsy from the most active lesion should be performed. *M. leprae* is best identified in tissue using the *Fite stain*. Lesions from patients with the lepromatous form reveal numerous AFB in clumps (globi), whereas patients with the tuberculoid form rarely have mycobacteria identified, but the diagnosis can be made by demonstration of well-formed noncaseating granulomas and nerve involvement. The presence of **neural inflammation** differentiates leprosy from other granulomatous disorders. Mycobacterial culture of lesions should be performed to exclude *M. tuberculosis* and nontuberculous cutaneous infections. If no resources are available, slit-skin (skin smear) biopsies represent an alternative. Slit-skin smears have high specificity but low sensitivity; only 30% of adults and 10–30% of children <15 years old are smear positive (usually patients with the lepromatous form). The bacterial index can range from 0 (no bacilli in 100 oil-immersion fields), as generally seen in paucibacillary disease, to 6+ (>1,000 bacilli/field), as can be seen in multibacillary disease.

Diagnostic and histopathologic consultation in the United States is available through the **National Hansen's Disease Program** (**NHDP**; http://www.hrsa.gov/hansens or 800-642-2477). Specimens (formalin or paraffin embedded) can be sent to the NHDP for pathologic analysis free of charge. A PCR test for *M. leprae* is not readily available in clinical practice but may be performed at the NHDP. In nonendemic areas, PCR may be useful for diagnosis when AFB are discernible in tissue but clinical and histopathologic features are not typical. *M. leprae* DNA is detectable by PCR in 95% of lepromatous disease and 55% of tuberculoid lepra. PCR has also allowed detection of the organism in nasal secretions from asymptomatic people. Molecular testing for mutations causing drug resistance is also available through the NHDP and is usually used in the setting of relapse.

Antibodies to *M. leprae* are present in 90% of patients with untreated lepromatous disease, 40–50% of patients with paucibacillary disease, and 1–5% of healthy controls. However, serologic testing is insensitive and is not used for diagnosis.

TREATMENT

The primary goal of treatment is early antimicrobial therapy to prevent permanent neuropathy. Leprosy is curable. Effective treatment requires multidrug therapy (MDT) with **dapsone**, **clofazimine**, and **rifampin**. Combination therapy is employed to prevent antimicrobial resistance. In the United States, clinical providers considering a diagnosis and treatment of a patient with HD should obtain **consultation from the NHDP**. The recommended combination MDT can be obtained free of charge from the NHDP (Table 262.1) and in other countries through the WHO (Table 262.2). Compared with the WHO, the NHDP advocates for a longer duration of treatment and daily rather than monthly administration of rifampin because shorter antimicrobial regimens have been associated with a greater risk of relapse. The recommended duration by the WHO for tuberculoid disease is 6 months and for lepromatous disease is 12 months. Since 2018, the WHO has advocated for a three-drug regimen for all leprosy forms; however, NHDP guidelines recommend two drugs (dapsone and rifampin) for the treatment of paucibacillary disease.

Before starting combination MDT, patients should be tested for glucose-6-phosphate dehydrogenase deficiency, have a baseline

Table 262.1 NHDP-Recommended Multidrug Therapy Regimens for Hansen Disease in the United States

TYPE OF LEPROSY	PATIENT POPULATION	ANTIMICROBIAL THERAPY	DURATION OF THERAPY
Multibacillary (LL, BL, BB)	Adult	Dapsone 100 mg/day *and* rifampin* 600 mg/day *and* clofazimine 50 mg/day	24 mo
	Pediatric†	Dapsone 1 mg/kg/day *and* rifampin 10-20 mg/kg/day *and* clofazimine 1 mg/kg/day‡	
Paucibacillary (TT, BT)	Adult	Dapsone 100 mg/day *and* rifampin 600 mg/day	12 mo
	Pediatric†	Dapsone 1 mg/kg/day *and* rifampin 10-20 mg/kg/day	

*Rifampin is taken monthly if the patient is on prednisone.
†Daily pediatric mg/kg dose should not exceed the adult daily maximum.
‡Clofazimine is only available through NHDP Investigational New Drug (IND) program; minimum formulation is 50 mg, and capsules should not be cut. Alternative dosing includes clofazimine 2 mg/kg every other day
NHDP, National Hansen's Disease Program; BB, borderline; BL, borderline lepromatous; BT, borderline tuberculoid; LL, lepromatous; TT, tuberculoid.
NHDP multidrug therapy is daily and of longer duration than WHO-recommended regimen. All drugs are administered orally. For immunologically compromised or elderly patients, these protocols may be modified. Consultation with the NHDP is advised.

Table 262.2 WHO-Recommended Multidrug Therapy (MDT) Regimens for Hansen Disease

TYPE OF LEPROSY	PATIENT POPULATION	ANTIMICROBIAL THERAPY	DURATION OF THERAPY
Multibacillary (LL, BL, BB)	Adult	Rifampicin 600 mg once monthly *and* dapsone 100 mg/day *and* clofazimine 300 mg once monthly and 50 mg/day	12 mo
	Pediatric*	Rifampicin 450 mg once monthly *and* dapsone 50 mg/day *and* clofazimine 150 mg once monthly and 50 mg every other day	
Paucibacillary (TT, BT)	Adult	Rifampicin 600 mg once monthly *and* dapsone 100 mg/day *and* clofazimine 300 mg once monthly and 50 mg/day	6 mo
	Pediatric*	Rifampicin 450 mg once monthly *and* dapsone 50 mg/day *and* clofazimine 150 mg once monthly and 50 mg every other day	

*In children <10 yr old, or <than 40Kg, MDT dosages should be in mg/kg, not to exceed the adult daily maximum: rifampicin 10 mg/kg once monthly, dapsone 2 mg/kg/day, and clofazimine100 mg once a month, 50 mg twice weekly.
WHO, World Health Organization; BB, borderline; BL, borderline lepromatous; BT, borderline tuberculoid; LL, lepromatous; TT, tuberculoid.

complete blood cell count and liver function testing, and be evaluated for evidence of active tuberculosis, in which monotherapy with rifampin should be avoided. Response to therapy is seen clinically as flattening or disappearance of skin lesions and improvement in nerve function, usually within 1-2 months after initiating MDT. Complete resolution or improvement may take 6-12 months, depending on the severity of infection. Most skin lesions heal without scarring. Identification of biomarkers for the optimal identification and management of leprosy continue to be under study. CXCL10 (IP-10) has been identified as a potential marker to help monitor treatment efficacy in patients with multibacillary disease, as higher levels of CXCL-10 are important for the control of bacillary load.

Alternative agents to treat HD include minocycline, clarithromycin, and some fluoroquinolones (levofloxacin, ofloxacin, moxifloxacin). Given limited data, these alternative antimicrobials are used in selected cases of intolerance to the routine combination MDT regimen or for documented resistance. It is important to note that some patients who have been adequately treated for HD may later show evidence of chronic reversal reactions and late neuropathies, but these are bacillus negative and thus should not be considered relapses. Neuritis must be treated promptly to minimize nerve injury and disability. Treatment with corticosteroids appears to improve nerve function in two thirds of patients.

Bone marrow suppression and hepatotoxicity have been reported and should be monitored every 3 months during therapy. A screening urinalysis should be performed annually. Other reactions, such as methemoglobinemia and hypersensitivity reactions to dapsone, are rare. An ophthalmologic evaluation should routinely be performed in all patients with HD because ocular complications can occur. Given the proclivity for testicular invasion in multibacillary leprosy with resultant testicular dysfunction and infertility, males should be screened for elevated follicle-stimulating hormone or luteinizing hormone concentrations and decreased testosterone levels.

After completion of MDT, annual follow-up for ≥5 years for paucibacillary and ≥10 years for multibacillary disease is warranted. Relapse of the disease after completion of MDT is rare (0.01–1.4%) and must be distinguished from the more common leprosy immunologic reactions. Patients who have a bacillary index of ≥4 pre-MDT or ≥3 at the completion of MDT have the highest risk of relapse (approximately 20%). When relapse occurs, it is usually within 5-10 years of MDT completion and a result of reactivation of drug-susceptible mycobacteria. Thus patients who are expected to relapse are generally treated with the same MDT regimen. Resistance to all three drugs has been documented, although it rarely occurs with combination therapy. There is no role for routine baseline resistance testing, but the NHDP can provide it if needed.

Leprosy Reactions

Immunologic reactions can occur before, during, and years after treatment and should be treated aggressively to prevent peripheral nerve damage. In general, antimycobacterial drugs should be continued. Fatigue, malaise, or fever can be present, and the inflammation associated with these reactions can cause severe nerve injury. Prompt therapy with corticosteroids with or without other antiinflammatory agents, adequate analgesia, and physical support are essential for patients with active neuritis to prevent nerve damage. **If corticosteroids are indicated for a prolonged time, the frequency of rifampicin administration should be decreased from daily to monthly** administration (to avoid drug interactions). In 2020, to aid with the management of leprosy reactions, the WHO published the technical guide: *Leprosy/Hansen Disease: Management of Reactions and Prevention of Disabilities*.

For severe **type 1 reactions**, **prednisone is recommended**, 1 mg/kg/day orally (40-60 mg) with a slow taper (decreasing by 5 mg every 2-4 weeks after evidence of improvement over 3-6 months) in addition to standard MDT. If there is evidence of peripheral nerve deterioration, higher doses and longer tapers may be needed. Nerve function improves after corticosteroid treatment in 30–80% of patients who did not have preexisting neuritis. In patients not responding to corticosteroids, cyclosporine may be used as a second-line agent.

For severe **type 2 reactions**, **prednisone is routinely used** at 1 mg/kg/day for 12 weeks. However, given the recurrence and chronicity of ENL, **corticosteroid-sparing agents should be considered** to avoid complications associated with their prolonged use. **Thalidomide** (100-400 mg/daily for 48-72 hours, tapering over 2 weeks to 100 mg/daily) is effective in treating these types of reactions. Given the teratogenicity of thalidomide (contraindicated for children <12 years old and women of childbearing age), the drug is only available through a restrictive distribution program approved by the U.S. Food and Drug Administration (FDA). **Clofazimine** (300 mg/day for several months, tapering to <100 mg/day, within a year) alone or in combination with corticosteroids, has also been useful in managing patients with chronic ENL and is generally used until all signs of the reaction have abated. Other immunosuppressive drugs have been used to treat type 2 reactions with inconsistent results, including cyclosporine, mycophenolate, and methotrexate. **Lucio phenomenon is managed similarly to ENL** and treatment of underlying infections.

LONG-TERM COMPLICATIONS

Leprosy is a leading cause of permanent physical disability among communicable diseases worldwide. The major chronic complications and deformities of leprosy are caused by **nerve injury**. Nerve impairment may be purely sensory, motor, or autonomic or may be a combination. The prognosis for arresting progression of tissue and nerve damage is good if therapy is started early, but recovery of lost sensory and motor function is variable and frequently incomplete. Nerve function impairment can occur before diagnosis, during MDT, or after MDT and can develop without overt signs of skin or nerve inflammation (silent neuropathy). Patients at highest risk of nerve impairment are those with multibacillary leprosy and preexisting nerve damage. These patients should undergo regular monthly surveillance during therapy and for at least 2 years from the time of diagnosis. In children, deformities can occur in 3–10% of cases and mainly in those with nerve enlargement. Other factors contributing to risk of deformities include increasing age in children, delay in accessing medical care, multiple skin lesions, multibacillary disease, smear positivity, multiple nerve involvement, and leprosy reaction at presentation.

PREVENTION

In addition to treating active leprosy cases, control measures for HD include the management of **contacts** of index patients. In endemic countries, close monitoring of household contacts of HD patients, particularly HD patients with multibacillary disease, is warranted to ensure that early treatment can be implemented if evidence of early HD develops. These household contacts should be examined at baseline and then yearly for 5 years. In nonendemic areas, disease presenting in the contacts of patients with HD is rare. A single dose of bacille Calmette-Guérin (BCG) vaccine has variable protective efficacy against leprosy, ranging from 10% to 80%; an additional dose results in increased protection. Any suspected or newly diagnosed case of leprosy in the United States should be reported to local and state public health departments, the Centers for Disease Control and Prevention (CDC), and NHDP. There are no leprosy vaccines available or recommended for use in the United States. In the hospital setting, **standard precautions** should be implemented. Hand hygiene is recommended for all people in contact with a patient with lepromatous leprosy. The use of chemoprophylaxis with a single dose of rifampin (SDR) within endemic areas is recommended by the WHO, but not the NHDP, for adults and children ≥2 years in contact with leprosy patients. Because leprosy is a highly stigmatized disease, caution must be exercised when implementing SDR in contacts, particularly for those outside the patient's family.

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Chapter 263

Nontuberculous Mycobacteria

Ericka V. Hayes

Nontuberculous mycobacteria **(NTM)**, also referred to as **atypical mycobacteria** and **mycobacteria other than tuberculosis** (MOTT), are all members of the genus *Mycobacterium* and include species other than *Mycobacterium tuberculosis* complex and *Mycobacterium leprae*. The NTM constitute a highly diverse group of bacteria that differ from *M. tuberculosis* complex bacteria in their pathogenicity, interhuman transmissibility, nutritional requirements, ability to produce pigments, enzymatic activity, and drug susceptibility. In contrast to the *M. tuberculosis* complex, NTM are acquired from environmental sources and not by person-to-person spread, although the latter is under debate, especially in patients with cystic fibrosis (CF). Their omnipresence in the environment means that the clinical relevance of NTM isolation from clinical specimens is sometimes unclear; a positive culture might reflect occasional presence or contamination rather than true NTM disease. NTM are associated with pediatric lymphadenitis, otomastoiditis, serious lung infections, and, rarely, disseminated disease. Treatment is long-term and cumbersome and often requires adjunctive surgical intervention. Comprehensive guidelines on diagnosis and treatment are provided by the American Thoracic Society (ATS) and British Thoracic Society (BTS).

ETIOLOGY

NTM are ubiquitous in the environment all over the world, existing as saprophytes in soil and water (including municipal water supplies, tap water, hot tubs, and shower heads), environmental niches that are the supposed sources of human infections. With the introduction of molecular identification tools such as 16S recombinant DNA gene sequencing, the number of identified NTM species has grown to more than 150; the *clinical relevance* (i.e., percentage of isolates that are causative agents of true NTM disease, rather than occasional contaminants) differs significantly by species.

Mycobacterium avium complex (**MAC**; i.e., *M. avium, Mycobacterium intracellulare,* and several closely related but rarer species) and *Mycobacterium kansasii* are most often isolated from clinical samples, yet the isolation frequency of these species differs significantly by geographic area. MAC bacteria have been frequently isolated from natural and synthetic environments, and cases of MAC disease have been successfully linked to home exposure to shower and tap water. Although the designation *M. avium* suggests that human infections are acquired from birds (Latin *avium*), molecular typing has established that *M. avium* strains that cause pediatric lymphadenitis and adult pulmonary disease represent the *M. avium* hominis suis subgrouping, mainly found in humans and pigs and not in birds.

Some NTM have well-defined ecologic niches that help explain infection patterns. The natural reservoir for *Mycobacterium marinum* is fish and other cold-blooded animals, and the **fish tank granuloma**, a localized skin infection caused by *M. marinum,* follows skin injury in an aquatic environment. *Mycobacterium fortuitum* complex bacteria and *Mycobacterium chelonae* are ubiquitous in water and have caused clusters of nosocomial surgical wound and venous catheter–related infections. *Mycobacterium ulcerans* is associated with severe, chronic skin infections **(Buruli ulcer disease)** and is endemic mainly in West Africa and Australia, although other foci exist. Its incidence is highest in children <15 years old. *M. ulcerans* had been detected in environmental samples by polymerase chain reaction (PCR) and has been recovered by culture from a water strider (an insect of the *Gerris* genus) from Benin.

EPIDEMIOLOGY

Humans are exposed to NTM on a daily basis. In rural U.S. counties, where *M. avium* is common in swamps, the prevalence of asymptomatic infections with *M. avium* complex, as measured by skin test sensitization, approaches 70% by adulthood. Still, the incidence and prevalence of the various NTM disease types remain largely unknown, especially for pediatric NTM disease. In Australian children, the overall incidence of NTM infection is 0.84 per 100,000, with lymphadenitis accounting for two thirds of cases. The incidence of pediatric NTM disease in the Netherlands is estimated at 0.77 infections per 100,000 children per year, with lymphadenitis making up 92% of all infections.

In comparison, estimations of the prevalence of NTM from respiratory samples in adults are 5-15 per 100,000 persons per year, with important differences between countries or regions. Because pulmonary NTM disease progresses slowly, over years rather than months, and usually takes several years to cure, the prevalence of pulmonary NTM disease is much higher than incidence rates would suggest.

The paradigm that NTM disease is a rare entity limited to resource-rich countries is changing. In recent studies in African countries with a high prevalence of HIV infection, it has been found that NTM might play a much larger role as a cause of tuberculosis-like disease of children and adults than previously assumed and thus confuse the diagnosis of tuberculosis.

Although it is generally believed that NTM infections are contracted from environmental sources, whole genome sequence analysis of *Mycobacterium abscessus* strains of patients in a CF clinic in the United Kingdom supports the possibility of nosocomial horizontal transmission among CF patients.

PATHOGENESIS

The histologic appearances of lesions caused by *M. tuberculosis* and NTM are often indistinguishable. The classic pathologic lesion consists of caseating granulomas. Compared with *M. tuberculosis* infections, NTM infections are more likely to result in **granulomas that are non-caseating**, poorly defined (nonpalisading), irregular or serpiginous, or even absent, with only chronic inflammatory changes observed. The histology likely reflects the immune status of the patient.

In patients with AIDS and disseminated NTM infection, the inflammatory reaction is usually scant, and tissues are filled with large numbers of histiocytes packed with acid-fast bacilli (AFB). These disseminated NTM infections typically occur only after the number of CD4 T lymphocytes has fallen below 50/μL in children ≥6 years, below 75/μL in children 2 to <6 years, below 500/μL in children 1 to <2 years, and below 750/μL in children <1 year, suggesting that specific T-cell products or activities are required for immunity to mycobacteria.

The pivotal roles of interferon (IFN)-γ, interleukin (IL)-12, and tumor necrosis factor (TNF)-α in disease pathogenesis are demonstrated by the high incidence of mostly disseminated NTM disease in children with IFN-γ and IL-12 pathway deficiencies and in persons treated with agents that neutralize TNF-α.

Observed differences in pathogenicity, clinical relevance, and spectrum of clinical disease associated with the various NTM species emphasize the importance of bacterial factors in the pathogenesis of NTM disease, although exact virulence factors remain largely unknown.

CLINICAL MANIFESTATIONS

Lymphadenitis of the superior anterior cervical or submandibular lymph nodes is the most common manifestation of NTM infection in children (Table 263.1). Preauricular, posterior cervical, axillary, and inguinal nodes are involved occasionally. Lymphadenitis is most

Table 263.1 Major Clinical Syndromes Associated with Nontuberculous Mycobacterial Infection

SYNDROME	MOST COMMON CAUSES	LESS FREQUENT CAUSES*
Chronic nodular disease (adults with bronchiectasis; cystic fibrosis)	MAC (*M. intracellulare, M. avium*), *M. kansasii, M. abscessus*	*M. xenopi, M. malmoense, M. szulgai, M. smegmatis, M. celatum, M. simiae, M. goodii, M. asiaticum, M. heckeshornense, M. branderi, M. lentiflavum, M. triplex, M. fortuitum, M. arupense, M. abscessus* subsp. *bolletii, M. phocaicum, M. aubagnense, M. florentinum, M. abscessus* subsp. *massiliense, M. nebraskense, M. saskatchewanense, M. seoulense, M. senuense, M. paraseoulense, M. europaeum, M. sherrisii, M. kyorinense, M. noviomagense, M. mantenii, M. shinjukuense, M. koreense, M. heraklionense, M. parascrofulaceum, M. arosiense*
Cervical or other lymphadenitis (especially children)	MAC	*M. scrofulaceum, M. malmoense* (northern Europe), *M. abscessus, M. fortuitum, M. lentiflavum, M. tusciae, M. palustre, M. interjectum, M. elephantis, M. heidelbergense, M. parmense, M. bohemicum, M. haemophilum, M. europaeum, M. florentinum, M. triplex, M. asiaticum, M. kansasii, M. heckeshornense*
Skin and soft tissue disease	*M. fortuitum* group, *M. chelonae, M. abscessus, M. marinum, M. ulcerans* (Australia, tropical countries only)	*M. kansasii, M. haemophilum, M. porcinum, M. smegmatis, M. genavense, M. lacus, M. novocastrense, M. houstonense, M. goodii, M. immunogenum, M. mageritense, M. abscessus* subsp. *massiliense, M. arupense, M. monacense, M. bohemicum, M. branderi, M. shigaense, M. szulgai, M. asiaticum, M. xenopi, M. kumamotense, M. setense, M. montefiorense* (eels), *M. pseudoshottsii* (fish), *M. shottsii* (fish)
Skeletal (bone, joint, tendon) infection	*M. marinum*, MAC, *M. kansasii, M. fortuitum* group, *M. abscessus, M. chelonae*	*M. haemophilum, M. scrofulaceum, M. heckeshornense, M. smegmatis, M. terrae/chromogenicum* complex, *M. wolinskyi, M. goodii, M. arupense, M. xenopi, M. triplex, M. lacus, M. arosiense*
Disseminated infection		*M. genavense, M. haemophilum, M. xenopi*
HIV-seropositive host	*M. avium, M. kansasii*	*M. marinum, M. simiae, M. intracellulare, M. scrofulaceum, M. fortuitum, M. conspicuum, M. celatum, M. lentiflavum, M. triplex, M. colombiense, M. sherrisii, M. heckeshornense*
HIV-seronegative host	*M. abscessus, M. chelonae*	*M. marinum, M. kansasii, M. haemophilum, M. chimaera, M. conspicuum, M. shottsii* (fish), *M. pseudoshottsii* (fish)
Catheter-related infections	*M. fortuitum, M. abscessus, M. chelonae*	*M. mucogenicum, M. immunogenum, M. mageritense, M. septicum, M. porcinum, M. bacteremicum, M. brumae*
Hypersensitivity pneumonitis (metal workers; hot tub users)	*M. immunogenum, M. avium*	

*The available information is sparse for selected pathogens such as *M. xenopi, M. malmoense, M. szulgai, M. celatum*, and *M. asiaticum* and the newly described species.
HIV, Human immunodeficiency virus; MAC, *Mycobacterium avium* complex.
From Brown-Elliott BA, Wallace RJ Jr. Infections caused by nontuberculous mycobacteria other than *Mycobacterium avium* complex. In Bennett JF, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of* Infectious *Diseases*, 8th ed. Philadelphia: Elsevier; 2015: Table 254-1.

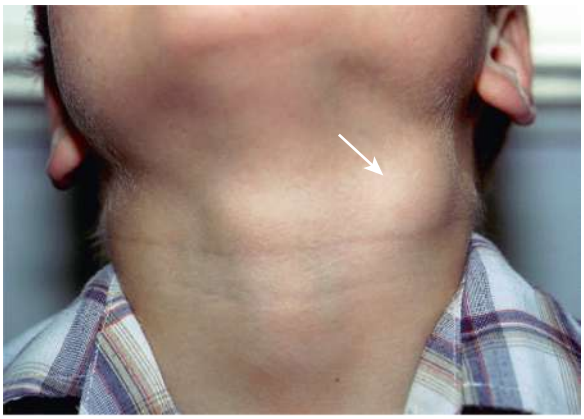

Fig. 263.1 Enlarging cervical lymph node infected with *Mycobacterium avium* complex infection. The node is firm, painless, freely movable, and not erythematous.

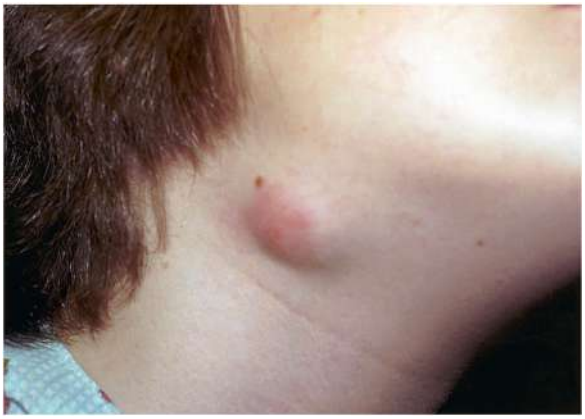

Fig. 263.2 Suppurating cervical lymph node infected with *Mycobacterium avium* complex.

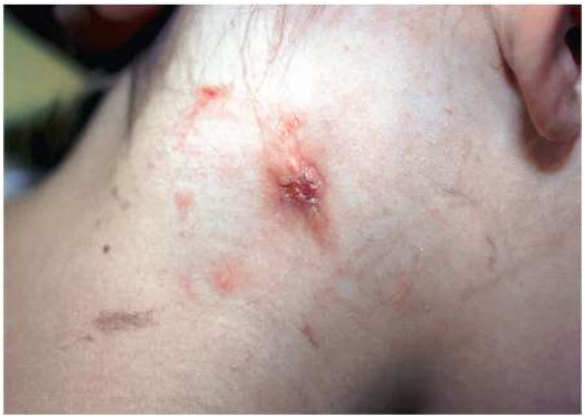

Fig. 263.3 Ruptured cervical lymph node infected with *Mycobacterium avium* complex, which resembles the classic scrofula of tuberculosis.

common in children 1-5 years of age and has been related to soil exposure (e.g., playing in sandboxes) and teething, although exact predisposing conditions have not been identified. Given the constant environmental exposure to NTM, the occurrence of these infections might also reflect an atypical immune response of a subset of the infected children during or after their first contact with NTM. However, in healthy children with isolated NTM lymphadenitis, immunodeficiency is quite rare.

Affected children usually lack constitutional symptoms and present with a unilateral, subacute, and slowly enlarging lymph node or group of closely approximated nodes >1.5 cm in diameter that are firm, painless, freely movable, and not erythematous (Fig. 263.1). The involved nodes occasionally resolve without progression, but most undergo rapid suppuration after several weeks (Fig. 263.2). The center of the node becomes fluctuant, and the overlying skin thins and becomes erythematous and often even violaceous. Eventually, the nodes rupture and can form cutaneous sinus tracts that can drain persistently, reminiscent of scrofula from tuberculosis (Fig. 263.3).

In the United States and Western Europe, MAC accounts for approximately 80% of NTM lymphadenitis in children. *M. kansasii* accounts for most other cases of lymphadenitis in the United States. *M. malmoense* and *M. haemophilum* have also been described as causative agents of lymphadenitis. *M. malmoense* is most common in Northwestern Europe. For *M. haemophilum,* underestimation of its importance is likely because the bacteria require specific culture conditions (hemin-enriched media, low incubation temperatures). On the basis of PCR analysis of lymph node samples from lymphadenitis cases in The Netherlands, *M. haemophilum* is the second most common cause of this infection, after MAC. One study suggests that children with MAC lymphadenitis are significantly younger than those infected by *M. haemophilum,* possibly related to age-specific environmental exposures. *Mycobacterium lentiflavum* is also an emerging NTM associated with lymphadenitis.

Cutaneous disease caused by NTM is rare in children (see Table 263.1). Infection usually follows percutaneous inoculation with fresh or salt water contaminated by *M. marinum.* Within 2-6 weeks after exposure, an erythematous papule develops at the site of minor abrasions on the elbows, knees, or feet **(swimming pool granuloma)** and on the hands and fingers of fish tank owners, mostly inflicted during tank cleaning **(fish tank granuloma)**. These lesions are usually nontender and enlarge over 3-5 weeks to form violaceous plaques. Nodules or pustules can develop and occasionally will ulcerate, resulting in a serosanguineous discharge. The lesions sometimes resemble sporotrichosis, with satellite lesions near the site of entry, extending along the superficial lymphatics. Lymphadenopathy is usually absent. Although most infections remain localized to the skin, penetrating *M. marinum* infections can result in tenosynovitis, bursitis, osteomyelitis, or arthritis.

M. ulcerans infection is the third most common mycobacterial infection in immunocompetent patients, after *M. tuberculosis* and *M. leprae* infection, and causes cutaneous disease in children living in tropical regions of Africa, South America, Asia, and parts of Australia. In some communities in West Africa, up to 16% of people have been affected. Children <15 years old are particularly affected in rural tropical counties, accounting for 48% of infected individuals in Africa. Infection follows percutaneous inoculation from minor trauma, such as pricks and cuts from plants or insect bites. After an incubation period of approximately 3 months, lesions appear as an erythematous nodule, usually on the legs or arms. The lesion undergoes central necrosis and ulceration. The lesion, often called a **Buruli ulcer** after the region in Uganda where a large case series was reported, has a characteristic undermined edge, expands over several weeks, and can result in extensive, deep soft tissue destruction or bone involvement (Fig. 263.4). Lesions are typically painless, and constitutional symptoms are unusual. Lesions might heal slowly over 6-9 months or might continue to spread, leading to deformities, contractures, and disability. Depending on the location of the ulcer, these can be significantly disfiguring.

Skin and soft tissue infections caused by **rapidly growing mycobacteria**, such as *M. fortuitum, M. chelonae,* or *M. abscessus,* are rare in children and usually follow percutaneous inoculation from puncture or surgical wounds, minor abrasions, or tattooing. There has been a large outbreak of *M. fortuitum* furunculosis related to nail salon footbaths. Clinical disease usually arises after a 4- to 6-week incubation period and manifests as localized cellulitis, painful nodules, or a draining abscess. *M. haemophilum* can cause painful subcutaneous nodules, which often ulcerate and suppurate in immunocompromised patients, particularly after kidney transplantation.

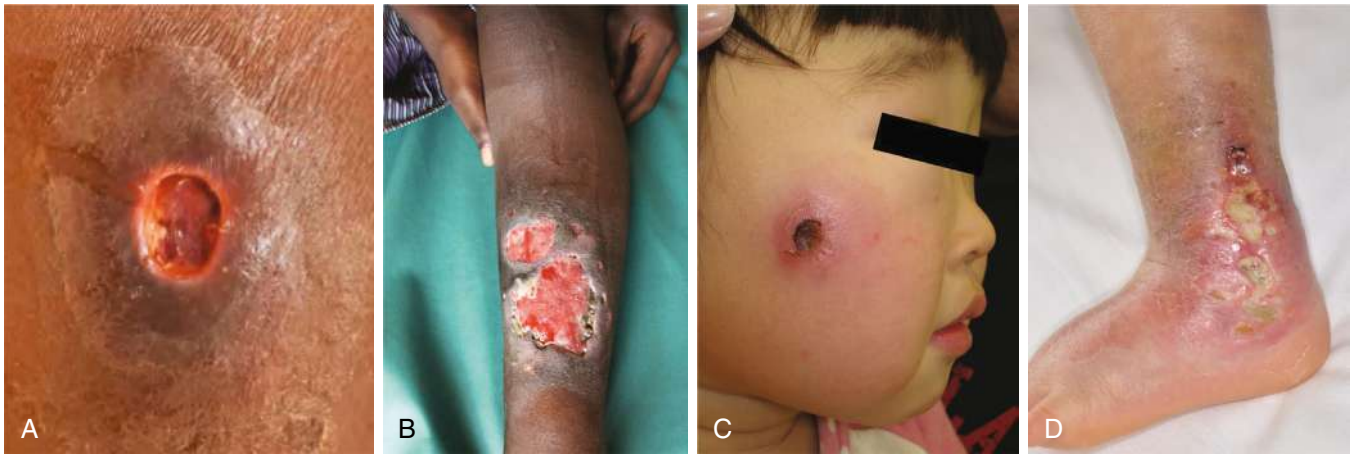

Fig. 263.4 Buruli ulcer lesions in patients from West Africa (**A** and **B**) and Japan (**C** and **D**). *(A, B from Röltgen K, Pluschke G. Buruli ulcer: history and disease burden. In: Pluschke G, Röltgen K, eds. Buruli Ulcer. Cham: Springer; 2019; C, D courtesy Dr Mikio Ohtsuka, Fukushima Medical University.)*

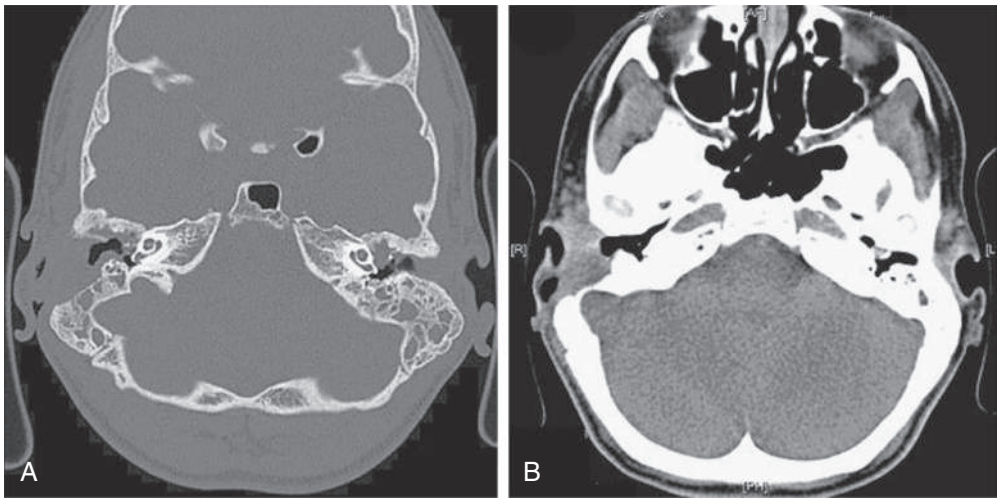

Fig. 263.5 CT images of the middle ear of 6-yr-old child infected with *Mycobacterium abscessus*, demonstrating extensive bone destruction in the right mastoid and associated right-sided mucosal swelling. **A,** Bone tissue window setting. **B,** Soft tissue window setting.

NTM are an uncommon cause of **catheter-associated infections** but are becoming increasingly recognized in this respect. Infections caused by *M. fortuitum, M. chelonae,* or *M. abscessus* can manifest as bacteremia or localized catheter tunnel infections.

Otomastoiditis, or chronic otitis media, is a rare extrapulmonary NTM disease type that specifically affects children with tympanostomy tubes and a history of topical antibiotic or steroid use. *M. abscessus* is the most common causative agent, followed by MAC (see Table 263.1). Patients present with painless, chronic otorrhea resistant to antibiotic therapy. CT can reveal destruction of the mastoid bone with mucosal swelling (Fig. 263.5).

Delayed or unsuccessful treatment can result in permanent hearing loss. In unusual circumstances, NTM cause other bone and joint infections that are indistinguishable from those produced by *M. tuberculosis* or other bacterial agents. Such infections usually result from operative incision or accidental puncture wounds. *M. fortuitum* infections from puncture wounds of the foot resemble infections caused by *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

Pulmonary infections are the most common form of NTM illness in adults but are rare in children. MAC bacteria, the most commonly identified organisms (see Table 263.1), are capable of causing acute pneumonitis, chronic cough, or wheezing associated with paratracheal or peribronchial lymphadenitis and airway compression in normal children. Associated constitutional symptoms such as fever, anorexia, and weight loss occur in 60% of these children. Chest radiographic findings are similar to those for primary tuberculosis, with unilateral infiltrates and hilar lymphadenopathy (Fig. 263.6). Pleural effusion is

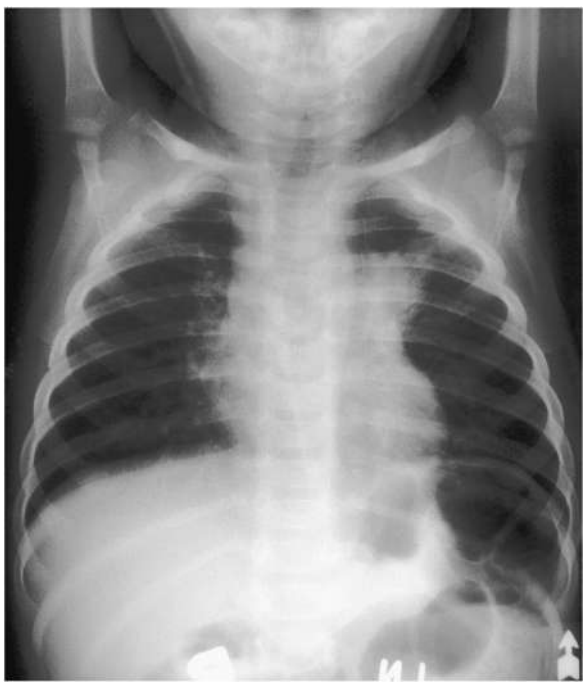

Fig. 263.6 Chest radiograph of 2-yr-old child infected with *Mycobacterium avium* complex, demonstrating a left upper lobe infiltrate and left hilar lymphadenopathy.

uncommon. Rare cases of progression to endobronchial granulation tissue have been reported.

Pulmonary infections usually occur in adults with underlying chronic lung disease. The onset is insidious and consists of cough and fatigue, progressing to weight loss, night sweats, low-grade fever, and generalized malaise in severe cases. Thin-walled cavities with minimal surrounding parenchymal infiltrates are characteristic, but radiographic findings can resemble those of tuberculosis. A separate disease manifestation occurs typically in postmenopausal women and is radiologically characterized by bronchiectasis and nodular lesions, often affecting the middle lobe and lingula (Lady Windemere's syndrome).

Chronic pulmonary infections specifically affect children with CF and are generally caused by *M. abscessus* or MAC. *M. abscessus* primarily affects children, and MAC is most common among adults. The percentage of CF patients with at least one sputum culture positive for NTM is 6–8.1% overall and increases with age; in CF patients <12 years old, a prevalence of 3.9% has been reported. The strong representation of *M. abscessus* in these patients is remarkable, because this bacterium is an uncommon isolate in other categories of patients. There are indications that NTM infections in CF patients further accelerate the decline in lung function; antimycobacterial therapy can result in weight gain and improved lung function in affected patients.

Disseminated disease is usually associated with MAC infection and occurs in immunocompromised children. The first category of patients with disseminated disease includes persons with mutations in genes coding for the interferon-γ receptor (IFNGR) or the IL-12 receptor or for IL-12 production. Patients with complete **IFNGR deficiency** have severe, difficult-to-treat disease. Those with partial IFNGR deficiency or IL-12 pathway mutations have milder disease that can respond to IFN-γ and antimycobacterial therapy. **Multifocal osteomyelitis** is particularly prevalent in persons with the IFNGR1 818del4 mutation. Recurrences, even years after a course of treatment, and multiple infections are well documented. The second category of patients affected by disseminated disease is patients with **AIDS**. Disseminated NTM disease in patients with AIDS usually appears when CD4 cell counts are <50/μL for children ≥6 years , <75/μL in children 2 to <6 years, <500/μL in children 1 to <2 years, and <750/μL in children <1 year. The most recent estimate of the incidence of disseminated NTM disease is 0.14-0.2 episodes per 100 person-years, a 10-fold decrease from its incidence before combination antiretroviral therapy (cART) was available.

Colonization of the respiratory or gastrointestinal (GI) tract probably precedes disseminated MAC infections, but screening studies of respiratory secretions or stool samples are not useful to predict dissemination. Continuous high-grade bacteremia is common, and multiple organs are infected, typically including the lymph nodes, liver, spleen, bone marrow, and GI tract. The thyroid, pancreas, adrenal gland, kidney, muscle, and brain can also be involved. The most common signs and symptoms of disseminated MAC infections in patients with AIDS are fever, night sweats, chills, anorexia, marked weight loss, wasting, weakness, generalized lymphadenopathy, and hepatosplenomegaly. Jaundice, elevated alkaline phosphatase or lactate dehydrogenase levels, anemia, and neutropenia can occur. Imaging studies usually demonstrate massive lymphadenopathy of hilar, mediastinal, mesenteric, or retroperitoneal nodes. Successful treatment of disseminated infection in children with AIDS requires immune reconstitution and cART in addition to specific NTM therapy. The survival in children with AIDS has improved considerably with the availability of cART.

Disseminated disease in children without any apparent immunodeficiency is exceedingly rare.

DIAGNOSIS

For infections of lymph nodes, skin, bone, and soft tissues, isolation of the causative NTM bacteria by *Mycobacterium* culture, preferably with histologic confirmation of granulomatous inflammation, normally suffices for diagnosis. The differential diagnosis of NTM lymphadenitis includes acute bacterial lymphadenitis, tuberculosis, cat scratch disease *(Bartonella henselae* infection*)*, mononucleosis, toxoplasmosis, brucellosis, tularemia, and malignancies, especially lymphomas.

Table 263.2 American Thoracic Society Clinical and Microbiologic Criteria for Diagnosis of Nontuberculous Mycobacteria (NTM) Pulmonary Disease

CLINICAL*	PULMONARY OR SYSTEMIC SYMPTOMS
Radiologic*	Nodular or cavitary opacities on chest radiograph or a high-resolution computed tomography (HRCT) scan that shows bronchiectasis with multiple small nodules
AND	Appropriate exclusion of other diagnoses
Microbiologic	1. Positive culture results from at least two separate expectorated sputum samples. If the results are nondiagnostic, consider repeat sputum AFB smears and cultures. or 2. Positive culture results from at least one bronchial wash or lavage. or 3. Transbronchial or other lung biopsy with mycobacterial histologic features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture-positive for NTM.

*Note: Both clinical and radiologic criteria are required.
AFB, Acid-fast bacilli.
From Daley CL, Iaccarino JM, Lange C, et al. Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline [published correction appears in Clin Infect Dis. 2020 Dec 31;71(11):3023]. *Clin Infect Dis.* 2020;71(4):e1–e36.

Differentiation between NTM and *M. tuberculosis* may be difficult, but children with NTM lymphadenitis usually have a Mantoux tuberculin skin test reaction of <15 mm induration, unilateral anterior cervical node involvement, a normal chest radiograph, and no history of exposure to tuberculosis. Definitive diagnosis requires excision of the involved nodes for culture and histology. Fine-needle aspiration for PCR and culture can enable earlier diagnosis, before excisional biopsy.

The diagnosis of pulmonary NTM infection in children is difficult because many species of NTM, including MAC, are omnipresent in our environment and can contaminate clinical samples or be present but not causative of disease. As a result, isolation of these bacteria from nonsterile specimens (respiratory and digestive tract) does not necessarily reflect true disease. To determine the clinical relevance of isolation of NTM, the ATS/BTS diagnostic criteria are an important support (Table 263.2). These criteria take into consideration clinical features and radiologic, pathologic, and microbiologic findings. Their hallmark is the need for multiple positive cultures yielding the same NTM species to make a definitive diagnosis of pulmonary NTM disease, though a single culture from bronchoalveolar lavage (BAL)/bronchial lavage is acceptable in patients who meet clinical and radiologic criteria. In children, definitive diagnosis often requires invasive procedures such as bronchoscopy and pulmonary or endobronchial biopsy; in CF patients, more aggressive sample pretreatment in the clinical microbiology laboratory is necessary to prevent overgrowth by other species, especially *Pseudomonas*. The chance of NTM isolation being clinically relevant differs significantly by species; some species are more likely causative agents of true pulmonary disease *(M. avium, M. kansasii*, *M. abscessus, M. malmoense)*, whereas others are more likely contaminants (*M. gordonae, M. fortuitum, M. chelonae)*.

Blood cultures are 90–95% sensitive in AIDS patients with disseminated infection. MAC may be detected within 7-10 days of inoculation in almost all patients by automated blood culture systems. In adults, some studies have shown that liver biopsy cultures and stains are more sensitive than blood culture or bone marrow biopsy workup. Commercially available DNA probes differentiate NTM from *M.*

tuberculosis. If DNA probes cannot identify the causative mycobacteria, DNA sequencing of bacterial housekeeping genes can yield a clue to the identity of these NTM. Identification of histiocytes containing numerous AFB from bone marrow and other biopsy tissues provides a rapid presumptive diagnosis of disseminated mycobacterial infection.

TREATMENT

Therapy for NTM infections is long-term and cumbersome; expert consultation is advised. Therapy involves medical, surgical, or often combined treatment (see Chapter 260, Table 260.3). Isolation of the infecting strain followed by drug-susceptibility testing is ideal, because it provides a baseline for drug susceptibility. Important discrepancies exist between in vitro drug susceptibility and in vivo response to treatment, explained in part by synergism, mainly among first-line antituberculosis drugs. In vitro, **slow growers** *(M. kansasii, M. marinum, M. xenopi, M. ulcerans, M. malmoense)* are usually susceptible to the first-line antituberculosis drugs **rifampin** and **ethambutol**; MAC bacteria are often resistant to these drugs alone but susceptible to the combination and have variable susceptibility to other antibiotics, most importantly the macrolides. **Rapid growers** *(M. fortuitum, M. chelonae, M. abscessus)* are highly resistant to antituberculosis drugs and often have inducible macrolide-resistance mechanisms. Susceptibility to macrolides, aminoglycosides, carbapenems, tetracyclines, and glycylcyclines are most relevant for therapy guidance. In all NTM infections, multidrug therapy (MDT) is essential to avoid development of resistance.

The preferred treatment of NTM lymphadenitis is complete surgical excision. Clinical trials revealed that surgery is more effective than antibiotic treatment (see Table 260.3). Nodes should be removed while still firm and encapsulated. Excision is more difficult if extensive caseation with extension to surrounding tissue has occurred, and complications of facial nerve damage or relapse of infection are more likely in such cases. Incomplete surgical excision is not advised, because chronic drainage can develop. If there are concerns or risk factors for possible *M. tuberculosis* infection, therapy with isoniazid, rifampin, ethambutol, and pyrazinamide should be administered until cultures confirm the cause to be NTM (see Chapter 261). If surgery of NTM lymphadenitis cannot be performed, or removal of infected tissue is incomplete, or recurrence or chronic drainage develops, a 3-month trial of antibiotic therapy should be considered. **Clarithromycin or azithromycin combined with rifampin or ethambutol are the most common therapy regimens reported for MAC lymphadenitis** (see Table 260.3). Suppuration may still occur on appropriate antibiotic therapy. In immunocompetent patients, **an observational approach** to NTM lymphadenitis can be chosen without antibiotic therapy, although resolution will take up to 12 months.

Posttraumatic cutaneous NTM lesions in immunocompetent patients usually heal spontaneously after incision and drainage without other therapy. *M. marinum* is susceptible to rifampin, amikacin, ethambutol, sulfonamides, trimethoprim-sulfamethoxazole, and tetracycline. Therapy with a combination of these drugs, particularly clarithromycin and ethambutol, may be given until 1 month after the lesion has disappeared. Corticosteroid injections should not be used. Superficial infections with *M. fortuitum* or *M. chelonae* usually resolve after surgical incision and open drainage, but deep-seated or catheter-related infections require removal of infected central lines and therapy with parenteral amikacin plus cefoxitin, ciprofloxacin, or clarithromycin.

Some localized forms of *M. ulcerans* skin disease (Buruli ulcer) can heal spontaneously; for most forms, excisional surgery with primary closure or skin grafting is recommended. **The combination of rifampin (10 mg/kg once daily) and clarithromycin (7.5 mg/kg twice daily) for 8 weeks results in excellent outcomes and is now the recommended treatment for early limited Buruli ulcer.** Another agent that shows great promise is telacebec (also known as *Q203*), a novel first-in-class antituberculosis drug targeting cellular energy production through inhibition of the mycobacterial cytochrome bc1 complex; animal studies have demonstrated significant potency against *M. ulcerans,* possibly allowing for shorter courses of treatment. In January 2021, the U.S. Food and Drug Administration granted orphan drug designation (ODD) to telacebec for Buruli ulcer treatment. **Physiotherapy** after surgery is essential to prevent contractures and functional disabilities.

For patients who meet diagnostic criteria for pulmonary NTM infections (see Table 263.2), treatment rather than observation is recommended, particularly with persistently positive sputum smears and/or cavitary lung disease. Although treatment offers possibility of cure, there can be significant adverse effects of treatment and low cure rates for some forms of infection. Patients who require treatment for NTM pulmonary disease should have isolates sent for susceptibility testing, with the caveat that this testing is helpful for NTM for antibiotics where there is a well-documented correlation between in vitro activity and microbiologic response to therapy. Drugs for which this correlation exist include macrolides (azithromycin, clarithromycin) and amikacin for MAC and *M. abscessus* and rifampin for *M. kansasii*. **For macrolide-susceptible MAC pulmonary disease, treatment with three drugs for at least 12 months after culture conversion is recommended, generally azithromycin, rifampin, and ethambutol.** For macrolide-resistant isolates, parenteral amikacin is often used, as MAC isolates are usually susceptible in vitro to this agent.

Macrolides are a mainstay in the treatment of *M. abscessus* pulmonary disease. However, macrolide resistance can develop via chromosomal mutation or through induction of the erm(41) gene. **For *M. abscessus* disease caused by strains without inducible or chromosomal macrolide resistance, a macrolide-containing treatment regimen is recommended, typically with at least three active drugs. If macrolide resistance (chromosomal or inducible) is present, at least four active drugs are recommended. Treatment regimens for *M. abscessus* are complex, usually with oral plus parental drugs. Regimens typically include two to three oral agents, which may include azithromycin, clofazimine, or linezolid, and at least one parenteral agent, with options including amikacin, imipenem, and tigecycline.** In CF patients, inhaled agents may also have a role. Choice of treatment regimens and duration of therapy should be guided by expert consultation. For select patients, surgical resection of severely diseased lung in addition to medical therapy may be indicated.

For *M. kansasii* pulmonary disease, susceptibility-based treatment for rifampin is recommended over empirical therapy. The recommended treatment regimen for rifampin-susceptible *M. kansasii* infections is rifampin, ethambutol, and either isoniazid or a macrolide for at least 12 months. Fluoroquinolones also have good activity against *M. kanasasii* but are reserved for rifampin-resistant *M. kansasii* infection treatment and for patients who have intolerance to one of the first-line antibiotics.

Patients with disseminated MAC and IL-12 pathway defects or IFNGR deficiency should be treated for at least 12 months with clarithromycin or azithromycin combined with rifampin or rifabutin and ethambutol. In vitro susceptibility testing for macrolides is important to guide therapy. Once the clinical illness has resolved, lifelong daily prophylaxis with azithromycin or clarithromycin is advisable to prevent recurrent disease. The use of IFN adjunctive therapy is determined by the specific genetic defect.

In children with AIDS, prophylaxis with azithromycin or clarithromycin is indicated to prevent infection with MAC. Although few pediatric studies exist, the U.S. Public Health Service recommends either **azithromycin** (20 mg/kg once weekly PO, maximum 1,200 mg/dose *or* 5 mg/kg once daily PO, maximum 250 mg/dose in patients intolerant of the larger dose) or **clarithromycin** (7.5 mg/kg/dose twice daily PO; maximum 500 mg/dose) for HIV-infected children with significant immune deficiency, as defined by the CD4 count (children ≥6 years old, CD4 count <50 cells/μL; 2 to <6 years old, <75/μL; 1 to <2 years old, <500/μL; <1 year old, <750/μL). Rifabutin may also be used. Primary prophylaxis may be safely discontinued in children >2 years old receiving stable highly active antiretroviral therapy (HAART) for >6 months and experiencing sustained (>3 months) CD4 cell recovery well above the age-specific target for initiation of prophylaxis: >100 cells/μL for children ≥6 years old and >200/μL for children 2-5 years old. For children <2 years old, no specific recommendations for discontinuing MAC prophylaxis exist.

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Section 8

Spirochetal Infections

Chapter 264

Syphilis (*Treponema pallidum*)

Alice I. Sato and H. Dele Davies

Syphilis is a chronic systemic sexually or vertically (mother to child) transmitted infection that can be easily treated if detected early but manifests with protean clinical symptoms and significant morbidity if left unchecked. (Please note that the terms *mother* and *maternal* are used to designate the birthing parent throughout this chapter and are not intended to exclude other birthing parents.)

ETIOLOGY

Syphilis is caused by *Treponema pallidum,* a delicate, tightly spiraled, motile spirochete with finely tapered ends belonging to the family Spirochaetaceae. The pathogenic members of this genus include *T. pallidum* subspecies *pallidum* (venereal syphilis), *T. pallidum* subspecies *pertenue* (yaws), *T. pallidum* subspecies *endemicum* (bejel or endemic syphilis), and *T. pallidum* subspecies *carateum* (pinta). Because these microorganisms stain poorly and are below the detection limits of conventional light microscopy, detection in clinical specimens requires dark-field, phase-contrast microscopy or direct immunofluorescent or silver staining. *T. pallidum* has only recently been successfully grown in vitro via co-culture with mammalian tissue culture cells, and a method has now been described for inoculation of fresh and frozen needle aspirates from primary experimental syphilis lesions onto culture plates but remains to be developed for clinical use. Use of nucleic acid amplification testing by polymerase chain reaction (PCR) may have a role in diagnosis, particularly in seronegative patients or those with discrepant serology results.

EPIDEMIOLOGY

Acquired syphilis is transmitted almost exclusively by sexual contact, including vaginal, anal, and oral exposure. Less common modes of transmission include transfusion of contaminated blood or direct contact with infected tissues. Syphilis in men who have sex with men (MSM) may be acquired in the absence of visible lesions. DNA-based *T. pallidum* testing has identified organisms in oral rinse or swab samples and in anal canal swabs, urine, semen, and peripheral blood; the risk is highest in secondary and early latent syphilis. The incubation period for acquired primary syphilis is about 3 weeks (range 10-90 days). After an epidemic resurgence of primary and secondary syphilis in the United States that peaked in 1989, the annual rate declined 90% to the lowest-ever rate by 2000. The total number of cases of primary and secondary syphilis has subsequently rebounded since 2000 (Fig. 264.1). MSM have been disproportionately impacted: ~46% of cases in 2021. Rates of primary and secondary syphilis in women remain lower than in men yet still have increased 55% during 2021. Cases of congenital syphilis reached an historic low in 2005 but have subsequently increased annually since 2013, reflecting the rates among women. In 2021, the US national congenital syphilis rate was 77.9 cases per 100,000 live births, representing a 30.5% increase from 2020 and a 219.3% increase from 2017 (Fig. 264.2); syphilitic still births also increased over this period. The increase occurs across every region and all races and ethnicities, but marked disparities exist,

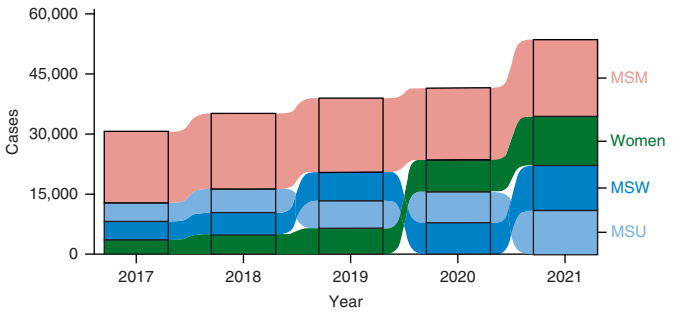


Fig 264.1 Primary and secondary syphilis – Reported cases by sex and sex of sex partners 2017–2021. Note: Over the 5-yr period, 0.2% of cases were missing sex and were not included. MSM, Gay, bisexual, and other men who have sex with men; MSU, Men with unknown sex of sex partners; MSW, men who have sex with women only. *(From Centers for Disease Control and Prevention. Sexually transmitted disease surveillance. National overview of STDs, 2021. https://www.cdc.gov/std/statistics/2021/overview.htm)*

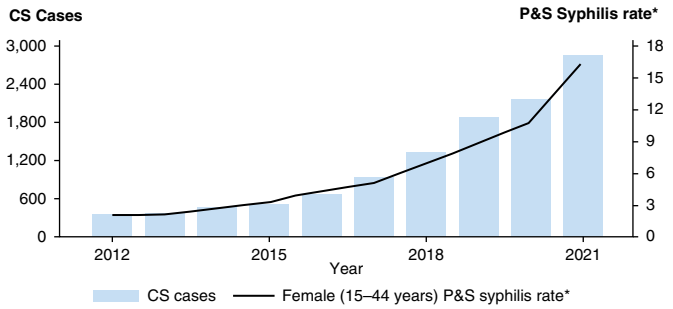


Fig. 264.2 Congenital syphilis — Reported cases by year of birth and rates of reported cases of primary and secondary syphilis among women age 15-44 years, United States, 2012–2021. *Per 100,000. CS, Congenital syphilis; P&S syphilis, Primary and secondary syphilis. *(From Centers for Disease Control and Prevention. Sexually transmitted disease surveillance. National overview of STDs, 2021. https://www.cdc.gov/std/statistics/2021/overview.htm)*

with minority groups, gay and bisexual men, and youth most affected. The COVID-19 pandemic disrupted screening programs and access to care, and increased cases are expected.

Congenital syphilis results from transplacental transmission of spirochetes or occasionally by intrapartum contact with infectious lesions or possibly involved mucosa without obvious lesions. Women with primary and secondary syphilis and spirochetemia are more likely to transmit infection to the fetus than are women with latent infection. Transmission can occur at any stage of pregnancy, resulting in early fetal loss, preterm or low birthweight infants, stillbirths, neonatal deaths, or infants born with congenital disease. The incidence of congenital infection in offspring of untreated or inadequately treated infected women remains highest during the first 4 years after acquisition of primary infection, secondary infection, and early latent disease. Maternal (parental) factors associated with congenital syphilis include limited access to healthcare, late or no prenatal care, drug use, multiple sex partners, unprotected sexual contact, incarceration, work in the sex trade, and inadequate treatment of syphilis during pregnancy. Congenital syphilis may be seen in the context of untreated, inadequately treated, or undocumented treatment before or during pregnancy. In addition, the mother may have been treated appropriately but did not have an adequate serologic response to therapy and the infant was inadequately evaluated, or the infant had documented congenital syphilis. Confirmed cases of both acquired and congenital syphilis must be reported to the local health department.

CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS

Many persons infected with syphilis are *asymptomatic for years,* or do not recognize the early signs of disease, or do not seek or have access

to treatment. The Centers for Disease Control and Prevention (CDC) recommends testing all pregnant persons and selective testing of adolescents, based on lesions or risk factors (those with other sexually transmitted diseases including HIV, MSM, incarcerated individuals, or persons who exchange sex for money or drugs). CDC/MMWR sexually transmitted infection (STI) guidelines should be consulted to ensure that all appropriate screening is performed. All 50 states and the District of Columbia explicitly allow minors to consent for STI services, though as of 2022, 18 states allow (but do not require) physicians to notify parents of STI services provided to a minor (https://www.cdc.gov/hiv/policies/law/states/minors.html). Periods of active clinical disease alternate with periods of latency (Fig. 264.3). **Primary syphilis** is characterized by a chancre and regional lymphadenitis. A **painless papule** (which may be overlooked) appears at the site of entry (usually the genitalia) 2-6 weeks after inoculation and develops into a clean, painless but highly contagious ulcer with raised borders **(chancre)** containing abundant *T. pallidum*. Extragenital chancres can occur at other sites of primary entry and pose a diagnostic challenge. Oral lesions can be mistaken for aphthous ulcers or herpes. Lesions on the nipple can be confused with cellulitis or eczema. Adjacent lymph nodes are generally enlarged and nontender. The chancre heals spontaneously within 4-6 weeks, leaving a thin scar.

Untreated patients develop manifestations of **secondary syphilis** related to spirochetemia 2-10 weeks after the chancre heals. Manifestations of secondary syphilis include a generalized nonpruritic maculopapular rash, notably involving the palms and soles (Fig. 264.4). Pustular lesions can also develop. **Condylomata lata**, gray-white to erythematous wartlike plaques, can occur in moist areas around the anus, scrotum, or vagina, and white plaques **(mucous patches)** may be found in mucous membranes. Secondary syphilis should be considered in the differential diagnosis of virtually any rash of unknown etiology. A **flulike illness** with low-grade fever, headache, malaise, anorexia, weight loss, sore throat, myalgias, arthralgias, and generalized lymphadenopathy is often present. Renal, hepatic, or ocular manifestations may be present. Meningitis occurs in about 30% of patients with untreated syphilis, occurring at any stage but most commonly in

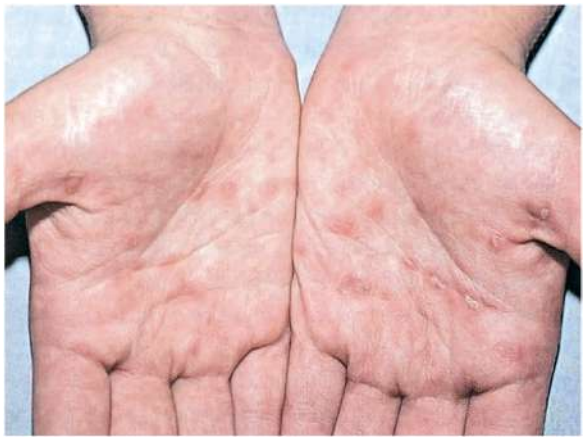


Fig. 264.4 Secondary syphilis. Ham-colored palmar macules on an adolescent with secondary syphilis. *(From Weston WL, Lane AT, Morelli J. Color Textbook of Pediatric Dermatology, 3rd ed. St. Louis: Mosby; 2002.)*

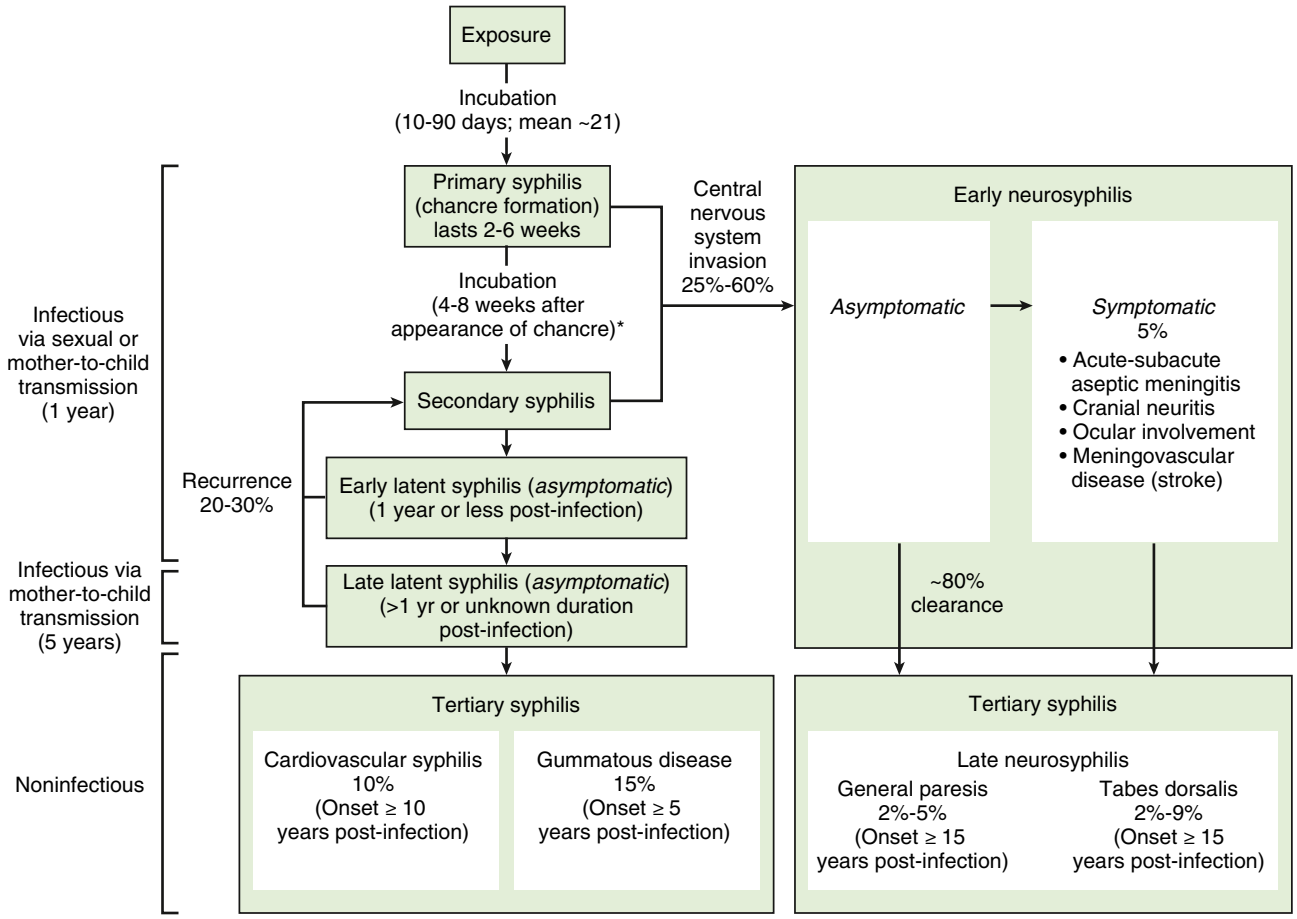


Fig. 264.3 Natural course of untreated syphilis. As of January 2018, the Centers for Disease Control and Prevention renamed early and late latent syphilis *early syphilis, nonprimary, nonsecondary* and *syphilis, unknown duration or late*, respectively. *HIV infection may modify the progression of syphilis; the chancre may coexist with the secondary syphilis stage, suggesting a more rapid progression to the secondary stage. *(Modified from Radolf JD, Tramont EC, Salazar JC. Syphilis [Treponema pallidum]. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 9th ed. Philadelphia: Elsevier; 2020: Fig. 237.5, p. 2874.)*

secondary syphilis (see Fig. 264.3). It is characterized by cerebrospinal fluid (CSF) pleocytosis and elevated protein level. Patients with meningitis might not show neurologic symptoms. Even without treatment, secondary infection becomes **latent** within 1-2 months after onset of rash. Relapses with secondary manifestations can occur during the first year of latency (the **early latent period**). **Late syphilis** follows and may be either asymptomatic **(late latent)** or symptomatic **(tertiary)**. Tertiary disease follows in about one-third of untreated cases and is marked by neurologic, cardiovascular, and **gummatous lesions** (nonsuppurative granulomas of the skin, bone, and liver resulting from the host cytotoxic T-cell response). In the preantibiotic era, neurologic manifestations of tertiary syphilis **(tabes dorsalis** and **paresis)** were common. The clinical course of syphilis and its tissue manifestations reflect the immunopathobiology of the host humoral and delayed-type hypersensitivity responses. A robust timeline of progression through the overlapping stages occurs in immunocompromised HIV patients

Congenital Infection

Untreated syphilis during pregnancy results in a vertical transmission rate approaching 100%, with profound effects on pregnancy outcome, reflecting obliterating endarteritis. Fetal or perinatal death occurs in 40% of affected infants. Premature delivery can also occur. Neonates can also be infected at delivery by contact with an active genital lesion. Most infected infants are asymptomatic at birth, including up to 40% with CSF seeding, and are identified only by routine prenatal screening. In the absence of treatment, symptoms develop within weeks or months. Among infants symptomatic at birth or in the first few months of life, manifestations have traditionally been divided into early and late stages. All stages of congenital syphilis are characterized by a vasculitis, with progression to necrosis and fibrosis. The **early signs** appear during the first 2 years of life, and the **late signs** appear gradually during the first 2 decades. Early manifestations vary and involve multiple organ systems, resulting from transplacental spirochetemia, and are analogous to the secondary stage of acquired syphilis. Hepatosplenomegaly, jaundice, and elevated liver enzymes are common. Histologically, liver involvement includes bile stasis, fibrosis, and extramedullary hematopoiesis. Lymphadenopathy tends to be diffuse and resolve spontaneously, although shotty nodes can persist.

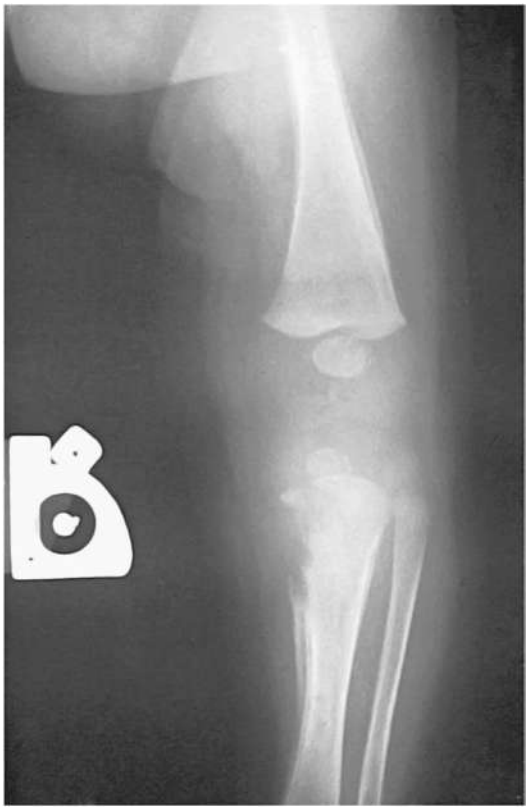


Fig. 264.5 Osteochondritis and periostitis in a newborn with congenital syphilis.

Coombs-negative hemolytic anemia is characteristic. Thrombocytopenia is often associated with platelet trapping in an enlarged spleen. Characteristic **osteochondritis** and **periostitis** (Fig. 264.5) and a mucocutaneous rash (Fig. 264.6A and B) manifesting with erythematous maculopapular or vesiculobullous lesions followed by desquamation involving the hands and feet (see Fig. 264.6C) are common. Mucous patches, persistent rhinitis **(snuffles)**, and condylomatous lesions (Fig. 264.7) are highly characteristic features of mucous membrane involvement containing abundant spirochetes. Blood and moist, open lesions from infants with congenital syphilis and children with acquired primary or secondary syphilis are infectious until 24 hours of appropriate treatment.

Bone involvement is common. Roentgenographic abnormalities include **Wimberger lines** (demineralization of the medial proximal tibial metaphysis); multiple sites of osteochondritis at the wrists, elbows, ankles, and knees; and periostitis of the long bones and, rarely, the skull. The osteochondritis is painful, often resulting in irritability and refusal to move the involved extremity **(pseudoparalysis of Parrot)**.

Congenital neurosyphilis is often asymptomatic in the neonatal period, although CSF abnormalities can occur even in asymptomatic infants. Failure to thrive, chorioretinitis, nephritis, and nephrotic syndrome can also be seen. Manifestations of renal involvement include hypertension, hematuria, proteinuria, hypoproteinemia, hypercholesterolemia, and hypocomplementemia, probably related to glomerular deposition of circulating immune complexes. Less common clinical manifestations of early congenital syphilis include gastroenteritis, peritonitis, pancreatitis, pneumonia, eye involvement (glaucoma and chorioretinitis), nonimmune hydrops, and testicular masses.

Late manifestations (children >2 years of age) are rarely seen in developed countries. These result primarily from chronic granulomatous inflammation of bone, teeth, and the central nervous system and are summarized in Table 264.1. Skeletal changes are caused by persistent or recurrent periostitis and associated thickening of the involved

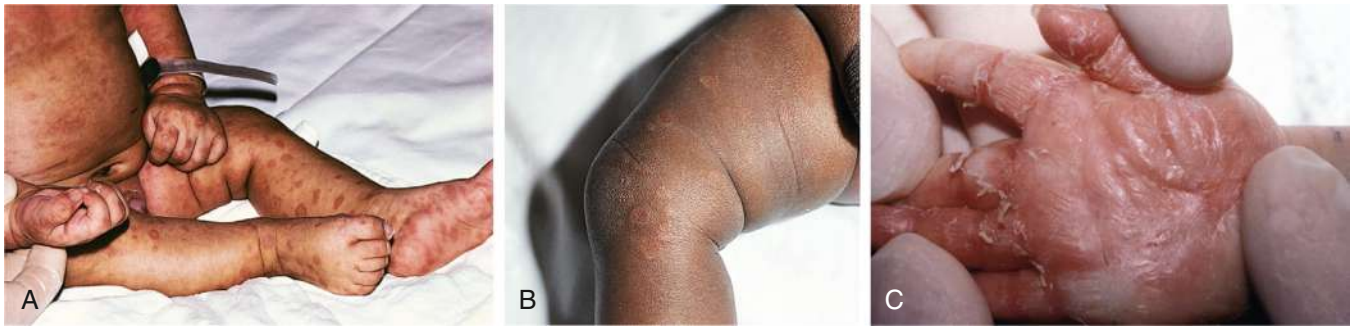


Fig. 264.6 A and B, Papulosquamous plaques in two infants with syphilis. C, Desquamation on the palm of a newborn's hand. *(A and B from Eichenfeld LF, Frieden IJ, Esterly NB, eds. Textbook of Neonatal Dermatology. Philadelphia: WB Saunders, 2001: p. 196; courtesy Dr. Patricia Treadwell.)*

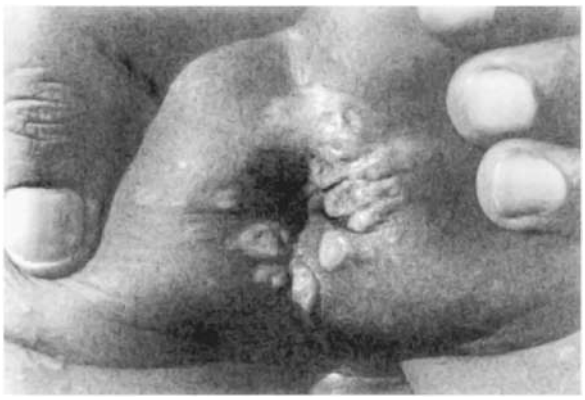


Fig. 264.7 Perianal condylomata lata. *(From Karthikeyan K, Thappa DM. Early congenital syphilis in the new millennium. Pediatr Dermatol. 2002;19:275–276.)*

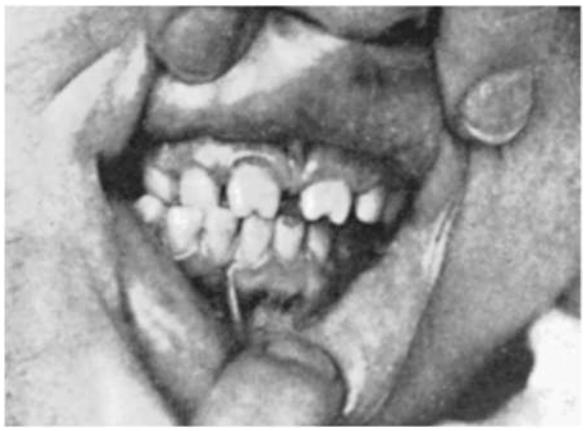


Fig. 264.8 Hutchinson teeth as a late manifestation of congenital syphilis.

Table 264.1 Late Manifestations of Congenital Syphilis

SYMPTOM/SIGN	DESCRIPTION/COMMENTS
Olympian brow	Bony prominence of the forehead caused by persistent or recurrent periostitis
Clavicular or Higoumenakis sign	Unilateral or bilateral thickening of the sternoclavicular third of the clavicle
Saber shins	Anterior bowing of the midportion of the tibia
Scaphoid scapula	Convexity along the medial border of the scapula
Hutchinson teeth	Peg-shaped upper central incisors; they erupt during sixth yr of life with abnormal enamel, resulting in a notch along the biting surface
Mulberry molars	Abnormal first lower (6 yr) molars characterized by small biting surface and excessive number of cusps
Saddle nose*	Depression of the nasal root, a result of syphilitic rhinitis destroying adjacent bone and cartilage
Rhagades	Linear scars that extend in a spokelike pattern from previous mucocutaneous fissures of the mouth, anus, and genitalia
Juvenile paresis	Latent meningovascular infection; it is rare and typically occurs during adolescence with behavioral changes, focal seizures, or loss of intellectual function
Juvenile tabes	Rare spinal cord involvement and cardiovascular involvement with aortitis
Hutchinson triad	Hutchinson teeth, interstitial keratitis, and eighth cranial nerve deafness
Clutton joint	Unilateral or bilateral painless joint swelling (usually involving the knees) from synovitis with sterile synovial fluid; spontaneous remission usually occurs after several weeks
Interstitial keratitis	Manifests with intense photophobia and lacrimation, followed within weeks or months by corneal opacification and complete blindness
Eighth cranial nerve deafness	May be unilateral or bilateral, appears at any age, manifests initially as vertigo and high-tone hearing loss, and progresses to permanent deafness

*A perforated nasal septum may be an associated abnormality.

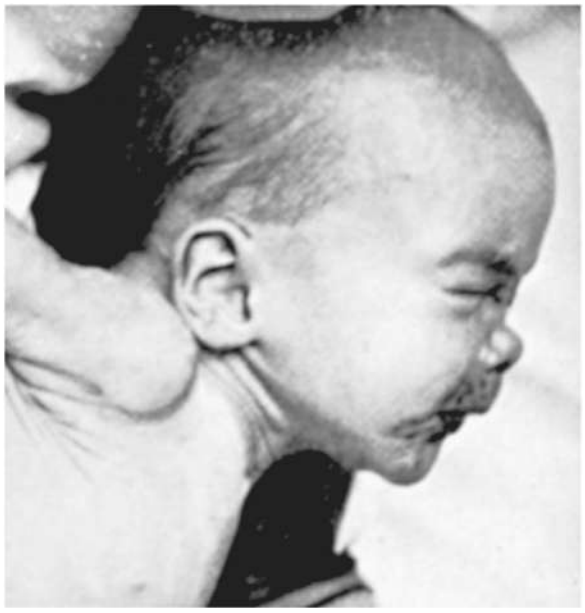


Fig. 264.9 Saddle nose in a newborn with congenital syphilis.

bone. Dental abnormalities, such as **Hutchinson teeth** (Fig. 264.8), are common. Defects in enamel formation lead to repeated caries and eventual tooth destruction. **Saddle nose** (Fig. 264.9) is a depression of the nasal root and may be associated with a perforated nasal septum.

Other late manifestations of congenital syphilis can manifest as hypersensitivity phenomena. These include unilateral or bilateral interstitial keratitis and the **Clutton joint** (see Table 264.1). Other common ocular manifestations include choroiditis, retinitis, vascular occlusion, and optic atrophy. Soft tissue gummas (identical to those of acquired disease) and paroxysmal cold hemoglobinuria are rare hypersensitivity phenomena.

DIAGNOSIS

Fundamental limitations of the currently available tests for syphilis are vexing, but results must always be interpreted in the context of patient history and physical examination. Physicians should remain aware of their local prevalence rates and treat presumptively when syphilis is suspected by clinical and epidemiologic data. The diagnosis of primary syphilis is confirmed when *T. pallidum* is demonstrated by dark-field microscopy or direct fluorescent antibody testing on specimens from skin lesions, placenta, or umbilical cord. Nucleic acid–based amplification assays, such as PCR, are also used in some specialized laboratories but are not commercially available. Despite the absence of a true

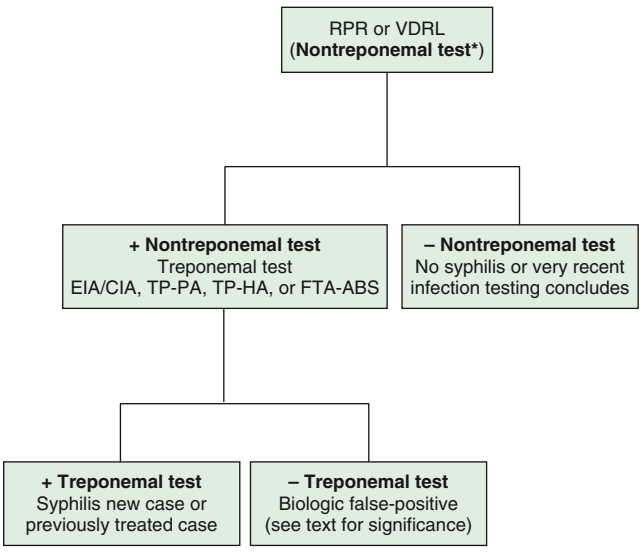
gold-standard serologic assay, serologic testing for syphilis remains the principal means for diagnosis and traditionally involves a two-step screening process with a nontreponemal test followed by a confirmatory treponemal test (Fig. 264.10A). Both test types are required for serologic-based diagnosis. False-negative tests may occur in early syphilis, and high-risk individuals may need repeat testing in 2-4 weeks if clinically indicated.

The **Venereal Disease Research Laboratory (VDRL)** and **rapid plasma reagin (RPR)** tests are sensitive **nontreponemal tests** that detect antibodies against phospholipid antigens on the treponeme surface that cross react with cardiolipin-lecithin-cholesterol antigens of damaged host cells. The quantitative results of these tests are helpful both in screening and in monitoring therapy. Titers increase with active disease, including treatment failure or reinfection, and decline with adequate treatment (Fig. 264.11). Nontreponemal tests usually become nonreactive within 1 year of adequate therapy for primary syphilis and within 2 years of adequate treatment for secondary disease. Fifteen to twenty percent of patients become **serofast** (nontreponemal titers persisting at low levels for long periods). In congenital infection, nontreponemal tests become nonreactive within a few months after adequate treatment. Certain conditions such as infectious mononucleosis and other viral infections, autoimmune diseases, and pregnancy can give false-positive VDRL results. False-positive results are less common with the use of purified cardiolipin-lecithin-cholesterol antigen. All pregnant women should be screened early in pregnancy and at delivery. All positive maternal (parental) serologic tests for syphilis, regardless of titer, necessitate thorough investigation. Antibody excess can give a false-negative reading unless the serum is diluted **(prozone effect) as the formation of the antigen-antibody lattice needed to visualize a positive flocculation test is disrupted.** False-negative results can also occur in early primary syphilis, in latent syphilis of long duration, and in late congenital syphilis.

Treponemal tests traditionally are used to confirm diagnosis and measure specific *T. pallidum* antibodies (immunoglobulin [Ig] G, IgM, and IgA), which appear earlier than nontreponemal antibodies. Treponemal tests include the *T. pallidum* particle agglutination test (TP-PA, which is the preferred treponemal test) and the fluorescent treponemal antibody absorption test (FTA-ABS). Treponemal antibody titers become positive soon after initial infection and usually remain positive for life, even with adequate therapy (see Fig. 264.11). These antibody titers do not correlate with disease activity. Traditionally they are useful for diagnosis of a first episode of syphilis and for distinguishing false-positive results of nontreponemal antibody tests but cannot accurately identify length of time of infection, response to therapy, or reinfection.

There is limited cross reactivity of treponemal antibody tests with other spirochetes, including the causative organisms of Lyme disease *(Borrelia burgdorferi),* yaws, endemic syphilis, and pinta. Only venereal syphilis and Lyme disease are found in the United States. Nontreponemal tests (VDRL, RPR) are uniformly nonreactive in Lyme disease.

Various enzyme-linked, chemiluminescence, and multiplex flow immunoassays to detect treponemal IgG and IgM have been developed. These assays have increased sensitivity and are amenable to automation and high-volume use. Rapid point-of-care tests are available to allow quality screening programs in resource-limited settings where the World Health Organization otherwise relies on syndromic management of STIs and patients are treated for all likely causes of their constellation of signs and symptoms. In the United States, use of immunoassays has confounded screening because it switches the traditional algorithm: the treponemal-specific testing is done before the nontreponemal testing. Because the former remain positive for life, clinical and epidemiologic data are required to provide guidelines to distinguish cured disease, early syphilis, untreated late latent disease, and true false-positive tests. Benefits of **reverse screening** are



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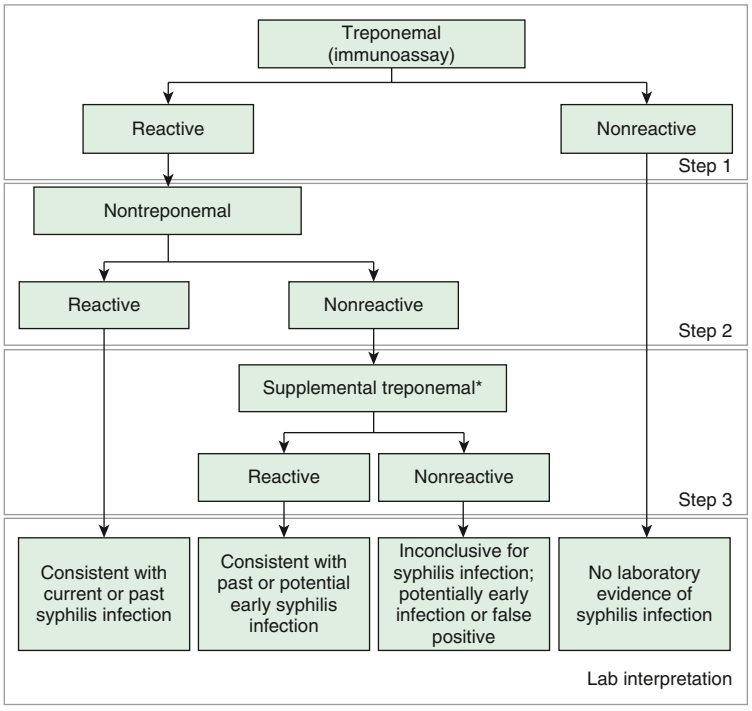
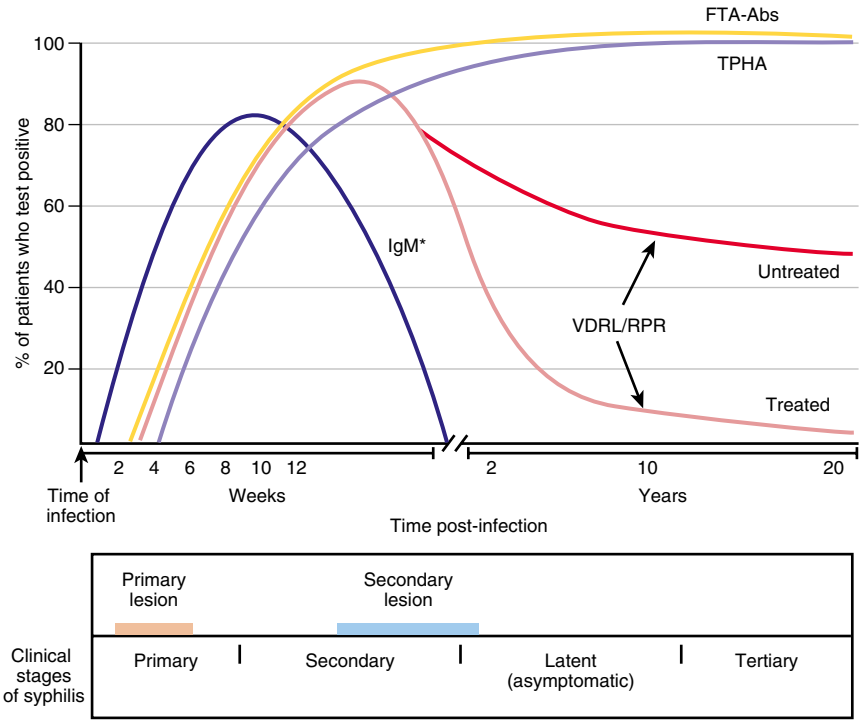


**The supplemental treponemal test should use a unique platform and/or antigen, different from the first treponemal test.*

B

Fig. 264.10 A, Traditional laboratory testing algorithm for syphilis. B, Suggested alternative testing algorithm. EIA/CIA, Enzyme immunoassay/chemiluminescence immunoassay; FTA-ABS, fluorescent treponemal antibody absorption; *RPR*, rapid plasma reagin; TP-HA, *Treponema pallidum* hemagglutination; TP-PA, *Treponema pallidum* particle agglutination; VDRL, Venereal Disease Research Laboratory. *If nontreponemal test is positive qualitatively, a titer is then quantitated. *(A based on data from Workowski KA, Berman S; Centers for Diseases Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep 2010;59[RR-12]:1–110. pp. 26–29.)*



*IgM by ELISA or FTA-ABS 195 or immunoblot.

Fig. 264.11 Common patterns of serologic reactivity in syphilis patients. *FTA-Abs*, fluorescent treponemal antibody absorption (test); *RPR*, rapid plasma reagin (test); *TPHA*, *Treponema pallidum* hemagglutination assay; *VDRL*, Venereal Disease Research Laboratory (test). IgM by immunoassay. *(From Peeling R, Ye H. Diagnostic tools for preventing and managing maternal and congenital syphilis: an overview. Bull World Health Organ. 2004;82[6]:439–446.)*

increased detection of transmissible early syphilis and of late latent disease to afford monitoring for tertiary disease. Although the CDC and American Academy of Pediatrics (AAP) Red Book continue to recommend the traditional screen ("conventional diagnostic approach"; see Fig. 264.10A), they have provided guidelines for interpretation of the reverse screening algorithm (see Fig. 264.10B). Reverse screening may yield false-positive results, particularly in low-prevalence populations where testing results should be interpreted with caution, as false-positive testing in children may have serious adverse consequences. If reverse testing yields a positive treponemal result but a negative nontreponemal result, a second treponemal test targeting a different treponemal antigen is needed for confirmation. Interpretation of nontreponemal and treponemal serologic tests in the newborn can be confounded by maternal IgG antibodies transferred to the fetus. Passively acquired antibody is suggested by a neonatal titer at least fourfold (i.e., a two-tube dilution) less than the maternal (parental) titer. This conclusion can be verified by a gradual decline in antibody in the infant, usually becoming undetectable by 3-6 months of age. Conversely, an infant nontreponemal titer fourfold higher than the mother's at the time of delivery or a persistent or rising nontreponemal titer in the infant suggests congenital infection.

Neurologic involvement can occur at any stage of syphilis. The diagnosis of neurosyphilis remains difficult but is often established by demonstrating pleocytosis and increased protein in the CSF and a positive CSF VDRL test along with neurologic symptoms. The CSF VDRL test is specific but relatively insensitive (22–69%) for neurosyphilis. CSF PCR and IgM immunoblot tests are being studied but not currently recommended for use in making the diagnosis of neurosyphilis.

Dark-field or direct fluorescent antibody microscopy of scrapings from primary lesions or congenital or secondary lesions can reveal *T. pallidum,* often before serology becomes positive, but these modalities are usually not available in clinical practice. Since 2015 different methods of PCR, including routine PCR, nested PCR, reverse-transcriptase PCR, and quantitative PCR targeting different DNA gene sequences, have been used by many laboratories as methods to detect *T. pallidum* in primary disease. However, there are currently no commercially available test kits, and each test must be validated for use in each laboratory. Furthermore, these tests are not useful for asymptomatic patients, and interpretation may be complicated by the fact that they amplify both dead and living organisms. Placental examination by gross and microscopic techniques can be useful in the diagnosis of congenital syphilis. The disproportionately large placentas are characterized histologically by focal proliferative villitis, endovascular and perivascular arteritis, and focal or diffuse immaturity of placental villi.

Congenital Syphilis

A diagnosis of congenital syphilis requires a thorough review of maternal (parental) history of syphilis treatment preconception and the testing, treatment, and dynamics of response during the current pregnancy. Regardless of maternal (parental) treatment and the presence/absence of symptoms in the infant, proactive evaluation and treatment of exposed neonates is critical (Fig. 264.12 and Table 264.2). Symptomatic infants should be thoroughly evaluated and treated. Figure 264.12 and Table 264.3 describe the guidelines for evaluating and managing asymptomatic infants who are considered at risk for congenital syphilis because the maternal (parental) nontreponemal and treponemal serology is positive. Internationally adopted, refugee, and immigrant children should also be screened, regardless of history or report of treatment. Diagnostic testing risk-stratifies infants to probability of congenital infection: proven or highly probable congenital syphilis, possible congenital syphilis, congenital syphilis less likely, or congenital syphilis unlikely.

A diagnosis of neurosyphilis in the newborn with syphilitic infection is confounded by poor sensitivity of the CSF VDRL test in this age-group and lack of CSF abnormalities. A positive CSF VDRL test in a newborn warrants treatment for neurosyphilis, even though it might reflect passive transfer of antibodies from serum to CSF. It is now accepted that all infants with a presumptive diagnosis of congenital syphilis should be treated with regimens effective for neurosyphilis because central nervous system involvement cannot be reliably excluded. A diagnosis of syphilis beyond early infancy should lead to consideration of possible child abuse.

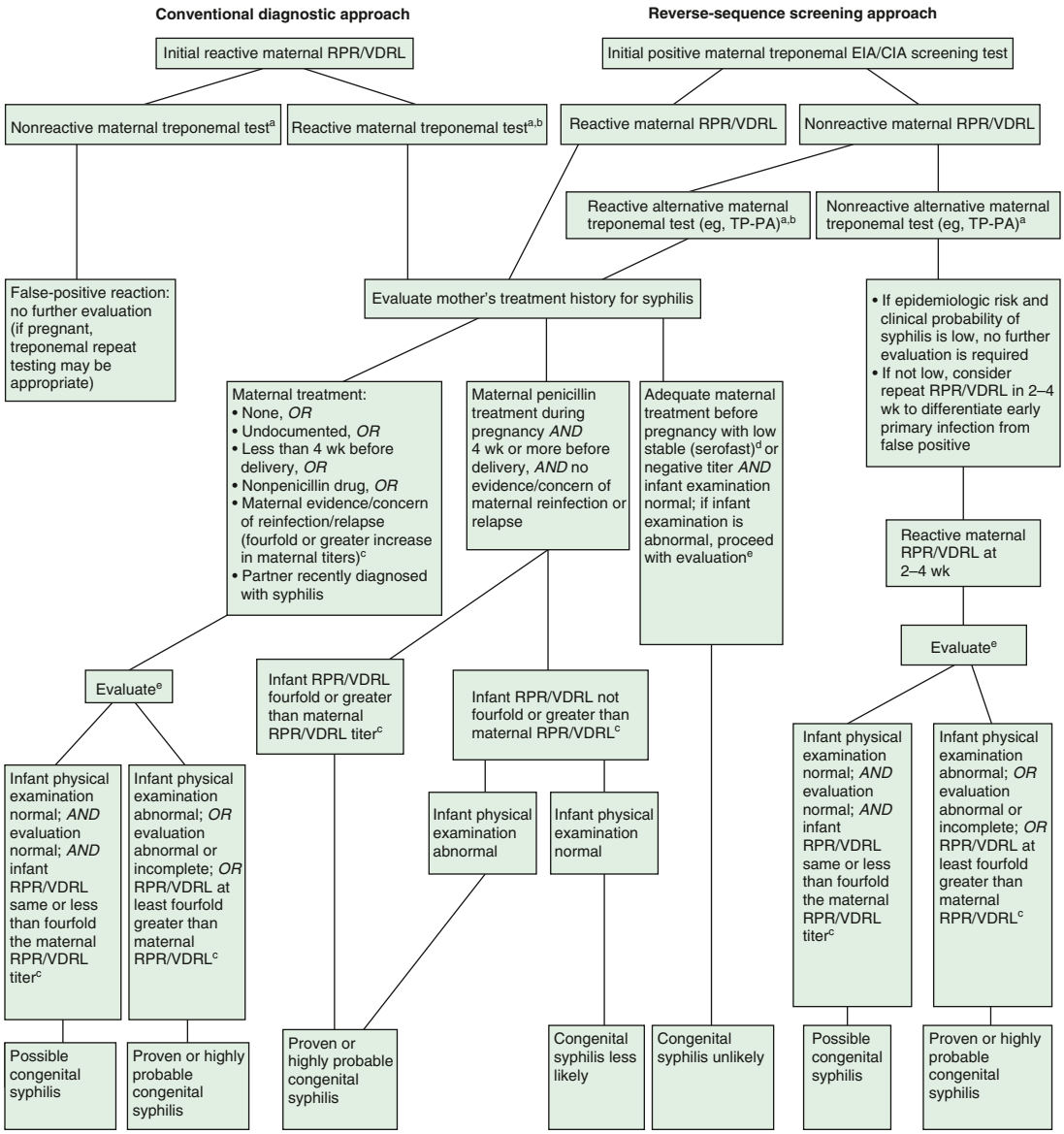


Fig. 264.12 Algorithm for the diagnostic approach of infants born to mothers (birthing parents) with reactive serologic tests for syphilis. [a]*Treponema pallidum* particle agglutination (TP-PA) (which is the preferred treponemal test) or fluorescent treponemal antibody absorption (FTA-ABS). [b]Test for human immunodeficiency virus (HIV) antibody. Infants of HIV-infected mothers do not require different evaluation or treatment for syphilis. [c]A fourfold change in titer is the same as a change of two dilutions. For example, a titer of 1:64 is fourfold greater than a titer of 1:16, and a titer of 1:4 is fourfold lower than a titer of 1:16. When comparing titers, the same type of nontreponemal test should be used (e.g., if the initial test was an RPR, the follow-up test should also be an RPR). [d]Stable VDRL titers 1:2 or less or RPR 1:4 or less beyond 1 year after successful treatment are considered low serofast. [e]Complete blood cell (CBC) and platelet count; cerebrospinal fluid (CSF) examination for cell count, protein, and quantitative VDRL; other tests as clinically indicated (e.g., chest radiographs, long-bone radiographs, eye examination, liver function tests, neuroimaging, and auditory brainstem response). For neonates, pathologic examination of the placenta or umbilical cord with specific fluorescent antitreponemal antibody staining, if possible. RPR, Rapid plasma regain; VDRL, Venereal Disease Research Laboratory. *(From American Academy of Pediatrics. Syphilis. In Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. Red Book: 2021–2024 Report of the Committee on Infectious Diseases, 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021: Fig. 3.15, p. 734.)*

For infants with proven or highly probable disease or abnormal physical findings, complete evaluation, including serologic tests (RPR or VDRL), complete blood count with differential and platelet count, liver function tests, long-bone radiographs, ophthalmology examination, auditory brainstem response, and other tests as indicated, should be performed. If possible, pathologic examination of the placenta and/or umbilical cord with specific fluorescent antitreponemal antibody staining is recommend by the AAP. For infants with a positive VDRL or RPR test result and normal physical examination whose mothers were inadequately treated, further evaluation is not necessary if 10 days of parenteral therapy are administered.

TREATMENT

The goals of early detection and treatment include treatment of current infection and prevention of both late-stage disease and sexual or vertical transmission. *T. pallidum* remains extremely sensitive to penicillin, with no evidence of emerging penicillin resistance, and thus penicillin remains the treatment drug of choice (additional information available in Table 264.4 and at http://www.cdc.gov/std/treatment for patients over 1 month old). Parenteral penicillin G is the only documented effective treatment for congenital syphilis, syphilis during pregnancy, and neurosyphilis and is recommended for treatment of syphilis in persons with HIV. Aqueous crystalline penicillin G is preferred over

Table 264.2 Clues that Suggest a Diagnosis of Congenital Syphilis

EPIDEMIOLOGIC BACKGROUND	CLINICAL FINDINGS
Untreated early syphilis in the mother	Osteochondritis, periostitis
Untreated latent syphilis in the mother	Snuffles, hemorrhagic or mucopurulent rhinitis
An untreated mother who has contact with a known patient with syphilis during pregnancy	Condylomata lata
Mother treated less than 30 days before delivery	Bullous lesions, palmar or plantar rash
Mother treated for syphilis during pregnancy with a drug other than penicillin	Mucous patches
Mother treated for syphilis during pregnancy without follow-up to demonstrate fourfold decrease in titer	Hepatomegaly, splenomegaly
Mother co-infected with HIV	Jaundice, hepatitis
	Nonimmune hydrops fetalis
	Generalized lymphadenopathy
	Central nervous system signs; elevated cell count or protein in cerebrospinal fluid
	Hemolytic anemia, diffuse intravascular coagulation, thrombocytopenia
	Pneumonitis
	Nephrotic syndrome
	Placental villitis or vasculitis (unexplained enlarged placenta)
	Intrauterine growth restriction

Arranged in decreasing order of confidence of diagnosis.
Modified from Remington JS, Klein JO, Wilson CB, et al., eds. *Infectious Diseases of the Fetus and Newborn Infant*, 6th ed. Philadelphia: WB Saunders; 2006:556.

Table 264.3 Confirmed Proven or Highly Probable Congenital Syphilis

DIAGNOSIS AND TREATMENT

Any neonate with:

- An abnormal physical examination that is consistent with congenital syphilis;
- A serum quantitative nontreponemal serologic titer that is fourfold (or greater) higher than the mother's titer at delivery (e.g., maternal titer = 1:2, neonatal titer ≥1:8 or maternal titer = 1:8, neonatal titer ≥1:32); or
- A positive dark-field test or PCR of placenta, cord, lesions, or body fluids or a positive silver stain of the placenta or cord.

Recommended evaluation:

- CSF analysis for VDRL, cell count, and protein
- Complete blood count (CBC) and differential and platelet count
- Long-bone radiographs
- Other tests as clinically indicated (e.g., chest radiograph, liver function tests, neuroimaging, ophthalmologic examination, and auditory brainstem response)

Recommended regimens, confirmed or highly probable congenital syphilis:

Aqueous crystalline penicillin G 100,000-150,000 units/kg body weight/day, administered as 50,000 units/kg body weight/dose by IV every 12 hr during the first 7 days of life and every 8 hr thereafter for a total of 10 days*

OR

Procaine penicillin G 50,000 units/kg body weight/dose IM in a single daily dose for 10 days

If >1 day of therapy is missed, the entire course should be restarted. Data are insufficient regarding use of other antimicrobial agents (e.g., ampicillin). When possible, a full 10-day course of penicillin is preferred, even if ampicillin was initially provided for possible sepsis. Using agents other than penicillin requires close serologic follow-up for assessing therapy adequacy.

*Preferred therapy per the 2021-2024 AAP Red Book
From Centers for Disease Control and Prevention. Congenital syphilis. Sexually Transmitted Diseases and Treatment Guidelines, 2021. Scenario 1. https://www.cdc.gov/std/treatment-guidelines/congenital-syphilis.htm.

procaine penicillin, because it better achieves and sustains the minimum concentration of 0.018 μg/mL (0.03 units/mL) needed for 7-10 days to achieve the prolonged treponemicidal levels required for the long dividing time of *T. pallidum*.

In 2023, due to manufacturing limitations and increased demand, the United States entered a period of penicillin G shortage, requiring prioritization of pregnant persons to receive this antibiotic, as no other medication is proven to prevent vertical transmission. Penicillin G is often preferred for IM injection in treatment of other syphilis infections as an approach to ensure adherence to therapy, and thus the shortage may lead to increased transmission.

For proven or highly probable congenital syphilis, procaine penicillin G (50,000 U/kg IM daily × 10 days) should only be used if access to IV penicillin G is limited (such as in a low-resource setting) or if IV access cannot be obtained. For infants with possible congenital syphilis, aqueous penicillin G (50,000 U/kg IV every 12 hours when 1 wk or younger, then every 8 hours for infants older than 1 wk, for a total of 10 days of therapy) is preferred, though procaine penicillin G (50,000 U/kg IM daily x 10 days) may be given. Benzathine penicillin G (50,000 U/kg IM) as a single dose can be considered but only if all components of the evaluation are normal and follow-up is certain. Infants in whom congenital syphilis is less likely may be treated with benzathine penicillin G (50,000 U/kg IM) as a single dose. If no treatment is given, infants must be closely followed until the nontreponemal test becomes nonreactive. If any portion of the assessment for congenital syphilis is abnormal or not obtained, or the CSF studies are uninterpretable, or outpatient follow-up cannot be assured, treatment with procaine penicillin G is preferred. Patients with persistent or increasing titers require repeat evaluation and treatment with a 10-day course of parenteral penicillin G, even if previously treated.

Although nonpenicillin regimens are available to the penicillin-allergic patient, desensitization followed by standard penicillin therapy is the most reliable strategy. Success of treatment also depends on the integrity of the host immune response. A transient acute systemic febrile reaction called the **Jarisch-Herxheimer reaction** (caused by massive release of endotoxin-like antigens during bacterial lysis) occurs in 15–20% of patients with acquired or congenital syphilis treated with penicillin. It is not an indication for discontinuing penicillin therapy. Use of other agents for congenital syphilis should only be done in consultation with a pediatric infectious diseases specialist and requires close clinical and serologic follow-up.

Acquired Syphilis

Primary, secondary, and early latent disease is treated with a single dose of benzathine penicillin G (50,000 units/kg IM, maximum 2.4 million units, in a single dose). Persons with late latent or tertiary disease require three doses at 1-week intervals. Nonpregnant penicillin-allergic patients without neurosyphilis may be treated with either doxycycline (4.4 mg/kg divided in 2 doses, max 200 mg per day, orally twice a day for 14 days) or tetracycline (25-50 mg/kg divided in 4 doses, max 2 g per day, orally for 14 days, for age ≥8 years). Emerging *azalide* and *macrolide resistance* has been documented throughout the United States (a 23S ribosomal NA [rRNA] point mutation at position 2058) and, more recently, worldwide (a 23S rRNA point mutation at position 2059), compromising the effective use of these antibiotics. Careful serologic follow-up is always necessary. Documentation of serologic cure is an essential part of syphilis treatment. Less than a fourfold decline in titer reflects treatment failure.

The CDC recommends that all persons with syphilis be tested for HIV and other STIs. Patients diagnosed with syphilis with a negative HIV test should undergo repeat testing 3 months later. Diagnosis of syphilis in high-risk individuals, particularly men or transgender women who have sex with men, is associated with increased risk of

Table 264.4 Recommended Treatment for Syphilis in People Older Than 1 Mo

STATUS	CHILDREN	ADULTS
Congenital syphilis in patients >1 mo old; OR children >2 mo with late and previously untreated congenital syphilis	Aqueous crystalline penicillin G 200,000-300,000 U/kg/day IV administered as 50,000 U/kg, every 4-6 hr for 10 days*	
Primary, secondary, and early latent syphilis†	Penicillin G benzathine‡ 50,000 U/kg IM, up to the adult dose of 2.4 million U in a single dose *If allergic to penicillin and not pregnant,* Doxycycline 4.4 mg/kg divided in 2 doses, max 200 mg per day, orally twice a day for 14 days (for ages ≥8 yr) *OR* Tetracycline 25-50 mg/kg divided in 4 doses, max 2 g per day, orally for 14 days (for ages ≥8 yr)	Penicillin G benzathine 2.4 million U IM in a single dose *OR* *If allergic to penicillin and not pregnant,* doxycycline 100 mg orally twice a day for 14 days *OR* Tetracycline 500 mg orally 4 times/day for 14 days
Late latent syphilis§	Penicillin G benzathine 50,000 U/kg IM, up to the adult dose of 2.4 million U, administered as 3 single doses at 1-wk intervals (total 150,000 U/kg, up to the adult dose of 7.2 million U) *If allergic to penicillin and not pregnant,* Doxycycline 4.4 mg/kg divided in 2 doses, max 200 mg per day, orally twice a day for 4 weeks (for ages ≥8 yr) *OR* Tetracycline 25-50 mg/kg divided in 4 doses, max 2 g per day, orally for 4 weeks (for ages ≥8 yr)	Penicillin G benzathine 7.2 million U total, administered as 3 doses of 2.4 million U IM, each at 1-wk intervals; pregnant women who have delays in any dose of therapy beyond 9 days between doses should repeat the full course of therapy *OR* *If allergic to penicillin and not pregnant,* Doxycycline 100 mg orally twice a day for 4 wk *OR* Tetracycline 500 mg orally, 4 times/day for 4 wk
Tertiary	—	Penicillin G benzathine 7.2 million U total, administered as 3 doses of 2.4 million U IM at 1-wk intervals *If allergic to penicillin and not pregnant, consult an infectious diseases expert*
Neurosyphilis‖	Aqueous crystalline penicillin G 200,000-300,000 U/kg/day IV every 4-6 hr for 10-14 days, in doses not to exceed the adult dose	Aqueous crystalline penicillin G 18-24 million U per day, administered as 3-4 million U IV every 4 hr for 10-14 days¶ *OR* Penicillin G procaine‡ 2.4 million U IM once daily PLUS probenecid 500 mg orally 4 times/day, both for 10-14 days¶

*If the patient has no clinical manifestations of disease, the cerebrospinal fluid (CSF) examination is normal, and the CSF Venereal Disease Research Laboratory (VDRL) test result is negative, some experts would treat with up to 3 weekly doses of penicillin G benzathine 50,000 U/kg IM. Some experts also suggest giving these patients a single dose of penicillin G benzathine 50,000 U/kg IM after the 10-day course of intravenous aqueous penicillin.
†Early latent syphilis is defined as being acquired within the preceding year.
‡Penicillin G benzathine and penicillin G procaine are approved for intramuscular administration only.
§Late latent syphilis is defined as syphilis beyond 1 year's duration.
‖Patients who are allergic to penicillin should be desensitized.
¶Some experts administer penicillin G benzathine 2.4 million U IM once per week for up to 3 weeks after completion of these neurosyphilis treatment regimens.
IV, Intravenously; *IM*, intramuscularly.
From American Academy of Pediatrics. Syphilis. In: Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2021–2024 Report of the Committee on Infectious Diseases*, 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021: Table 3.67, pp. 741–742.

subsequent HIV acquisition, and preexposure prophylaxis (PrEP) should be considered. Patients co-infected with HIV are at increased risk for neurologic complications and higher rates of treatment failure. CDC guidelines recommend the same treatment of primary and secondary syphilis as for patients who are not infected with HIV, but some experts recommend three weekly doses of benzathine penicillin G. HIV-infected patients with late latent syphilis or latent syphilis of unknown duration should have a CSF evaluation for neurosyphilis before treatment.

Sex partners of infected persons of any stage should be evaluated and treated. Persons exposed for 90 days or less preceding diagnosis in a sex partner should be treated presumptively even if seronegative. Persons exposed for more than 90 days before the diagnosis in a sex partner should be treated if seropositive or if serologic tests are not available. Follow-up serology should be performed on treated patients to establish adequacy of therapy, and all patients should be tested for other sexually transmitted diseases, including HIV. Children with acquired primary, secondary, or latent syphilis should undergo evaluation for possible sexual assault or abuse.

Syphilis in Pregnancy

When clinical or serologic findings suggest active infection or when the diagnosis of active syphilis cannot be excluded with certainty, treatment is indicated. The goals of treatment of the pregnant person include eradication of maternal (parental) disease, prevention of parent-to-child transmission, and treatment of fetal infection. Patients should be treated immediately with the penicillin regimen appropriate for the pregnant person's stage of syphilis. Those who have been

adequately treated in the past do not require additional therapy unless quantitative serology suggests evidence of reinfection **(fourfold elevation in titer)**.

Penicillin G is the only agent known to be effective for treating fetal infection and for prevention of congenital infection. Pregnant patients who are allergic to penicillin should be desensitized and treated with penicillin. If doses for late latent syphilis are delayed beyond 9 days from the prior dose, the full course of therapy needs to be repeated. Additional therapy may be considered for pregnant persons with primary, secondary, or early latent syphilis or when syphilis is diagnosed during the second half of pregnancy and sonographic evidence of fetal or placental syphilis is noted. In these cases, a second dose of benzathine penicillin G (2.4 million units IM given 1 week after the initial dose) may decrease the risk of vertical transmission. Jarisch-Herxheimer reaction in the second half of pregnancy may induce premature labor or fetal distress, and patients with reactions should seek obstetric attention promptly.

Congenital Syphilis

Adequate maternal (parental) treatment at least 30 days before delivery is likely to prevent congenital syphilis. All infants born to pregnant persons with syphilis should be followed until nontreponemal serology is negative. The infant should be treated if there is any uncertainty about the adequacy of maternal (parental) treatment. The goal of infant treatment is prevention of organ damage, skeletal deformity, and developmental delay. Any infant at risk of congenital syphilis should be evaluated for HIV.

Congenital syphilis is treated in infants up to 1 month of age with aqueous penicillin G (100,000-150,000 units/kg/24 hr IV divided every 12 hours for the first week of life and every 8 hours thereafter) or procaine penicillin G (50,000 units/kg IM once daily) given for 10 days. Both penicillin regimens are recognized as adequate therapy for congenital syphilis, but higher concentrations of penicillin are achieved in the CSF of infants treated with intravenous aqueous penicillin G than in those treated with intramuscular procaine penicillin. Treated infants should be closely monitored at 2-, 4-, 6-, and 12-month well child care visits and serologic nontreponemal titers repeated every 2-3 months until nonreactive. Titers generally decrease by 3 months of age and become nonreactive by 6 months of age if adequately treated or if antibody was merely transplacentally acquired without infection. Infants diagnosed and treated for congenital syphilis after 1 month of age should be treated with aqueous crystalline penicillin G 200,000-300,000 U/kg/day IV administered as 50,000 U/kg, every 4-6 hr for 10 days (Table 264.4). Nontreponemal titers may resolve more slowly if the patient was treated after 1 month old. Increasing or persistent stable titers 6-12 months after initial treatment suggest possible ongoing infection, and repeat evaluation, including CSF, is indicated. Repeat treatment (penicillin G IV for 10 days) may be indicated. Infants with a negative nontreponemal test born to a person seroreactive at the time of delivery could have incubating congenital infection and so should be retested at 3 months. Infants with initial abnormal CSF studies only require repeat lumbar puncture if they have persistent nontreponemal serologic titers at 6-12 months old. If CSF has a persistent positive VDRL or abnormal indices not attributable to another ongoing illness, retreatment is indicated after 2 years of follow-up. At age 2 previously treated infants should receive a full developmental assessment. In a very low-risk neonate who is asymptomatic and whose mother was treated appropriately, without evidence of relapse or reinfection but with a low and stable VDRL titer (serofast), no evaluation is necessary. Some specialists, however, would treat such an infant with a single dose of benzathine penicillin G 50,000 units/kg IM.

PREVENTION

Syphilis, including congenital syphilis, is a reportable disease in all 50 states and the District of Columbia. Testing is indicated at any time for persons with suspicious lesions, a history of recent sexual exposure to a person with syphilis, or diagnosis of another sexually transmitted infection, including HIV infection. Screening for syphilis in asymptomatic, nonpregnant persons at increased risk for infection has received an A recommendation from the US Preventive Services Task Force (USPSTF) as providing significant benefit. Direct-to-consumer test services for STIs (or "home tests") have become more acceptable following consumer experience with similar testing during the COVID-19 pandemic, and best practices for implementation are an area of intense research. As of late 2023, the US CDC had posted request for comment on proposed guidelines for the use of doxycycline as post-exposure prophylaxis for bacterial STI prevention, including syphilis, to be offered to MSM and transgender women with a history of at least one bacterial STI in the last 12 months; insufficient evidence is currently available to give recommendations for other groups, including children, cisgender women or heterosexual men, transgender men, or other queer and nonbinary individuals. The resurgence of syphilis compels clinicians to remain cognizant of its protean manifestations to avoid missed or late diagnosis. Timely treatment lessens risk of community spread. Despite the genome sequencing of *T. pallidum* in 1998, vaccine development remains elusive, confounded by the treponeme's ability to evade the immune system.

Congenital Syphilis

Congenital syphilis is a preventable disease, a sentinel event indicating multiple missed opportunities. Primary prevention is tied to prevention of syphilis in women of childbearing age, and secondary prevention with early diagnosis and prompt treatment of women and their partners. Access to and use of comprehensive prenatal care is key, with careful history taking (including interim sexual partners) at each visit. Routine prenatal screening for syphilis remains the most important factor in identifying infants at risk for developing congenital syphilis. Screening all women at the beginning of prenatal care is an evidence-based standard of care and legally required in all states. In pregnant women without optimal prenatal care, serologic screening for syphilis should be performed at the time pregnancy is diagnosed. Any person who is delivered of a stillborn infant at 20 weeks or fewer of gestation should be tested for syphilis. In communities and populations with a high prevalence of syphilis and in patients at high risk (pregnant persons with a history of incarceration, drug use, or multiple or concurrent partners), testing should be performed at least two additional times: at the beginning of the third trimester (28 weeks) and at delivery. Some states mandate repeat testing at delivery for all pregnant persons, underscoring the importance of preventive screening. Those at high risk for syphilis should be screened even more frequently, either monthly or, pragmatically (in the case of inconsistent prenatal care), at every medical encounter because they can have repeat infections during pregnancy or reinfection late in pregnancy. Follow-up serologic testing of all treated pregnant persons should be done after treatment to document titer decline, relapse, or reinfection.

No newborn should leave the hospital without the mother's (parent's) syphilis status having been determined at least once during pregnancy or at delivery. In states conducting newborn screening for syphilis, both the parent's and infant's serologic results should be known before discharge. Appropriate follow-up for the treated or exposed infant should be arranged. In addition, all previously uninvestigated infants of an infected mother should be screened. Strong linkages between clinicians and public health practitioners remain essential for comprehensive prevention of acquired and congenital syphilis.

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Chapter 265

Nonvenereal Treponemal Infections

Stephen K. Obaro and H. Dele Davies

Nonvenereal treponemal infections—yaws, bejel (endemic syphilis), and pinta—are caused by different subspecies of *Treponema pallidum* and occur in tropical and subtropical areas. The causative agents of nonvenereal treponematoses—*T. pallidum pertenue, T. pallidum* subspecies *endemicum,* and *Treponema carateum*—cannot be distinguished from *T. pallidum* subspecies *pallidum* by morphologic or serologic tests.

In general, nonvenereal treponematoses have prominent cutaneous manifestations and relapsing courses, as in venereal syphilis, but they are not found in urban centers, they are not sexually transmitted, and they are not congenitally acquired. Transmission is primarily through body contact, poor hygiene, crowded conditions, and poor access to healthcare. Children also serve as the primary reservoirs for these organisms, spreading infection via skin-to-skin and skin–to–mucous membrane contact, and possibly via fomites as well.

Penicillin remains the treatment of choice for syphilis and nonvenereal treponemal infections.

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265.1 Yaws (*Treponema pertenue*)

Stephen K. Obaro and H. Dele Davies

Yaws is the most prevalent nonvenereal treponematosis. The causative agent, *Treponema pertenue,* bears very close genomic resemblance to *T. pallidum* subspecies *pallidum*. The overall sequence identity between the genomes of *T. pallidum pertenue* and *T. pallidum* subspecies *pallidum is* 99.8%. Yaws is a contagious, chronic, relapsing infection involving the skin and bony structures caused by the spirochete *T. pertenue,* which is identical to *T. pallidum* microscopically and serologically. This disease occurs in tropical regions with heavy rainfall and annual temperatures ≥27°C (80°F). Almost all cases occur in children in tropical and subtropical countries. It is also referred to as "framboesia," "pian," "parangi," and "bouba." A high percentage of the population is infected in endemic areas.

T. pertenue is transmitted by direct contact from an infected lesion through a skin abrasion or laceration. Transmission is facilitated by overcrowding and poor personal hygiene in the rainforest areas of the world. Yaws predominantly affects children, with approximately 75% of cases being reported in children younger than 15 years of age. This population also constitutes the reservoir for disease transmission. The initial papular lesion, which constitutes **primary yaws**, also described as the **mother yaw,** occurs 2-8 weeks after inoculation. This lesion typically involves the buttocks or lower extremities. The papule develops into a raised, raspberry-like papilloma and is often accompanied by regional lymphadenopathy. The skin pathology is similar to that of venereal syphilis, consisting of epidermal hyperplasia and papillomatosis (Fig. 265.1). Healing of the mother yaw leaves a hypopigmented scar. The **secondary-stage** lesions can erupt anywhere on the body before or after the healing of the mother yaw and may be accompanied by lymphadenopathy, anorexia, and malaise. Multiple cutaneous lesions (daughter yaws, pianomas, or framboesias) appear, spread diffusely, ulcerate, and are covered by exudates containing treponemes. Secondary lesions heal without scarring. Recurrent lesions are common within 5 years after the primary lesion.

The lesions are often associated with bone pain resulting from underlying periostitis or osteomyelitis, especially of the fingers, nose, and tibia. The initial period of clinical activity is followed by a 5- to 10-year period of latency. The appearance of tertiary-stage lesions develops in approximately 10% of infected patients, with onset typically at puberty, with solitary and destructive lesions. These lesions occur as painful papillomas on the hands and feet, gummatous skin ulcerations, or osteitis. Bony destruction and deformity, juxtaarticular nodules, depigmentation, and painful

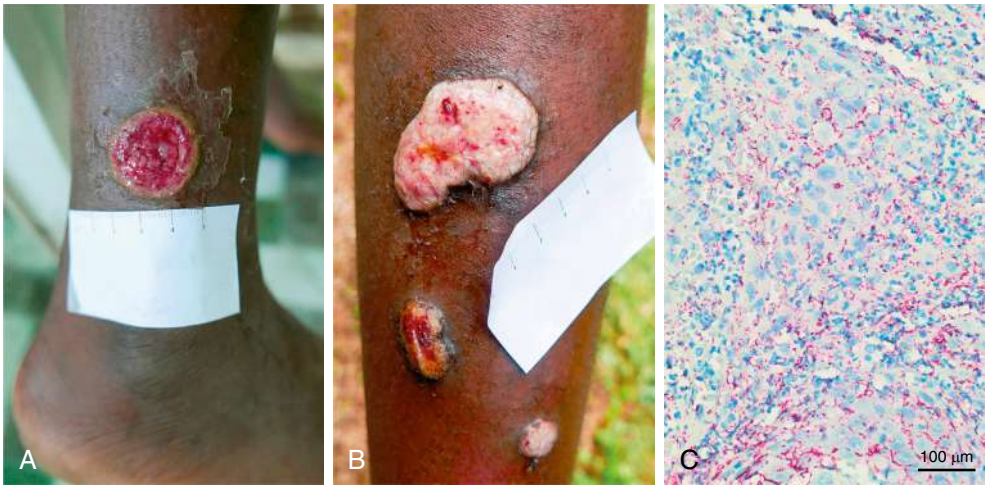

Fig. 265.1 Yaws lesions in a patient with treatment failure associated with macrolide-resistant *T p pertenue*. **A,** Primary lesion (red, moist 2.5-cm ulcer) on the left leg of an 11-yr-old patient with yaws observed at the 30-mo survey. Lesional swab PCR was positive for *T p pertenue* with wild-type 23S rRNA. **B,** Secondary yaws papillomas (multiple nodules with yellow granular surface) seen at 36-mo survey. These lesions were PCR positive for *T p pertenue* with A2059G mutation in 23S rRNA. **C,** Photomicrograph of skin biopsy of the larger papilloma lesion in panel **B** with abundant spirochete organisms stained bright red by the *Treponema pallidum* immunohistochemical stain (×400 magnification). *T p pertenue*, *Treponema pallidum* subspecies pertenue. *(From Mitja O, Godornes C, Houinei W, et al. Re-emergence of yaws after single mass azithromycin treatment followed by targeted treatment: a longitudinal study. Lancet. 2018;391:1599–1606, Fig. 2.)*

hyperkeratosis **(dry crab yaws)** of the palms and soles are common. Approximately 10% of patients may progress and develop tertiary-stage lesions after 5 years or more of untreated infection, although this outcome is now rare.

The diagnosis is based on the characteristic clinical manifestations of the disease in an endemic area. Dark-field examination of cutaneous lesions for treponemes and both treponemal and nontreponemal serologic tests for syphilis, which are positive because of cross reactivity, are used to confirm the diagnosis. The nontreponemal agglutination tests, such as the rapid plasma reagin and Venereal Diseases Research Laboratory tests, are positive in untreated cases, and these tests can be used for test of cure, because they revert to negative after treatment. However, the treponemal tests (*T. pallidum* hemagglutination assay, *T. pallidum* particle agglutination assay, and fluorescent treponemal antibody absorption) are more specific and remain positive for life. New immunochromatographic test strips that can be applied for testing both whole blood and serum are simple, cheap, and easy to use and do not require refrigeration. However, they have lower sensitivity compared with the antibody assays and appear to work best in persons with more active disease.

The differential diagnosis includes other conditions with similar cutaneous manifestations such as eczema, psoriasis, excoriated chronic scabies, tungiasis, leishmaniasis, tropical ulcer cutaneous mycoses, and verrucae. Involvement of the bone may mimic dactylitis that is commonly associated with sickle cell disease.

Treatment of yaws consists of a single dose of the long-acting benzathine penicillin G (1.2 million units IM for adults and 0.6 million units for children <10 years) for index patients and all contacts. Patients allergic to penicillin may be treated with erythromycin, doxycycline, or tetracycline at appropriate doses for venereal syphilis (see Chapter 264). One oral dose of azithromycin (30 mg/kg; maximum: 2 g) is as effective as benzathine penicillin. Treatment cures the lesions of active yaws, renders them noninfectious, and prevents relapse. Family members, contacts, and patients with latent infection should receive the same dose as those with active disease. Eradication of yaws from some endemic areas has been accomplished by treating the entire population (mass treatment) with azithromycin, although reemergence has been reported in those who did not receive mass treatment. In 2023, due to manufacturing limitations and increased demand, the United States entered a period of penicillin G shortage, potentially causing treatment to shift to erythromycin, doxycycline, or tetracycline until the shortages are resolved.

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265.2 Bejel (Endemic Syphilis; *Treponema pallidum endemicum*)

Stephen K. Obaro and H. Dele Davies

Bejel, or endemic syphilis, affects children in remote rural communities living in poor hygienic conditions. Unlike yaws, bejel can occur in temperate and dry, hot climates. Infection with *T. pallidum* subspecies *endemicum* follows penetration of the spirochete through traumatized skin or mucous membranes. In experimental infections, a primary papule forms at the inoculation site after an incubation period of 3 weeks. A primary lesion is almost never visualized in human infections; however, primary ulcers have been described surrounding the nipples of nursing mothers with infected children.

The clinical manifestations of the **secondary stage** typically occur 3-6 months after inoculation and are confined to the skin and mucous membranes. They consist of highly infectious mucous patches on the oral mucosa and condyloma-like lesions on the moist areas of the body, especially the axilla and anus. These mucocutaneous lesions resolve spontaneously over a period of several months, but recurrences are common. The secondary stage is followed by a variable latency period before the onset of late or tertiary bejel. The tertiary stage can occur as early as 6 months or as late as several years after resolution of initial symptoms. The lesions in the tertiary stage are identical to those of yaws and include gumma formation in skin, subcutaneous tissue, and bone, resulting in painful destructive ulcerations, swelling, and deformity.

The diagnosis is based on the characteristic clinical manifestations of the disease in an endemic area. Dark-field examination of cutaneous lesions for treponemes and both treponemal and nontreponemal serologic tests for syphilis, which are positive because of cross reactivity, are used to confirm the diagnosis.

Differentiation from venereal syphilis is extremely difficult in an endemic area. Bejel is distinguished by the absence of a primary chancre and lack of involvement of the central nervous system and cardiovascular system during the late stage.

Treatment of early infection consists of a single dose of benzathine penicillin G (1.2 million units IM for adults and 0.6 million units for children <10 years). Late infection is treated with three injections of the same dosage at intervals of 7 days. Patients allergic to penicillin may be treated with erythromycin or tetracycline. Similarly, when penicillin G is unavailable because of manufacturing limitations, treatment with erythromycin or tetracycline is appropriate.

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265.3 Pinta (*Treponema carateum*)

Stephen K. Obaro and H. Dele Davies

Pinta is a chronic, nonvenereally transmitted infection caused by *T. pallidum* subsp. *carateum,* a spirochete morphologically and serologically indistinguishable from other human treponemes. This is perhaps the mildest of the nonvenereal treponematoses. The disease is endemic in Mexico, Central America, South America, and parts of the West Indies and largely affects children younger than 15 years of age.

Infection follows direct inoculation of the treponeme through abraded skin. After a variable incubation period of days, the **primary** lesion appears at the inoculation site as a small asymptomatic erythematous papule resembling localized psoriasis or eczema. The regional lymph nodes are often enlarged. Spirochetes can be visualized on dark-field examination of skin scrapings or from biopsy of the involved lymph nodes. After a period of enlargement, the primary lesion disappears. Unlike primary yaws, the lesion does not ulcerate but can expand with central depigmented resolution. **Secondary** lesions follow within 6-8 months and consist of small macules and papules on the face, scalp, and other sun-exposed portions of the body. These pigmented, highly infectious lesions are scaly and nonpruritic and can coalesce to form large plaquelike elevations resembling psoriasis. In the late or **tertiary** stage, atrophic and depigmented lesions develop on the hands, wrists, ankles, feet, face, and scalp. Hyperkeratosis of palms and soles is uncommon.

The diagnosis is based on the characteristic clinical manifestations of the disease in an endemic area. Dark-field examination of cutaneous lesions for treponemes and both treponemal and nontreponemal serologic tests for syphilis, which are positive because of cross reactivity, are used to confirm the diagnosis.

Treatment consists of a single dose of benzathine penicillin G (1.2 million units IM for adults and 0.6 million units for children <10 years). Tetracycline and erythromycin are alternatives for patients allergic to penicillin and during periods when penicillin G is unavailable because of manufacturing limitations. Treatment campaigns and improvement of standards of living are necessary for reduction and elimination of the disease.

Chapter 266

Leptospira

H. Dele Davies and Kari A. Simonsen

Leptospirosis is a common and widespread zoonosis caused by aerobic, motile spirochetes of the genus *Leptospira*.

ETIOLOGY

Leptospira spp. are thin, helix-shaped members of the phylum Spirochaetes. There are 22 species identified within the genus *Leptospira,* and these are further divided into over 300 serovars. There are at least 10 pathogenic *Leptospira* species, with serovars demonstrating preferential host specificity.

EPIDEMIOLOGY

Leptospirosis has a worldwide distribution, but most human cases occur in tropical and subtropical countries with disease burden disproportionately affecting resource-poor populations. Leptospires survive for days to weeks in warm and damp environmental conditions, including water and moist soil. In the United States, the CDC estimates 100-200 annual cases; Hawaii reports about 50% of U.S. cases, with Pacific Coast and Southern states having a higher incidence than the remainder of the country. Leptospires infect many species of animals, including rats, mice, and moles; livestock such as cattle, goats, sheep, horses, and pigs; wild mammals like raccoons or opossums; and domestic dogs. Infected animals excrete spirochetes in their urine for prolonged periods. Globally, most human cases result from exposure to water or soil contaminated with rat urine; however, the major animal reservoir in the United States is the dog. Groups at high risk for leptospirosis include persons exposed occupationally or recreationally to contaminated soil, water, or infected animals. High-risk occupations include agricultural workers, veterinarians, abattoir workers, meat inspectors, rodent control workers, laboratory workers, sewer workers, and military personnel. Cases are more frequent in the late summer and fall and often after heavy rainfalls. Exposure to contaminated floodwaters is also a documented source of infection. Transmission via animal bites and directly from person to person has been rarely reported.

PATHOLOGY AND PATHOGENESIS

Leptospires enter human hosts through mucous membranes (primarily the eyes, nose, and mouth), transdermally through abraded skin, or by ingestion of contaminated water. After penetration, they circulate in the bloodstream, causing endothelial damage of small blood vessels with secondary ischemic damage to end organs.

CLINICAL MANIFESTATIONS

The spectrum of human leptospirosis ranges from asymptomatic infection to severe disease (5–10% of infections) with multiorgan dysfunction and death. The onset is usually abrupt, and the illness may follow a monophasic or the classically described biphasic course (Fig. 266.1). The incubation period ranges from 2 to 30 days, after which there is an **initial** or **septicemic phase** lasting 2-7 days, during which leptospires can be isolated from the blood, cerebrospinal fluid (CSF), and other tissues. This phase may be followed by a brief period of well-being before onset of a second symptomatic **immune** or **leptospiruric phase**. This phase is associated with the appearance of circulating IgM antibody, disappearance of organisms from the blood and CSF, and appearance of signs and symptoms associated with localization of leptospires in the tissues. Despite the presence of circulating antibody, leptospires can persist in the kidney, urine, and aqueous humor. The immune phase can last for several weeks. Symptomatic infection may be anicteric or icteric.

Anicteric Leptospirosis

The **septicemic phase** of anicteric leptospirosis has an abrupt onset with flulike signs of fever, shaking chills, lethargy, severe headache, malaise, nausea, vomiting, and severe debilitating myalgia most prominent in the lower extremities, lumbosacral spine, and abdomen. Bradycardia and hypotension can occur, but circulatory collapse is uncommon. Conjunctival suffusion with photophobia and orbital pain (in the absence of chemosis and purulent exudate),

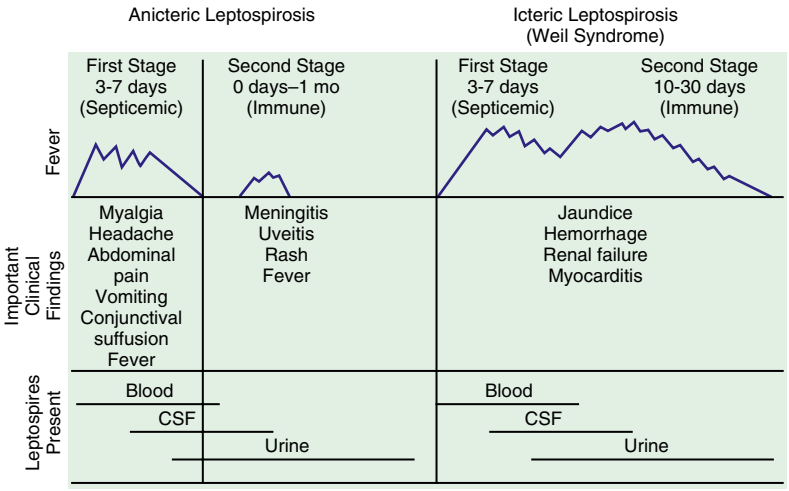

Fig. 266.1 Stages of anicteric and icteric leptospirosis. Correlation between clinical findings and presence of leptospires in body fluids. *CSF*, Cerebrospinal fluid. *(From Feigin RD, Anderson DC. Human leptospirosis. CRC Crit Rev Clin Lab Sci. 1975;5:413–467. Copyright CRC Press, Inc., Boca Raton, FL.)*

generalized lymphadenopathy, and hepatosplenomegaly may also be present. A transient (<24 hours) erythematous maculopapular, urticarial, petechial, purpuric, or desquamating rash occurs in 10% of cases. Rarer manifestations include pharyngitis, pneumonitis, arthritis, carditis, cholecystitis, and orchitis. The **second** or **immune phase** can follow a brief asymptomatic interlude and is characterized by recurrence of fever and aseptic meningitis. Although 80% of infected children have abnormal CSF profiles, only 50% have clinical meningeal manifestations. CSF abnormalities include a modest elevation in pressure, pleocytosis with early polymorphonuclear leukocytosis followed by mononuclear predominance rarely exceeding 500 cells/mm^3, normal or slightly elevated protein levels, and normal glucose values. Encephalitis, cranial and peripheral neuropathies, papilledema, and paralysis are uncommon. A self-limited unilateral or bilateral uveitis can occur during this phase, rarely resulting in permanent visual impairment. Central nervous system symptoms usually resolve spontaneously within 1 week, with almost no mortality.

Icteric Leptospirosis (Weil Syndrome)

Weil syndrome is a severe form of leptospirosis seen more commonly in adults (>30 years) than in children. The initial manifestations are similar to those described for anicteric leptospirosis. However, the immune phase is characterized by jaundice, acute renal dysfunction, thrombocytopenia, and, in fulminant cases, pulmonary hemorrhage and cardiovascular collapse. Hepatic involvement leads to right upper quadrant pain, hepatomegaly, direct and indirect hyperbilirubinemia, and modestly elevated serum levels of hepatic enzymes. Liver function usually returns to normal after recovery. Patients have abnormal findings on urinalysis (hematuria, proteinuria, and casts), and azotemia is common, often associated with oliguria or anuria. Acute kidney failure occurs in 16–40% of cases. Abnormal electrocardiograms are present in 90% of cases, but congestive heart failure is uncommon. Transient thrombocytopenia occurs in >50% of cases. Rarely, hemorrhagic manifestations occur, including epistaxis, hemoptysis, and pulmonary, gastrointestinal, and adrenal hemorrhage. Patients with pulmonary hemorrhage syndrome may have >50% mortality rate, although the overall mortality rate for severe disease is lower, about 5–15%.

DIAGNOSIS

Leptospirosis should be considered in the differential diagnosis of acute flulike febrile illnesses with a history of direct contact with animals or with soil or water contaminated with animal urine. The disease may be difficult to distinguish clinically from dengue or malaria in endemic areas.

The diagnosis is most often confirmed by serologic testing and less often confirmed by isolation of the infecting organism from clinical specimens. The gold-standard diagnostic method is the microscopic agglutination test, a serogroup-specific assay using live antigen suspension of leptospiral serovars and dark-field microscopy for agglutination. A fourfold or greater increase in titer in paired sera confirms the diagnosis. Agglutinins usually appear by the 12th day of illness and reach a maximum titer by the third week. Low titers can persist for years. Approximately 10% of infected persons do not have detectable agglutinins, presumably because available antisera do not identify all *Leptospira* serotypes. Additionally, enzyme-linked immunosorbent assay (ELISA) methods, latex agglutination, and immunochromatography are commercially available, and DNA PCR diagnostics have been developed. Phase-contrast and dark-field microscopy are insensitive for spirochete detection, but organisms may be identified using Warthin-Starry silver stain or fluorescent antibody staining of tissue or body fluids. Unlike other pathogenic spirochetes, leptospires can be recovered from the blood or CSF during the first 10 days of illness and from urine after the second week by repeated culture of small inoculum (i.e., one drop of blood or CSF in 5 mL of medium) on commercially available selective media. However, the inoculum in clinical specimens is small, and growth can take up to 16 weeks.

TREATMENT

Leptospira spp. demonstrate in vitro susceptibility to penicillin and tetracyclines, but in vivo effectiveness of these antibiotics in treating human leptospirosis is unclear because of the naturally high spontaneous recovery rates. Some studies suggest that initiation of treatment before the seventh day shortens the clinical course and decreases the severity of the infection; thus treatment with penicillin G, ceftriaxone, or doxycycline (in children ≥8 years of age) should be instituted early when the diagnosis is suspected. There is evidence that a short (<2 weeks) course of doxycycline may be safely used in children >2 years of age. Parenteral penicillin G (6-8 million U/m^2/day divided every 4 hours IV for 7 days) is recommended, with doxycycline 2 mg/kg/day divided in two doses with a maximum of 100 mg twice daily as an alternative for patients allergic to penicillin. Ceftriaxone, and azithromycin have been evaluated in clinical trials and have demonstrated equivalent effectiveness with doxycycline. These antibiotics can be used as alternatives in patients for whom doxycycline is contraindicated. In mild illness, oral doxycycline, amoxicillin, and ampicillin have been used successfully. In severe illness, supportive care with specific attention given to cardiopulmonary status, renal function, coagulopathy, and fluid and electrolyte balance is warranted.

PREVENTION

Prevention of human leptospirosis infection is facilitated through rodent control measures and avoidance of contaminated water and soil. Immunization of livestock and domestic dogs is recommended as a means of reducing animal reservoirs. Human vaccine development has been challenging because of the diversity of *Leptospira* serovars and their variable geographic distribution. Protective clothing (i.e., boots, gloves, and goggles) should be worn by persons at risk for occupational exposure. In hospital settings, in addition to standard precautions, contact precautions are recommended for potential exposures to infected urine. Leptospirosis was successfully prevented in American soldiers stationed in the tropics by administering prophylactic doxycycline (200 mg PO once a week). This approach may be similarly effective for travelers to highly endemic areas for short periods; however, there are no specific pediatric data to support any prophylaxis regimen.

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Chapter 267

Relapsing Fever *(Borrelia)*

Stephen K. Obaro and H. Dele Davies

Relapsing fever is characterized by recurring fevers and flulike symptoms such as headaches, myalgia, arthralgia, and rigors.

ETIOLOGY

Relapsing fever is an arthropod (lice or tick)-transmitted infection caused by spirochetes of the genus *Borrelia*.

Louse-borne (epidemic) relapsing fever is caused by *Borrelia recurrentis* and is transmitted from person to person by *Pediculus humanus,* the human body louse. Human infection occurs as a result of crushing lice during scratching, facilitating entry of infected hemolymph through abraded or normal skin or mucous membranes.

Tick-borne (endemic) relapsing fever is caused by several species of *Borrelia* and is transmitted to humans by *Ornithodoros* ticks. *Borrelia hermsii* and *Borrelia turicatae* are the common species in the western United States, whereas *Borrelia dugesii* is the major cause of disease in Mexico and Central America. Human infection occurs when saliva, coxal fluid, or excrement is released by the tick during feeding, thereby permitting spirochetes to penetrate the skin and mucous membranes.

Borrelia miyamotoi has been identified in the Japanese *Ixodes persulcatus* tick and in the *Ixodes dammini* tick, the agent that transmits Lyme disease in the northeastern United States. This *Borrelia* species causes a Lyme disease–like illness rather than relapsing fever.

EPIDEMIOLOGY

Louse-borne relapsing fever tends to occur in epidemics associated with war, poverty, famine, and poor personal hygiene, often in association with typhus. This form of relapsing fever is no longer seen in the United States but is endemic in parts of East Africa. Using 16S ribosomal RNA (rRNA) polymerase chain reaction assays for molecular detection, up to 20.5% of all unexplained fever in the Horn of Africa, including northwestern Morocco where the population traditionally lives in mud huts, is caused by tick-borne relapsing fever, making this the most common cause of bacterial infections.

Ornithodoros ticks, which transmit endemic relapsing fever and are distributed worldwide, including in the western United States, prefer warm, humid environments and high altitudes and are found in rodent burrows, caves, and other nesting sites (Fig. 267.1). Rodents (e.g., squirrels and chipmunks) are the principal reservoirs. Infected ticks gain access to human dwellings on the rodent host. Human contact is often unnoticed because these soft ticks have a painless bite and detach immediately after a short blood meal.

PATHOLOGY AND PATHOGENESIS

Relapsing fever is cyclical because the *Borrelia* organisms undergo antigenic (phase) variation. Multiple variants evolve simultaneously during the first relapse, with one type becoming predominant. Spirochetes isolated during the primary febrile episode differ antigenically from those recovered during a subsequent relapse. During febrile episodes, spirochetes enter the bloodstream, induce the development of specific immunoglobulin M and G antibodies, and undergo agglutination, immobilization, lysis, and phagocytosis. During remission, *Borrelia* spirochetes may remain in the bloodstream, but spirochetemia is insufficient to produce symptoms. The number of relapses in untreated patients depends on the number of antigenic variants of the infecting strain.

CLINICAL MANIFESTATIONS

Relapsing fever is characterized by febrile episodes lasting 2-9 days, separated by afebrile intervals of 2-7 days. Louse-borne disease has an incubation period of 2-14 days, longer periods of pyrexia, fewer relapses, and longer remission periods than tick-borne disease. The incubation period of tick-borne disease is usually 7 days (range: 2-9 days). Each form of relapsing fever is characterized by sudden onset of high fever, lethargy, headache, photophobia, nausea, vomiting, myalgia, and arthralgia. Additional symptoms may appear later and include abdominal pain, a productive cough, mild respiratory distress, and bleeding manifestations, including epistaxis, hemoptysis, hematuria, and hematemesis. During the end of the primary febrile episode, a diffuse, erythematous, macular, or petechial rash lasting up to 2 days may develop over the trunk and shoulders. There may also be lymphadenopathy, pneumonia, and splenomegaly. Hepatic tenderness associated with hepatomegaly is a common sign, with jaundice in half of affected children. Central nervous system manifestations include lethargy, stupor, meningismus, convulsions, peripheral neuritis, focal neurologic deficits, and cranial nerve paralysis and may be the principal feature of late relapses in tick-borne disease. Severe manifestations include myocarditis, hepatic failure, and disseminated intravascular coagulopathy.

The initial symptomatic period characteristically ends with a crisis in 2-9 days, marked by abrupt diaphoresis, hypothermia, hypotension, bradycardia, profound muscle weakness, and prostration. In untreated patients, the first relapse occurs within 1 week, followed by usually 3 but up to 10 relapses, with symptoms during each relapse becoming milder and shorter as the afebrile remission period lengthens.

DIAGNOSIS

Diagnosis depends on demonstration of spirochetes by dark-field microscopy or in thin or thick blood smears stained with Giemsa or Wright stain and by blood culture (Fig. 267.2). During afebrile remissions, spirochetes are not found in the blood. Serologic tests have not been standardized, are generally not available, and produce cross reactions with other spirochetes, including *Borrelia burgdorferi,* the agent of Lyme disease. Central nervous system involvement may be associated with lymphocytic pleocytosis. Molecular methods, including nested polymerase chain reaction or 16S rRNA polymerase chain reaction assays, have been used for detection of tick-borne and louse-borne recurrent fever and have been found to have improved sensitivity and specificity compared with blood smears. However, these assays are not yet routinely available for commercial use.

TREATMENT

Oral or parenteral tetracycline or doxycycline is the drug of choice for louse-borne and tick-borne relapsing fever. For children older than 8 years of age and young adults, tetracycline 500 mg PO every 6 hours or doxycycline 100 mg PO every 12 hours for 10 days is effective. Single-dose treatment with tetracycline (500 mg PO) or

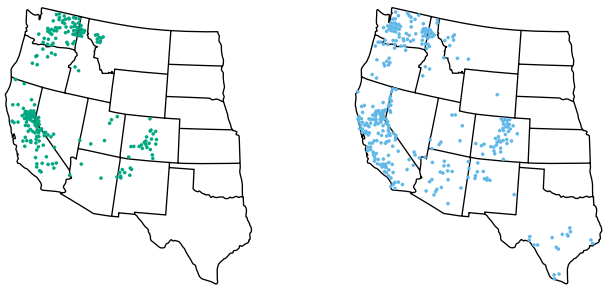

Fig. 267.1 Cases of tickborne relapsing fever–United States, 1990–2011. During the years 1990–2011, 483 cases of tickborne relapsing fever were reported in the western United States, with infections being transmitted most frequently in California, Washington, and Colorado. *(From Centers for Disease Control and Prevention [CDC]. Tick-borne relapsing fever: distribution. Available at:* http://www.cdc.gov/relapsing-fever/distribution*)*

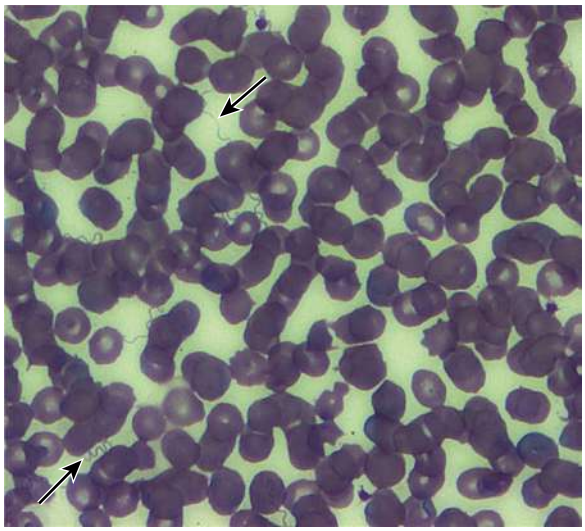

Fig. 267.2 Stained thin smear of a newborn's peripheral blood showing the presence of numerous spirochetes (indicated by *arrows*) at ×63 magnification—Colorado, 2011. *(From Centers for Disease Control and Prevention [CDC]. Tickborne relapsing fever in a mother and newborn child–Colorado, 2011. MMWR Morb Mortal Wkly Rep. 2012;61:174–176.)*

erythromycin is efficacious in adults, but experience in children is limited. In children younger than 8 years of age, erythromycin (50 mg/kg/day divided every 6 hours PO) for a total of 10 days is recommended, although there is evidence that doxycycline given for durations of less than 2 weeks is safe in children >2 years of age. Penicillin and chloramphenicol are also effective. Central nervous system involvement is usually responsive to intravenous ceftriaxone or penicillin.

Resolution of each febrile episode either by natural crisis or as a result of antimicrobial treatment is often accompanied by the Jarisch-Herxheimer reaction, which is caused by massive antigen release. Corticosteroid or antipyretic pretreatment does not prevent this reaction.

PROGNOSIS

With adequate therapy, the mortality rate for relapsing fever is <5%. A majority of patients recover from their illness with or without treatment after the appearance of anti-*Borrelia* antibodies, which agglutinate, kill, or opsonize the spirochete. However, pregnant women and their neonates are at increased risk for tick-borne recurrent fever-associated complications, including adult respiratory distress syndrome, Jarisch-Herxheimer reaction, and precipitous or premature delivery. Neonates have up to a 33% case fatality rate. The risk of Jarisch-Herxheimer reaction appears to be much higher in louse-borne relapsing fever (LBRF) (55.8%) compared to TBRF (19.3%). However, they have similar overall case fatality rates, TBRF (6.5%) and LBRF (4–10.2%).

PREVENTION

No vaccine is available. Disease control requires avoidance or elimination of the arthropod vectors. In epidemics of louse-borne disease, good personal hygiene and delousing of persons, dwellings, and clothing with commercially available insecticides can prevent dissemination. The risk for tick-borne disease can be minimized in endemic areas by maintaining rodent-free dwellings. Giving prophylactic doxycycline for 4 days after a tick bite may prevent tick-borne relapsing fever caused by *Borrelia persica.*

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Chapter 268

Lyme Disease *(Borrelia burgdorferi)*

Sanjeev K. Swami

Lyme disease is the most common vector-borne disease in the United States and is an important public health problem.

ETIOLOGY

Lyme disease is a zoonotic infection caused by the transmission of the spirochete *Borrelia burgdorferi* sensu lato (broad sense) to humans via the bite of an infected tick of the *Ixodes* genus. In North America, *B. burgdorferi* sensu stricto (strict sense) causes almost all cases; another species in the upper Midwestern United States, *Borrelia mayonii* (belonging to the group *B. burgdorferi* sensu lato), also causes Lyme disease, but the illness is slightly different, with more diffuse rashes and gastrointestinal symptoms. In Europe, the species *Borrelia afzelii* and *Borrelia garinii* also cause disease. The three major outer-surface proteins, called *OspA, OspB,* and *OspC* (which are highly charged basic proteins of molecular weights of about 31, 34, and 23 kDa, respectively), and the 41-kDa flagellar protein are important targets for the immune response. Differences in the molecular structure of the different species are associated with differences in the clinical manifestations of Lyme borreliosis in Europe and the United States. These differences include the higher incidence of radiculoneuritis in Europe.

TRANSMISSION

In the eastern and midwestern United States, the vector for Lyme disease is ***Ixodes scapularis***, the black-legged tick that is commonly known as the **deer tick**. It is responsible for most cases in the United States. The vector on the Pacific Coast is *Ixodes pacificus,* the western black-legged tick. *Ixodes* ticks have a 2-year, three-stage life cycle. The larvae hatch in the early summer and are usually uninfected with *B. burgdorferi.* The tick can become infected at any stage of its life cycle by feeding on a host, usually a small mammal such as the white-footed mouse *(Peromyscus leucopus)*, which is a natural reservoir for *B. burgdorferi.* The larvae overwinter and emerge the following spring in the nymphal stage, which is the stage of the tick most likely to transmit the infection. The nymphs molt to adults in the fall, and then adults spend the second winter attached to white-tailed deer *(Odocoileus virginianus)*. The females lay their eggs the following spring before they die, and the 2-year life cycle begins again.

Several factors are associated with increased risk for transmission of *B. burgdorferi* from ticks to humans. The proportion of infected ticks varies by geographic area and by the stage of the tick's life cycle. In endemic areas in the northeastern and midwestern United States, 15–25% of nymphal ticks and 35–50% of adult ticks are infected with *B. burgdorferi.* By contrast, *I. pacificus* often feeds on lizards, which are not a competent reservoir for *B. burgdorferi,* reducing the chance that these ticks will be infected. The risk for transmission of *B. burgdorferi* from infected *Ixodes* ticks is related to the duration of feeding. Experiments in animals show that infected nymphal ticks must feed for 36-48 hours and infected adults must feed for 48-72 hours before the risk for transmission of *B. burgdorferi* becomes substantial. If the tick is recognized and removed promptly, transmission of *B. burgdorferi* will not occur. *Most patients with Lyme disease do not remember the tick bite that transmitted the infection.*

The habitat of tick species that carry *B. burgdorferi* may be geographically expanding in the United States because of climate change. *I. scapularis* also transmits other microorganisms, namely *Anaplasma*

phagocytophilum and *Babesia microti,* as well as *Borrelia miyamotoi.* Simultaneous transmission can result in co-infections with these organisms and *B. burgdorferi.*

EPIDEMIOLOGY

Lyme disease has been reported in more than 50 countries, including forested areas of Asia; northwestern, central, and eastern Europe; and eastern and midwestern United States. In Europe, most cases occur in the Scandinavian countries and in central Europe, especially Germany, Austria, and Switzerland, whereas in the United States, 92% of cases occurred in 16 states in 2019: Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, North Carolina, Pennsylvania, Rhode Island, Vermont, Virginia, West Virginia, and Wisconsin (Fig. 268.1).

In 2019, the most recent year for which U.S. data are available, more than 23,000 confirmed cases and more than 11,000 probable cases were reported. The 3-year averaged national incidence is estimated at 7.8 cases per 100,000 population, and in recent years the national incidence has ranged from a low of 7.0 cases per 100,000 (2012) to a high of 9.1 cases per 100,000 (2017). In endemic areas, the reported annual incidence ranges from 20 to 100 cases per 100,000 population, although this figure may be as high as 600 cases per 100,000 population in hyperendemic areas. The reported incidence of disease by age is bimodal. There is an initial peak among children age 5-14 followed by a second peak among adults 55-69. In the United States, Lyme disease is diagnosed in males slightly more often than in females. Early Lyme disease usually occurs from spring to early fall, corresponding to deer tick activity. Late disease (primarily arthritis) occurs year-round. Among adults, outdoor occupation and leisure activities are risk factors; for children, location of residence in an endemic area is the most important risk for infection.

Lyme disease is designated a nationally notifiable disease by the CDC and Council for State and Territorial Epidemiologists. Healthcare providers, hospitals, laboratories, and other parties are required by law to notify local health departments when a confirmed or probable case of Lyme disease occurs. The local health departments report cases to the state and territorial health departments; it is voluntary in turn for these authorities to report data to the CDC, and therefore the actual number of Lyme disease cases and incidence are likely underreported and underestimated. Lyme disease was the sixth most common notifiable disease reported to the CDC in 2019 (following *Chlamydia trachomatis,* gonorrhea, syphilis, campylobacteriosis, and salmonellosis).

PATHOLOGY AND PATHOGENESIS

Similar to other spirochetal infections, untreated Lyme disease is characterized by asymptomatic infection, clinical disease that can occur in stages, and a propensity for cutaneous and neurologic manifestations. The skin is the initial site of infection by *B. burgdorferi.* Disseminated Lyme disease results from the spread of spirochetes through the bloodstream to tissues throughout the body. The spirochete adheres to the surfaces of a wide variety of different types of cells, but the principal target organs are the skin, central and peripheral nervous systems, joints, heart, and eyes. Because the organism can persist in tissues for prolonged periods, symptoms can appear very late after initial infection.

The symptoms of disseminated Lyme disease are a result of inflammation mediated by interleukin-1 and other lymphokines in response to the presence of the organism. It is likely that relatively few organisms actually invade the host, but cytokines serve to amplify the inflammatory response and lead to much tissue damage. Lyme disease is characterized by inflammatory lesions that contain both T and B lymphocytes, macrophages, plasma cells, and mast cells. The refractory symptoms of disseminated Lyme disease can have an immunogenetic basis. Persons with certain HLA-DR allotypes may be genetically predisposed to develop chronic Lyme arthritis. An autoinflammatory response in the synovium can result in clinical symptoms long after the bacteria have been killed by antibiotics.

CLINICAL MANIFESTATIONS

The clinical manifestations of Lyme disease are divided into early and disseminated stages. Older nomenclature included early localized disease, early disseminated disease, and late disease; early disseminated and late disease have been combined into disseminated disease in the current nomenclature (Table 268.1). Untreated patients can progressively develop clinical symptoms of each stage of the disease, or they can present with disseminated disease without having had any symptoms of the early Lyme disease.

Early Disease

The first clinical manifestation of Lyme disease in many patients is **erythema migrans** (Fig. 268.2). Although it usually occurs 7-14 days after the bite, the onset of the rash has been reported from 3 to 30 days later. The initial lesion occurs at the site of the bite. The rash is generally either uniformly erythematous or a target lesion with central clearing; rarely, there are vesicular or necrotic areas

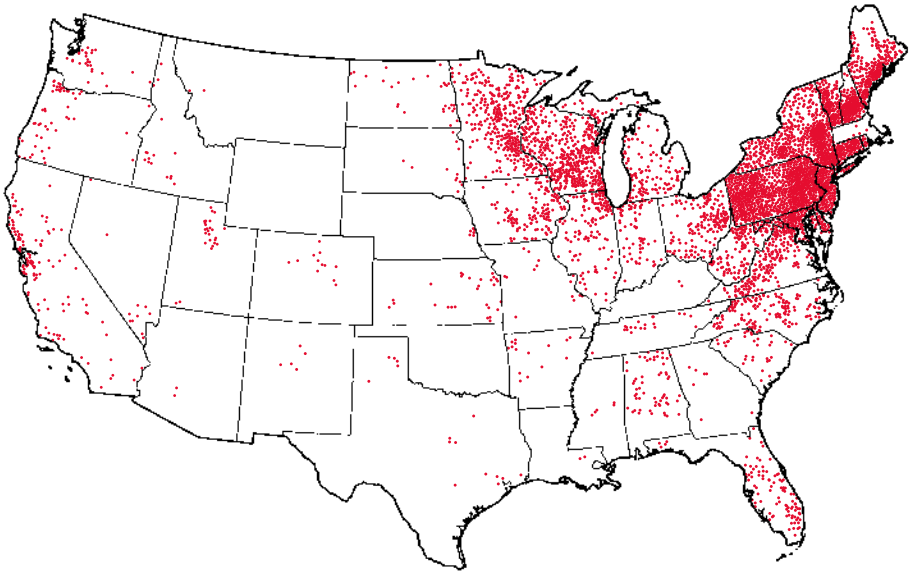

Fig. 268.1 The geographic distribution of Lyme disease cases in the United States. *(From the Centers for Disease Control and Prevention. Reported cases of Lyme disease—United States, 2019. Available at: https://www.cdc.gov/lyme/datasurveillance/maps-recent.html)*

Table 268.1 Clinical Stages of Lyme Disease

DISEASE STAGE	TIMING AFTER TICK BITE	TYPICAL CLINICAL MANIFESTATIONS
Early localized	3-30 days	Erythema migrans (single), variable constitutional symptoms (headache, fever, myalgia, arthralgia, fatigue)
Disseminated	3-12 wk	Erythema migrans (single or multiple), worse constitutional symptoms, cranial neuritis, meningitis, carditis, ocular disease
Disseminated	>2 mo	Arthritis

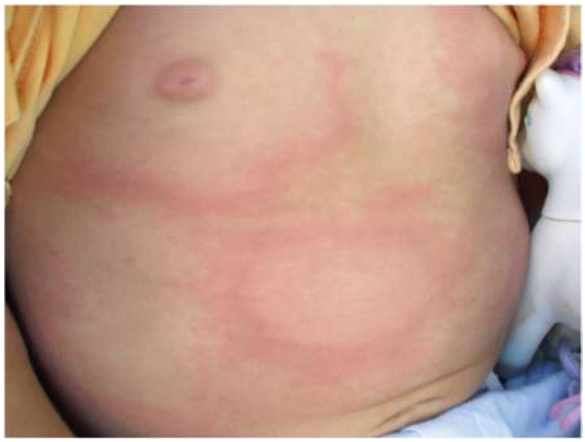

Fig. 268.3 Multiple erythema migrans in early disseminated Lyme disease.

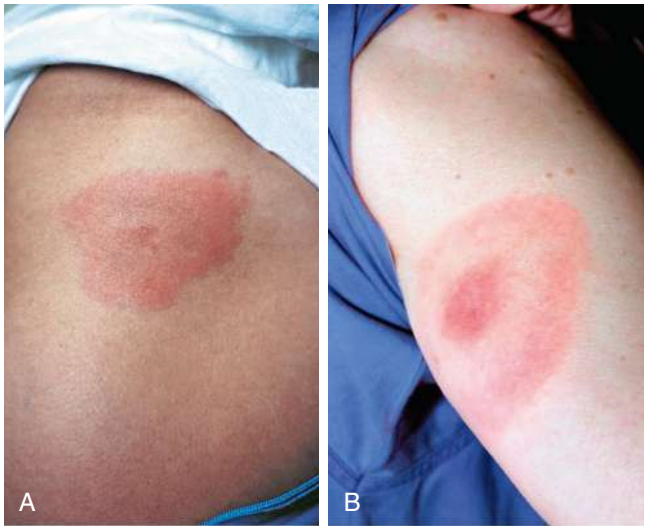

Fig. 268.2 Skin manifestations of Lyme borreliosis. **A,** Erythema migrans on the upper leg, showing central clearing. **B,** Erythema migrans of the arm showing "bull's-eye" appearance. *(A from Stanek G, Strle F. Lyme borreliosis. Lancet. 2003;362:1639–1647.)*

in the center of the rash. Occasionally the rash is itchy or painful, although usually it is asymptomatic. The lesion can occur anywhere on the body, but the most common locations are the axilla, periumbilical area, thigh, and groin. It is not unusual for the rash to occur on the neck, face, or hairline, especially in young children. Without treatment, the rash gradually expands (hence the name *migrans*) to an average diameter of 15 cm and typically remains present for 1-2 weeks. Erythema migrans may be associated with systemic features, including fever, myalgias, arthralgias, headache, or malaise; gastrointestinal symptoms are rare. Co-infection with *B. microti* or *A. phagocytophilum* during early infection with *B. burgdorferi* is associated with more severe systemic symptoms. **Co-infections** should be suspected with unusual features of Lyme disease, poor response to appropriate antibiotics, prolonged fever, or laboratory abnormalities that include anemia, leukopenia, thrombocytopenia, or elevated liver enzymes.

Disseminated Disease

In the United States, approximately 20% of patients with acute *B. burgdorferi* infection develop secondary (multiple) erythema migrans lesions, a common manifestation of disseminated Lyme disease, caused by hematogenous spread of the organisms to multiple skin sites (Fig. 268.3). The secondary lesions, which can develop several days or weeks after the first lesion, are usually smaller than the primary lesion and are often accompanied by more severe constitutional symptoms. The lesions may not have the classic appearance of erythema migrans; they may lack central clearing, appear oval in shape, or have irregular borders. The most common neurologic manifestations are **peripheral facial nerve palsy** and **meningitis**. Peripheral (or cranial) nerves other than the facial nerve may be affected, and patients can present with multiple concurrent nerve palsies. Lyme meningitis usually has an indolent onset with days to weeks of symptoms (longer than viral meningitis) that can include headache, neck pain and stiffness, and fatigue. Fever is variably present. Patients can present with both peripheral nerve palsy *and* meningitis, but typically they have either central nervous system or peripheral nervous system disease.

The clinical findings of papilledema, cranial neuropathy (especially cranial nerve VII), and erythema migrans, which are present individually or together in up to 90% of cases, help differentiate Lyme meningitis from viral meningitis, in which these findings are rarely present. The aseptic meningitis caused by Lyme disease can be accompanied by significant elevations of intracranial pressure, which can sometimes last weeks or even months. All the cranial nerves except the olfactory have been reported to be involved with Lyme disease, but the most common are VI and especially VII. In endemic areas, Lyme disease is the leading cause of peripheral facial nerve palsy. It is often the initial or the only manifestation of Lyme disease and is sometimes bilateral. The facial paralysis usually lasts 2-8 weeks and resolves completely in most cases. Radiculoneuritis and other peripheral neuropathies can occur but are more common in Europe.

Cardiac involvement occurs in 5–15% of disseminated Lyme disease (overall <1% of Lyme infections) and usually takes the form of **heart block**, which can be first, second, or third degree, and the rhythm can fluctuate rapidly. Rarely, myocardial dysfunction (myocarditis) can occur. Patients presenting with suspected or proven disseminated Lyme disease should have a careful cardiac examination, and electrocardiography should be strongly considered, especially if patients report chest pain, palpitations, or presyncopal symptoms. Lyme carditis is a treatable condition and is the only manifestation of Lyme disease that has been fatal.

Papilledema and uveitis are most common ocular conditions associated with Lyme disease; optic neuritis has also been reported.

Arthritis is the most common manifestation of disseminated Lyme disease and begins weeks to months (possibly years) after the initial infection. Lyme arthritis is classically a monoarticular, nonmigratory arthritis affecting the large joints. The knee is the

most commonly infected joint followed by the hip. Lyme arthritis can occasionally be oligoarticular or migratory. The hallmark of Lyme arthritis is joint swelling, which is a result of synovial effusion and sometimes synovial hypertrophy. The swollen joint may be only mildly symptomatic, or less often, it may be painful and tender, although patients usually do not experience the severe pain and systemic toxicity that are common with pyogenic arthritis. Micromotion tenderness is rare with Lyme arthritis. If untreated, the arthritis can last several weeks, resolve, and then be followed by recurrent attacks in the same or other joints.

Other manifestations of Lyme disease involving the central nervous system, sometimes termed *late neuroborreliosis,* are rarely reported in children. In adults, chronic encephalitis and polyneuritis have been attributed to Lyme disease. The term *Lyme encephalopathy* has been used to describe chronic encephalitis (demonstrable by objective measures), but other literature has also used this term in reference to memory loss and other cognitive sequelae after Lyme disease has been treated. At times, the vague and mistaken term *chronic Lyme disease* has been used to describe symptomatology in persons who might have never had well-documented infection with *B. burgdorferi* at all, have serologic evidence of prior infection but current symptoms not consistent with Lyme disease, or have persistent symptoms after having received appropriate antibiotic therapy. Prolonged treatment does not treat the chronic neuropsychiatric symptoms and at times has harmed the patient.

Some patients experience prolonged symptoms after treatment of early or disseminated Lyme disease; these symptoms frequently include fatigue, headaches, myalgias, arthralgias, and difficulty thinking. This phenomenon is termed **posttreatment Lyme disease syndrome**. The etiology for this process is unclear, but prolonged antibiotic treatment has not been shown to hasten recovery and has been associated with harm. Most patients have symptom resolution by 6 months without antibiotic therapy.

Congenital Lyme Disease

In endemic areas, infection can occur during pregnancy, and although congenital infection appears to be a rare event, there is no recognized congenital infection syndrome associated with Lyme disease. *B. burgdorferi* has been identified from several abortuses and from a few live-born children with congenital anomalies; however, the tissues in which the spirochete has been identified usually have not shown histologic evidence of inflammation. Severe skin and cardiac manifestations have been described in a few cases, but studies conducted in endemic areas have indicated that there is no difference in the prevalence of congenital malformations among the offspring of women with serum antibodies against *B. burgdorferi* and the offspring of those without such antibodies.

LABORATORY FINDINGS

Standard laboratory tests rarely are helpful in diagnosing Lyme disease because any associated laboratory abnormalities usually are nonspecific. The peripheral white blood cell count may be either normal or elevated. The erythrocyte sedimentation rate (ESR) may be mildly elevated. Liver transaminases are occasionally mildly elevated. In Lyme arthritis, the white blood cell count in joint fluid can range from 25,000 to 100,000/mL, often with a preponderance of polymorphonuclear cells. A lower ESR (≤40) and C-reactive protein and a peripheral blood absolute neutrophil count of less than 10,000 may help to differentiate Lyme from septic arthritis. When meningitis is present, there usually is a low-grade pleocytosis with a lymphocytic and monocytic predominance. The cerebrospinal fluid (CSF) protein level may be elevated, but the glucose concentration usually is normal. Gram stain and routine bacterial cultures are negative. Imaging of the central nervous system (e.g., magnetic resonance imaging and single-photon emission computed tomography) occasionally reveals abnormalities, but there is no definitive pattern in Lyme disease. The main role of imaging is to exclude other diagnoses.

DIAGNOSIS

In the appropriate epidemiologic setting (endemic area, season), typical erythema migrans is pathognomonic. Occasionally, the diagnosis of erythema migrans may be difficult because the rash initially can be confused with nummular eczema, tinea corporis, granuloma annulare, an insect bite reaction, southern tick–associated rash illness, or cellulitis. The relatively rapid expansion of erythema migrans helps distinguish it from these other skin lesions. The other clinical manifestations of Lyme disease are less specific and may be confused with other conditions; the monoarticular or oligoarticular arthritis sometimes is confused with a septic joint or other causes of arthritis in children, such as juvenile idiopathic arthritis or rheumatic fever; the facial nerve palsy caused by Lyme disease is clinically indistinguishable from Bell palsy, although bilateral involvement is much more common with Lyme disease; Lyme meningitis generally occurs in the warmer months, the same period that enteroviral meningitis is prevalent. Therefore for all disease manifestations other than erythema migrans, it is recommended to have laboratory confirmation of infection with *B. burgdorferi.*

Although *B. burgdorferi* has been isolated from the blood, skin, CSF, myocardium, and synovium of patients with Lyme disease, the organism is difficult to isolate in culture (cultivation is largely relegated to research laboratories). Infection is usually identified by the detection of antibody in serum. Although some laboratories offer polymerase chain reaction as a diagnostic test for Lyme disease, its sensitivity is poor because of the low concentrations of bacteria in many sites, especially CSF. Other antigen-based tests, including a test for *B. burgdorferi* antigens in urine, are unreliable. Clinicians should be aware that some laboratories use alternative diagnostic tests and/or alternative interpretive criteria that are not evidence based, leading to a false diagnosis of Lyme disease. The CDC and the Food and Drug Administration recommend against using these tests.

Serology

After the transmission of *B. burgdorferi* from a tick bite, specific immunoglobulin (Ig) M antibodies appear first, usually within 2 weeks, peak at 6-8 weeks, and subsequently decline. Sometimes a prolonged or recurrent elevation of IgM antibodies occurs despite effective antimicrobial treatment. Elevated IgM levels after 6-8 weeks are often false positives. Specific IgG antibodies usually appear between 2 and 6 weeks, peak after 4-6 months, and can remain elevated for years, particularly in patients with arthritis. The antibody response to *B. burgdorferi* may be blunted in patients with early Lyme disease who are treated promptly with an effective antimicrobial agent. *Serodiagnosis during the first 4 weeks of infection is not sensitive and may need to be repeated.*

Historically, the most common method used to detect IgG and IgM antibodies has been the enzyme-linked immunosorbent assay **(ELISA)**. *This method is sensitive but not optimally specific*. The ELISA sometimes produces false-positive results because of antibodies that cross react with other spirochetal infections (e.g., *B. miyamotoi,* syphilis, leptospirosis, or relapsing fever), or certain viral infections (e.g., Epstein-Barr virus), or that occur in certain autoimmune diseases (e.g., systemic lupus erythematosus). The positive predictive value of the ELISA result depends primarily on the plausibility that the patient has Lyme disease based on the clinical and epidemiologic history and the physical examination **(the pretest probability)**. For patients who have been in endemic areas with opportunities for *Ixodes* tick exposure and who have typical clinical manifestations of Lyme disease, the pretest probability is high, and positive ELISA results are usually true positives. For patients who are from nonendemic areas and/or who have little risk for *Ixodes* tick exposures and/or have nonspecific symptoms (low pretest probability), rates of false-positive results are high. Infection with *B. miyamotoi* may cause false-positive ELISA tests for Lyme disease. This syndrome of relapsing fever, headache, and myalgia

but no rash with neutropenia or thrombocytopenia is uncommon in Lyme disease.

Western immunoblotting is well-standardized, and there are accepted criteria for interpretation. Five of 10 IgG bands and 2 of 3 IgM bands are considered reactive. The Western blot is not as sensitive as ELISA, especially in early infection, but is highly specific. Any positive or equivocal ELISA can be confirmed with Western blotting. The CDC recommends using IgM and IgG Western blot confirmation when symptoms have been present ≤30 days and IgG only when symptoms have been present longer than 30 days.

Two-tier testing is the recommended laboratory evaluation of most cases of Lyme disease and is associated with a high degree of sensitivity and specificity when used appropriately. Two-tier assays using serial ELISAs have been developed that have similar or better sensitivity and specificity when compared with ELISA followed by Western blot. The serial ELISA methodology can have improved turn-around time and has two quantitative tests rather than a quantitative test followed by a test that requires interpretation. Stand-alone ELISAs have also been developed that have similar sensitivity and specificity when compared with two-tier testing.

Clinicians should be aware that Lyme disease might not be the cause of a patient's symptoms despite the presence of antibodies to *B. burgdorferi*. The test result may be falsely positive (as described for ELISA), or the patient might have been infected previously. Antibodies to *B. burgdorferi* that develop with infection can persist for many years despite adequate treatment and clinical cure of the disease. In addition, because some people who become infected with *B. burgdorferi* are asymptomatic, the background rate of seropositivity among patients who have never had clinically apparent Lyme disease may be substantial in endemic areas. Finally, because antibodies against *B. burgdorferi* persist after successful treatment, there is no reason to obtain follow-up serologic tests.

TREATMENT

Table 268.2 provides treatment recommendations. Most patients can be treated with oral antibiotics. Young children are generally treated with amoxicillin. Doxycycline has the advantages of good central nervous system penetration and activity against *A. phagocytophilum,* which may be transmitted at the same time as *B. burgdorferi* in certain geographic areas. Historically, children <8 years were not treated with doxycycline because of the risk of staining of the permanent teeth. Data from the CDC have shown that this is not a concern for treatment courses <2 weeks. Doxycycline oral solution is still challenging to find, so most younger children are prescribed amoxicillin. There are no data that show a difference in efficacy between amoxicillin and doxycycline for the treatment of Lyme disease. Patients who are treated with doxycycline should be alerted to the risk for developing photosensitivity in sun-exposed areas while taking the medication; thus long sleeves, long pants, and a hat are recommended for activities in direct sunlight. The only oral cephalosporin proved to be effective for the treatment of Lyme disease is cefuroxime axetil, which is an alternative for persons who cannot take doxycycline or who are allergic to penicillin. There is no reported resistance of *B. burgdorferi* to these antibiotics. Macrolide antibiotics, including azithromycin, appear to have limited activity and are only recommended for patients allergic to all of the other active medications.

Parenteral therapy is usually recommended for patients with higher degrees of heart block or central nervous system involvement, although oral therapy for meningitis is also considered acceptable for ambulatory patients. Patients with arthritis that fails to resolve after an initial course of oral therapy can be retreated with an oral regimen or can receive intravenous antibiotic therapy. Ceftriaxone is favored because of its excellent anti-*Borrelia* activity, tolerability, and once-daily dosing regimen, which can usually be done on an outpatient basis.

Table 268.2 Recommended Treatment of Lyme Disease

DRUG	PEDIATRIC DOSING
Amoxicillin	50 mg/kg/day in 3 divided doses (max: 1,500 mg/day)
Doxycycline	4.4 mg/kg/day in 2 divided doses (max: 200 mg/day) (see text regarding doxycycline use in children)
Cefuroxime axetil	30 mg/kg/day in 2 divided doses (max: 1,000 mg/day)
Ceftriaxone (IV)*,†	50-75 mg/kg/day once daily (max: 2,000 mg/day)
Azithromycin‡	10 mg/kg/day once daily ×7 days
RECOMMENDED THERAPY BASED ON CLINICAL MANIFESTATION	
Erythema migrans	Doxycycline ×10 days Amoxicillin ×14 days Cefuroxime ×14 days
Meningitis, radiculopathy	Doxycycline ×14-21 days or Ceftriaxone ×14 days (14-21 for hospitalized patients)
Cranial nerve palsy§	Doxycycline ×14-21 days
Cardiac disease	Oral regimen or ceftriaxone 14-21 days (see text for specifics)
Arthritis	Oral regimen 28 days
Persistent or recurrent arthritis after initial treatment	Oral regimen ×28 days or Ceftriaxone 14-28 days
Borrelial lymphocytoma	Doxycycline, amoxicillin, cefuroxime 14 days

*Penicillin G is an alternative parenteral agent but requires more frequent dosing.
†Doses of 100 mg/kg/day should be used for meningitis.
‡For those unable to take amoxicillin or doxycycline.
§Treatment is to prevent late disease, not to treat the cranial palsy; avoid corticosteroids.

Peripheral facial nerve palsy can be treated using an oral antibiotic. Experts are divided on whether every patient with Lyme-associated facial palsy needs a CSF analysis, but clinicians should consider lumbar puncture for patients with significant headache, neck pain or stiffness, or papilledema.

Patients with symptomatic cardiac disease, second- or third-degree heart block, or significantly prolonged PR interval should be hospitalized and monitored closely. These patients should receive a parenteral antibiotic for their initial treatment. Patients with first-degree heart block can be treated with an oral antibiotic, and patients with high degrees of heart block can be transitioned to oral treatment as their heart block resolves.

Some patients develop a Jarisch-Herxheimer reaction soon after treatment is initiated; this results from lysis of the *Borrelia*. The manifestations of this reaction are low-grade fever and achiness. These symptoms resolve spontaneously within 24-48 hours, and administration of nonsteroidal antiinflammatory drugs often is beneficial. Nonsteroidal antiinflammatory drugs also may be useful in treating symptoms of early Lyme disease and of Lyme arthritis. *Co-infections with other pathogens transmitted by Ixodes ticks should be treated according to standard recommendations.*

There is no clear evidence that posttreatment Lyme disease syndrome is related to persistence of the organism. Studies in adults have

Table 268.3 Personal Prevention Measures

BEFORE VENTURING OUTSIDE	DURING AND/OR AFTER EXPOSURE TO TICK HABITAT†
Personal prevention measures*	Conduct a thorough tick check of extremities, torso, and areas where ticks may be visually obscured (e.g., axilla, nape of neck, hairline, in and around ears, umbilicus, groin, popliteal fossa)
Avoid risky habitats	Bathe or shower within 2 hr
Wear light-colored clothing	Dry clothes on high heat for at least 10 min; if not possible, wash clothes in hot water
Wear long sleeves and pants	
Tuck pants into socks or footwear	
Wear permethrin-treated clothing	
Use an EPA-approved repellent or insecticide as per manufacturer's instructions	***If an attached tick is detected***
	Remove properly and clean bite area
DEET	https://www.cdc.gov/lyme/removal/index.html
Picaridin	Tip: Store tick (e.g., in sealed container/plastic bag, wrapped in clear tape, or taped to a piece of paper). Label with date and likely geographic location of exposure.
IR3535	See clinician and show tick if concerned that it is an *Ixodes* spp. and has fed at least 36 hr.
Oil of lemon eucalyptus (OLE)	Monitor health for symptoms of Lyme disease and other tick-borne diseases
p-Methane-3,8-diol (PMD)	
2-undecanone	
Permethrin (for application to clothing and gear only)	

*Tip: Have handy a fine-tipped tweezers, tick storage container, and hand sanitizer.
†Continue to conduct a tick check whenever possible to detect and remove feeding ticks as soon as possible.
DEET, N,N-Diethyl-meta-toluamide; EPA, Environmental Protection Agency.
From Lantos PM, Rumbaugh J, Bockenstedt LK, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR): 2020 Guidelines for the Prevention, Diagnosis and Treatment of Lyme Disease. *Clin Infect Dis.* 2021;72(1):e1–e48, Table 5, p. e13.

not shown benefit with prolonged or repeated treatment with oral or parenteral antibiotics.

PROGNOSIS

There is a widespread misconception that Lyme disease is difficult to cure and that chronic symptoms and clinical recurrences are common. The most likely reason for apparent treatment failure is an incorrect diagnosis of Lyme disease.

The prognosis for children treated for Lyme disease is excellent. Children treated for erythema migrans rarely develop symptoms of late Lyme disease. The long-term prognosis for patients who are treated beginning in the later stages of Lyme disease also is excellent. Although chronic and recurrent arthritis may occur, especially among patients with certain human leukocyte antigen allotypes (an autoimmune process), most children who are treated for Lyme arthritis are cured and have no sequelae. Although there are rare reports of adults who have developed late neuroborreliosis, usually among persons with Lyme disease in whom treatment was delayed for months or years, similar cases in children are rare.

Table 268.4 Management of a Suspected *Ixodes* Tick Bite in the United States

DO	DO NOT
1. Remove tick with clean fine-tipped tweezers (or other comparable device).	1. Do not use other nonmechanical methods for tick removal.
2. Identify tick. Send to a laboratory, refer to an online resource.	2. Do not test tick for pathogens (e.g., send for PCR).
3. Determine if tick meets high-risk criteria. a. Identified as *Ixodes* vector species b. Bite occurred in a highly endemic area c. Attached for ≥36 hr	3. Do not initiate prophylaxis in any other scenario.
Consider initiating prophylaxis if a, b, and c are met AND it is within 72 hr of tick removal. See dosing in the footnote*.	

*Doxycycline is given as a single oral dose, 200 mg for adults and 4.4 mg/kg (up to a maximum dose of 200 mg) for children.
PCR, Polymerase chain reaction.
From Lantos PM, Rumbaugh J, Bockenstedt LK, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR): 2020 Guidelines for the Prevention, Diagnosis and Treatment of Lyme Disease. *Clin Infect Dis.* 2021;72(1):e1–e48, Table 6, p. e13.

PREVENTION

The best way to avoid Lyme disease is to avoid tick-infested areas (Table 268.3). Children should be examined for deer ticks after known or potential exposure (although many people are not able to identify the species or the stage of the tick). If a tick attachment is noted, the tick should be grasped at the mouthparts with a forceps or tweezers; if these are not available, the tick should be covered with a tissue (Table 268.4). The recommended method of tick removal is to pull directly outward without twisting; infection is usually preventable if the tick is removed before 36 hours of attachment; at this time the ticks are flat and nonengorged (Fig. 268.4).

The overall risk for acquiring Lyme disease after a tick bite is low (1–3%) in most endemic areas. If the tick is engorged and present for >72 hours (a high-risk tick bite), the risk of infection may increase to 25% in *hyperendemic* areas. Patients and families should be advised to watch the area for development of erythema migrans and to seek medical attention if the rash or constitutional symptoms occur. If infection develops, early treatment of the infection is highly effective. Prophylaxis after a high-risk tick bite with a single dose of oral doxycycline in adults (200 mg) or 4.4 mg/kg in children is effective in reducing the risk of Lyme disease. The routine testing of ticks that have been removed from humans for evidence of *B. burgdorferi* is not recommended because the value of a positive test result for predicting infection in the human host is unknown.

Personal protective measures that may be effective in reducing the chance of tick bites include wearing protective clothing (long pants tucked into socks, long-sleeved shirts) when entering tick-infested areas, checking for and promptly removing ticks, and using tick repellents such as *N,N*-diethyl-3-methylbenzamide (DEET) (see Table 268.3). This chemical can safely be used on pants, socks, and shoes; care must be used with heavy or repeated application on skin,

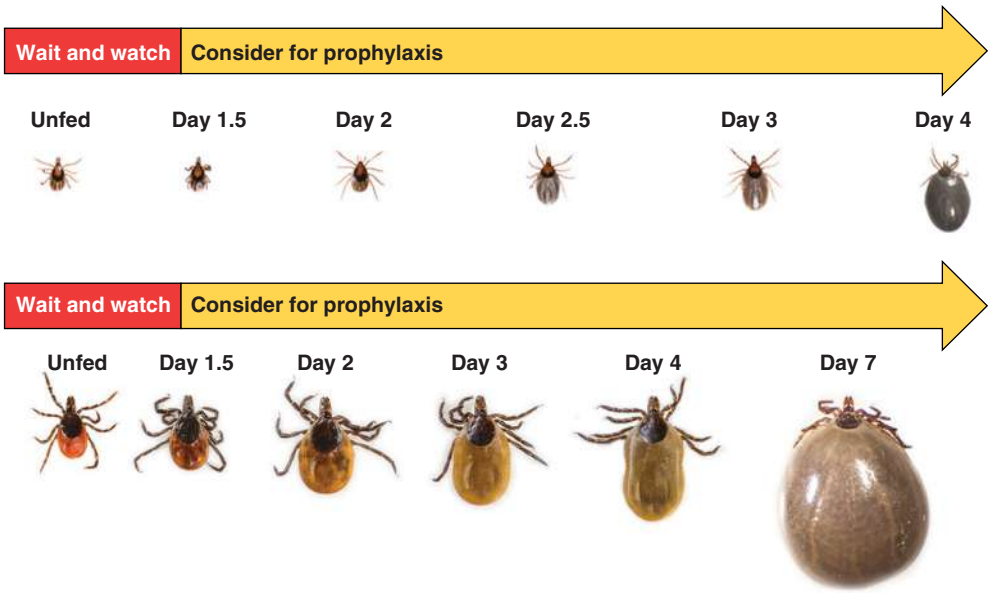

Fig. 268.4 Relative sizes of engorging nymphal and adult female *Ixodes scapularis* (black-legged = deer tick) as a function of time spent feeding (= attachment time). Transmission of *Borrelia burgdorferi* requires 36-48 hr of feeding, and therefore antibiotic prophylaxis is recommended only if the tick has been attached for at least 36 hr, or 1.5 days. By itself, duration of feeding is insufficient for recommending antibiotic prophylaxis. *(Top)* Nymphs (Feeding time: Unfed = 0 hr; Day 1.5 = 36 hr; Day 2 = 48 hr; Day 2.5 = 60 hr; Day 3 = 72 hr; Day 4 = 96 hr). *(Bottom)* Adult females over the same period. Unfed nymph and adult female are the sizes of poppy and sesame seeds, respectively. Not actual size. *(Courtesy of URI TickEncounter Resource Center, TickEncounter.org; From Lantos PM, Rumbaugh J, Bockenstedt LK, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America [IDSA], American Academy of Neurology [AAN], and American College of Rheumatology [ACR]: 2020 Guidelines for the Prevention, Diagnosis and Treatment of Lyme Disease. Clin Infect Dis. 2021;72[1]:e1–e48, Fig. 6.)*

particularly in infants, because of the risk of systemic absorption and toxicity. Permethrin treatment of clothing is also an effective prevention strategy.

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Section 9

Mycoplasmal Infections

Chapter 269

Mycoplasma pneumoniae

Asuncion Mejias and Octavio Ramilo

Among the few *Mycoplasma* species isolated from the human respiratory tract, *Mycoplasma pneumoniae* remains the most common species causing respiratory infections in school-age children and young adults and is associated with a variety of clinical manifestations.

THE ORGANISM

Mycoplasmas are the smallest self-replicating prokaryotes known to cause disease in humans. Their size of 150-250 nm is more on the order of viruses than bacteria. *M. pneumoniae* is a fastidious double-stranded DNA bacterium that is distinguished by a small genome (~800,000 base pairs) and a long doubling time, which makes culturing it a slow process (5-20 days) compared to other bacteria. *M. pneumoniae* isolates can be classified in two major genetic groups (subtypes 1 and 2) based on the P1 adhesion protein. Distinguishing these two subtypes is important for epidemiologic purposes. Like other mycoplasmas, *M. pneumoniae* is distinguished by the complete absence of a cell wall, resulting in (1) their dependence on host cells for obtaining essential nutrients, (2) their intrinsic resistance to β-lactam agents, and (3) their pleomorphic shape and lack of visibility on Gram staining.

EPIDEMIOLOGY

M. pneumoniae infections occur worldwide and throughout the year. This organism is a frequent cause of community-acquired pneumonia (CAP) in children >5 years of age and adults, accounting for ~20% of all CAP in middle school and high school children and up to 50% of CAP in college students and military recruits. The proportion of cases increases according to age, as recently shown in a large population-based study of CAP conducted in the United States (3% in <5 years, 17% in 5-9 years, and 24% in 10-17 years).

In contrast to the acute, short-lived epidemics associated with some respiratory viruses, *M. pneumoniae* infection occurs endemically worldwide. Epidemic outbreaks of variable intensity occur every few years and are likely related to the alternative circulation of the two *M. pneumoniae* subtypes. Transmission occurs through the respiratory route by large droplet spread during close contact with a symptomatic person. Community outbreaks have been described in closed settings (colleges, boarding schools, military bases) and can spread largely through school contacts. Attack rates within families are high, with transmission rates of 40–80% for household adult and children contacts, respectively. In contrast to many other respiratory infections, the incubation period is 2-3 weeks; hence, the course of infection in a specific population (family) may last several weeks.

The occurrence of mycoplasma illnesses is related, in part, to age and preexposure immunity. Overt illness is less common before 3 years of age but can occur. Children younger than 5 years of age appear to have milder illnesses associated with upper respiratory tract involvement, vomiting, and diarrhea. Immunity after infection is not long-lasting, as evidenced by the frequency of reinfections over time. Other pathogens

are frequently co-detected in children with *M. pneumoniae,* especially in those younger than 2 years of age, where viral co-infections have been identified in up to 30% of cases. *Asymptomatic carriage* after infection can last up to 4 months despite antibiotic therapy and may contribute to prolonged outbreaks. Children are often the reservoir from whom mycoplasma spreads. In the clinical setting, there are no available tools yet to differentiate carriage vs infection.

PATHOGENESIS

The pathogenicity of *M. pneumoniae* is dependent on its extracellular attachment and the initiation of the host cell immune response. The mechanisms by which *M. pneumoniae* causes disease include (1) direct bacterial invasion that initiates in the cells of the ciliated respiratory epithelium, the target cells of *M. pneumoniae* infection; (2) toxin mediated through the production of the adenosine diphosphate–ribosylating and vacuolating toxin termed *community-acquired respiratory distress syndrome* (CARDS), an exotoxin that may damage the respiratory tract and has been associated with more severe or even fatal disease; and (3) indirect immune-mediated effects, by altering antigens in the cell surface and inducing the production of autoantibodies.

The organism is an elongated snakelike structure with a one-end organelle, which mediates the attachment to sialic acid receptors in the cilia through a complex set of adhesion transmembrane proteins (P1, P30, proteins B and C, P116, and HMW1-3). Virulent organisms attach to ciliated respiratory epithelial cell surfaces located in the bronchi, bronchioles, alveoli, and possibly upper respiratory tract and burrow down between cells, resulting in ciliostasis and eventual sloughing of the cells. This bacterium is capable of forming biofilms, with strain-specific phenotypic differences, which hinder antibiotic penetration and recognition by the immune system.

Once *M. pneumoniae* reaches the lower respiratory tract, it promotes the polyclonal activation of B lymphocytes and $CD4^+$ T cells and amplifies the immune response with the production of various proinflammatory and antiinflammatory cytokines and chemokines, such as tumor necrosis factor-α, interleukin (IL)-8, IL-1β, Il-6, and IL-10.

Although it is well documented that specific cell-mediated immunity and antibody titers against *M. pneumoniae* increase with age (and therefore probably follow repeated infections), the immune mechanisms that protect against or clear the infection are not well defined. In humans, nasal IgA antibodies correlated with protection after experimental challenge. A distinct aspect of *M. pneumoniae* is its ability to induce the production of cold agglutinins (IgM antibodies) directed against the I antigen on the erythrocyte's surface. Even though antibody responses do not confer complete protection against reinfections, the importance of a robust humoral response is apparent, because patients with congenital antibody deficiencies, such as those with hypogammaglobulinemia, can develop severe and prolonged disease and have a higher risk of extrapulmonary manifestations. In children with sickle cell disease or sickle-related hemoglobinopathies, *M. pneumoniae* is a common infectious trigger of acute chest syndrome. These children and also children with Down syndrome can develop severe *Mycoplasma* pneumonia. On the other hand, *M. pneumoniae* does not seem to be a common infectious agent in patients with AIDS.

M. pneumoniae has been detected by polymerase chain reaction (PCR) in many nonrespiratory sites, including blood, pleural fluid, cerebrospinal fluid (CSF), and synovial fluid. The mechanisms of extrapulmonary disease associated with *M. pneumoniae* are unclear and appear to be different according to the duration of symptoms at the time of presentation: direct invasion vs immune-mediated.

CLINICAL MANIFESTATIONS

M. pneumoniae is a frequent cause of upper and lower respiratory tract infections in children and adolescents. The clinical manifestations of *M. pneumoniae* can be divided into respiratory (more common) and extrapulmonary (less common).

Respiratory Tract Disease

Tracheobronchitis and atypical pneumonia are the most commonly recognized clinical syndromes associated with *M. pneumoniae*. This agent is responsible for up to 20% of all cases of CAP. The clinical manifestations of *M. pneumoniae* pneumonia evolve according to the stage of the disease. The onset is usually characterized by gradual development of headache, malaise, fever, and sore throat, followed by progression of lower respiratory symptoms, including hoarseness and nonproductive cough. The gradual onset in children with atypical pneumonia is in contrast to the sudden onset of lobar pneumonia. Coryza and gastrointestinal manifestations are unusual and suggest a viral etiology, if present. Approximately 10% of children will develop a cutaneous maculopapular rash. Although the clinical course in untreated patients is variable, cough, the clinical hallmark of *M. pneumoniae* infection, usually worsens during the first week of illness. Symptoms generally resolve within 2 weeks, although cough can last up to 4 weeks and may be accompanied by wheezing.

Chest examination may be unrevealing, even in patients with severe cough. There may be no auscultative or percussive findings or only minimum dry rales. Clinical findings are often less severe than suggested by the chest radiograph, explaining why the term "walking pneumonia" is often used to describe CAP caused by *M. pneumoniae*. Radiographic findings are variable and nonspecific, not allowing differentiation from viral or bacterial pathogens. Bilateral diffuse infiltrates, lobar pneumonia, or hilar lymphadenopathy can occur in up to 30% of patients. Although unusual, large pleural effusions associated with lobar infiltrates and necrotizing pneumonia have been described in patients with immunodeficiency, Down syndrome, chronic cardiopulmonary disease, and sickle cell disease. The white blood cell and differential counts are usually normal, whereas the erythrocyte sedimentation rate and C-reactive protein are often elevated. Appropriate antibiotics shorten the duration of illness but do not reliably eradicate the organism from the respiratory tract.

Other respiratory illnesses occasionally caused by *M. pneumoniae* include undifferentiated upper respiratory tract infections; intractable, nonproductive cough; pharyngitis (usually without marked cervical lymphadenopathy); sinusitis; croup; and bronchiolitis. *M. pneumoniae* is a common trigger of wheezing in asthmatic children and can cause chronic colonization in the airways, resulting in lung dysfunction in adolescent and adult asthmatic patients. Otitis media and bullous myringitis, which also occur with other viral and bacterial infections, have been described but are rare, and their absence should not exclude the diagnosis of *M. pneumoniae*.

Extrapulmonary Disease

Despite the reportedly rare isolation of *M. pneumoniae* from nonrespiratory sites, the improved sensitivity of PCR for *M. pneumoniae* DNA detection has led to increasing identification of this bacterium in nonrespiratory sites, particularly the central nervous system (CNS). Patients with or without respiratory symptoms can have involvement of the skin, CNS, blood, heart, gastrointestinal tract, and joints. Extrapulmonary manifestations have been documented in 11–26% of children with *M. pneumoniae* infection and include:

1. ***CNS disease:*** Occurs in 0.1% of all patients with *M. pneumoniae* infection and in 7% of those requiring hospitalization. Manifestations include encephalitis, acute disseminated encephalomyelitis (ADEM), transverse myelitis, cerebellar ataxia, aseptic meningitis, Guillain-Barré syndrome, Bell palsy, and peripheral neuropathy. CNS disease manifestations occur 3-23 days (mean: 10 days) after onset of respiratory illness but may not be preceded by any signs of respiratory infection in up to 20% of cases. Studies in children suggest that there are two pathogenic mechanisms for *M. pneumoniae*–associated neurologic disease: the first pattern is characterized by almost absent or no prodromal respiratory symptoms (<7 days) and nonreactive IgM responses. On the other hand, the second pattern is characterized by the presence of respiratory symptoms (most commonly cough) for ≥7 days and reactive IgM in acute serum. In the first group *M. pneumoniae* is usually identified in CSF by PCR but not in the respiratory tract, whereas in children presenting with ≥7 days of respiratory symptoms, the opposite is true. These studies suggest that encephalitis occurring more than 7 days after onset of prodromal symptoms is more likely to be caused by an autoimmune response to *M. pneumoniae,* whereas its occurrence early in the course of the disease may be associated with direct bacterial invasion of the CNS. Involvement of the brainstem can result in severe

dystonia and movement disorders. The CSF may be normal or have mild mononuclear pleocytosis and/or increased CSF protein concentrations with normal glucose. Diagnosis is confirmed with positive CSF PCR, positive PCR from a throat swab, or demonstration of seroconversion. Findings on MRI include focal ischemic changes, ventriculomegaly, diffuse edema, or multifocal white matter inflammatory lesions consistent with postinfectious ADEM. Long-term sequelae have been reported in 23–64% of cases.

2. ***Mucocutaneous disease:*** Up to 25% of children with *M. pneumoniae* infections can have associated skin and mucosal exanthems, most notably maculopapular rashes, urticaria, and *Mycoplasma*-induced rash and mucositis syndrome (MIRM) or Stevens-Johnson syndrome (SJS). Gianotti-Crosti syndrome and erythema nodosum are also associated with *M. pneumoniae* infections. Approximately 10% of children with *M. pneumoniae* CAP will exhibit a maculopapular rash. *Mycoplasma*-induced rash and mucositis usually develop 3-21 days after initial respiratory symptoms, last less than 14 days, and are rarely associated with severe complications (Figs. 269.1 and 269.2). *M. pneumoniae* may also produce an isolated oral mucositis in absence of a rash.
3. ***Hematologic abnormalities:*** Include mild degrees of hemolysis with a positive Coombs test and minor reticulocytosis 2-3 weeks after the onset of illness. Severe hemolysis is associated with high titers of cold hemagglutinins (≥1:512) and occurs rarely. Thrombocytopenia, aplastic anemia, hemophagocytic syndrome, and coagulation defects occur occasionally.

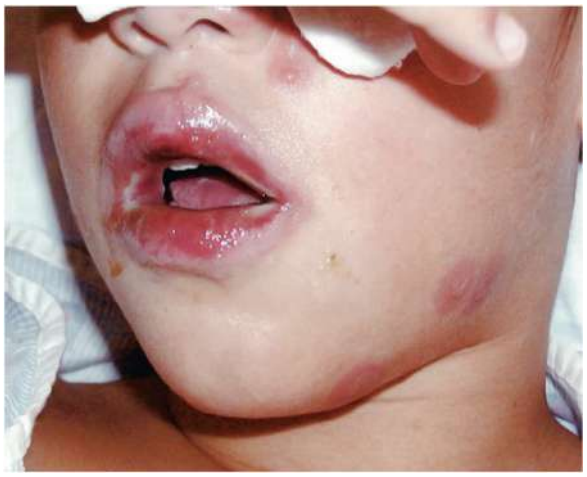

Fig. 269.1 Lip changes found in *Mycoplasma pneumoniae*–associated mucositis.

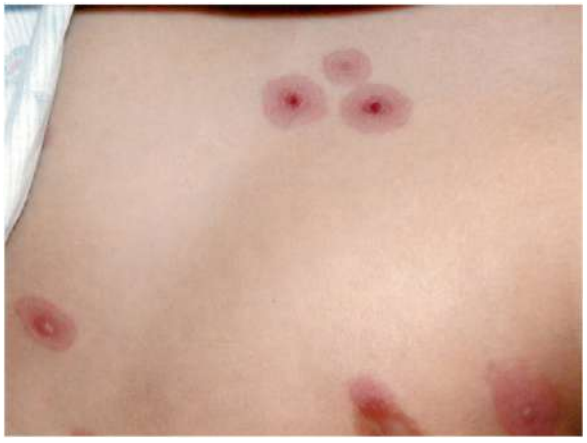

Fig. 269.2 Classic skin lesions found in *Mycoplasma pneumoniae*–associated rash.

4. ***Musculoskeletal:*** Arthritis appears to be less common in children than in adults, but monoarthritis, polyarthritis, and migratory arthritis have been described. Rhabdomyolysis has also been documented, often associated with other organ system manifestations.
5. ***Other conditions,*** such as mild hepatitis, gastroenteritis, pancreatitis, acute glomerulonephritis, iritis or uveitis, and cardiac complications (pericarditis, myocarditis, and rheumatic fever–like syndrome, most commonly seen in adults) are also described. Fatal *M. pneumoniae* infections are rare.

DIAGNOSIS

No specific clinical, epidemiologic, or laboratory parameters allow for a definite diagnosis of *M. pneumoniae* infection. Nevertheless, pneumonia in school-age children and young adults with a gradual onset and cough as prominent findings suggests *M. pneumoniae* infection. The best method for diagnosis is a combination of PCR from respiratory samples and serology (acute and convalescent), as *M. pneumoniae* colonizes the airway and has been identified in 17–25% of asymptomatic children.

Cultures on special media (SP4 agar media) of the throat or sputum might demonstrate the classic *M. pneumoniae* "mulberry" colonies, but growth generally requires incubation for more than 2-3 weeks. The fastidious nutritional requirements of *Mycoplasma* make cultures slow and impractical, and few laboratories maintain the capability of culturing *M. pneumoniae*.

Serologic tests (immunofluorescence tests, enzyme-linked immune assays [EIAs]) to detect serum immunoglobulin (Ig) M, IgA, and IgG antibodies against *M. pneumoniae* are commercially available. IgM antibodies have a high rate of false-positive and false-negative results. In most cases, IgM antibodies are not detected within the first week after symptom onset or in children with recurrent infections and may be positive for up to 6-12 months after infection, or even years, and thus may not indicate acute infection. A fourfold or greater increase in IgG antibody titers against *M. pneumoniae* between acute and convalescent sera obtained 2-4 weeks apart is diagnostic. Complement fixation assays are less sensitive and specific than EIA or immunofluorescent assays.

Cold hemagglutinins (cold-reacting antibodies [IgM] against red blood cells) can be detected in approximately 50% of patients with *M. pneumoniae* pneumonia. These antibodies are nonspecific, especially at titers <1:64, as modest increases in cold hemagglutinins can be observed in other viral infections. Cold agglutinin antibodies should not be used for the diagnosis of *M. pneumoniae* infections if other methods are available.

Nucleic acid amplification test (NAATs) for *M. pneumoniae* have replaced other diagnostic tests. PCR of a nasopharyngeal or throat swab (the combination of both increases sensitivity) for *M. pneumoniae* genomic DNA carries a sensitivity and a specificity of 80% to >97%. Different primers have been used to identify gene sequences of the P1 cytoadhesion protein or the ribosomal (r) 16S RNA. PCR allows a more rapid diagnosis in acutely ill patients and can be positive earlier in the course of infection than serologic tests. Identification of *M. pneumoniae* by PCR (or culture) from a patient with compatible clinical manifestations suggests causation.

The diagnosis of extrapulmonary disease associated with *M. pneumoniae* is challenging. Although *M. pneumoniae* has been identified by PCR in the CSF of children with encephalitis, there are currently no reliable tests for the diagnosis of CNS or other nonrespiratory sites associated with *M. pneumoniae*. Because the extrapulmonary manifestations of *M. pneumoniae* may have an immunologic base, measuring acute and convalescent IgM and IgG antibody levels is advisable.

TREATMENT

M. pneumoniae illness is usually mild, and most cases of pneumonia can be managed without the need for hospitalization. Because mycoplasmas lack a cell wall, they are inherently resistant to β-lactam agents that act by inhibiting the cell wall synthesis. In addition, drugs from other classes, such as trimethoprim, rifampin, or linezolid, are inactive against *M. pneumoniae*. Studies regarding the effectiveness of antimicrobial therapy for *M. pneumoniae* infections in children are contradictory. Nevertheless, empiric treatment is often initiated in hospitalized children with CAP or severe extrapulmonary manifestations based on clinical suspicion because of the difficulty of a definitive diagnosis.

Antimicrobial Therapy

M. pneumoniae is typically sensitive to macrolides (erythromycin, clarithromycin, azithromycin), tetracyclines, and quinolones in vitro. Treatment of *Mycoplasma* does not assure eradication. Data from observational studies showed that macrolide treatment of children with *M. pneumoniae* CAP shortened the course of illness. Treatment may be more effective when started within 3-4 days of illness onset. Although macrolides do not have bactericidal activity, they are preferred in children younger than 8 years of age. Two multicenter studies of pediatric CAP demonstrated comparable clinical and bacteriologic success rates between erythromycin and clarithromycin or azithromycin. However, the newer macrolides were better tolerated. The recommended treatment is **clarithromycin (15 mg/kg/day divided into two doses PO for 10 days; maximum daily dose 1 g) or azithromycin (10 mg/kg PO once on day 1 [maximum dose 500 mg] and 5 mg/kg once daily [maximum dose 250 mg] PO on days 2-5)**. Doxycycline (2-4 mg/kg/day PO twice a day for 7 days, maximum daily dose 200 mg) in children of all ages and fluoroquinolones such as levofloxacin (10 mg/kg per dose twice a day in children <5 years; 10 mg/kg/day once a day in children ≥5 years—maximum daily dose 750 mg—for 7-10 days) are effective but have higher minimum inhibitory concentrations (MICs) compared with macrolides and currently are not recommended as a first-line therapy in children.

Macrolide-resistant *M. pneumoniae* infections should be suspected in patients with severe infections not responding to macrolide therapy within the first 48 hours of treatment, especially if they have a history of exposure to macrolides. Macrolide-resistant *M. pneumoniae* strains have been reported in Asia (70–90% in Japan and China), Europe (with great variability from country to country: 0% in the Netherlands vs 26% in Italy), and Israel. In the United States and Canada, the rates of resistance have varied from 2.8% to 13% of cases. The clinical significance of macrolide-resistant infections has not been completely elucidated. However, if macrolide-resistant *M. pneumoniae* is suspected, switching to a nonmacrolide antimicrobial regimen such as doxycycline or levofloxacin might be prudent.

Adjunctive Therapy

There is no evidence that treatment of upper respiratory tract or nonrespiratory tract disease with antimicrobial agents alters the course of illness. However, patients with severe manifestations of extrapulmonary disease may benefit from antimicrobial treatment because direct involvement of the bacterium cannot be excluded. Oftentimes antibiotics are administered in combination with immunomodulatory therapy. In this regard, corticosteroids with or without intravenous immunoglobulin are the most commonly used agents for managing severe *M. pneumoniae* extrapulmonary manifestations, particularly for patients with CNS involvement or rash and mucositis. Although definitive data are lacking, case studies suggest the associated clinical benefit of steroids in the management of severe lung disease, SJS, and hemolytic anemia.

PREVENTION

Trials with inactivated and live attenuated vaccines for *M. pneumoniae* have been conducted with disappointing results. In hospitalized patients, standard and droplet precautions are recommended for the duration of symptoms. It is important to emphasize that *Mycoplasma* infection remains contagious as long as cough persists and despite successful antibiotic therapy. Prophylaxis with tetracyclines or azithromycin substantially reduces the secondary attack rates in institutional outbreaks and family close contacts. Antimicrobial prophylaxis is not recommended routinely; however, it can be considered in patients at high risk for severe disease, such as children with sickle cell disease.

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Chapter 270

Genital Mycoplasmas (*Mycoplasma hominis, Mycoplasma genitalium,* and *Ureaplasma urealyticum*)

María I. Sánchez Códez and Asuncion Mejias

ETIOLOGY

Mycoplasma species are small pleomorphic bacteria that typically lack a cell wall and are bound by a cell membrane. Many of the biologic properties of mycoplasmas are in fact the result of the absence of a rigid cell wall, including resistance to β-lactam antibiotics. These ubiquitous organisms are difficult to cultivate using routine media and belong to the family Mycoplasmataceae in the class Mollicutes and represent the smallest self-replicating organisms known to date. The entire genome of many of the *Mycoplasma* species is among the smallest of the prokaryotic genomes. The family Mycoplasmataceae is composed of two genera responsible for human infection: *Mycoplasma* and *Ureaplasma.* Of those, *Mycoplasma hominis, Mycoplasma genitalium,* and *Ureaplasma* spp., which include *Ureaplasma urealyticum* (biovar 2) and *Ureaplasma parvum* (biovar 1), are considered human urogenital pathogens and are reviewed in this chapter. The main feature that distinguishes *Ureaplasma* spp. from *Mycoplasma* spp. is the ability of the former to hydrolyze urea for energy production.

Genital mycoplasmas are often associated with sexually transmitted infections such as cervicitis and nongonococcal urethritis (NGU) or with puerperal infections such as endometritis. *M. hominis* and *Ureaplasma* spp. commonly colonize the female genital tract and can cause chorioamnionitis, colonization of neonates, and perinatal infections. The role of *M. genitalium* in pregnant women has not been well defined.

EPIDEMIOLOGY

Genital mycoplasmas are part of the normal flora and are commonly present in the genitourinary (GU) tract of postpubertal women and men and the upper respiratory tract. The prevalence of genital colonization with these bacteria has been directly associated with low socioeconomic status, hormonal changes, and ethnicity and increases proportionally according to sexual activity, being highest among individuals with multiple sexual partners. Female colonization is greatest in the vagina (and less in the endocervix, urethra, and endometrium), with rates varying from 40% to 80% for *Ureaplasma* spp. and 21–50% for *M. hominis* among sexually active asymptomatic women. *Ureaplasma* is isolated less often from urine than from the cervix, but *M. hominis* is present in the urine and in the cervix with approximately the same frequency. Male colonization is less common and occurs primarily in the urethra. Among prepubertal children and sexually inactive adults, colonization rates are <10%. *M. genitalium* is implicated in approximately 15–20% of NGU cases in men and in 10–30% of women with cervicitis and also plays a role in pelvic inflammatory disease in women. Studies using polymerase chain reaction (PCR) show that colonization of the female lower urogenital tract with *M. genitalium* is less common than with *M. hominis* or *Ureaplasma* spp.

TRANSMISSION

Genital mycoplasmas are transmitted by sexual contact or by vertical transmission from mother to infant. As with other perinatal infections, vertical transmission can occur through ascending intrauterine infection or hematogenous spread from placental infection but most often occurs through a colonized birth canal at the time of delivery. Transmission rates among neonates born to women colonized with *Ureaplasma* spp. range from 18% to 88%. Neonatal colonization rates are higher among infants who weigh <1,000 g, infants who are born in the presence of chorioamnionitis, and infants born to mothers who are heavily colonized and of lower socioeconomic status. Neonatal colonization is transient and decreases proportionally with age. Organisms may be recovered from the newborn's throat, vagina, rectum, and, occasionally, conjunctiva and respiratory tract.

PATHOGENESIS

Genital mycoplasmas can cause chronic inflammation of the GU tract and amniotic membranes. These bacteria usually live in a state of adherence to the respiratory or urogenital tract but can disseminate to other organs when there is a disruption of the mucosa or a weakened or immature immune system, such as in premature infants. *Ureaplasma* spp. can infect the amniotic sac early in gestation without rupturing the amniotic membranes, resulting in a clinically silent, chronic chorioamnionitis characterized by an intense inflammatory response. In addition, mycoplasmas and *Ureaplasma* spp. hydrolyze arginine or urea into ammonium for energy production. Ammonium causes an increase in the genital pH that leads to bacterial dysbiosis with a reduction in *Lactobacillus* and overgrowth of other genital bacteria that can promote preterm labor, premature rupture of membranes, and chorioamnionitis.

Attachment to fetal human tracheal epithelium can cause ciliary disarray, clumping, and loss of epithelial cells. In vitro studies show that *Ureaplasma* spp. stimulates macrophage production of interleukin (IL)-6 and tumor necrosis factor-α. In addition, high concentrations of proinflammatory cytokines possibly associated with development of bronchopulmonary dysplasia (BPD) of prematurity, such as monocyte chemoattractant protein-1 and IL-8, have been found in tracheal secretions from very low birthweight infants colonized with *Ureaplasma* spp. Immunity appears to require serotype-specific antibody. Thus lack of maternal antibodies might account for a higher disease risk in premature newborns.

CLINICAL MANIFESTATIONS

The main syndromes associated with *Ureaplasma* spp., *M. genitalium,* and *M. hominis* are displayed in Table 270.1.

Intrauterine and Neonatal Infections

Chorioamnionitis and Early Onset Infections

Genital mycoplasmas are associated with a variety of fetal and neonatal infections. *Ureaplasma* spp. have been associated with clinically inapparent chorioamnionitis, resulting in spontaneous abortion, increased fetal death, or premature delivery, although the causative role remains uncertain. Studies have shown that women with *Ureaplasma* spp. detected by PCR in amniotic fluid in the first or second trimester of gestation have an increased risk of preterm labor and delivery. In addition, *Ureaplasma* spp. are the microorganism most commonly identified by PCR in women with premature rupture of membranes, and data suggest that *U. parvum* plays a bigger role than *U. urealyticum* in prematurity.

Table 270.1 Clinical Syndromes and Antibiotic Therapy for Ureaplasmas and Mycoplasmas Infection

	UREAPLASMA SPP.	*M. HOMINIS*	*M. GENITALIUM*
INTRAUTERINE AND NEONATAL INFECTIONS			
Chorioamnionitis	++	++	–
Preterm delivery	++	+	++
Postpartum fever	++	+++	UK
BPD	+++	+	UK
CNS infections	+	+	UK
NEC	+	UK	UK
GENITOURINARY INFECTIONS			
NGU (acute/chronic)	++*	–	+++
Cervicitis	–	–	+++
PID	+	++	+++
NON-NEONATAL/NONGENITOURINARY INFECTIONS			
CNS disease†	+	++	–
Bacteremia	+	++	–
Surgical wound infections	++	++	–
Arthritis	+	++	–
TREATMENT			
Macrolides	++	–	++
Quinolones‡	+	++	+
Clindamycin	–	++	+
Tetracyclines (doxycycline)	++	+	+

*Only *Ureaplasma urealyticum* (not *parvum*).
†CNS disease include meningitis, hydrocephalus, brain abscess, subdural empyema, intraventricular hemorrhage, and nonfunctioning CNS shunts.
‡The most commonly used quinolones are ciprofloxacin, levofloxacin, and moxifloxacin.
BPD, Bronchopulmonary dysplasia; CNS, central nervous system; NEC, necrotizing enterocolitis; NGU, nongonococcal urethritis; PID, pelvic inflammatory disease; UK, unknown.

Ureaplasma spp. can also be recovered from tracheal, blood, cerebrospinal fluid (CSF), or lung biopsy specimens in up to 50% of sick infants younger than 34 weeks of gestation. In a study of 351 mother/infant dyads, isolation of *Ureaplasma* spp. or *M. hominis* from cord blood was documented in 23% of infants born between 23 and 32 weeks of gestation and correlated with the development of systemic inflammatory response syndrome.

Bronchopulmonary Dysplasia

The role of these organisms in causing severe respiratory insufficiency, the need for mechanical ventilation, the development of BPD, or death remains controversial. Nevertheless, meta-analyses of published studies have identified respiratory colonization with *Ureaplasma* spp. as an independent risk factor for the development of BPD. However, trials using erythromycin or azithromycin therapy in high-risk preterm infants with tracheobronchial colonization of *Ureaplasma* spp. have failed to show any difference in the development of BPD in treated vs. nontreated infants. Similarly, treatment with azithromycin in pregnant women colonized with *Ureaplasma* spp. did not show a reduction in the risk of BPD in neonates. To date there is not enough evidence to support the use of antibiotic therapy in preterm infants at risk for or with confirmed *Ureaplasma* spp. infection to prevent the development of BPD.

Central Nervous System Infections

M. hominis and *Ureaplasma* spp. have been isolated from the CSF of premature infants and, less commonly, full-term infants. These bacteria may represent true pathogens and may be associated with CNS disease based on the host susceptibility/gestational age and bacteria pathogenicity. However, the clinical significance of recovering *M. hominis* and *Ureaplasma* spp. from the CSF is uncertain, as most infants have no overt signs of CNS disease, CSF pleocytosis is not consistent, and spontaneous clearance of mycoplasmas has been documented without specific therapy.

Ureaplasma spp. have been associated with the development of subdural empyema and meningitis associated with intraventricular hemorrhage (IVH) and hydrocephalus. Limited data suggest that meningitis caused by *M. hominis* can also be associated with IVH, hydrocephalus, and brain abscess, particularly in low birthweight or preterm neonates and in infants with neural tube defects. In a review of 29 reported neonatal cases with *M. hominis* meningitis, 8 (28%) neonates died and 8 (28%) developed neurologic sequelae. The age of onset of meningitis ranges from 1 to 196 days of life, and organisms can persist in the CSF without therapy for days to weeks. Pachymeningitis may be evident on MRI.

Other: *M. hominis* and *Ureaplasma* spp. have also been associated with neonatal conjunctivitis, abscesses (mainly at the scalp electrode site and associated with *M. hominis*), pneumonia, bacteremia, and necrotizing enterocolitis (NEC).

Genitourinary Infections

In sexually active adolescents and adults, genital mycoplasmas are associated with sexually transmitted diseases and are rarely associated with focal infections outside the genital tract. *U. urealyticum* (not *U. parvum*) and *M. genitalium* are recognized etiologic agents of NGU, mainly in men, and represent the second most common cause of urethritis after *Chlamydia trachomatis*. *M. genitalium* has been identified in 30% of patients with persistent or recurrent NGU, because this bacterium is relatively resistant to the antibiotics recommended for the treatment of NGU. Rare complications of NGU include epididymitis and prostatitis. Salpingitis, cervicitis, pelvic inflammatory disease, and endometritis have been described in women associated with *M. genitalium* and, to a lesser extent, with *M. hominis*.

Nongenital Infections

Ureaplasma spp. and *M. hominis* infections are rarely described outside the neonatal period. These infections have been reported in both immunocompetent and immunocompromised children, including patients with hypogammaglobulinemia, lymphoma, or solid organ transplant recipients, who appear to be at higher risk of infection.

Cases of *Ureaplasma* spp. pneumonia, osteomyelitis, arthritis, meningitis, mediastinitis, bacteremia, infection of aortic grafts, and surgical site infections have been reported. Recent data suggest that *Ureaplasma* spp. is associated with posttransplant hyperammonemia syndrome, a rare but potentially fatal complication.

M. hominis is most commonly reported in systemic infections and has been associated with CNS disease (including meningitis, brain abscesses, subdural empyema, and nonfunctioning shunts), surgical wound infections, arthritis (associated in up to 50% of cases with prior manipulation of the GU tract), prosthetic and naïve endocarditis, osteomyelitis, and pneumonia. There are reports of life-threatening mediastinitis, sternal wound infections, pleuritis, peritonitis, and pericarditis, with high mortality rates in patients after organ transplantation. These infections should be suspected in culture-negative systemic or local infections, when samples have been properly collected and before initiation of antibiotic therapy.

DIAGNOSIS

All Mollicutes lack a cell wall and are therefore not visible on Gram stain. *M. hominis* and *Ureaplasma* spp. can grow in cell-free media and require sterols for growth, producing characteristic colonies on agar. Colonies of *M. hominis* are 200-300 μm in diameter with a fried-egg appearance, whereas colonies of *Ureaplasma* spp. are smaller (16-60 μm in diameter). *M. genitalium* is a fastidious organism and can be isolated with difficulty in cell culture systems, requiring up to 8 weeks to be detected. Most clinical microbiology laboratories do not routinely test for these pathogens, and nucleic acid–based tests are the preferred method for diagnosis. PCR-based assays have greater sensitivity than culture (90% vs 40%, respectively) and provide a more practical method for detection. Serologic assays for genital mycoplasmas have limited value in the clinical setting and are not commercially available for diagnostic purposes. In addition, serologic studies for *Ureaplasma* spp. are not useful because of the high prevalence of colonization in healthy children and adults.

Genital Tract Infection

Confirmation of genital tract infection is challenging because of the high colonization rates in the vagina and urethra. NGU is typically defined as new-onset urethral discharge or dysuria with Gram stain of urethral discharge showing ≥5 polymorphonuclear leukocytes per oil-immersion field in the absence of gram-negative diplococci (i.e., *Neisseria gonorrhoeae*). The lack of cell wall prevents the identification of these bacteria by routine Gram stain. Detection of *Ureaplasma* spp. or *M. hominis* by PCR is available for a variety of specimens, including urine and swabs of the cervix, urethra, and vagina. *M. genitalium* is often identified by nucleic acid amplification tests (NAATs) of first-void urine specimens in men and vaginal swabs in women.

Neonates

Ureaplasma spp. and *M. hominis* have been isolated from urine, blood, CSF, tracheal aspirates, pleural fluid, abscesses, and lung tissue. Premature neonates who are clinically ill with pneumonitis, focal abscesses, or CNS disease (particularly progressive hydrocephalus with or without pleocytosis) for whom bacterial cultures are negative or in whom there is no improvement with standard antibiotic therapy warrant further workup to rule out genital mycoplasmas. Isolation of *Ureaplasma* spp. and *M. hominis* requires special media using urea for the former and arginine for the latter, and clinical specimens must be cultured immediately or frozen at −70°C (−94°F) to prevent loss of organisms. *M. hominis* can also be detected sometimes using routine laboratory media such as blood agar or chocolate agar. When inoculated into broth containing arginine (for *M. hominis*) or urea (for *Ureaplasma* spp.), growth is indicated by an alkaline pH. Identification of

Ureaplasma spp. on agar requires 1-3 days of growth and visualization with the dissecting microscope, whereas *M. hominis* is apparent to the eye but can require 2-7 days to grow. PCR-based assays are available and will shed light on the causality of these pathogens when sterile sites are tested (e.g., CSF, joint fluid).

TREATMENT

These organisms lack a cell wall, and thus **β-lactam agents or glycopeptides are not effective**. These bacteria are also resistant to sulfonamides and trimethoprim because they do not synthesize folic acid. Rifamycins do not have activity against Mollicutes (see Table 270.1).

Unlike other mycoplasmas and ureaplasmas, ***M. hominis* is resistant to macrolides** but generally susceptible to clindamycin and quinolones. **Most *Ureaplasma* spp. are susceptible to macrolides and advanced-generation quinolones**, such as levofloxacin or moxifloxacin, but are intrinsically resistant to aminoglycosides and often resistant to ciprofloxacin and clindamycin. Susceptibility to tetracyclines is variable for both organisms, with increasing resistance being reported. ***M. genitalium* is typically susceptible to macrolides and moxifloxacin**, with variable resistance to tetracyclines and clindamycin.

Adolescents and Adults

Recommended treatment for NGU should include antibiotics with activity against *C. trachomatis* with either doxycycline (100 mg PO twice daily for 7 days) or azithromycin (1 g PO as a single dose). If adherence to a multiday regimen is not a concern, azithromycin administered over a 5-day course (500 mg on day 1 followed by 250 mg daily for 4 days) is an alternative and may limit the development of resistance. Recurrent NGU after completion of treatment suggests the presence of doxycycline or azithromycin-resistant *M. genitalium*. If the initial empiric regimen did not include macrolides, retreatment with an azithromycin-based regimen may be indicated. Azithromycin is also preferred in children younger than 8 years and in those with allergy to tetracyclines. On the other hand, if patients received azithromycin initially, retreatment with moxifloxacin may be most effective. Before the introduction of azithromycin, up to 60% of patients with *M. genitalium* NGU developed recurrent or chronic urethritis despite 1-2 weeks of treatment with doxycycline.

Sexual partners should also be treated to avoid recurrent disease in the index case. Nongenital mycoplasmal infections may require surgical drainage and prolonged antibiotic therapy.

Neonates

Treatment of these infections in neonates is challenging, and **no optimal treatment has been established**. Doxycycline and quinolones are generally avoided at this age because of their associated toxicities. In addition, attributing causality may be difficult. In general, therapy for neonates with genital mycoplasma infections is indicated if infections are associated with pure growth of the organism or if the organism is detected by PCR from a normally sterile site in conjunction with compatible disease manifestations to assure the treatment of an infectious process rather than merely colonization.

Treatment is usually based on predictable antimicrobial sensitivities because susceptibility testing is not readily available for individual isolates (see Table 270.1). The treatment of BPD with **azithromycin** for the treatment of ***Ureaplasma* spp.** remains controversial. For infants with symptomatic central nervous system (CNS) infection, cures have been described with chloramphenicol, doxycycline, and quinolones, as they have better penetration into the CSF than macrolides. The long-term consequences of asymptomatic CNS infection associated with genital mycoplasmas, especially in the absence of pleocytosis, are unknown. Because mycoplasmas can spontaneously clear from the CSF, therapy should involve minimal risks.

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Section 10

Chlamydial Infections

Chapter 271

Chlamydia pneumoniae

Stephan A. Kohlhoff and Margaret R. Hammerschlag

Chlamydia pneumoniae is a common cause of lower respiratory tract diseases, including pneumonia in children and bronchitis and pneumonia in adults. This organism was briefly known as *Chlamydophila pneumoniae,* and that name is still used as an alternative designation in some sources.

ETIOLOGY

Chlamydiae are obligate intracellular pathogens that have established a unique niche in host cells. Chlamydiae cause a variety of diseases in animal species at virtually all phylogenic levels. The most significant human pathogens are *C. pneumoniae* and *C. trachomatis* (see Chapter 272). *C. psittaci* is the cause of psittacosis, an important zoonosis (see Chapter 273). There are now nine recognized chlamydial species.

Chlamydiae have a gram-negative envelope without detectable peptidoglycan, although recent genomic analysis has revealed that both *C. pneumoniae* and *C. trachomatis* encode proteins forming a nearly complete pathway for synthesis of peptidoglycan, including penicillin-binding proteins. Chlamydiae also share a group-specific lipopolysaccharide antigen and use host adenosine triphosphate for the synthesis of chlamydial proteins. Although chlamydiae are auxotrophic for three of four nucleoside triphosphates, they encode functional glucose-catabolizing enzymes that can be used to generate adenosine triphosphate. As with peptidoglycan synthesis, for some reason, these genes are turned off. All chlamydiae also encode an abundant surface-exposed protein called the *major outer membrane protein.* The major outer membrane protein is the major determinant of the serologic classification of *C. trachomatis* and *C. psittaci* isolates.

EPIDEMIOLOGY

C. pneumoniae is primarily a human respiratory pathogen. The organism has also been isolated from nonhuman species, including horses, koalas, reptiles, and amphibians, where it also causes respiratory infection, although the role that these infections might play in transmission to humans is unknown. *C. pneumoniae* appears to affect individuals of all ages. The proportion of community-acquired pneumonias associated with *C. pneumoniae* infection is 2–19%, varying with geographic location, the age-group examined, and the diagnostic methods used. Several studies of the role of *C. pneumoniae* in lower respiratory tract infection in pediatric populations have found evidence of infection in 0–18% of patients based on serology or culture for diagnosis. In one study, almost 20% of the children with *C. pneumoniae* infection were co-infected with *Mycoplasma pneumoniae. C. pneumoniae* may also be responsible for 10–20% of episodes of acute chest syndrome in children with sickle cell disease, up to 10% of asthma exacerbations, 10% of episodes of bronchitis, and 5–10% of episodes of pharyngitis in children. Asymptomatic infection appears to be common based on epidemiologic studies.

Transmission probably occurs from person to person through respiratory droplets. Spread of the infection appears to be enhanced by close proximity, as is evident from localized outbreaks in enclosed populations, such as military recruits and in nursing homes.

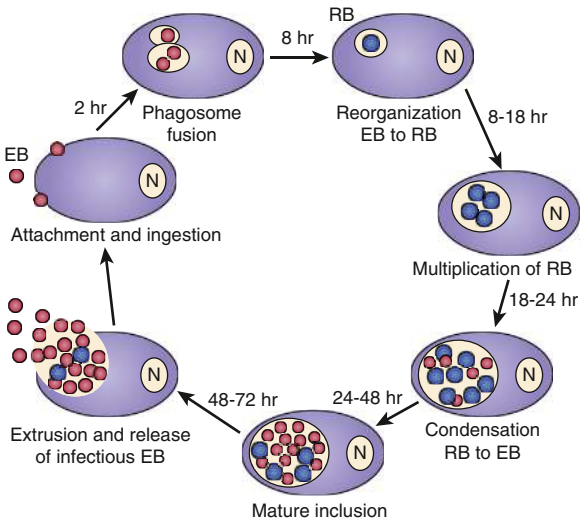

Fig. 271.1 Life cycle of chlamydiae in epithelial cells. *EB,* Elementary body; *RB,* reticulate body. *(From Hammerschlag MR. Infections due to Chlamydia trachomatis and Chlamydia pneumoniae in children and adolescents. Pediatr Rev. 2004;25:43–50.)*

PATHOGENESIS

Chlamydiae are characterized by a unique developmental cycle (Fig. 271.1) with morphologically distinct infectious and reproductive forms: the elementary body (EB) and reticulate body (RB). After infection, the infectious EBs, which are 200-400 μm in diameter, attach to the host cell by a process of electrostatic binding and are taken into the cell by endocytosis that does not depend on the microtubule system. Within the host cell, the EB remains within a membrane-lined phagosome. The phagosome does not fuse with the host cell lysosome. The inclusion membrane is devoid of host cell markers, but lipid markers traffic to the inclusion, which suggests a functional interaction with the Golgi apparatus. The EBs then differentiate into RBs that undergo binary fission. After approximately 36 hours, the RBs differentiate into EBs. At approximately 48 hours, release can occur by cytolysis or by a process of exocytosis or extrusion of the whole inclusion, leaving the host cell intact. Chlamydiae can also enter a persistent state after treatment with certain cytokines such as interferon-γ, treatment with antibiotics, or restriction of certain nutrients. While chlamydiae are in the persistent state, metabolic activity is reduced. The ability to cause prolonged, often subclinical, infection is one of the major characteristics of chlamydiae.

CLINICAL MANIFESTATIONS

Infections caused by *C. pneumoniae* cannot be readily differentiated from those caused by other respiratory pathogens, especially *M. pneumoniae.* The pneumonia usually occurs as a classic atypical (or nonbacterial) pneumonia characterized by mild to moderate constitutional symptoms, including fever, malaise, headache, cough, and often pharyngitis. Severe pneumonia with pleural effusions and empyema has been described. Milder respiratory infections have been described, manifesting as a pertussis-like illness.

C. pneumoniae can serve as an infectious trigger for asthma, can cause pulmonary exacerbations in patients with cystic fibrosis, and can produce acute chest syndrome in patients with sickle cell anemia. *C. pneumoniae* has been isolated from middle ear aspirates of children with acute otitis media, most of the time as co-infection with other bacteria. Asymptomatic respiratory infection has been documented in 2–5% of adults and children and can persist for 1 year or longer.

DIAGNOSIS

It is not possible to differentiate *C. pneumoniae* from other causes of atypical pneumonia on the basis of clinical findings. Auscultation reveals the presence of rales and often wheezing. The chest radiograph often appears worse than the patient's clinical status would indicate and can show mild, diffuse involvement or lobar infiltrates with small pleural effusions. The complete blood count may be elevated with a left shift but is usually unremarkable.

Specific diagnosis of *C. pneumoniae* infection has been based on isolation of the organism in tissue culture. *C. pneumoniae* grows best in cycloheximide-treated HEp-2 and HL cells. The optimum site for culture is the posterior nasopharynx; the specimen is collected with wire-shafted swabs in the same manner as that used for *C. trachomatis.* The organism can be isolated from sputum, throat cultures, bronchoalveolar lavage fluid, and pleural fluid, but few laboratories perform such cultures because of technical difficulties. There are two U.S. Food and Drug Administration (FDA)–cleared multiplexed nucleic acid amplification testing assays available for detection of respiratory viruses; pneumonia pathogens; and *C. pneumoniae, M. pneumoniae,* and *Bordetella pertussis* on upper respiratory samples. These systems combine nucleic acid extraction, amplification, detection, and data analysis.

Serologic diagnosis can be accomplished using the microimmunofluorescence (MIF) or the complement fixation tests. The complement fixation test is genus specific and is also used for diagnosis of lymphogranuloma venereum (see Chapter 272.4) and psittacosis (see Chapter 273). Its sensitivity in hospitalized patients with *C. pneumoniae* infection and children is variable. The Centers for Disease Control and Prevention (CDC) has proposed modifications in the serologic criteria for diagnosis. Although the MIF test was considered to be the only currently acceptable serologic test, the criteria were made significantly more stringent. Acute infection, using the MIF test, was defined by a fourfold increase in immunoglobulin (Ig) G titer or an IgM titer of ≥16; use of a single elevated IgG titer was discouraged. An IgG titer of ≥16 was thought to indicate past exposure, but neither elevated IgA titers nor any other serologic marker was thought to be a valid indicator of persistent or chronic infection. Because diagnosis would require paired sera, this would be a retrospective diagnosis. The CDC did not recommend the use of any enzyme-linked immune assay for detection of antibody to *C. pneumoniae* because of concern about the inconsistent correlation of these results with culture results. Studies of *C. pneumoniae* infection in children with pneumonia and asthma show that more than 50% of children with culture-documented infection have no detectable serum anti–*C. pneumoniae* antibody. Because of the availability of FDA-cleared nucleic acid test technology, diagnosis of acute infection should not be made using serology.

TREATMENT

The optimum dose and duration of antimicrobial therapy for *C. pneumoniae* infections remain uncertain. Most treatment studies have used only serology for diagnosis, and thus microbiologic efficacy cannot be assessed. Prolonged therapy for 2 weeks or longer is required for some patients, because recrudescent symptoms and persistent positive cultures have been described after 2 weeks of erythromycin and 30 days of tetracycline or doxycycline.

Tetracyclines, macrolides (erythromycin, azithromycin, and clarithromycin), and quinolones show in vitro activity. Like *C. psittaci, C. pneumoniae* is resistant to sulfonamides. The results of treatment studies have shown that erythromycin (40 mg/kg/day PO divided twice a day for 10 days), clarithromycin (15 mg/kg/day PO divided twice a day for 10 days), and azithromycin (10 mg/kg PO on day 1 and then 5 mg/kg/day PO on days 2-5) are effective for eradication of *C. pneumoniae* from the nasopharynx of children with pneumonia in approximately 80% of cases. Resistance to these commonly used drug classes has not been conclusively demonstrated. Persistent symptoms may, however, reflect persistent infection caused by the latent nature of the organism or another etiology and should prompt a thorough reevaluation.

PROGNOSIS

Clinical response to antibiotic therapy varies. Coughing often persists for several weeks even after therapy.

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Chapter 272

Chlamydia trachomatis

Margaret R. Hammerschlag

Chlamydia trachomatis is subdivided into two biovars, namely, lymphogranuloma venereum (LGV) and trachoma, which is the agent of human oculogenital diseases other than LGV. Although the strains of both biovars have almost complete DNA homology, they differ in growth characteristics and virulence in tissue culture and animals. In developed countries, *C. trachomatis* is the most prevalent sexually transmitted disease, causing urethritis in men, cervicitis and salpingitis in women, and conjunctivitis and pneumonia in infants.

272.1 Trachoma

Margaret R. Hammerschlag

Trachoma is the most important preventable cause of blindness in the world. It is caused primarily by the A, B, Ba, and C serotypes of *C. trachomatis.* It is endemic in the Middle East and Southeast Asia and among Navajo Indians in the southwestern United States. In areas that are endemic for trachoma, genital chlamydial infection is caused by the serotypes responsible for oculogenital disease: D, E, F, G, H, I, J, and K. The disease is spread from eye to eye. Flies are a common vector.

Trachoma begins as a **follicular conjunctivitis**, usually in early childhood. The follicles heal, leading to conjunctival scarring that can result in an entropion, with the eyelid turning inward so that the lashes abrade the cornea. It is the corneal ulceration secondary to the constant trauma that leads to scarring and blindness. Bacterial superinfection can also contribute to scarring. Blindness occurs years after the active disease.

Trachoma can be diagnosed clinically. The World Health Organization suggests that at least two of four criteria must be present for a diagnosis of trachoma: lymphoid follicles on the upper tarsal conjunctivae, typical conjunctival scarring, vascular pannus, and limbal follicles. The diagnosis is confirmed by culture or staining tests for *C. trachomatis* performed during the active stage of disease. Serologic tests are not helpful clinically because of the long duration of the disease and the high seroprevalence in endemic populations.

Poverty and lack of sanitation are important factors in the spread of trachoma. As socioeconomic conditions improve, the incidence of the disease decreases substantially. Endemic trachoma is managed by mass drug administration (MDA) with azithromycin in affected communities. Endemic communities should receive MDA until clinical signs of active disease in children 1-9 years of age falls below 5%. MDA with a single dose of azithromycin to all the residents of a village dramatically reduces the prevalence and intensity of infection. This effect continues for 2 years after treatment, probably by interrupting the transmission of ocular *C. trachomatis* infection.

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272.2 Genital Tract Infections

Margaret R. Hammerschlag

EPIDEMIOLOGY

There are an estimated 3 million new cases of chlamydial sexually transmitted infections each year in the United States. *C. trachomatis* is a major cause of epididymitis and is the cause of 23–55% of all cases of nongonococcal urethritis. As many as 50% of men with gonorrhea may be co-infected with *C. trachomatis.* The prevalence of chlamydial cervicitis among sexually active women is 2–35%. Rates of infection among girls 15-19 years of age exceed 20% in many urban populations and can be as high as 15% in suburban populations.

Children who have been sexually abused can acquire anogenital *C. trachomatis* infection, which is usually asymptomatic. However, because perinatally acquired rectal and vaginal *C. trachomatis* infections can persist for 3 years or longer, the detection of *C. trachomatis* in the vagina or rectum of a young child is not absolute evidence of sexual abuse.

CLINICAL MANIFESTATIONS

The trachoma biovar of *C. trachomatis* causes a spectrum of disease in sexually active adolescents and adults. Up to 75% of women with *C. trachomatis* have no symptoms of infection. *C. trachomatis* can cause urethritis (acute urethral syndrome), epididymitis, cervicitis, salpingitis, proctitis, and pelvic inflammatory disease. The symptoms of chlamydial genital tract infections are less acute than those of gonorrhea, consisting of a discharge that is usually mucoid rather than purulent. Asymptomatic urethral infection is common in sexually active men. Autoinoculation from the genital tract to the eyes can lead to concomitant inclusion conjunctivitis.

DIAGNOSIS

Diagnosis of genital chlamydial infection is now accomplished by nucleic acid amplification tests (NAATs). These tests have high sensitivity, detecting 10–20% more cases than culture, while retaining high specificity. Six FDA-approved NAATs are commercially available for detecting *C. trachomatis,* including polymerase chain reaction (PCR; Amplicor Chlamydia test, Roche Molecular Diagnostics, Nutley, NJ), strand displacement amplification (ProbeTec, BD Diagnostic Systems, Sparks, MD), transcription-mediated amplification (Amp CT, Hologic, San Diego, CA), and GeneXpert CT/NG assay (Cepheid, Sunnyvale, CA). PCR and strand displacement amplification are DNA amplification tests that use primers that target gene sequences on the cryptogenic *C. trachomatis* plasmid that is present at approximately 10 copies in each infected cell. Transcription-mediated amplification is a ribosomal RNA amplification assay. GeneXpert is an on-demand, qualitative, real-time PCR. All these assays are also available as co-amplification tests for simultaneously detecting *C. trachomatis* and *Neisseria gonorrhoeae.*

The available commercial NAATs are FDA-approved for cervical and vaginal swabs from adolescent girls and women, urethral swabs from adolescent boys and men, and urine, pharyngeal, and rectal swabs from adolescents and adults. Use of urine avoids the necessity for a clinical pelvic examination and can greatly facilitate screening in certain populations, especially adolescents, although several studies have now demonstrated that endocervical specimens and vaginal swabs are superior to urine for NAAT. Self-collected vaginal specimens appear to be as reliable as specimens obtained by a healthcare professional.

Data on the use of NAATs for vaginal specimens or urine from children are very limited and are insufficient to allow making a recommendation for their use. NAATs can be used, but confirmatory testing must be done. Because of the low prevalence of infection in this population, the positive predictive values of a positive test can be less than 30%. Confirmatory testing should consist of testing the original sample with a second FDA-approved NAAT that targets a different gene sequence from the initial test or repeating the testing **before** treatment. Use of non-FDA-cleared assays is strongly discouraged.

The etiology of most cases of nonchlamydial nongonococcal urethritis is unknown, although *Ureaplasma urealyticum* and possibly *Mycoplasma genitalium* are implicated in up to one third of cases (see Chapter 270). Proctocolitis may develop in individuals who have a rectal infection with an LGV strain (see Chapter 272.4).

TREATMENT

The first-line treatment regimen now recommended by the CDC for uncomplicated *C. trachomatis* genital and rectal infection in adult and adolescent men and nonpregnant women is doxycycline (100 mg PO twice a day for 7 days). Recent studies have documented that doxycycline is significantly more effective than single-dose azithromycin. Alternative regimens are azithromycin (1 g orally in a single dose) or levofloxacin (500 mg PO once daily for 7 days). Doxycycline and quinolones are contraindicated in pregnant women, and quinolones are contraindicated in persons younger than 18 years. For pregnant women, the recommended treatment regimen is azithromycin (1 g PO as a single dose) or amoxicillin (500 mg PO 3 times a day for 7 days).

Empirical treatment without microbiologic diagnosis is recommended only for patients at high risk for infection who are unlikely to return for follow-up evaluation, including adolescents with multiple sex partners. These patients should be treated empirically for both *C. trachomatis* and *N. gonorrhoeae*.

Sex partners of patients with nongonococcal urethritis should be treated if they have had sexual contact with the patient during the 60 days preceding the onset of symptoms. The most recent sexual partner should be treated even if the last sexual contact was more than 60 days from onset of symptoms.

COMPLICATIONS

Complications of genital chlamydial infections in women include perihepatitis (Fitz-Hugh–Curtis syndrome) and salpingitis. Of women with untreated chlamydial infection who develop pelvic inflammatory disease, up to 40% will have significant sequelae; approximately 17% will suffer from chronic pelvic pain, approximately 17% will become infertile, and approximately 9% will have an ectopic (tubal) pregnancy. Adolescent girls may be at higher risk for developing complications, especially salpingitis, than older women. Salpingitis in adolescent girls is also more likely to lead to tubal scarring, subsequent obstruction with secondary infertility, and increased risk for ectopic pregnancy. Approximately 50% of neonates born to pregnant women with untreated chlamydial infection will acquire *C. trachomatis* infection (see Chapter 272.3). Women with *C. trachomatis* infection have a threefold to fivefold increased risk for acquiring HIV infection.

PREVENTION

Timely treatment of sex partners is essential for decreasing the risk for reinfection. Sex partners should be evaluated and treated if they had sexual contact during the 60 days preceding onset of symptoms in the patient. The most recent sex partner should be treated even if the last sexual contact was >60 days. Patients and their sex partners should abstain from sexual intercourse until 7 days after a single-dose regimen or after completion of a 7-day regimen.

Annual routine screening for *C. trachomatis* is recommended for all sexually active female adolescents, for all women 20-25 years of age, and for older women with risk factors such as new or multiple partners or inconsistent use of barrier contraceptives. Sexual risk assessment might indicate more frequent screening of some women.

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272.3 Conjunctivitis and Pneumonia in Newborns

Margaret R. Hammerschlag

EPIDEMIOLOGY

Chlamydial genital infection is reported in 5–30% of pregnant women, with a risk for vertical transmission at parturition to newborn infants of approximately 50%. The infant may become infected at one or more sites, including the conjunctivae, nasopharynx, rectum, and vagina. Transmission is rare after cesarean section with intact membranes. The introduction of systematic prenatal screening for *C. trachomatis* infection and treatment of pregnant women has resulted in a dramatic decrease in the incidence of neonatal chlamydial infection in the United States. However, in countries where prenatal screening is not done, such as the Netherlands, *C. trachomatis* remains an important cause of neonatal infection, accounting for >60% of neonatal conjunctivitis.

Inclusion Conjunctivitis

Approximately 30–50% of infants born to mothers with active, untreated chlamydial infection develop clinical conjunctivitis. Symptoms usually develop 5-14 days after delivery, or earlier in infants born after prolonged rupture of membranes. The presentation is extremely variable and ranges from mild conjunctival injection with scant mucoid discharge to severe conjunctivitis with copious purulent discharge, chemosis, and pseudomembrane formation. The conjunctiva may be very friable and may bleed when stroked with a swab. Chlamydial conjunctivitis must be differentiated from gonococcal ophthalmia, which is sight-threatening. At least 50% of infants with chlamydial conjunctivitis also have nasopharyngeal infection.

Pneumonia

Pneumonia caused by *C. trachomatis* can develop in 10–20% of infants born to women with active, untreated chlamydial infection. Only approximately 25% of infants with nasopharyngeal chlamydial infection develop pneumonia. *C. trachomatis* pneumonia of infancy has a characteristic presentation. Onset usually occurs between 1 and 3 months of age and is often insidious, with persistent cough, tachypnea, and absence of fever. Auscultation reveals rales; wheezing is occasionally present but is uncommon. The absence of fever and wheezing generally helps to distinguish *C. trachomatis* pneumonia from respiratory syncytial virus pneumonia. A distinctive laboratory finding is the presence of peripheral eosinophilia (>400 cells/μL). The most consistent finding on chest radiograph is hyperinflation accompanied by minimal interstitial or alveolar infiltrates.

Infections at Other Sites

Infants born to mothers with *C. trachomatis* can develop infection in the rectum or vagina. Although infection in these sites appears to be totally asymptomatic, it can cause confusion if it is identified later. Perinatally acquired rectal, vaginal, and nasopharyngeal infections can persist for 3 years or longer.

DIAGNOSIS

Definitive diagnosis is achieved by isolation of *C. trachomatis* in cultures of specimens obtained from the conjunctiva or nasopharynx. Data on the use of NAATs for diagnosis of *C. trachomatis* in children are limited but suggest that PCR may be equivalent to culture for detecting *C. trachomatis* in the conjunctiva of infants with conjunctivitis. However, NAATs are not currently FDA-cleared for use with conjunctival or nasopharyngeal specimens from infants. Laboratories can do internal validation delineated in the CDC 2014 *C. trachomatis* and *N. gonorrhoeae* laboratory guidelines.

TREATMENT

The recommended treatment regimens for *C. trachomatis* conjunctivitis or pneumonia in infants are erythromycin (base or ethylsuccinate, 50 mg/kg/day divided 4 times a day PO for 14 days) or azithromycin suspension (20 mg/kg/day once daily PO for 3 days). The rationale for using oral therapy for conjunctivitis is that 50% or more of these infants have concomitant nasopharyngeal infection or disease at other sites, and studies demonstrate that topical therapy with sulfonamide drops and erythromycin ointment is not effective. The failure rate with oral erythromycin remains 10–20%, and some infants require a second

course of treatment. Mothers (and their sexual contacts) of infants with *C. trachomatis* infections should be empirically treated for genital infection. An association between treatment with oral erythromycin or oral azithromycin and infantile hypertrophic pyloric stenosis has been reported in infants younger than 6 weeks of age.

PREVENTION

Neonatal gonococcal prophylaxis with topical erythromycin ointment does not prevent chlamydial ophthalmia or nasopharyngeal colonization with *C. trachomatis* or chlamydial pneumonia. *The most effective method of controlling perinatal chlamydial infection is screening and treatment of pregnant women.* In 2015, the Canadian Pediatric Society recommended that neonatal ocular prophylaxis be discontinued and that prenatal screening for chlamydia be enhanced. The program was implemented in 2016. In the United States, implementation of prenatal screening and treatment of pregnant women has resulted in a dramatic decrease in perinatal chlamydial infections. For treatment of *C. trachomatis* infection in pregnant women, the CDC currently recommends either azithromycin (1 g PO as a single dose) or amoxicillin (500 mg PO 3 times a day for 7 days) as first-line regimens. Erythromycin base (250 mg PO 4 times a day for 14 days) and erythromycin ethylsuccinate (800 mg 4 times a day for 7 days, or 400 mg PO 4 times a day for 14 days) are listed as alternative regimens. Reasons for failure of maternal treatment to prevent infantile chlamydial infection include poor compliance and reinfection from an untreated sexual partner.

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272.4 Lymphogranuloma Venereum

Margaret R. Hammerschlag

LGV is a systemic sexually transmitted disease caused by the L_1, L_2, and L_3 serotypes of the LGV biovar of *C. trachomatis*. Unlike strains of the trachoma biovar, LGV strains have a predilection for lymphoid tissue. Fewer than 1,000 cases are reported in adults in the United States annually. There has been a resurgence of LGV infections among men who have sex with men in Europe and the United States. Many of the men were HIV infected and used illicit drugs, specifically methamphetamines. The only pediatric case that has been reported since the emergence of the new clusters of HIV-associated cases in 2003 was a 16-year-old boy who presented with LGV proctocolitis after having receptive unprotected anal intercourse with a 30-year-old man he met on the Internet. This history was obtained after the boy was found to be HIV-positive. The diagnosis of LGV, particularly when it presents with proctocolitis, relies on a high index of suspicion that would lead to emphasizing certain aspects of the history and ordering the pertinent diagnostic tests. Many pediatricians and pediatric gastroenterologists might not be familiar with the entity and might not entertain it as a diagnostic consideration in pediatric patients. The diagnosis can be further suggested by *C. trachomatis* testing: commonly by NAATs or culturing the organism if culture is available. Currently available NAATs will not differentiate LGV from other *C. trachomatis* serovars. NAATs for *C. trachomatis* are also not FDA-cleared for testing rectal specimens, but laboratories can do an internal validation as recommended in the CDC 2014 *C. trachomatis* and *N. gonorrhoeae* laboratory guidelines. NAATs have been found in several clinical studies to perform well with rectal specimens. Typing of the *C. trachomatis* specimen can be done by sequencing from the NAAT specimen by many state laboratories. Trying to ascertain the *C. trachomatis* serovar for confirmation of LGV has therapeutic implications, as LGV needs to be treated with a 3-week course of doxycycline; a single-dose of azithromycin will not eradicate the infection.

CLINICAL MANIFESTATIONS

The **first stage of LGV** is characterized by the appearance of the primary lesion, a painless, usually transient papule on the genitals. The **second stage** is characterized by usually unilateral femoral or inguinal lymphadenitis with enlarging, painful buboes. The nodes may break down and drain, especially in men. In women, the vulvar lymph drains to the retroperitoneal nodes. Fever, myalgia, and headache are common. The **third stage** is a genitoanorectal syndrome with rectovaginal fistulas, rectal strictures, and urethral destruction. Among men who have sex with men, rectal infection with LGV can produce a severe, acute proctocolitis, which can be confused with inflammatory bowel disease or malignancy.

DIAGNOSIS

LGV can be diagnosed by serologic testing or by culture of *C. trachomatis* or molecular testing for *C. trachomatis* from a specimen aspirated from a bubo. Most patients with LGV have complement-fixing antibody titers of >1:16. Chancroid and herpes simplex virus can be distinguished clinically from LGV by the concurrent presence of painful genital ulcers. Syphilis can be differentiated by serologic tests. However, co-infections can occur.

TREATMENT

Doxycycline (100 mg PO bid for 21 days) is the recommended treatment. Alternative regimens are azithromycin (1 g PO once weekly for 3 weeks) or erythromycin base (500 mg PO 4 times a day for 21 days). As the azithromycin regimen has not been validated, it is recommended that a test of cure with a *C. trachomatis* NAAT 4 weeks after completion of therapy be performed. Sex partners of patients with LGV should be treated if they have had sexual contact with the patient during the 30 days preceding the onset of symptoms.

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Chapter 273

Psittacosis *(Chlamydia psittaci)*

Stephan A. Kohlhoff and Margaret R. Hammerschlag

Chlamydia psittaci, the agent of psittacosis (also known as **parrot fever** and **ornithosis**), is primarily an animal pathogen and rarely causes human disease. In birds, *C. psittaci* infection is known as *avian chlamydiosis*.

ETIOLOGY

C. psittaci affects both psittacine birds (e.g., parrots, parakeets, macaws) and nonpsittacine birds (ducks, turkeys); the known host range includes 130 avian species. The life cycle of *C. psittaci* is the same as for *C. pneumoniae* (see Chapter 271). Strains of *C. psittaci* have been analyzed by patterns of pathogenicity, inclusion morphology in tissue culture, DNA restriction endonuclease analysis, and monoclonal antibodies, which indicate that there are seven avian serovars. The organism has also been found in nonavian domestic animals,

including cattle, sheep, pigs, goats, and cats. Nonavian *C. psittaci* has rarely caused disease in humans. Two of the avian serovars, psittacine and turkey, are of major importance in the avian population of the United States. Each is associated with important host preferences and disease characteristics. There are four other *Chlamydia* species that have birds as their primary hosts: *C. avium* (pigeons, parrots), *C. gallinacea* (chickens, turkeys, ducks), *C. ibdis* (ibis), and *C. buteonis* (hawks, buzzards). *C. gallinacea* may have the potential to cause outbreaks in poultry plants.

EPIDEMIOLOGY

On average, 11 cases of psittacosis per year in the United States were reported from 2000 to 2017. However, experts believe the disease is potentially underreported and underdiagnosed. In 2018, a multistate psittacosis outbreak among poultry plant workers had 13 laboratory-confirmed cases. The majority of cases were associated with exposure to birds, including 70% after exposure to caged pet birds, which were usually psittacine birds, including cockatiels, parakeets, parrots, and macaws. Chlamydiosis among caged nonpsittacine birds occurs most often in pigeons, doves, and mynah birds. Persons at highest risk for acquiring psittacosis include workers in poultry plants, bird fanciers, owners of pet birds, and pet shop employees. Reported cases most likely underestimate the number of actual infections owing to a lack of awareness and readily available diagnostic tests.

Inhalation of aerosols from feces, fecal dust, and nasal secretions of animals infected with *C. psittaci* is the primary route of infection. Source birds are either asymptomatic or have anorexia, ruffled feathers, lethargy, and watery green droppings. Psittacosis is uncommon in children, in part because children may be less likely to have close contact with infected birds. One high-risk activity is cleaning the cage.

CLINICAL MANIFESTATIONS

Infection with *C. psittaci* in humans ranges from clinically inapparent to severe disease, including pneumonia and multiorgan involvement. The mean incubation period is 15 days after exposure, with a range of 5-21 days. Onset of disease is usually abrupt, with fever, cough, headache, myalgia, and malaise. The fever is high and is often associated with rigors and sweats. The headache can be so severe that meningitis is considered. The cough is usually nonproductive. Gastrointestinal symptoms are occasionally reported. Crackles may be heard on auscultation. Chest radiographs are usually abnormal and are characterized by the presence of variable infiltrates, sometimes accompanied by pleural effusions. The white blood cell count is usually normal but is sometimes mildly elevated. Elevated levels of aspartate aminotransferase, alkaline phosphatase, and bilirubin are common. Nonpulmonary complications include pericarditis, endocarditis, and myocarditis. Mortality occurs in 5% of cases.

DIAGNOSIS

Psittacosis can be difficult to diagnose because of the varying clinical presentations. A history of exposure to birds or association with an active case can be important clues, but as many as 20% of patients with psittacosis have no known contact. Person-to-person spread has been suggested but not proved. Other infections that cause pneumonia with high fever, unusually severe headache, and myalgia include routine bacterial and viral respiratory infections as well as *Coxiella burnetii* infection (Q fever), *Mycoplasma pneumoniae* infection, *C. pneumoniae* infection, tularemia, tuberculosis, fungal infections, and Legionnaires' disease.

A patient is considered to have a confirmed case of psittacosis if clinical illness is compatible with psittacosis and the case is laboratory confirmed by identification of *C. psittaci* by polymerase chain reaction (PCR) from respiratory specimens (e.g., sputum, pleural fluid, or lung tissue), blood, or stool. Serologic methods are most available, but these tests have poor specificity and require testing of paired specimens collected weeks apart, delaying or preventing confirmation of the clinical diagnosis in a timely fashion. A patient is considered to have a probable case of psittacosis if the clinical illness is compatible with psittacosis and there is an epidemiologic exposure. Lower respiratory tract samples are the specimen of choice, although 5 of 13 (38%) of the patients in the 2018 multistate outbreak also had *C. psittaci* DNA detected in their stool specimens.

Although *C. psittaci* will grow in the same culture systems used for isolation of *C. trachomatis* and *C. pneumoniae,* very few laboratories culture for *C. psittaci,* mainly because of the potential biohazard. Real-time PCR assays can distinguish *C. psittaci* from other chlamydial species and identify different *C. psittaci* genotypes. Currently real-time PCR for *C. psittaci* is only available at the CDC.

TREATMENT

Recommended treatment regimens for psittacosis are doxycycline (100 mg PO twice daily) or tetracycline (500 mg PO 4 times a day) for at least 10-14 days after the fever abates. The initial treatment of severely ill patients is doxycycline hyclate (4.4 mg/kg/day divided every 12 hours IV; maximum: 100 mg/dose). Erythromycin (500 mg PO 4 times a day) and azithromycin (10 mg/kg PO on day 1, not to exceed 500 mg, followed by 5 mg/kg PO on days 2-5, not to exceed 250 mg) are alternative agents if tetracyclines are contraindicated (e.g., children <8 years of age and pregnant women) but may be less effective. Remission is usually evident within 48-72 hours. Reinfection and clinical disease can develop within 2 months of treatment, indicating that initial infection does not appear to be followed by long-term immunity.

PROGNOSIS

The mortality rate of psittacosis is 15–20% with no treatment but is <1% with appropriate treatment. Severe illness leading to respiratory failure and fetal death has been reported among pregnant women.

PREVENTION

Several control measures are recommended to prevent transmission of *C. psittaci* from birds. Bird fanciers should be cognizant of the potential risk. *C. psittaci* is susceptible to heat and to most disinfectants and detergents but is resistant to acid and alkali. Accurate records of all bird-related transactions aid in identifying sources of infected birds and potentially exposed persons. Newly acquired birds, including birds that have been to shows, exhibitions, fairs, or other events, should be isolated for 30-45 days or tested or treated prophylactically before adding them to a group of birds. Care should be taken to prevent transfer of fecal material, feathers, food, or other materials between birdcages. Birds with signs of avian chlamydiosis (e.g., ocular or nasal discharge, watery green droppings, or low body weight) should be isolated and should not be sold or purchased. Their handlers should wear protective clothing and a disposable surgical cap and use a respirator with an N95 or higher efficiency rating (not a surgical mask) when handling them or cleaning their cages. Infected birds should be isolated until fully treated, which is generally 45 days.

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Section 11

Rickettsial Infections

Chapter 274

Spotted Fever Group Rickettsioses

Megan E. Reller and J. Stephen Dumler

Rickettsia species were classically divided into *spotted fever* and *typhus* groups based on serologic reactions and the presence or absence of the outer membrane protein A gene *(ompA)*. Sequencing of over 150 complete genomes has refined distinctions. However, there is controversy regarding phylogeny, and some data suggest that diversity and pathogenicity are the result of gene loss and lateral gene transfer from other prokaryotes or even eukaryotes, which further obscures accurate taxonomic classification. One proposal is to divide existing species into spotted fever and *transitional* groups based on genetic relatedness; both include pathogenic species and species not now known to cause human disease (Table 274.1). Although increasingly more is understood about the molecular basis by which these bacteria cause human illness, an alternative classification system based on pathogenetic mechanisms has not been defined.

The list of pathogens and potential pathogens in the spotted fever group has expanded dramatically in recent years. Unfortunately, the most common diagnostic approach uses a serologic method that cannot distinguish among related species; thus the CDC classifies serologically defined cases as "spotted fever rickettsiosis" to reflect this uncertainty. Among the etiologic agents of spotted fever rickettsiosis are the tick-borne agents *Rickettsia rickettsii,* the cause of Rocky Mountain or Brazilian spotted fever (RMSF); *R. conorii,* the cause of Mediterranean spotted fever (MSF) or boutonneuse fever; *R. sibirica,* the cause of North Asian tick typhus; *R. japonica,* the cause of Oriental or Japanese spotted fever; *R. honei,* the cause of Flinders Island spotted fever or Thai tick typhus; *R. africae,* the cause of African tick bite fever; *R. akari,* the cause of mite-transmitted rickettsialpox; *R. felis*, the cause of cat flea–transmitted typhus; and *R. australis,* the cause of tick-transmitted Queensland tick typhus. The recognition that *R. parkeri* and "*R. philipii*" (*Rickettsia* 364D) both cause mild spotted fever in North America and the association of high seroprevalence for spotted fever group *Rickettsia* infections in humans where *Amblyomma* ticks frequently contain *R. amblyommatis* suggest that the full range of agents that can cause spotted fever is still to be discerned.

Infections with other members of the spotted fever and transitional groups are clinically similar to MSF, with fever, maculopapular rash, and eschar at the site of the tick bite. Israeli spotted fever (*R. conorii* infection) is generally associated with a more severe course in children, including death. African tick bite fever is relatively mild, can include a vesicular rash, and often manifests with multiple eschars. New potentially pathogenic rickettsial species have been identified, including *R. slovaca,* the cause of tick-borne lymphadenopathy or *Dermacentor*-borne necrosis and lymphadenopathy. *R. aeschlimannii, R. heilongjiangensis, R. helvetica, R. massiliae,* and *R. raoultii* are all reported to cause mild to moderate illnesses in humans, although few cases have been described. Fortunately, the vast majority of infections respond well to doxycycline treatment if instituted early in illness; however, this is a significant challenge.

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274.1 Rocky Mountain Spotted Fever *(Rickettsia rickettsii)*

Megan E. Reller and J. Stephen Dumler

RMSF is the most severe rickettsial disease in the United States and Western Hemisphere. Although spotted fever rickettsiosis is the most common vector-borne disease in the United States after Lyme disease, the proportion of these cases caused by *R. rickettsii* is not known. Although considered uncommon, RMSF is believed to be greatly underdiagnosed and underreported. RMSF should be considered in the differential diagnosis of fever, headache, and rash in the summer months, especially after tick exposure. Because fulminant disease and death are associated with delays in treatment, patients in whom the illness is clinically suspected should be treated promptly.

ETIOLOGY

RMSF results from systemic infection of endothelial cells by the obligate intracellular bacterium *R. rickettsii.*

EPIDEMIOLOGY

The term **Rocky Mountain spotted fever** is historical, because the agent was discovered in the Bitterroot Range of the Rocky Mountains of Montana. Few cases are reported from this region. Cases have been reported throughout the continental United States (except Vermont and Maine), southwestern Canada, Mexico, Central America, and South America, but not from outside of the Western Hemisphere. In 2010, the CDC reporting criteria for RMSF changed to **spotted fever group rickettsiosis**, because serology often does not distinguish *R. rickettsii* from infection by other spotted fever group *Rickettsia*. Additionally, cases detected by enzyme immunoassay were classified as probable. Thus in 2012, 2,802 confirmed and probable cases of spotted fever rickettsiosis were reported in *Morbidity and Mortality Weekly Reports* Summary of Notifiable Diseases. Unlike in prior years, most cases were reported from the west southcentral states, especially from Arkansas, Oklahoma, and Missouri; high numbers of cases were also reported from North Carolina, Tennessee, Virginia, New Jersey, Georgia, Alabama, and Arizona (Fig. 274.1). The incidence of RMSF cycles over 25- to 35-year intervals, but spotted fever rickettsioses have steadily increased since 1998 over which time approximately 14% occur in individuals younger than 19 years. Habitats favored by ticks, including wooded areas or coastal grassland and salt marshes, and, in the southwestern United States and Mexico, shaded areas where dogs congregate and acquire infected ticks are those that place children at increased risk for infection. Foci of intense risk for infection are found both in rural and urban areas, most recently in Mexico and South America. Clustering of cases within families likely reflects shared environmental exposures. In the United States, 90% of cases occur between April and September, months in which humans spend the most time outdoors. The highest age-specific incidence of RMSF among children is seen in those older than 10 years of age, with males outnumbering females; however, the highest case fatality rate for RMSF is observed in those less than 10 years of age.

TRANSMISSION

Ticks are the natural hosts, reservoirs, and vectors of *R. rickettsii* and maintain the infection in nature by transovarial transmission (passage of the organism from infected ticks to their progeny). Ticks harboring rickettsiae are substantially less fecund than uninfected ticks; thus horizontal transmission (acquisition of rickettsiae by taking a blood meal from transiently rickettsemic hosts such as small mammals or dogs) contributes to maintenance of rickettsial infections in ticks. Uninfected ticks that simultaneously feed (co-feed) with infected transmitting ticks easily become infected, even if feeding on an immune host, and are also likely to be major contributors to natural transmission and maintenance. Ticks transmit the infectious agent to mammalian hosts (including humans) via infected saliva during feeding. The pathogen *R. rickettsii* in ticks becomes virulent after exposure to blood or increased temperature; thus the longer the tick is attached, the greater the risk of transmission. The principal tick

Table 274.1 Summary of Rickettsial Diseases of Humans, Including *Rickettsia, Orientia, Ehrlichia, Anaplasma, Neorickettsia,* and *Coxiella*

GROUP OR DISEASE AGENT		ARTHROPOD VECTOR, TRANSMISSION HOSTS		GEOGRAPHIC DISTRIBUTION	PRESENTING CLINICAL FEATURES*	COMMON LAB ABNORMALITIES	DIAGNOSTIC TESTS	TREATMENT†
SPOTTED FEVER GROUP								
Rocky Mountain spotted fever	*Rickettsia rickettsii*	Tick bite: *Dermacentor* species (wood tick, dog tick) *Rhipicephalus sanguineus* (brown dog tick)	Dogs Rodents	Western hemisphere	Fever, headache, rash,* emesis, diarrhea, myalgias	AST, ALT ↓Na (mild) ↓Platelets ±Leukopenia Left shift	Early: IH, DFA, PCR After first wk: IFA	**Doxycycline** Tetracycline Chloramphenicol
Mediterranean spotted fever (boutonneuse fever)	*Rickettsia conorii*	Tick bite: *R. sanguineus* (brown dog tick)	Dogs Rodents	Africa, Mediterranean, India, Middle East	Painless eschar (tache noir) with regional lymphadenopathy, fever, headache, rash,* myalgias	AST, ALT ↓Na (mild) ↓Platelets ±Leukopenia Left shift	Early: IH, DFA, PCR After first wk: IFA	**Doxycycline** Tetracycline Chloramphenicol Azithromycin Clarithromycin Fluoroquinolones
African tick-bite fever	*Rickettsia africae*	Tick bite	Cattle Goats?	Sub-Saharan Africa, Caribbean	Fever, single or multiple eschars, regional lymphadenopathy, rash* (can be vesicular)	AST, ALT ↓Platelets	Early: IH, DFA After 1st wk: IFA	**Doxycycline**
Tickborne lymphadenopathy (TIBOLA); Dermacentor-borne necrosis and lymphadenopathy (DEBONEL)	*Rickettsia slovaca, Rickettsia raoultii, Rickettsia sibirica mongolotimonae*	Tick bite: *Dermacentor*	?	Europe	Eschar (scalp), painful lymphadenopathy	?	PCR	**Doxycycline**
Rickettsia spp., 364D genotype	"*Rickettsia philippii*"	*Dermacentor occidentalis* (Pacific coast tick)		California	Eschar, fever, headache, lymphadenopathy, malaise	Unremarkable	PCR	Doxycycline
Flea-borne spotted fever	*Rickettsia felis*	Flea bite	Opossums Cats Dogs	Western hemisphere, Europe	Fever, rash,* headache	?	Early: PCR After first wk: IFA	Doxycycline
TRANSITIONAL GROUP								
Rickettsialpox	*Rickettsia akari*	Mite bite	Mice	North America, Russia, Ukraine, Adriatic, Korea, South Africa	Painless eschar, ulcer or papule; tender regional lymphadenopathy, fever, headache, rash* (can be vesicular)	↓WBC	Early: IH, DFA After first wk: IFA	**Doxycycline** Chloramphenicol
Queensland tick typhus	*Rickettsia australis*	*Ixodes holocyclus, I. tasmani*	Bandicoots and Rodents	Australia, Tasmania	Fever, eschar, headache, myalgia, lymphadenopathy	↓WBC, ↓platelets	Early: PCR on eschar or eschar swab; After first wk: IFA	**Doxycycline**
TYPHUS GROUP								
Murine typhus	*Rickettsia typhi*	Flea feces	Rats Opossums	Worldwide	Fever, headache, rash,* myalgias, emesis, lymphadenopathy, hepatosplenomegaly	AST, ALT ↓Na (mild) ↓WBC ↓ Platelets	Early: DFA, PCR After first wk: IFA	**Doxycycline** Chloramphenicol

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Table 274.1 Summary of Rickettsial Diseases of Humans, Including *Rickettsia, Orientia, Ehrlichia, Anaplasma, Neorickettsia,* and *Coxiella*—cont'd

GROUP OR DISEASE AGENT		ARTHROPOD VECTOR, TRANSMISSION HOSTS		GEOGRAPHIC DISTRIBUTION	PRESENTING CLINICAL FEATURES*	COMMON LAB ABNORMALITIES	DIAGNOSTIC TESTS	TREATMENT†
Epidemic (louse-borne) typhus (recrudescent form: Brill-Zinsser disease)	*Rickettsia prowazekii*	Louse feces	Humans	South America, Central America, Mexico, Africa, Asia, Eastern Europe	Fever, headache, abdominal pain, rash,* CNS involvement	AST, ALT ↓Platelets	Early: none After first wk: IgG/IgM, IFA	**Doxycycline** Tetracycline Chloramphenicol
Flying squirrel (sylvatic) typhus	*Rickettsia prowazekii*	Louse feces? Flea feces or bite?	Flying squirrels	Eastern United States	Same as above (often milder)	AST, ALT ↓Platelets	Early: none After first wk: IFA	**Doxycycline** Tetracycline Chloramphenicol
SCRUB TYPHUS								
Scrub typhus	*Orientia tsutsugamushi, Orientia chuto "Orientia chiloensis"*	Chigger bite: *Leptotrombidium* spp.	Rodents?	South Asia, Japan, Indonesia, Korea, China, Russia, Australia, Africa, Middle East, Chile	Fever, rash,* headache, painless eschar, hepatosplenomegaly, gastrointestinal symptoms	↓Platelets AST, ALT	Early: none After first wk: IFA	**Doxycycline** Tetracycline Chloramphenicol **Rifampicin** Azithromycin
EHRLICHIOSIS AND ANAPLASMOSIS								
Human monocytic ehrlichiosis	*Ehrlichia chaffeensis*	Tick bite: *Amblyomma americanum* (lone star tick)	Deer Dogs	United States, Mexico	Fever, headache, malaise, myalgias, rash*‡, hepatosplenomegaly,‡ swollen hands/feet‡	AST, ALT ↓WBC ↓Platelets ↓Na (mild)	Early: PCR After first wk: IFA	**Doxycycline** Tetracycline
Human granulocytic anaplasmosis	*Anaplasma phagocytophilum*	Tick bite: *Ixodes* species *Haemaphysalis longicornis*	Rodents Deer Ruminants	United States, Europe, Asia	Fever, headache, malaise, myalgias	AST, ALT ↓WBC, ↓ANC ↓Platelets	Early: PCR, blood smear After first wk: IFA	**Doxycycline** Tetracycline Rifampin
Ewingii ehrlichiosis	*Ehrlichia ewingii*	Tick bite: *Amblyomma americanum* (lone star tick)	Dogs Deer	United States (south-central, southeast)	Fever, headache, malaise, myalgias	AST, ALT, ↓WBC ↓Platelets	Early: PCR serology not available	**Doxycycline** Tetracycline
Ehrlichia muris eauclairensis infection	*Ehrlichia muris* ssp. *eauclairensis*	*Ixodes scapularis*	?	Minnesota, Wisconsin	Fever, headache, malaise, myalgias	AST, ALT ↓WBC, ↓Platelets	Early: PCR specific serology not available	**Doxycycline**
Neoehrlichiosis	*Neoehrlichia mikurensis*	*Ixodes ricinus*	Small mammals?	Europe, Asia	Fever, headache, myalgias, thrombosis	Neutrophilia, anemia, elevated CRP, AST, ALT	PCR	**Doxycycline**
Sennetsu neorickettsiosis	*Neorickettsia sennetsu*	Ingestion of fish helminth?, ingestion of fermented fish	Fish, trematodes	Japan, Malaysia, Laos	Fever, "mononucleosis" symptoms, postauricular and posterior cervical lymphadenopathy	Atypical lymphocytosis	Early: none After first wk: IFA	**Doxycycline** Tetracycline

Continued

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Table 274.1 Summary of Rickettsial Diseases of Humans, Including *Rickettsia, Orientia, Ehrlichia, Anaplasma, Neorickettsia,* and *Coxiella*—cont'd

GROUP OR DISEASE AGENT		ARTHROPOD VECTOR, TRANSMISSION HOSTS		GEOGRAPHIC DISTRIBUTION	PRESENTING CLINICAL FEATURES*	COMMON LAB ABNORMALITIES	DIAGNOSTIC TESTS	TREATMENT†
Q FEVER								
Q Fever: acute (for chronic, see text)	*Coxiella burnetii*	Inhalation of infected aerosols: contact with parturient animals, abattoir, contaminated cheese and milk, ?ticks	Cattle Sheep Goats Cats Rabbits	Worldwide	Fever, headache, arthralgias, myalgias, gastrointestinal symptoms, cough, pneumonia, rash (children)	AST, ALT WBC ↓ Platelets Interstitial infiltrate	Early: PCR After first wk: IFA	**Doxycycline** Tetracycline Fluoroquinolones Trimethoprim-sulfamethoxazole

*Rash is infrequently present at initial presentation but appears during the first wk of illness.
†Preferred treatment is in **bold**.
‡Often present in children but not adults.
ALT, Alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CNS, central nervous system; DFA, direct fluorescent antibody; IFA, indirect fluorescent antibody; IgG, immunoglobulin G; IgM, immunoglobulin M; IH, immunohistochemistry; PCR, polymerase chain reaction; WBC, white blood cell count.

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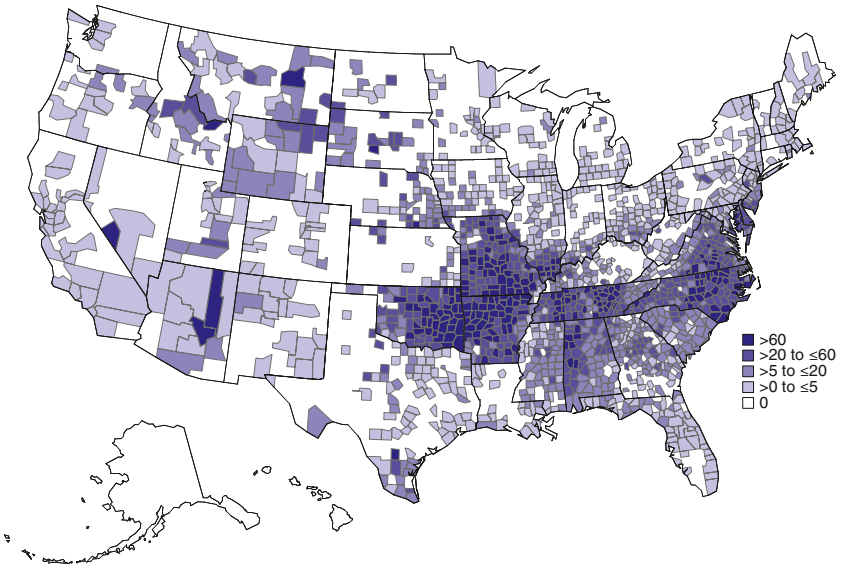

Fig. 274.1 Reported incidence rate* of spotted fever rickettsiosis,† by county—United States, 2000–2013. *As reported through national surveillance, per 1,000,000 persons per year. Cases are reported by county of residence, which is not always where the infection was acquired. †Includes Rocky Mountain spotted fever (RMSF) and other spotted fever group rickettsioses. In 2010, the name of the reporting category changed from RMSF to spotted fever rickettsiosis. *(From Biggs HM, Behravesh CB, Bradley KK, et al. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever and other spotted fever group rickettsioses, ehrlichioses, and anaplasmosis—United States. MMWR Recomm Rep. 2016;65:1–44. Fig. 1.)*

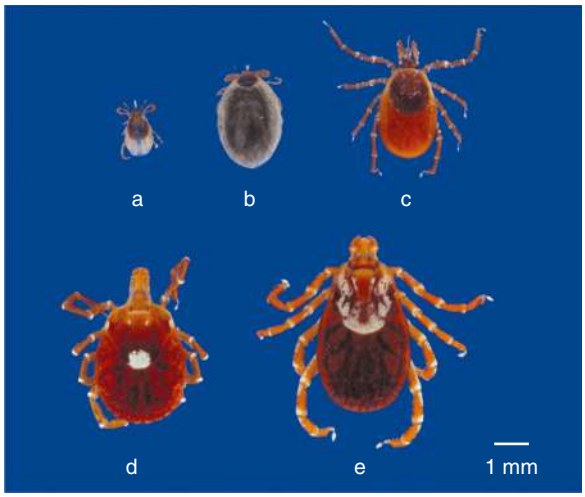

Fig. 274.2 Tick vectors of agents of human rickettsial diseases. An unengaged nymph *(a)*, engorged nymph *(b)*, and adult female *(c)* of *Ixodes scapularis* (deer tick), the vector of *Anaplasma phagocytophilum* and *Ehrlichia muris*–like agent (EMLA), the causes of human granulocytic anaplasmosis and EMLA ehrlichiosis, respectively. An adult female *(d)* of *Amblyomma americanum* (lone star tick), the vector of *Ehrlichia chaffeensis* and *Ehrlichia ewingii*, the causes of human monocytic ehrlichiosis and ewingii ehrlichiosis, respectively. An adult female *(e)* of *Dermacentor variabilis* (American dog tick), the vector of *Rickettsia rickettsii*, the cause of Rocky Mountain spotted fever.

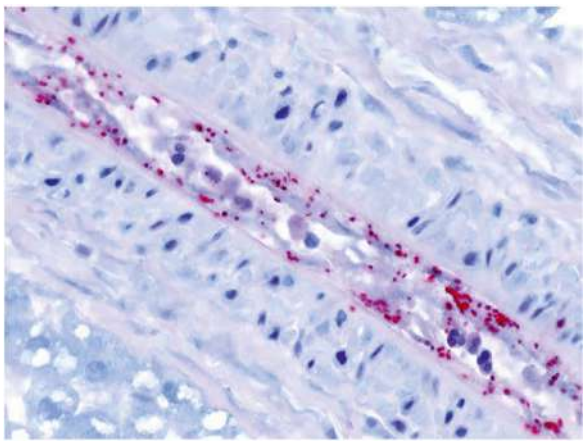

Fig. 274.3 Immunohistochemical stain demonstrating *Rickettsia (red)* in infection of blood vessel endothelial cells. *(From Biggs HM, Behravesh CB, Bradley KK, et al. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever and other spotted fever group rickettsioses, ehrlichioses, and anaplasmosis—United States. MMWR Recomm Rep. 2016;65:1–44, Fig. 20.)*

hosts of *R. rickettsii* are *Dermacentor variabilis* (the American dog tick) in the eastern United States and Canada, *Dermacentor andersoni* (the wood tick) in the western United States and Canada, *Rhipicephalus sanguineus* (the common brown dog tick) in the southwestern United States and in Mexico, and several *Amblyomma* spp. in Central and South America (Fig. 274.2).

Dogs can serve as reservoir hosts for *R. rickettsii*, can develop RMSF themselves, and can bring infected ticks into contact with humans. Serologic studies suggest that many patients with RMSF likely acquired the illness from ticks carried by the family dog.

Humans can also become infected when trying to remove an attached tick, because *R. rickettsii*–containing tick fluids or feces can be rubbed into the open wound at the bite site or into the conjunctivae by contaminated fingers. Inhalation of aerosolized rickettsiae has caused severe infections and deaths in laboratory workers, highlighting another mechanism of infection.

PATHOLOGY AND PATHOGENESIS

Systemic infection is most obvious on the skin (rash), but nearly all organs and tissues are affected. After inoculation of tick saliva into the dermis, rickettsial outer surface proteins bind to the vascular endothelial cell surface proteins, which signals focal cytoskeletal changes and endocytosis. Thereafter, rickettsia phospholipase-mediated dissolution of the endosomal membranes allows escape into the cytosol. Members of the spotted fever group actively nucleate actin polymerization on one pole to achieve directional movement, allowing some to propel into neighboring cells despite minimal initial host cell damage. The rickettsiae proliferate and injure host cells by oxidative membrane alterations, protease activation, or continued phospholipase activity. It is likely that some aspects of intracellular infection are mediated by rickettsial protein effectors delivered into the host cell by bacterial secretion systems.

The histologic correlate of the initial macular or maculopapular rash is perivascular infiltration of lymphoid and histiocytic cells with edema but without significant endothelial damage. Proliferation of rickettsiae within the cytoplasm of infected endothelial cells leads to endothelial injury and **lymphohistiocytic or leukocytoclastic vasculitis** of small venules and capillaries, which allows extravasation of intravascular erythrocytes into the dermis and manifests as a petechial rash (Fig. 274.3). This process is systemic and ultimately results in widespread microvascular leakage,

tissue hypoperfusion, and possibly septic shock or end-organ ischemic injury. Infrequently, inflammation leads to nonocclusive thrombi. Very rarely, small and large vessels become completely obliterated by thrombi, leading to tissue infarction or hemorrhagic necrosis. Interstitial pneumonitis and vascular leakage in the lungs can lead to noncardiogenic pulmonary edema, and meningoencephalitis can cause significant cerebral edema and herniation.

The presence of the infectious agent initiates an inflammatory cascade, including release of cytokines and chemokines such as tumor necrosis factor, interleukin-1β, interferon-γ, and regulated upon activation, normal T-cell expressed and secreted (RANTES). Infection of endothelial cells by *R. rickettsii* induces surface E-selectin expression and procoagulant activity followed by chemokine recruitment of lymphocytes, macrophages, and, occasionally, neutrophils. Local inflammatory and immune responses are suspected to contribute to the vascular injury; however, the benefits of effective innate immunity are greater. Blockade of tumor necrosis factor and interferon-γ in animal models diminishes survival and increases morbidity; reactive oxygen intermediates, nitric oxide expression, and sequestration of tryptophan from rickettsiae are mechanisms by which rickettsiae are killed within cells. Direct contact of infected endothelial cells with perforin-producing CD8 T lymphocytes and interferon-γ-producing natural killer cells, accompanied by rickettsia antibody, helps control the infection. The timing and balance between rickettsia-mediated increases in vascular permeability and the benefits of induction of innate and adaptive immunity are likely the major determinants of severity and outcome.

CLINICAL MANIFESTATIONS

The incubation period of RMSF in children varies from 2 to 14 days (median: 7 days). In 49% of cases, patients or their parents report a history of removing an attached tick, although the site of the tick bite is usually inapparent. Epidemiologic clues include living in or visiting an endemic area, playing or hiking in the woods, typical season, similar illness in family members, and close contact with a dog. In patients presenting for care, the illness is initially nonspecific, and most patients are not diagnosed during their first visit with a healthcare practitioner. Manifestations often (>50%) include fever, rash (frequently involving the palms or soles), nausea and vomiting, and headache and, less often (<50%), myalgias, abdominal pain, diarrhea, conjunctival injection, altered mental status, lymphadenopathy, and peripheral edema. Pain and tenderness of calf muscles are particularly common in children.

The typical **clinical triad of fever, headache, and rash** is observed in 58% of pediatric patients overall, and rash involving the soles and palms first appearing after day 3 is associated with significantly higher risk of death. Fever and headache persist if the illness is untreated. Fever can exceed 40°C (104°F) and can remain persistently elevated or can fluctuate dramatically. Headache is severe, unremitting, and unresponsive to analgesics.

Rash usually appears after only 1-2 days of illness, and an estimated 3–5% of children never develop a rash that is recognized. Initially, discrete, pale, rose-red blanching macules or maculopapules appear; characteristically, this initial rash is observed on the extremities, including the wrists, ankles, or lower legs (Fig. 274.4). In 65% of patients, the initial rash spreads rapidly to involve the entire body, including the soles and palms. The rash can become petechial or even hemorrhagic, sometimes with palpable purpura.

In severe disease, the petechiae can enlarge into ecchymoses, which can become necrotic (Fig. 274.5). Severe vascular obstruction secondary to the rickettsial vasculitis and thrombosis is uncommon but can result in gangrene of the digits, earlobes, scrotum, nose, or an entire limb.

Central nervous system infection usually manifests as changes in mental status (33%) or as photophobia (18%), seizure (17%), or meningismus (16%). Patients can also manifest ataxia, coma, or auditory deficits. Cerebrospinal fluid parameters are usually normal, but one third have pleocytosis (<10-300 cells/μL), either mononuclear or, less often, neutrophil-dominated. Some (20%) have elevated protein (<200 mg/dL) in the cerebrospinal fluid; hypoglycorrhachia is rare.

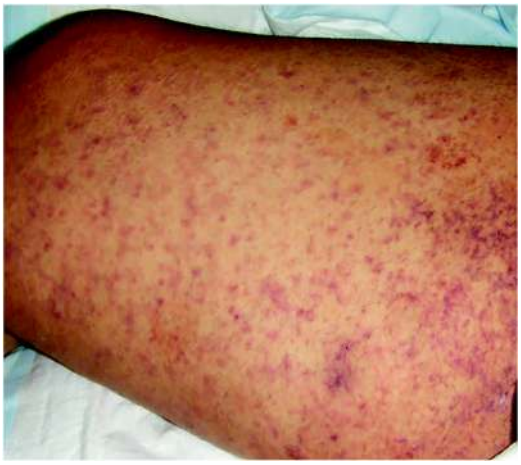

Fig. 274.4 Maculopapular rash with central petechiae associated with Rocky Mountain spotted fever. *(From Biggs HM, Behravesh CB, Bradley KK, et al. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever and other spotted fever group rickettsioses, ehrlichioses, and anaplasmosis—United States. MMWR Recomm Rep. 2016;65:1–44, Fig. 21.)*

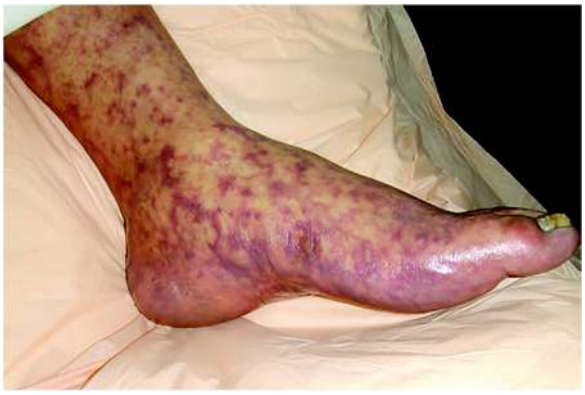

Fig. 274.5 Late-stage petechial purpuric rash involving the sole of the foot in a patient with Rocky Mountain spotted fever. *(From Biggs HM, Behravesh CB, Bradley KK, et al. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever and other spotted fever group rickettsioses, ehrlichioses, and anaplasmosis—United States. MMWR Recomm Rep. 2016;65:1–44, Fig. 22.)*

Neuroimaging studies often reveal only subtle abnormalities. However, with advanced disease and neurologic signs, a unique but nonspecific "starry sky" appearance may be observed on brain MRI that reflects the same systemic vasculitis observed with skin lesions.

Other

Pulmonary disease occurs more often in adults than in children. However, 33% of children examined have a chest radiograph interpreted as an infiltrate or pneumonia. The clinical presentation in these cases can manifest as rales, infiltrates, and noncardiogenic pulmonary edema. Other findings can include conjunctival suffusion, periorbital edema, dorsal hand and foot edema, and hepatosplenomegaly. Severe disease can include myocarditis, acute renal failure, and vascular collapse.

Persons with glucose-6-phosphate dehydrogenase deficiency are at increased risk for fulminant RMSF, defined as death from *R. rickettsii* infection within 5 days. The clinical course of fulminant RMSF is characterized by profound coagulopathy and extensive thrombosis leading to kidney, liver, and respiratory failure. Features associated with increased risk of death include altered mental status, admission to an intensive care unit, need for inotropic support, coma, and need for rapidly administered intravenous fluid.

Occasionally, clinical signs and symptoms suggest a localized process such as appendicitis or cholecystitis. Thorough evaluation usually reveals evidence of a systemic process, and unnecessary surgical interventions are avoided.

LABORATORY FINDINGS

Laboratory abnormalities are common but nonspecific. Thrombocytopenia occurs in 60%, and the total white blood cell count is most often normal, with leukocytosis in 24% and leukopenia in 9%. Other characteristic abnormalities include a left-shifted leukocyte differential, anemia (33%), hyponatremia (<135 mEq/mL in 52%), and elevated serum aminotransferase levels (50%).

DIAGNOSIS

Delays in diagnosis and treatment are associated with severe disease and death. Because no reliable diagnostic test is readily available to confirm RMSF during illness, which lasts from 10 days to not more than 3 weeks, the decision to treat must be based on compatible epidemiologic, clinical, and laboratory features. RMSF should be considered in patients presenting spring through fall with an acute febrile illness accompanied by headache and myalgia (particularly if they report exposure to ticks or contact with a dog or have been in forested or tick-infested rural areas). A history of tick exposure, a rash (especially if on the palms or soles), a normal or low leukocyte count with a marked left shift, a relatively low or decreasing platelet count, and a low serum sodium concentration are all clues that can support a diagnosis of RMSF. In patients without a rash or in dark-skinned patients in whom a rash can be difficult to appreciate, the diagnosis can be exceptionally elusive and delayed. One half of pediatric deaths occur within 9 days of onset of symptoms. Thus treatment should not be withheld pending definitive laboratory results for a patient with clinically suspected illness. Further, prompt response to early treatment is diagnostically helpful.

If a rash is present, a vasculotropic rickettsial infection can be diagnosed as early as day 1 or 2 of illness with biopsy of a petechial lesion and immunohistochemical or immunofluorescent demonstration of a specific rickettsial antigen in the endothelium. Although highly specific, the sensitivity of this method is probably 70% at most. Furthermore, it can be adversely influenced by prior antimicrobial therapy, suboptimal selection of skin lesions for biopsy, and examination of insufficient tissue because of the focal nature of the infection. Tissue or blood can also be evaluated for *R. rickettsii* nucleic acids by polymerase chain reaction (PCR) at the CDC and selected public health or reference laboratories; PCR on blood is less sensitive than PCR on tissue and of similar sensitivity to tissue immunohistochemistry, probably because the level of rickettsemia is generally very low (<6 rickettsiae/mL). Because eschars are rare with RMSF, scab scrapings or skin swabs are not useful specimens for the detection of rickettsemia by PCR.

Definitive diagnosis is most often accomplished by serology, which is retrospective, because a rise in titer is not seen until after the first week of illness. The gold standard for the diagnosis of RMSF is a fourfold increase in immunoglobulin G antibody titer by indirect fluorescent antibody assay between paired acute and convalescent (at 2-4 weeks) sera, including in the case of seroconversion. A single IgG titer is neither sensitive (patients can die before seroconversion) nor specific (an elevated titer can represent prior infection). IgM is nonspecific and does not confirm acute infection. With current serologic methods, RMSF cannot be reliably distinguished from other spotted fever group rickettsiae infections, some of which are not known to be pathogenic. Therefore confirming acute spotted fever group rickettsia infection requires a compatible clinical illness. Cross reactions of spotted fever group rickettsiae with typhus group rickettsiae also occur, but titers may be lower for the typhus group. Cross reactions are not seen with *Ehrlichia* or *Anaplasma* infections. Currently, enzyme-linked immunosorbent assay (ELISA) serologic methods can only provide "probable" rather than confirmed evidence of infection. Weil-Felix antibody testing should not be performed because it lacks both sensitivity and specificity. RMSF and other spotted fever group rickettsioses are reportable diseases in the United States; however, few reported cases include paired IgG serology, PCR with sequencing, and epidemiologic and clinical metadata. Therefore little is known about the breadth, pathogenicity, and epidemiology of different spotted fever group rickettsiae in the United States or across the globe. Chronic infections by spotted fever group rickettsiae are not documented, such that positive serologic tests after 1 month or more do not reflect ongoing spotted fever group rickettsia infection.

DIFFERENTIAL DIAGNOSIS

Other rickettsial infections are easily confused with RMSF, especially all forms of human ehrlichiosis and murine typhus and novel spotted fever group rickettsioses that result from *R. parkeri* or "*R. philipii*" str. 364D infections. RMSF can also mimic a variety of other diseases, such as meningococcemia and enterovirus infections. Negative blood cultures can exclude meningococcemia. PCR can differentiate enterovirus from *R. rickettsii* in patients with aseptic meningitis and cerebrospinal fluid pleocytosis. Other diseases in the differential diagnosis are typhoid fever, secondary syphilis, Lyme disease, leptospirosis, rat-bite fever, scarlet fever, toxic shock syndrome, rheumatic fever, rubella, parvovirus infection, Kawasaki disease, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, Henoch-Schönlein purpura, hemolytic uremic syndrome, aseptic meningitis, acute gastrointestinal illness, acute abdomen, hepatitis, infectious mononucleosis, hemophagocytic and macrophage activation syndromes, dengue fever, and drug reactions.

TREATMENT

The time-proven effective therapies for RMSF are tetracyclines and chloramphenicol. The treatment of choice for suspected RMSF in patients of all ages, including children under 8 years of age, is doxycycline (4 mg/kg/day divided every 12 hours PO or IV; maximum: 200 mg/day). Tetracycline (25-50 mg/kg/day divided every 6 hours PO; maximum: 2 g/day) is an alternative. Chloramphenicol (50-100 mg/kg/day divided every 6 hours IV; maximum: 4 g/day) should be reserved for patients with doxycycline allergy and for pregnant women because chloramphenicol is an independent risk factor for increased mortality vs tetracyclines. If used, chloramphenicol should be monitored to maintain serum concentrations of 10-30 μg/mL. Chloramphenicol is preferred for pregnant women because of potential adverse effects of doxycycline on fetal teeth and bone and maternal liver function. RMSF is a life-threatening illness for which prompt therapy is imperative, and multiple recent studies demonstrate a negligible risk for tooth discoloration in children younger than 8 years of age with the use of doxycycline. Chloramphenicol is rarely associated with aplastic anemia and is no longer available as an oral preparation in the United States. An additional benefit of doxycycline over chloramphenicol is its effectiveness against potential concomitant *Ehrlichia* or *Anaplasma* infection. Sulfonamides should not be used because they are associated with greater morbidity and mortality with all rickettsial infections. Other antibiotics, including penicillins, cephalosporins, and aminoglycosides, are not effective. The use of alternative antimicrobial agents, such as fluoroquinolones and the macrolides (azithromycin and clarithromycin), has not been evaluated.

Therapy should be continued for a minimum of 5-7 days and until the patient has been afebrile for at least 3 days. Treated patients usually defervesce within 48 hours, so the duration of therapy is usually <10 days. Spotted fever group rickettsia infection resolves within several weeks if treated appropriately; thus patients with remitting clinical manifestations after 1 month do not benefit from continued or additional treatment.

SUPPORTIVE CARE

Most infections resolve rapidly with appropriate antimicrobial therapy and do not require hospitalization or other supportive care. Among those hospitalized, 36% require intensive care. Particular attention to hemodynamic status is mandatory in severely ill children because iatrogenic pulmonary or cerebral edema could be easily precipitated owing to diffuse microvascular injury of the lungs, meninges, and

brain. Judicious use of corticosteroids for meningoencephalitis has been advocated by some, but no controlled trials have been conducted.

COMPLICATIONS

Complications of RMSF include noncardiogenic pulmonary edema from pulmonary microvascular leakage, cerebral edema from meningoencephalitis, and multiorgan damage (hepatitis, pancreatitis, cholecystitis, epidermal necrosis, and gangrene) mediated by rickettsial vasculitis and/or the accumulated effects of hypoperfusion and ischemia (acute renal failure). Long-term neurologic sequelae can occur in any child with RMSF but are more likely to occur in those hospitalized for ≥2 weeks. Examples of neurologic sequelae include speech or swallowing disorders; global encephalopathy; cerebellar, vestibular, and motor dysfunction; hearing loss; and cortical blindness. Learning disabilities and behavioral problems are the most common neurologic sequelae among children who have survived severe disease.

PROGNOSIS

Delays in diagnosis and therapy are significant factors associated with severe illness or death. Before the advent of effective antimicrobial therapy for RMSF, the case fatality rate was 10% for children and 30% for adults. The overall case fatality rate decreased to a historic low (0.3–0.4%) from 2003 to 2012; however, many experts attribute this decrease to detection and reporting of other less virulent emerging forms of spotted fever group rickettsioses that cannot be readily differentiated from RMSF using current serologic tests. The overall case fatality rate of children 0-9 years of age was 1.4%, but rates as high as 8.5% and 11.8% were documented in Texas (1986–1996) and in Arizona (1999–2007), respectively, and rates as high as 30–40% are now reported from outbreaks in Mexico, Brazil, and other parts of South America. Diagnosis based on serology alone underestimates the true mortality of RMSF, because death occurs at a median of 7 days (before developing a serologic response). Deaths occur despite the availability of effective therapeutic agents, indicating the need for clinical vigilance and a low threshold for early empiric therapy. Even with administration of appropriate antimicrobials, delayed therapy can lead to irreversible vascular or end-organ damage and long-term sequelae or death. Early therapy in uncomplicated cases usually leads to rapid defervescence within 1-3 days and recovery within 7-10 days. A slower response may be seen if therapy is delayed. In those who survive despite no treatment, fever subsides in 2-3 weeks.

PREVENTION

No vaccines are available. Prevention of RMSF is best accomplished by preventing or treating tick infestation in dogs, avoiding areas where ticks reside, using insect repellents containing N,*N*-diethyl-3-methylbenzamide (DEET) or new alternatives (https://www.epa.gov/insect-repellents/find-repellent-right-you), wearing protective clothing, and carefully inspecting children after play in areas where they are potentially exposed to ticks. Recovery from infection yields lifelong immunity.

Prompt and complete removal of attached ticks helps reduce the risk for transmission because rickettsiae in the ticks need to be reactivated to become virulent, and this requires at least several hours to days of exposure to body heat or blood. Contrary to popular belief, the application of petroleum jelly, 70% isopropyl alcohol, fingernail polish, or a hot match are not effective in removing ticks. A tick can be safely removed by grasping the mouth parts with a pair of forceps at the site of attachment to the skin and applying gentle and steady pressure to achieve retraction without twisting, thereby removing the entire tick and its mouth parts. The site of attachment should then be disinfected. Ticks should not be squeezed or crushed, because their fluids may be infectious. The removed tick should be soaked in alcohol or flushed down the toilet, and hands should be washed to avoid accidental inoculation into conjunctivae, mucous membranes, or breaks in skin. Typically, prophylactic antimicrobial therapy is not recommended because tetracyclines and chloramphenicol are only rickettsiastatic; however, the evidence to support this position is meager.

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274.2 Mediterranean Spotted Fever or Boutonneuse Fever (*Rickettsia conorii*)

Megan E. Reller and J. Stephen Dumler

MSF, or boutonneuse fever, is caused by *R. conorii;* it is also called by other names, such as *Kenya tick typhus, Indian tick typhus, Israeli spotted fever,* and *Astrakhan fever*. It is a moderately severe vasculotropic rickettsiosis in adults but comparatively milder in children, with more frequent lymphadenopathy; often, MSF is initially associated with an eschar at the site of the tick bite. Minor differences in clinical presentation could be associated with genetic diversity of this species.

ETIOLOGY

MSF is caused by systemic endothelial cell infection by the obligate intracellular bacterium *R. conorii*. Similar species are distributed globally, such as *R. sibirica, R. heilongjiangensis,* and *R. mongolotimonae* in Russia, China, Mongolia, and Pakistan; *R. australis* and *R. honei* in Australia; *R. japonica* in Japan; *R. africae* in South Africa; and *R. parkeri* and "*R. philippii*" str. 364D in the Americas (see Table 274.1). Analysis of antigens and related DNA sequences show that all are closely related within a broad genetic clade that includes spotted fever group *Rickettsia* species such as *R. rickettsii*, the cause of RMSF.

EPIDEMIOLOGY

R. conorii is distributed over a large geographic region, including India, Pakistan, Russia, Ukraine, Georgia, Israel, Morocco, southern Europe, Ethiopia, Kenya, and South Africa. Reported cases of MSF in southern Europe have steadily increased since 1980, and the seroprevalence is 11–26% in some areas. The peak in reported cases occurs during July and August in the Mediterranean basin; in other regions it occurs during warm months when ticks are active.

TRANSMISSION

Transmission occurs after the bite of the brown dog tick, *R. sanguineus,* or for other *Rickettsia* spp. tick genera such as *Dermacentor, Haemaphysalis, Amblyomma, Hyalomma,* and *Ixodes.* Clustering of human cases of boutonneuse fever, infected ticks, and infected dogs implicates the household dog as a potential vehicle for transmission.

PATHOLOGY AND PATHOGENESIS

The underlying pathology seen with MSF is nearly identical to that of RMSF, except that eschars are often present at the site of a tick bite where inoculation of rickettsiae occurs. The histopathology of the resultant lesion includes necrosis of dermal and epidermal tissues with a superficial crust; a dermis densely infiltrated by lymphocytes, histiocytes, and scattered neutrophils; and damaged capillaries and venules in the dermis. Immunohistochemical stains and nucleic acid amplification tests confirm that the lesions contain rickettsia-infected endothelial cells and potentially other cells such as macrophages. The necrosis results from both direct rickettsia-mediated vasculitis and resultant extensive local inflammation. Thus rickettsiae have ready access to lymphatics and venous blood and disseminate to cause systemic disease.

CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS

Typical findings in children include fever (37–100%), a maculopapular rash that appears 3-5 days after onset of fever (94–100%), hepatosplenomegaly (20–83%), myalgias and arthralgias (10–42%), headache (8–63%), nausea, vomiting, or diarrhea (5–28%), and lymphadenopathy (52–54%). In 60–90% of patients, a **painless eschar**, or **tache noire**, appears at the site of the tick bite, often on the scalp, with accompanying regional lymphadenopathy (50–60%) (Fig. 274.6). The infection can be severe, mimicking RMSF, although morbidity and fatalities in children

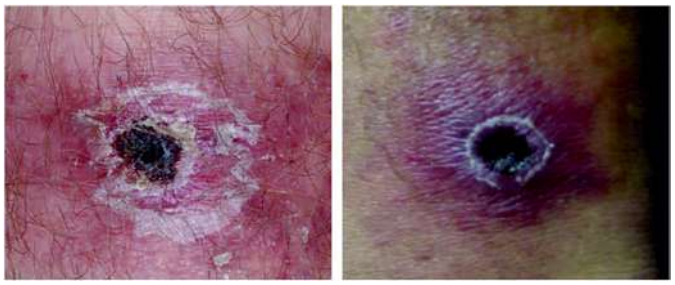

Fig. 274.6 Various appearances of eschars associated with *Rickettsia parkeri* rickettsiosis. *(From Biggs HM, Behravesh CB, Bradley KK, et al. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever and other spotted fever group rickettsioses, ehrlichioses, and anaplasmosis—United States. MMWR Recomm Rep. 2016;65:1–44, Fig. 24.)*

are less frequent than in adults. Findings can include seizures, purpuric skin lesions, meningitis and neurologic deficits, respiratory and/or acute renal failure, and severe thrombocytopenia. Even though the case fatality rate can be as high as 10% in adults and severe infections occur in approximately 9% of children, pediatric deaths are rare. As with RMSF, a particularly severe form occurs in patients with glucose-6-phosphate dehydrogenase deficiency and in patients with underlying conditions such as alcoholic liver disease or diabetes mellitus.

DIAGNOSIS

Laboratory diagnosis of MSF and related spotted fever group rickettsioses is the same as that for RMSF. Cases can be confirmed by immunohistologic or immunofluorescent demonstration of or amplification of nucleic acids from rickettsiae in eschar crust or skin biopsies, or demonstration of seroconversion, or accompanied by a fourfold rise in serum antibody titer to spotted fever group rickettsiae between acute and convalescent sera. Antibodies to spotted fever group antigens cross react, so RMSF or other spotted fever group rickettsiosis in the United States or MSF in Europe, Africa, and Asia cannot be distinguished by these methods. When eschars are present, biopsy of the eschar with submission of tissue or a swab of the base for PCR provides considerably higher sensitivity than PCR on blood and is advocated, if available. In vitro cultivation via centrifugation-assisted shell vial tissue culture is rarely used for clinical diagnosis. Treatment should not be withheld while waiting for diagnostic test results.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes conditions also associated with single eschars, such as anthrax, bacterial ecthyma, brown recluse spider bite, rat-bite fever (caused by *Spirillum minus*), and other rickettsioses (such as rickettsialpox, African tick-bite fever, *R. parkeri* or "*R. philipii*" str. 364D rickettsiosis, and scrub typhus). The spotted fever group rickettsia *R. africae* causes African tick-bite fever, a milder illness than MSF that is often associated with multiple eschars and occasionally a vesicular rash. African tick-bite fever can be contracted in North Africa, where MSF also occurs, and is a common infection of travelers to sub-Saharan Africa who encounter bush or high grasslands on safari. *R. parkeri* and "*R. philipii*" str. 364D rickettsiosis are emerging infections in North and South America and in the U.S. western states, respectively. Both often present with an eschar and milder clinical manifestations similar to those observed with African tick-bite fever.

TREATMENT AND SUPPORTIVE CARE

In adults, MSF is effectively treated with tetracycline, doxycycline, chloramphenicol, ciprofloxacin, ofloxacin, levofloxacin, azithromycin, or clarithromycin. For children, the treatment of choice is doxycycline (4 mg/kg/day divided every 12 hours PO or IV; maximum: 200 mg/day). Tetracycline and chloramphenicol are alternatives, as for RMSF. Azithromycin (10 mg/kg/day once daily PO for 3 days) and clarithromycin (15 mg/kg/day divided twice daily PO for 7 days) are also used. Specific fluoroquinolone regimens effective for children have not been established, although recent reports suggest that the use of fluoroquinolones is associated with increased disease severity as compared with doxycycline. Intensive care may be required.

COMPLICATIONS

The complications of MSF are similar to those of RMSF. Overall, the case fatality rate is less than 2%, but fatalities are rare in children. Particularly severe infections have been noted in patients with underlying medical conditions, including glucose-6-phosphate dehydrogenase deficiency and diabetes mellitus.

PREVENTION

MSF is transmitted by tick bites, and prevention is the same as recommended for RMSF. No vaccine is currently available.

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274.3 Rickettsialpox *(Rickettsia akari)* and Flea-Borne Spotted Fever

Megan E. Reller and J. Stephen Dumler

Rickettsialpox is caused by *R. akari,* a transitional-group *Rickettsia* species that is transmitted by the mouse mite, *Allodermanyssus sanguineus.* The mouse host for this mite is widely distributed in cities in the United States, Europe, and Asia. Seroepidemiologic studies suggest a high prevalence of this infection in urban settings. The disease is uncommon and is usually mild. Unlike the situation with most forms of rickettsiosis, the macrophage is an important target cell for *R. akari.*

Rickettsialpox is best known because of its association with a varicelliform rash. In fact, this rash is a modified form of an antecedent typical macular or maculopapular rash like those seen in other vasculotropic rickettsioses and is occasionally seen with other rickettsioses such as African tick-bite fever. Clinical descriptions in children are infrequent. At presentation, most patients have fever, headache, and chills. In up to 90% of cases, there is a painless papular, ulcerative lesion, or eschar at the initial site of inoculation, which can be associated with tender regional lymphadenopathy. In some patients, the maculopapular rash becomes vesicular, involving the trunk, head, and extremities. The infection generally resolves spontaneously and does not require therapy. However, a short course of doxycycline hastens resolution and is sometimes used in patients older than 8 years of age and in young children with relatively severe illness. Complications and fatalities are rare; however, clear examples of severe disease in children like that observed with RMSF are described.

Flea-borne spotted fever, caused by *Rickettsia felis,* is often considered within the typhus group because of flea transmission; however, phylogenetic studies place it close to the *Rickettsia* genus spotted fever or within the "transitional" group. Similarly, a related cat flea–associated agent, *R. asembonensis,* was isolated from cat fleas; it and other related rickettsiae in fleas have been identified in environmental samples over broad geographic regions but are not known to cause human disease. Since the discovery of *R. felis* in a febrile patient from Texas by use of molecular amplification methods, and its subsequent isolation from infected cat fleas, molecular and cross reactive serologic tests have purported to identify human infections globally, some at high rates of prevalence. Clinical isolates have yet to be made from infected humans, and many patients identified by molecular methods lack serologic responses or even clinical signs. Its identification within mosquitoes and in conjunction with malaria further confound its role as a human pathogen. Until many of the discrepant findings observed with *R. felis* are resolved, its role as an important infectious agent in humans remains to be resolved.

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Chapter 275

Scrub Typhus (*Orientia tsutsugamushi*)

Megan E. Reller and J. Stephen Dumler

Scrub typhus is an important cause of acute febrile illness in South and East Asia and the Pacific and could be emerging in the Middle East, Africa, and South America. The causative agent is distinct from, but related to, *Rickettsia* species. The infection is transmitted via chigger (larval mite) bites and involves many antigenically diverse strains of *Orientia tsutsugamushi* or emerging *Orientia* spp. such as "*O. chuto*" and "*O. chiloensis,*" hampering vaccine development.

ETIOLOGY

The causative agent of scrub typhus, or tsutsugamushi fever, is *O. tsutsugamushi,* which is distinct from other spotted fever and typhus group rickettsiae (see Table 274.1 in Chapter 274). *O. tsutsugamushi* lacks both lipopolysaccharide and peptidoglycan in its cell wall. Like other vasculotropic rickettsiae, *O. tsutsugamushi* infects endothelial cells and causes vasculitis, the predominant clinicopathologic feature of the disease. However, the organism also infects macrophages and cardiac myocytes. A new *Candidatus* species, "*Orientia chuto,*" was isolated from a patient in the Middle East, and definitive evidence of infection based on serology and/or PCR amplification of *O. tsutsugamushi* genes from acute-phase blood suggests a wider range for scrub typhus and related infections. Similarly, a scrub typhus–like illness in southern Chile has been attributed to infection by a new species, "*Orientia chiloensis*."

EPIDEMIOLOGY

At least 1 million infections occur each year, and it is estimated that more than 1 billion people are at risk. Scrub typhus is recognized mostly in Asia, including areas delimited by Korea, Pakistan, and northern Australia. Outside these tropical and subtropical regions, the disease occurs in Japan, the Primorsky of far eastern Russia, Tajikistan, Nepal, and nontropical China, including Tibet. Cases imported to the United States and other parts of the world are reported. Endemic scrub typhus has historically been confined to Asia and Oceania and the tsutsugamushi triangle; however, *Orientia* may be distributed more broadly, with confirmed cases in South America and possible cases in Africa. Most infections in children are acquired in rural areas. In Thailand and Sri Lanka, scrub typhus is the cause of 1–8% of acute fevers of unknown origin. Infections are most common during rainy months, usually June through November. Reported cases in boys are higher than in girls.

TRANSMISSION

O. tsutsugamushi is transmitted via the bite of the larval stage (chigger) of a trombiculid mite (*Leptotrombidium* in Asia, *Herpetacarus* in Chile, and *Microtrombicula* in Africa), which serves as both vector and reservoir. Vertical transovarial transmission (passage of the organism from infected mites to their progeny) is the major mechanism for maintenance in nature. Because only the larval stage takes blood meals, a role for horizontal transmission from infected rodent hosts to uninfected mites has not been proved, but transmission among co-feeding larval mites is a possibility. Multiple serotypes of *O. tsutsugamushi* are recognized, and some share antigenic cross reactivity; however, they do not stimulate protective cross-immunity.

PATHOLOGY AND PATHOGENESIS

The pathogenesis of scrub typhus is uncertain. The process may be stimulated by widespread infection of vascular endothelial cells, which corresponds to the distribution of disseminated vasculitic and perivascular inflammatory lesions observed in histopathologic examinations. In autopsy series, the major result of the vascular injury appears to be hemorrhage. However, data support the concept that vascular injury initiated by the infection is sustained by immune-mediated inflammation that together cause significant vascular leakage. The net result is significant vascular compromise and ensuing end-organ injury, most often manifested in the brain and lungs, as with other vasculotropic rickettsioses.

CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS

Scrub typhus can be mild or severe in children and can affect almost every organ system. Most patients present with fever for 9-11 days (range: 1-30 days) before seeking medical care. Regional or generalized lymphadenopathy is reported in 23–93%, hepatomegaly in about two thirds, and splenomegaly in about one third of children with scrub typhus. Gastrointestinal symptoms, including abdominal pain, vomiting, and diarrhea, occur in up to 40% of children at presentation. A **single painless eschar** with an erythematous rim at the site of the chigger bite is seen in 7–68% of cases, and a maculopapular rash is present in less than half; both can be absent. Hemophagocytic lymphohistiocytosis has been described. Leukocyte and platelet counts are most commonly within normal ranges, although thrombocytopenia occurs in one quarter to one third of children, and leukocytosis is observed in approximately 40% of children. Clinical manifestations often respond dramatically to appropriate treatment. Adverse outcomes in fetuses and newborn infants of infected mothers have been described, resulting from vertical transmission.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Owing to the potential for severe complications, diagnosis and decision to initiate treatment should be based on clinical suspicion. The reference diagnostic standard for acute scrub typhus remains demonstration of a fourfold rise in IgG antibody titer by indirect fluorescent antibody testing of acute-phase and convalescent-phase (obtained at 2- to 4-week follow-up) sera. The IgG indirect fluorescent antibody assay is >90% sensitive with 11 days or more of fever but does not distinguish acute from past infection in those residing in endemic regions. A positive acute-phase IgM is also not definitive evidence of acute scrub typhus. Although the rickettsiae can be cultivated using tissue culture methods, polymerase chain reaction tests are not highly sensitive, and these diagnostic methods are not widely available. The differential diagnosis includes fever of unknown origin, enteric fever, typhoid fever, dengue hemorrhagic fever, other rickettsioses, tularemia, anthrax, dengue, leptospirosis, malaria, and infectious mononucleosis.

TREATMENT AND SUPPORTIVE CARE

The recommended treatment regimen for scrub typhus is doxycycline (4 mg/kg/day PO or IV divided every 12 hours; maximum: 200 mg/day). Alternative regimens include tetracycline (25-50 mg/kg/day PO divided every 6 hours; maximum: 2 g/day) or chloramphenicol (50-100 mg/kg/day divided every 6 hours IV; maximum: 4 g/24 hr). If used, chloramphenicol should be monitored to maintain serum concentrations of 10-30 μg/mL. Alternatives now supported by data from randomized trials include azithromycin (10 mg/kg PO on day 1, then 5 mg/kg PO; maximum: 500 mg/day) or clarithromycin (15-30 mg/kg/day PO divided every 12 hours; maximum: 1 g/day). Therapy should be continued for a minimum of 5 days and until the patient has been afebrile for at least 3 days to avoid relapse. However, a single dose of oral doxycycline was reported effective for all 38 children treated with this regimen in a large series from Thailand. Most children respond rapidly to doxycycline or chloramphenicol within 1-2 days (range: 1-5 days). Strains of *O. tsutsugamushi* with modestly higher doxycycline minimal inhibitory concentrations are reported in some regions of Thailand. Clinical trials showed that azithromycin could be as effective and that rifampicin is superior to doxycycline in such cases and could have a role as an alternative therapy, especially for pregnant women. The use of ciprofloxacin in pregnant women resulted in an adverse outcome in

five of five pregnancies among Indian women. Intensive care may be required for hemodynamic management of severely affected patients.

COMPLICATIONS

Serious complications include pneumonitis in 20–35% and meningoencephalitis in approximately 10–25% of children. Acute renal failure, myocarditis, and septic shock occur less often. Cerebrospinal fluid examination shows a mild mononuclear pleocytosis with normal glucose levels. Chest radiographs reveal transient perihilar or peribronchial interstitial infiltrates in most children who are examined. The reported case fatality rate varies widely; among 883 patients <20 years of age in 18 published studies, the case fatality rate was 11%; the median for the studies was 1.6–1.8% and ranged as high as 33%. In a contemporary systematic review and meta-analysis of Indian children, the case fatality rate was 1.1%.

PREVENTION

Prevention is based on avoidance of the chiggers that transmit *O. tsutsugamushi.* Protective clothing is the next most useful mode of prevention. Infection provides immunity to reinfection by homologous but not heterologous strains; however, because natural strains are highly heterogeneous, infection does not always provide complete protection against reinfection. No vaccines are currently available.

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Chapter 276

Typhus Group Rickettsioses

Megan E. Reller and J. Stephen Dumler

Members of the typhus group of rickettsiae (see Table 274.1 in Chapter 274) include *Rickettsia typhi,* the cause of murine typhus, and *Rickettsia prowazekii,* the cause of louse-borne or epidemic typhus. *R. typhi* is transmitted to humans by fleas, and *R. prowazekii* is transmitted in the feces of body lice. Louse-borne or epidemic typhus is widely considered to be the most virulent of the rickettsial diseases, with a high case fatality rate even with treatment. Murine typhus is moderately severe and likely underreported worldwide; global warming and increased precipitation may increase cases and spread. The genomes of both *R. typhi* and *R. prowazekii* are similar.

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276.1 Murine (Endemic or Flea-Borne) Typhus *(Rickettsia typhi)*

Megan E. Reller and J. Stephen Dumler

ETIOLOGY

Murine typhus is caused by *R. typhi,* a rickettsia transmitted from infected fleas to rats, other rodents, or opossums and back to fleas. Transovarial transmission (passage of the organism from infected fleas to their progeny) in fleas is inefficient. Transmission depends on infection from the flea to uninfected mammals that then sustain transient rickettsemia and serve as sources of the bacterium for uninfected fleas that bite during the period of rickettsemia.

EPIDEMIOLOGY

Murine typhus has a worldwide distribution and occurs especially in warm coastal ports, where it is primarily maintained in a cycle involving rat fleas *(Xenopsylla cheopis)* and rats (*Rattus* species). Peak incidence occurs when rat populations are highest during spring, summer, and fall. Sentinel surveillance studies suggest that travel-acquired murine typhus occurs most often in those visiting Southeast Asia and Africa. In the United States, murine typhus was prevalent before eradication efforts using DDT in the 1940s and is now re-emerging. The disease is recognized most often in south Texas and Southern California. However, seroprevalence studies among children indicate that murine typhus is acquired across the southeast and southcentral United States, thus expanding the endemic areas in which pediatricians must be alert for this infection. In the coastal areas of south Texas and in Southern California, the disease is seen in all months, but predominantly from January through July, and is associated with a *sylvatic cycle* involving opossums and cat fleas *(Ctenocephalides felis)*. The marked increase in reported cases in the past decade likely relates to increased recognition, improved surveillance, and ecologic factors.

TRANSMISSION

R. typhi normally cycles between rodents or midsize animals such as opossums and their fleas. Human acquisition of murine typhus occurs when rickettsiae-infected flea feces contaminate flea bite wounds. Direct inoculation via flea bite is possible, but inefficient.

PATHOLOGY AND PATHOGENESIS

R. typhi is a vasculotropic rickettsia that causes disease in a manner similar to *Rickettsia rickettsii* (see Chapter 274.1). *R. typhi* organisms in flea feces deposited on the skin as part of the flea feeding reflex are inoculated into the pruritic flea bite wound. After an interval for local proliferation, the rickettsiae spread systemically via lymphatics to the blood, after which they infect the endothelium in many tissues. As with spotted fever group rickettsiae, typhus group rickettsiae infect endothelial cells, but unlike the spotted fever group rickettsiae, they polymerize intracellular actin poorly, have limited intracellular mobility, and probably cause cellular injury by either enzymatic membrane or mechanical lysis after accumulating in large numbers within the endothelial cell cytoplasm. Intracellular infection leads to endothelial cell damage, recruitment of inflammatory cells, and vasculitis. The inflammatory cell infiltrates bring in a number of effector cells, including macrophages that produce proinflammatory cytokines, and CD4, CD8, and natural killer lymphocytes, which can produce immune cytokines such as interferon-γ or participate in cell-mediated cytotoxic responses. Intracellular rickettsial proliferation of typhus group rickettsiae is inhibited by cytokine-mediated mechanisms and nitric oxide–dependent and –independent mechanisms.

Pathologic findings include systemic vasculitis in response to rickettsiae within endothelial cells. This vasculitis manifests as interstitial pneumonitis, meningoencephalitis, interstitial nephritis, myocarditis, and mild hepatitis with periportal lymphohistiocytic infiltrates. As vasculitis and inflammatory damage accumulate, multiorgan damage can ensue.

CLINICAL MANIFESTATIONS

In children, murine typhus is generally a self-limited infection, but can be severe, similar to other vasculotropic rickettsioses. The incubation period varies from 1 to 2 weeks. The initial presentation is often nonspecific and mimics typhoid fever; fever of undetermined origin is the most common presentation. Pediatric patients with murine typhus exhibit symptoms classically attributed to other vasculotropic rickettsioses, such as rash (48–80%), myalgias (29–57%), vomiting (29–45%), cough (15–40%), headache (19–77%), and diarrhea or abdominal pain (10–40%). A petechial rash is observed in <15% of children, and the usual appearance is that of macules or maculopapules distributed on the trunk and extremities. The rash can involve both the soles and palms. Among common clinical features, only abdominal pain, diarrhea, and sore throat are more common in children than in adults, underscoring

the mild nature of most cases in children. Murine typhus–associated hemophagocytic lymphohistiocytosis (HLH) is described. Although neurologic involvement is a common finding in adults with murine typhus, photophobia, confusion, stupor, coma, seizures, meningismus, and ataxia are seen in <20% of hospitalized children and <6% of infected children treated as outpatients. Poor neonatal outcomes are reported with infection during pregnancy; however, frequency and clinical spectrum are not well documented.

LABORATORY FINDINGS

Although nonspecific, laboratory findings are less severe than in adults. Helpful findings include mild leukopenia (28–40%) with a moderate left shift, mild to marked thrombocytopenia (30–60%), hyponatremia (20–66%), hypoalbuminemia (30–87%), and elevated aspartate aminotransferase (82%) and alanine aminotransferase (38%). Elevations in serum urea nitrogen are usually a result of prerenal mechanisms.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Delays in diagnosis and therapy are associated with increased morbidity and mortality; thus diagnosis must be based on clinical suspicion. Occasionally, patients present with findings suggesting pharyngitis, bronchitis, hepatitis, gastroenteritis, or sepsis; thus the differential diagnosis may be extensive. Murine typhus can also mimic SARS-CoV-2–associated multisystem inflammatory syndrome in children (MIS-C).

Confirmation of the diagnosis is usually accomplished by comparing acute- and convalescent-phase antibody titers obtained with the indirect fluorescent antibody assay (IFA) to demonstrate a fourfold rise in titer. Current objective studies of the diagnostic yield of *R. typhi* nucleic acid amplification from acute-phase whole blood show disappointingly low sensitivity, and rickettsial culture is not readily available. Thus paired (acute and convalescent) serology to demonstrate a fourfold rise in immunoglobulin (Ig) G antibody titer by IFA remains the standard for confirming acute infection. Use of IgM serologic tests is discouraged for diagnosis of rickettsial infections because of both limited sensitivity and specificity.

TREATMENT

A meta-analysis of murine typhus in children reviewed treatment in 261 children, including 54 who received no antimicrobial therapy. Although 15% had complications, there were no deaths. The standard therapy for murine typhus in children was similar to that for adults and focused on use of tetracyclines or chloramphenicol. Quinolones have been used in children, and limited clinical studies show that ciprofloxacin is as effective as doxycycline and chloramphenicol to treat murine typhus; however, treatment failures are reported. In vitro experiments suggest that minimal inhibitory concentrations of azithromycin and clarithromycin for *R. typhi* should be easily achieved. However, in adult patients, a prospective randomized clinical trial showed that either a 3- or 7-day course of doxycycline was superior to 3 days of azithromycin for fever clearance.

Therefore the time-honored recommended treatment for murine typhus remains doxycycline (4 mg/kg/day divided every 12 hours PO or IV; maximum: 200 mg/day). Alternative regimens include tetracycline (25-50 mg/kg/day divided every 6 hours PO; maximum: 2 g/day) or chloramphenicol (50-100 mg/kg/day divided every 6 hours IV; maximum: 4 g/day). Therapy should be for a minimum of 3 days and continued until the patient has been afebrile for at least 3 days.

SUPPORTIVE CARE

Although disease is usually mild, 15% of children have complications and 2–7% require intensive care for management of meningoencephalitis, a disseminated intravascular coagulation–like condition, or other conditions. As for other rickettsial infections with significant systemic vascular injury, careful hemodynamic management is mandatory to avoid pulmonary or cerebral edema.

COMPLICATIONS

Complications of murine typhus in pediatric patients are uncommon; however, relapse, stupor, facial edema, dehydration, splenic rupture, and meningoencephalitis are reported. Predominance of abdominal pain has led to surgical exploration to exclude a perforated viscus.

PREVENTION

Control of murine typhus was dependent on elimination of the flea reservoir and control of flea hosts, and this approach remains important. However, with the recognition of cat fleas as potentially significant reservoirs and vectors, the presence of these flea vectors and their mammalian hosts in suburban areas where close human exposures occur poses increasingly difficult control problems. It is not known with certainty if infection confers protective immunity; reinfection appears to be rare.

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276.2 Epidemic (Louse-Borne) Typhus (*Rickettsia prowazekii*)

Megan E. Reller and J. Stephen Dumler

ETIOLOGY

Humans are considered the principal reservoir of *R. prowazekii,* the causative agent of epidemic or louse-borne typhus and its recrudescent form, Brill-Zinsser disease. Another reservoir exists in flying squirrels, their ectoparasites, and potentially ticks in a sylvatic cycle with small rodents. *R. prowazekii* is the most pathogenic member of the genus *Rickettsia* and multiplies to very large intracellular quantities before rupture of infected endothelial cells.

EPIDEMIOLOGY

The infection is characteristically seen in winter or spring and especially during times of poor hygienic practices associated with crowding, war, famine, extreme poverty, and civil strife. As observed in a recent outbreak among youths at a rehabilitation center in Rwanda, infections in children under these conditions can lead to severe adverse outcomes. *R. prowazekii* has also been associated with sporadic cases of a mild, typhus-like illness in the United States; such cases are associated with exposure to flying squirrels harboring infected lice or fleas. *R. prowazekii* organisms isolated from these squirrels appear to be genetically similar to isolates obtained during typical outbreaks.

Most cases of louse-borne typhus in the developed world are sporadic, but outbreaks have been identified in Africa (Ethiopia, Nigeria, Rwanda, and Burundi), Mexico, Central America, South America, Eastern Europe, Afghanistan, Russia, northern India, and China within the past 25 years. After the Burundi Civil War in 1993, 35,000-100,000 cases of epidemic typhus were diagnosed in displaced refugees, resulting in an estimated 6,000 deaths.

TRANSMISSION

Human body lice *(Pediculus humanus)* become infected by feeding on persons who have rickettsiae circulating in their blood owing to endothelial cell infection. The ingested rickettsiae infect the midgut epithelial cells of the lice and are passed into the feces, which, in turn, are introduced into a susceptible human host through abrasions or perforations in the skin, through the conjunctivae, or rarely, through inhalation as fomites in clothing, bedding, or furniture.

CLINICAL MANIFESTATIONS

Louse-borne typhus can be mild or severe in children. The incubation period is usually <14 days. The typical clinical manifestations include fever, severe headache, abdominal tenderness, and rash in most patients, as well as chills (82%), myalgias (70%), arthralgias (70%), anorexia (48%), nonproductive cough (38%), dizziness (35%),

photophobia (33%), nausea (32%), abdominal pain (30%), tinnitus (23%), constipation (23%), meningismus (17%), visual disturbances (15%), vomiting (10%), and diarrhea (7%). However, investigation of recent African outbreaks has shown a lower incidence of rash (25%) and a high incidence of delirium (81%) and cough associated with pneumonitis (70%). The rash is initially pink or erythematous and blanches. In one third of patients, red, nonblanching macules and petechiae appear predominantly on the trunk. Infections identified during the preantibiotic era typically produced a variety of central nervous system findings, including delirium (48%), coma (6%), and seizures (1%). Estimates of case fatality rates range between 3.5% and 20% in outbreaks.

Brill-Zinsser disease is a form of typhus that becomes recrudescent months to years after the primary infection, thus rarely affecting children. When bacteremic with rickettsiae, these infected patients can transmit the agent to lice, potentially providing the initial event that triggers an outbreak if hygienic conditions permit.

TREATMENT

Recommended treatment regimens for louse-borne or sylvatic typhus are identical to those used for murine typhus. The treatment of choice is doxycycline (4 mg/kg/day divided every 12 hours PO or IV; maximum: 200 mg/day). Alternative treatments include tetracycline (25-50 mg/kg/day divided every 6 hours PO; maximum: 2 g/day) or chloramphenicol (50-100 mg/kg/day divided every 6 hours IV; maximum: 4 g/day). Therapy should be continued for a minimum of 5 days and until the patient is afebrile for at least 3 days. Evidence exists that doxycycline as a single 200-mg oral dose (4.4 mg/kg if <45 kg) is also efficacious.

PREVENTION

Immediate destruction of vectors with an insecticide is important in the control of an epidemic. Lice live in clothing rather than on the skin; thus searches for ectoparasites should include examination of clothing. For epidemic typhus, antibiotic therapy and delousing measures interrupt transmission, reduce the prevalence of infection in the human reservoir, and diminish the impact of an outbreak. Dust containing excreta from infected lice is stable and capable of transmitting typhus, and care must be taken to prevent its inhalation. Infection confers solid protective immunity. However, recrudescence can occur years later with Brill-Zinsser disease, implying that immunity is not complete.

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Chapter 277

Ehrlichiosis and Anaplasmosis

Megan E. Reller and J. Stephen Dumler

ETIOLOGY

Ehrlichiosis in humans was first described in 1987, when clusters of bacteria confined within cytoplasmic vacuoles of circulating leukocytes (morulae), particularly **mononuclear** leukocytes, were detected in the peripheral blood of a patient with suspected Rocky Mountain spotted fever (RMSF). The etiologic agent, *Ehrlichia chaffeensis,* was cultivated from blood of an infected patient in 1990 and identified as the predominant cause of human ehrlichiosis. Investigations showed that infection by *E. chaffeensis* is transmitted by *Amblyomma americanum* ticks and occurs more often than RMSF in some geographic areas. By 1994, other cases in which morulae were found only in **neutrophils** and lacked serologic evidence for *E. chaffeensis* infection led to the recognition of the species classified as *Anaplasma phagocytophilum,* which encompasses several previously described veterinary pathogens on at least two different continents and causes **anaplasmosis**.

Since these discoveries, additional species in the Anaplasmataceae family were identified as human pathogens, including (1) *Ehrlichia ewingii* in 1996, a veterinary pathogen of canine neutrophils transmitted by *A. americanum* ticks; (2) the *Ixodes scapularis*–transmitted *Ehrlichia muris* subsp. *eauclairensis* in 2009, only present so far in patients from Minnesota and Wisconsin in the United States; (3) infections by *Candidatus* Neoehrlichia mikurensis, presumably *Ixodes* spp. or *Haemaphysalis concinna* tick-transmitted, recognized in 2010 as a cause of sepsis-like infections of immune-compromised patients in Europe, and later as a cause of mild febrile illness in healthy individuals in China; (4) Panola Mountain *Ehrlichia,* a bacterium rarely associated with infections in humans but present in *A. americanum* ticks in the United States and with genetic features of the ruminant pathogen *Ehrlichia ruminantium*; (5) *Ehrlichia canis,* the established canine pathogen that has infected humans in Venezuela and possibly Costa Rica; and (6) *Anaplasma capra,* the cause of mild fever after *Ixodes persulcatus* tick bites, so far only identified in China. The latter five have not yet been established as causes of infection in children.

Although the infections caused by these various genera have been called ehrlichiosis, further study has identified substantial differences in biology and diagnostic approaches such that the CDC now generally separates these into ehrlichiosis, anaplasmosis, or undetermined ehrlichiosis/anaplasmosis. **Human monocytic ehrlichiosis (HME)**, or simply ehrlichiosis, describes disease characterized by infection of predominantly monocytes and is caused by *E. chaffeensis;* **human granulocytic anaplasmosis (HGA)**, now "anaplasmosis," describes disease related to infection of circulating neutrophils by *Anaplasma phagocytophilum;* and **ewingii ehrlichiosis** is caused by infection of granulocytes by *E. ewingii* (see Table 274.1 in Chapter 274).

All of these organisms are tick-transmitted and are small, obligate intracellular bacteria with gram-negative-type cell walls. *Neorickettsia sennetsu* is another related bacterium that is rarely recognized as a cause of human disease and is not transmitted by ticks. *E. chaffeensis* alters host signaling and transcription once inside the cell. It survives in an endosome that enters a receptor recycling pathway to avoid phagosome-lysosome fusion and growth into a **morula**, an intravacuolar aggregate of bacteria. *A. phagocytophilum* survives in a unique vacuole that becomes decorated by microbial proteins that prevent normal endosomal trafficking and lysosome fusion. Little is known about the vacuoles in which *E. ewingii* and *E. muris* subsp. *eauclairensis* grow. These bacteria are pathogens of phagocytic cells in mammals, and characteristically each species has a specific host cell affinity: *E. chaffeensis* infects mononuclear phagocytes, and *A. phagocytophilum* and *E. ewingii* infect neutrophils. Infection leads to direct modifications in function, in part the result of changes in intracellular signal transduction or modulation of transcription of the host cell that diminishes host defenses toward the bacterium. Yet host immune and inflammatory reactions are still activated and in part account for many of the clinical manifestations in ehrlichiosis, such as overlaps with macrophage activation syndrome or hemophagocytic lymphohistiocytosis.

EPIDEMIOLOGY

Infections with *E. chaffeensis* occur across the southeastern, south central, and Mid-Atlantic States of the United States in a distribution that parallels that of RMSF; cases have also been reported in northern California. Reported cases of ehrlichiosis have more than doubled since adoption of the current surveillance case definition in 2008. Suspected cases with appropriate serologic and occasionally molecular evidence have been reported in Europe, Africa, South America, and the Far East, including China and Korea. Human infections with *E. ewingii* have only been identified in the United States in

photophobia (33%), nausea (32%), abdominal pain (30%), tinnitus (23%), constipation (23%), meningismus (17%), visual disturbances (15%), vomiting (10%), and diarrhea (7%). However, investigation of recent African outbreaks has shown a lower incidence of rash (25%) and a high incidence of delirium (81%) and cough associated with pneumonitis (70%). The rash is initially pink or erythematous and blanches. In one third of patients, red, nonblanching macules and petechiae appear predominantly on the trunk. Infections identified during the preantibiotic era typically produced a variety of central nervous system findings, including delirium (48%), coma (6%), and seizures (1%). Estimates of case fatality rates range between 3.5% and 20% in outbreaks.

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EPIDEMIOLOGY

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areas where *E. chaffeensis* also exists, perhaps owing to the shared tick vector. Canine infections are documented in both sub-Saharan Africa and South America.

Although the median age of patients with ehrlichiosis and anaplasmosis is generally older (>51 years), many infected children have been identified, and for ehrlichiosis, the case fatality rate is 4% in those <5 years of age. Perinatal transmission of ehrlichiosis and anaplasmosis has been documented in case reports. Little is known about the epidemiology of *E. ewingii* infections; although infections in children occur, they are recognized at a rate 100-fold less than for *E. chaffeensis*. All infections are strongly associated with tick exposure and tick bites and are identified predominantly during May through September. Although both nymphal and adult ticks can transmit infection, nymphs are more likely to transmit disease because they are most active during the summer.

TRANSMISSION

The predominant tick species that harbors *E. chaffeensis* and *E. ewingii* is *A. americanum,* the lone star tick (see Fig. 274.2*d* in Chapter 274). The tick vectors of *A. phagocytophilum* are *Ixodes* spp., including *I. scapularis* (black-legged or deer tick) in the eastern United States (see Fig. 274.1 in Chapter 274), *Ixodes pacificus* (western black-legged tick) in the western United States, *Ixodes ricinus* (sheep tick) in Europe, *Ixodes persulcatus* in Eurasia, and *Haemaphysalis* spp. in China. The *Ixodes* spp. ticks also transmit *Borrelia burgdorferi, Borrelia miyamotoi, Borrelia mayonii, Babesia microti,* and tick-borne encephalitis-associated flaviviruses in Europe and Powassan viruses and *E. muris* subsp. *eauclairensis* in North America. Co-infections with these agents and *A. phagocytophilum* are documented in children and adults.

Ehrlichia and *Anaplasma* species are maintained in nature predominantly by horizontal transmission (tick to mammal to tick) because the organisms are not transmitted to the progeny of infected adult female ticks (transovarial transmission). The major reservoir for *E. chaffeensis* is the white-tailed deer *(Odocoileus virginianus)*, which is found abundantly in many parts of the United States. A reservoir for *A. phagocytophilum* in the eastern United States appears to be the white-footed mouse, *Peromyscus leucopus.* Deer or domestic ruminants can sustain persistent asymptomatic infections, but the genetic variants in these reservoirs might not be infectious for humans. Efficient transmission requires persistent infections of mammals. Although *E. chaffeensis* and *A. phagocytophilum* can cause persistent infections in animals, clear evidence of chronic infections in humans is exceedingly rare. Transmission of *Ehrlichia* can occur within hours of tick attachment, in contrast to the 1-2 days of attachment required for transmission of *B. burgdorferi* to occur. Transmission of *A. phagocytophilum* is via the bite of the small nymphal stage of *Ixodes* spp., including *I. scapularis* (see Fig. 274.2a in Chapter 274), and is effective only after 36 hours of attachment on laboratory mice.

PATHOLOGY AND PATHOGENESIS

Although ehrlichiosis and anaplasmosis often clinically mimic RMSF or typhus, vasculitis is rare. Pathologic findings include mild, diffuse perivascular lymphohistiocytic infiltrates; Kupffer cell hyperplasia and mild lobular hepatitis with infrequent apoptotic hepatocytes and, less frequently, centrilobular necrosis, cholestasis, and steatosis; infiltrates of mononuclear phagocytes in the spleen, lymph nodes, and bone marrow with occasional hemophagocytosis; granulomas of the liver and bone marrow in patients with *E. chaffeensis* infections; and hyperplasia of one or more bone marrow hematopoietic lineages.

The exact pathogenetic mechanisms are poorly understood, but histopathologic examinations suggest diffuse macrophage activation and poorly regulated host immune and inflammatory reactions. This activation results in moderate to profound leukopenia and thrombocytopenia despite a hypercellular bone marrow, and deaths often are related to hemorrhage or secondary opportunistic infections. Hepatic and other organ-specific injury occurs by a mechanism that appears to be triggered by the bacterium but is more closely related to induction of innate and adaptive immune effectors that are dysregulated in severely affected patients. Meningoencephalitis with a mononuclear cell pleocytosis in the cerebrospinal fluid (CSF) occurs with ehrlichiosis but is rare with anaplasmosis.

CLINICAL MANIFESTATIONS

The clinical manifestations of ehrlichiosis, anaplasmosis, and ewingii ehrlichiosis are similar. Many well-characterized infections of ehrlichiosis and anaplasmosis of variable severity have been reported in children, including deaths. Whereas anaplasmosis is more common in children, ehrlichiosis appears to be more severe. Children with ehrlichiosis are often ill for 4-12 days, shorter than in adults. Abdominal pain may occur disproportionately in children vs adults with anaplasmosis. In a series of children with ehrlichiosis, most required hospitalization and many (25%) required intensive care; these statistics might represent preferential reporting of severe cases. However, review of case reports and electronic surveillance of anaplasmosis to the CDC identified that 42% of patients 5-9 years of age required hospitalization, and the case fatality rate is 4% among children <5 years of age. Population-based studies document that seroconversion often occurs in children who are well or who have only a mild illness. Many fewer pediatric cases of *E. ewingii* infection are reported, so the clinical manifestations related to this infection are less well characterized. The incubation period (time from last tick bite or exposure) appears to range from 2 days to 3 weeks. Nearly 25% of patients do not report a tick bite.

Clinically, ehrlichiosis and anaplasmosis are undifferentiated febrile illnesses. In ehrlichiosis, fever (~100%), headache (77%), and myalgia (77%) are most common, but many patients also report abdominal pain, nausea, and vomiting. Altered mental status accompanied by other signs of central nervous system involvement is present in 36%. Rash is a common feature (~60%) in children. The rash is usually macular or maculopapular, but petechial lesions can occur. The triad of fever, headache, and rash is observed in ~50%. Photophobia, conjunctivitis, pharyngitis, and arthralgias can occur but are less consistently present. Lymphadenopathy, hepatomegaly, and splenomegaly are detected in nearly 50% of children with ehrlichiosis. Edema of the face, hands, and feet occurs more commonly in children than in adults, but arthritis is uncommon.

Similar but less severe manifestations occur with anaplasmosis in children, including fever (93%), headache (73%), myalgia (73%), and rigors (60%). Nausea, vomiting, abdominal pain, and anorexia occur in 30% or less of patients. Cough is present in 20%. Rash is infrequent in anaplasmosis and most often is erythema migrans that results from concurrent Lyme disease.

Meningoencephalitis with a lymphocyte-predominant CSF pleocytosis is an uncommon but potentially severe complication of ehrlichiosis that appears to be rare with anaplasmosis. CSF protein may be elevated, and glucose may be mildly depressed in adults with ehrlichiosis meningoencephalitis, but CSF protein and glucose in affected children are typically normal. In one series, 19% of adult patients with central nervous system symptoms and abnormal CSF died despite normal CTs of the brain.

Chronic or persistent disease with low or absent fever is very unlikely to be any form of ehrlichiosis.

LABORATORY FINDINGS

Characteristically, most children with ehrlichiosis and anaplasmosis present with leukopenia (57–80%) and thrombocytopenia (38–93%); cytopenias reach a nadir several days into the illness. Lymphopenia is common in both ehrlichiosis and anaplasmosis. Leukocytosis can also occur, but usually after the first week of illness or with effective antimicrobial treatment. Adults with pancytopenia often have a cellular or reactive bone marrow examination, and in nearly 75% of bone marrow specimens from adults with ehrlichiosis, granulomas and granulomatous inflammation are present; this finding is not a feature of adults with anaplasmosis. Mild to markedly elevated serum hepatic transaminase levels are frequent in both ehrlichiosis (85–92%) and anaplasmosis (40–50%). Hyponatremia (<135 mEq/L) is present in most cases. A clinical picture similar to disseminated intravascular coagulopathy has also been reported.

DIAGNOSIS

Any delays in diagnosis or treatment are major contributors to increased morbidity or mortality in adults, where those not started on doxycycline at hospital admission are much more likely to require intensive care and undergo a significantly longer course of illness and hospitalization. Tick bites are not always reported; thus treatment must begin as early as possible based on epidemiologic (geographic) and clinical suspicion. Because both ehrlichiosis and anaplasmosis can be fatal, therapy should not be withheld while waiting for the results of confirmatory testing. In fact, prompt response to therapy supports the diagnosis.

Although several reports document pediatric patients with *E. chaffeensis* infection diagnosed based on typical *Ehrlichia* morulae in peripheral blood leukocytes (Fig. 277.1A), this finding is too infrequent to be considered a useful diagnostic approach. In contrast, anaplasmosis in adults presents with a small but significant percentage (1–40%) of circulating neutrophils (see Fig. 277.1B) containing typical morulae in 20–60% of patients.

E. chaffeensis and *A. phagocytophilum* infections are currently most frequently established by specific polymerase chain reaction assays used during the acute phase of illness when antibodies are often not detected. Both infections can be confirmed by demonstrating a fourfold change in immunoglobulin G titer by indirect immunofluorescence assay between paired sera. Serologic tests during the acute phase of infection are often negative; consequently, confirmation of acute infection requires demonstration of a fourfold rise in IgG titer in paired samples. A single specific titer of ≥128 is suggestive, but the use of IgM testing is discouraged owing to a lack of specificity. Identification of morulae in monocytes or macrophages for *E. chaffeensis* or in neutrophils or eosinophils for *A. phagocytophilum* by microscopy is suggestive. Demonstration of specific antigen in a tissue sample by immunohistochemistry and isolation of the organism in cell culture are not timely and are used infrequently. *E. ewingii* infection can only be confirmed by polymerase chain reaction because it has not been cultured and serologic antigens are not available. *E. ewingii* antibodies cross react with *E. chaffeensis* in routine serologic tests. Up to 15% of patients with anaplasmosis have serologic cross reactions with *E. chaffeensis;* thus serodiagnosis depends on testing with both *E. chaffeensis* and *A. phagocytophilum* antigens and demonstrating a fourfold or higher difference between titers.

DIFFERENTIAL DIAGNOSIS

Because of the nonspecific presentation, ehrlichiosis mimics other arthropod-borne infections such as RMSF, tularemia, babesiosis, Lyme disease, murine typhus, relapsing fever, and Colorado tick fever. Other potential diagnoses often considered include otitis media, streptococcal pharyngitis, infectious mononucleosis, Kawasaki disease, endocarditis, respiratory or gastrointestinal viral syndromes, hepatitis, leptospirosis, Q fever, collagen-vascular diseases, hemophagocytic syndromes, and leukemia. If rash and disseminated intravascular coagulopathy predominate, meningococcemia, bacterial sepsis, and toxic shock syndrome should also be suspected. Meningoencephalitis might suggest aseptic meningitis caused by enterovirus or herpes simplex virus, bacterial meningitis, or RMSF. Severe respiratory disease may be confused with bacterial, viral, and fungal causes of pneumonia. Mounting evidence suggests that ehrlichiosis and anaplasmosis may be precipitating factors for hemophagocytic lymphohistiocytosis.

TREATMENT

Both ehrlichiosis and anaplasmosis are effectively treated with tetracyclines, especially doxycycline, and the majority of patients improve within 48 hours. In vitro tests document that both *E. chaffeensis* and *A. phagocytophilum* have minimal inhibitory concentrations to chloramphenicol above blood levels that can be safely achieved. Therefore a short course of doxycycline is the recommended regimen. Doxycycline is used safely in children younger than 8 years of age because tooth discoloration is dose dependent and the need for multiple courses is unlikely; experience has demonstrated that adverse consequences of doxycycline use in children <8 years of age are extremely rare, in particular if courses are relatively short. Few data exist to recommend alternative therapies; however, both *E. chaffeensis* and *A. phagocytophilum* are susceptible in vitro to rifampin, which has been used successfully to treat anaplasmosis in pregnant women and children.

The recommended regimen for patients of all ages with severe or complicated ehrlichiosis and anaplasmosis is doxycycline (for those who weigh <45 kg, 4 mg/kg/day PO or IV divided every 12 hours; maximum 200 mg/day). An alternative regimen is tetracycline (25-50 mg/kg/day divided every 6 hours PO; maximum 2 g/day). For children who weigh more than 45 kg, the adult dose, 100 mg twice daily by oral or intravenous route, can be used. Therapy should be continued for ≥5 days and until the patient has been afebrile for ≥2-4 days.

Other broad-spectrum antibiotics, including penicillins, cephalosporins, aminoglycosides, and macrolides, are not effective. In vitro studies suggest that fluoroquinolones are active against *A. phagocytophilum,* although at least one patient relapsed when levofloxacin was discontinued. *E. chaffeensis* is naturally resistant to fluoroquinolones owing to a single nucleotide change in *gyrA,* which suggests that *A. phagocytophilum* could also become resistant to fluoroquinolones rapidly.

COMPLICATIONS AND PROGNOSIS

Fatal ehrlichiosis has been reported in occasional pediatric patients, where the findings included pulmonary involvement and respiratory failure in patients with or without immune compromise. The pattern of severe pulmonary involvement culminating in diffuse alveolar damage and acute respiratory distress syndrome and secondary nosocomial

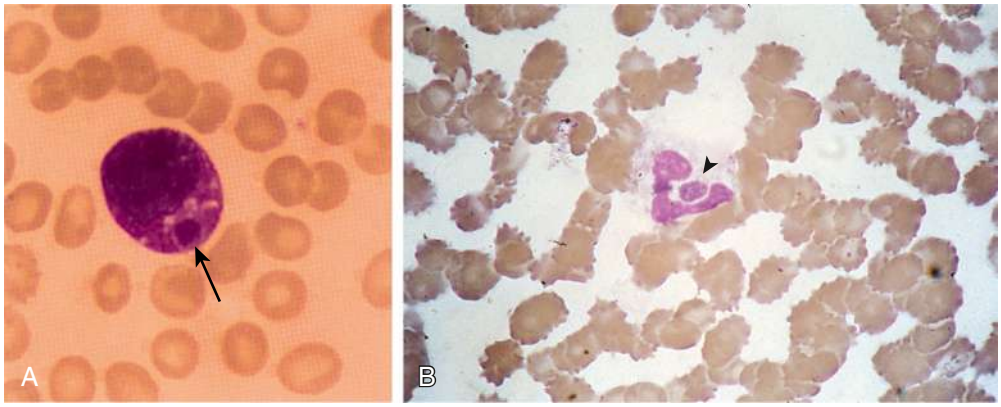

Fig. 277.1 Morulae in peripheral blood leukocytes in patients with human monocytic ehrlichiosis and human granulocytic anaplasmosis. **A,** A morula *(arrow)* containing *Ehrlichia chaffeensis* in a monocyte. **B,** A morula *(arrowhead)* containing *Anaplasma phagocytophilum* in a neutrophil. Wright stains, original magnifications ×1,200. *E. chaffeensis* and *A. phagocytophilum* have similar morphologies but are serologically and genetically distinct.

or opportunistic infections is now well-documented with ehrlichiosis and anaplasmosis in adults. Of greater concern is the frequency with which secondary hemophagocytic lymphohistiocytosis is diagnosed with ehrlichiosis and anaplasmosis in children. Children and adults who are immunocompromised (e.g., HIV infection, high-dose corticosteroid therapy, cancer chemotherapy, immunosuppression for organ transplantation) are at high risk for fulminant *E. chaffeensis* infection, for *E. ewingii* infection, and for severe anaplasmosis.

PREVENTION

Ehrlichiosis, anaplasmosis, and ewingii ehrlichiosis are tick-borne diseases, and any activity that increases exposure to ticks increases risk. Avoiding tick-infested areas, wearing appropriate light-colored clothing, spraying tick repellents on clothing, carefully inspecting for ticks after exposure, and promptly removing any attached ticks diminish the risk. The interval between tick attachment and transmission of the agents may be as short as 4 hours; thus attached ticks should be removed promptly. A role of prophylactic therapy for ehrlichiosis and anaplasmosis after tick bites has not been investigated. It is not known if infection confers protective immunity; however, reinfection appears to be rare.

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Chapter 278

Q Fever (*Coxiella burnetii*)

Megan E. Reller and J. Stephen Dumler

Q fever (for query fever, the name given after an outbreak of febrile illness in an abattoir in Queensland, Australia) is rarely reported in children but is probably underdiagnosed. Symptomatic patients can have acute or chronic disease.

ETIOLOGY

Although previously classified within the order Rickettsiales, *Coxiella burnetii* (the causative agent of Q fever) is genetically distinct from the genera *Rickettsia, Orientia*, *Ehrlichia,* and *Anaplasma*. Hence, based on small genome analysis, it best aligns with the order Legionellales, family Coxiellaceae. *C. burnetii* is highly infectious for both humans and animals; even a single organism can cause infection. The agent has been nationally notifiable since 1999 and is listed as a Category B agent of bioterrorism by the Centers for Disease Control and Prevention (CDC). Unlike *Rickettsia,* the organism can enter a sporogenic differentiation cycle, which renders it highly resistant to chemical and physical treatments.

C. burnetii resides intracellularly within macrophages. In vitro, the organism undergoes a lipopolysaccharide phase variation similar to that described for smooth and rough strains of Enterobacteriaceae. Unlike *Ehrlichia, Anaplasma,* and *Chlamydia, C. burnetii* survives and proliferates within acidified phagosomes to form aggregates of >100 bacteria.

EPIDEMIOLOGY

The disease is reported worldwide, except in New Zealand. Although seroepidemiologic studies suggest that infection occurs just as often in children as in adults, children less often present with clinical disease than adults. During the large outbreak of Q fever in the Netherlands in 2007–2009, only 3.5% of those diagnosed with Q fever were age 19 years or younger. Infections are recognized more often in men than in women. Historically, reported cases in boys and girls have been equal, although a recent study reported male predominance. Approximately 60% of infections are asymptomatic, and only 5% of symptomatic patients require hospitalization. Seroprevalence surveys show that 6–70% of children in endemic European and African communities have evidence of past infection. In France, the overall incidence of Q fever is estimated to be 50 cases per 100,000 persons. A similar estimate is not available for Africa, where cases are likely misdiagnosed as malaria. The seroprevalence of Q fever in the United States is estimated to be 3.1%. Reported cases of Q fever in the United States have been received from every state, but 35% are reported from four states (California, Texas, Colorado, and Illinois). In the United States, reported Q fever cases increased by greater than ninefold from 17 cases in 2000 to 167 cases in 2008, reflecting an increase in incidence, increased reporting after September 11, 2001, improved diagnostic tools, or a combination of factors. Cases decreased significantly in 2008–2013 relative to 2007 but returned to previous high levels in 2014 (173 cases, including 147 acute and 39 chronic). Beginning in 2008, reported cases in the United States have been classified as acute or chronic. Between 2002 and 2014, more than 50% of recognized cases in the United States required hospitalization. Reported cases in Asia and Australia have also increased. Most infections in children are identified during the lamb birthing season in Europe (January through June), after farm visits, or after exposure to placentas of dogs, cats, and rabbits. The largest (~4,000 human cases) community outbreak ever described occurred in the Netherlands in 2007–2012 and was associated with intensive farming of dairy goats and dairy sheep. In 2011, the first multistate outbreak of Q fever in humans was linked to interstate sale of infected goats; an outbreak of unknown source was also reported. From 2000 to 2010, 60% of cases reported to the CDC occurred in individuals without reported exposure to livestock. More than 20% of cases of clinically recognized acute or chronic Q fever occur in immunosuppressed hosts or in persons with prosthetic valves or damaged native valves or vessels. These findings highlight the need for considering Q fever in those with clinically compatible illness, especially but not exclusively in those with likely exposures and in vulnerable hosts. Epidemiologic investigations and control efforts require a One Health approach, with consideration of the interactions between humans, animals, environment, and public health.

TRANSMISSION

In contrast to other rickettsial infections, humans usually acquire *C. burnetii* by inhaling infectious aerosols (e.g., contaminated barnyard dust) or ingesting (and likely aspirating) contaminated foods. Ticks are rarely implicated. Cattle, sheep, and goats are the primary reservoirs, but infection in other livestock and domestic pets is also described. Organisms are excreted in milk, urine, and feces of infected animals, but especially in amniotic fluids and the placenta. An increase in incidence is associated with the seasonal mistral winds in France that coincide with lamb birthing season and with consumption of cheese among children in Greece. In Nova Scotia and Maine, exposure to newborn animals, especially kittens, has been associated with small outbreaks of Q fever in families. Exposure to domestic ruminants is the major risk in Europe and Australia, although many urban dwellers in France also acquire Q fever without such an exposure. Person-to-person transmission is possible but rare. Clinical Q fever during pregnancy can result from primary infection or reactivation of latent infection and is associated with miscarriage, intrauterine growth retardation, and premature births. Obstetricians and other related healthcare workers are at risk for acquiring infection because of the quantity of *C. burnetii* sequestered in the placenta. Sexual transmission and cases attributable to blood transfusion or bone marrow transplantation are also reported. Transmission after *live cell therapy* (injected live animal cells) has also been reported.

PATHOLOGY AND PATHOGENESIS

The pathology of Q fever depends on the mode of transmission, route of dissemination, specific tissues involved, and course of the infection. When acquired via inhalation, a mild interstitial lymphocytic pneumonitis and macrophage- and organism-rich intraalveolar exudates are

often seen. When the liver is involved, a mild to moderate lymphocytic lobular hepatitis can be seen. Inflammatory pseudotumors can develop in the pulmonary parenchyma or other tissues. Classic fibrin-ring ("doughnut") granulomas, generally associated with acute, self-limited infections, are occasionally identified in liver, bone marrow, meninges, and other organs. Typically, infected tissues are also infiltrated by lymphocytes and histiocytes.

Recovery from symptomatic or asymptomatic acute infection can result in persistent subclinical infection, possibly maintained by dysregulated cytokine responses. The persistence of *C. burnetii* in tissue macrophages at sites of preexisting tissue damage elicits low-grade chronic inflammation and, depending on the site of involvement, can result in irreversible cardiac valve damage, persistent vascular injury, or osteomyelitis. Endocarditis of native or prosthetic valves is characterized by infiltrates of macrophages and lymphocytes in necrotic fibrinous valvular vegetations and an absence of granulomas.

CLINICAL MANIFESTATIONS AND COMPLICATIONS

Children are less likely to develop symptoms compared with adults. Only approximately 40–50% of people infected with *C. burnetii* develop symptoms. Historically, two forms of symptomatic disease have been thought to occur. **Acute Q fever**, now better characterized as **primary Q fever**, is more common and usually manifests as self-limited undifferentiated fever or an influenza-like illness with interstitial pneumonitis. Persistent localized infection with *C. burnetii* can cause what has historically been referred to as **chronic Q fever**. In adults, persistent localized infection usually involves the cardiovascular system—native heart valves, especially those with preexisting valvulopathy, prosthetic valves, or other endovascular prostheses. Q fever osteomyelitis is less common but proportionally more common as a manifestation of infection in children. Less common persistent localized *C. burnetii* infections include lymphadenitis, genital infection, and pericarditis.

Primary (Acute) Q Fever

Acute Q fever develops approximately 3 weeks (range: 14-39 days) after exposure to the causative agent. The severity of illness in children ranges from subclinical infection to a systemic illness of sudden onset characterized by high fever, severe frontal headache, nonproductive cough, chest pain, vomiting, diarrhea, abdominal pain, arthralgias, and myalgias. Approximately 40% of children with acute Q fever present with fever, 25% with pneumonia or an influenza-like illness, >10% with meningoencephalitis, and >10% with myocarditis. Other manifestations include pericarditis, hepatitis, hemophagocytic lymphohistiocytosis, rhabdomyolysis, and a hemolytic uremic–like syndrome. Rash, ranging from maculopapular to purpuric lesions, is an unusual finding in adults with Q fever but is observed in approximately 50% of pediatric patients. Rigors and night sweats are common in adults with Q fever and occur less often in children. Prominent clinical findings that can create diagnostic confusion include fatigue, vomiting, abdominal pain, and meningismus. Hepatomegaly and splenomegaly may be detected in some patients.

Routine laboratory investigations in pediatric acute Q fever are usually normal but can reveal mild leukocytosis and thrombocytopenia. Up to 85% of children have modestly elevated serum hepatic transaminase levels that usually normalize within 10 days. Hyperbilirubinemia is uncommon in the absence of complications. C-reactive protein may not be elevated in pediatric Q fever. Chest radiographs are abnormal in nearly 30% of all patients; in children, the most common findings include single or multiple bilateral infiltrates with reticular markings in the lower lobes.

Primary Q fever in children is usually a self-limited illness, with fever persisting for only 7-10 days compared with 2-3 weeks in adults. However, severe manifestations of acute illness, such as myocarditis requiring cardiac transplantation, meningoencephalitis, pericarditis, hemophagocytosis, thrombosis with antiphospholipid antibody syndrome, and a relapsing febrile illness lasting for several months, have been reported.

Persistent Localized Q Fever Infection

The risk for developing persistent localized Q fever infection, historically called *chronic Q fever,* is strongly correlated with advancing age and underlying conditions such as cardiac valve damage or immunosuppression; persistent localized Q fever infection is rarely diagnosed in children. A review identified only five cases of Q fever endocarditis and six cases of osteomyelitis among children, none of whom had known predisposing immune deficiencies. Four of the five cases of endocarditis occurred in children with underlying congenital heart abnormalities and involved the aortic, pulmonary, and tricuspid valves. Four of the six children with Q fever osteomyelitis had a prior diagnosis or clinical course consistent with idiopathic chronic recurrent multifocal osteomyelitis. A long interval before diagnosis and lack of high fever are common in pediatric cases of persistent localized Q fever infection—historically chronic Q fever.

Although Q fever endocarditis often results in death (23–65% of cases) in adults, mortality has not been reported for children. Endocarditis associated with persistent or chronic Q fever can occur months to years after acute infection and can occur in the absence of recognized acute Q fever and in the absence of clinically recognized valvulopathy. Chronic hepatitis has also been reported.

LABORATORY FINDINGS

Laboratory features in children with chronic Q fever are poorly documented; adult patients often have an erythrocyte sedimentation rate of >20 mm/hr (80% of cases), hypergammaglobulinemia (54%), and hyperfibrinogenemia (67%). In children, the presence of rheumatoid factor in >50% of cases and circulating immune complexes in nearly 90% suggest an autoimmune process. The presence of antiplatelet antibodies, anti–smooth muscle antibodies, antimitochondrial antibodies, circulating anticoagulants, positive direct Coombs tests, and antiphospholipid antibodies also suggest this possibility.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Although uncommonly diagnosed, Q fever in children most often mimics other childhood respiratory infections. It should be considered in children who have an influenza-like illness, lower or upper respiratory tract infection, fever of unknown origin, myocarditis, meningoencephalitis, culture-negative endocarditis, or recurrent osteomyelitis and who live in rural areas or who are in close contact with domestic livestock, cats, or animal products.

The diagnosis of primary (acute) Q fever is most easily and commonly confirmed by testing acute and convalescent sera (3-6 weeks apart), which show a fourfold increase in indirect fluorescent immunoglobulin G antibody titers to phase II *C. burnetii* antigens. The phase II antibody response to *C. burnetii* appears first and is higher than the phase I antibody response. Phase II immunoglobulin G antibodies can remain elevated for months to years, regardless of initial symptoms or lack thereof. In contrast, persistent localized (chronic) Q fever is characterized by a phase I immunoglobulin G antibody titer greater than 800 that is sustained for 6 months or more, such as occurs with Q fever endocarditis in patients with valvular heart disease. Cross-reactions with antibodies to *Legionella* and *Bartonella* can occur.

Although culture has been considered the gold standard, sensitivity (compared with a composite standard including serology and polymerase chain reaction [PCR]) is low. *C. burnetii* has been cultivated in tissue culture cells, which can become positive within 48 hours, but isolation and antimicrobial susceptibility testing of *C. burnetii* should be attempted only in specialized biohazard facilities. Testing by PCR can be performed on blood, serum, and tissue samples and is available only in some public health, reference, or research laboratories. PCR has been helpful in patients with equivocal titers, as occurs with early infection. PCR usually remains positive for 7-10 days after acute infection. Sensitivity has been improved by real-time methods and the use

of repeated sequences as targets. Immunohistochemical staining has also been used but is not readily available. PCR should be performed either before or shortly after initiation of treatment. PCR can also confirm a serologic diagnosis of endocarditis in untreated patients. Genotyping has aided epidemiologic investigations to confirm the source of infection. The differential diagnosis depends on the clinical presentation. In patients with respiratory disease, *Mycoplasma pneumoniae, Chlamydophila pneumoniae,* legionellosis, psittacosis, and Epstein-Barr virus infection should be considered. In patients with granulomatous hepatitis, tuberculous and nontuberculous mycobacterial infections, salmonellosis, visceral leishmaniasis, toxoplasmosis, Hodgkin disease, monocytic ehrlichiosis, brucellosis, cat scratch disease *(Bartonella henselae)*, or autoimmune disorders such as sarcoidosis should be considered. **Culture-negative endocarditis** suggests infection with *Brucella, Bartonella,* HACEK organisms *(Haemophilus, Aggregatibacter, Cardiobacterium hominis, Eikenella corrodens, Kingella)*, partially treated bacterial endocarditis, nonbacterial endocarditis, or potentially noninfectious inflammatory conditions, including chronic recurrent multifocal osteomyelitis and antiphospholipid syndrome.

TREATMENT

Selection of an appropriate antimicrobial regimen for children is difficult owing to the lack of rigorous studies, the limited therapeutic window for drugs that are known to be efficacious, and the potential length of therapy required to preclude relapse.

Most pediatric patients with Q fever have a self-limited illness that is identified only on retrospective serologic evaluation. However, to prevent potential complications, treatment should be considered for patients who present with suspected acute Q fever within 3 days of onset of symptoms, because therapy started more than 3 days after the onset of illness has little effect on the course of acute Q fever. Early treatment is effective in shortening illness duration and severity. Doxycycline (100 mg orally 2 times/day for children 8 years or older or 4 mg/kg/day orally divided 2 times/day for children younger than 8 years, maximum: 200 mg/day, for 14 days) is the drug of choice. Doxycycline may cause permanent tooth discoloration for children younger than 8 years if used repeatedly but is generally safe when used for short courses. Children younger than 8 years with mild illness, pregnant adolescents, and patients allergic to doxycycline can be treated with trimethoprim-sulfamethoxazole.

For persistent focal Q fever, especially endocarditis and mostly in adults, therapy for 18-36 months is mandatory, because treatment is more difficult and relapses can occur despite appropriate therapy. The current recommended regimen for Q fever endocarditis is a combination of doxycycline and hydroxychloroquine for 18 months or longer. For patients with heart failure, valve replacement could be necessary.

PREVENTION

Recognition of the disease in livestock or other domestic animals should alert communities to the risk for human infection by aerosol exposures within 15 km. Milk from infected herds must be pasteurized at temperatures sufficient to destroy *C. burnetii. C. burnetii* is resistant to significant environmental conditions but can be inactivated with a solution of 1% Lysol, 1% formaldehyde, or 5% hydrogen peroxide. Special isolation measures are not required because person-to-person transmission is rare, except when others are exposed to the placenta of an infected patient. A vaccine is available and provides protection against Q fever for at least 5 years in abattoir workers; however, it is not licensed in the United States. Prospective studies of vaccination in children at high risk are needed. Clusters of cases resulting from intense natural exposures, such as in slaughterhouses or on farms, are well documented. Clusters of cases that occur in the absence of such an exposure should be investigated as potential sentinel events for bioterrorism.

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Section 12

Fungal Infections

Chapter 279

Principles of Antifungal Therapy

William J. Steinbach

Invasive fungal infections are a major cause of morbidity and mortality in the growing number of immunocompromised children. The antifungal armamentarium has markedly increased in recent years (Tables 279.1 and 279.2).

POLYENES

Amphotericin B

The prototype of the oldest antifungal class, the polyene macrolides, is amphotericin B deoxycholate. Amphotericin B was once the preferred treatment for most invasive fungal infections and the standard of comparison for all newer antifungal agents. Amphotericin B is so named because it is amphoteric, forming soluble salts in both acidic and basic environments. However, because of its insolubility in water, amphotericin B for clinical use is actually amphotericin B mixed with the detergent deoxycholate. Amphotericin B binds to ergosterol, the major sterol found in fungal cytoplasmic membranes, and acts by creating transmembrane channels. The fungicidal activity is the result of a damaged barrier and subsequent cell death through leakage of essential nutrients from the fungal cell.

Amphotericin B is released from its carrier and distributes efficiently with lipoproteins and is then taken up preferentially by organs of the reticuloendothelial system. After an initial 24- to 48-hour distributional half-life, there is very slow release and a subsequent terminal elimination half-life of up to 15 days. In addition to conventional amphotericin B deoxycholate, two fundamentally different lipid-associated formulations are currently available that offer the advantage of an increased daily dosage of the parent drug, better delivery to the primary reticuloendothelial organs (lungs, liver, spleen), and reduced toxicity. Amphotericin B lipid complex (ABLC) is a tightly packed ribbon-like structure of a bilayered membrane, and liposomal amphotericin B (L-amphotericin B) consists of small uniformly sized vesicles of a lipid bilayer of amphotericin B. Lipid formulations of amphotericin B generally have a slower onset of action, presumably owing to the required disassociation of free amphotericin B from the lipid vehicle. The ability to safely administer higher daily doses of the parent drugs improves their efficacy, comparing favorably with amphotericin B deoxycholate but with less toxicity. Lipid formulations have the added benefit of increased tissue concentrations compared with conventional amphotericin B, specifically in the liver, lungs, and spleen. Tolerance to amphotericin B deoxycholate is limited by its acute and chronic toxicities. In addition to interacting with fungal ergosterol, the drug also interacts with cholesterol in human cell membranes, likely accounting for its toxicity. Up to 80% of patients receiving amphotericin B develop either infusion-related toxicity or nephrotoxicity, especially with concomitant therapy with nephrotoxic drugs such as aminoglycosides, vancomycin, cyclosporine, or tacrolimus. Renal function usually returns to normal after cessation of amphotericin B, although permanent renal impairment can occur after larger doses. Amphotericin B nephrotoxicity is generally less severe in infants and children than in adults, likely because of the more rapid clearance of the drug in children. Lipid formulations appear to stabilize

Table 279.1 Suggested Dosing of Antifungal Agents in Children and Neonates

DRUG	FORMULATIONS	SUGGESTED PEDIATRIC DOSAGE	COMMENTS
Amphotericin B deoxycholate	IV	1 mg/kg/day	Generally less toxicity in children than adults; do not start with smaller test doses
Lipid amphotericin B formulations	IV	5 mg/kg/day	Generally, all lipid formulations are dosed the same; there is no clear indication of one formulation over another for clinical efficacy
Fluconazole	IV, PO	12 mg/kg/day	Loading dose (25 mg/kg) is recommended in neonates based on pharmacokinetic simulations and likely suggested in children, but insufficiently studied
Itraconazole	PO	2.5 mg/kg/dose bid	Divide dosage twice daily in children; follow trough levels
Voriconazole	IV, PO	8 mg/kg/dose bid IV maintenance; 9 mg/kg/dose bid oral maintenance	Linear pharmacokinetics in children requires higher dosing than in adults; 9 mg/kg/dose bid IV loading, followed by maintenance dosing; follow trough levels carefully
Posaconazole	IV, PO	At least 18 mg/kg/day divided tid for oral suspension; IV and new powder for oral suspension 6 mg/kg/day once daily (given bid as a loading dose on first day)	Dosage unclear in children at present In adults, max dosage for oral suspension is 800 mg/day, and optimally divide this into 2 or 3 doses; follow trough levels; adult dosing for IV and extended-release tablet is 300 mg twice on first day, then 300 mg once daily
Isavuconazole	PO, IV	10 mg/kg (q8h on days 1 and 2 and then once daily thereafter)	Adult dosing for IV and tablet is 200 mg 3 times on first day, then 200 mg once daily
Micafungin	IV	2-10 mg/kg/day	Highest dosages in neonates (10 mg/kg/day) and lower dosages in children; >8 yr of age, use adult dosage
Anidulafungin	IV	1.5 mg/kg/day	Loading dose of 3 mg/kg/day
Caspofungin	IV	50 mg/m^2/day; neonates 25 mg/m^2/day	Load with 70 mg/m^2/day, then 50mg/m^2/day as maintenance dosage

amphotericin B in a self-associated state so that it is not available to interact with the cholesterol of human cellular membranes.

A clinical trial comparing L-amphotericin B at doses of 3 mg/kg/day versus 10 mg/kg/day found no efficacy benefit for the higher dose and only greater toxicity. Therefore it is generally not recommended to use any lipid amphotericin B preparations at very high dosages (>5 mg/kg/day), although some experts report using higher dosing in very difficult infections where a lipid amphotericin B formulation is the first-line therapy (e.g., mucormycosis).

PYRIMIDINE ANALOGS

5-Fluorocytosine

5-Fluorocytosine (5-FC) is a fluorinated analog of cytosine and has antifungal activity resulting from the rapid conversion into 5-fluorouracil (5-FU) within susceptible fungal cells. Clinical and microbiologic antifungal resistance develops quickly to 5-FC monotherapy, so clinicians have reserved it for combination approaches. Fungistatic 5-FC is thought to enhance the antifungal activity of amphotericin B, especially in anatomic sites where amphotericin B penetration is often suboptimal, such as cerebrospinal fluid (CSF). 5-FC penetrates well into most body sites because it is small, highly water-soluble, and not bound by serum proteins to any great extent. One explanation for the synergy detected with the combination of amphotericin B plus 5-FC is that the membrane-permeabilizing effects of low concentrations of amphotericin B facilitate penetration of 5-FC to the cell interior. 5-FC is only available as an oral formulation in the United States, and the dosage is 150 mg/kg/day in four divided doses.

5-FC can exacerbate myelosuppression in patients with neutropenia, and toxic levels can develop when used in combination with amphotericin B, owing to nephrotoxicity of the amphotericin B and decreased renal clearance of 5-FC. Routine serum 5-FC level monitoring is warranted in high-risk patients, and levels should be obtained after 3-5 days of therapy, with a goal to achieve a 2-hour postdose peak <100 µg/mL (and ideally 30-80 µg/mL). Levels >100 µg/mL are associated with bone marrow aplasia. Toxicities can include azotemia, renal tubular acidosis, leukopenia, thrombocytopenia, and others and appear in approximately 50% of patients in the first 2 weeks of therapy.

Nearly all clinical studies involving 5-FC for cryptococcal meningitis are combination antifungal protocols with amphotericin B. The use of 5-FC for *Candida* meningitis in premature neonates is discouraged. A study evaluating risk factors and mortality rates of neonatal candidiasis among extremely premature infants showed that infants with *Candida* meningitis who received amphotericin B in combination with 5-FC had a prolonged time to sterilization of the CSF compared with infants receiving amphotericin B monotherapy.

AZOLES

The azole antifungals inhibit the fungal cytochrome $P450_{14DM}$ (also known as *lanosterol 14α-demethylase*), which catalyzes a late step in fungal cell membrane ergosterol biosynthesis. Of the older first-generation, itraconazole has activity against *Aspergillus,* but fluconazole is ineffective against *Aspergillus* and other molds. Second-generation triazoles (voriconazole, posaconazole, and isavuconazole) have an expanded antifungal spectrum of activity, including activity against molds, and generally greater in vitro antifungal activity.

Fluconazole

Fluconazole is fungistatic, and this activity is not influenced by concentration once the maximal fungistatic concentration is surpassed (concentration independent), in contrast to the concentration-dependent

Table 279.2 Suggested Antifungals for Specific, More Common Fungal Pathogens

FUNGAL SPECIES	AMP	FLU	ITR	VOR	POS	ISA	FLUC	CMA
Aspergillus calidoustus	++	–	–	–	–	–	–	++
Aspergillus fumigatus	+	–	±	++	+	++	–	+
Aspergillus terreus	–	–	+	++	+	++	–	+
Blastomyces dermatitidis	++	+	++	+	+	+	–	–
Candida albicans	+	++	+	+	+	+	+	++
Candida glabrata	+	–	±	±	±	±	+	±
Candida krusei	+	–	–	+	+	+	+	++
Candida lusitaniae	–	++	+	+	+	+	+	+
Candida parapsilosis	++	++	+	+	+	+	+	±
Coccidioides immitis	++	+	++	+	++	+	–	–
Cryptococcus spp.	++	+	+	+	+	+	++	–
Fusarium spp.	±	–	–	++	+	+	–	–
Histoplasma capsulatum	++	+	++	+	+	+	–	–
Mucor spp.	++	–	±	–	+	+	–	–
Scedosporium apiospermum	–	–	±	+	+	+	–	±
Scedosporium prolificans	–	–	±	±	±	±	–	±

AMP, amphotericin B formulations; FLU, fluconazole; ITR, itraconazole; VOR, voriconazole; POS, posaconazole; ISA, isavuconazole; FLUC, flucytosine; CMA, caspofungin, micafungin, or anidulafungin.
++, preferred therapy(ies); +, usually active; ±, variably active; –, usually not active.

fungicidal activity of amphotericin B. Fluconazole is available as either an oral or intravenous form, and oral administration has a bioavailability of approximately 90% relative to intravenous administration. Fluconazole passes into tissues and fluids quite rapidly, probably because of its relatively low lipophilicity and limited degree of binding to plasma proteins. Concentrations of fluconazole are 10- to 20-fold higher in the urine than in blood, making it an ideal agent for treating fungal urinary tract infections. Concentrations in the CSF and vitreous humor of the eye are approximately 80% of those found simultaneously in blood.

Simple conversion of the corresponding adult dosage of fluconazole on a weight basis is inappropriate for pediatric patients. Fluconazole clearance is generally more rapid in children than in adults, with a mean plasma half-life of approximately 20 hours in children and approximately 30 hours in adult patients. Therefore to achieve comparable exposure in pediatric patients, the daily fluconazole dosage needs to be essentially doubled. Correct pediatric fluconazole dosages should be proportionately higher than adult dosages, generally 12 mg/kg/day. In neonates, the volume of distribution is significantly greater and more variable than in infants and children, and doubling the dosage for neonatal patients is necessary to achieve comparable plasma concentrations. The increased volume of distribution is thought to be the result of the larger amount of body water found in the total body volume of neonates. A pharmacokinetic study in premature infants suggests that maintenance fluconazole dosages of 12 mg/kg/day are necessary to achieve exposures similar to those in older children and adults. In addition, a loading dose of 25 mg/kg in neonates has achieved steady-state concentrations sooner. Although a fluconazole loading dose has been studied in adult and neonatal patients, this approach has never been formally studied in children, yet makes clinical sense. Side effects of fluconazole are uncommon but generally include gastrointestinal upset (vomiting, diarrhea, nausea) and skin rash.

Fluconazole plays an important role in the treatment of invasive candidiasis. Consensus guidelines suggest that use of the fungistatic fluconazole for invasive candidiasis is acceptable as step-down therapy after a good clinical response to initial therapy with an echinocandin. Other clinical scenarios for fluconazole include patients who are not critically ill and who are considered unlikely to have a fluconazole-resistant *Candida* species. Although most isolates of *Candida albicans* remain susceptible to fluconazole, for certain *Candida* species, fluconazole is not an ideal agent: *C. krusei* is generally resistant, and *C. glabrata* is often resistant. There is no confirmed role for combination antifungal therapy with fluconazole and another antifungal against invasive candidiasis.

Prophylaxis with fluconazole to prevent neonatal candidiasis remains a controversial topic. In the first prospective, randomized double-blind trial of 100 infants with birthweights <1,000 g, infants who received fluconazole for 6 weeks had a decrease in fungal colonization and a decrease in the development of invasive fungal infection (0% vs 20%) compared with placebo. Other studies have yielded similarly encouraging results and have demonstrated that use of fluconazole prophylaxis for 4-6 weeks in high-risk infants does not increase the incidence of fungal colonization and infections caused by natively fluconazole-resistant *Candida* species. A more recent large trial studied fluconazole prophylaxis in extremely low birthweight infants in nurseries with a lower incidence of candidiasis and found that fluconazole

prophylaxis led to a decreased incidence of candidiasis but had no effect on mortality. The universal implementation of such a strategy across nurseries is discouraged, because the rate of *Candida* infections varies greatly among centers. Consensus guidelines now recommend fluconazole prophylaxis only in centers with high rates (>10%) of neonatal candidiasis.

Itraconazole

Compared to fluconazole, itraconazole has the benefit of antifungal activity against *Aspergillus* species but comes with several practical constraints, such as erratic oral absorption in high-risk patients and significant drug interactions. These pharmacokinetic concerns have been addressed with a better-absorbed oral solution to replace the unpredictable capsules used earlier. Itraconazole has a high volume of distribution and accumulates in tissues, and tissue-bound levels are probably more clinically relevant to infection treatment than serum levels. Dissolution and absorption of itraconazole are affected by gastric pH. Patients with achlorhydria or taking H_2-receptor antagonists might demonstrate impaired absorption, and co-administration of the capsule with acidic beverages such as colas or cranberry juice can enhance absorption. Administration with food significantly increases the absorption of the capsule formulation, but the oral suspension with a cyclodextrin base is better absorbed on an empty stomach.

Side effects are relatively few and include nausea and vomiting (10%), elevated transaminases (5%), and peripheral edema. There have been reports in adults of development of cardiomyopathy. Because of important drug interactions, prior or concurrent use of rifampin, phenytoin, carbamazepine, and phenobarbital should be avoided.

Itraconazole has its largest role in treating less serious infections with endemic mycoses (histoplasmosis, coccidioidomycosis, and blastomycosis). The plethora of drug interactions make itraconazole a concern in complex patients receiving other medications. As with most azole antifungals, monitoring itraconazole serum levels is a key principle in management (generally itraconazole trough levels should be 1-2 μg/mL; trough levels >5 μg/mL may be associated with increased toxicity). Concentrations should be checked after 5 days of therapy to ensure adequate drug exposure. When measured by high-pressure liquid chromatography, both itraconazole and its bioactive hydroxyitraconazole metabolite are reported, the sum of which should be considered in assessing drug levels.

Voriconazole

Voriconazole is a second-generation triazole and a synthetic derivative of fluconazole. Voriconazole generally has the spectrum of activity of itraconazole and the high bioavailability of fluconazole. Importantly, it is fungicidal against *Aspergillus* and fungistatic against *Candida*. It is extensively metabolized by the liver and has approximately 90% oral bioavailability in adults but appears to be closer to 50–60% bioavailability in children. The cytochrome P450 2C19 (CYP2C19) enzyme appears to play a major role in the metabolism of voriconazole, and polymorphisms in CYP2C19 are associated with slow voriconazole metabolism. As many as 20% of non-Indian Asians have low CYP2C19 activity and develop voriconazole levels as much as fourfold higher than those in homozygous subjects, leading to potentially increased toxicity.

Voriconazole is available as an oral tablet, an oral suspension, and an intravenous solution. In adults, voriconazole exhibits nonlinear pharmacokinetics, has a variable half-life of approximately 6 hours with large interpatient variation in blood levels, and achieves good CSF penetration. In contrast to the situation in adults, elimination of voriconazole is linear in children. A multicenter safety, population pharmacokinetic study of intravenous voriconazole dosages in immunocompromised pediatric patients showed that body weight was more influential than age in accounting for the observed variability in voriconazole pharmacokinetics, and voriconazole needs to be dosed higher in pediatric patients than in adult patients. Adult patients load with 6 mg/kg/dose and then transition to a maintenance dosage of 4 mg/kg/dose, but children should begin and continue with 9 mg/kg/dose intravenously (see Table 279.1) and continue maintenance dosing at 8 mg/kg/dose. This need for an increased dosage in treating children is crucial to understand and is mandated by the fundamentally different pharmacokinetics of this drug in pediatric patients. Obtaining voriconazole serum levels (to achieve ≥2 μg/mL) is critical for therapeutic success. Oral voriconazole is best absorbed on an empty stomach. Generally a trough level greater than the minimum inhibitory concentration (MIC) of the infecting organism is preferred, and very high voriconazole levels have been associated with toxicity (generally >6 μg/mL). However, many studies have shown an inconsistent relationship between dosing and levels, highlighting the need for close monitoring after the initial dosing scheme and then dose adjustment as needed in the individual patient. Trough levels should be monitored approximately 5 days after initiation of therapy and repeated the following week to confirm the patient remains in the therapeutic range or repeated 4 days after change of dose. The main side effects of voriconazole include reversible dosage-dependent visual disturbances (increased brightness, blurred vision) in as many as one third of treated patients, elevated hepatic transaminases with increasing dosages, and occasional skin reactions likely caused by photosensitization. In some rare long-term (mean of 3 years of therapy) cases, this voriconazole phototoxicity has developed into cutaneous squamous cell carcinoma. Discontinuing voriconazole is recommended in patients experiencing chronic phototoxicity.

The largest prospective clinical trial of voriconazole as primary therapy for invasive aspergillosis compared initial randomized therapy with voriconazole versus amphotericin B and demonstrated improved response and survival with voriconazole over amphotericin B. **Voriconazole is guideline-recommended as the preferred primary therapy against invasive aspergillosis.** Voriconazole also has a role in treating candidiasis, but its fungistatic nature makes it often less than ideal for treating critically ill or neutropenic patients where the fungicidal echinocandin antifungals are preferred.

Posaconazole

Posaconazole is a second-generation triazole that is a derivative of itraconazole and is currently available as an oral suspension, an intravenous formulation, and a delayed-release tablet. The antimicrobial spectrum of posaconazole is similar to that of voriconazole; however, the former is active against mucormycosis, and voriconazole is not active against these particular mold infections.

Effective absorption of the less desirable oral suspension strongly requires taking the medication with food, ideally a high-fat meal; taking posaconazole on an empty stomach will result in approximately one fourth of the absorption as in the fed state, emphasizing the importance of diet to increase serum levels of oral suspension posaconazole (the opposite of voriconazole). Posaconazole exposure is maximized with acidic beverages, administration in divided doses, and the absence of proton pump inhibitors. The tablet formulation has much better absorption because of its delayed release in the small intestine, but absorption will still be slightly increased with food. If the patient can take the large-sized tablets, the delayed-release tablet is the preferred form because of the ability to easily obtain higher and more consistent drug levels. Importantly, the delayed-release tablet cannot be broken for use due to its chemical coating. As a result of the low pH (<5) of IV posaconazole, a central venous catheter is required for administration. The IV formulation contains only slightly lower amounts of the cyclodextrin vehicle than voriconazole, so similar theoretical renal accumulation concerns exist. Posaconazole causes transient hepatic reactions, including mild to moderate elevations in liver transaminases, alkaline phosphatase, and total bilirubin.

In adult patients, dosages of the oral suspension at >800 mg/day do not result in increased serum levels, and division of daily dosing into three or four doses/day results in greater serum levels than a once- or twice-daily dosing scheme when using the oral suspension. The pediatric oral suspension dose recommended by some experts for treating invasive disease is estimated to be at least 18 mg/kg/day divided 3 times daily, but even that dose did not achieve target levels when studied. A study with a new pediatric formulation for suspension, essentially the tablet form that is able to be suspended, showed a dose of 6 mg/

kg (given twice a day as a loading dose on the first day and then once daily) achieved target exposures necessary for antifungal prophylaxis, with a safety profile similar to adult patients. A subsequent study suggested that posaconazole dosing for the delayed-release tablets and IV formulation requires greater daily doses for children <13 years old. Pediatric dosing with the current IV or extended-release tablet dosing is not yet fully defined, but adolescents can likely follow the adult dosing schemes. Similar to itraconazole and voriconazole, posaconazole should be monitored with trough levels (to achieve ≥1 μg/mL for treatment and ≥0.07 μg/mL for prophylaxis).

In an international randomized, single-blinded study of posaconazole versus fluconazole or itraconazole in neutropenic patients undergoing chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes, posaconazole was superior in preventing invasive fungal infections. Another multisite international randomized, double-blinded study in patients with allogeneic hematopoietic stem cell transplantation and graft versus host disease showed that posaconazole was not inferior to fluconazole in the prevention of invasive fungal infections. **Posaconazole is approved for prophylaxis against invasive fungal infections but has shown great efficacy in clinical experience with recalcitrant mold infections.**

In patients with chronic granulomatous disease (CGD) and proven invasive fungal infection refractory to standard therapy, posaconazole was proved to be well tolerated and quite effective and is the preferred agent against invasive aspergillosis in this patient population.

Isavuconazole

Isavuconazole is a triazole that was FDA approved in 2015 for treatment of invasive aspergillosis and invasive mucormycosis with oral (capsules only) and IV formulations. Isavuconazole has an antifungal spectrum similar to that of voriconazole and some activity against *Zygomycetes* such as mucormycosis (yet potentially not as potent against *Zygomycetes* as posaconazole). A phase 3 clinical trial in adult patients demonstrated noninferiority versus voriconazole against invasive aspergillosis and other mold infections, whereas another study showed good clinical activity against mucormycosis. Isavuconazole is dispensed as the prodrug isavuconazonium sulfate. Dosing in adult patients is loading with isavuconazole 200 mg (equivalent to 372-mg isavuconazonium sulfate) every 8 hours for 2 days (6 doses), followed by 200 mg once daily for maintenance dosing. The half-life is long (>5 days), there is 98% bioavailability in adults, and there is no reported food effect with oral isavuconazole. Unlike voriconazole, the IV formulation does not contain the vehicle cyclodextrin, possibly making it more attractive in patients with renal failure. Early experience suggests a much lower rate of photosensitivity and skin disorders as well as visual disturbances compared with voriconazole. A recently completed pediatric pharmacokinetic study reported that a dose of 10 mg/kg (q8h on days 1 and 2 and once daily thereafter) resulted in similar exposures and safety as seen in adults.

ECHINOCANDINS

The echinocandins are a class of antifungals that interfere with cell wall biosynthesis by noncompetitive inhibition of 1,3-β-D-glucan synthase, an enzyme present in fungi but absent in mammalian cells. 1,3-β-glucan is an essential cell wall polysaccharide and provides structural integrity for the fungal cell wall. Echinocandins are generally fungicidal in vitro against *Candida* species, although not as rapidly as amphotericin B, and are fungistatic against *Aspergillus*. As a class, these agents are not metabolized through the CYP enzyme system, lessening some of the drug interactions and side effects seen with the azole class. The echinocandins appear to have a prolonged and dosage-dependent fungicidal antifungal effect on *C. albicans* compared with the fungistatic fluconazole. Three compounds in this class (caspofungin, micafungin, and anidulafungin) are FDA approved for use, but there are others (rezafungin) in late-stage clinical trials. Owing to the large size of the molecules, the current echinocandins are only available in an intravenous formulation. Because 1,3-β-glucan is a selective target present only in fungal cell walls and not in mammalian cells, drug-related toxicity is minimal, with no apparent myelotoxicity or nephrotoxicity with the agents. **The echinocandins are the preferred primary therapy for invasive candidiasis.**

Caspofungin

Caspofungin is administered to adults as a 70-mg loading dose followed by a daily maintenance 50-mg dosage. Caspofungin has been evaluated at double the recommended dosage (100 mg/day in adults) with no adverse effects, and it is unclear if higher dosage of this relatively safe agent results in greater clinical efficacy. At present there is no known maximum tolerated dosage and no toxicity-determined maximum length of therapy for caspofungin.

Pharmacokinetics are slightly different in children, with caspofungin levels lower in smaller children and with a reduced half-life. A study evaluated the pharmacokinetics of caspofungin in children with neutropenia and showed that in patients receiving 50 mg/m^2/day (maximum, 70 mg/day), the levels were similar to those in adults receiving 50 mg/day and were consistent across age ranges. In this study, weight-based dosing (1 mg/kg/day) was suboptimal when compared with body surface area regimens, so caspofungin should be appropriately dosed in children as a loading dose of 70 mg/m^2/day, followed by daily maintenance dosing of 50 mg/m^2/day.

Echinocandins like caspofungin are guideline-recommended initial therapy for invasive candidiasis but should be used against invasive aspergillosis only in the setting of potential combination therapy or for resistant or refractory disease. In a multicenter trial of patients with invasive candidiasis, 73% of patients who received caspofungin had a favorable response at the end of therapy compared with 62% in the amphotericin B group. Importantly, caspofungin treatment performed equally well to amphotericin B treatment for all the major *Candida* species. Earlier studies suggested that some infections with *C. parapsilosis* do not potentially clear as effectively with an echinocandin, but the echinocandins are still preferred empiric therapy against invasive candidiasis. Caspofungin was also evaluated against L-amphotericin B in the empirical treatment of patients with persistent fever and neutropenia and was not inferior to liposomal amphotericin B. A study in children with acute myeloid leukemia demonstrated that caspofungin prophylaxis resulted in a significantly lower incidence of invasive fungal disease compared with fluconazole prophylaxis. A study comparing caspofungin with triazole prophylaxis in pediatric allogeneic hematopoietic stem cell transplant recipients found no difference in the agents.

Caspofungin in newborns (25 mg/m^2/day) has been used for refractory cases of disseminated candidiasis. Neonates with invasive candidiasis are at high risk for central nervous system involvement; it is not known if the dosages of caspofungin studied provide sufficient exposure to penetrate the central nervous system at levels necessary to cure infection. Therefore caspofungin is not recommended as standard monotherapy in neonatal candidiasis.

Micafungin

The pharmacokinetics of micafungin have been evaluated in children and young infants. An inverse relation between age and clearance was observed, where mean systemic clearance was significantly greater and mean half-life was significantly shorter in patients 2-8 years of age compared to patients 9-17 years of age. Therefore dosing of micafungin in children is age-related and needs to be higher in children <8 years old. Doses in children are generally 2 mg/kg/day, with higher doses needed for neonates, infants, and younger patients, and with a dose of 10 mg/kg/day for preterm neonates. Several pharmacokinetic studies in term and preterm infants have shown that micafungin has a shorter half-life and a more rapid rate of clearance in infants compared with published data in older children and adults. Adult micafungin dosing (100 or 150 mg once daily) is to be used in patients who weigh more than 40 kg. Unlike the other echinocandins, a loading dose is not required for micafungin.

Clinical trials, including those of micafungin used for treatment of invasive candidiasis, as well as prophylaxis studies in patients after

stem cell transplantation, have demonstrated fewer adverse events compared with liposomal amphotericin B and fluconazole. The most common adverse events experienced by these patients are related to the gastrointestinal tract (nausea, diarrhea). Hypersensitivity reactions associated with micafungin have been reported, and liver enzymes are elevated in 5% of patients receiving this agent. Hyperbilirubinemia, renal impairment, and hemolytic anemia related to micafungin use have also been identified in postmarketing surveillance of the drug.

Micafungin at dosages of 100 and 150 mg daily was also noninferior to caspofungin in an international, randomized, double-blinded study of adults with candidemia or invasive candidiasis and was found to be superior to fluconazole in the prevention of invasive fungal infections in a randomized study of adults undergoing hematopoietic stem cell transplantation.

Of the three drugs within the echinocandin class, micafungin has been the one most extensively studied in children. A pediatric substudy as part of a double-blind, randomized, multinational trial comparing micafungin (2 mg/kg/day) with liposomal amphotericin B (3 mg/kg/day) as first-line treatment for invasive candidiasis showed similar success for micafungin and liposomal amphotericin B. In general, micafungin was better tolerated than liposomal amphotericin B, as evidenced by fewer adverse events leading to discontinuation of therapy.

Anidulafungin

Anidulafungin has the longest half-life of all the echinocandins (approximately 18 hours). In a study of 25 neutropenic children receiving anidulafungin as empirical therapy, four patients in the group receiving 0.75 mg/kg/day experienced adverse events such as facial erythema and rash, elevation in serum blood urea nitrogen, and fever and hypotension. In a pharmacokinetic study in neonates and young infants, anidulafungin exposures comparable to adults were achieved with doses of 1.5 mg/kg/day (3 mg/kg loading dose). One infant in this cohort supported by extracorporeal membrane oxygenation achieved the lowest exposure, which suggests that dose adjustments are required in this population. The adult dose for invasive candidiasis is a loading dose of 200 mg on the first day, followed by 100 mg daily. An open-label study of invasive candidiasis in children showed similar efficacy and minimal toxicity, comparable to the other echinocandins. An additional study showed similar and acceptable pharmacokinetics in patients 1 month to 2 years of age.

Ibrexafungerp

Ibrexafungerp was approved in 2021 for adults with vulvovaginal candidiasis after two phase 3 studies (VANISH203 and VANISH 306). This is the first new class of antifungals (also called "fungerps"). Similar to the echinocandins, ibrexafungerp noncompetitively inhibits β-1,3-glucan synthase and is also fungicidal against *Candida* spp. and *Aspergillus* spp. The binding site on the glucan synthase enzyme is not the same as the echinocandins. Resistance or reduced susceptibility to the echinocandins is largely through two hot-spot pathogenic variants in the *FKS1* gene, whereas many resistance mutations to ibrexafungerp are caused by the *FKS2* gene, and ibrexafungerp does have activity against some echinocandin-resistant isolates. Ibrexafungerp is the first orally available glucan synthase inhibitor and has a long half-life, suggesting once-daily dosing for clinical use. Similar to the echinocandins, initial studies show limited to no distribution to the central nervous system and variable distribution to the eye. In a phase 2 study, ibrexafungerp as step-down therapy after initial echinocandin therapy for invasive candidiasis was well-tolerated and achieved a favorable global response similar to the standard of care. There is an ongoing co-administration study with voriconazole in pulmonary invasive aspergillosis (SCYNERGIA) and an ongoing recurrent vulvovaginal candidiasis study (CANDLE), yet no completed pediatric studies.

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Chapter 280
Candida

Jessica E. Ericson and Daniel K. Benjamin Jr.

Candidiasis encompasses many clinical syndromes that may be caused by several species of *Candida*. Invasive candidiasis (*Candida* infections of the blood and other sterile body fluids) is a leading cause of infection-related mortality in hospitalized immunocompromised patients.

C. albicans accounts for most human infections, but *C. parapsilosis, C. tropicalis, C. krusei, C. lusitaniae, C. glabrata,* and several other species are commonly isolated from hospitalized children. Species identification and susceptibility testing are important owing to increasing frequency of fluconazole resistance and increasing prevalence of non-*albicans Candida* species. *C. auris* is an emerging multiresistant invasive pathogen that has a global presence and affects immunocompromised patients; nosocomial spread has been reported.

Treatment of invasive *Candida* infections is complicated by the emergence of non-*albicans* strains. Amphotericin B deoxycholate is inactive against approximately 20% of strains of *C. lusitaniae.* Fluconazole is useful for many *Candida* infections but is inactive against all strains of *C. krusei* and 5–25% of strains of *C. glabrata.* Most *Candida* are susceptible to echinocandins, but resistance is occasionally seen, most often among *C. krusei* and *C. glabrata*. **Susceptibility testing of these clinical isolates is recommended.**

280.1 Neonatal Infections

Jessica E. Ericson and Daniel K. Benjamin Jr.

Candida is a common cause of oral mucous membrane infections **(thrush)** and perineal skin infections **(*Candida* diaper dermatitis)** in young infants. Rare presentations include **congenital cutaneous candidiasis**, caused by an ascending infection into the uterus during gestation, and **invasive fungal dermatitis**, a postnatal skin infection resulting in positive blood cultures. Invasive candidiasis is a common infectious complication in the neonatal intensive care unit (NICU) because of improved survival of extremely preterm infants.

EPIDEMIOLOGY

Candida species are a common cause of bloodstream infection in premature infants. The incidence varies greatly by individual NICU. Among centers in the National Institutes of Health–sponsored Neonatal Research Network, the cumulative incidence of candidiasis among infants <1,000 g birthweight ranges from 2% to 28%. Colonization is associated with a significantly increased risk of future invasive *Candida* infection. Up to 10% of full-term infants are colonized as the result of vertical transmission from the mother at birth, with slightly higher rates of colonization in premature infants. Colonization rates increase to >50% among infants admitted to the NICU by 1 month of age. Histamine-2 blockers, corticosteroids, and broad-spectrum antibiotics facilitate *Candida* colonization and overgrowth.

Significant risk factors for neonatal invasive candidiasis include prematurity, low birthweight, exposure to broad-spectrum antibiotics, abdominal surgery, endotracheal intubation, and presence of a central venous catheter.

PATHOGENESIS

Immunologic immaturity along with an underdeveloped layer of skin, need for invasive measures (endotracheal tubes, central venous catheters), and exposure to broad-spectrum antibiotics places preterm infants at great risk for invasive candidiasis. Premature infants are also at high risk for spontaneous intestinal perforations and

necrotizing enterocolitis. Both conditions require abdominal surgery, prolonged exposure to broad-spectrum antibiotics, and total parenteral nutrition administration requiring placement of central venous catheters. Each of these factors increases the risk of invasive candidiasis by decreasing the physiologic barriers that protect against invasive infection.

CLINICAL MANIFESTATIONS

The manifestations of neonatal candidiasis vary in severity from oral thrush and *Candida* diaper dermatitis (see Chapter 280.2) to invasive candidiasis that can manifest with overwhelming sepsis (see Chapter 280.3). Signs of invasive candidiasis among premature infants are often nonspecific and include temperature instability, lethargy, apnea, hypotension, respiratory distress, abdominal distention, and thrombocytopenia.

Central nervous system involvement is common and is most accurately described as meningoencephalitis. *Candida* infections involving the central nervous system often result in abscesses, leading to unremarkable cerebrospinal fluid parameters (white blood cell count, glucose, protein) even though central nervous system infection is present. Endophthalmitis is an uncommon complication affecting <5% of infants with invasive candidiasis, but candidemia is associated with an increased risk of severe retinopathy of prematurity. Renal involvement commonly complicates neonatal invasive candidiasis. Renal involvement may be limited to candiduria or can manifest with diffuse infiltration of *Candida* throughout the renal parenchyma or the presence of *Candida* and debris within the collecting system. Because of the poor sensitivity of blood cultures for *Candida*, candiduria should be considered a surrogate marker of candidemia in premature infants. Other affected organs include the heart, bones, joints, liver, and spleen.

DIAGNOSIS

Mucocutaneous infections are most often diagnosed by direct clinical exam. Scrapings of skin lesions may be examined with a microscope after Gram staining or suspension in KOH. Definitive diagnosis of invasive disease requires histologic demonstration of the fungus in tissue specimens or recovery of the fungus from normally sterile body fluids. Hematologic parameters are sensitive but not specific. Thrombocytopenia occurs in more than 80% of premature infants with invasive candidiasis, but also occurs in 75% of premature infants with gram-negative bacterial sepsis and nearly 50% of infants with gram-positive bacterial sepsis. Blood cultures have very low sensitivity for invasive candidiasis. In a study of autopsy-proven candidiasis in adult patients, the sensitivity of multiple blood cultures for detecting single-organ disease was 28%. Blood culture volumes in infants are often only 0.5-1 mL, making the sensitivity in this population almost certainly lower. Blood culture volume should be maximized as much as possible to increase sensitivity.

Further assessment of infants in the presence of documented candidemia should include ultrasound or computerized tomography of the head to evaluate for abscesses; ultrasound of the liver, kidney, and spleen; cardiac echocardiography; ophthalmologic exam; lumbar puncture; and urine culture. These tests are necessary to determine if more than one body system is infected, which is commonly the case.

PROPHYLAXIS

NICUs with a high incidence of invasive candidiasis should consider prophylaxis with fluconazole in infants <1,000 g birthweight as a cost-effective method of reducing invasive candidiasis. Twice-weekly fluconazole at 3 or 6 mg/kg/dose decreases rates of both colonization with *Candida* species and invasive fungal infections. Use of this dosing strategy has not been shown to increase the frequency of infections caused by fluconazole-resistant strains, but use of an alternative antifungal class for cases of breakthrough infection is suggested.

TREATMENT

In the absence of systemic manifestations, **topical antifungal therapy is the treatment of choice for congenital cutaneous candidiasis in full-term infants**. Congenital cutaneous candidiasis in preterm infants can progress to systemic disease, and therefore systemic therapy is warranted in these patients.

Every attempt should be made to **remove or replace central venous catheters** once the diagnosis of candidemia is confirmed. Delayed removal has been consistently associated with increased mortality and morbidity, including poor neurodevelopmental outcomes.

Although no well-powered randomized controlled trials exist to guide the length and type of therapy**, 21 days of systemic antifungal therapy from the last positive *Candida* culture is recommended in infants**. Antifungal therapy should be targeted based on susceptibility testing. Amphotericin B deoxycholate has been the mainstay of therapy for systemic candidiasis and is active against both yeast and mycelial forms. Nephrotoxicity, hypokalemia, and hypomagnesemia are common, but amphotericin B deoxycholate is better tolerated in infants than in adult patients. *C. lusitaniae,* an uncommon pathogen in infants, is often resistant to amphotericin B deoxycholate. Liposomal amphotericin is associated with worse outcomes in infants and should be used only when urinary tract involvement can reliably be excluded. Fluconazole is often used instead of amphotericin B deoxycholate for treatment of invasive neonatal *Candida* infections because of its effectiveness and low incidence of side effects. It is particularly useful for urinary tract infections, obtaining high concentrations in the urine. A loading dose should be given to obtain therapeutic serum concentrations in a timely manner. Fluconazole is inactive against all strains of *C. krusei* and some isolates of *C. glabrata.* Additionally, in centers where fluconazole prophylaxis is used, another agent, such as amphotericin B deoxycholate, should be used for treatment. The echinocandins have excellent activity against most *Candida* species and have been used successfully in patients with resistant organisms or in whom other therapies have failed. Two trials comparing an echinocandin with amphotericin B deoxycholate were stopped early because of low recruitment but found similar efficacy for the two treatments among the included patients. Several studies have described the pharmacokinetics of antifungals in infants (Table 280.1).

PROGNOSIS

Mortality after invasive candidiasis in premature infants has been consistently reported to be around 20% in large studies but can be as high as 50% in infants <1,500 g birthweight. Candidiasis is also associated with poor neurodevelopmental outcomes, chronic lung disease, and severe retinopathy of prematurity.

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280.2 Infections in Immunocompetent Children and Adolescents

Jessica E. Ericson and Daniel K. Benjamin Jr.

ORAL CANDIDIASIS

Oral thrush is a superficial mucous membrane infection that affects approximately 2–5% of normal neonates. *C. albicans* is the most commonly isolated species. Oral thrush can develop as early as 7-10 days of age. The use of antibiotics, especially in the first year of life, can lead to recurrent or persistent thrush. It is characterized by pearly white, curdish material visible on the tongue, palate, and buccal mucosa. Oral thrush may be asymptomatic or can cause pain, fussiness, and decreased feeding, leading to inadequate nutritional intake and dehydration. It is uncommon after 1 year of age but can occur in older children treated with antibiotics. Persistent or recurrent thrush with no obvious predisposing reason, such as recent antibiotic treatment, warrants investigation of an underlying immunodeficiency, especially vertically transmitted HIV infection or a primary congenital immune defect.

Treatment of mild cases might not be necessary. When treatment is warranted, the most commonly prescribed antifungal agent is topical

Table 280.1 Dosing of Antifungal Agents Studied in Infants* with Reported Pharmacokinetic (PK) Parameters

DRUG	PK STUDIED IN INFANTS	SUGGESTED DOSE
Amphotericin B deoxycholate	Yes (multiple)	1 mg/kg/day
Amphotericin B lipid complex	Yes (single)	5 mg/kg/day
Liposomal amphotericin B	Yes (single)	5 mg/kg/day
Amphotericin B colloidal dispersion	No	5 mg/kg/day
Fluconazole†	Yes (best studied with ~250 infant contributing PK samples)	12 mg/kg/day
Voriconazole	No – drug concentrations reported for a single infant with neonatal candidiasis	
Posaconazole	No – drug concentrations reported for a single infant with cutaneous rhizopus infection	
Micafungin‡	Yes (multiple)	10 mg/kg/day
Caspofungin§	Yes (single)	50 mg/m^2/day
Anidulafungin‡	Yes (single)	1.5 mg/kg/day

*Voriconazole and posaconazole dosing have not been investigated in the nursery. Doses are those suggested by experts.
†A loading dose of 25 mg/kg of fluconazole is necessary to achieve therapeutic serum and cerebrospinal fluid concentrations in the early days of therapy.
‡Micafungin has been studied in infants <120 days of life at this dosage.
§Caspofungin and anidulafungin should generally be avoided because dosing sufficient to penetrate brain tissue has not been studied.

nystatin. For recalcitrant or recurrent infections, a single dose of fluconazole may be useful. In breastfed infants, simultaneous treatment of infant and mother with topical nystatin or oral fluconazole may be indicated.

DIAPER DERMATITIS

Diaper dermatitis is the most common infection caused by *Candida* (see Chapter 707) and is characterized by a confluent erythematous rash with satellite pustules. *Candida* diaper dermatitis often complicates other noninfectious diaper dermatitides and often occurs after a course of oral antibiotics.

A common practice is to presumptively treat any diaper rash that has been present for longer than 3 days with topical antifungal therapy such as nystatin, clotrimazole, or miconazole. If significant inflammation is present, the addition of hydrocortisone 1% may be useful for the first 1-2 days, but topical corticosteroids should be used cautiously in infants because the relatively potent topical corticosteroid can lead to adverse effects. Frequent diaper changes and short periods without diapers are important adjunctive treatments.

UNGUAL AND PERIUNGUAL INFECTIONS

Paronychia and onychomycosis may be caused by *Candida,* although *Trichophyton* and *Epidermophyton* are more common causes. *Candida* onychomycosis differs from tinea infections by its propensity to involve the fingernails and not the toenails and by the associated paronychia. *Candida* paronychia often responds to treatment consisting of keeping the hands dry and using a topical antifungal agent. Psoriasis and immune dysfunction, including HIV and primary immunodeficiencies, predispose to *Candida* ungual infections. Ungual infections often require systemic antifungal therapy. **Once-weekly fluconazole for 4-12 months is an effective treatment strategy with fairly low toxicity.**

VULVOVAGINITIS

Vulvovaginitis is a common *Candida* infection of pubertal and postpubertal female patients. Predisposing factors include pregnancy, use of oral contraceptives, and use of oral antibiotics. Prepubertal children with *Candida* vulvovaginitis usually have a predisposing factor such as diabetes mellitus or prolonged antibiotic treatment. Clinical manifestations can include pain or itching, dysuria, vulvar or vaginal erythema, and an opaque white or cheesy exudate. More than 80% of cases are caused by *C. albicans.*

***Candida* vulvovaginitis can be effectively treated with either vaginal creams or troches of nystatin, clotrimazole, or miconazole. Oral therapy with a single dose of fluconazole is also effective.**

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280.3 Infections in Immunocompromised Children and Adolescents

Jessica E. Ericson and Daniel K. Benjamin Jr.

ETIOLOGY

Candida albicans is the most common cause of invasive candidiasis among immunocompromised pediatric patients and is associated with higher rates of mortality and end-organ involvement than are non-*albicans* species.

CLINICAL MANIFESTATIONS

HIV-Infected Children

Oral thrush and diaper dermatitis are the most common *Candida* infections in HIV-infected children. Besides oral thrush, three other types of oral *Candida* infections can occur in HIV-infected children: atrophic candidiasis, which manifests as a fiery erythema of the mucosa or loss of papillae of the tongue; chronic hyperplastic candidiasis, which presents with oral symmetric white plaques; and angular cheilitis, in which there is erythema and fissuring of the angles of the mouth. Topical antifungal therapy may be effective, but **systemic treatment with fluconazole or itraconazole is usually necessary**. Symptoms of dysphagia or poor oral intake can indicate progression to *Candida* esophagitis, requiring systemic antifungal therapy. In HIV patients, esophagitis can also be caused by cytomegalovirus, herpes simplex virus, reflux, or lymphoma; *Candida* is the most common cause, and *Candida* esophagitis can occur in the absence of thrush.

Candida dermatitis and onychomycosis are more common in HIV-infected children. These infections are generally more severe than they are in immunocompetent children and can require systemic antifungal therapy.

Cancer and Transplant Patients

Fungal infections, especially *Candida* and *Aspergillus* infections, are a significant problem in oncology patients with chemotherapy-associated neutropenia (see Chapter 223). Greater than 5 days of fever during a neutropenic episode is associated with presence of an invasive fungal infection. Accordingly, empirical antifungal therapy should be started if fever and neutropenia persist for 5 or more days. **An echinocandin should be used until sensitivity testing results are available.** High-risk oncology patients warrant prophylaxis against invasive *Candida* infection. Both fluconazole and echinocandins are used for this indication, typically at lower doses than those used for treatment. If an echinocandin is used for prophylaxis, liposomal amphotericin B should be used if empirical treatment becomes warranted.

Bone marrow transplant recipients have a much higher risk of fungal infections because of the dramatically prolonged duration of neutropenia. Voriconazole prophylaxis decreases the incidence of candidemia in bone marrow transplant recipients with the additional benefit over fluconazole of mold prophylaxis. The use of granulocyte colony-stimulating factor reduces the duration of neutropenia after chemotherapy and is associated with decreased risk for candidemia. When *Candida* infection occurs in this population, the lung, spleen, kidney, and liver are involved in more than 50% of cases.

Solid organ transplant recipients are also at increased risk for superficial and invasive *Candida* infections. Studies in liver transplant recipients demonstrate the utility of antifungal prophylaxis with amphotericin B deoxycholate, fluconazole, voriconazole, or caspofungin in high-risk patients (those with prolonged surgical time, comorbidities, recent antibiotic exposure, or bile leak).

Catheter-Associated Infections

Central venous catheter infections occur most often in oncology patients but can affect any patient with a central catheter. Neutropenia, use of broad-spectrum antibiotics, and parenteral alimentation are associated with increased risk for *Candida* central catheter infection. Treatment typically requires removing or replacing the catheter followed by a 2- to 3-week course of systemic antifungal therapy. **Removal of the central catheter in place at the time of a positive blood culture and use of a peripheral IV or enteral support for at least 48 hours before obtaining central access is advocated.** Removal of the original catheter followed by immediate replacement with a new central catheter in a different anatomic location is acceptable if an interval without central access is not feasible. Delays in catheter removal are associated with increased risks of metastatic complications and death.

DIAGNOSIS

The diagnosis is often presumptive in neutropenic patients with prolonged fever because positive blood cultures for *Candida* occur only in a minority of patients who are later found to have disseminated infection. If isolated, *Candida* grows readily on routine blood culture media, with ≥90% of positive cultures identified within 72 hours. CT scan may demonstrate findings consistent with invasive fungal infection but also is limited by nonspecific findings and false negatives. The role of screening by CT scan has not been well defined. In high-risk patients, serial serum assays for (1,3)-β-D-glucan, a polysaccharide component of the fungal cell wall, may contribute to the diagnosis of invasive Candida infection. However, this test is not sensitive or specific enough to be used without a careful assessment of the limitations of the assay.

Table 280.2 Dosing of Antifungal Agents in Children Older Than 1 Year of Age for Treatment of Invasive Disease

DRUG	SUGGESTED DOSE
Amphotericin B deoxycholate	1 mg/kg/day
Amphotericin B lipid complex	5 mg/kg/day
Liposomal amphotericin B	5 mg/kg/day
Amphotericin B colloidal dispersion	5 mg/kg/day
Fluconazole†	12 mg/kg/day
Voriconazole*,‡	8 mg/kg every 12 hr
Micafungin	2-4 mg/kg/day
Caspofungin	50 mg/m²/day
Anidulafungin	1.5 mg/kg/day

*Use adult dosages in children older than 12 yr of age for voriconazole and older than 8 yr of age for micafungin.
†Loading doses should be used for fluconazole (25 mg/kg), voriconazole (9 mg/kg q 12 × 24 hr), caspofungin (70 mg/m²), and anidulafungin (3 mg/kg).
‡Dosing should be adjusted based on the results of therapeutic drug monitoring.

TREATMENT

Echinocandins are favored as empirical therapy for moderately or severely ill children and for those with neutropenia; fluconazole is acceptable for those who are infected with a susceptible organism and are less critically ill; amphotericin B products are also acceptable. Definitive antifungal selection should be made based on susceptibility testing results. Fluconazole is not effective against *C. krusei* and some isolates of *C. glabrata. C. parapsilosis* has occasional resistance to the echinocandins, but the overall rate is still low. Amphotericin B deoxycholate is inactive against approximately 20% of the strains of *C. lusitaniae,* and therefore susceptibility testing should be performed for all strains (Table 280.2). *C. auris,* a species first identified in 2009 that has caused nosocomial infections worldwide, is resistant to most antifungals. An echinocandin should be used until sensitivity results are available.

PRIMARY IMMUNE DEFECTS

Chronic mucocutaneous candidiasis involves *Candida* infections of the oral cavity, esophagus, and/or genital mucosa, as well as involvement of skin and nails, that is recurrent or persistent and difficult to treat. There is a broad spectrum of genetic immune defects associated with chronic mucocutaneous candidiasis mostly related to severe T-cell defects or disorders of interleukin-17 production. Genes or disorders associated with chronic mucocutaneous candidiasis include severe combined immunodeficiency syndrome, NEMO or IKBG deficiency, DOCK8 deficiency, STAT3 deficiency (autosomal dominant hyperimmunoglobulin E syndrome), autoimmune polyendocrinopathy type 1, CARD9 deficiency, *STAT1* gain-of-function mutations, and *IL17RA* mutations.

Primary immunodeficiencies associated with an increased risk of invasive *Candida* infections include severe congenital neutropenia, CARD9 deficiency, chronic granulomatous disease, and leukocyte adhesion deficiency type 1.

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Chapter 281

Cryptococcus neoformans and *Cryptococcus gattii*

David L. Goldman

ETIOLOGY

More than 30 cryptococcal species have been described; however, 2 species (*Cryptococcus neoformans* and *Cryptococcus gattii*) cause the vast majority of disease in children and adults. Both *C. neoformans* and *C. gattii* are encapsulated, facultative intracellular yeasts that are recognized for their tendency to cause central nervous system (CNS) infection, especially in immunocompromised patients. Although there is significant overlap in the disease caused by these pathogens, there are key differences in epidemiology and clinical presentation, which will be reviewed here. Cryptococcal disease may rarely be caused by other species (e.g., *C. laurentii* and *C. albidus*), especially in immunocompromised individuals (including neonates). These latter species will not be covered in this chapter.

EPIDEMIOLOGY

Cryptococcosis is primarily acquired from exposure to contaminated environments. *C. neoformans* is distributed in temperate climates predominantly in soil contaminated with droppings from certain avian species, including pigeons, canaries, and cockatoos. It may also be found on rotting wood, fruits, and vegetables and may be carried by cockroaches. Transmission from pet birds to their owners and via solid organ transplantation of infected organs are uncommon, but have also been described.

Disease secondary to *C. neoformans* occurs primarily in immunocompromised individuals and especially in those with defects in cellular immunity, though apparently normal individuals can also be affected. A large increase in the incidence of cryptococcosis was noted in association with the AIDS epidemic, with disease generally occurring with severe immunosuppression ($CD4^+$ T cells <100/μL). However, since the development of effective antiretroviral therapies (ART), the incidence of AIDS-associated cryptococcosis has decreased dramatically, except in resource-limited areas of the world such as sub-Saharan Africa, where ART is not readily available.

Other risk factors for cryptococcal infection include immunosuppression associated with organ transplantation, diabetes mellitus, renal failure, cirrhosis, corticosteroids, rheumatologic conditions, chemotherapeutics, and immune-modulating monoclonal antibodies (e.g., etanercept, infliximab, and alemtuzumab). In patients who have undergone organ transplantation, cryptococcosis is the third most common fungal infection after candidiasis and aspergillosis. Children with certain primary immunodeficiency diseases may also be at increased risk for cryptococcosis, including those with hyper-IgM syndrome, severe combined immunodeficiency, idiopathic $CD4^+$ lymphopenia, autoantibodies to granulocyte-macrophage colony-stimulating factor or interferon-γ, CD40 ligand deficiency, and monoMAC syndrome (monocytopenia, B and natural killer cell lymphopenia).

C. gattii was initially recognized for its tendency to cause disease in tropical regions, especially among the native peoples of Australasia, where the organism can be found in association with eucalyptus trees. In these regions, affected individuals are typically immunocompetent. *C. gattii* disease has also been observed outside these tropical regions. An outbreak of *C. gattii* disease involving British Columbia and extending into the Pacific Northwest region of the United States was first recognized in 1999. Affected individuals were typically adults, with disease occurring in both immunocompetent and immunocompromised individuals. However, comorbid conditions were often present, including chronic lung and heart disease. A disproportionate fraction of patients (relative to those infected with *C. neoformans*) presented with pulmonary disease. An incubation period ranging from 2 to 12 months is typical. Thus in the appropriate clinical context, cryptococcosis should be considered in the differential diagnosis of residents of the Pacific Northwest and returning travelers.

Overall, cryptococcosis (both caused by *C. neoformans* and *C. gattii*) is significantly less common in children than in adults. The basis for this discrepancy is poorly understood but could be related to differences in exposure or immune response. Serologic studies suggest that subclinical infection is common among children living in urban areas after age 2 years. Reactivation of latent infection is thought to be an important mechanism of cryptococcal pathogenesis. It is reasonable to postulate that children do not have enough exposures to establish latent infection. During the early AIDS epidemic, the incidence of cryptococcosis in the United States was reported to be on the order of 10% in adults and 1% in children. The largest series of pediatric cryptococcosis comes from South Africa and describes 361 cases, accounting for 2% of the cryptococcosis cases over a 2-year period.

PATHOGENESIS

Like many fungi, *C. neoformans* and *C. gattii* survive as saprophytes in the environment. Their virulence characteristics appear to have evolved as an adaptive response to environmental stressors and predators, such as amoeba. Several key factors have been identified, including the ability to grow at 37°C, encapsulation, and melanin production. These same traits allow the organisms to successfully replicate within the host cell. The polysaccharide capsule, which is readily recognized by India ink staining of cerebrospinal fluid (CSF), is an essential virulence factor. Disease secondary to acapsular strains is exceedingly rare. The capsular material exhibits a variety of biologic activities that are important in the pathogenesis of disease, including interference with opsonization, inhibition of chemotaxis, and enhancement of nonprotective type 2 helper T cells (TH2) inflammation. Capsular material is shed by the organism into body tissues and fluids during infection and has been implicated in the development of increased intracranial pressure (ICP), a hallmark of cryptococcal meningoencephalitis. Detection of shed capsular antigen in the serum and CSF is key to the diagnosis of cryptococcal disease. The organism also has the ability to undergo phenotypic variation in response to environmental changes through a variety of mechanisms and can form large giant cells (on the order 20 times its normal size), which are resistant to phagocytosis. Other recognized virulence factors include a secreted urease, which may promote intraphagolysosomal survival.

In most cases, infection is believed to be acquired by inhalation of desiccated forms of the organism, which upon deposition within the lungs are engulfed by alveolar macrophages. An additional portal of entry is the transplantation of infected organs. Furthermore, direct inoculation can lead to cutaneous or ophthalmic infection. After entry into the respiratory tract, infection can be latent and later progress (i.e., reactivate) in the context of immunodeficiency, in a manner similar to tuberculosis. Alternatively, infection can immediately progress and disseminate to produce symptomatic disease. Cell-mediated immunity that leads to macrophage activation is the most important host defense and is associated with granulomatous inflammation, which effectively contains infection. The precise mechanism of entry of this yeast into the CNS is not known, though several mechanisms have been hypothesized, including transit via infected macrophages (Trojan horse model), direct uptake by endothelial cells, and entry between the tight junctions of endothelial cells.

CLINICAL MANIFESTATIONS

The manifestations of cryptococcal infection reflect the route of inoculation, the infecting strain, and the immune status of the host. Sites of infection include the lung, CNS, blood, skin, bone, eyes, and lymph nodes.

Meningitis/Meningoencephalitis

CNS disease is the most commonly recognized manifestation of cryptococcosis. The disease is characteristically subacute or chronic (evolving over weeks to months). Although the term *meningitis* is commonly used to describe CNS involvement, some degree of encephalitis is also typically present, with occasional patients developing intracerebral masses, known as *cryptococcomas*. Importantly, meningeal signs and fever (typical of other forms of meningitis) may be lacking. In a review of pediatric cryptococcosis from Colombia, the most common symptoms were headache (78%), fever (69%), nausea and vomiting (66%), confusion (50%), and meningismus (38%). Other symptoms include decreased level of consciousness, changes in personality, ataxia, hearing deficits, and visual deficits. Increased intracranial pressure is thought to occur as a result of impaired absorption of CSF and has been reported to occur in more than 50% of adults with cryptococcal meningitis.

Despite antifungal therapy, the mortality rate for cryptococcosis remains high, ranging from 15–40%. Most deaths occur within several weeks of diagnosis. Factors associated with a poor prognosis reflect a high fungal burden and poor host response, including altered mentation, high CSF fungal burden, low CSF white blood cell (WBC) number (<10 cells/mm^3), and failure to rapidly sterilize the CSF. Increased ICP is a key factor in the morbidity and mortality of cryptococcal meningitis and is especially problematic for patients with *C. gattii* disease. Appropriate management of increased ICP is therefore essential to the appropriate management of cryptococcal meningitis (see later). Postinfectious sequelae are common and include hydrocephalus, decreased visual acuity, deafness, cranial nerve palsies, seizures, and ataxia.

Pneumonia

Cryptococcosis is acquired via inhalation, and pneumonia is the most commonly recognized form of disease after meningitis. As with meningitis, pneumonia occurs in both immunocompetent and immunocompromised individuals. Pulmonary disease can present in isolation or in the context of disseminated disease/meningitis, which is typical among immunocompromised individuals. Among adults with AIDS-associated cryptococcal pneumonia, over 90% had concomitant CNS infection. Thus clinicians should have a high suspicion for cryptococcal meningitis/disseminated disease in patients with cryptococcal pneumonia, especially among immunocompromised individuals, and should pursue a workup to exclude dissemination.

Cryptococcal pneumonia is often asymptomatic and may be detected because of radiographs performed for other reasons. In this regard, asymptomatic pulmonary nodules secondary to *C. neoformans* can be found in children with sarcomas, who are being evaluated for metastatic disease. Among symptomatic patients, a wide array of symptoms has been reported, including fever, cough, pleuritic chest pain, and constitutional symptoms like weight loss. Severe disease may result in respiratory failure. Chest radiographic findings are variable and may demonstrate a poorly localized bronchopneumonia, nodules, masses, or lobar consolidations. Pulmonary cavities and pleural effusions are rare. Immunocompromised patients with disseminated disease can have alveolar and interstitial infiltrates that mimic the pattern of disease seen in some patients with *Pneumocystis* pneumonia.

Cutaneous Infection

Cutaneous disease occurs most commonly in the context of disseminated cryptococcosis but rarely can result from local inoculation. The appearance of cutaneous cryptococcosis is both nondistinct and variable and includes papules, ulcers, subcutaneous nodules, and rarely, cellulitis. The lesions are typically subacute, evolving over weeks to months. Early lesions are often erythematous, are variably indurated and tender, and may be single or multiple. Lesions often become ulcerated with central necrosis and raised borders. Cutaneous cryptococcosis in immunocompromised patients can also resemble molluscum contagiosum. Given the variable and nondistinct nature of this disease, a high suspicion of disease, especially in the appropriate clinical context (e.g., immunocompromised host), is needed to make the diagnosis.

Skeletal Infection

Skeletal infection occurs in approximately 5% of patients with disseminated infection but rarely in HIV-infected patients. Interestingly, chronic infection of the tibia was the first recognized manifestation of cryptococcal disease and was described in 1894. Like other forms of cryptococcosis, the onset of symptoms is insidious and chronic. Bone involvement is typified by soft tissue swelling and tenderness, and arthritis is characterized by effusion, erythema, and pain on motion. Skeletal disease is unifocal in approximately 75% of cases. The vertebrae are the most common site of infection, followed by the tibia, ileum, rib, femur, and humerus. Concomitant bone and joint disease can result from contiguous spread.

Sepsis Syndrome

Sepsis syndrome is a rare manifestation of cryptococcosis and occurs almost exclusively among HIV-infected patients. Fever is followed by respiratory distress and multiorgan system disease that is often fatal.

Immune Reconstitution Inflammatory Syndrome

Cryptococcal-associated immune reconstitution inflammatory syndrome (C-IRIS) occurs in the setting of AIDS and in solid organ transplantation. Improvement of immune function resulting from the administration of ART in AIDS patients (or the reduction of immunosuppression in transplant recipients) is thought to enhance and dysregulate inflammation, leading to an exacerbation of symptoms. This situation is similar to IRIS seen with other opportunistic pathogens. More commonly, C-IRIS presents as a worsening of symptoms in someone with a known diagnosis of cryptococcosis, often within 1-2 months of initiation of ART. Occasionally, C-IRIS, which presents as a meningitis or lymphadenitis, occurs in individuals who were never known to have cryptococcosis (unmasking-IRIS). IRIS is particularly problematic in CNS cryptococcosis and may result in worsening of increased ICP. Although cases of C-IRIS have been described in children, the incidence is not well defined.

DIAGNOSIS

The approach to the diagnosis of cryptococcosis depends on the organ system involved. Recovery of the fungus by culture or demonstration of the fungus in histologic sections of infected tissue or body fluids by India ink staining is definitive. Cryptococci readily grow on standard fungal and bacterial culture media. Colonies can be seen within 48-72 hours when grown aerobically at standard temperatures. The CSF profile in patients with cryptococcal meningitis typically reveals a mild lymphocytosis and elevated protein, but findings can also be normal.

Detection of cryptococcal polysaccharide in the CSF, which can be done by several different methods, is key to the diagnosis of CNS infection. One of the earliest detection tests to be developed is the latex agglutination test, which can detect cryptococcal antigen in serum and CSF. Titers of ≥1:4 in bodily fluid strongly suggest infection, and titers of >1:1,024 reflect high burden of yeast, poor host immune response, and greater likelihood of therapeutic failure. Serial monitoring of cryptococcal antigen levels is not useful in guiding

therapy, as the polysaccharide antigen is actively shed into the tissue and may persist for prolonged periods. Patients with localized pneumonia typically do not have elevated serum antigen levels (though occasionally low levels of antigen, <1:4, may be detected). Higher serum antigen levels in patients with pulmonary disease are indicative of dissemination outside the lungs. A point-of-care, lateral flow assay for polysaccharide detection has been developed and has comparable sensitivity to the latex-agglutination assay, with the advantage of being less labor intensive. This assay provides a qualitive positive/negative result, but can also be performed to provide a semiquantitative result. False negatives for both latex agglutination and lateral flow assays may occur in the context of antigen excess, so samples are typically run both undiluted and diluted. False-positive results can occur with other fungal infections, including infection with *Trichosporon* spp. and, rarely, by disinfectants. A commercially available ELISA also allows for the detection of cryptococcal polysaccharide in body fluids. Several PCR-based film arrays have also been developed for the diagnosis of cryptococcosis. These assays allow for the detection of *C. neoformans* DNA in the CSF as part of a panel of meningitis/encephalitis-associated pathogens. Nonetheless, both false positives and false negatives (especially in the context of low-burden disease) have been well documented.

TREATMENT

The choice of treatment for cryptococcosis depends on the sites of involvement and the host immune status. These regimens have not been rigorously studied in children and generally represent extrapolations from studies done in adults. Guidelines for the treatment of pediatric cryptococcosis have been developed by the Infectious Diseases Society of America (IDSA) and the World Health Organization (WHO).

Pulmonary Disease

The immunocompetent patient with asymptomatic or mild disease limited to the lungs should be treated with oral fluconazole (pediatric dose 6-12 mg/kg/day and adult dose 400 mg/day) for 6-12 months to prevent dissemination and progression of disease. Alternative treatments include itraconazole in solution form (pediatric dose 5-10 mg/kg/day divided every 12 hours and adult dose 400 mg/day), voriconazole, and posaconazole. Fluconazole therapy can also be used for immunocompromised individuals with isolated mild to moderate pulmonary disease in the absence of dissemination or CNS disease. Longer maintenance therapy with fluconazole to prevent recurrence should be considered in this cohort, especially among AIDS patients if the $CD4^+$ T cells remain less than 100/μL. Adjunctive surgical management of pulmonary lesions that are not responsive to surgical management should be considered. Patients with diffuse pulmonary disease or those with severe symptoms (e.g., acute respiratory distress syndrome) should be treated in the same manner as those with meningitis.

Disseminated Disease and Meningitis

For more severe forms of disease, including meningitis and any form of disseminated disease, an initial induction regimen to promote rapid decline in fungal burden is indicated. According to Infectious Diseases Society of America (IDSA) guidelines, induction therapy should consist of amphotericin B (1 mg/kg/day) plus flucytosine (100-150 mg/kg/day divided every 6 hours, assuming normal kidney function) for a minimum of 2 weeks, keeping serum flucytosine concentrations between 40 and 60 μg/mL. Lipid amphotericin B has replaced standard amphotericin B for the treatment of severe cryptococcosis in adults, primarily based on its lower toxicity profile. Strong consideration should be given to the use of lipid complex amphotericin B (3-6 mg/kg/day) in all affected pediatric patients, especially those with underlying kidney disease or at risk for kidney disease. Alternative induction therapies as outlined by the WHO guidelines include (1) 1 week of amphotericin B in combination with flucytosine, followed by 1 week of high-dose fluconazole with amphotericin B; and (2) 2 weeks of amphotericin B in combination with high-dose fluconazole. Repeat lumbar puncture is generally recommend at the end of induction therapy to document sterilization of CSF. Longer periods of induction (4-6 weeks) should be considered in the following scenarios: (1) immunocompetent patients with cryptococcal meningitis, (2) meningitis secondary to *C. gattii,* (3) failure to sterilize CSF, and (4) neurologic complications (including cryptococcomas). After induction, consolidation therapy with oral fluconazole (pediatric dose 10-12 mg/kg/day, adult dose 400-800 mg/day) should be given for 8 weeks. In patients with ongoing immunosuppression, maintenance fluconazole should be used to prevent recurrence. In organ transplant recipients, current recommendations are for 6-12 months of maintenance therapy with fluconazole (pediatric dose 6 mg/kg/day, adult dose 200-400 mg/day). In patients with AIDS, prolonged maintenance therapy should be given. Studies in adults suggest that maintenance therapy can be discontinued once the patient has achieved immune reconstitution (as indicated by $CD4^+$ T cells >100/μL and an undetectable or very low HIV RNA level that is sustained for greater than 3 months). A minimum of 12 months of antifungal therapy is indicated. Use of adjuvant interferon gamma for patients with refractory cryptococcal meningitis has been described in adults, but not in pediatric patients.

Increased ICP. Increased ICP contributes greatly to the morbidity and mortality of cryptococcal meningitis, and aggressive management of this phenomenon is indicated. Current guidelines indicate that in patients with increased ICP (>25 cm H_2O), CSF should be removed to establish a pressure ≤20 cm H_2O or by 50% if ICP is extremely high. Serial lumbar punctures may be needed to ensure normalization of ICP, and ventriculoperitoneal shunts can be considered for patients with persistently elevated increased ICP. Corticosteroids, mannitol, and acetazolamide are generally not indicated in the treatment of increased ICP, though anecdotal reports describe use in association with cryptococcoma (in patients with *C. gattii* infection) and C-IRIS.

C-IRIS. To prevent the development of C-IRIS, most experts recommend delaying the institution of ART for 4-6 weeks after the initiation of antifungal therapy. Recurrence of disease and emergence of antifungal resistance should be excluded in the context of a diagnosis of C-IRIS. Treatment strategies have not been well studied but generally consist of antifungal therapy along with antiinflammatory agents (e.g., NSAIDs and corticosteroids). Reduction of increased ICP through therapeutic lumbar puncture may be necessary.

PREVENTION

Persons at high risk for cryptococcosis should be advised to avoid exposures to bird droppings. Effective ART for persons with HIV infection significantly reduces the risk of cryptococcal disease. For adolescent patients with AIDS, regular cryptococcal antigen testing with subsequent diagnostic evaluation and therapy should be considered for individuals with $CD4^+$ lymphocyte counts <100/μL. Cryptococcal antigen screening should also be done before the initiation of antiretroviral therapy in patients newly diagnosed with HIV infection. In the absence of ability to perform regular screening, fluconazole prophylaxis for all patients with $CD4^+$ lymphocyte counts <100/μL can be considered. However, in children for whom the incidence of cryptococcosis is relatively low, screening and prophylaxis are generally not needed.

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Chapter 282

Malassezia

Ashley M. Maranich

Members of the genus *Malassezia* are lipophilic yeasts that are a significant component of the skin microbiome. They have a predilection for the sebum-rich areas of the skin and are considered normal skin flora. Colonization is established just after birth and rises before puberty, with distribution (both in species and number) related to numerous factors, including age, body site, and geographic location.

The history of *Malassezia* nomenclature is complex and can be confusing. Yeast forms may appear oval or round, resulting in early designations of both *Pityrosporum ovale* and *Pityrosporum orbiculare*. Additionally, newer technologies, such as matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS), are allowing for an improved classification system. The genus *Malassezia* has recently been assigned its own class, Malasseziomycetes, with 18 currently recognized species. Disease is facilitated by transformation of the yeast form to a hyphal form, with clusters of thick-walled blastospores with the hyphae producing the characteristic **spaghetti-and-meatballs** appearance of *Malassezia* spp. under light microscopy.

Malassezia can cause a number of dermatologic conditions, more commonly in tropical environments, to include **tinea versicolor** (also **pityriasis versicolor**) (Fig. 282.1; see Chapter 707), neonatal acne, seborrheic dermatitis, dandruff, *Malassezia* folliculitis, and onychomycosis and are linked with atopic dermatitis and psoriasis. *M. sympodialis, M. globosa,* and *M. furfur* are the major causes of tinea versicolor. *Malassezia* spp. may be isolated from sebum-rich skin areas of asymptomatic persons, emphasizing that demonstration of the fungus does not equate with infection.

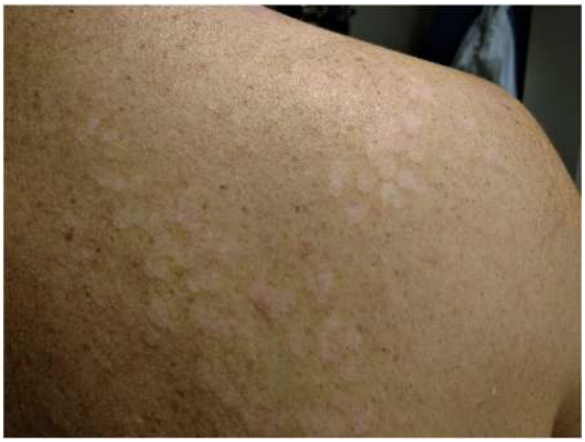

Fig. 282.1 A young adult with tinea versicolor. Notice the characteristic hypopigmented scaling macules. *(Courtesy Ashley M. Maranich, MD.)*

Invasive infections, namely catheter-associated **fungemia**, can occur, with premature infants and immunocompromised individuals (especially those with malignancies) the most high-risk populations. *M. furfur* is the species most commonly causing fungemia, with *M. pachydermatis* implicated in neonatal intensive care unit outbreaks. The use of lipid emulsions containing medium-chain triglycerides inhibits the growth of *Malassezia* spp. and can prevent infection. Symptoms of catheter-associated fungemia are indistinguishable from other causes of catheter-associated infections but should be suspected in patients, especially neonates, receiving intravenous lipid infusions. Compared with other causes of fungal sepsis, it is unusual for catheter-related *Malassezia* fungemia to be associated with secondary focal infection.

Malassezia species do not grow readily on standard fungal media, and successful culture requires overlaying the agar with olive oil. Recovery of *Malassezia* from blood culture is optimized by supplementing the medium with olive oil or palmitic acid and allowing for prolonged incubation for at least 2 weeks.

Topical treatment of skin-related conditions is considered first-line to minimize the risk of side effects. **The traditional primary therapy for tinea versicolor is daily use of topical selenium sulfide 2.5% applied to affected areas for 10 minutes for a week. Additional regimens for skin disorders include topical azole creams, ketoconazole 2% shampoo applied daily for 3 days, and terbinafine 1% cream applied 1-2 times daily for 1-2 weeks. *Malassezia*-associated skin diseases limited to the head and neck can be managed with either 1% ciclopirox, ketoconazole, or zinc pyrithione shampoos.** Regardless of the agent chosen, recovery time can be prolonged, with repigmentation not occurring for several months. **Continued application of topical treatment on a weekly or monthly basis is frequently recommended to prevent relapse.** Recurrence is common and usually responds well to the original treatment regimen.

Oral therapy for tinea versicolor with fluconazole or itraconazole is easier to administer (especially with large areas of skin involved) but is more expensive, has higher side effect risks, and may be less effective than topical therapy. **Various dosing regimens have been used with success, including fluconazole 300 mg weekly for 2-4 weeks, fluconazole as a single 400-mg dose, and itraconazole 200 mg daily for 5-7 days or 100 mg daily for 2 weeks.** Recent studies have examined alternative therapies, with early data suggesting that essential oils might be a possible option for long-term therapy of *Malassezia* skin infections, with additional studies needed.

Treatment of *Malassezia* fungemia is complicated by the lack of standardized susceptibility testing references. **Recent consensus recommendations name liposomal amphotericin B as first-line treatment for systemic *Malassezia* infections, with amphotericin B deoxycholate as an alternative. Additionally, the involved catheter should be removed and any lipid infusion should be discontinued. Itraconazole, posaconazole, or voriconazole may be alternative agents, but fluconazole should be avoided, given that many patients with *Malassezia* bloodstream infections in existing clinical series were receiving fluconazole prophylaxis at the time of developing the infection.**

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Chapter 283
Aspergillus

William J. Steinbach

The genus *Aspergillus* contains approximately 250 species, but most human disease is caused by *Aspergillus fumigatus, A. flavus*, *A. niger*, *A. terreus,* and *A. nidulans*. Invasive disease is most commonly caused by *A. fumigatus*. Most cases of *Aspergillus* disease **(aspergillosis)** are caused by inhalation of airborne spores (conidia) that subsequently germinate into fungal hyphae and invade host tissue. When inhaled by an immunocompetent person, conidia are rarely deleterious, presumably because they are efficiently cleared by phagocytic cells. Macrophage- and neutrophil-mediated host defenses are required for resistance to invasive disease.

Aspergillus is a relatively unusual pathogen in that it can create very different disease states depending on the host characteristics, including allergic (hypersensitivity), saprophytic (noninvasive), chronic, or invasive disease. Immunodeficient hosts are at risk for invasive disease, whereas immunocompetent atopic hosts tend to develop allergic disease. Disease manifestations include primary allergic reactions; colonization of the lungs or sinuses; localized infection of the lung or skin; chronic infection of the lung; invasive pulmonary disease; or widely disseminated disease of the lungs, brain, skin, eye, bone, heart, and other organs. Clinically, these syndromes often manifest with mild, nonspecific, and late-onset symptoms, particularly in the immunosuppressed host, complicating accurate diagnosis and timely treatment.

283.1 Allergic Disease (Hypersensitivity Syndromes)

William J. Steinbach

ASTHMA

Attacks of atopic asthma can be triggered by inhalation of *Aspergillus* conidia, producing allergic responses and subsequent bronchospasm. Exposure to fungi, especially *Aspergillus,* needs to be considered as a trigger in a patient with an asthma flare, especially in those patients with severe or recalcitrant asthma.

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity disease resulting from immunologic sensitization to *Aspergillus* antigens. It is primarily seen in patients with asthma or cystic fibrosis. Inhalation of conidia produces noninvasive colonization of the bronchial airways, resulting in persistent inflammation and development of hypersensitivity inflammatory responses. Disease manifestations are the result of abnormal immunologic responses to *A. fumigatus* antigens and include wheezing, pulmonary infiltrates, bronchiectasis, and even fibrosis.

There are eight primary diagnostic criteria for ABPA: episodic bronchial obstruction, peripheral eosinophilia, immediate cutaneous reactivity to ***Aspergillus*** antigens, precipitating IgE antibodies to *Aspergillus* antigen, elevated total IgE, serum precipitin (specific IgG) antibodies to *A. fumigatus,* pulmonary infiltrates, and central bronchiectasis. Secondary diagnostic criteria include repeated detection of *Aspergillus* from sputum by identification of morphologically consistent fungal elements or direct culture and coughing of brown plugs or specks. Radiologically, bronchial wall thickening, pulmonary infiltrates, and central bronchiectasis can be seen.

Treatment depends on relieving inflammation via an extended course of systemic corticosteroids. Addition of oral antifungal agents, such as itraconazole or voriconazole, is used to decrease the fungal burden and diminish the inciting stimulus for inflammation. Because disease activity is correlated with serum IgE levels, these levels are used as one marker to define duration of therapy. An area of research interest is the utility of anti-IgE antibody therapy in the management of ABPA.

ALLERGIC *ASPERGILLUS* SINUSITIS

Allergic *Aspergillus* sinusitis is thought to be similar in etiology to ABPA. It has been primarily described in young adult patients with asthma and may or may not be seen in combination with ABPA. Patients often present with symptoms of chronic sinusitis or recurrent acute sinusitis, such as congestion, headaches, and rhinitis, and are found to have nasal polyps and opacification of multiple sinuses on imaging. Laboratory findings can include elevated IgE levels, precipitating antibodies to *Aspergillus* antigen, and immediate cutaneous reactivity to *Aspergillus* antigens. Sinus tissue specimens might contain eosinophils, Charcot-Leyden crystals, and fungal elements consistent with *Aspergillus* species. **Surgical drainage is an important aspect of treatment, often accompanied by courses of either systemic or inhaled steroids. Use of an antifungal agent may also be considered.**

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283.2 Saprophytic (Noninvasive) Syndromes

William J. Steinbach

PULMONARY ASPERGILLOMA

Aspergillomas are masses of fungal hyphae, cellular debris, and inflammatory cells that proliferate without vascular invasion, generally in the setting of preexisting cavitary lesions or ectatic bronchi. These cavitary lesions can occur as a result of infections such as tuberculosis, histoplasmosis, or resolved abscesses or secondary to congenital or acquired defects such as pulmonary cysts or bullous emphysema. Patients may be asymptomatic, with diagnosis made through imaging for other reasons, or may present with hemoptysis, cough, or fever. On imaging, initially there may be thickening of the walls of a cavity, and later on there is a solid round mass separated from the cavity wall as the fungal ball develops. Detection of *Aspergillus* antibody in the serum suggests this diagnosis. Treatment is indicated for control of complications, such as hemoptysis. **Surgical resection is the definitive treatment but has been associated with significant risks. Systemic antifungal treatment with azole-class agents is indicated in certain patients.**

CHRONIC PULMONARY ASPERGILLOSIS

Chronic aspergillosis can occur in patients with normal immune systems or mild degrees of immunosuppression, including intermittent corticosteroids. Three major categories, each with overlapping clinical features, have been proposed to describe different manifestations of chronic aspergillosis. The first is chronic **cavitary pulmonary aspergillosis** (CCPA), which is similar to aspergilloma, except that multiple cavities form and expand with occupying fungal balls. The second is **chronic fibrosing pulmonary aspergillosis**, where the multiple individual lesions progress to significant pulmonary fibrosis. The final is **subacute invasive aspergillosis** (IA), which was previously called *chronic necrotizing pulmonary aspergillosis,* a slowly progressive process found in patients with mild to moderate immune impairment.

Treatment based on consensus guidelines can sometimes involve surgical resection, although long-term antifungal therapy is often indicated. Management of semi-IA is similar to that of invasive pulmonary aspergillosis; however, the disease is more indolent, and thus there is a greater emphasis on oral therapy. Direct instillation of antifungals into the lesion cavity has been employed with some success.

OTOMYCOSIS

Aspergillus can colonize the external auditory canal, with possible extension to the middle ear and mastoid air spaces if the tympanic membrane is disrupted by concurrent bacterial infection. Symptoms include pain, itching, decreased unilateral hearing, or otorrhea.

Otomycosis is more often seen in patients with impaired mucosal immunity, such as patients with hypogammaglobulinemia, diabetes mellitus, chronic eczema, or HIV and those using chronic steroids. **Treatments have not been well studied, but topical treatment with acetic or boric acid instillations or oral azoles such as voriconazole, itraconazole, and posaconazole have been described.**

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283.3 Invasive Disease

William J. Steinbach

IA is primarily a disease of immunocompromised hosts, and common risk factors in adults include cancer or chemotherapy-induced neutropenia, particularly if severe and/or prolonged; hematopoietic stem cell transplantation, especially during the initial preengraftment phase or if complicated by graft-versus-host disease; neutrophil or macrophage dysfunction, as occurs in severe combined immunodeficiency (SCID) or chronic granulomatous disease (CGD); prolonged high-dose steroid use; solid organ transplantation; and rarely, HIV. The most common site of primary infection is the lung, but primary invasive infection is also seen in the sinuses and skin and rarely elsewhere. Secondary infection can be seen after hematogenous spread, often to the skin, central nervous system (CNS), eye, bone, and heart.

INVASIVE PULMONARY ASPERGILLOSIS

Invasive pulmonary aspergillosis is the most common form of aspergillosis and plays a significant role in morbidity and mortality in the patient populations mentioned at increased risk for IA. Presenting symptoms can include fever despite initiation of empirical broad-spectrum antibacterial therapy, cough, chest pain, hemoptysis, and pulmonary infiltrates. Patients on high-dose steroids are less likely to present with fever. Symptoms in these immunocompromised patients can be very vague, and thus maintaining a high index of suspicion when confronted with a high-risk patient is essential.

Diagnosis

Imaging can be helpful, although no finding is pathognomonic for invasive pulmonary aspergillosis. Characteristically, multiple ill-defined nodules can be seen, though lobar or diffuse consolidation is not uncommon, and normal chest x-rays do not rule out disease. Classic radiologic signs on CT during neutropenia include the **halo sign**, when angioinvasion produces a hemorrhagic nodule surrounded by ischemia (Fig. 283.1). Early on there is a rim of ground-glass opacification surrounding a nodule. Over time, these lesions evolve into cavitary lesions or lesions with an **air crescent sign** when the lung necroses around the fungal mass, often seen during recovery from neutropenia. Unfortunately, these findings are not specific to invasive pulmonary aspergillosis and can also be seen in other pulmonary fungal infections, and in pulmonary hemorrhage and organizing pneumonia. In addition, several reviews of imaging results of pediatric aspergillosis cases suggest that cavitation and air crescent formation are less common among these patients than among adult patients. On MRI, the typical finding for pulmonary disease is the **target sign**, a nodule with a lower central signal compared with the rim-enhancing periphery.

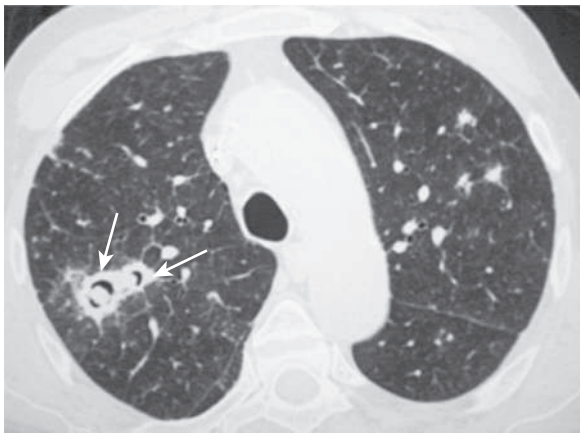

Fig. 283.1 Angioinvasive aspergillosis. CT section at the level of the lower trachea shows a consolidation with an eccentric cavitation and air crescent sign *(arrows)*. This finding in this neutropenic patient is highly diagnostic of angioinvasive aspergillosis. *(From Franquet T. Nonneoplastic parenchymal lung disease. In: Haaga JR, Boll DT, eds. CT and MRI of the Whole Body, 6th ed. Philadelphia: Elsevier; 2017: Fig. 36.14.)*

Conclusive diagnosis requires culture of *Aspergillus* from a normally sterile site and histologic identification of tissue invasion by fungal hyphae consistent with *Aspergillus* morphology. In addition, depending on the specimen type, a positive result from culture can represent colonization rather than infection; however, all positive cultures should be interpreted conservatively in high-risk patients. Serology can be useful in the diagnosis of allergic ***Aspergillus*** syndromes and in aspergilloma but is low yield for invasive disease, likely because of deficient immune responses in the high-risk immunocompromised population. Bronchoalveolar lavage (BAL) can be useful, but negative culture results cannot be used to rule out disease, owing to inadequate sensitivity. Proven disease requires histologic confirmation or microbiologic recovery of the organism, whereas probable disease diagnosis includes radiographic findings coupled with molecular biologic assays such as galactomannan antigen detection either in the serum or from the BAL. This galactomannan assay has been shown to be the most sensitive in detecting disease in cancer patients or hematopoietic stem cell transplant recipients, with less utility in solid organ transplant recipients. Earlier reports of increased false-positive reactions in children versus adults have been refuted, and the galactomannan assay is effective in diagnosing IA in children. This test does possess high rates of false negativity in patients with congenital immunodeficiency (e.g., CGD) and invasive ***Aspergillus*** infections. The beta-glucan assay is a nonspecific molecular fungal assay that detects the major component of the fungal cell wall. Unlike the galactomannan assay, which is specific for *Aspergillus*, the beta-glucan assay will not discriminate which fungal organism is infecting the patient. Polymerase chain reaction (PCR)–based assays are in development for the diagnosis of aspergillosis but are still being optimized.

Treatment

Successful treatment of IA hinges on the ability to reconstitute normal immune function and use of effective antifungal agents until immune recovery can be achieved. Therefore lowering overall immunosuppression, specifically via cessation of corticosteroid use, is vital to improve the ultimate outcome. **Multiple published guidelines recommend that primary therapy for all forms of IA is voriconazole**, based on several studies showing both improved response rates and improved survival in patients receiving voriconazole when compared with amphotericin B. Guideline-recommended alternative therapies include liposomal amphotericin B, isavuconazole, and other lipid formulations of amphotericin B. European guidelines recommend isavuconazole and voriconazole for treatment of pulmonary disease with a similar strength of recommendation, mentioning fewer adverse effects with isavuconazole than with voriconazole and use of liposomal amphotericin B as an alternative. Posaconazole is another triazole antifungal that is approved for antifungal prophylaxis and may be considered an alternative agent for first-line treatment of IA.

The echinocandin class of antifungals may also a play a role in treatment of IA, but to date, these agents are generally employed as second-line medications, particularly for salvage therapy. Combination antifungal therapy has revealed disparate results. The U.S. guidelines state that combination primary antifungal therapy with voriconazole plus an echinocandin may be considered in select patients with documented IA; however, this is not a recommendation. Importantly, primary therapy with an echinocandin is not recommended, but an echinocandin can be used in the settings in which azole or polyene antifungals are contraindicated. Unfortunately, even with newer

antifungals, complete or partial response rates for treatment of IA are only approximately 50%. To augment antifungal therapies, patients have been treated with growth factors to increase neutrophil counts, granulocyte transfusions, interferon-γ, and surgery. Treatment of IA should be continued for a minimum of 6-12 weeks; however, many experts feel that treatment should continue until complete clinical and radiographic resolution of disease.

Special Populations

Patients with CGD represent a pediatric population at particular risk for pulmonary aspergillosis. Invasive pulmonary aspergillosis can be the first serious infection identified in these patients, and the lifetime risk of developing pulmonary aspergillosis is estimated to be 33%. Unlike classical IA in cancer patients, the onset of symptoms is often gradual, with slow development of fever, fatigue, pneumonia, and elevated sedimentation rate. The neutrophils of patients with CGD surround the collections of fungal elements but cannot kill them, thereby permitting local invasion with extension of disease to the pleura, ribs, and vertebrae, though angioinvasion is not seen. Imaging in these patients is much less likely to reveal the halo sign, infarcts, or cavitary lesions and instead generally shows areas of tissue destruction caused by the ongoing inflammatory processes.

CUTANEOUS ASPERGILLOSIS

Cutaneous aspergillosis can occur as a primary disease or as a consequence of hematogenous dissemination or spread from underlying structures. Primary cutaneous disease classically occurs at sites of skin disruption, such as intravenous access device locations, adhesive dressings, or sites of injury or surgery. Premature infants are at particular risk, given their immature skin and need for multiple access devices. Cutaneous disease in transplant recipients tends to reflect hematogenous distribution from a primary site of infection, often the lungs. Lesions are erythematous, indurated papules that progress to painful, ulcerated, necrotic lesions. Treatment depends on the combination of surgical debridement and antifungal therapy, with systemic voriconazole recommended as primary therapy.

INVASIVE SINONASAL DISEASE

Invasive *Aspergillus* sinusitis represents a difficult diagnosis because the clinical presentation tends to be highly variable. Patients can present with congestion, rhinorrhea, epistaxis, headache, facial pain or swelling, orbital swelling, fever, or abnormal appearance of the nasal turbinates. Because noninvasive imaging can be normal, diagnosis rests on direct visualization via endoscopy and biopsy. Sinus mucosa may be pale, discolored, granulating, or necrotic, depending on the stage and extent of disease. The infection can invade adjacent structures, including the eye and brain. This syndrome is difficult to distinguish clinically from other types of invasive fungal disease of the sinuses such as mucormycosis, rendering obtaining specimens for culture and histology extremely important. If the diagnosis is confirmed, treatment should be with voriconazole similar to invasive pulmonary disease. Because voriconazole is not active against mucormycosis, amphotericin B formulations should be considered in invasive fungal sinusitis pending definitive identification.

CENTRAL NERVOUS SYSTEM

The primary site of *Aspergillus* infection tends to be the lungs, but as the hyphae invade into the vasculature, fungal elements can dislodge and travel through the bloodstream, permitting establishment of secondary infection sites. One of the sites commonly involved in disseminated disease is the CNS. Cerebral aspergillosis can also arise secondary to local extension of sinus disease. The presentation of cerebral aspergillosis is highly variable but can include changes in mental status, seizures, paralysis, coma, and ophthalmoplegia. As the hyphae invade the CNS vasculature, hemorrhagic infarcts develop that convert to abscesses. Biopsy is required for definitive diagnosis, but patients are often too ill to tolerate surgery. Imaging can be helpful for diagnosis, and MRI is preferred. In general, the prognosis for CNS aspergillosis is extremely poor, likely owing to the late onset at presentation. Reversal of immunosuppression is extremely important, when possible. Surgical resection of lesions may be useful. Voriconazole is the best therapy, usually at high doses.

EYE

Fungal endophthalmitis and keratitis may be seen in patients with disseminated *Aspergillus* infection. Pain, photophobia, and decreased visual acuity may be present, though many patients are asymptomatic. Emergent ophthalmologic evaluation is important when these entities are suspected. Endophthalmitis is treated with intravitreal injection of either amphotericin B or voriconazole along with surgical intervention and systemic antifungal therapy with voriconazole. Keratitis requires topical and systemic antifungal therapy.

BONE

Aspergillus osteomyelitis can occur, most commonly in the vertebrae. Rib involvement occurs as a result of extension of disease in patients with CGD and is most often caused by *A. nidulans*. Treatment depends on the combination of surgical debridement and systemic antifungals. Arthritis can develop after hematogenous dissemination or local extension, and treatment depends on joint drainage combined with antifungal therapy. Voriconazole is the preferred first-line therapy.

HEART

Cardiac infection can occur as a result of surgical contamination, secondary to disseminated infection, or after direct extension from a contiguous focus of infection and includes endocarditis, myocarditis, and pericarditis. Treatment requires surgical intervention in the case of endocarditis and pericarditis, along with systemic antifungals, sometimes lifelong because of the possibility of recurrent infection.

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Chapter 284

Histoplasmosis (*Histoplasma capsulatum*)

Matthew C. Washam and Lara A. Danziger-Isakov

ETIOLOGY

Histoplasmosis is caused by *Histoplasma capsulatum,* a dimorphic fungus found in the environment as a saprobe in the mycelial (mold) form and in tissues in the parasitic form as yeast.

EPIDEMIOLOGY

Two varieties of *Histoplasma* cause human histoplasmosis. The most common variety, *H. capsulatum* var. *capsulatum,* is found in soil as the saprotrophic form throughout the midwestern United States, primarily along the Ohio and Mississippi rivers. In parts of Kentucky and Tennessee, almost 90% of the population older than 20 years of age have positive skin test results for histoplasmin. Sporadic cases have also been reported in nonendemic states in patients without a travel history. Worldwide, *H. capsulatum* var. *capsulatum* is endemic to parts of Central and South America, the Caribbean, China, India, Southeast Asia, and the Mediterranean. The less common variety, *H. capsulatum* var. *duboisii,* is endemic to certain areas of western and central sub-Saharan Africa.

H. capsulatum thrives in soil rich in nitrates such as areas that are heavily contaminated with bird or bat droppings or decayed wood. Fungal spores are often carried on the wings of birds. Focal outbreaks of histoplasmosis have been reported after aerosolization of microconidia

resulting from construction in areas previously occupied by starling roosts or chicken coops or by chopping decayed wood or burning bamboo exposed to a blackbird roost. Unlike birds, bats are actively infected with *Histoplasma.* Focal outbreaks of histoplasmosis have also been reported after intense exposure to bat guano in caves and along bridges frequented by bats. Horizontal person-to-person transmission does not occur, although transplacental transmission of *H. capsulatum* has been reported in immunocompromised mothers.

PATHOGENESIS

Inhalation of microconidia (fungal spores) is the initial stage of human infection. The conidia reach the alveoli, germinate, and proliferate as yeast. Alternatively, spores can remain as mold with the potential for activation. Most infections are asymptomatic or self-limited. When disseminated disease occurs, any organ system can be involved. The initial infection is a bronchopneumonia. As the initial pulmonary lesion ages, giant cells form, followed by formation of caseating or noncaseating granulomas and central necrosis. Granulomas contain viable yeast, and disease can relapse. At the time of spore germination, yeast cells are phagocytosed by alveolar macrophages, where they replicate and gain access to the reticuloendothelial system via the pulmonary lymphatic system and hilar lymph nodes. Dissemination with splenic involvement typically follows the primary pulmonary infection. In normal hosts, specific cell-mediated immunity follows in approximately 2 weeks, enabling sensitized T cells to activate macrophages and kill the organism. The initial pulmonary lesion resolves within 2-4 months but may undergo calcification resembling the Ghon complex of tuberculosis. Alternatively, buckshot calcifications involving the lung and spleen may be seen. Unlike tuberculosis, reinfection with *H. capsulatum* may occur and can lead to exaggerated host responses in some cases.

Children with immune deficiencies, specifically deficiencies involving cell-mediated immunity, are at increased risk for disseminated histoplasmosis. Primary immunodeficiencies involving pathogenic genetic variants in the interleukin (IL)-12/interferon (IFN)-γ pathway have been reported in children with disseminated histoplasmosis, including IL-12Rβ1 deficiency and IFN-γ R1 deficiency. Other primary immunodeficiencies identified in children with disseminated disease include *STAT1* gain-of-function pathogenic genetic variants, idiopathic CD4 lymphopenia, AR-DOCK8 deficiency, AD-GATA2 deficiency, and X-linked CD40L deficiency. Children with certain secondary immunodeficiencies (cancer patients, solid organ transplant recipients, children with HIV infection, and children receiving immunomodulatory therapy with tumor necrosis factor [TNF]-α inhibitors) are also at increased risk for disseminated disease.

CLINICAL MANIFESTATIONS

Exposure to *Histoplasma* is common in endemic areas, although most infections are subclinical. Less than 1% of those infected display the following clinical manifestations:

Acute pulmonary histoplasmosis follows initial or recurrent respiratory exposure to microconidia. Symptomatic disease occurs more often in young children; in older patients, symptoms follow exposure to large inocula in closed spaces (e.g., chicken coops or caves) or prolonged exposure (e.g., camping on contaminated soil, chopping decayed wood). The median incubation time is 14 days. The prodrome is not specific and usually consists of flulike symptoms, including headache, fever, chest pain, cough, and myalgias. Hepatosplenomegaly occurs more often in infants and young children. Symptomatic infections may be associated with significant respiratory distress and hypoxia and can require intubation, mechanical ventilation, and steroid therapy. Acute pulmonary disease can also manifest with a prolonged illness (10 days to 3 weeks) consisting of weight loss, dyspnea, high fever, asthenia, and fatigue. Children with symptomatic disease typically have a patchy bronchopneumonia; hilar lymphadenopathy is variably present (Fig. 284.1). In young children, the pneumonia can coalesce. Focal or buckshot calcifications are convalescent findings in patients after acute pulmonary infection.

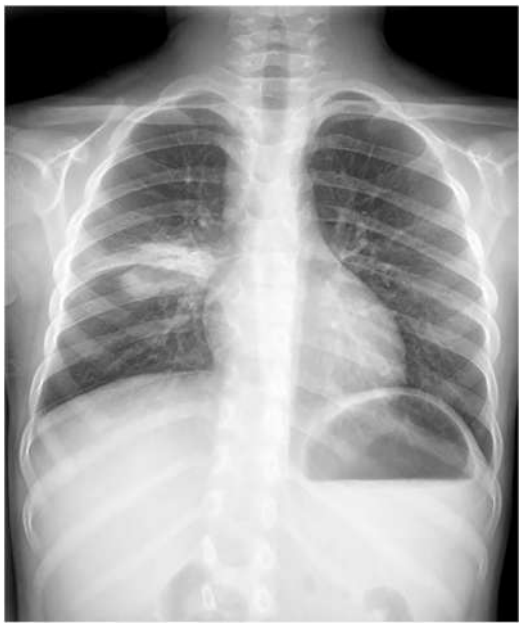

Fig. 284.1 Radiograph of a 5-yr-old child with acute pulmonary histoplasmosis showing right perihilar lymphadenopathy.

Complications of pulmonary histoplasmosis occur secondary to exaggerated host responses to fungal antigens within the lung parenchyma or hilar lymph nodes. **Histoplasmomas** are of parenchymal origin and are usually asymptomatic. These fibroma-like lesions are often concentrically calcified and single. Rarely, these lesions produce broncholithiasis associated with "stone spitting," wheezing, and hemoptysis. In endemic regions, these lesions can mimic parenchymal tumors and are occasionally diagnosed at lung biopsy. **Mediastinal granulomas** form when reactive hilar lymph nodes coalesce and mat together. Although these lesions are usually asymptomatic, huge granulomas can compress the mediastinal structures, producing symptoms of esophageal, bronchial, or vena caval obstruction. Local extension and necrosis can produce pericarditis or pleural effusions. **Mediastinal fibrosis** is a rare complication of mediastinal granulomas and represents an uncontrolled fibrotic reaction arising from the hilar nodes. Structures within the mediastinum become encased within a fibrotic mass, producing obstructive symptomatology. Superior vena cava syndrome, pulmonary venous obstruction with a mitral stenosis–like syndrome, and pulmonary artery obstruction with congestive heart failure have been described. Dysphagia accompanies esophageal entrapment, and a syndrome of cough, wheeze, hemoptysis, and dyspnea accompanies bronchial obstruction. Rarely, children develop a sarcoid-like disease with arthritis or arthralgia, erythema nodosum, keratoconjunctivitis, iridocyclitis, and pericarditis. **Pericarditis**, with effusions both pericardial and pleural, is a self-limited benign condition that develops as a result of an inflammatory reaction to adjacent mediastinal disease. The effusions are exudative, and the organism is rarely culturable from fluid. **Progressive disseminated histoplasmosis** can occur in infants and in children with deficient cell-mediated immunity. Disseminated disease may occur either during the initial acute infection in children with primary or secondary immunodeficiencies affecting T-cell function (see "Pathogenesis"), in infants, or as a reactivation of a latent focus of infection within the reticuloendothelial system in children who acquire an immunosuppressive condition years after primary infection. Disseminated histoplasmosis in an HIV-infected patient is an AIDS-defining illness. Fever is the most common finding and can persist for weeks to months before the condition is diagnosed. The majority of patients have hepatosplenomegaly, lymphadenopathy, and interstitial pulmonary disease. Extrapulmonary infection is a characteristic of disseminated disease and can include destructive bony lesions, Addison

disease, meningitis, multifocal chorioretinitis, and endocarditis. Some patients develop mucous membrane ulcerations and skin findings such as nodules, ulcers, or molluscum-like papules. A sepsis-like syndrome has been identified in a small number of HIV-infected patients with disseminated histoplasmosis and is characterized by the rapid onset of shock, multiorgan failure, and coagulopathy. Reactive hemophagocytic syndrome has been described in immunocompromised patients with severe disseminated histoplasmosis. Many children with disseminated disease experience transient hyperglobulinemia. Elevated acute-phase reactants and hypercalcemia are typically seen but are nonspecific. Anemia, thrombocytopenia, and pancytopenia are variably present; elevated liver function tests and high serum concentrations of angiotensin-converting enzyme may be observed. Chest radiographs are normal in more than half of children with disseminated disease.

Chronic pulmonary histoplasmosis is an opportunistic infection in adult patients with centrilobular emphysema. **Chronic progressive disseminated histoplasmosis** is a slowly progressive infection caused by *Histoplasma* that occurs in older adults without obvious immunosuppression that is uniformly fatal if untreated. These entities are rare in children.

DIAGNOSIS

Optimal diagnosis of suspected histoplasmosis depends on the clinical presentation and underlying immune status of the patient. Using serum and urine antigen tests along with serum antibody tests via complement fixation and immunodiffusion yields a diagnostic sensitivity >90% for acute pulmonary and disseminated forms of histoplasmosis. Diagnostic testing options include the following:

Antigen detection is the most widely available diagnostic study for patients with suspected pulmonary histoplasmosis or progressive disseminated histoplasmosis. Current laboratory methodology uses enzyme immunoassay (EIA) to detect *H. capsulatum* polysaccharide antigen in urine, blood, bronchoalveolar lavage fluid, and cerebrospinal fluid. In patients at risk for disseminated disease, antigen can be demonstrated in the urine, blood, or bronchoalveolar lavage fluid in more than 90% of cases. Antigenuria has been shown to correlate with severity of disseminated histoplasmosis. Serum, urine, and bronchoalveolar lavage fluid from patients with acute or chronic pulmonary infections are variably antigen positive. In one study, antigenuria was present in 83% of patients with acute pulmonary disease and 30% of patients with subacute pulmonary disease. False-positive results on urinary antigen testing can occur in patients with *Blastomyces dermatitidis, Coccidioides immitis, Coccidioides posadasii, Paracoccidioides brasiliensis,* and *Penicillium marneffei*. Testing both urine and serum samples for histoplasma antigen increases the sensitivity compared with testing only the urine or serum alone. Sequential measurement of serum antigen levels in patients with disseminated disease is useful for monitoring response to therapy; persistent low-level antigenuria may occur in some patients who have completed therapy and have no evidence of active infection.

Antibody tests continue to be useful for the diagnosis of acute pulmonary histoplasmosis, its complications, and chronic pulmonary disease. Serum antibody to yeast and mycelium-associated antigens is classically measured by complement fixation. Although titers of >1:8 are found in more than 80% of patients with histoplasmosis, titers of ≥1:32 are most significant for the diagnosis of recent infection. Complement-fixation antibody titers are often not significant early in the infection and do not become positive until 4-6 weeks after exposure. A fourfold increase in either yeast or mycelial-phase titers or a single titer of ≥1:32 is presumptive evidence of active infection. Complement-fixation titers may be falsely positive in patients with other systemic mycoses such as *B. dermatitidis* and *C. immitis* and may be falsely negative in immunocompromised patients. Antibody detection by immunodiffusion is less sensitive but more specific than complement fixation and is used to confirm questionably positive complement-fixation titers. An EIA-based method that has improved sensitivity and specificity compared with other serologic methods has been developed. The highest sensitivity for antibody testing can be achieved by combining methodologies.

Culture sensitivity of tissue or body fluid samples is generally highest for children with progressive disseminated histoplasmosis or acute pulmonary histoplasmosis caused by a large inoculum of organisms. *Histoplasma* typically grows within 6 weeks on Sabouraud agar at 25°C (77°F). Identification of tuberculate macroconidia allows for only a presumptive diagnosis, because *Sepedonium* species form similar structures. A confirmatory test using a chemiluminescent DNA probe for *H. capsulatum* is necessary to establish a definitive identification. The yeast can be recovered from blood or bone marrow in >90% of patients with progressive disseminated histoplasmosis. Sputum cultures are rarely obtained and are variably positive in normal hosts with acute pulmonary histoplasmosis; cultures of bronchoalveolar lavage fluid appear to have a slightly higher yield than sputum cultures. Blood cultures are sterile in patients with acute pulmonary histoplasmosis, and cultures from any source are typically sterile in patients with the sarcoid form of the disease.

Histologic examination can identify yeast forms in tissue from patients with complicated forms of acute pulmonary disease (histoplasmoma and mediastinal granuloma). Tissue should be stained with methenamine silver or periodic acid–Schiff stains, and yeast can be found within or outside of macrophages. In children with disseminated disease, organisms can be identified from bone marrow, liver, and mucocutaneous lesions. In those who are severely ill, Wright stain of peripheral blood can demonstrate fungal elements within leukocytes. Examination of fibrotic tissue from children with mediastinal fibrosis usually demonstrates no organisms.

Real-time polymerase chain reaction has been used on formalin-fixed, paraffin-embedded biopsy tissue and has an analytical sensitivity of at least 6 pg/μL from tissue-extracted DNA and a clinical sensitivity and specificity of 88.9% and 100%, respectively. Although not widely available, molecular methods may ultimately provide a more timely and accurate diagnosis.

Skin testing is useful only for epidemiologic studies, as cutaneous reactivity is lifelong and intradermal injection can elicit an immune response in otherwise seronegative persons. Reagents are no longer commercially available.

TREATMENT

Acute pulmonary histoplasmosis does not require antifungal therapy for asymptomatic or mildly symptomatic children. Oral itraconazole (4-10 mg/kg/day in two divided doses, not to exceed 400 mg daily) for 6-12 weeks should be considered in patients with acute pulmonary infections who fail to improve clinically within 1 month. Although it appears to be less effective, fluconazole may be considered as an alternative therapy in children intolerant to itraconazole. Clinical experience in treating histoplasmosis with the newer azoles (voriconazole and posaconazole) is increasing, with posaconazole having increased in vitro activity. *Patients with pulmonary histoplasmosis who become hypoxemic or require ventilatory support* should receive amphotericin B deoxycholate (0.7-1.0 mg/kg/day) or amphotericin B lipid complex (3-5 mg/kg/day) until improved, and adjunctive corticosteroids (intravenous methylprednisolone at a dose of 0.5-1 mg/kg/day) can be considered for 1-2 weeks; continued therapy with oral itraconazole for a minimum of 12 wk is also recommended. The lipid preparations of amphotericin are not preferentially recommended in children with pulmonary histoplasmosis, as the classic preparation is generally well tolerated in this patient population. Patients with severe obstructive symptoms caused by granulomatous mediastinal disease may be treated sequentially with amphotericin B followed by itraconazole for 6-12 months, and inclusion of adjunctive corticosteroids should be considered for the first 1-2 weeks. Patients with milder mediastinal disease may be treated with oral itraconazole alone. Some experts recommend that surgery be reserved for patients who fail to improve after 1 month of intensive amphotericin B therapy. Sarcoid-like disease with or without pericarditis may be treated with nonsteroidal antiinflammatory agents for 2-12 weeks.

Progressive disseminated histoplasmosis usually requires amphotericin B deoxycholate (1.0 mg/kg/day for 4-6 weeks) or amphotericin B lipid complex (3-5 mg/kg/day). Alternatively, amphotericin B may be given for 2-4 weeks followed by oral itraconazole (4-10 mg/kg/day in two divided doses) as maintenance therapy for 12 months,

depending on *Histoplasma* antigen status. Longer therapy may be needed in patients with severe disease, immunosuppression, or primary immunodeficiency syndromes. It is recommended to monitor blood levels of itraconazole during treatment, aiming for a concentration of ≥1 μg/mL but <10 μg/mL to avoid potential drug toxicity. It is also recommended to monitor urine antigen levels during therapy and for 12 months after therapy has ended to ensure cure. Relapses in immunocompromised patients with progressive disseminated histoplasmosis are relatively common. Lifelong suppressive therapy with daily itraconazole (5 mg/kg/day up to adult dose of 200 mg/day) may be required if immunosuppression cannot be reversed. For severely immunocompromised HIV-infected children living in endemic regions, itraconazole (2-5 mg/kg every 12-24 hours) may be used prophylactically. Care must be taken to avoid interactions between antifungal azoles and protease inhibitors.

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Chapter 285

Blastomycosis

Gregory M. Gauthier and Bruce S. Klein

ETIOLOGY

The etiologic agents of blastomycosis belong to a species complex and include *Blastomyces dermatitidis, B. gilchristii, B. helicus, B. emzantsi, B. percursus, B. parvus,* and *B. silverae*. The latter two species *(B. parvus, B. silverae)* rarely cause human infection. All *Blastomyces* species exhibit thermal dimorphism in which they grow as mold and produce spores in the soil at environmental temperature (22–25°C [71.6–77°F]) and as pathogenic yeast at core human body temperature (37°C [98.6°F]). Once in tissue, *Blastomyces* infection results in pyogranulomatous inflammation, which is characterized by neutrophil infiltration and granuloma formation. *Blastomyces* yeast can be differentiated from other fungi by the presence of a broad-based budding pattern between dividing yeast cells, which occurs in all *Blastomyces* species.

EPIDEMIOLOGY

Blastomyces species cause disease in immunocompetent and immunocompromised children. Approximately 2–13% of blastomycosis cases occur in the pediatric population (average age: 9.1-12.9 years; range: 19 days to 18 years). Blastomycosis of newborns and infants is rare. In North America, the traditional geographic range of blastomycosis cases is restricted to the Midwest, southcentral, and southeastern United States and parts of Canada bordering the Great Lakes and Saint Lawrence River Valley. In these geographic regions, several areas are hyperendemic for blastomycosis (e.g., Marathon and Vilas counties, Wisconsin; central and southcentral Mississippi; Kenora, Ontario). Outside of North America, autochthonous infections have been reported from Africa (~100 cases), India (<12 cases), and Israel. *B. dermatitidis* is not endemic to Central America, South America, Europe, Asia, or Australia.

In North America, *B. dermatitidis* and *B. gilchristii* grow in an ecologic niche characterized by forested, sandy soils with an acidic pH that have decaying vegetation and are near water. *B. dermatitidis* is located throughout the traditional geographic range, whereas *B. gilchristii* is restricted to Minnesota, Wisconsin, Canada, and areas along the St. Lawrence River. *B. helicus* is located in the western United States (California, Montana, Idaho, Colorado, Nebraska, Texas) and Canada (Saskatchewan, Alberta); however, its environmental niche remains to be determined. In Africa, there are multiple species of *Blastomyces,* including *B. dermatitidis, B. gilchristii, B. percursus,* and *B. emzantsi.* Knowledge about the ecological niche and geographic distribution of *Blastomyces* species in Africa is limited. *B. percursus* has been reported from Israel.

Most *Blastomyces* infections are sporadic, but at least 20 outbreaks have been reported, and most of these outbreaks have included pediatric patients. Outbreaks have been associated with construction or outdoor activities (camping, hiking, fishing, rafting on a river, using a community compost pile); however, some outbreaks have no identifiable risk factors other than geography. Although blastomycosis is often thought to be an infection that primarily affects persons residing in or visiting rural areas, outbreaks and sporadic cases of blastomycosis are well reported in urban areas. Blastomycosis outbreak investigations in Wisconsin suggested that persons of Hmong ethnicity are at increased risk for the disease, which may be the result of polymorphisms in the interleukin-6 (IL-6) gene. These polymorphisms result in reduced IL-6 cytokine production and $CD4^+$ T lymphocytes that produce IL-17, which in turn, impairs activation of neutrophils and macrophages against *Blastomyces*. Although persons of Hmong ethnicity are at increased risk for blastomycosis, they do not appear to be at risk for disseminated infection. Increased incidence of blastomycosis has also been reported in indigenous persons living in the United States and Canada.

The severity of infection is influenced by the size of the inhaled inoculum and the integrity of the patient's immune system. Solid organ transplant recipients are at risk for severe pulmonary blastomycosis, including acute respiratory distress syndrome (ARDS); however, they are not at higher risk for disseminated infection. Although blastomycosis is uncommon in persons immunosuppressed with AIDS, there is an increased risk for dissemination to the central nervous system (CNS). Persons receiving tumor necrosis factor-α inhibitors are at risk for blastomycosis, but rates of dissemination or severe disease are not well defined.

PATHOGENESIS

The ability of mycelial fragments and spores to convert to yeast in the lung is a crucial event in the pathogenesis of infection with *Blastomyces* and other dimorphic fungi. This temperature-dependent morphologic shift, which is known as the *phase transition,* enables *Blastomyces* to evade the host immune system and establish infection. In the yeast form, the essential virulence factor BAD1 (B*lastomyces* ad*hesin*-1; formerly WI-1) is secreted into the extracellular milieu and binds back to chitin on the fungal cell wall. BAD1 is a multifunctional protein that promotes binding of yeast to alveolar macrophages (via CR3 and CD14 receptors) and lung tissue (via heparan sulfate), blocks the deposition of complement on the yeast surface, binds calcium, suppresses the host's ability to produce cytokines (tumor necrosis factor-α, IL-17, interferon-gamma), and inhibits activation of $CD4^+$ T lymphocytes. Deletion of *BAD1* abolishes virulence of *Blastomyces* yeast in a murine model of pulmonary infection.

The phase transition between mold and yeast forms is a complex event that involves alteration in cell wall composition, metabolism, intracellular signaling, and gene expression. The morphologic shift to yeast is regulated in part by a histidine kinase known as DRK1 (*d*imorphism *r*egulating *k*inase-1). This sensor kinase controls not only the conversion of mold to yeast but also spore production, cell wall composition, and *BAD1* expression; the loss of *DRK1* gene expression through gene disruption renders *B. dermatitidis* avirulent in a murine model of pulmonary blastomycosis. The function of DRK1 is conserved in other thermally dimorphic fungi, including *Histoplasma capsulatum* and *Talaromyces marneffei* (formerly *Penicillium marneffei*).

The phase transition is reversible, and after a drop in temperature from 37°C (98.6°F) to 22°C (71.6°F), yeast convert to sporulating mold. Growth as mold promotes survival in the soil, allows for sexual reproduction to enhance genetic diversity, and facilitates transmission to new hosts (via spores and mycelial fragments). The transition from

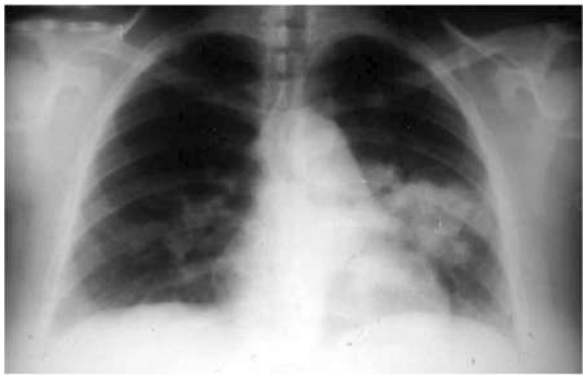

Fig. 285.1 Left lung infection in a patient with symptoms resembling acute bacterial pneumonia. Organisms of *Blastomyces* in the sputum seen with potassium hydroxide preparation, and subsequent culture confirmed the diagnosis. *(From Bradsher RW Jr. Blastomycoses. In: Bennett JE, Blaser MJ, Dolin R, et al, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th ed, Philadelphia: Saunders; 2015: Fig. 266-5.)*

yeast to mold is influenced by SREB (siderophore biosynthesis repressor in *Blastomyces*) and *N*-acetylglucosamine transporters (NGT1, NGT2). Deletion of *SREB,* which encodes a GATA transcription factor, results in the failure of *B. dermatitidis* yeast to complete the conversion to mold at 22°C. *N*-Acetylglucosamine, which polymerizes to form chitin, accelerates the transition to hyphae via NGT1 and NGT2 transporters.

Innate and adaptive immune systems are required to effectively control infection; humoral immunity is dispensable. Macrophages and neutrophils are capable of ingesting and killing *Blastomyces* conidia. In contrast, yeast are poorly killed by nonactivated macrophages, are resistant to reactive oxygen species, and suppress nitric oxide production. Adaptive immunity is mediated by T lymphocytes (Th1 and Th17), which activate macrophages and neutrophils to facilitate clearance of infection. After infection, cell-mediated immunity against *Blastomyces* can last for at least 2 years.

CLINICAL MANIFESTATIONS

The clinical manifestations of blastomycosis are diverse and include subclinical infection, symptomatic pneumonia, and disseminated disease. Clinical disease develops 3 weeks to 3 months after inhalation of spores or mycelial fragments. Asymptomatic or subclinical infections are estimated to occur in 50% of patients.

The most common clinical manifestation of blastomycosis is **pneumonia**, which can range from acute to chronic. Acute symptoms resemble community-acquired pneumonia and include fever, dyspnea, cough, chest pain, and malaise (Fig. 285.1). Respiratory failure, including ARDS, can occur in patients with an overwhelming burden of infection. The most common chest imaging pattern is air space consolidation with or without air bronchograms. Any lobe of the lung can be involved, and multiple lobe involvement is not uncommon. Other radiographic features include masslike consolidation, nodules with cavity formation, reticulonodular pattern, and miliary disease. Hilar adenopathy and pleural effusions occur in approximately 20% of cases. Because the clinical and radiographic features often mimic bacterial pneumonia, patients can be mistakenly treated with antibiotics, resulting in disease progression, which can result in disseminated disease or respiratory failure, including ARDS. Patients with subacute or chronic pneumonia experience fevers, chills, night sweats, cough, weight loss, hemoptysis, dyspnea, and chest pain. Mass lesions and cavitary disease on chest roentgenography can mimic malignancy and tuberculosis, respectively.

Extrapulmonary blastomycosis most often affects the skin or bone but can involve almost any organ. The incidence of **extrapulmonary blastomycosis** in children ranges from 38% to 50%, similar to rates in adult patients (15–48%). *B. dermatitidis* is more likely to cause disseminated infection, whereas *B. gilchristii* is more likely to remain localized to the lungs. The skin is the most common site for extrapulmonary blastomycosis, which is usually the result of hematogenous dissemination. Direct inoculation of *B. dermatitidis* into the skin from trauma or a laboratory accident can result in primary cutaneous blastomycosis. Skin manifestations include plaques, papules, ulcers, nodules, and verrucous lesions. Erythema nodosum is rare in blastomycosis. Dissemination of *B. dermatitidis* to the bone results in lytic destruction, pain, soft tissue swelling, sinus tract formation, and ulceration. The ribs, skull, spine, and long bones are most commonly affected. Patients with osteomyelitis often have pulmonary or cutaneous involvement. Vertebral osteomyelitis can be complicated by paraspinal abscess, psoas abscess, and vertebral body collapse. Extension of long bone osteomyelitis can result in pathologic fracture or septic arthritis. Genitourinary blastomycosis occurs in just under 10% of adults but is rare in children.

CNS blastomycosis (brain abscess, meningitis) occurs in <10% of immunocompetent patients but in up to 40% of persons with AIDS. The majority of patients with CNS blastomycosis have clinically apparent infection at non-CNS sites (e.g., lung, skin, mass lesion). Symptoms of CNS infection include headache, altered mental status, memory loss, seizure, cranial nerve deficits, and focal neurologic deficits. Complications include hydrocephalus, cerebral herniation, infarction, panhypopituitarism, residual weakness, and poor functioning in school. Lumbar puncture demonstrates leukocytosis with a neutrophil or lymphocyte predominance, elevated protein, and low glucose. Growth of *Blastomyces* in culture from cerebrospinal fluid occurs in less than 50% of affected patients.

Blastomycosis can complicate pregnancy, and clinical information is limited to case reports. Disseminated infection involving the lungs, skin, and bone is common. Spread of infection to the placenta has been documented by histopathology; however, the frequency of placental blastomycosis remains unknown. Transmission of *Blastomyces* to the fetus is uncommon and is postulated to occur through transplacental transmission or aspiration of infected vaginal secretions. Although clinical data are limited, blastomycosis during pregnancy does not appear to increase the risk for congenital malformations.

DIAGNOSIS

The diagnosis of blastomycosis requires a high index of suspicion because the clinical and radiographic manifestations can mimic other diseases, including community-acquired pneumonia, tuberculosis, and malignancy. The misdiagnosis of blastomycosis, most often as community-acquired pneumonia, results in a delay of therapy and progression of disease, including dissemination and respiratory failure. In addition, absence of exposure to traditional environmental risk factors for blastomycosis can lead to a delay in diagnosis. Blastomycosis should be included in the differential diagnosis for patients with pneumonia who (1) live in or visit areas in which this pathogen is endemic, (2) fail to respond to a treatment course of antibiotics, or (3) have concomitant skin lesions or osteomyelitis. A detailed medical history regarding exposure risks (e.g., canoeing, rafting, hiking, fishing, playing in outdoor forts, beaver dam exploration, home remodeling, nearby road or building construction, woodpile for a wood burning stove, and use of a community compost pile) should be obtained. In addition, the health of family pets such as dogs should be ascertained, as canine disease may be a harbinger of human infection. Studies from Wisconsin and Minnesota have demonstrated that 7.7–10% of persons with blastomycosis have a dog with concomitant or prior blastomycosis. The incidence of canine blastomycosis is 10-fold higher than human blastomycosis, and canine infection suggests a common source of environmental *Blastomyces* exposure.

Growth of *Blastomyces* in culture from sputum, skin, bone, or other clinical specimens provides a definitive diagnosis. Sputum specimens should be stained with 10% potassium hydroxide or calcofluor white. Histopathology shows neutrophilic infiltration with noncaseating

granulomas (pyogranulomas). *Blastomyces* yeast in tissue samples can be visualized using Gomori methenamine silver or periodic acid–Schiff stains. Yeasts are 4-29 μm in size, have a double refractile cell wall, and are characterized by broad-based budding between mother and daughter cells.

Nonculture diagnostic techniques should be used in conjunction with fungal smears and cultures to facilitate the diagnosis of blastomycosis. The development of a *Blastomyces* antigen test has supplanted insensitive serologic methods such as complement fixation and immunodiffusion. Urine, serum, cerebrospinal fluid, and bronchoalveolar fluid specimens can be collected for the *Blastomyces* antigen test. Sensitivity of the urine antigen test ranges from 85% to 93% and is influenced by the burden of infection. The antigen test has similar sensitivity for *B. dermatitidis* and *B. gilchristii,* but ability to detect other species is poorly characterized. The antigen test can cross react with other dimorphic fungi, including *Histoplasma capsulatum, Paracoccidioides brasiliensis,* and *Penicillium marneffei,* decreasing the specificity to 76.9–79%. An antibody test against the BAD1 protein has been developed and has a sensitivity of 87.8% and a specificity of 94–99%; however, this test is not yet commercially available. Combination antigen and BAD1 antibody testing can increase diagnostic sensitivity to 97.6%.

TREATMENT

Antifungal therapy is influenced by the severity of the infection, involvement of the CNS, the integrity of the host's immune system, and pregnancy. All persons diagnosed with blastomycosis should receive antifungal therapy. **Newborns** with blastomycosis should be treated with amphotericin B deoxycholate 1 mg/kg/day. **Children with mild to moderately severe infection** can be treated with itraconazole 10 mg/kg/day (maximum: 400 mg/day) for 6-12 months. **Children with severe disease, immunodeficiency, or immunosuppression** should be treated with amphotericin B deoxycholate 0.7-1.0 mg/kg/day or lipid amphotericin B 3-5 mg/kg/day until there is clinical improvement, generally 7-14 days, and then itraconazole 10 mg/kg/day (maximum: 400 mg/day) for a total of 12 months. **Central nervous system blastomycosis** requires therapy with lipid amphotericin B 5 mg/kg/day for 4-6 weeks, followed by itraconazole, fluconazole, or voriconazole for ≥12 months.

All pediatric patients of childbearing age should undergo pregnancy testing before initiation of azole antifungals. Itraconazole can increase the risk for spontaneous abortion, and fluconazole can cause craniofacial defects resembling Antley-Bixler syndrome. Voriconazole and posaconazole cause skeletal abnormalities in animal models. Treatment of blastomycosis in **pregnant patients** consists of lipid amphotericin B 3-5 mg/kg/day for 6-8 weeks.

For patients receiving itraconazole, the oral antifungal of choice, therapeutic drug monitoring should be performed 14 days into therapy (goal total itraconazole level 1-5 μg/mL), and liver function tests should be monitored periodically. Because of the long half-life of itraconazole, serum drug levels can be obtained at any time of the day, irrespective of when the drug was administered. Total itraconazole level is determined by adding itraconazole and hydroxyitraconazole concentrations; hydroxyitraconazole is a metabolite that possesses antifungal activity. Voriconazole, posaconazole, and isavuconazonium sulfate have activity against *B. dermatitidis*. Clinical experience with these drugs is growing, and treatment outcomes are promising. Therapeutic drug monitoring is recommended for voriconazole and posaconazole (goal trough levels 1-5 μg/mL) and can be considered with isavuconazonium sulfate. The echinocandins (caspofungin, micafungin, and anidulafungin) should not be used to treat blastomycosis. Serial measurement of urine antigen levels to assess response to therapy can be a helpful adjunct in monitoring response to antifungal therapy.

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Chapter 286

Coccidioidomycosis (*Coccidioides* Species)

Felicia A. Scaggs Huang and Rebecca C. Brady

ETIOLOGY

Coccidioidomycosis (valley fever, San Joaquin fever, desert rheumatism, coccidioidal granuloma) is caused by *Coccidioides* spp., a soil-dwelling dimorphic fungus. *Coccidioides* spp. grow in the environment as spore-bearing (arthroconidia-bearing) mycelial forms. In their parasitic form, they appear as unique, endosporulating spherules in infected tissue. The two recognized species, *C. immitis* and *C. posadasii,* cause clinically indistinguishable illnesses.

EPIDEMIOLOGY

Coccidioides spp. inhabit soil in arid regions. *C. immitis* is primarily found in California's San Joaquin Valley. *C. posadasii* is endemic to southern regions of Arizona, Utah, Nevada, New Mexico, western Texas, and regions of Mexico and Central and South America. The risk of infection among long-term residents in endemic regions is 3% per year.

Population migrations into endemic areas and increasing numbers of immunosuppressed persons have caused coccidioidomycosis to become an important health problem. From 2000 to 2012 in California, 4,582 cases, 1,301 hospitalizations, and 11 deaths associated with coccidioidomycosis were reported in children, who accounted for 9.2% of total cases. From 2015 to 2016, the rate of coccidioidomycosis cases among California children increased from 2.1 per 100,000 to 5.2 per 100,000. Case and hospitalization rates were highest in males and those 12-17 years. Another recent California study showed that 55% of children were hospitalized, with a median length of stay of 44 days.

Infection results from inhalation of aerosolized spores. Incidence increases during windy, dry periods that follow rainy seasons. Seismic events, archaeologic excavations, and other activities that disturb contaminated sites have caused outbreaks. Person-to-person transmission does not occur. Rarely, infections result from spores that contaminate fomites or grow beneath casts or wound dressings of infected patients. Infection has also resulted from transplantation of organs from infected donors and from mother to fetus. Visitors to endemic areas can acquire infections, and diagnosis may be delayed when they are evaluated in nonendemic areas. Spores are highly virulent, and *Coccidioides* spp. are potential agents of bioterrorism (see Chapter 763).

PATHOGENESIS

Inhaled spores reach terminal bronchioles, where they transform into septated spherules that resist phagocytosis and within which many endospores develop. Released endospores transform into new spherules, and the process results in an acute focus of infection. Endospores can also disseminate lymphohematogenously. Eventually, a granulomatous reaction predominates. Both recovery and protection upon reexposure depend on effective cellular immunity.

Children with congenital primary immunodeficiency disorders may be at increased risk for infection; these disorders include interleukin-12Rβ1 deficiency, interferon-γR1 deficiency, and *STAT1* gain-of-function mutations.

CLINICAL MANIFESTATIONS

The clinical spectrum (Fig. 286.1) encompasses pulmonary and extrapulmonary disease. Pulmonary infection occurs in 95% of cases and can be divided into primary, complicated, and residual

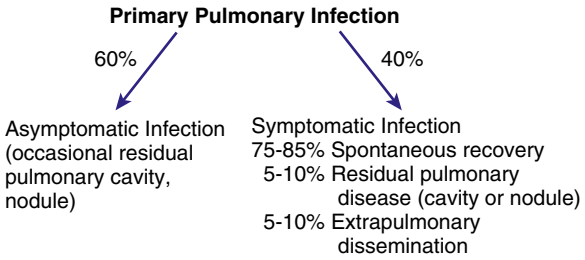

Fig. 286.1 Natural history of coccidioidomycosis.

infections. Approximately 60% of infections are asymptomatic. Symptoms in children are often milder than those in adults. The incidence of extrapulmonary dissemination in children approaches that of adults.

Primary Coccidioidomycosis

The incubation period is 1-4 weeks, with an average of 10-16 days. Early symptoms include malaise, chills, fever, and night sweats. Chest discomfort occurs in 50–70% of patients and varies from mild tightness to severe pain. Headache and/or backache are sometimes reported. Evanescent, generalized, fine macular, erythematous or urticarial eruptions may be seen within the first few days of infection. Erythema nodosum can occur (more often in females) and is sometimes accompanied by erythema multiforme, usually 3-21 days after the onset of symptoms. The clinical constellation of erythema nodosum, fever, chest pain, and arthralgias (especially knees and ankles) is called *desert rheumatism* and *valley fever.* Profound fatigue can occur and lasts weeks to months. Of note, extrapulmonary manifestations of a primary pulmonary infection do not necessarily represent disseminated disease. In hospitalized children, pulmonary symptoms are most common. The chest examination is often normal even if radiographic findings are present. Dullness to percussion, friction rub, or fine rales may be present. Pleural effusions can occur and can become large enough to compromise respiratory status. Hilar and mediastinal lymphadenopathy are common (Fig. 286.2).

Complicated Pulmonary Infection

Complicated infections include severe and persistent pneumonia, progressive primary coccidioidomycosis, progressive fibrocavitary disease, transient cavities that develop in areas of pulmonary consolidation, and empyema that follows rupture of a cavity into the pleural space. Some cavities persist, are thin walled and peripheral, and cause no symptoms; occasionally there is mild hemoptysis, and rarely there is serious hemorrhage. Rarely, acute respiratory insufficiency occurs after intense exposure; this condition is associated with high mortality rates.

Residual Pulmonary Coccidioidomycosis

Residual pulmonary coccidioidomycosis includes fibrosis and persisting pulmonary nodules. Nodules are present in 5–7% of infections and sometimes require differentiation from malignancy in adults.

Disseminated (Extrapulmonary) Infection

Clinically apparent dissemination occurs in 0.5% of patients. Its incidence is increased in infants; men; pregnant women who become infected during the second and third trimesters; persons of Filipino, African, and Latin American ancestry; and persons from other Asian backgrounds. Primary or acquired disorders of cellular immunity (Table 286.1) markedly increase the risk of dissemination. A convenience sample of 108 children in California reported that diagnosis occurred a median of 57 days after symptom onset in those with disseminated infection (compared to 16 days in those with acute or pulmonary coccidioidomycosis).

Symptoms usually occur within 6 months of primary infection. Prolonged fever, toxicity, skin lesions, subcutaneous and/or osseous cold abscesses, and laryngeal lesions can herald the onset. Skin lesions have a predilection for the nasolabial area and appear initially as papules, which evolve to form pustules, plaques, abscesses, and verrucous plaques. Biopsy of these lesions demonstrates spherules. **Basilar meningitis** is the most common manifestation and may be accompanied by ventriculitis, ependymitis, cerebral vasculitis, abscess, and syringomyelia. Headache, vomiting, meningismus, and cranial nerve dysfunction are often present. Untreated meningitis is almost invariably fatal. Hydrocephalus is the most common complication in surviving patients. Bone infections account for 20–50% of extrapulmonary manifestations, are often multifocal, and can affect adjacent structures. Miliary dissemination and peritonitis can mimic tuberculosis.

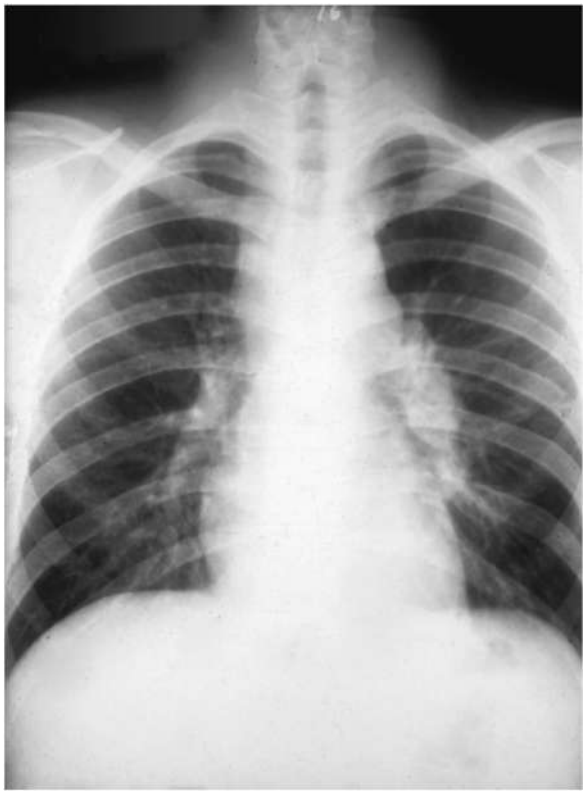

Fig. 286.2 Chest radiograph of a 19-yr-old male with acute primary coccidioidomycosis. There is prominent hilar lymphadenopathy and mediastinal widening.

Table 286.1 Risk Factors for Poor Outcome in Patients with Active Coccidioidomycosis

PRIMARY INFECTIONS
Severe, prolonged (≥6 wk), or progressive infection
RISK FACTORS FOR EXTRAPULMONARY DISSEMINATION
Primary or acquired cellular immune dysfunction (including patients receiving tumor necrosis factor inhibitors or high-dose glucocorticoids)
Neonates, infants, the elderly
Male sex (adult)
Filipino, African, Native American, or Latin American ethnicity
Late-stage pregnancy and early postpartum period
Standardized complement fixation antibody titer >1:16 or increasing titer with persisting symptoms
Blood group B
Human leukocyte antigen class II allele-DRBI*1301
Diabetes mellitus

DIAGNOSIS

Nonspecific tests have limited usefulness. Most routine laboratory evaluations are unremarkable. Complete blood count might show an elevated eosinophil count; marked eosinophilia can accompany dissemination. As a result, a high index of suspicion is required to direct an appropriate workup, especially in patients who have visited or reside in an endemic area.

Culture, Histopathologic Findings, and Antigen Detection

Any isolation of *Coccidioides* spp. from a patient specimen is considered definitive evidence of infection because the fungus is not part of the normal human microbiome. However, although diagnostic, culture is positive in only 8.3% of respiratory tract specimens and in 3.2% of all other sites. It may take several days for a specimen to grow. *Coccidioides* spp. is isolated from clinical specimens as the spore-bearing mold form, and thus the laboratory should be informed and use special precautions when the diagnosis is suspected. Inappropriate biocontainment procedures can lead to infection of exposed laboratory staff. The observation of endosporulating spherules in histopathologic specimens using potassium hydroxide (KOH) preparations, calcofluor white, or hematoxylin and eosin (H&E) stains is diagnostic. Periodic acid Schiff–or Gomori–methenamine silver stains also may be used to demonstrate the fungus.

A quantitative enzyme immunoassay (EIA) (MiraVista Diagnostics, Indianapolis, IN) that detects coccidioidal galactomannan in urine, serum, plasma, cerebrospinal fluid (CSF), or bronchoalveolar lavage fluid has excellent specificity and is positive in 70% of patients with severe infections. Although the EIA can cross react with other endemic mycoses, interpretation is often straightforward because there is negligible geographic overlap with areas endemic for other mycoses. In addition, a real-time polymerase chain reaction (PCR) assay has been developed to directly detect the fungus in tissue samples. The specificity is high, but sensitivity is not greater than that of routine cultures. Presently, *Coccidioides* spp. PCR is available through reference laboratories.

CSF analysis should be performed in patients with suspected dissemination. Findings in meningitis are similar to those seen with tuberculous meningitis (see Chapter 261). Eosinophilic pleocytosis may be present. Fungal stains and culture are usually negative. Volumes of 10 mL in adults have improved the yield of culture.

Serology

Serologic tests provide valuable diagnostic information but may be falsely negative early in self-limited infections and in immunocompromised patients. Three major methods are used, including EIA, complement fixation (CF), and immunodiffusion. EIA and CF tests are best done in experienced reference laboratories because false-positive results may be reported.

Immunoglobulin (Ig) M–specific antibody becomes measurable in 50% of infected patients 1 week after onset and in 90% of infected patients by 3 weeks. EIA is sensitive and can detect IgM and IgG antibody. It is less specific than other methods; confirmation with immunodiffusion or CF may be needed. IgG antibodies measured by CF appear between the second and third week but can take several months; follow-up testing is needed if tests are negative and clinical suspicion persists. In the presence of CF titers of 1:2 or 1:4, a positive immunodiffusion test can help corroborate significance because it is less sensitive but more specific than EIA. IgG-specific antibody can persist for months, with titers elevated in proportion to the severity of illness. CF titers >1:16 are suggestive of dissemination. Direct comparison of the results of CF (IgG) antibody tests measured by different methodologies should be interpreted with caution. IgG antibody titers used to monitor disease activity should be tested concurrently with serum samples taken earlier in the illness using the same methodology.

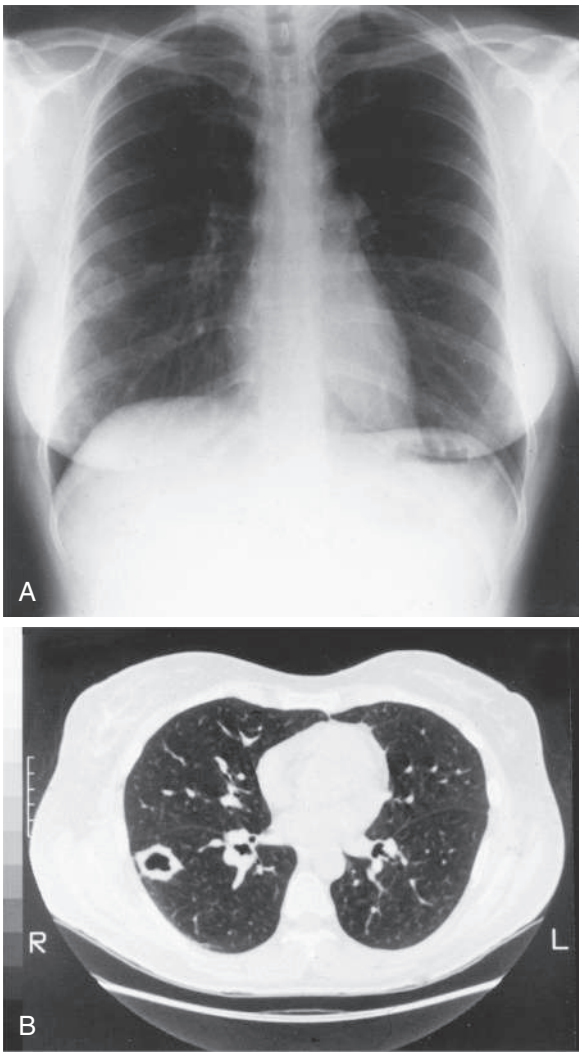

Fig. 286.3 A, Chest radiograph revealing a chronic cavitary lesion in the right lung of a female with coccidioidomycosis. B, CT showing the same cavity in the right lung.

C. immitis antibody is present in CSF in 95% of patients with meningitis and is usually diagnostic. Rarely, "spillover" in patients without meningitis but with high IgG titers in serum can be present in CSF. Isolation of *Coccidioides* spp. from CSF culture of patients with meningitis is uncommon, although culture of large volumes of CSF may improve sensitivity.

Imaging Procedures

During primary infection, chest radiography may be normal or demonstrate consolidation, single or multiple circumscribed lesions, or soft pulmonary densities. Pulmonary infiltrates in the upper lobes are more common in coccidioidal infection than in classic bacterial pneumonia. Hilar and subcarinal lymphadenopathy is often present (see Fig. 286.2). Cavities tend to be thin walled (Fig. 286.3). Pleural effusions vary in size. The presence of miliary or reticulonodular lesions is prognostically unfavorable. Isolated or multiple osseous lesions are usually lytic and affect cancellous bone. Lesions can affect adjacent structures, and vertebral lesions can affect the spinal cord.

TREATMENT

Based on the few rigorous clinical trials performed in adults and the opinions of experts in the management of coccidioidomycosis, consensus treatment guidelines have been developed (Table 286.2).

Table 286.2 Indications for Treatment of Coccidioidomycosis in Adults

INDICATION	TREATMENT
Acute pneumonia, mild	Observe without antifungal treatment at 1- to 3-mo intervals for 2 yr; some experts recommend antifungal treatment
Weight loss >10%; night sweats >3 wk; infiltrates at least half of one lung or parts of both lungs; prominent or persistent hilar lymphadenopathy; complement fixation titers >1:16; inability to work, symptoms >2 mo	Treat with an azole daily for 3-6 mo, with follow-up at 1- to 3-mo intervals for 2 yr
Uncomplicated acute pneumonia, special circumstances: immunosuppression, late pregnancy, Filipino or African ancestry, age >55 yr, other chronic diseases (diabetes, cardiopulmonary disease), symptoms >2 mo	Treat with an azole daily for 3-6 mo, with follow-up at 1- to 3-mo intervals for 2 yr Treat with amphotericin B if in late pregnancy
Diffuse pneumonia: reticulonodular or miliary infiltrates suggest underlying immunodeficiency and possible fungemia	Treat initially with amphotericin B if significant hypoxia or rapid deterioration, followed by an azole for ≥1 yr In mild cases, an azole for ≥1 yr
Chronic pneumonia	Treat with an azole for ≥1 yr
Disseminated disease, nonmeningeal	Treat with an azole for ≥1 yr except in severe or rapidly worsening cases, for which amphotericin B is recommended
Disseminated disease, meningeal	Treat with fluconazole (some add intrathecal amphotericin B) and treat indefinitely

Consultation with experts in an area of endemicity should be considered when formulating a management plan. Many patients with mild primary coccidioidomycosis do not require antifungal therapy. However, those at risk of severe or complicated disease should receive treatment.

Treatment is recommended for HIV-infected patients with active coccidioidomycosis and CD4 counts <250/μL. After successful treatment, antifungals may be stopped if the CD4 count exceeds 250/μL. Treatment should be continued if the CD4 count remains less than 250/μL and should be given indefinitely in all HIV-infected patients with coccidioidal meningitis. Patients with other forms of chronic immunosuppression (e.g., solid organ transplant recipients) may also require lifelong therapy.

First-line agents include oral and intravenous preparations of **fluconazole** (6-12 mg/kg; max 400-1200 mg/day) and itraconazole (2-5 mg/kg PO twice daily; max 400 mg/day). Fluconazole is often the first-line therapy because it has high bioavailability and few side effects. Serum concentrations of itraconazole should be monitored.

Amphotericin B is preferred for initial treatment of severe infections. Amphotericin B deoxycholate is less costly than lipid formulations and is often well tolerated in children. Once a daily dose of amphotericin B deoxycholate of 0.5-1.5 mg/kg/day is achieved, the frequency of administration can be reduced to 3 times weekly. The recommended total dosage ranges from 15-45 mg/kg and is determined by the clinical response. Lipid formulations of amphotericin are recommended for patients with impaired renal function, for patients receiving other nephrotoxic agents, or if amphotericin B deoxycholate is not tolerated. Some experts prefer liposomal amphotericin to treat central nervous system infections because it achieves higher levels in brain parenchyma. Amphotericin B preparations do not cross the blood-brain barrier to effectively treat *Coccidioides* spp., but they can mask the signs of meningitis. Infections during pregnancy should be treated with amphotericin B, because the azoles are potentially teratogenic. Isavuconazole, voriconazole, and posaconazole have been used successfully as salvage therapy.

Primary Pulmonary Infection

Primary pulmonary coccidioidomycosis resolves in 95% of patients without risk factors for dissemination; antifungal therapy does not lessen the frequency of dissemination or pulmonary residua. When it is elected to defer antifungal therapy, visits are recommended at 1- to 3-month intervals for 2 years and as needed.

Patients with significant or prolonged symptoms are more likely to incur benefit from antifungal agents, but there are no established criteria upon which to base the decision. Table 286.2 summarizes commonly used indicators in adults. A treatment trial in adults with primary respiratory infections examined outcomes of antifungal therapy prescribed on the basis of severity and compared them with an untreated group with less severe symptoms; complications occurred only in patients in the treatment group and only in those in whom treatment was stopped. If treatment is elected, a 3- to 6-month course of fluconazole (12 mg/kg/day) or itraconazole (10 mg/kg/day) is recommended.

Diffuse Pneumonia

Diffuse reticulonodular densities or miliary infiltrates, sometimes accompanied by severe illness, can occur in dissemination or after exposure to a large fungal inoculum. In this setting, amphotericin B is recommended for initial treatment, followed thereafter by extended treatment with high-dose fluconazole (see Table 286.2).

Disseminated (Extrapulmonary) Infection

For nonmeningeal infection (see Table 286.2), oral fluconazole and itraconazole are effective for treating disseminated coccidioidomycosis that is not extensive, is not progressing rapidly, and has not affected the central nervous system. Some experts recommend higher doses for adults than were used in clinical trials. A subgroup analysis showed a tendency for improved response of skeletal infections that were treated with itraconazole. Amphotericin B deoxycholate is used as an alternative, especially if there is rapid worsening and lesions are in critical locations. Voriconazole has been used successfully as salvage therapy. The optimal duration of therapy with the azoles has not been clearly defined. Late relapses have occurred after lengthy treatment and favorable clinical response.

Meningitis

Therapy with oral or IV fluconazole is currently preferred for coccidioidal meningitis. In adults, a dosage of 400-1,200 mg/day is recommended. For children, the dose is 12 mg/kg/day. Some experts use intrathecal, intraventricular, or intracisternally administered amphotericin B in addition to an azole, believing that the clinical response may be faster. Patients who respond to the azole should continue treatment indefinitely. Hydrocephalus is common and not necessarily a marker of treatment failure. In the event of treatment failure with azoles, intrathecal amphotericin B deoxycholate is indicated, with or without the azole. Cerebral vasculitis can occur and may predispose to cerebral ischemia, infarction, or hemorrhage. The efficacy of high-dose steroids is unresolved. Salvage therapy with isavuconazole or voriconazole has been effective.

Surgical Management

If a pulmonary cavity is located peripherally or there is recurrent bleeding or pleural extension, excision may be needed. Infrequently, bronchopleural fistula or recurrent cavitation occurs as a surgical

complication; rarely, dissemination can result. Perioperative intravenous amphotericin B may be considered. Drainage of cold abscesses, synovectomy, and curettage or excision of osseous lesions are sometimes needed. Surgical consultation is appropriate if vertebral involvement is identified to evaluate for spinal cord involvement. Local and systemic administration of amphotericin B can be used to treat coccidioidal articular disease.

Monitoring

Patients should be followed closely because late relapses can occur despite treatment, especially in those who are immunosuppressed or have severe manifestations. Testing for CF antibodies should be obtained every 12 weeks during treatment. Most titers decline as the patient improves and ultimately become undetectable. However, titers may remain positive in recovered patients. Progressive or disseminated disease should be considered when titers are persistently elevated (>1:32). These individuals may need thorough physical examinations and imaging studies. After completion of therapy, patients should be evaluated yearly for at least 2 years because some patients relapse (28% of adults who completed 12 months of fluconazole, 18% for itraconazole).

Refractory Disease

In patients who do not improve clinically on appropriate therapy, develop new symptoms, or have persistently elevated CF titers, investigations are indicated for complicated and disseminated disease. Evaluations should assess for joint effusions, skin lesions, and neurologic dysfunction. Consultation with a physician experienced in the management of coccidioidal infections should be considered.

PREVENTION

Prevention relies on education about ways to reduce exposure. Physicians practicing in nonendemic regions should incorporate careful travel histories when evaluating patients with symptoms compatible with coccidioidomycosis.

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Chapter 287

Paracoccidioides brasiliensis

Andrew P. Steenhoff

ETIOLOGY

Paracoccidioidomycosis (South American or Brazilian blastomycosis, Lutz-Splendore-Almeida disease) is the most common systemic mycosis in Latin America. It is a fungal infection that is endemic in South America, with cases also reported in Mexico and Central America. Brazil accounts for more than 80% of all reported cases. The etiologic agent, *Paracoccidioides brasiliensis,* is a thermally dimorphic fungus found in the environment in the mycelial (mold) form and in tissues as yeast.

EPIDEMIOLOGY

P. brasiliensis is a soil-inhabiting microorganism and is ecologically unique to Central and South America. Endemic outbreaks occur mainly in the tropical rainforests of Brazil, with cases scattered in Argentina, Colombia, and Venezuela. There is an increased incidence in areas with moderately high altitude, with high humidity and rainfall, and where coffee and tobacco are grown. Armadillos appear to be a natural reservoir for *P. brasiliensis.* The most common route of infection is by inhalation of conidia. The disease is not usually thought to be contagious, and person-to-person transmission has not been confirmed. Paracoccidioidomycosis is more common among boys after puberty because of the role of estrogen in preventing the transition of conidia to the yeast form. Children account for <10% of the total number of cases.

PATHOGENESIS

Invasion of *P. brasiliensis* into the human body is based on a myriad of fungal components and strategies to bypass host defense mechanisms. With the emergence of CRISPR technology and full access to diverse databanks (such as genomes, transcriptomes, proteomes, metabolomes, lipidomes), investigators are poised to better understand the virulence processes of *P. brasiliensis,* hopefully allowing translation into benefits for patients.

The entry route into the body is via the respiratory tract, and the lungs are the site of primary infection, although not all patients have respiratory symptoms. Once the conidia or hyphal fragments reach the alveoli, yeast transformation takes place. The infection then spreads to the mucous membranes of the nose, mouth, and gastrointestinal tract. Cell-mediated immunity, mainly through lymphocytes and the production of Th-1 cytokines, is crucial to containing the infection. Tumor necrosis factor-α and interferon-γ activated macrophages are responsible for intracellular killing of *P. brasiliensis*. If the initial immune response is not successful, the response may shift toward a Th-2 pattern, which is unable to contain the infection, resulting in clinical progression. The yeast can disseminate by the lymphohematogenous route to skin, lymph nodes, and other organs and remain dormant in lymph nodes, producing a latent infection with reactivation occurring later in life. There are cases of patients who developed disease 30 or more years after leaving an endemic region.

Histopathologically, the yeastlike cells are round, with the parent cell being quite large and surrounded by small buds, giving it the appearance of a ship's wheel. A mixed suppurative and granulomatous inflammatory reaction with areas of necrosis is seen in pulmonary infections. In chronic infections, fibrosis and calcification may be seen. Mucocutaneous infections are typified by ulceration and pseudoepitheliomatous hyperplasia.

CLINICAL MANIFESTATIONS

There are two clinical forms of disease. The **acute** form (juvenile paracoccidioidomycosis) is rare, occurs almost exclusively in children and persons with impaired immunity, and targets the reticuloendothelial system. Pulmonary symptoms may be absent, although chest radiographs often show patchy, confluent, or nodular densities. Patients typically present acutely with fever, malaise, wasting, lymphadenopathy, and abdominal enlargement from intraabdominal lymphadenopathy. Hepatomegaly and splenomegaly are nearly constant. Localized bony lesions have been reported in children and can progress to systemic disease. Multifocal osteomyelitis, arthritis, and pericardial effusions can also occur. Nonspecific laboratory findings include anemia, eosinophilia, and hypergammaglobulinemia. Acute paracoccidioidomycosis has a 25% mortality rate. Hepatic involvement associated with jaundice and hypoalbuminemia may confer a worse prognosis.

Adults develop a **chronic** progressive illness that manifests initially with flulike symptoms, fever, and weight loss (adult paracoccidioidomycosis). Pulmonary infection develops with dyspnea, cough, chest pain, and hemoptysis. Findings on physical examination are scant, although chest radiographs can show infiltrates that are disproportionate with mild clinical findings. Mucositis involving the mouth and its structures as well as the nose can manifest as localized pain, change in voice, or dysphagia. Lesions can extend beyond the oral cavity onto the skin. Generalized lymphadenopathy, hepatosplenomegaly, and

adrenal involvement (seen in 15–50% of cases) can lead to Addison disease. Meningoencephalitis and central nervous system granulomas can occur as presenting or secondary symptoms. Adults with extensive exposure to soil, such as farmers, are most likely to develop the chronic form of the disease.

DIAGNOSIS

Demonstration of the fungus by direct wet mount (potassium hydroxide) preparation of sputum, exudate, or pus supports the diagnosis in many cases. Histopathologic examination of biopsy specimens using special fungal staining techniques is also diagnostic. Immunohistochemistry using monoclonal antibodies to specific glycoproteins can also be done on tissue sections. Culture of the fungus on Sabouraud dextrose or yeast extract agar confirms the diagnosis. Antibodies to *P. brasiliensis* can be demonstrated in most patients. Serial antibody titers and lymphocyte proliferative responses to fungal antigens are useful for monitoring the response to therapy. The 43-kDa glycoprotein (gp43) is present in sera of more than 90% of patients with paracoccidioidomycosis by immunodiffusion (the most commonly used diagnostic test) and in 100% of patients by immunoblotting. A latex particle agglutination test using pooled crude fungal exoantigens is being developed for the detection of anti–*P. brasiliensis* antibodies and has shown 92% agreement with the immunodiffusion test. Newer diagnostic methods that might prove to be very useful in the future include polymerase chain reaction, detection of gp43, and capture enzyme-linked immunosorbent assay to detect specific immunoglobulin E in patient sera. Skin testing with paracoccidioidin is not reliable, because 30–50% of patients with active disease are nonreactive initially, and a positive test indicates previous exposure but not necessarily active disease.

TREATMENT

Itraconazole (5-10 mg/kg/day with a maximum dose of 200 mg/day) orally for 6 months is the treatment of choice for paracoccidioidomycosis. **Fluconazole has also been used**, but high doses (≥600 mg/day) and longer treatment periods are required. A small number of patients have been treated with other azoles, including **voriconazole, posaconazole, and isavuconazole**. These drugs are potential substitutes for itraconazole but are more costly and can have interactions with other drugs. **Terbinafine** is an allylamine that has potent in vitro activity against *P. brasiliensis* and has been used for successful treatment of paracoccidioidomycosis. **Amphotericin B** is recommended for disseminated disease and if other therapies fail. Therapy with sulfonamide compounds, including sulfadiazine, TMP-SMX (trimethoprim 8-10 mg/kg/day to maximum of 160 mg, sulfamethoxazole 40-50 mg/kg/day to maximum of 800 mg), and dapsone, have been used historically and are generally less expensive than the newer azoles and allylamines. The primary disadvantage is that the treatment course is very long, lasting months to years, depending on the agent selected. Relapse can occur after any form of therapy, including with amphotericin B. In selected patients with intense inflammation in sites such as the central nervous system or with lung lesions causing respiratory insufficiency, there is some evidence that use of prednisone for 1-2 weeks concomitantly with antifungal therapy reduces inflammation more effectively and may be of benefit. Occasionally children develop paradoxical clinical worsening during treatment, including new lymph node enlargement, fistula formation, fever, and weight loss. In this circumstance, steroids are also recommended.

Two therapies currently under investigation include the use of **curcumin**, an antioxidant found in the Indian spice turmeric, and the calcineurin inhibitor **cyclosporine**. Curcumin was found to have more antifungal activity than fluconazole against *P. brasiliensis* when studied in vitro using human buccal epithelial cells. Cyclosporine blocks the thermodimorphism of *P. brasiliensis*. Animal models demonstrate that fungal whole cells, purified antigens, peptides, and DNA vaccines have great potential toward the development of a vaccine for use in humans.

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Chapter 288

Sporotrichosis (*Sporothrix schenckii*)

Andrew P. Steenhoff

ETIOLOGY

Sporotrichosis is a rare fungal infection that occurs worldwide, both sporadically and in outbreaks, and is caused by *Sporothrix schenckii,* which exhibits temperature dimorphism, existing as a mold at environmental temperatures (25–30°C [77–86°F]) and as a yeast in vivo (37°C [98.6°F]). *S. schenckii* comprises a group of cryptic, phylogenetically related species, including *S. brasiliensis, S. chilensis, S. globosa, S. luriei, S. mexicana,* and *S. pallida*. *S brasiliensis* is the most virulent species.

EPIDEMIOLOGY

S. schenckii is found throughout the world, but most cases of sporotrichosis are reported from South America, Central America, and Asia, including Japan, India, and China. In the United States, the majority of cases have occurred in the Midwest, particularly in areas along the Mississippi and Missouri rivers. The fungus is found in decaying vegetation and has been isolated most commonly from sphagnum moss, rosebushes, barberry, straw, and some types of hay. Sporotrichosis can occur as an occupational disease among farmers, gardeners, veterinarians, and laboratory workers. Transmission from bites and scratches of animals, most commonly cats and armadillos, has occurred. Reports of human-to-human transmission are rare. Sporotrichosis has rarely been reported in infants. The mechanism of transmission in children may be zoonotic but usually is unclear. In one endemic area of Peru, the incidence of infection is greater in children than in adults; risk factors for infection in these children are playing in crop fields, living in houses with dirt floors, and owning a cat.

PATHOGENESIS

Disease in humans usually follows cutaneous inoculation of the fungus into a minor wound. Pulmonary infection can result from the inhalation of large numbers of spores. Disseminated infection is unusual but can occur in immunocompromised patients after ingestion or inhalation of spores. The cellular immune response to *S. schenckii* infection is both neutrophilic and monocytic. Histologically, the coexistence of noncaseating granulomas and microabscess formation is characteristic. T-cell–mediated immunity appears to be important in limiting infection, and antibody does not protect against infection. As a result of the paucity of organisms, it is usually difficult to demonstrate the fungi in biopsy specimens.

CLINICAL MANIFESTATIONS

Cutaneous sporotrichosis is the most common form of disease in all age-groups. Cutaneous disease may either be lymphocutaneous or fixed cutaneous, the former being much more common (Fig. 288.1). Lymphocutaneous sporotrichosis accounts for more than 75% of reported cases in children and occurs after traumatic subcutaneous inoculation. After a variable and often prolonged incubation period (1-12 weeks), an isolated, painless erythematous papule develops at the inoculation site. The initial lesion is usually on an extremity in adults but is often on the face in children. The original papule enlarges and ulcerates. Although the infection might remain limited to the inoculation site (fixed cutaneous form), satellite lesions follow lymphangitic spread and appear as multiple tender subcutaneous nodules tracking along the lymphatic channels that drain the lesion. These secondary nodules are subcutaneous granulomas that adhere to the overlying skin and subsequently ulcerate. Sporotrichosis does not heal spontaneously, and these ulcerative lesions can persist for years if untreated. Systemic signs and symptoms are uncommon.

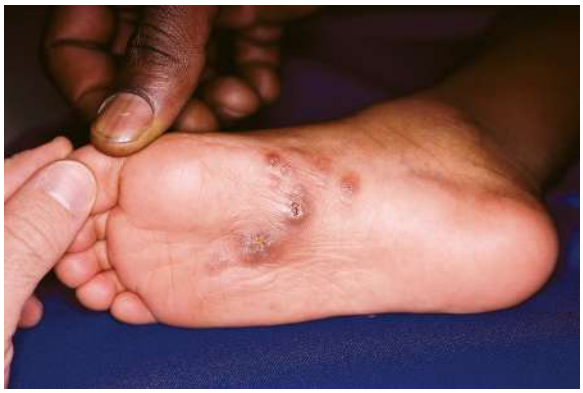

Fig. 288.1 Sporotrichosis. Erythematous papules and nodules on the plantar surface with early lymphangitic (sporotrichoid) spread. *(From Paller AS, Mancini AJ. Hurwitz Clinical Pediatric Dermatology, 5th ed. Philadelphia: Elsevier; 2016: Fig. 17.48.)*

Extracutaneous sporotrichosis is rare in children, and most cases are reported in adults with underlying medical conditions, including AIDS and other immunosuppressing diseases. The most common form of extracutaneous sporotrichosis involves infection of the bones and joints. Pulmonary sporotrichosis usually manifests as a chronic pneumonitis similar to the presentation of pulmonary tuberculosis. Erythema nodosum is an immunoreactive manifestation.

DIAGNOSIS

Cutaneous and lymphocutaneous sporotrichosis must be differentiated from other causes of nodular lymphangitis, including atypical mycobacterial infection, nocardiosis, leishmaniasis, tularemia, melioidosis, cutaneous anthrax, and other systemic mycoses, including coccidioidomycosis. Definitive diagnosis requires isolation of the fungus from the site of infection by culture. Special histologic staining such as periodic acid–Schiff and methenamine silver is required to identify yeast forms in tissues, which are typically oval or cigar-shaped. In spite of special staining techniques, diagnostic yield from biopsy specimens is low because of the small number of organisms present in the tissues. In cases of disseminated disease, demonstration of serum antibody against *S. schenckii*–related antigens can be diagnostically useful. Serologic testing is not commercially available but is offered by specialized laboratories, including the Centers for Disease Control and Prevention in the United States.

TREATMENT

Although comparative trials and extensive experience in children are not available, **itraconazole is the recommended treatment of choice for infections outside the central nervous system**. The recommended dosage for children is 5-10 mg/kg/day orally, with an initial maximum dose of 200 mg daily, which may be increased up to 400 mg daily if there is no initial response. Alternatively, **younger children with cutaneous disease only may be treated with a saturated solution of potassium iodide** (1 drop, 3 times daily by mouth, increasing as tolerated to a maximum of 1 drop/kg of body weight or 40-50 drops, 3 times daily, whichever is lowest). Adverse reactions, usually in the form of nausea and vomiting, should be managed with temporary cessation of therapy and reinstitution at a lower dosage. Therapy is continued 2-4 weeks after cutaneous lesions have resolved, which usually takes at least 6-12 weeks. **Terbinafine has been used successfully to treat cutaneous sporotrichosis but is reported to have lower cure rates and higher relapse rates than itraconazole.** Further clinical efficacy data are needed to routinely recommend its use. **Amphotericin B is the treatment of choice for pulmonary infections, disseminated infections, central nervous system disease, and infections in immunocompromised persons.** Oral **fluconazole** 12 mg/kg daily (maximum dose, 400-800 mg daily) can be used if other agents are not tolerated. **Posaconazole** shows promise, but further data are needed.

Therapy with azoles or a saturated solution of potassium iodide should not be used in pregnant women. **Amphotericin B can be used safely for cases of pulmonary or disseminated disease in pregnancy.** Pregnant patients with cutaneous disease can be treated with local hyperthermia or can have therapy delayed until the pregnancy is completed. Hyperthermia involves heating the affected area to 42–45°C (107.6–113°F) using water baths or heating pads and works by inhibiting growth of the fungus. Dissemination to the fetus does not occur, and the disease is not worsened by pregnancy. **Surgical debridement has a role in the treatment of some cases of sporotrichosis, particularly in osteoarticular disease.**

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Chapter 289

Mucormycosis

Rachel L. Wattier and William J. Steinbach

ETIOLOGY

Mucormycosis refers to opportunistic invasive fungal infections caused by fungi of the order Mucorales. These organisms are found commonly in soil and decaying organic matter and are distributed worldwide. Mucormycosis was previously called *zygomycosis,* but this terminology has been abandoned because of reclassification of organisms using molecular phylogenetic analysis. The most common disease-causing genera of Mucorales are *Rhizopus, Mucor,* and *Lichtheimia* (formerly *Absidia*). Infections caused by organisms of the genera *Rhizomucor, Cunninghamella, Saksenaea*, *Apophysomyces,* and others are less common. Mucormycosis in humans is characterized by a rapidly evolving course, tissue necrosis, and blood vessel invasion.

EPIDEMIOLOGY

Mucormycosis is primarily a disease of persons with underlying conditions that impair host immunity, though it can sometimes manifest with cutaneous and soft tissue infections at sites of trauma in immunocompetent hosts. Predisposing factors include poorly controlled diabetes, especially if complicated by ketoacidosis, and profound immunocompromise resulting from therapy for hematologic malignancies (especially with prolonged neutropenia), stem cell or organ transplantation, and/or high-dose corticosteroid therapy. Other risk factors include iron overload and prematurity. Mucormycosis may develop as a breakthrough infection in patients receiving voriconazole antifungal prophylaxis; voriconazole lacks activity against the Mucorales. Therefore breakthrough infections or nonresponse to voriconazole should prompt increased consideration of mucormycosis.

Mucormycosis is the second most common invasive mold infection in immunocompromised hosts after aspergillosis, and its incidence is increasing because of an increase in the number and improved survival of immunocompromised persons at risk. A contemporary review of reported pediatric cases from 2008 to 2017 found a 32% case fatality rate across all included cases. Mortality rates vary depending on disease manifestations of mucormycosis and underlying patient conditions, with worse outcomes observed in patients with more extensive disease manifestations and those with irreversible predisposing risk factors. However, observational studies suggest that pediatric patients with mucormycosis generally have more favorable outcomes compared to adults and that outcomes may be improving over time with contemporary therapeutic approaches.

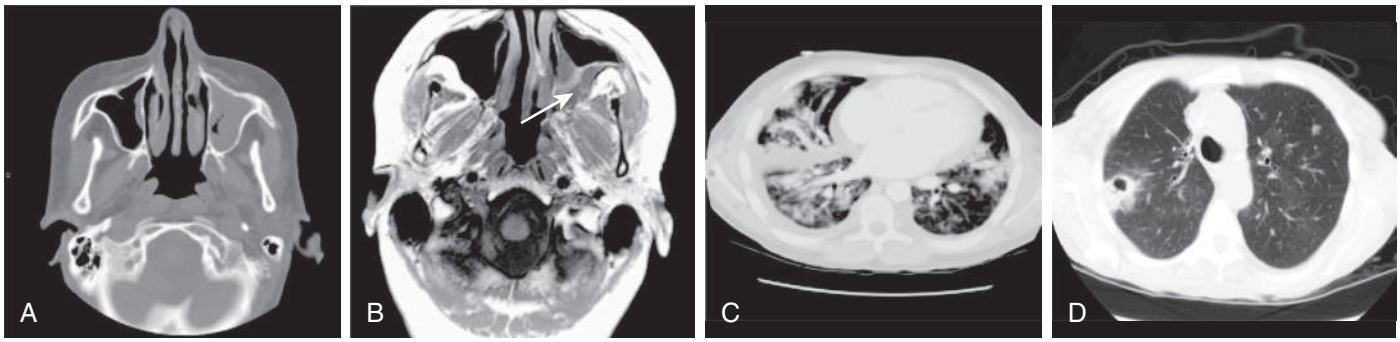

Fig. 289.1 Radiographic findings in mucormycosis. **A,** CT scan shows left maxillary sinus air-fluid level, similar to bacterial sinusitis. **B,** Magnetic resonance image reveals T2 signal hyperintensity in the left pterygoid musculature *(arrow)* in conjunction with a left maxillary sinus air-fluid level. **C,** Multiple heterogeneous nodular and consolidative lesions with a large pulmonary vessel infarct and modest pleural effusions are shown in a patient with cancer and pulmonary mucormycosis. **D,** Contrast-enhanced CT scan demonstrates a cavity within a dense infiltrate in a patient with acute myelogenous leukemia and pulmonary mucormycosis. *(Courtesy Dr. Edith Marom, University of Texas, MD Anderson Cancer Center, Houston, Texas.)*

PATHOGENESIS

Spores can be inhaled from the environment into the upper and/or lower airways, inoculated at sites of cutaneous trauma, or, less commonly, ingested. If, because of impaired immune response, spores are not cleared by macrophages and neutrophils, they germinate into hyphae, resulting in local invasion and tissue destruction. Mucormycosis is characterized by extensive angioinvasion, resulting in thrombosis, infarction, and tissue necrosis, which can limit the delivery of antifungal agents and leukocytes to the site of infection and contribute to dissemination of the infection to other organs.

Many of the Mucorales can scavenge iron, an element essential for cell growth, from the host. The iron chelator deferoxamine paradoxically increases iron availability and uptake by members of the Mucorales. Acidosis diminishes the phagocytic and chemotactic ability of neutrophils while increasing the availability of unbound iron, likely explaining the susceptibility to mucormycosis among individuals with uncontrolled acidosis.

CLINICAL MANIFESTATIONS

Mucormycosis can occur as any of several clinical syndromes, including rhinocerebral, pulmonary, cutaneous or subcutaneous, gastrointestinal, or disseminated disease. The initial symptoms and signs of each may be subtle and not easily distinguishable from other infections, so it is important to have a high index of suspicion for the disease in patients at risk.

Rhinocerebral mucormycosis is the most common form and can involve the palate, sinuses, orbit, and/or adjacent structures with potential progression to the brain. Initial symptoms are similar to sinusitis and include headache, retroorbital pain, fever, and nasal discharge. Infection can evolve rapidly or be slowly progressive. Orbital involvement manifests as periorbital edema, proptosis, ptosis, and/or ophthalmoplegia. The nasal discharge may be dark and bloody; involved tissues become red, then violaceous, and then black as vessel thrombosis and tissue necrosis occur. Extension beyond the nasal cavity into the mouth is common and may be apparent as palatal lesion(s). Destructive paranasal sinusitis with bone involvement and possible intracranial extension can be demonstrated by computed tomography (CT) or magnetic resonance imaging (MRI) (Fig. 289.1). Rhinocerebral mucormycosis can be complicated by cavernous sinus thrombosis or thrombosis of the internal carotid artery. Intracranial extension can occur directly from the nasal cavity and sinuses, usually to the frontal or frontotemporal lobes, or hematogenously, commonly involving the occipital lobe or brainstem.

Pulmonary mucormycosis usually occurs in profoundly neutropenic patients and presents similarly to other pulmonary invasive mold infections. Manifestations can include fever, tachypnea, productive cough, pleuritic chest pain, and hemoptysis; however, initial symptoms may be minimal. A wide range of pulmonary radiographic findings, including pulmonary nodules, consolidation, cavitary lesion(s), and lung infarct(s), are recognized (see Fig. 289.1). Although the radiographic findings overlap with other pulmonary invasive fungal infections, the presence of multiple nodules (≥10), pleural effusion(s), or the **reverse halo sign**, a focal area of ground-glass opacity surrounded by a ring of consolidation, is more suggestive of mucormycosis.

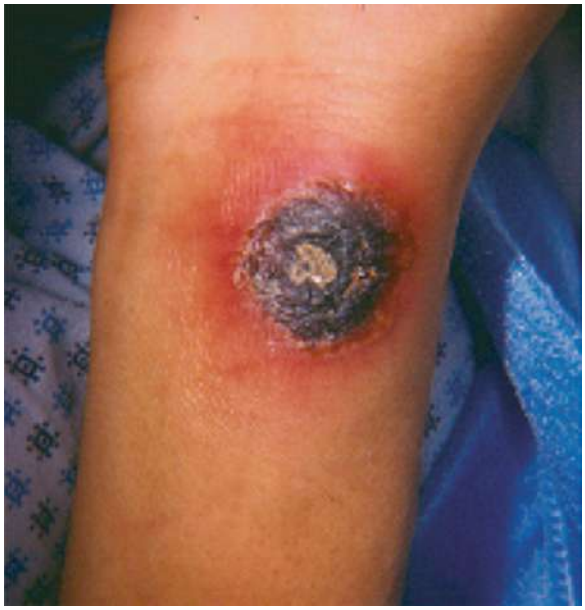

Fig. 289.2 Cutaneous presentation of mucormycosis. Chronic, nonhealing ulcer with necrosis after traumatic inoculation. *(From Kontoyiannis DP, Lewis RE. Agents of mucormycosis and entomophthoramycosis. In Bennett JF, Dolin R, Blaser MJ (eds). Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th ed. Philadelphia: Elsevier, 2015. Fig. 260-6A; Courtesy Drs. Gerald Bodey and Saud Ahmed, University of Texas, MD Anderson Cancer Center, Houston, TX.)*

Cutaneous and soft tissue mucormycosis can be primary, resulting from direct inoculation at sites of trauma, including burns, surgical sites, or vascular access sites, or secondary, resulting from hematogenous dissemination to the skin from another primary site. Primary cutaneous lesions manifest initially as painful erythematous papules that ulcerate, leaving a black necrotic center. In contrast, secondary cutaneous lesions from hematogenous seeding tend to be nodular, with minimal destruction of the epidermis. Either may be invasive locally, progressing through multiple tissue layers, including muscle, fascia, and bone (Fig. 289.2), with accompanying tissue necrosis.

Gastrointestinal mucormycosis is the least common form of disease except in preterm neonates, in whom it is the most commonly reported form of mucormycosis. Manifestations include abdominal pain, nausea, vomiting, gastrointestinal bleeding, obstruction, and perforation. Any part of the gastrointestinal tract can be involved, with the stomach followed by colon and ileum being the most commonly

affected. The clinical presentation in neonates mimics necrotizing enterocolitis, sometimes with a palpable abdominal mass. Recognition of gastrointestinal mucormycosis is challenging given its rarity and overlap in presentation with other gastrointestinal diseases. It is associated with particularly high mortality and commonly not diagnosed until postmortem examination.

Disseminated mucormycosis can develop from any site of primary disease but is more commonly associated with initial pulmonary disease. It carries the highest mortality rates seen with mucormycosis, especially among immunocompromised persons. The clinical presentation varies based on the involved sites. Dissemination of mucormycosis to the brain is of particular concern and alters management and prognosis, so many experts recommend brain imaging routinely, even in the absence of neurologic symptoms.

DIAGNOSIS

All forms of mucormycosis are considered medically emergent, and some (e.g., rhinocerebral) are also surgical emergencies. Diagnostic evaluation and initiation of treatment should be pursued simultaneously with a coordinated multidisciplinary approach. The diagnosis depends on early recognition of compatible clinical findings in a patient with predisposing risk factors. Once mucormycosis is suspected, cross-sectional imaging should be performed to define the site(s) of disease as indicated based on the clinical presentation, and tissue from the site of disease should be obtained for diagnostic evaluation, along with initial surgical debridement for rhinocerebral or cutaneous mucormycosis. The diagnosis relies on direct morphologic identification of mycotic elements from culture or tissue biopsy specimens. Mucorales appear as broad (5-25 μm in diameter), infrequently septate (denoted as aseptate or pauci-septate on pathology), thin-walled hyphae, branching irregularly at right angles when stained with Gomori methenamine silver (GMS) or hematoxylin and eosin. Organisms may be challenging to identify reliably by morphology from tissue specimens; immunohistochemistry or molecular diagnostic tests can provide more reliable identification to the species level.

Mucorales can be cultured on standard laboratory media; however, cultures from nontissue specimens, such as bronchoalveolar lavage fluid, have poor sensitivity. Mucorales hyphae can also be easily disrupted, decreasing the yield of cultures. Submitting fresh tissue with careful handling to avoid disruption (e.g., grinding) can improve yield. When an organism is visualized by histopathology but not recovered in culture, molecular methods may improve detection. Though Mucorales can be culture contaminants, isolation in a susceptible host should prompt consideration of clinical disease. Noninvasive fungal biomarkers, such as galactomannan and 1,3-β-D-glucan, do not detect the causative agents of mucormycosis. Though molecular tests are available to detect Mucorales and other fungal pathogens directly from blood samples, these have not yet been sufficiently validated to replace tissue-based diagnosis.

TREATMENT

Though mucormycosis can be aggressive and difficult to treat, with high mortality rates, more favorable outcomes can be achieved via early recognition and prompt institution of medical therapy combined with extensive surgical debridement of devitalized tissue to the extent possible. It is essential to reverse predisposing factors, such as neutropenia, hyperglycemia, and/or acidosis, and to withdraw immunosuppression or deferoxamine therapy, if applicable.

Given the rarity of mucormycosis, there are few clinical trials to guide optimal therapy. Based on clinical experience, observational data, and small clinical trials, the European Confederation of Medical Microbiology and the Mycoses Study Group published "global guidelines" for mucormycosis in 2019. **Lipid formulations of amphotericin B, with preference for liposomal amphotericin B, are strongly recommended as first-line therapy for all forms of mucormycosis in all age-groups.** It is recommended to initiate therapy with the full dose of liposomal amphotericin B of at least 5 mg/kg/day, with consideration up to 10 mg/kg/day, and 10 mg/kg/day is recommended for treatment of central nervous system infection. Other antifungals with activity against the Mucorales include isavuconazole (administered as the prodrug isavuconazonium sulfate) and posaconazole; however, there is less experience with these antifungals for initial or "primary therapy" of mucormycosis, and their activity can vary based on causative species and specific antifungal susceptibility patterns. Guidelines moderately recommend primary therapy with IV formulations of either posaconazole or isavuconazole in patients with significant preexisting renal impairment, because of potential nephrotoxicity with amphotericin B formulations. However, some experts prefer liposomal amphotericin B for patients with severe or progressive mucormycosis even in the setting of renal impairment.

There is increasing pharmacokinetic and safety data supporting the use of isavuconazole and posaconazole in pediatric patients, though posaconazole pharmacokinetics vary by formulation, and the immediate-release oral suspension does not reliably achieve optimal target concentrations. Therefore IV or delayed-release formulations of posaconazole are preferred. **Isavuconazole or posaconazole is recommended for specific roles in the treatment of mucormycosis, the most established role being for "salvage therapy" in patients who either do not respond adequately to initial amphotericin B–based therapy or who develop intolerance precluding continuation of amphotericin B-based therapy.** In the case of inadequate response, many experts recommend combination therapy, including liposomal amphotericin B with either isavuconazole or posaconazole, so that the "backbone" therapy with liposomal amphotericin B can also be continued. Given the rapidly progressive course and severe outcomes associated with mucormycosis, primary combination therapy (a regimen with multiple antifungal agents from the beginning) is also frequently used in practice. However, there is currently insufficient evidence to determine whether initial combination therapy is beneficial over monotherapy with liposomal amphotericin B. The results of animal model studies and observational clinical studies have varied, and some of the better-quality observational studies have not shown a clear benefit. **Combination therapy with liposomal amphotericin B and isavuconazole or posaconazole is therefore marginally recommended in the global mucormycosis guidelines.** Some clinicians have given combination therapy with an echinocandin antifungal (e.g., caspofungin) added to amphotericin B–based therapy based on animal model data and limited clinical studies showing potential benefit with this combination. However, this combination has been less preferred recently, partly because echinocandins lack intrinsic activity against the Mucorales and because increasing data favor isavuconazole or posaconazole for salvage therapy.

Given the complex considerations when selecting and monitoring antifungal therapy for mucormycosis, and also considering surgical approaches, which are well-established for rhinocerebral and cutaneous mucormycosis and favored when possible for localized pulmonary mucormycosis, a multidisciplinary approach with expert guidance is necessary. Patients with mucormycosis should be monitored with frequent repeat imaging to evaluate their response to therapy, and multiple surgical procedures are often necessary to achieve stabilization of disease.

The duration of antifungal therapy is individualized but is usually continued until all clinical and radiographic findings have resolved and the patient shows reconstitution or significant improvement of their immune response. Patients with a good response to initial IV antifungal therapy may be converted to maintenance therapy with enteral isavuconazole or posaconazole.

Various adjunctive therapies have been reported for mucormycosis; the most commonly used are treatments such as hematopoietic growth factors to reverse neutropenia as a predisposing factor. Hyperbaric oxygen has been used anecdotally as an adjunctive therapy but is not well established and not routinely recommended. Iron chelation with deferasirox has been tried as salvage therapy in refractory mucormycosis but is currently not recommended because of adverse outcomes in a small clinical trial. The overall emphasis of disease management should remain on optimizing the antifungal and surgical therapies and reversing any modifiable predisposing conditions.

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Chapter 290

Pneumocystis jirovecii

Francis Gigliotti and Terry W. Wright

Pneumocystis jirovecii pneumonia (interstitial plasma cell pneumonitis) in an immunocompromised person is a life-threatening infection. Primary infection in the immunocompetent individual is usually subclinical and goes unrecognized. The disease most likely results from new or repeat acquisition of the organism rather than reactivation of latent organisms. Even in the most severe cases, with rare exceptions, the pathogen remains localized to the lungs.

ETIOLOGY

The genus ***Pneumocystis*** contains a group of common extracellular **fungal pathogens,** which are found worldwide and exist exclusively in the lungs of mammalian hosts as **obligate biotrophs**. The initial taxonomic placement of *Pneumocystis* was ambiguous. However, comparative genomics definitively positioned *Pneumocystis* among the ascomycetous fungi, despite sharing certain morphologic features and drug susceptibility profiles with protozoa. Detailed information on the basic biology and life cycle of *Pneumocystis* is incomplete because of the inability to grow these organisms in culture. However, phenotypic and genotypic analyses show that the *Pneumocystis* organisms infecting each individual mammalian host are unique and restricted to that host. Current knowledge suggests that a distinct *Pneumocystis* evolved in each host species and ultimately adapted to its specific host in a manner that prevented transmission and replication in heterologous host species.

The clear biological distinction of *Pneumocystis* from different mammalian hosts led to the **division of *Pneumocystis* into multiple species** that are named according to the host from which they are derived. Current convention uses the name ***P. jirovecii*** to refer to the *Pneumocystis* species infecting humans, whereas those infecting rats and mice are designated *P. carinii* and *P. murina*, respectively. Clinicians should be aware that the term *P. carinii* was originally used for all *Pneumocystis* regardless of host species of origin and may sometimes refer to human-derived *Pneumocystis* in older medical literature.

EPIDEMIOLOGY

P. jirovecii is found worldwide, but a natural habitat outside of the human host has not been identified. Serologic surveys show that most humans are exposed to *P. jirovecii* before 4 years of age, and polymerase chain reaction (PCR) analyses has confirmed the prevalence of *P. jirovecii* in both children and adults. Full genome sequencing of three *Pneumocystis* species, including *P. jirovecii*, revealed that ***Pneumocystis* has lost critical genes required for autonomous survival and growth**. Thus currently available evidence suggests that *P. jirovecii* only lives in the lungs of humans and that it persists in the human population through repeat subclinical or mild infection of immunocompetent adults and children. Gene loss helps to explain the inability to either culture *Pneumocystis* or identify a natural reservoir outside the host. The universal prevalence of *P. jirovecii* in the human population likely explains why *P. jirovecii* is a common opportunistic infection in immunocompromised people not receiving prophylaxis.

The mode of *Pneumocystis* transmission to humans is undefined, but animal-to-animal airborne transmission has been clearly demonstrated. Animal-to-human transmission is unlikely because of the stringent host-species restriction of *Pneumocystis* species. Person-to-person transmission is likely but has not been directly proven. However, the appearance of geographically clustered *Pneumocystis* cases caused by genetically similar *P. jirovecii* strains supports the occurrence of community spread among immunocompromised patients. In addition, *P. jirovecii* has been detected in air samples collected in close proximity to patients with *Pneumocystis* pneumonia. **Thus it seems likely that *P. jirovecii* is passed from human to human through an airborne route**.

Most humans are infected with *P. jirovecii* during early childhood. In the immunocompetent child, these infections are usually asymptomatic or mild and indistinguishable from other common childhood respiratory infections. Pneumonia caused by *P. jirovecii* occurs almost exclusively in severely immunocompromised hosts, including those with congenital or acquired immunodeficiency disorders, malignancies, or transplanted organs. Patients with primary immunodeficiency diseases at risk for infection include severe combined immunodeficiency disease, X-linked CD40 ligand deficiency, major histocompatibility complex class II deficiency, nuclear factor kappa B essential modulator (NEMO) deficiency, dedicator of cytokinesis 8 (DOCK8) deficiency, Wiskott-Aldrich syndrome, and caspase recruitment domain 11 (CARD11) deficiency. *P. jirovecii* can be found in the lungs of infants who have died with the diagnosis of sudden infant death syndrome (SIDS). However, further study concluded that *P. jirovecii* is likely not the cause of SIDS but instead that there is overlap in the timing of the primary *P. jirovecii* infection and the onset of SIDS. Recent studies have described pathologic changes in the lungs of infants during primary infection and have suggested a possible association of *P. jirovecii* with respiratory distress syndrome in preterm infants.

Without chemoprophylaxis, approximately 40% of infants and children with AIDS, 70% of adults with AIDS, 12% of children with leukemia, and 10% of patients with organ transplants develop *P. jirovecii* pneumonia. Epidemics that occurred among debilitated infants in Europe during and after World War II are attributed to malnutrition. Currently, **the use of novel immunosuppressive agents for the treatment of inflammatory syndromes, autoimmune disease, and malignancy has expanded the at-risk population**. For example, the addition of anti–tumor necrosis factor (TNF) therapy to the management of patients with inflammatory bowel disease or rheumatoid arthritis has resulted in a demonstrable increase in *P. jirovecii* pneumonia in these patient populations. The use of rituximab or ibrutinib in patients with hematologic malignancies also increases the risk of *Pneumocystis* pneumonia.

PATHOGENESIS

Two forms of *P. jirovecii* are found in the alveolar spaces: the cyst form (or ascus), which are 5-8 μm in diameter and contain up to eight pleomorphic intracystic bodies (sporozoites or ascospores); and trophic forms (or trophozoites), which are 2-5 μm cells derived from excysted sporozoites. The names sporozoite and trophozoite were based on the morphologic similarities to protozoa. However, the inclusion of *Pneumocystis* among the fungi led to the adoption of names such as ascus and ascospore, which are derived from fungal terminology. The cyst form accounts for 5–10% of the *Pneumocystis* in the lung. The cyst has a thick wall composed of β-glucan, which is thought to be a major driver of pulmonary inflammation during *Pneumocystis* pneumonia. *P. jirovecii* trophic forms typically constitute approximately 90% of the *Pneumocystis* in the lungs and have the ability to suppress inflammation induced by the cyst form. Trophic forms attach firmly to the type 1 pneumocytes lining the alveoli, possibly by adhesive bridging proteins such as fibronectin or mannose-dependent ligands. The consequences of this interaction are unclear, but it may provide signals or nutrients to *Pneumocystis* to stimulate growth. As the infection progresses, this interaction may contribute to the characteristic alveolar damage.

Control of *P. jirovecii* infection in immunocompetent people requires functional cell-mediated immunity, and patients with AIDS show an increased incidence of *Pneumocystis* pneumonia as $CD4^+$ T-lymphocyte counts decrease. Before widespread prophylaxis of AIDS patients, life-threatening *Pneumocystis* pneumonia occurred in a high percentage of these patients when $CD4^+$ T cell counts dropped below 200 cells/mm^3. **$CD4^+$ T cell counts provide a useful indicator in both older children and adults of the need for prophylaxis against *Pneumocystis* pneumonia**. Although normally functioning $CD4^+$ T cells are central to controlling *P. jirovecii* infection, the final effector pathway for destruction of *P. jirovecii* is poorly understood but likely requires macrophages. $CD4^+$ T cells may activate macrophages for phagocytosis and clearance of *Pneumocystis* through local cytokine secretion, and also provide help for the production of specific antibody.

Anti-*Pneumocystis* antibody has the potential to facilitate fungal clearance through opsonization, complement activation, or interfering with *Pneumocystis* binding to lung epithelial cells.

Clinical investigation as well as work in animal models has revealed that the host's immune response to *Pneumocystis* infection is a major contributor to the pathogenesis of *Pneumocystis* pneumonia. Human studies found that the severity of disease correlates with the degree of lung inflammation but not with fungal burden. Furthermore, patients with profound AIDS-related immunosuppression present with higher *P. jirovecii* burdens but better lung function than non-AIDS patients with *Pneumocystis* pneumonia and with greater retained immune function. A classic AIDS-related presentation of *Pneumocystis* pneumonia can be modeled in $CD4^+$ T cell–depleted rodents and simian immune virus–infected nonhuman primates. In the absence of $CD4^+$ T cells a progressive accumulation of $CD8^+$ T cells occurs in a likely attempt to fight the infection. These cells do not provide effective host defense against *Pneumocystis*, but instead directly contribute to *Pneumocystis* pneumonia–related immunopathogenesis and lung injury. Similar to humans with *Pneumocystis* pneumonia, polymorphonuclear leukocytes (PMNs) also accumulate in the lungs of animals as *Pneumocystis* pneumonia progresses. These phagocytes do not contribute meaningfully to either *Pneumocystis* eradication or immunopathogenesis. However, as is the case in human patients, there is a strong correlation between the number of PMNs in the lung and the severity of disease.

In the complete absence of an adaptive immune response, as can be modeled in severe combined immunodeficient (SCID) mice, *Pneumocystis* infection produces little alteration in lung histology or function until late in the course of the disease. However, if congenic lymphocytes are transferred to *Pneumocystis*-infected SCID mice, an acute $CD4^+$ T cell–dependent immune response is mounted against the *Pneumocystis*. There is rapid onset of pulmonary inflammation, surfactant dysfunction, severe respiratory impairment, and significant hypoxia, mimicking the characteristic changes of *Pneumocystis* pneumonia in humans. The functional $CD4^+$ T cells generate an effective immune response against the existing infection, but also cause inflammation and lung injury. $CD8^+$ T cells are typically ineffective in the eradication of *Pneumocystis* but may modulate the $CD4^+$ T cell response to lessen the immune-mediated damage. **The functional interactions of T cell subsets in patients with differing and often fluctuating immune status are likely responsible for the variations in presentation and outcome of *Pneumocystis* pneumonia**.

PATHOLOGY

The histopathologic features of *P. jirovecii* pneumonia are of two types. The first type is infantile interstitial plasma cell pneumonitis, which was observed in epidemic outbreaks in debilitated infants 3-6 months of age. Extensive infiltration with thickening of the alveolar septum occurs, and plasma cells are prominent. The second type is a diffuse desquamative alveolar pneumonitis found in immunocompromised children and adults. The alveoli contain large numbers of *P. jirovecii* in a foamy exudate with alveolar macrophages active in the phagocytosis of organisms. The alveolar septum is not infiltrated to the extent it is in the infantile type, and plasma cells are usually absent.

CLINICAL MANIFESTATIONS

There are at least three distinct clinical presentations of *P. jirovecii* pneumonia. In patients with profound congenital immunodeficiency or in AIDS patients with very few $CD4^+$ T cells, the onset of hypoxia and symptoms is subtle and often without fever, with tachypnea progressing to nasal flaring; intercostal, suprasternal, and infrasternal retractions; and cyanosis in severe cases. In children and adults with immunodeficiency resulting from immunosuppressive medications, the onset of hypoxia and symptoms is often more abrupt, with fever, tachypnea, dyspnea, and cough, progressing to severe respiratory compromise. This type accounts for the majority of cases, although the severity of clinical expression can vary. *Rales are usually not detected on physical examination.* The third pattern of *Pneumocystis* pneumonia is reported in severely immunocompromised patients who appear to be responding to therapy but then have an acute and seemingly paradoxical deterioration thought to be associated with the restoration of immune function. This condition is referred to as *immune reconstitution inflammatory syndrome* and is most commonly seen in patients with newly diagnosed AIDS who present with *P. jirovecii* pneumonia and who have a rapid response to antiretroviral therapy that is instituted at the same time as anti-*Pneumocystis* therapy. It can also occur in stem cell transplant recipients who engraft while infected with *P. jirovecii*.

LABORATORY FINDINGS AND DIAGNOSIS

The chest radiograph reveals bilateral diffuse interstitial or alveolar ground glass infiltrates (Fig. 290.1). The earliest densities are perihilar, and progression proceeds peripherally, sparing the apical areas until last. The arterial oxygen tension (Pao_2) is invariably decreased. The major role of the laboratory in establishing a diagnosis of *P. jirovecii* pneumonia is to identify organisms in lung specimens by a variety of methods. **Definitive diagnosis requires visualization of *P. jirovecii* in the lung in the presence of clinical signs and symptoms of the infection**. Organisms can be detected in specimens collected by bronchoalveolar lavage (BAL), tracheal aspirate, transbronchial lung biopsy, bronchial brushings, percutaneous transthoracic needle aspiration, and open lung biopsy. Hypertonic saline–induced sputum samples are helpful if *P. jirovecii* is found, but the absence of the organisms in induced sputum does not exclude the infection and BAL should be performed. Open lung biopsy is the most reliable method, although BAL is more practical in most cases. Estimates of the diagnostic yield of the various specimens are 20–40% for induced sputum, 50–60% for tracheal aspirate, 75–95% for BAL, 75–85% for transbronchial biopsy, and 90–100% for open lung biopsy.

Once obtained, the specimens are typically stained with one of four commonly used stains: Grocott-Gomori silver stain and toluidine blue stain for the cyst form, polychrome stains such as Giemsa stain for the trophic forms and ascospores, and the fluorescein-labeled monoclonal antibody stains for both trophic forms and cysts. **Many clinical laboratories have adopted polymerase chain reaction analysis of respiratory specimens for the diagnosis of *Pneumocystis* pneumonia**. Serum lactate dehydrogenase (LDH) levels are often elevated during *Pneumocystis* pneumonia, and although elevated LDH is not a specific or definitive diagnosis, high levels should raise suspicion.

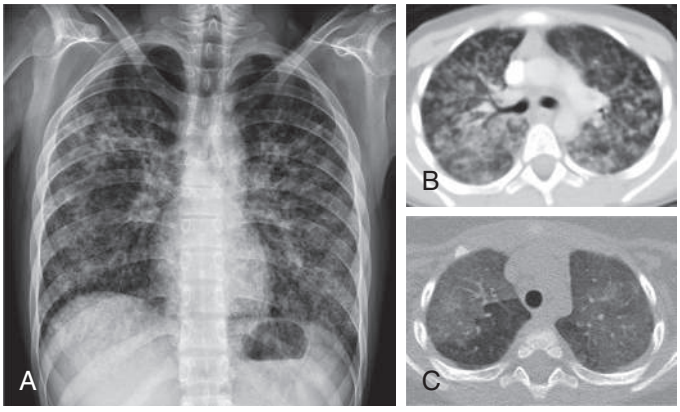

Fig. 290.1 *Pneumocystis jirovecii* infection in a 17-yr-old male with acute lymphoblastic leukemia and immunodeficiency, who presented with dyspnea, fever, nonproductive cough, and decreased white blood cell counts. A, Radiograph shows diffuse bilateral interstitial opacity throughout the lungs. B, Contrast-enhanced computed tomography confirms the bilateral patchy and ground-glass opacities in both lungs. The diagnosis was confirmed by a positive polymerase chain reaction test from bronchial lavage fluid. C, CT in a different patient demonstrates a typical "crazy paving" pattern in both upper lobes. *(From Westra SJ, Yikilmaz A, Lee EY. Pulmonary infection. In: Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 13th ed. Philadelphia: Elsevier; 2019: Fig. 54.30.)*

TREATMENT

The recommended therapy for *P. jirovecii* pneumonia is trimethoprim-sulfamethoxazole (TMP-SMX) (15-20 mg TMP and 75-100 mg SMX/kg/day in four divided doses) administered intravenously or orally if there is mild disease and no malabsorption or diarrhea. The duration of treatment is 3 weeks for patients with AIDS and 2 weeks for other patients. Unfortunately, adverse reactions often occur with TMP-SMX, especially rash and neutropenia in patients with AIDS. For patients who cannot tolerate or who fail to respond to TMP-SMX after 5-7 days, pentamidine isethionate (4 mg/kg/day as a single dose IV) may be used. Adverse reactions are frequent and include renal and hepatic dysfunction, hyperglycemia or hypoglycemia, rash, and thrombocytopenia. Atovaquone (750 mg twice daily with food, for patients >13 years of age) is an alternative treatment that has been used primarily in adults with mild to moderate disease. Limited experience is available for younger children. Pharmacokinetic studies of atovaquone show that a dose of 30 mg/kg/day PO in two divided doses for children 0-3 months of age and older than 2 years of age is adequate and safe; a dose of 45 mg/kg/day PO in two divided doses is needed for children between 4 months and 2 years of age. Other effective therapies include trimetrexate glucuronate or combinations of trimethoprim plus dapsone or clindamycin plus primaquine. The combination of caspofungin and TMP-SMX is also being assessed as a treatment for *Pneumocystis* pneumonia and may help control inflammation in some patients.

Some studies in adults suggest that administration of **corticosteroids as adjunctive therapy to suppress the inflammatory response** increases the chances for survival in moderate and severe cases of *P. jirovecii* pneumonia. The recommended regimen of corticosteroids for adolescents older than 13 years of age and for adults is oral prednisone, 80 mg/day PO in two divided doses on days 1-5, 40 mg/day PO once daily on days 6-10, and 20 mg/day PO once daily on days 11-21. A reasonable regimen for children is oral prednisone, 2 mg/kg/day for the first 7-10 days, followed by a tapering regimen for the next 10-14 days.

SUPPORTIVE CARE

Basic supportive care is dictated by the condition of the patient, with careful attention to maintain appropriate hydration and oxygenation. Only 5–10% of patients with AIDS require mechanical ventilation compared with 50–60% of patients without AIDS, consistent with the hypothesis that the patient's ability to mount an immune/inflammatory response correlates with severity and outcome of *Pneumocystis* pneumonia. There are anecdotal reports of giving surfactant to children with severe *P. jirovecii* pneumonia, although the use of surfactant to treat adult-type respiratory distress syndrome is controversial.

COMPLICATIONS

Most complications occur as adverse events associated with the treatment drugs or as a consequence of mechanical ventilation. The most severe pulmonary complication of *P. jirovecii* pneumonia is adult-type respiratory distress syndrome. Rarely, *P. jirovecii* infection affects extrapulmonary sites (e.g., retina, spleen, and bone marrow), but such infections are usually not symptomatic and also respond to treatment.

PROGNOSIS

Without treatment, *P. jirovecii* pneumonitis is fatal in almost all immunocompromised hosts within 3-4 weeks of onset. The mortality rate varies with patient population and is related to inflammatory response rather than organism burden. Patients with AIDS have a mortality rate of 5–10%, and patients with other diseases such as malignancies have mortality rates as high as 20–25%. Patients who require mechanical ventilation have mortality rates of 60–90%. Patients remain at risk for *P. jirovecii* pneumonia as long as they are immunocompromised. Continuous prophylaxis should be initiated or reinstituted at the end of therapy for patients with AIDS (see Chapter 322).

PREVENTION

Patients at high risk for *P. jirovecii* pneumonia should be placed on chemoprophylaxis. Prophylaxis in infants born to HIV-infected mothers and for HIV-infected infants and children is based on age and CD4 cell counts (see Chapter 322). Because CD4 counts fluctuate rapidly during the first year of life, infants born to HIV-infected mothers should be placed on prophylaxis during the first year of life until HIV infection is ruled out. Patients with severe combined immunodeficiency disease, patients receiving intensive immunosuppressive therapy for cancer or other diseases, and organ transplant recipients are also candidates for prophylaxis. **TMP-SMX (5 mg/kg TMP and 25 mg SMX/kg PO once daily or divided into two doses daily) is the drug of choice and may be given for 3 consecutive days each week or, alternatively, each day**. Alternatives for prophylaxis include **dapsone** (2 mg/kg/day PO, maximum: 100 mg/dose; or 4 mg/kg PO once weekly, maximum: 200 mg/dose), **atovaquone** (30 mg/kg/day PO for infants 1-3 months and ≥24 months of age; 45 mg/kg/day for infants and toddlers 4-23 months of age), and **aerosolized pentamidine** (300 mg/mo by Respirgard II nebulizer), but all of these agents are inferior to TMP-SMX. Finally, limited clinical experience suggests that pentamidine can be given intravenously once monthly to prevent *P. jirovecii* pneumonia. Prophylaxis must be continued as long as the patient remains immunocompromised. Some patients with AIDS who reconstitute adequate immunity during highly active antiretroviral therapy may have prophylaxis withdrawn. Recent animal studies suggest that vaccines may be effective at preventing *Pneumocystis* pneumonia in immunocompromised hosts, but to date none have been tested in humans.

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Chapter 291

Other Pathogenic Fungi

William J. Steinbach

Less common fungi that were once innocent or only contaminants are now emerging as lethal pathogens in a world of increasingly immunocompromised patients. Although there are reports of countless previously considered nonpathogenic fungi infecting severely immunocompromised patients, this chapter focuses on the most common and relevant miscellaneous fungi causing disease.

PHAEOHYPHOMYCOSIS: *CLADOPHIALOPHORA BANTIANA, BIPOLARIS* SPP., AND OTHERS

Phaeohyphomycosis is a heterogeneous group of fungal species commonly found in the soil and characterized by dematiaceous (darkly pigmented brown or black) hyphal forms in tissue. This staining can help distinguish between *Aspergillus* infections, and hyphae often appear more fragmented that seen with *Aspergillus* infections. The characteristic color of the hyphae is related to the presence of melanin in the fungal cell wall, which likely plays a role in fungal pathogenesis. *Phaeo* comes from Greek, meaning "dark," and has been commonly used to describe infections with these fungi as phaeohyphomycosis. It has been suggested that the term *dematiaceous* is not appropriate given its etymologic derivation from the Greek *deme*, meaning "bundle," although it has become fairly entrenched in medical mycologic literature. The term *melanized* is also used, given its specific meaning.

Phaeohyphomycosis has been attributed to more than 150 species of fungi. Among the most prevalent causes of human infection are *Alternaria alternata*, *Acrophialophora fusispora*, *Aureobasidium pullulans*, *Bipolaris* spp., *Curvularia* spp., *Chaetomium* spp., *Cladophialophora*

bantiana, *Exserohilum*, *Fonsecaea*, *Hortaea werneckii*, *Neoscytalidium dimidiatum*, *Verruconis gallopava* (previously *Ochroconis gallopava*), *Phaeoacremonium*, *Phoma*, *Pyrenochaeta*, *Rhinocladiella*, *Veronaea botryosa*, *Wangiella dermatitidis* (previously *Exophiala dermatitidis*), and *Phialophora* spp.

In the multicenter CDC-funded epidemiologic TRANSNET study, 26 cases of phaeohyphomycosis were identified in hematopoietic stem cell transplant (HSCT) recipients analyzed, representing 2.6% of all reported invasive fungal disease in the HSCT cohort. The median time from transplant to diagnosis was 100 days, and 92% of cases were seen in allogeneic HSCT recipients. The mortality rate was 42% at 90 days after diagnosis. There was a higher incidence of phaeohyphomycosis noted from transplant centers in the southern United States versus other regions of the country. Phaeohyphomycosis also represented 2.5% of the overall number of invasive fungal disease in solid organ transplant (SOT) recipients in the TRANSNET study. The median time from transplant to diagnosis was much longer at 18 months, and 53% of cases were specifically diagnosed in lung transplant recipients. There was a 10% mortality rate at 90 days after diagnosis. Overall, cutaneous disease was more common in SOT recipients, whereas pulmonary disease was more common in hematopoietic stem cell transplant recipients. In this series, bloodstream and central nervous system (CNS) infections were seen only in hematopoietic stem cell transplant recipients.

Historically, organisms causing phaeohyphomycosis have been largely associated with cutaneous and subcutaneous infections occurring mostly in immunocompetent persons in tropical and subtropical regions. However, they have emerged with increasing frequency as causes of invasive disease in immunocompromised persons worldwide. Infections can manifest as a range of clinical entities, including localized cutaneous infection and subcutaneous nodules, mycetomas (localized infections involving the cutaneous and subcutaneous tissue, fascia, and bone, often of the lower extremities, and characterized by mycotic granules), chromoblastomycosis (sclerotic bodies in tissues usually seen in tropical regions), keratitis, pulmonary infections, localized deep infections, cerebral abscesses, disseminated infection, allergic fungal sinusitis, and allergic bronchopulmonary mycosis.

C. bantiana is the etiology for the majority of CNS phaeohyphomycosis, including patients that may have no apparent immunosuppression. CNS disease commonly presents with a headache and a focal neurologic deficit, frequently a hemiparesis, or seizures. The most common CNS manifestation is a solitary brain abscess. Though the pathophysiology is not well understood, these are thought to originate via hematogenous dissemination from occult pulmonary or cutaneous foci.

Diagnosis of phaeohyphomycosis relies on pathologic examination of cultures and biopsies, often with expert gross and microscopic examination required. There are no serologic or antigen tests to detect these fungi in blood or tissue, and PCR is in its infancy for this group of organisms. Almost all allergic disease and eosinophilia is caused by either *Bipolaris* spp. or *Curvularia* spp.

Treatment

Treatment recommendations for the rare molds causing phaeohyphomycosis are unfortunately primarily based on in vitro susceptibility data, case reports, and expert opinion. Recommendations can be found in European and Australian guidelines and the American Transplant Society Infectious Diseases Community of Practice Guidelines. European antifungal treatment guidelines highlight the sparse data on preferred therapy, including in vitro data, limited animal model studies, and expert opinion. **There are no clearly defined standard therapies, but the guideline panel generally recommended voriconazole, posaconazole, or itraconazole, because those agents demonstrate the most consistent in vitro antifungal activity against this group of fungi. Specifically, voriconazole is likely the best for CNS infections because of its excellent CNS penetration. For invasive infections, surgery is crucial to the overall treatment.** For phaeohyphomycosis, there is substantial variability in susceptibility both between and within species of a given genus, making correct species identification and susceptibility testing especially critical in guiding therapy for these infections. Combination therapy is suggested in some circumstances for disseminated or CNS infection and for organisms for which no single agent has predictably favorable activity.

Therapy for CNS infections with *C. bantiana* is often unsuccessful despite susceptibility of this organism to several antifungal agents, and it is unclear whether antifungal therapy alters outcome, because survival without complete abscess resection is exceedingly rare. Some experts recommend combination therapy, particularly for cases in which the abscess cannot be completely resected. Surgery is particularly important for brain abscesses secondary to *C. bantiana* infection; regardless of host immune status and antifungal therapy, survival is extremely poor if the abscess is not completely resected. If an invasive mold infection is associated with an intravenous catheter or a peritoneal dialysis catheter, removal of the catheter is recommended.

Including only culture-positive cases of CNS phaeohyphomycosis, the survival rate for this infection is only 35%. A series of 30 cases revealed those patients with single, encapsulated CNS lesions did much better than those with multifocal disease. However, no patient who did not undergo surgery survived. Whether patients underwent neurosurgery alone or with antifungal therapy, the most important factor for cure was resectability of the lesion; antifungal therapy itself was not associated with improved survival.

HYALOHYPHOMYCOSIS: *FUSARIUM* AND *SCEDOSPORIUM* SPP. AND OTHERS

In contrast to phaeohyphomycosis, hyalohyphomycosis refers to infections caused by hyaline (colorless, nonpigmented, nonmelanized) septate fungal hyphae. The major hyalohyphomycotic pathogens are *Fusarium* spp., *Scedosporium* spp., *Paecilomyces* spp., *Trichoderma* spp., *Acremonium* spp., *Scopulariopsis* spp., and *Purpureocillium* spp. These species are often misidentified as *Aspergillus* spp., but they can be differentiated by their conidia and phialide morphologies. This section focuses on *Fusarium* and *Scedosporium* spp., which are usually the third and fourth most common invasive mold diseases in immunocompromised hosts, after invasive aspergillosis and mucormycosis.

The majority of human cases of fusariosis are caused by members of the *Fusarium solani, Fusarium oxysporum,* and *Fusarium fujikuroi* spp. complexes, with the *F. solani* spp. complex demonstrating greater pathogenicity. Nomenclature of organisms causing scedosporiosis can be confusing and has undergone recent changes. The genus name *Pseudallescheria* applies to the sexual state (teleomorph) whereas *Scedosporium* applies to the asexual state (anamorph) of these organisms. *Scedosporium apiospermum* was once thought to be the anamorph of *Pseudallescheria boydii*, but these organisms are now known to be distinct species. The *S. apiospermum* spp. complex encompasses *S. apiospermum*, *Scedosporium boydii*, *Scedosporium aurantiacum*, *Scedosporium dehoogii*, and *Scedosporium minutispora*. The organism formerly known as *Scedosporium prolificans* is now renamed *Lomentospora prolificans* and is phylogenetically distinct from the *Scedosporium* spp.

In addition to the usual airborne and cutaneous inoculation routes of acquisition common to other invasive molds, *Fusarium* can be transmitted via contaminated water sources (e.g., shower heads) and can cause infection associated with intravenous catheters. Both *Fusarium* and *Scedosporium/Lomentospora* spp. can cause infection in immunocompetent hosts, primarily localized infections such as keratitis or onychomycosis. In immunocompromised patients, *Fusarium* can disseminate from initially localized infections such as onychomycosis or intertrigo. The major predisposing factors for invasive disease are profound and prolonged neutropenia and severe cell-mediated immunodeficiency.

Among HSCT recipients in the TRANSNET study, fusariosis accounted for 3% of invasive fungal disease. Identified risk factors for fusariosis in HSCT recipients include history of cytomegalovirus infection, receipt of an umbilical cord blood transplant (compared with other stem cell sources), receipt of antithymocyte globulin, and

hyperglycemia. Risk factors specific to development of fusariosis beyond day 40 after transplant include graft-versus-host disease and prior invasive mold disease. Scedosporiosis is less common among HSCT recipients compared with fusariosis, with only 16 cases identified in the TRANSNET study compared with 31 cases of fusariosis and 77 cases of mucormycosis. Among 1208 invasive fungal infections in the TRANSNET study of SOT recipients, there were 6 cases of fusariosis and 11 cases of scedosporiasis, compared with 28 cases of mucormycosis. In a literature review of *L. prolificans* cases, SOT recipients constituted 8.6% of cases. Scedosporiasis is most common among lung transplant recipients, in whom colonization of the airways can occur pretransplantation (particularly in patients with cystic fibrosis), or posttransplantation, and may progress to invasive infection. Among patients undergoing therapy for cancer, fusariosis primarily occurs in those with hematologic malignancy, especially acute myelogenous leukemia. In a single center study of 44 cases, the most commonly identified risk factors for fusariosis in patients with hematologic malignancy were active leukemia, prolonged and profound neutropenia, and high-dose corticosteroid exposure.

Clinical Presentations

The most common sites of invasive fusariosis in immunocompromised persons are the skin (60–80% of cases), lungs (50–80% of cases), and sinuses (20–30% of cases). *Fusarium* can develop yeastlike adventitious sporulation within infected tissue, which facilitates dissemination, seen in 70% of cases. Unlike other molds that infrequently cause detectable fungemia and are difficult to recover in standard blood culture media, blood cultures are positive for *Fusarium* in 40–50% of cases.

Radiographic series comparing findings of pulmonary fusariosis to those of invasive aspergillosis and mucormycosis note that the halo sign (a nodule surrounded by ground glass opacity) is frequently absent in cases of fusariosis. Cutaneous lesions of invasive fusariosis are distinctive, consisting of painful, circular macules or papules, usually with central necrosis and surrounding erythema. Appearance of cutaneous lesions in invasive fusariosis is usually secondary to hematogenous dissemination to the skin, rather than direct inoculation into the skin.

Invasive disease caused by *S. apiospermum* spp. complex most frequently involves the skin, lungs, and CNS. CNS disease develops in the context of hematogenous dissemination and can manifest as brain abscess(es) or meningoencephalitis. Other manifestations include sinusitis and endogenous endophthalmitis. Skin lesions of *S. apiospermum* spp. complex can manifest as nodules, erythematous or violaceous papules, or bullae, which may develop necrosis. They are usually secondary to hematogenous dissemination rather than primary cutaneous lesions from direct inoculation of the skin. Lymphangitic or sporotrichoid spreading patterns have been described. Blood cultures are positive in approximately 30% of cases of invasive infection with *S. apiospermum* spp. complex. Similar manifestations are seen in invasive *L. prolificans* infections, but the propensity to disseminate is higher and positive blood cultures are reported in over 50% of cases. Hematogenous dissemination of *L. prolificans* to the CNS is common.

Diagnosis

Diagnosis of fusariosis or scedosporiasis requires isolation and identification of the causative organism from the affected site(s). The causative organisms have thin septate hyphae with acute angle branching; they are not morphologically distinguishable from *Aspergillus* when examined in tissue. Culture is necessary for definitive identification of these organisms, though distinguishing between *Fusarium* spp. complexes may be difficult using conventional methods. Organisms causing fusariosis and scedosporiosis can be detected in conventional blood cultures; however, they may be initially reported out as "yeast" because of the appearance of conidia produced by adventitious sporulation.

The *Aspergillus* serum galactomannan assay is positive in approximately half of patients with invasive fusariosis and detection of serum galactomannan above threshold has been shown to precede diagnosis of invasive fusariosis in a high prevalence setting.

Treatment

Treatment recommendations for fusariosis and scedosporiasis are provided in European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and European Confederation of Medical Mycology (ECMM) joint guidelines, and in Australian consensus guidelines. The optimal therapy is unknown; recommendations are primarily based on case reports, clinical experience, and in vitro data, given a lack of clinical trials for these rare diseases. **The ESCMID/ECMM guidelines recommend voriconazole or a lipid-based amphotericin B formulation for treatment of fusariosis, with preference for voriconazole.** Australian guidelines do not state a preference for either agent on the basis of inadequate data. Voriconazole treatment has been associated with higher treatment responses and improved survival, though these should be interpreted with caution because of potential confounding by earlier diagnosis or other interventions.

Because in vitro susceptibility of *Fusarium* isolates to both voriconazole and amphotericin B varies widely, some experts routinely use combination therapy with voriconazole and lipid-based amphotericin B to ensure that at least one agent is active. Some reports describe successful combination therapy with terbinafine and either liposomal amphotericin B or voriconazole, and in vitro data show synergy between terbinafine and voriconazole. Isavuconazole has been studied in few adult cases; based on in vitro susceptibilities it appears to be less active than voriconazole. *Fusarium* spp. are resistant to the echinocandins and to itraconazole.

The activity of antifungal agents against members of the *S. apiospermum* spp. complex is variable, and there are species-based differences in susceptibility pattern. Amphotericin B–based therapy is not recommended due to in vitro resistance and poor clinical responses. Voriconazole is the most active agent and the recommended first-line therapy. In a large observational study, the response rate to voriconazole therapy for *S. apiospermum* infections was 66%. The echinocandins, itraconazole, and posaconazole have variable activity. Isavuconazole is active in vitro but so far has been studied in only a handful of adults with scedosporiasis, limiting conclusions about its utility.

L. prolificans is highly resistant to all antifungal agents currently available. Successful treatment of infections caused by this organism depends on reversal of predisposing conditions and aggressive surgical debridement. Voriconazole is the antifungal with best demonstrated activity, but minimum inhibitory concentrations tend to be high and clinical responses to voriconazole therapy are suboptimal. Combination therapy is typically used, including voriconazole and other agents; successful outcomes have been reported with voriconazole or posaconazole and terbinafine or voriconazole with an echinocandin. Australian guidelines recommend the combination of voriconazole with terbinafine. However, terbinafine is highly protein-bound with distribution primarily to skin and adipose tissue, leading some experts to doubt its utility in treating systemic fungal infections. There have been reports of combination therapy including miltefosine, which is typically used in the treatment of leishmaniasis but demonstrates some in vitro antifungal activity against *L. prolificans*. It is important to recognize that publication bias likely has an impact on reporting of outcomes and no particular antifungal regimen has convincing evidence to support efficacy against *L. prolificans*.

Surgical debridement of infected and necrotic tissue is recommended to facilitate cure, particularly in *L. prolificans* infection, for which surgery and immune reconstitution are the primary effective therapies. Removal of intravenous catheters is recommended for catheter-associated fusariosis.

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Section 13
Viral Infections

Chapter 292
Principles of Antiviral Therapy
Mark R. Schleiss

Antiviral chemotherapy typically requires a delicate balance between targeting critical steps in viral replication without interfering with host cellular function. Because viruses require cellular functions to complete replication, many antiviral agents exert significant host cellular toxicity, a limitation that has hindered antiviral drug development. In spite of this limitation, a number of agents are licensed for use against viruses, particularly herpesviruses, respiratory viruses, and hepatitis viruses (Table 292.1).

In making the decision to commence antiviral drugs, it is important for the clinician to obtain appropriate diagnostic specimens, which can help clarify the antiviral of choice. The choice of a specific antiviral is based on the recommended agent of choice for a particular clinical condition, pharmacokinetics, toxicities, cost, and the potential for development of resistance (Table 292.2). Intercurrent conditions in the patient, such as renal insufficiency, should also be considered. Clinicians must monitor antiviral therapy closely for adverse events or toxicities, both anticipated and unanticipated.

In vitro sensitivity testing of virus isolates to antiviral compounds usually involves a complex tissue culture system. The potency of an antiviral is determined by the **50% inhibitory dose (ID_{50}),** which is the antiviral concentration required to inhibit the growth in cell culture of a standardized viral inoculum by 50%. Because of the complexity of these assays, the results vary widely, and the actual relationship between antiviral sensitivity testing and antiviral therapy outcomes is sometimes unclear. Because these assays are often not readily available and take considerable time to complete, **genotypic analysis** for antiviral susceptibility is increasingly being offered. Such assays may be useful for patients on long-term antiviral therapy.

Clinical context is essential in making decisions about antiviral treatment, along with knowledge of a patient's immune status. For example, antiviral treatment is rarely if ever indicated in an immunocompetent child shedding cytomegalovirus (CMV) but may be lifesaving when administered to an immunocompromised solid organ transplant (SOT) or hematopoietic stem cell transplant (HSCT) patient. Antivirals can be used with a variety of clinical goals in mind. Antivirals can be used for **treatment** of active end-organ disease, as **prophylaxis** to prevent viral infection or disease, or as **preemptive therapy** aimed at reducing risk of progression to disease (i.e., a positive signal indicating viral replication but in the absence of clinical evidence of end-organ disease). In preemptive therapy, a patient will usually have a positive signal for polymerase chain reaction–based identification of viral nucleic acids in a clinical sample (blood or body fluid) but have no symptoms. However, SOT and HSCT patients are at high risk of developing disease in this setting (particularly due to CMV infection), a scenario that warrants preemptive treatment with an antiviral agent. In contrast, prophylaxis is administered to seropositive patients who are at risk to reactivate latent viral infection but do not yet have evidence of active viral replication or shedding.

A fundamental concept important in the understanding of the mechanism of action of most antivirals is that viruses must use host cell components to replicate. Thus mechanisms of action for antiviral compounds must be selective to virus-specific functions whenever possible, and antiviral agents may have significant toxicities to the host if these compounds impact cellular physiology. Some of the more commonly targeted sites of action for antiviral agents include viral entry, absorption, penetration, and uncoating (amantadine, rimantadine); transcription or replication of the viral genome (acyclovir, valacyclovir, cidofovir, famciclovir, letermovir, maribavir, penciclovir, foscarnet, ganciclovir, valganciclovir, ribavirin, trifluridine); viral protein synthesis (interferons [IFNs]) or protein modification (protease inhibitors); and viral assembly, release, or deaggregation (baloxavir, oseltamivir, peramivir, zanamivir, IFNs).

An understudied and underappreciated issue in antiviral therapy is emergence of resistance, particularly in the setting of high viral load, high intrinsic viral mutation rate, and prolonged or repeated courses of antiviral therapy. Resistant viruses are more likely to develop or be selected for in immunocompromised patients because these patients are more likely to have multiple or long-term exposures to an antiviral agent.

ANTIVIRALS USED FOR HERPESVIRUSES

The herpesviruses are important pediatric pathogens, particularly in newborns and immunocompromised children. Most of the licensed antivirals are nucleoside analogs that inhibit viral DNA polymerase, inducing premature chain termination during viral DNA synthesis in infected cells.

Acyclovir

Acyclovir is a safe and effective therapy for herpes simplex virus (HSV) infections. The favorable safety profile of acyclovir derives from its requirement for activation to its active form via phosphorylation by a viral enzyme, thymidine kinase (TK). Thus acyclovir can be activated only in cells already infected with HSV that express the viral TK enzyme, a strategy that maximizes selectivity and reduces the potential for cellular toxicity in uninfected cells. Acyclovir is most active against HSV and is also active against varicella-zoster virus (VZV); therapy is indicated for infections with these viruses in a variety of clinical settings. Activity of acyclovir against CMV is less pronounced, and activity against Epstein-Barr virus is minimal, both in vitro and clinically. Therefore, under most circumstances, acyclovir should not be used to treat CMV or Epstein-Barr virus infections.

The biggest impact of acyclovir in clinical practice is in the treatment of primary and recurrent genital HSV infections. Oral nucleoside therapy plays an important role in the management of acute primary genital herpes, treatment of episodic symptomatic reactivations, and prophylaxis against reactivation. Acyclovir is also indicated in the management of suspected or proven HSV encephalitis in patients of all ages and for treatment of neonatal HSV infection, with or without central nervous system (CNS) involvement. With respect to neonatal HSV infection, the routine empirical use of acyclovir against presumptive or possible HSV infection in infants admitted with fever and no focus in the first 4 weeks of life is controversial. Acyclovir should be used routinely in infants born to women with risk factors for primary genital herpes or infants presenting with any combination of vesicular lesions, seizures, meningoencephalitis, hepatitis, pneumonia, or disseminated intravascular coagulation. Some experts advocate the initiation of acyclovir in all febrile neonates. Other experts have argued that a selective approach based on the history and physical examination is more appropriate when making decisions about the use of acyclovir in febrile infants. Given the safety of the drug, prudence would dictate the use of acyclovir in such patients if HSV infection cannot be excluded.

Acyclovir is indicated for the treatment of primary HSV gingivostomatitis and for primary genital HSV infection. Long-term suppressive therapy for genital HSV and for recurrent oropharyngeal infections (herpes labialis) is also effective. Acyclovir is also recommended for

Table 292.1 Currently Licensed Antiviral Drugs

ANTIVIRAL	TRADE NAME	MECHANISM OF ACTION/COMMENTS
Acyclovir	Zovirax	Inhibits viral DNA polymerase
Adefovir	Hepsera	Nucleotide reverse transcriptase inhibitor
Amantadine*	Symmetrel	Blocks M2 protein ion channel
Baloxavir	Xofluza	Inhibits polymerase acidic endonuclease, blocking viral replication
BMS-791325	Beclabuvir	Inhibitor of HCV NS5B Evaluated in combination with asunaprevir and daclatasvir; active against HCV genotype 1
Boceprevir†	Victrelis	Inhibitor of HCV NS3 serine protease Active against HCV genotype 1
Cidofovir	Vistide	Inhibits viral DNA polymerase
Daclatasvir	Daklinza	Inhibitor of HCV NS5A Used in varying combinations with sofosbuvir, ribavirin, and interferon
Dasabuvir	Exviera	Inhibitor of HCV NS5B Used together with the combination medication ombitasvir/paritaprevir/ritonavir (Viekira Pak) Activity limited to HCV genotype 1
Elbasvir	(Zepatier)	Inhibitor of HCV NS5A Used in combination with the NS3/4A protease inhibitor grazoprevir under the trade name Zepatier, either with or without ribavirin
Entecavir	Baraclude	Nucleoside reverse transcriptase inhibitor Active against HBV
Famciclovir†	Generic	Inhibits viral DNA polymerase
Fomivirsen‡	Vitravene	Phosphorothioate oligonucleotide inhibits viral replication via antisense mechanism
Foscarnet	Foscavir	Inhibits viral DNA polymerase and reverse transcriptase at pyrophosphate-binding site
Ganciclovir	Cytovene	Inhibits viral DNA polymerase
Grazoprevir	Zepatier	Inhibitor of HCV NS3-4A serine protease Used in combination with elbasvir under the trade name Zepatier, either with or without ribavirin
Idoxuridine Ophthalmic†	Herplex	Inhibits viral DNA polymerase
Interferon-α	Intron-A (interferon-α2b) Roferon-A (interferon-α2a) Infergen (interferon alfacon-1)	Produces multiple effector proteins that exert antiviral effects; also directly interacts with immune system components
Interferon-α2b plus ribavirin	Rebetron	Not established
Lamivudine (3TC)	Epivir	Inhibits viral DNA polymerase and reverse transcriptase; active against HBV With dolutegravir, Dovato; with tenofovir, Delstrigo; with zidovudine, Combivir; with abacavir and dolutegravir, Triumeq.
Ledipasvir	(with Sofosbuvir: Harvoni)	Inhibitor of HCV NS5A
Letermovir	Prevymis	Prophylaxis against CMV following HSCT
Maribavir	Livtencity	Treatment of refractory CMV disease when treated with conventional antiviral therapy
Molnupiravir	Lagevrio	Treatment of SARS-CoV-2 Induces viral RNA mutations during replication
Nirmatrelvir/ritonavir	Paxlovid	Treatment of SARS-CoV-2 Protease inhibitor
Ombitasvir	(Viekira Pak)	Inhibitor of HCV NS5A Used in combination with paritaprevir, ritonavir and dasabuvir in Viekira Pak Active against HCV genotype 1

Continued

Table 292.1 Currently Licensed Antiviral Drugs—cont'd

ANTIVIRAL	TRADE NAME	MECHANISM OF ACTION/COMMENTS
Oseltamivir	Tamiflu	Neuraminidase inhibitor; interference with deaggregation and release of viral progeny
Paritaprevir	(Viekira Pak) (Technivie†/Viekirax)	Inhibitor of HCV NS3-4A serine protease Used in combination with ombitasvir, ritonavir and dasabuvir (Viekira Pak), or in combination with ombitasvir and ritonavir (Technivie†/Viekirax)
Pegylated interferon	PEG-Intron (α2b), Pegasys (α2a)	Same as interferon
Penciclovir (topical)	Denavir	Inhibits viral DNA polymerase
Peramivir	Rapivab	Neuraminidase inhibitor
Remdesivir	Veklury	Treatment of SARS-CoV-2 Inhibits viral RNA polymerase
Ribavirin	Virazole, Rebetol, Copegus	Interference with viral messenger RNA
Rimantadine*	Flumadine	Blocks M2 protein ion channel
Simeprevir†	Olysio	Inhibitor of HCV NS3-4A serine protease Active against genotype 1 ± genotype 4 Used in combinations with sofosbuvir or ribavirin and pegylated interferon-alfa†
Sofosbuvir	(Harvoni)	Inhibitor of HCV NS5B Used in combination with ledipasvir (Harvoni) Approved in children >6 years of age and >17 kg
Telaprevir†	Incivek Incivo VX-950	Inhibitor of HCV NS3-4A serine protease Active against HCV genotype 1 No longer available in United States
Telbivudine†	Tyzeka	Interferes with HBV DNA replication No longer available in United States
Tenofovir	Viread Vemlidy	Nucleoside reverse transcriptase inhibitor Active against HBV
Trifluridine	Viroptic	Inhibits viral DNA polymerase
Valacyclovir	Valtrex	Same as acyclovir
Valganciclovir	Valcyte	Same as ganciclovir
Velpatasvir	(Epclusa, Sofosvel, Velpanat)	Inhibitor of HCV NS5A Used in combination with sofosbuvir (Epclusa, Sofosvel, Velpanat) Active against all 6 HCV genotypes
Vidarabine	Ara-A	Inhibits viral DNA polymerase (and to lesser extent, cellular DNA polymerase)
Zanamivir	Relenza	Neuraminidase inhibitor; interference with deaggregation and release of viral progeny
FDA-APPROVED COMBINATION THERAPIES WITH INTERFERONS		
Interferon-α2b + ribavirin	Rebetron (Intron-A plus Rebetol† [ribavirin])	Discontinuation of Rebetol announced by FDA in 2019
Interferon-α2a + ribavirin	Roferon-A† + ribavirin	Discontinuation of Roferon announced by manufacturer in 2020
Pegylated interferon-α2b + ribavirin (3 yr and older)	PEG-Intron PegIntron Sylatron ViraferonPeg PEG-Intron/Rebetol (with ribavirin)	Indicated for chronic hepatitis C
Pegylated interferon-α2a ± ribavirin (5 yr and older)	Pegasys + Copegus	Approved for the treatment of chronic hepatitis C (in combination with ribavirin) and treatment of chronic hepatitis B (can be used alone) Has been used in the treatment of mycosis fungoides (a T-cell lymphoma)

*No longer recommended by Centers for Disease Control and Prevention for treatment of influenza.
†No longer marketed in United States.
‡No longer available.

Table 292.2 Antiviral Therapies for Non-HIV Clinical Conditions*

*VIRUS	CLINICAL SYNDROME	ANTIVIRAL AGENT OF CHOICE	ALTERNATIVE ANTIVIRAL AGENTS
Influenza A and B	Treatment	Oseltamivir (>2 wk old)	Zanamivir (>7 yr old) Peramivir (>2 yr old) Baloxavir (>12 yr old)
	Prophylaxis	Oseltamivir (>3 mo old)	Zanamivir (>5 yr old)
Respiratory syncytial virus	Bronchiolitis or pneumonia in high-risk host	Ribavirin aerosol	
COVID-19	Pneumonia MIS-C†	Remdesivir	Nirmatrelvir-ritonavir Molnupiravir
Adenovirus	In immunocompromised patients: Pneumonia Viremia Nephritis Hemorrhagic cystitis	Cidofovir	
CMV	Congenital CMV infection (symptomatic disease)	Valganciclovir (long-term oral valganciclovir may improve developmental and hearing outcomes)	Ganciclovir
	Retinitis in AIDS patients	Valganciclovir	Ganciclovir Cidofovir Foscarnet Ganciclovir ocular insert
	Pneumonitis, colitis; esophagitis in immunocompromised patients	Ganciclovir (IV)	Foscarnet Cidofovir Valganciclovir Maribavir
	Prophylaxis for HSCT or SOT	Acyclovir (high-dose; oral)	Valganciclovir Letermovir
HSV	Neonatal herpes	Acyclovir (IV)	
	Suppressive therapy following neonatal herpes	Acyclovir (PO)	
	HSV encephalitis	Acyclovir (IV)	
	HSV gingivostomatitis	Acyclovir (PO)	Acyclovir (IV) Valacyclovir (PO)
	First episode genital infection	Acyclovir (PO)	Valacyclovir
			Acyclovir (IV) (severe disease)
	Recurrent genital herpes	Acyclovir (PO)	Valacyclovir
	Suppression of genital herpes	Acyclovir (PO)	Valacyclovir
	Cutaneous HSV (whitlow, herpes gladiatorum)	Acyclovir (PO)	Penciclovir (topical)
	Eczema herpeticum	Acyclovir (PO)	Acyclovir (IV) (severe disease)
	Mucocutaneous infection in immunocompromised host (mild)	Acyclovir (IV)	Acyclovir (PO) (if outpatient therapy acceptable)
	Mucocutaneous infection in immunocompromised host (moderate to severe)	Acyclovir (IV)	
	HSV prophylaxis in bone marrow transplant recipients	Acyclovir (IV)	Valacyclovir
	Acyclovir-resistant HSV	Foscarnet	Cidofovir
	Keratitis or keratoconjunctivitis	Trifluridine	Vidarabine

Continued

Table 292.2 Antiviral Therapies for Non-HIV Clinical Conditions*—cont'd

*VIRUS	CLINICAL SYNDROME	ANTIVIRAL AGENT OF CHOICE	ALTERNATIVE ANTIVIRAL AGENTS
Varicella-zoster virus	Chickenpox, healthy child	Supportive care	Acyclovir (PO)
	Chickenpox, immunocompromised child	Acyclovir (IV)	
	Zoster (not ophthalmic branch of trigeminal nerve), healthy child	Supportive care	Acyclovir (PO)
	Zoster (ophthalmic branch of trigeminal nerve), healthy child	Acyclovir (IV)	
	Zoster, immunocompromised child	Acyclovir (IV)	Valacyclovir

*For antiviral agents for hepatitis B and hepatitis C, see Table 292.1.
†For MIS-C, adjunctive therapies also include steroids, immunomodulatory therapy; see Chapter 449.1.
CMV, Cytomegalovirus; HSV, herpes simplex virus.

less commonly encountered HSV infections, including herpetic whitlow, eczema herpeticum, and herpes gladiatorum. In addition, acyclovir is commonly used for prophylaxis against HSV reactivation in SOT and HSCT patients. Severe end-organ HSV disease, including disseminated infection, is occasionally encountered in immunocompromised or pregnant patients, representing another clinical scenario in which acyclovir therapy is warranted.

Acyclovir modifies the course of primary VZV infection, although the effect is modest. Acyclovir or another nucleoside analog should always be used in localized or disseminated VZV infections in immunocompromised patients. Primary VZV infection in pregnancy is another setting in which acyclovir is indicated; this is a high-risk scenario and can be associated with a substantial risk of maternal mortality, particularly if pneumonia is present.

Acyclovir is available in topical (5% ointment), parenteral, and oral formulations, including an oral suspension formulation for pediatric use. Topical therapy has little role in pediatric practice and should be avoided in favor of alternative modes of delivery, particularly in infants with vesicular lesions compatible with herpetic infection, where topical therapy should never be used. The bioavailability of oral formulations is modest, with only 15–30% of the oral dose being absorbed. There is widespread tissue distribution after systemic administration, and high concentrations of drug are achieved in the kidneys, lungs, liver, myocardium, and skin vesicles. Cerebrospinal fluid concentrations are approximately 50% of plasma concentrations. Acyclovir crosses the placenta, and breast milk concentrations are approximately 3 times plasma concentrations, although there are no data on efficacy of in utero therapy or impact of acyclovir therapy on nursing infants. Acyclovir therapy in a nursing mother is not a contraindication to breastfeeding. The main route of elimination is renal, and dosage adjustments are necessary for renal insufficiency. Hemodialysis also eliminates acyclovir.

Acyclovir has an exceptional safety profile. Toxicity is observed typically only in exceptional circumstances: for example, if administered by rapid infusion to a dehydrated patient or a patient with underlying renal insufficiency, acyclovir can crystallize in renal tubules and produce a reversible obstructive uropathy. High doses of acyclovir are associated with neurotoxicity, and prolonged use can cause neutropenia. The favorable safety profile of acyclovir is underscored by recent studies of its safe use during pregnancy, and suppressive therapy in pregnant women with histories of recurrent genital HSV infection, typically with valacyclovir (see later), has become standard of care among many obstetricians. One uncommon but important complication of long-term use of acyclovir is the selection for acyclovir-resistant HSV strains, which usually occurs from pathogenic variants in the HSV *TK* gene. Resistance is rarely observed in pediatric practice but should be considered in any patient who has been on long-term antiviral therapy and who has an HSV or VZV infection that fails to clinically respond to acyclovir therapy.

Valacyclovir

Valacyclovir is the L-valyl ester of acyclovir and is rapidly converted to acyclovir after oral administration. This agent has a safety and activity profile similar to that of acyclovir but has a bioavailability of >50%, 3-5–fold greater than that of acyclovir. Plasma concentrations approach those observed with intravenous acyclovir. Valacyclovir is available only for oral administration. A suspension formulation is not commercially available, but an oral suspension (25 mg/mL or 50 mg/mL) may be prepared extemporaneously from 500-mg caplets for use in pediatric patients for whom a solid dosage form is not appropriate. Suppressive therapy with valacyclovir is commonly prescribed in the second and third trimesters of pregnancy in women who have a clinical history of recurrent genital herpes. *It is important to be aware that perinatal transmission of HSV can occur, leading to symptomatic disease in spite of maternal antenatal antiviral prophylaxis.* In such settings, the possibility of emergence of acyclovir-resistant virus should be considered.

Penciclovir and Famciclovir

Penciclovir is an acyclic nucleoside analog that, like acyclovir, inhibits the viral DNA polymerase after phosphorylation to its active form. Compared with acyclovir, penciclovir has a substantially longer intracellular half-life, which in theory can confer superior antiviral activity at the intracellular level; however, there is no evidence that this effect confers clinical superiority. Penciclovir is licensed only as a topical formulation (1% penciclovir cream), and this formulation is indicated for therapy of cutaneous HSV infections. Topical therapy for primary or recurrent herpes labialis or cutaneous HSV infection is an appropriate use of penciclovir in children older than 2 years of age.

Famciclovir is the prodrug formulation (diacetyl ester) of penciclovir. After oral administration, famciclovir is deacetylated to the parent drug, penciclovir. The efficacy of famciclovir for HSV and VZV infections appeared equivalent to that of acyclovir, although the pharmacokinetic profile was more favorable. As of 2016, the drug has been discontinued.

Ganciclovir and Valganciclovir

Ganciclovir is a nucleoside analog with structural similarity to that of acyclovir. Like acyclovir, ganciclovir must be phosphorylated for antiviral activity, which is targeted against the viral polymerase. The gene responsible for ganciclovir phosphorylation is not TK but rather the virally encoded UL97 phosphotransferase gene. Antiviral resistance in CMV can be observed with prolonged use of nucleoside antivirals, and resistance should be considered in patients on long-term therapy who appear to fail to respond clinically and virologically. Ganciclovir is broadly active against many herpesviruses, including HSV and VZV, but is most valuable for its activity against CMV. Ganciclovir was

the first antiviral agent licensed specifically to treat and prevent CMV infection. It is indicated for prophylaxis against and therapy of CMV infections in high-risk patients, including HIV-infected patients and SOT or HSCT recipients. Of particular importance is the use of ganciclovir in the management of CMV retinitis, a sight-threatening complication of HIV infection. Ganciclovir is also of benefit for newborns with symptomatic congenital CMV infection and may be of value in partially ameliorating the sensorineural hearing loss and developmental disabilities that are common complications of congenital CMV infection.

Ganciclovir is supplied in parenteral and oral (as the prodrug, valganciclovir) formulations. Ganciclovir ocular implants are also available for the management of CMV retinitis. The bioavailability of oral ganciclovir is poor, <10%, and therefore oral ganciclovir therapy has been supplanted by the oral prodrug valganciclovir, which is well absorbed from the gastrointestinal tract and quickly converted to ganciclovir by intestinal or hepatic metabolism. Bioavailability of ganciclovir (from valganciclovir) is approximately 60% from tablet and solution formulations. Significant concentrations are found in the aqueous humor, subretinal fluid, cerebrospinal fluid, and brain tissue (enough to inhibit susceptible strains of CMV). Subretinal concentrations are comparable with plasma concentrations, but intravitreal concentrations are lower. Drug concentrations in the CNS range from 24% to 70% of plasma concentrations. The main route of elimination is renal, and dosage adjustments are necessary for renal insufficiency. Dose reduction is proportional to the creatinine clearance. Hemodialysis efficiently eliminates ganciclovir, so administration of additional doses after dialysis is necessary.

Ganciclovir has several important toxicities. Reversible myelosuppression is the most important toxicity and commonly requires either discontinuation of therapy or the intercurrent administration of granulocyte colony–stimulating factor. There are also the theoretical risks of carcinogenicity and gonadal toxicity; although these effects have been observed in some animal models, they have never been observed in patients. The decision to administer ganciclovir to a pediatric patient is complex and should be made in consultation with a pediatric infectious disease specialist.

Foscarnet

Foscarnet has a unique profile, insofar as it is not a nucleoside analog but rather a pyrophosphate analog. The drug has broad activity against most herpesviruses. Like the nucleoside analogs, foscarnet inhibits viral DNA polymerase. On the other hand, foscarnet does not require phosphorylation to exert its antiviral activity, thus differing from the nucleoside analogs. It binds to a different site on the viral DNA polymerase to exert its antiviral effect and therefore retains activity against strains of HSV and CMV that are resistant to nucleoside analogs. Its clinical utility is as a second-line agent for management of CMV infections in high-risk patients who cannot tolerate ganciclovir and as an alternative for patients with persistent or refractory HSV, CMV, or VZV disease with suspected or documented antiviral drug resistance.

Foscarnet is available only as a parenteral formulation and is a toxic agent that must be administered cautiously. Nephrotoxicity is common, and reversible renal insufficiency is often observed, as evidenced by an increase in serum creatinine. Abnormalities in calcium and phosphorus homeostasis are common, and electrolytes and renal function must be monitored carefully during treatment.

Cidofovir

Cidofovir is an acyclic nucleotide analog that requires phosphorylation to its active form, cidofovir diphosphate, to exert its antiviral effect. Analogous to penciclovir, it has an extended intracellular half-life that contributes to its prolonged antiviral activity. Cidofovir is active against HSV, VZV, and CMV. In contrast to most of the other agents with activity against herpesviruses, cidofovir also exhibits broad-spectrum activity against other DNA viruses, most notably the poxviruses. Cidofovir has activity against the BK virus, a polyomavirus, and therapy may be warranted in some settings of BK reactivation after HSCT and SOT. Cidofovir is useful in the management of adenovirus infections in the immunocompromised host. Cidofovir is also useful in the management of CMV disease caused by strains with documented ganciclovir resistance.

Cidofovir is administered intravenously and is cleared renally by tubular secretion. Extensive prehydration and co-administration of probenecid are recommended. Nephrotoxicity is commonly encountered, even with appropriate prehydration; cidofovir must be co-administered with care with other nephrotoxic medications. Other potential toxicities include reproductive toxicity and carcinogenesis.

Trifluridine

Trifluridine is a pyrimidine nucleoside analog with activity against HSV, CMV, and adenovirus. It is formulated as a 1% ophthalmic solution and approved for topical use in the treatment of HSV keratitis and keratoconjunctivitis. Trifluridine is the treatment of choice for HSV keratitis, a disease that should always be managed in consultation with an ophthalmologist.

Vidarabine

Vidarabine is a nucleoside analog that has activity against HSV. It was the first parenteral antiviral agent for HSV infection, although it is no longer available for intravenous administration. A topical preparation remains available to treat HSV keratitis and is considered a second-line agent for this indication.

Fomivirsen

Fomivirsen is an anti-CMV compound that was used as a second-line agent for CMV retinitis by direct injection into the vitreous space. It is an antisense 21-mer DNA oligonucleotide that binds directly to complementary messenger RNA. This agent is of interest because it was the first antisense antiviral agent approved by the U.S. Food and Drug Administration (FDA). The drug is no longer marketed.

Letermovir

Letermovir is a highly orally bioavailable agent with a novel mechanism of antiviral action, functioning through interference with the viral terminase complex. This agent demonstrates substantial promise as an alternative to more toxic antivirals in patients at high risk for CMV disease, particularly in the transplantation setting. It is licensed for prophylaxis for CMV infection and disease in adult CMV-seropositive recipients of allogeneic HSCT.

Maribavir

Maribavir is a licensed orally bioavailable agent that targets the CMV gene product UL97, in the process blocking viral replication. The drug is indicated to treat patients >12 years of age who weigh >35 kg and have evidence of posttransplant CMV infection and/or disease that does not respond to other antiviral agents.

ANTIVIRALS USED FOR RESPIRATORY VIRAL INFECTIONS

Antiviral therapies are available for many respiratory pathogens, including respiratory syncytial virus (RSV), influenza A, and influenza B. Antiviral therapy for respiratory viral infections is of particular value for infants, children with chronic lung disease, and immunocompromised children.

Ribavirin

Ribavirin is a guanosine analog that has broad-spectrum activity against a variety of viruses, particularly RNA viruses. Its precise mechanism of action is incompletely understood but is probably related to interference with viral messenger RNA processing and translation. Ribavirin is available in oral, parenteral, and aerosolized formulations. Although intravenous ribavirin is highly effective in

the management of Lassa fever and other hemorrhagic fevers, this formulation is not licensed for use in the United States. The only licensed formulations in the United States are an aqueous formulation for aerosol administration (indicated for RSV infection) and an oral formulation that is combined with IFN-α for the treatment of hepatitis C. (For more information about antivirals for hepatitis, see Chapter 406.) Administration of ribavirin by aerosol should be considered for serious RSV lower respiratory tract disease in immunocompromised children, young infants with serious RSV-associated illness, and high-risk infants and children (children with chronic lung disease or cyanotic congenital heart disease). In vitro testing and uncontrolled clinical studies also suggest efficacy of aerosolized ribavirin for parainfluenza, influenza, and measles infections.

Ribavirin is generally nontoxic, particularly when administered by aerosol. Oral ribavirin is used in combination with other agents for therapy of hepatitis C (discussed later). There is no role for the use of oral ribavirin in the treatment of community-acquired viral respiratory tract infections. Ribavirin and its metabolites concentrate in red blood cells and can persist for several weeks and, in rare instances, may be associated with anemia. Conjunctivitis and bronchospasm have been reported after exposure to aerosolized drug. Care must be taken when using aerosolized ribavirin in children undergoing mechanical ventilation to avoid precipitation of particles in ventilator tubing; the drug is not formally approved for use in the mechanically ventilated patient, although there is published experience with this approach, which can be considered for mechanically ventilated patients, particularly in a "high-dose, short-duration" regimen (6 g/100 mL water given for a period of 2 hours 3 times a day). Concerns regarding potential teratogenicity from animal studies have not been borne out in clinical practice, although care should be taken to prevent inadvertent exposure to aerosolized drug in pregnant healthcare providers.

Amantadine and Rimantadine

Amantadine and rimantadine are tricyclic amines (adamantanes) that share structural similarity. Both were indicated for prophylaxis and therapy of influenza A. The mechanism of action of the tricyclic amines against influenza A virus was unclear, but they appeared to exert their antiviral effect at the level of uncoating of the virus. Both agents are extremely well absorbed after oral administration and are eliminated via the kidneys (90% of the dose is unchanged), necessitating dosage adjustments for renal insufficiency. The toxicities of the tricyclic amines are modest and include CNS adverse effects such as anxiety, difficulty concentrating, and lightheadedness and gastrointestinal adverse effects such as nausea and loss of appetite.

Although these agents are still manufactured and available, the Centers for Disease Control and Prevention (CDC) no longer recommends the use of the adamantane agents in treatment or prophylaxis against influenza, because of the emergence of widespread resistance.

Oseltamivir, Peramivir, Zanamivir (Neuraminidase Inhibitors)

These agents are active against both influenza A and B, although the importance of this broader spectrum of antiinfluenza activity in disease control is modest because influenza B infection is typically a much milder illness. Emerging strains of influenza, including H5N1 and the 2009 to 2010 pandemic strain, H1N1 (swine flu), are susceptible to oseltamivir and zanamivir but resistant to amantadine. Therefore these agents have emerged as the antivirals of choice for influenza infection. These agents have no appreciable activity against other respiratory viruses. The mechanism of antiviral activity of oseltamivir, zanamivir, and peramivir is via inhibition of the influenza neuraminidase. Unfortunately, oseltamivir resistance may occur as a result of a mutation in 2009 H1N1 viruses, resulting in treatment failure.

Zanamivir has poor oral bioavailability and is licensed only for inhalational administration. With inhaled administration, >75% of the dose is deposited in the oropharynx and much of it is swallowed. The actual amount distributed to the airways and lungs depends on factors such as the patient's inspiratory flow. Approximately 13% of the dose appears to be distributed to the airways and lungs, with approximately 10% of the inhaled dose distributed systemically. Local respiratory mucosal drug concentrations greatly exceed the drug concentration needed to inhibit influenza A and B viruses. Elimination is via the kidneys, and no dosage adjustment is necessary with renal insufficiency, because the amount systemically absorbed is low.

Oseltamivir is administered as an esterified prodrug that has high oral bioavailability. It is eliminated by tubular secretion, and dosage adjustment is required for patients with renal insufficiency. Gastrointestinal adverse effects, including nausea and vomiting, are occasionally observed. The drug is indicated for both treatment and prophylaxis. The usual adult dosage for treatment of influenza is 75 mg twice daily for 5 days. Treatment should be initiated within 2 days of the appearance of symptoms. Recommended treatment dosages for children vary by age and weight. The recommended dose for children younger than 1 year of age is 3 mg/kg/dose twice a day. For children older than 1 year of age, doses are 30 mg twice a day for children weighing ≤15 kg, 45 mg twice a day for children weighing 15-23 kg, 60 mg twice a day for those weighing 23-40 kg, and 75 mg twice a day for children weighing ≥40 kg. Dosages for chemoprophylaxis are the same for each weight group in children older than 1 year, but the drug should be administered only once daily rather than twice daily. Oseltamivir is FDA approved for therapy of influenza A and B treatment in children 2 weeks of age and older, whereas zanamivir is recommended for treatment of children 7 years of age and older. Current treatment and dosage recommendations for treatment of influenza in children and for chemoprophylaxis are available at https://www.cdc.gov/flu/highrisk/children-antiviral.htm. Oseltamivir has been described to produce neuropsychiatric (narcolepsy) and psychologic (suicidal events) side effects in some patient populations; the drug should be discontinued if behavioral or psychiatric side effects are observed. In late 2014 the FDA approved the neuraminidase inhibitor peramivir for treatment of influenza in pediatrics. It is available as a single-dose, intravenous option. The drug is currently approved for use in children >2 years. The dose is 12 mg/kg dose, up to 600 mg maximum, by intravenous infusion for a minimum of 15 minutes in children from 2 to 12 years. Children 13 and older should receive the adult dose (600 mg IV in a single, one-time dose).

Baloxavir

Baloxavir is dosed as baloxavir marboxil, a prodrug that is converted by hydrolysis to baloxavir, the active agent. It is active against influenza A and B. Baloxavir inhibits the endonuclease activity of the influenza polymerase acidic (PA) protein, in the process inhibiting virus replication. It is administered as a single dose of 40 mg in individuals 40-80 kg, and 80 mg in those >80 kg.

Oral baloxavir marboxil (Xofluza) is approved by the FDA for treatment of acute uncomplicated influenza within 2 days of illness onset in people ≥12 years. The safety and efficacy of baloxavir for the treatment of influenza have been established in pediatric patients ≥12 years and older weighing at least 40 kg. Safety and efficacy in patients <12 years or weighing less than 40 kg have not been established. Baloxavir efficacy is based on clinical trials in outpatients 12 to 64 years of age; people with underlying medical conditions and adults >65 years were not included in the initial published clinical trials. There are no available data for baloxavir treatment of hospitalized patients with influenza.

ANTIVIRALS USED FOR COVID-19

The advent of the COVID-19 pandemic has necessitated the urgent development of antivirals active against the SARS-CoV-2 virus. **Remdesivir** is an adenosine analog that was originally developed as a therapeutic option for Ebola virus. It is metabolized to its active metabolite, remdesivir triphosphate, which is a structural analog of adenosine triphosphate and results in delayed chain termination during viral replication. It reduces early-stage COVID-19 mortality and the need for mechanical

ventilation among hospitalized COVID-19 patients. The dose for pediatric patients less than 12 years of age and weighing at least 3 kg (and <40 kg) is a single loading dose of 5 mg/kg on day 1 followed by 2.5 mg/kg once daily for up to 5 days; for hospitalized patients requiring invasive mechanical ventilation and/or ECMO, up to 10 days total therapy can be administered. **Paxlovid** (also variably referred to as ritonavir-boosted nirmatrelvir) is a therapeutic combination consisting of two compounds: nirmatrelvir, an oral inhibitor of SARS-CoV-2 protease, and ritonavir, an inhibitor of the HIV-1 protease. Ritonavir is also a potent inhibitor of cytochrome P-450 (CYP) 3A; thus its inclusion results in higher levels of PF-07321332. In patients with SARS-CoV-2 infection who were treated with Paxlovid within 3 days of symptom onset, hospitalization and mortality rates were statistically significantly lower compared with placebo. The FDA Emergency Use Authorization (EUA) includes treatment of children over 12 years of age with a body weight of >40 kg, with a suggested dose of 300 mg nirmatrelvir (two 150-mg tablets) with 100 mg ritonavir (one 100-mg tablet), with all three tablets taken together, twice daily, by oral administration, for 5 days. **Molnupiravir** (Lagevrio) was originally developed as an influenza antiviral agent. It is a prodrug of a synthetic nucleoside hydroxycytidine derivative. Its antiviral effect is mediated by the introduction of copying errors during the SARS-CoV-2 RNA replication cycle. The reported efficacy against hospitalization or death in an adult study of mild or moderate COVID-19 disease was approximately 30%. The drug is not authorized for patients <18 years of age because of concerns that it may affect cartilage and bone growth.

ANTIVIRALS USED FOR HEPATITIS

Seven antiviral agents have been approved by the FDA for treatment of adults with chronic hepatitis B in the United States. These agents are categorized as either IFN-α2b and peginterferon-α2a) or nucleoside or nucleotide analogs (lamivudine, adefovir, entecavir, tenofovir, telbivudine). Lamivudine is currently considered the first-line therapy in adult patients, but experience in children is limited. In 2012 tenofovir was FDA approved for children with chronic hepatitis B age ≥12 years weighing >35 kg. Entecavir was approved in the United States for use in children 2 years and older with chronic HBV and evidence of active viral replication and disease activity and, with IFN-α, is emerging as a first-line antiviral regimen for children with hepatitis B who are candidates for antiviral therapy.

Adefovir demonstrates a favorable safety profile and is less likely to select for resistance than lamivudine, but virologic response was limited to adolescent patients and was lower than that of lamivudine. Most experts recommend watchful waiting of children with chronic hepatitis B infection, because current therapies are only modestly effective at best and evidence of long-term benefit is scant. Young children are often thought to be immune tolerant of hepatitis B infection (i.e., they have viral DNA present in serum but normal transaminase levels and no evidence of active hepatitis). These children should have transaminases and viral load monitored but are not typically considered to be candidates for antiviral therapy.

Various formulations of IFNs and ribavirin have been approved by the FDA to treat adults and children with chronic hepatitis C (see Tables 292.1 and 292.2). The impact of hepatitis C genotype had formerly been a major issue in treatment response. Previous studies using ribavirin and pegylated IFNs demonstrated significant genotype-dependent differences in responsiveness to antiviral therapy; patients with genotype 1 had the lowest levels of sustained virologic response, and patients with genotype 2 or 3 had the highest response. The development of novel and highly effective antivirals for HCV has revolutionized the care of hepatitis C patients. Novel drugs include ledipasvir, sofosbuvir, daclatasvir, elbasvir, beclabuvir, grazoprevir, paritaprevir, ombitasvir, velpatasvir, and dasabuvir. Ledipasvir, ombitasvir, daclatasvir, elbasvir, and velpatasvir inhibit the virally encoded phosphoprotein NS5A, which is involved in viral replication, assembly, and secretion, whereas sofosbuvir is metabolized to a uridine triphosphate mimic, which functions as an RNA chain terminator when incorporated into the nascent RNA by the NS5B polymerase enzyme. Dasabuvir and beclabuvir are also NS5B inhibitors. Paritaprevir and grazoprevir inhibit the nonstructural protein 3 (NS3/4) serine protease, a viral nonstructural protein that is the 70-kDa cleavage product of the hepatitis C virus polyprotein.

Sofosbuvir in a fixed-dose combination was originally licensed for treatment of hepatitis C in adults. It is highly effective (>90%) for hepatitis C genotypes 1 through 6. In 2020, it was licensed for treatment in children ages 6 years and older and weighing at least 17 kilograms for any of the six HCV genotypes in patients without cirrhosis or with mild cirrhosis. Epclusa in combination with ribavirin is indicated for the treatment of pediatric patients 6 years and older or weighing at least 17 kilograms with severe cirrhosis.

ANTIVIRAL IMMUNE GLOBULINS

Immune globulins are useful adjuncts in the management of viral disease. However, they are most valuable when administered as prophylaxis against infection and disease in high-risk patients; their value as therapeutic agents in the setting of established infection is less clear. **Varicella-zoster immune globulin (human)** is valuable for prophylaxis against VZV in high-risk children, particularly newborns and immunocompromised children (see Chapter 300). **CMV immune globulin** is warranted for children at high risk for CMV disease, particularly SOT and HSCT patients, and can play a role in preventing injury to the infected fetus when administered to the pregnant patient (see Chapter 302). **Palivizumab,** a monoclonal antibody with anti-RSV activity, is effective for preventing severe RSV lower respiratory tract disease in high-risk premature infants and has replaced **RSV immune globulin** (see Chapter 307). **Hepatitis B immune globulin** is indicated in infants born to hepatitis B surface antigen–positive mothers (see Chapter 406). A variety of monoclonal antibodies had received FDA EUA clearance for prophylaxis and/or therapy of SARS-CoV-2 infection, including **bamlanivimab** (LY-CoV555; administered alone or in combination with **etesevimab**), the combination of **casirivimab** and **imdevimab** (REGEN-COV), and the combination of **tixagevimab** (AZD8895) and **cilgavimab** (AZD1061), also known as Evusheld. As of late 2023, these products are no longer available due to their lack of effectiveness against emerging circulating variants of the SARS-CoV-2 virus. The US Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices has also recently recommended the routine use of **nirsevimab**, a monoclonal antibody targeting the prefusion conformation of the RSV F protein, for the prevention of RSV lower respiratory tract disease (see Chapter 307). Treatment is recommended for newborns and infants younger than 8 months of age during, or entering, their first RSV season, as well as for children up to 24 months of age at increased risk of developing RSV disease entering their second RSV season. A single dose of 50 mg administered intramuscularly is recommended for infants <5 kg, and 100 mg is recommended for infants ≥5 kg. Nirsevimab should not be given to children ≥8 months and older who are not at increased risk of severe RSV disease. For the 2023-24 respiratory virus season, and in light of shortage and distribution issues with nirsevimab, the CDC has recommended (https://emergency.cdc.gov/han/2023/han00499.asp) assigning the highest priority for nirsevimab 100 mg doses for infants at the highest risk for severe RSV disease: young infants (age <6 months and >5 kg) and infants with underlying conditions that place them at highest risk for severe RSV disease. The CDC also recommended that providers not use nirsevimab in palivizumab-eligible children ages 8–19 months for the 2023–24 RSV season; instead, they should receive palivizumab per American Academy of Pediatrics (AAP) recommendations https://publications.aap.org/pediatrics/article/152/1/e2023061803/192153/Palivizumab-Prophylaxis-in-Infants-and-Young?autologincheck=redirected).

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Chapter 293

Measles

Hayley A. Gans

Measles is highly contagious, but endemic transmission has been interrupted in the United States as a result of widespread vaccination; imported cases have resulted in epidemics in the United States in unimmunized or partially immunized individuals. In some areas of the world, measles remains a major cause of morbidity and mortality in children (Fig. 293.1).

ETIOLOGY

Measles virus is a negative sense single-stranded, lipid-enveloped RNA virus in the family Paramyxoviridae and genus *Morbillivirus.* Other members of the genus *Morbillivirus* affect a variety of mammals, such as rinderpest virus in cattle and distemper virus in dogs, but humans are the only host of measles virus. Of the six major structural proteins of measles virus, the two most important in terms of induction of immunity are the hemagglutinin (H) protein and the fusion (F) protein. The neutralizing antibodies are directed against the H protein, and antibodies to the F protein limit proliferation of the virus during infection. Small variations in genetic composition have also been identified that result in no effect on protective immunity but provide molecular markers that can distinguish between viral types. Related genotypes have been grouped by clades, and the World Health Organization (WHO) recognizes 8 clades, A-H, and 23 genotypes. These markers have been useful in the evaluation of endemic and epidemic spread of measles.

EPIDEMIOLOGY

The measles vaccine has changed the epidemiology of measles dramatically. Once worldwide in distribution, endemic transmission of measles has been interrupted in many countries where there is widespread vaccine coverage. Historically, measles caused universal infection in childhood in the United States, with 90% of children acquiring the infection before 15 years of age. Morbidity and mortality associated with measles decreased before the introduction of the vaccine as a result of improvements in healthcare and nutrition. However, the incidence declined dramatically following the introduction of the measles vaccine in 1963. The attack rate fell from 313 cases per 100,000 population in 1956–1960 to 1.3 cases per 100,000 in 1982–1988.

A nationwide indigenous measles outbreak occurred in the United States in 1989–1991, resulting in more than 55,000 cases, 11,000 hospitalizations, and 123 deaths, demonstrating that the infection had not yet been controlled. This resurgence was attributed to vaccine failure in a small number of school-age children, low coverage of preschool-age children, and more rapid waning of maternal antibodies in infants born to mothers who had never experienced wild-type measles infection. Implementation of the two-dose vaccine policy and more intensive immunization strategies resulted in interruption of endemic transmission, and in 2000 measles was declared eliminated from the United States.

Measles continues to be imported into the United States; therefore continued maintenance of >90% immunity through vaccination is necessary to prevent widespread outbreaks from occurring (see Fig. 293.1).

Since elimination in 2000, there have been several measles epidemics, with the two largest occurring in 2014 with 667 cases and in 2019 with 1,282 cases. In 2014 there were 23 outbreaks reported, compared with a median of 4 outbreaks reported annually during 2001–2010. The majority of cases were associated with importations from other countries (returning tourists, adoptees, refugees), particularly from the Philippines, with prior year epidemics associated with epidemics in the WHO European Region. Measles cases were largely restricted to unvaccinated individuals. The epidemic in 2019 resulted in the highest number of cases since 1992, with 89% of cases in unvaccinated or unknown vaccination status, and 10% of cases requiring hospitalization. There were 22 outbreaks in 17 states (7 were multistate outbreaks), and 85% of cases were in close-knit, isolated communities where standard control measures that generally quickly contain outbreaks were difficult to implement.

Population levels of measles immunity of ~95% are required to interrupt the endemic spread of measles. In the United States this can be achieved through the current two-dose immunization strategies when coverage rates are high (>90% one-dose coverage at 12-15 months and >95% two-dose coverage in school-age children). Although measles-mumps-rubella coverage remains high (~95% for 2011–2020), pockets of lower coverage rates exist because of reluctance of parents to vaccinate their children. This variability in vaccination has contributed to outbreaks among children in recent years.

TRANSMISSION

The portal of entry of measles virus is through the respiratory tract or conjunctivae following contact with large droplets or small-droplet aerosols in which the virus is suspended. Individuals are infectious from 3 days before to up to 4-6 days after the onset of rash. Approximately 90% of exposed susceptible individuals experience measles. Face-to-face contact is not necessary, because viable virus may be suspended in air for as long as 2 hours after the source case leaves a room. Secondary cases from spread of aerosolized virus have been reported in airplanes, physicians' offices, and hospitals.

PATHOLOGY

Measles infection causes necrosis of the respiratory tract epithelium and an accompanying lymphocytic infiltrate. Measles produces a small-vessel vasculitis on the skin and on the oral mucous membranes. Histology of the rash and exanthem reveals intracellular edema and dyskeratosis associated with formation of epidermal syncytial giant cells with up to 26 nuclei. Viral particles have been identified within these giant cells. In lymphoreticular tissue, lymphoid hyperplasia is prominent. Fusion of infected cells results in multinucleated giant cells, the **Warthin-Finkeldey giant cells** that are pathognomonic for measles, with up to 100 nuclei and intracytoplasmic and intranuclear inclusions.

PATHOGENESIS

Measles infection consists of four phases: incubation period, prodromal illness, exanthematous phase, and recovery. During incubation, measles virus migrates to regional lymph nodes. A primary viremia ensues that disseminates the virus to the reticuloendothelial system. A secondary viremia spreads virus to body surfaces. The prodromal illness begins after the secondary viremia and is associated with epithelial necrosis and giant cell formation in body tissues. Cells are killed by cell-to-cell plasma membrane fusion associated with viral replication that occurs in many body tissues, including cells of the central nervous system. Virus shedding begins in the prodromal phase. With onset of the rash, antibody production begins, and viral replication and symptoms begin to subside. Measles virus also infects $CD4^+$ T cells, resulting in suppression of the Th1 immune response and a multitude of other immunosuppressive effects.

Measles virus attaches to specific cell receptors to infect host cells. Studies in primates show that the initial targets for measles virus are alveolar macrophages, dendritic cells, and lymphocytes. The cell receptor in these cells appears to be the signaling lymphocyte-activating molecule CD150. Subsequently, respiratory epithelial cells become infected by attachment to the PVRL4 receptor (Nectin4), which is expressed on cells in the trachea, oral mucosa, nasopharynx, and lungs.

CLINICAL MANIFESTATIONS

Measles is a serious infection characterized by high fever, an enanthem, cough, coryza, conjunctivitis, and a prominent exanthem (Fig. 293.2). After an incubation period of 8-12 days, the prodromal phase begins with a mild fever followed by the onset of conjunctivitis with photophobia, coryza, a prominent cough, and increasing fever. **Koplik spots**

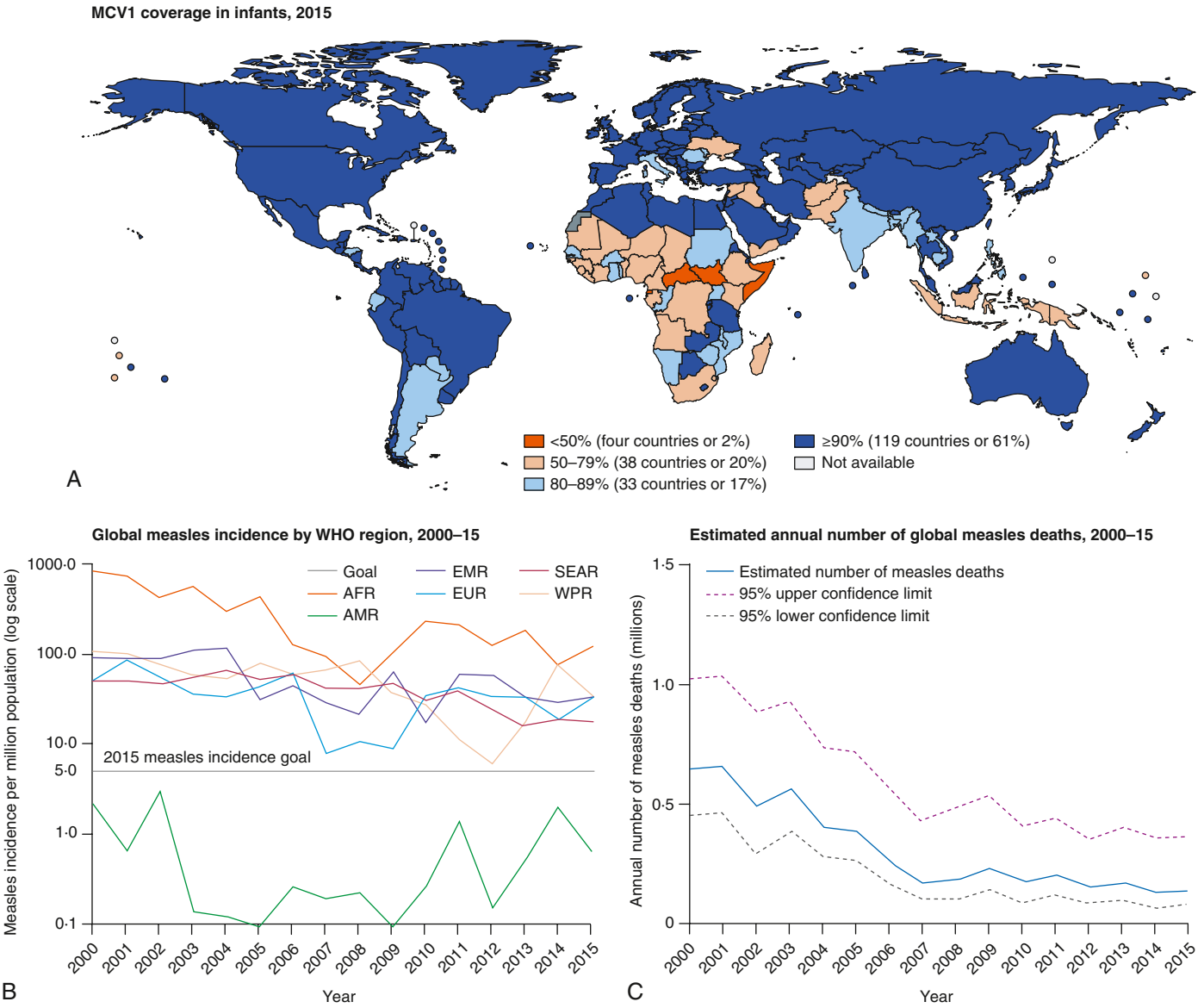

Fig. 293.1 Progress toward achieving global measles milestones for measles vaccine coverage (A), measles incidence (B), and measles mortality (C). A, Milestone 1: increase routine coverage with the first dose of measles-containing vaccine (MCV1) for children age 1 yr to ≥90% nationally and ≥80% in every district. Progress: The number of countries with ≥90% MCV1 coverage increased from 84 (44%) in 2000 to 119 (61%) in 2015. Among countries with ≥90% MCV1 coverage nationally, the percentage with ≥80% coverage in every district was only 39% of 119 countries in 2015. B, Milestone 2: reduce global measles incidence to <5 cases/1 million population. Progress: reported global annual measles incidence decreased 75% from 2000 to 2015, but only the Region of the Americas achieved the milestone of <5 cases/1 million population. C, Milestone 3: reduce global measles mortality by 95% from the 2000 estimate. Progress: the number of estimated global annual measles deaths decreased 79% from 2000 to 2015. AFR, African Region; AMR, Region of the Americas; EMR, Eastern Mediterranean Region; EUR, European Region; SEAR, South-East Asia Region; WPR, Western Pacific Region. *(From Moss WJ. Measles. Lancet. 2017;390:2490–2502. Fig. 2; with data from Patel MK, Gacic-Dobo M, Strebel PM, et al. Progress toward regional measles elimination—worldwide, 2000–2015. MMWR Morb Mortal Wkly Rep. 2016;65:1228–1233.)*

represent the enanthem and are the pathognomonic sign of measles, appearing 1-4 days before the onset of the rash (Fig. 293.3). They first appear as discrete red lesions with bluish-white spots in the center on the inner aspects of the cheeks at the level of the premolars. They may spread to involve the lips, hard palate, and gingiva. They also may occur in conjunctival folds and in the vaginal mucosa. Koplik spots have been reported in 50–70% of measles cases but probably occur in the great majority.

Symptoms increase in intensity for 2-4 days until the first day of the rash. The rash begins on the forehead (around the hairline), behind the ears, and on the upper neck as a red maculopapular eruption. It then spreads downward to the torso and extremities, reaching the palms and soles in up to 50% of cases. The exanthem frequently becomes confluent on the face and upper trunk (Fig. 293.4).

With the onset of the rash, symptoms begin to subside. The rash fades over about 7 days in the same progression as it evolved, often leaving a fine desquamation of skin in its wake. Of the major symptoms of measles, the cough lasts the longest, often up to 10 days. In more severe cases, generalized lymphadenopathy may be present, with cervical and occipital lymph nodes especially prominent.

MODIFIED MEASLES INFECTION

In individuals with passively acquired antibody, such as infants and recipients of blood products, a subclinical form of measles may occur. The rash may be indistinct, brief, or, rarely, entirely absent. Similarly, some individuals who have been vaccinated may have a rash but few other symptoms after exposure to measles. Persons with modified measles are not considered highly contagious.

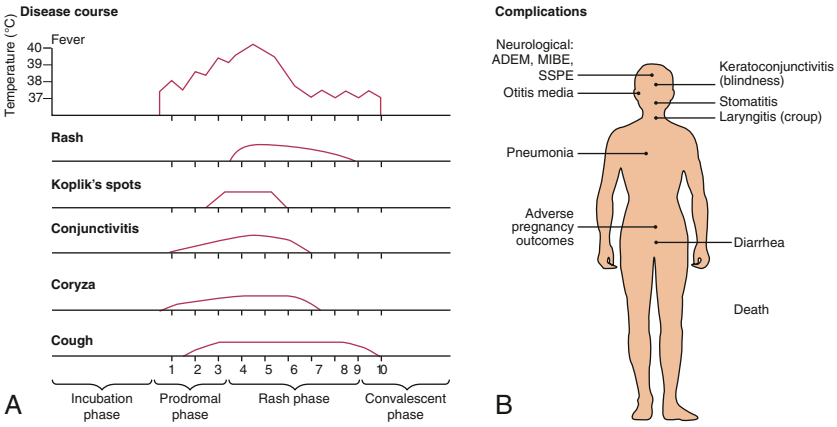

Fig. 293.2 Measles disease course (A) and complications (B). ADEM, Acute demyelinating encephalomyelitis; MIBE, measles inclusion body encephalitis; SSPE, subacute sclerosing panencephalitis. *(Modified from Moss WJ. Measles. Lancet. 2017;390:2490–2502. Fig. 4.)*

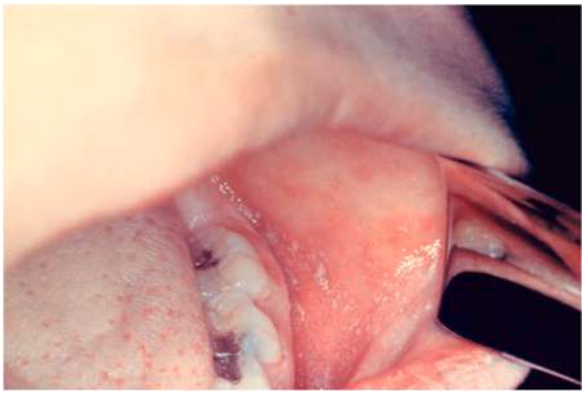

Fig. 293.3 Koplik spots on the buccal mucosa during the third day of rash. *(From Centers for Disease Control and Prevention [CDC]. Public health image library, image 4500. https://phil.cdc.gov/Details.aspx?pid=4500.)*

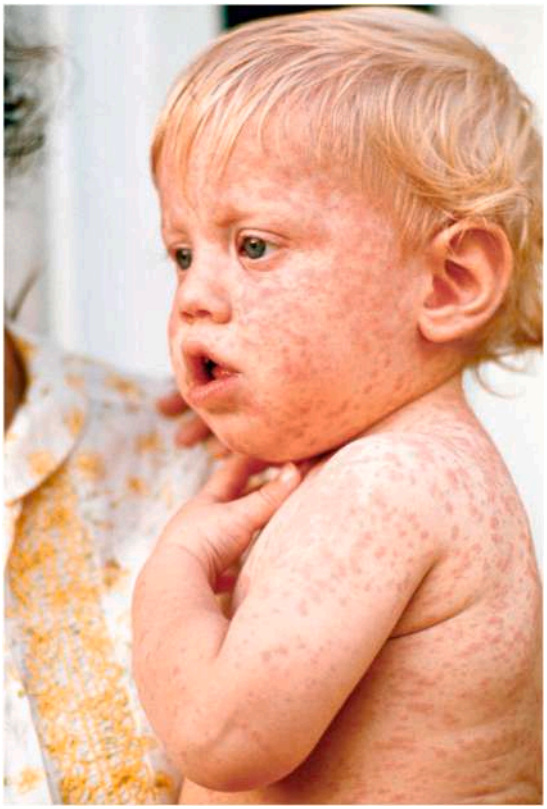

Fig. 293.4 A child with measles displaying the characteristic red blotchy pattern on his face and body. *(From Kremer JR, Muller CP. Measles in Europe—there is room for improvement. Lancet. 2009;373:356–358.)*

LABORATORY FINDINGS

The diagnosis of measles is almost always based on clinical and epidemiologic findings. Laboratory findings in the acute phase include reduction in the total white blood cell count, with lymphocytes decreased more than neutrophils. However, absolute neutropenia has been known to occur. In measles not complicated by bacterial infection, the erythrocyte sedimentation rate and C-reactive protein level are usually normal.

DIAGNOSIS

Isolation of measles from blood, urine, or respiratory secretions can be accomplished by culture at the CDC or local or state laboratories. Molecular detection by polymerase chain reaction (PCR) can be performed on specimens from nasopharyngeal aspirates, throat swabs, or urine. Serologic confirmation is most conveniently made by identification of immunoglobulin (Ig) M antibody in serum. IgM antibody appears 1-2 days after the onset of the rash and remains detectable for about 1 month. If a serum specimen is collected <72 hours after onset of rash and is negative for measles antibody, a second specimen should be obtained. Serologic confirmation may also be made by demonstration of a fourfold rise in IgG antibodies in acute and convalescent specimens collected 2-4 weeks apart. Collection of both a throat swab specimen for PCR and a serum specimen for IgM detection is recommended from all patients with clinical features compatible with measles. In addition, samples should be sent to local state public health laboratories or the CDC for genotyping.

DIFFERENTIAL DIAGNOSIS

Typical measles is unlikely to be confused with other illnesses, especially if Koplik spots are observed. Measles in the later stages or modified or atypical infections may be confused with a number of other exanthematous immune-mediated illnesses and infections, including rubella, adenovirus infection, enterovirus infection, and Epstein-Barr virus infection. Exanthem subitum (in infants) and erythema infectiosum (in older children) may also be confused with measles. *Mycoplasma pneumoniae* and group A *Streptococcus* may also produce rashes similar to that of measles. Kawasaki syndrome can cause many of the same findings as measles but lacks discrete intraoral lesions (Koplik spots) and a severe prodromal cough and typically leads to elevations of neutrophils and acute-phase reactants. In addition, the characteristic thrombocytosis of Kawasaki syndrome is absent in measles (see Chapter 208). Drug eruptions may occasionally be mistaken for measles.

TABLE 293.1 Complications by Age for Reported Measles Cases, United States, 1987–2000

COMPLICATION	OVERALL (67,032 CASES WITH AGE INFORMATION)	NO. (%) OF PERSONS WITH COMPLICATION BY AGE GROUP				
		<5 YR (*N* = 28,730)	5-9 YR (*N* = 6,492)	10-19 YR (*N* = 18,580)	20-29 YR (*N* = 9,161)	<30 YR (*N* = 4,069)
Any	19,480 (29.1)	11,883 (41.4)	1,173 (18.1)	2,369 (12.8)	2,656 (29.0)	1,399 (34.4)
Death	177 (0.3)	97 (0.3)	9 (0.1)	18 (0.1)	26 (0.3)	27 (0.7)
Diarrhea	5,482 (8.2)	3,294 (11.5)	408 (6.3)	627 (3.4)	767 (8.4)	386 (9.5)
Encephalitis	97 (0.1)	43 (0.2)	9 (0.1)	13 (0.1)	21 (0.2)	11 (0.3)
Hospitalization	12,876 (19.2)	7,470 (26.0)	612 (9.4)	1,612 (8.7)	2,075 (22.7)	1,107 (27.2)
Otitis media	4,879 (7.3)	4,009 (14.0)	305 (4.7)	338 (1.8)	157 (1.7)	70 (1.7)
Pneumonia	3,959 (5.9)	2,480 (8.6)	183 (2.8)	363 (2.0)	554 (6.1)	379 (9.3)

From Perry RT, Halsey NA. The clinical significance of measles: a review. *Clin Infect Dis.* 2004;189(Suppl. 1):S4–S16.

COMPLICATIONS

Complications of measles are largely attributable to the pathogenic effects of the virus on the respiratory tract and immune system (Table 293.1, see Fig. 293.2). Several factors make complications more likely. Morbidity and mortality from measles are greatest in individuals younger than 5 years of age (especially <1 year of age) and older than 20 years of age. In resource poor countries, higher case fatality rates have been associated with crowding, possibly attributable to larger inoculum doses after household exposure. Severe malnutrition in children results in a suboptimal immune response and higher morbidity and mortality with measles infection. Low serum retinol levels in children with measles are associated with higher measles morbidity and mortality in developing countries and in the United States. Measles infection lowers serum retinol concentrations, so subclinical cases of hyporetinolemia may be made symptomatic during measles. Measles infection in immunocompromised persons is associated with increased morbidity and mortality. Among patients with malignancy in whom measles develops, pneumonitis occurs in 58% and encephalitis occurs in 20%.

Pneumonia is the most common cause of death in measles. It may manifest as **giant cell pneumonia** caused directly by the viral infection or as superimposed bacterial infection. The most common bacterial pathogens are *Streptococcus pneumoniae, Haemophilus influenzae,* and *Staphylococcus aureus*. Following severe measles pneumonia, the final common pathway to a fatal outcome is often the development of bronchiolitis obliterans.

Croup, tracheitis, and bronchiolitis are common complications in infants and toddlers with measles. The clinical severity of these complications frequently requires intubation and ventilatory support until the infection resolves.

Acute otitis media is the most common complication of measles and was of particularly high incidence during the epidemic of the late 1980s and early 1990s because of the relatively young age of affected children. Sinusitis and mastoiditis also occur as complications. Viral and/or bacterial tracheitis is seen and can be life-threatening. Retropharyngeal abscess has also been reported.

Measles infection is known to suppress skin test responsiveness to purified tuberculin antigen. There may be a higher rate of activation of pulmonary tuberculosis in populations of individuals infected with *Mycobacterium tuberculosis* who are then exposed to measles.

Diarrhea and vomiting are common symptoms associated with acute measles, and diffuse giant cell formation is found in the epithelium in the gastrointestinal tract. Dehydration is a common consequence, especially in young infants and children. Appendicitis or abdominal pain may occur from obstruction of the appendiceal lumen by lymphoid hyperplasia.

Febrile seizures occur in <3% of children with measles. Encephalitis following measles is a long-associated complication, often with an unfavorable outcome. Rates of 1-3 in 1,000 cases of measles have been reported, with greater numbers occurring in adolescents and adults than in preschool- or school-age children. Encephalitis is a postinfectious, immunologically mediated process and is not the result of a direct effect by the virus. Clinical onset begins during the exanthem and manifests as seizures (56%), lethargy (46%), coma (28%), and irritability (26%). Findings in cerebrospinal fluid include lymphocytic pleocytosis in 85% of cases and elevated protein concentrations. Approximately 15% of patients with measles encephalitis die. Another 20–40% of patients suffer long-term sequelae, including cognitive impairment, motor disabilities, and deafness.

Measles encephalitis in immunocompromised patients results from direct damage to the brain by the virus. Subacute measles encephalitis manifests 1-10 months after measles in immunocompromised patients, particularly those with AIDS, lymphoreticular malignancies, and immunosuppressive therapy. Signs and symptoms include seizures, myoclonus, stupor, and coma. In addition to intracellular inclusions, abundant viral nucleocapsids and viral antigen are seen in brain tissue. Progressive disease and death almost always occur. A severe form of encephalitis called measles inclusion-body encephalitis (MIBE) is being increasingly recognized in immunocompromised hosts, typically occurring within a year of infection or vaccination and almost universally resulting in death. Although the pathophysiology is incompletely understood, the measles viruses implicated in MIBE are usually replication-defective, with their genomes possessing numerous mutations. Diagnosis is confirmed by detection of virus via immunohistochemistry of brain tissue.

A severe form of measles rarely seen nowadays is **hemorrhagic measles** or **black measles.** It manifested as a hemorrhagic skin eruption and was often fatal. Keratitis, appearing as multiple punctate epithelial foci, resolved with recovery from the infection.

Myocarditis is a rare complication of measles. Miscellaneous bacterial infections have been reported, including bacteremia, cellulitis, and toxic shock syndrome. Measles during pregnancy is associated with high rates of maternal morbidity, fetal wastage, and stillbirths, with congenital malformations in 3% of liveborn infants.

Subacute Sclerosing Panencephalitis

Subacute sclerosing panencephalitis (SSPE) is a chronic complication of measles with a delayed onset and an outcome that is nearly always fatal. It appears to result from a persistent infection with an altered measles virus that is harbored intracellularly in the central nervous system for several years. After 7-10 years the virus apparently regains virulence and attacks the cells in the central nervous system that offered the virus protection. This "slow virus infection" results in inflammation and cell death, leading to an inexorable neurodegenerative process.

SSPE is a rare disease and generally follows the prevalence of measles in a population. The incidence in the United States in 1960 was 0.61 cases per million persons younger than age 20 years. By 1980 the rate had fallen to 0.06 cases per million. Between 1956 and 1982 a total of 634 cases of SSPE had been reported to the national SSPE registry. After 1982 ~5 cases/year were reported annually in the United States, and only 2-3 cases/year were reported in the early 1990s. However, between 1995 and 2000, reported cases in the United States increased and 13 cases were reported in 2000. Of the 13 cases, 9 occurred in foreign-born individuals. This "resurgence" may be the result of an increased incidence of measles between 1989 and 1991. Although the age of onset ranges from <1 year to <30 years, the illness is primarily one of children and adolescents. Measles at an early age favors the development of SSPE: 50% of patients with SSPE have had primary measles before 2 years of age, and 75% have had measles before 4 years of age. Males are affected twice as often as females, and there appear to be more cases reported from rural than urban populations. Recent observations from the registry indicate a higher prevalence among children of Hispanic origin.

The pathogenesis of SSPE remains enigmatic. Factors that seem to be involved include defective measles virus and interaction with a defective or immature immune system. The virus isolated from brain tissue of patients with SSPE is missing one of the six structural proteins, the matrix or M protein. This protein is responsible for assembly, orientation, and alignment of the virus in preparation for budding during viral replication. Immature virus may be able to reside, and possibly propagate, within neuronal cells for long periods. The fact that most patients with SSPE were exposed at a young age suggests that immune immaturity is involved in pathogenesis.

Clinical manifestations of SSPE begin insidiously 7-13 years after primary measles infection. Subtle changes in behavior or school performance appear, including irritability, reduced attention span, and temper outbursts. This initial phase **(stage I)** may at times be missed because of brevity or mildness of the symptoms. Fever, headache, and other signs of encephalitis are absent. The hallmark of the **second stage** is massive myoclonus, which coincides with extension of the inflammatory process site to deeper structures in the brain, including the basal ganglia. Involuntary movements and repetitive myoclonic jerks begin in single muscle groups but give way to massive spasms and jerks involving both axial and appendicular muscles. Consciousness is maintained. In the **third stage**, involuntary movements disappear and are replaced by choreoathetosis, immobility, dystonia, and lead pipe rigidity that result from destruction of deeper centers in the basal ganglia. The sensorium deteriorates into dementia, stupor, and then coma. The **fourth stage** is characterized by loss of critical centers that support breathing, heart rate, and blood pressure. Death soon ensues. Progression through the clinical stages may follow courses characterized as acute, subacute, or chronic progressive.

The diagnosis of SSPE can be established through documentation of a compatible clinical course and at least one of the following supporting findings: (1) measles antibody detected in cerebrospinal fluid, (2) characteristic electroencephalographic findings, and (3) typical histologic findings in and/or isolation of virus or viral antigen from brain tissue obtained by biopsy or postmortem examination.

Cerebrospinal fluid analysis reveals normal cells but elevated IgG and IgM antibody titers in dilutions >1:8. Electroencephalographic patterns are normal in stage I, but in the myoclonic phase, suppression-burst episodes are seen that are characteristic of, but not pathognomonic for, SSPE. Brain biopsy is no longer routinely indicated for diagnosis of SSPE.

Management of SSPE is primarily supportive and similar to care provided to patients with other neurodegenerative diseases. Clinical trials using isoprinosine with or without interferon suggest significant benefit (30–34% remission rate) compared with patients without treatment (5–10% with spontaneous remissions).

It is recognized that carbamazepine is of significant benefit in the control of myoclonic jerks in the early stages of the illness.

Virtually all patients eventually succumb to SSPE. Most die within 1-3 years of onset from infection or loss of autonomic control mechanisms. Prevention of SSPE depends on prevention of primary measles infection through vaccination. SSPE has been described in patients who have no history of measles infection and exposure only to the vaccine virus. However, wild-type virus, not vaccine virus, has been found in brain tissue of at least some of these patients, suggesting that they had subclinical measles previously.

TREATMENT

Management of measles is supportive because there is no specific antiviral therapy approved for treatment of measles. Maintenance of hydration, oxygenation, and comfort are goals of therapy. Antipyretics for comfort and fever control are useful. For patients with respiratory tract involvement, airway humidification and supplemental oxygen may be of benefit. Respiratory failure from croup or pneumonia may require ventilatory support. Oral rehydration is effective in most cases, but severe dehydration may require intravenous therapy. Prophylactic antimicrobial therapy to prevent bacterial infection is not indicated.

Measles infection in immunocompromised patients is highly lethal. Ribavirin is active in vitro against measles virus. Anecdotal reports of ribavirin therapy with or without intravenous gamma globulin suggest some benefit in individual patients. Although no controlled trials have been performed, many experts favor use of ribavirin for treatment of measles pneumonia in patients <12 months, patients ≥12 months with pneumonia requiring ventilatory support, and patients with severe immunosuppression. Ribavirin dosing is 15-20 mg/kg/day orally in two divided doses. The optimal duration of therapy is not known; a duration of 5-7 days may be reasonable, guided by the patient's clinical status (respiratory symptoms and chest radiograph findings). Several investigational treatments have been used in individuals with SSPE with the goal of stabilization and delay of progression, including Isoprinosine (inosine pranobex) and interferon-α and interferon-β.

Vitamin A

Vitamin A deficiency in children in resource poor countries has long been known to be associated with increased mortality from a variety of infectious diseases, including measles. In the United States, studies in the early 1990s documented that 22–72% of children with measles had low retinol levels. In addition, one study demonstrated an inverse correlation between the level of retinol and severity of illness. Several randomized controlled trials of vitamin A therapy in the developing world have demonstrated reduced morbidity and mortality from measles. Use of vitamin A for treatment of measles in developed countries has not been evaluated in a large clinical trial, but a small study showed no effect on morbidity. Given the potential for benefit, the WHO and the CDC recommend that vitamin A be administered to all children with acute measles, even in countries where measles is not usually severe. Vitamin A should be administered once daily for 2 days at doses of 200,000 IU for children 12 months of age or older; 100,000 IU for infants 6-11 months of age; and 50,000 IU for infants younger than 6 months of age. In children with signs and symptoms of vitamin A deficiency, a third age-appropriate dose is recommended 2-4 weeks after the second dose.

PROGNOSIS

In the early 20th century, deaths from measles in the United States varied between 2,000 and 10,000 per year, or about 10 deaths per 1,000 cases of measles. With improvements in healthcare and antimicrobial therapy, better nutrition, and decreased crowding, the death-to-case ratio fell to 1 per 1,000 cases. Between 1982 and 2002, the CDC estimated that there were 259 deaths caused by measles in the United States, with a death-to-case ratio of 2.5-2.8 per 1,000 cases of measles. Pneumonia and encephalitis were complications in most of the fatal cases, and immunodeficiency conditions were identified in 14–16% of deaths. In 2011, of the 222 cases reported in the United States, 70

(32%) were hospitalized, including 17 (24%) with diarrhea, 15 (21%) with dehydration, and 12 (17%) with pneumonia. No cases of encephalitis or deaths were reported. In 2019, 10% of cases were hospitalized, 5% had pneumonia, and one (0.1%) had encephalitis, but no deaths were reported.

PREVENTION

Patients shed measles virus from 7 days after exposure to 4-6 days after the onset of rash. Exposure of susceptible individuals to those with measles should be avoided during this period. In hospitals, standard and airborne precautions should be observed for this period. Immunocompromised individuals with measles will shed virus for the duration of the illness, so isolation should be maintained throughout the disease.

Vaccine

Vaccination against measles is the most effective and safe prevention strategy. Measles vaccine in the United States is available as a combined vaccine with measles-mumps-rubella vaccine (Table 293.2). After the measles resurgence of 1989–1991, a second dose of measles vaccine was added to the schedule. The current recommendations include a first dose at 12-15 months of age and a second dose at 4-6 years of age. However, the second dose can be given any time after 30 days following the first dose, and the current schedule is a convenience schedule. Seroconversion is slightly lower in children who receive the first dose before or at 12 months of age (87% at 9 months, 95% at 12 months, and 98% at 15 months) because of persisting maternal antibody; however, this is an evolving situation, with children currently as young as 6 months unprotected from maternal antibodies and susceptible to measles infection. For children who have not received two doses by 11-12 years of age, a second dose should be provided. Infants who receive a dose before 12 months of age should be given two additional doses, one at 12-15 months and another at 4-6 years of age. Children who are traveling should be offered either primary measles immunization even as young as 6 months or a second dose even if <4 years.

Adverse events from the measles-mumps-rubella vaccine include fever (usually 6-12 days after vaccination), rash in approximately 5% of vaccinated persons, and, rarely, transient thrombocytopenia. Children prone to febrile seizures may experience an event following vaccination, so the risks and benefits of vaccination should be discussed with parents. Encephalopathy and autism have not been shown to be causally associated with the measles-mumps-rubella vaccine or vaccine constituents.

A review of the effect of measles vaccination on the epidemiology of SSPE has demonstrated that measles vaccination protects against SSPE

TABLE 293.2 Recommendations for Measles Immunization

CATEGORY	RECOMMENDATIONS
Unimmunized, no history of measles (12-15 mo of age)	MMR or MMRV vaccine is recommended at 12-15 mo of age; a second dose is recommended at least 28 days after the first dose (or 90 days for MMRV) and usually is administered at 4 through 6 yr of age
Children 6-11 mo of age in epidemic situations or before international travel	Immunize with MMR vaccine, but this dose is not considered valid, and 2 valid doses administered on or after the first birthday are required. The first valid dose should be administered at 12-15 mo of age; the second valid dose is recommended at least 28 days later and usually is administered at 4 through 6 yr of age. MMRV should not be administered to children <12 mo of age.
Students in kindergarten, elementary, middle, and high school who have received 1 dose of measles vaccine at 12 mo of age or older	Administer the second dose
Students in college and other postsecondary institutions who have received 1 dose of measles vaccine at 12 mo of age or older	Administer the second dose
History of immunization before the first birthday	Dose not considered valid; immunize (2 doses)
History of receipt of inactivated measles vaccine or unknown type of vaccine, 1963–1967	Dose not considered valid; immunize (2 doses)
Further attenuated or unknown vaccine administered with immunoglobulin	Dose not considered valid; immunize (2 doses)
Allergy to eggs	Immunize; no reactions likely
Neomycin allergy, nonanaphylactic	Immunize; no reactions likely
Severe hypersensitivity (anaphylaxis) to neomycin or gelatin	Avoid immunization
Tuberculosis	Immunize; if patient has untreated tuberculosis disease, start antituberculosis therapy before immunizing
Measles exposure	Immunize or give immunoglobulin, depending on circumstances
HIV infected	Immunize (2 doses) unless severely immunocompromised; administration of immunoglobulin if exposed to measles is based on degree of immunosuppression and measles vaccine history
Personal or family history of seizures	Immunize; advise parents of slightly increased risk of seizures
Immunoglobulin or blood recipient	Immunize at the appropriate interval

MMR, Measles-mumps-rubella vaccine; MMRV, measles-mumps-rubella-varicella vaccine.
From American Academy of Pediatrics. Measles. In Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book 2018 Report of the Committee on Infectious Diseases,* 31st ed. Itasca, IL: American Academy of Pediatrics, 2018: Table 3.39, p. 543.

TABLE 293.3 Suggested Intervals Between Immunoglobulin Administration and Measles Immunization*

INDICATION FOR IMMUNOGLOBULIN	ROUTE	DOSE		
		UNITS (U) OR MILLILITERS (ML)	MG IgG/KG	INTERVAL (MO)†
Tetanus (as tetanus Ig)	IM	250 U	10	3
Hepatitis A prophylaxis (as Ig):				
Contact prophylaxis	IM	0.02 mL/kg	3.3	3
International travel	IM	0.06 mL/kg	10	3
Hepatitis B prophylaxis (as hepatitis B Ig)	IM	0.06 mL/kg	10	3
Rabies prophylaxis (as rabies Ig)	IM	20 IU/kg	22	4
Varicella prophylaxis (as VariZIG)	IM	125 U/10 kg (maximum 625 U)	20-40	5
Measles prophylaxis (as Ig):				
Standard	IM	0.50 mL/kg	80	6
Immunocompromised host	IV		400 mg/kg	8
Respiratory syncytial virus prophylaxis (palivizumab monoclonal antibody)‡	IM	—	15 mg/kg (monoclonal)	None
Cytomegalovirus immune globulin	IV	3 mL/kg	150	6
Blood transfusion:				
Washed RBCs	IV	10 mL/kg	Negligible	0
RBCs, adenine-saline added	IV	10 mL/kg	10	3
Packed RBCs	IV	10 mL/kg	20-60	6
Whole blood	IV	10 mL/kg	80-100	6
Plasma or platelet products	IV	10 mL/kg	160	7
Replacement (or therapy) of immune deficiencies (as IVIG)	IV	—	300-400	8
ITP (as IVIG)	IV	—	400	8
ITP	IV	—	1,000	10
ITP or Kawasaki disease	IV	—	1,600-2,000	11

*Immunization in the form of measles-mumps-rubella (MMR), measles-mumps-rubella-varicella (MMRV), or monovalent measles vaccine.
†These intervals should provide sufficient time for decreases in passive antibodies in all children to allow for an adequate response to measles vaccine. Physicians should not assume that children are fully protected against measles during these intervals. Additional doses of Ig or measles vaccine may be indicated after exposure to measles.
‡Monoclonal antibodies, such as palivizumab, do not interfere with the immune response to vaccines.
Ig, Immunoglobulin; IgG, immunoglobulin G; ITP, immune (formerly termed "idiopathic") thrombocytopenic purpura; IVIG, intravenous Ig; RBCs, red blood cells.
From American Academy of Pediatrics. *Red Book: 2015 Report of the Committee on Infectious Diseases*, 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015: Table 1.10, p. 39.

and does not accelerate the course of SSPE or trigger the disease in those already infected with wild measles virus.

Passively administered immune globulin may inhibit the immune response to live measles vaccine, and administration should be delayed for variable amounts of time based on the dose of Ig (Table 293.3).

Live vaccines should not be administered to pregnant women or to immunodeficient or immunosuppressed patients. However, patients with HIV who are not severely immunocompromised should be immunized. Because measles virus may suppress the cutaneous response to tuberculosis antigen, skin testing for tuberculosis should be performed before or at the same time as administration of the vaccine. Individuals infected with *M. tuberculosis* should be receiving appropriate treatment at the time of administration of measles vaccine.

Postexposure Prophylaxis

Susceptible individuals exposed to measles may be protected from infection either by vaccine administration or with Ig. The vaccine is effective in prevention or modification of measles if given within 72 hours of exposure. Ig may be given up to 6 days after exposure to prevent or modify infection. Immunocompetent children should receive 0.5 mL/kg (maximum dose in both cases is 15 mL/kg) intramuscularly. For severely immunocompromised children and pregnant woman without evidence of measles immunity, immunoglobulin intravenously (IGIV) is the recommended Ig at 400 mg/kg. Ig is indicated for susceptible household contacts of patients with measles, especially infants <6 months of age, pregnant women, and immunocompromised persons.

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Chapter 294

Rubella

Hayley A. Gans

Rubella (**German measles** or **3-day measles**) is a mild, often exanthematous disease of childhood that is typically more severe and associated with more complications in adults. Its major clinical significance is transplacental infection and fetal damage as part of the **congenital rubella syndrome (CRS)**.

ETIOLOGY

Rubella virus is a member of the family Togaviridae and is the only species of the genus *Rubivirus.* It is a positive-sense single-stranded RNA virus with a lipid envelope and three structural proteins, including a nucleocapsid protein (C) that is associated with the nucleus and two glycoproteins, E1 and E2, that are associated with the envelope, carry the main epitopes, and therefore are the major antigenic sites of the virus. The virus is sensitive to heat, ultraviolet light, and extremes of pH but is relatively stable at cold temperatures. Humans are the only known reservoir.

EPIDEMIOLOGY

Rubella is found worldwide and circulates predominantly in late winter and early spring. In the United States, in the prevaccine era, rubella appeared to occur in major epidemics every 6-9 years, with smaller peaks interspersed every 3-4 years, and was most common in preschool-age and school-age children. During the rubella epidemic of 1964–1965 there were an estimated 12.5 million cases of rubella associated with 2,000 cases of encephalitis, more than 13,000 abortions or perinatal deaths, and 20,000 cases of CRS. After introduction of the rubella vaccine in 1969 in the United States, the incidence of rubella fell 78% and CRS cases fell 69% by 1976 (Fig. 294.1). Further decline in rubella and CRS cases occurred when certain at-risk populations were added to those for whom rubella immunization is indicated, including adolescents and college students. After years of decline, a resurgence of rubella and CRS cases occurred during 1989–1991 in association with the epidemic of measles during that period (see Fig. 294.1). Subsequently, a two-dose recommendation for rubella vaccine was implemented and resulted in a decrease in incidence of rubella from 0.45 per 100,000 population in 1990 to 0.1 per 100,000 population in 1999 and a corresponding decrease of CRS, with an average of six infants with CRS reported annually from 1992 to 2004. Mothers of these infants tended to be young, Hispanic, or foreign born. The number of reported cases of rubella continued to decline through the 1990s and the first decade of this century.

The endemic spread of rubella was declared eliminated in the United States in 2004 and eliminated in the Americas in 2015. However, cases of rubella continue to be imported into the United States from countries where it remains endemic. Accelerated global vaccine efforts have resulted in declines of rubella cases worldwide from 94,277 in 2012 to 10,194 in 2020. Rubella elimination has been verified in 93 (48%) of 194 countries, with 70% of infants globally receiving a rubella vaccine in 2020. From 2004 to 2016 there were 101 cases of rubella and 11 cases of CRS reported in the United States, all of which were imported cases of unknown source. Three of the CRS cases were acquired in Africa. This information highlights the need for continued maintenance of high levels of immunity in the United States.

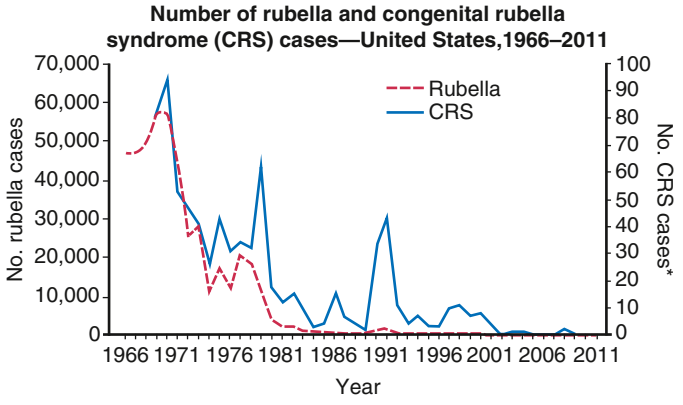

Fig. 294.1 Number of rubella and congenital rubella syndrome cases—United States, 1966–2011. Rubella and CRS data provided were reported voluntarily to Centers for Disease Control and Prevention from state health departments. *(From McLean HQ, Fiebelkorn AP, Temte JL, et al. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013. MMWR Recomm Rep. 2013;62[RR-04]:1–34.)*

PATHOLOGY

Little information is available on the pathologic findings in rubella occurring postnatally. The few reported studies of biopsy or autopsy material from cases of rubella revealed only nonspecific findings of lymphoreticular inflammation and mononuclear perivascular and meningeal infiltration. The pathologic findings for CRS are often severe and may involve nearly every organ system (Table 294.1).

PATHOGENESIS

The viral mechanisms for cell injury and death in postnatal or congenital rubella are not well delineated. The main mechanisms of transmission is respiratory for postnatal infection and transplacental in CRS. The incubation period following respiratory exposure averages 14 days, with a range from 12 to 23 days. After infection, the virus replicates in the respiratory epithelium and then spreads to regional lymph nodes (Fig. 294.2). Viremia ensues and is most intense from 10 to 17 days after infection. Viral shedding from the nasopharynx begins approximately 10 days after infection and may be detected up to 2 weeks after onset of the rash. The period of highest communicability is from 5 days before to 6 days after the appearance of the rash.

Congenital infection occurs during maternal viremia. After infecting the placenta, the virus spreads through the vascular system of the developing fetus and may infect any fetal organ. The most important risk factor for severe congenital defects is the stage of gestation at the time of infection. Maternal infection during the first 8 weeks of gestation results in the most severe and widespread defects. The risk for congenital defects has been estimated at 90% for maternal infection before 11 weeks of gestation, 33% at 11-12 weeks, 11% at 13-14 weeks, and 24% at 15-16 weeks. Defects occurring after 16 weeks of gestation are uncommon, even if fetal infection occurs.

Causes of cellular and tissue damage in the infected fetus may include tissue necrosis due to vascular insufficiency, reduced cellular multiplication time, chromosomal breaks, and production of a protein inhibitor causing mitotic arrests in certain cell types. The most distinctive feature of congenital rubella is chronicity. Once the fetus is infected early in gestation, the virus persists in fetal tissue until well beyond delivery. Persistence suggests the possibility of ongoing tissue damage and reactivation, most notably in the brain.

CLINICAL MANIFESTATIONS

Postnatal infection with rubella is typically a mild disease not easily discernible from other viral infections, especially in children. After an incubation period of 12-23 days, a prodrome consisting of low-grade fever, sore throat, red eyes with or without eye pain, headache, malaise, anorexia, and lymphadenopathy begins. Suboccipital, postauricular, and anterior cervical lymph nodes are most prominent. In children, the first manifestation of rubella is usually the rash, which is variable and not distinctive, often more prominent with heat. It begins on the face and neck as small, irregular pink macules that coalesce, and it spreads centrifugally to involve the torso and extremities, where

it tends to occur as discrete macules (Fig. 294.3). About the time of onset of the rash, examination of the oropharynx may reveal tiny, rose-colored lesions **(Forchheimer spots)** or petechial hemorrhages on the soft palate. The rash fades from the face as it extends to the rest of the body so that the whole body may not be involved at any one time. The duration of the rash is generally 3 days, and it usually resolves without desquamation. Subclinical infections are common, and 25–40% of children may not have a rash. Teenagers and adults tend to be more symptomatic and have systemic manifestations, with up to 70% of females demonstrating arthralgias and arthritis.

TABLE 294.1 Pathologic Findings in Congenital Rubella Syndrome

SYSTEM	PATHOLOGIC FINDINGS
Cardiovascular	Patent ductus arteriosus Pulmonary artery stenosis Ventriculoseptal defect Myocarditis
Central nervous system	Chronic meningitis Parenchymal necrosis Vasculitis with calcification
Eye	Microphthalmia Cataract Iridocyclitis Ciliary body necrosis Glaucoma Retinopathy
Ear	Cochlear hemorrhage Endothelial necrosis
Lung	Chronic mononuclear interstitial pneumonitis
Liver	Hepatic giant cell transformation Fibrosis Lobular disarray Bile stasis
Kidney	Interstitial nephritis
Adrenal gland	Cortical cytomegaly
Bone	Malformed osteoid Poor mineralization of osteoid Thinning cartilage
Spleen, lymph node	Extramedullary hematopoiesis
Thymus	Histiocytic reaction Absence of germinal centers
Skin	Erythropoiesis in dermis

LABORATORY FINDINGS

Leukopenia, neutropenia, and mild thrombocytopenia have been described during postnatal rubella.

DIAGNOSES

A specific diagnosis of rubella is important for epidemiologic reasons, for diagnosis of infection in pregnant women, and for confirmation of the diagnosis of congenital rubella. The most common diagnostic test is rubella immunoglobulin (Ig) M enzyme immunosorbent assay, which is typically present ~4 days after the appearance of the rash. As with any serologic test, the positive predictive value of testing decreases in populations with low prevalence of disease and in immunized individuals. Tests should be performed in the context of a supportive history of exposure or consistent clinical findings. The relative sensitivity and specificity of commercial kits used in most laboratories range from 96–99% and 86–97%, respectively. A caveat for testing of congenitally infected infants early in infancy is that false-negative results may occur owing to competing IgG antibodies circulating in these patients. In

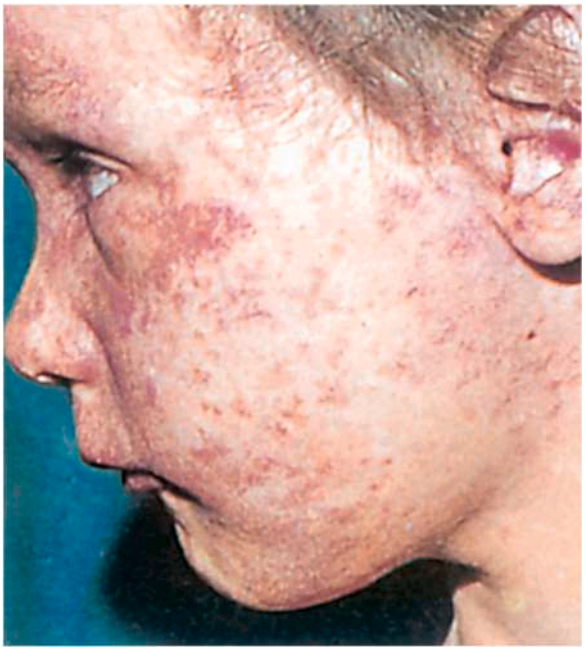

Fig. 294.3 Rash of rubella.

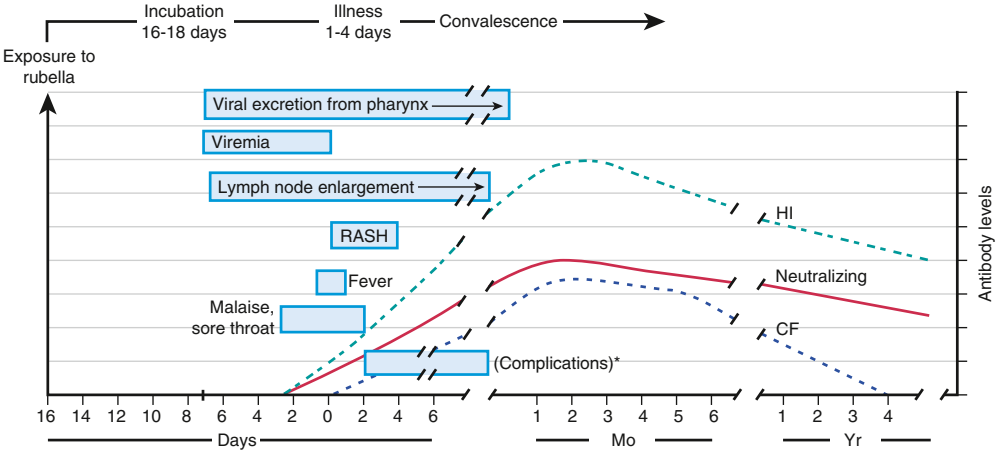

Fig. 294.2 Pathophysiologic events in postnatally acquired rubella virus infection. *Possible complications include arthralgia and/or arthritis, thrombocytopenic purpura, and encephalitis. CF, Complement fixation titer; HI, hemagglutination-inhibition titer. *(From Lamprecht CL. Rubella virus. In: Beshe RB, ed. Textbook of Human Virology, 2nd ed. Littleton, MA: PSG Publishing; 1990:685.)*

such patients, an IgM capture assay, reverse transcriptase polymerase chain reaction (PCR) test, or viral culture should be performed for confirmation. Virus can be detected by PCR in nasal, throat, urine, blood, and cerebrospinal fluid (CSF) specimens up to 10 days after rash onset (with highest yield within 3 days). Viral isolation by culture or PCR of nasopharyngeal secretions, urine in the newborn (as close to birth as possible), or cord blood or placenta can be used to diagnose congenital infection. PCR testing of amniotic fluid during pregnancy is also an appropriate approach to diagnose congenital infection. If CRS is confirmed, infants should be screened for viral shedding monthly after the age of 3 months until two consecutive negative tests are obtained. Viral shedding may be detected for up to 1 year.

DIFFERENTIAL DIAGNOSES

Rubella may manifest as distinctive features suggesting the diagnosis. It is frequently confused with other infections because it is uncommon, is similar to other viral exanthematous diseases, and demonstrates variability in the presence of typical findings. In severe cases, it may resemble measles. The absence of Koplik spots, a severe prodrome, and a shorter course, allow for differentiation from measles. Other diseases frequently confused with rubella include infections caused by adenoviruses, parvovirus B19 (erythema infectiosum), Epstein-Barr virus, enteroviruses, roseola, and *Mycoplasma pneumoniae*.

COMPLICATIONS

Complications following postnatal infection with rubella are infrequent and generally not life threatening.

Postinfectious **thrombocytopenia** occurs in approximately 1 in 3,000 cases of rubella and occurs more frequently among children and in girls. It manifests about 2 weeks after the onset of the rash as petechiae, epistaxis, gastrointestinal bleeding, and hematuria and is usually self-limited.

Arthritis following rubella occurs more commonly among adults, especially women. It begins within 1 week of onset of the exanthem and classically involves the small joints of the hands. It is self-limited and resolves within weeks without sequelae. There are anecdotal reports and some serologic evidence linking rubella with rheumatoid arthritis, but a true causal association remains speculative.

Encephalitis is the most serious complication of postnatal rubella. It occurs in two forms: a postinfectious syndrome following acute rubella and a rare progressive panencephalitis manifesting as a neurodegenerative disorder years after rubella.

Postinfectious encephalitis is uncommon, occurring in 1 in 5,000 cases of rubella. It appears within 7 days after onset of the rash, consisting of headache, seizures, confusion, coma, focal neurologic signs, and ataxia. Fever may recrudesce with the onset of neurologic symptoms. CSF may be normal or have a mild mononuclear pleocytosis and/or elevated protein concentration. Virus is rarely, if ever, isolated from CSF or brain, suggesting a noninfectious pathogenesis. Most patients recover completely, but mortality rates of 20% and long-term neurologic sequelae have been reported.

Progressive rubella panencephalitis (PRP) is an extremely rare complication of either acquired rubella or CRS. It has an onset and course similar to those of the subacute sclerosing panencephalitis associated with measles (see Chapter 293). However, unlike in the postinfectious form of rubella encephalitis, rubella virus may be isolated from brain tissue of the patient with PRP, suggesting an infectious pathogenesis, albeit a slow one. The clinical findings and course are indistinguishable from those of subacute sclerosing panencephalitis and transmissible spongiform encephalopathies (see Chapter 324). Death occurs 2-5 years after onset.

Other neurologic syndromes rarely reported with rubella include Guillain-Barré syndrome and peripheral neuritis. Myocarditis is a rare complication.

Congenital Rubella Syndrome

In 1941 an ophthalmologist first described a syndrome of cataracts and congenital heart disease that he correctly associated with rubella infections in the mothers during early pregnancy (Table 294.2). Shortly after the first description, hearing loss was recognized as a common finding often associated with microcephaly. In 1964 to 1965 a pandemic of rubella occurred, with 20,000 cases reported in the United States, leading to more than 11,000 spontaneous or therapeutic abortions and 2,100 neonatal deaths. From this experience emerged the expanded definition of CRS that includes numerous other transient or permanent abnormalities.

TABLE 294.2 Clinical Manifestations of Congenital Rubella Syndrome in 376 Children After Maternal Rubella*

MANIFESTATION	RATE (%)
Deafness	67
Ocular	71
Cataracts	29
Retinopathy	39
Heart disease†	48
Patent ductus arteriosus	78
Right pulmonary artery stenosis	70
Left pulmonary artery stenosis	56
Valvular pulmonic stenosis	40
Low birthweight	60
Psychomotor delay	45
Neonatal purpura	23
Death	35

*Other findings: hepatitis, linear streaking of bone, hazy cornea, congenital glaucoma, delayed growth.
†Findings in 87 patients with congenital rubella syndrome and heart disease who underwent cardiac angiography.
From Cooper LZ, Ziring PR, Ockerse AB, et al. Rubella: clinical manifestations and management. *Am J Dis Child.* 1969;118:18–29.

Nerve deafness is the single most common finding among infants with CRS. Most infants have some degree of intrauterine growth restriction. Retinal findings described as **salt-and-pepper retinopathy** are the most common ocular abnormality but have little early effect on vision. Unilateral or bilateral cataracts are the most serious eye finding, occurring in about a third of infants (Fig. 294.4). Cardiac abnormalities occur in half of the children infected during the first 8 weeks of gestation. Patent ductus arteriosus is the most frequently reported cardiac defect, followed by lesions of the pulmonary arteries and valvular disease. Interstitial pneumonitis leading to death in some cases has been reported. Neurologic abnormalities are common and may progress following birth. Meningoencephalitis is present in 10–20% of infants with CRS and may persist for up to 12 months. Longitudinal follow-up through 9-12 years of infants without initial retardation revealed progressive development of additional sensory, motor, and behavioral abnormalities, including hearing loss and autism. PRP has also been recognized rarely after CRS. Subsequent postnatal growth retardation and ultimate short stature have been reported in a minority of cases. Rare reports of immunologic deficiency syndromes have also been described.

A variety of late-onset manifestations of CRS have been recognized. In addition to PRP, they include diabetes mellitus (20%), thyroid dysfunction (5%), and glaucoma and visual abnormalities associated with the retinopathy, which had previously been considered benign.

TREATMENT

There is no specific treatment available for either acquired rubella or CRS.

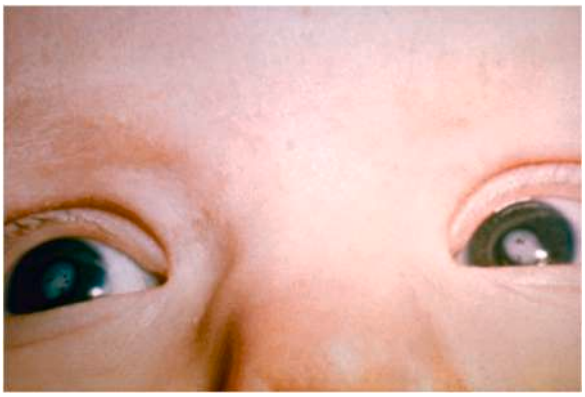

Fig. 294.4 Bilateral cataracts in infant with congenital rubella syndrome.

SUPPORTIVE CARE

Postnatal rubella is generally a mild illness that requires no care beyond antipyretics and analgesics. Intravenous immunoglobulin or corticosteroids can be considered for severe, nonremitting thrombocytopenia.

Management of children with CRS is more complex and requires pediatric, cardiac, audiologic, ophthalmologic, and neurologic evaluation and follow-up because many manifestations may not be readily apparent initially or may worsen with time. Hearing screening is of special importance because early intervention may improve outcomes in children with hearing problems caused by CRS.

PROGNOSIS

Postnatal infection with rubella has an excellent prognosis. Long-term outcomes of CRS are less favorable and somewhat variable. In an Australian cohort evaluated 50 years after infection, many had chronic conditions but most were married and had made good social adjustments. A cohort from New York from the mid-1960s epidemic had less-favorable outcomes, with 30% leading normal lives, 30% in dependent situations but functional, and 30% requiring institutionalization and continuous care.

Reinfection with wild virus occurs postnatally in both individuals who were previously infected with wild-virus rubella and vaccinated individuals. Reinfection is defined serologically as a significant increase in IgG antibody level and/or an IgM response in an individual who has a documented preexisting rubella-specific IgG above an accepted cutoff. Reinfection may result in an anamnestic IgG response, an IgM and IgG response, or clinical rubella. There are 29 reports in the literature of CRS following maternal reinfection. Reinfection with serious adverse outcomes to adults or children is rare and of unknown significance.

PREVENTION

Patients with postnatal infection should be isolated from susceptible individuals for 7 days after onset of the rash. Standard plus droplet precautions are recommended for hospitalized patients. Children with CRS may excrete the virus in respiratory secretions up to 1 year of age, so contact precautions should be maintained for them until 1 year of age, unless repeated cultures of urine and pharyngeal secretions are negative. Similar precautions apply to patients with CRS with regard to attendance in school and out-of-home childcare.

Exposure of susceptible pregnant women poses a potential risk to the fetus. For pregnant women exposed to rubella, a blood specimen should be obtained as soon as possible for rubella IgG-specific antibody testing; a frozen aliquot also should be saved for later testing. If the rubella antibody test result is positive, the mother is likely immune. If the rubella antibody test is negative, a second specimen should be obtained 2-3 weeks later and tested concurrently with the saved specimen. If both of these samples test negative, a third specimen should be obtained 6 weeks after exposure and tested concurrently with the saved specimen. If both the second and third specimens test negative, infection has not occurred. A negative first specimen and a positive test result in either the second or third specimen indicate that seroconversion has occurred in the mother, suggesting recent infection. Counseling should be provided about the risks and benefits of termination of pregnancy. The routine use of immunoglobulin for susceptible pregnant women exposed to rubella is not recommended and is considered only if termination of pregnancy is not an option because of maternal preferences. In such circumstances, immunoglobulin 0.55 mL/kg intramuscularly may be given with the understanding that prophylaxis may reduce the risk for clinically apparent infection but does not guarantee prevention of fetal infection.

VACCINATION

Rubella vaccine in the United States consists of the attenuated Wistar RA 27/3 strain that is usually administered in combination with measles and mumps (MMR) or also with varicella (MMRV) in a two-dose regimen at 12-15 months and 4-6 years of age. It theoretically may be effective as postexposure prophylaxis if administered within 3 days of exposure. Vaccine should not be administered to severely immunocompromised patients. Patients with HIV infection who are not severely immunocompromised may benefit from vaccination. Fever is not a contraindication, but if a more serious illness is suspected, immunization should be delayed. Immunoglobulin preparations may inhibit the serologic response to the vaccine (see Chapter 215). Vaccine should not be administered during pregnancy. If pregnancy occurs within 28 days of immunization, the patient should be counseled on the theoretical risks to the fetus. Studies of more than 200 women who had been inadvertently immunized with rubella vaccine during pregnancy showed that none of their offspring developed CRS. Therefore interruption of pregnancy is probably not warranted.

Following a single dose of rubella RA 27/3 vaccine, 95% of persons 12 months of age and older develop serologic immunity, and after two doses 99% have detectable antibody. Rubella RA 27/3 vaccine is highly protective, because 97% of those vaccinated are protected from clinical disease after one dose. Detectable antibodies remain for 15 years in most individuals vaccinated after one dose, and 91–100% had antibodies after 12-15 years after two doses. Although antibody levels may wane, especially after one dose of vaccine, increased susceptibility to rubella disease does not occur.

Adverse reactions to rubella vaccination are uncommon in children. MMR administration is associated with fever in 5–15% of vaccinees and with rash in approximately 5% of vaccinees. Arthralgia and arthritis are more common after rubella vaccination in adults. Approximately 25% of postpubertal women experience arthralgia, and 10% of postpubertal women experience arthritis. Peripheral neuropathies and transient thrombocytopenia may also occur.

As part of the worldwide effort to eliminate endemic rubella virus transmission and occurrence of CRS, maintaining high population immunity through vaccination coverage and high-quality integrated measles-rubella surveillance have been emphasized as being vital to its success.

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Chapter 295

Mumps

Hayley A. Gans

Mumps is an acute self-limited infection that was once commonplace but is now uncommon in countries with widespread use of vaccination. It is characterized by fever, bilateral or unilateral parotid swelling and tenderness, and the frequent occurrence of meningoencephalitis and orchitis. Although infrequent in countries with extensive vaccination programs, mumps remains endemic in the rest of the world, warranting continued vaccine protection. Nonetheless, outbreaks of mumps have been reported in highly vaccinated populations in the United States, particularly among students.

ETIOLOGY

Mumps virus is in the family Paramyxoviridae and the genus *Rubulavirus*. It is a negative-sense single-stranded nonsegmented RNA virus encapsulated in a lipoprotein envelope possessing seven structural proteins. Surface glycoproteins called HN (hemagglutinin-neuraminidase) and F (fusion) mediate absorption of the virus to host cells and penetration of the virus into cells, respectively. Both proteins stimulate production of protective antibodies. Mumps virus exists as a single serotype with up to 12 known genotypes, and humans are the only natural host.

EPIDEMIOLOGY

In the prevaccine era, mumps occurred primarily in young children between the ages of 5 and 9 years and in epidemics about every 4 years. Mumps infection occurred more often in the winter and spring months. In 1968, just after the introduction of the mumps vaccine, 185,691 cases were reported in the United States. Following the recommendation for routine use of mumps vaccine in 1977, the incidence of mumps fell dramatically in young children (Fig. 295.1) and shifted instead to older children, adolescents, and young adults. Outbreaks continued to occur *even in highly vaccinated* populations as a result of primary vaccine failure with one dose of vaccine and because of undervaccination of susceptible persons. After implementation of the two-dose recommendation for the measles-mumps-rubella (MMR) vaccine for measles control in 1989, the number of mumps cases declined further. During 2001–2003, fewer than 300 mumps cases were reported each year. In 2006 the largest mumps epidemic in the past 20 years occurred in the United States. A total of 6,584 cases occurred, 85% of them in 8 midwestern states. Twenty-nine percent of the cases occurred in patients 18-24 years old, most of whom were attending college. An analysis of 4,039 patients with mumps seen in the first 7 months of the epidemic indicated that 63% had received more than two doses of the MMR vaccine. Subsequently, several outbreaks of mumps have been documented in highly vaccinated populations in the United States, several in school settings including universities and in Guam. This phenomenon is reported globally as well. The majority of cases in vaccinated persons represent close contact thought to provide intense exposure that may overcome vaccine immunity and perhaps genotype mismatch between circulating mumps genotypes and those in the vaccine. Through 2020, mumps outbreaks have continued to occur, with a peak in 2016 with 6,366 cases, which dropped to 154 in 2021.

Mumps is spread from person to person by respiratory droplets. Virus appears in the saliva from up to 7 days before to as long as 7 days after onset of parotid swelling. The period of maximum infectiousness is 1-2 days before to 5 days after onset of parotid swelling. Viral shedding before onset of symptoms and in asymptomatic infected individuals impairs efforts to contain the infection in susceptible populations. The risk of spreading the virus increases the longer and the closer the contact a person has with someone who has mumps. The U.S. Centers for Disease Control and Prevention, the American Academy of Pediatrics, and the Health Infection Control Practices Advisory Committee recommend an isolation period of 5 days after onset of parotitis for patients with mumps in both community and healthcare settings.

PATHOLOGY AND PATHOGENESIS

Mumps virus targets the salivary glands, central nervous system (CNS), pancreas, testes, and, to a lesser extent, thyroid, ovaries, heart, kidneys, liver, and joint synovia.

After infection, initial viral replication occurs in the epithelium of the upper respiratory tract. Infection spreads to the adjacent lymph nodes by the lymphatic drainage, and viremia ensues, spreading the virus to targeted tissues, including the meninges, salivary glands, pancreas, testes, and ovaries. Mumps virus causes necrosis of infected cells and is associated with a lymphocytic inflammatory infiltrate. Salivary gland ducts are lined with necrotic epithelium, and the interstitium is infiltrated with lymphocytes. Swelling of tissue within the testes may result in focal ischemic infarcts. The cerebrospinal fluid (CSF) frequently contains a mononuclear pleocytosis, even in individuals without clinical signs of meningitis.

CLINICAL MANIFESTATIONS

The incubation period for mumps ranges from 12-25 days but is usually 16-18 days. Mumps virus infection may result in clinical presentation

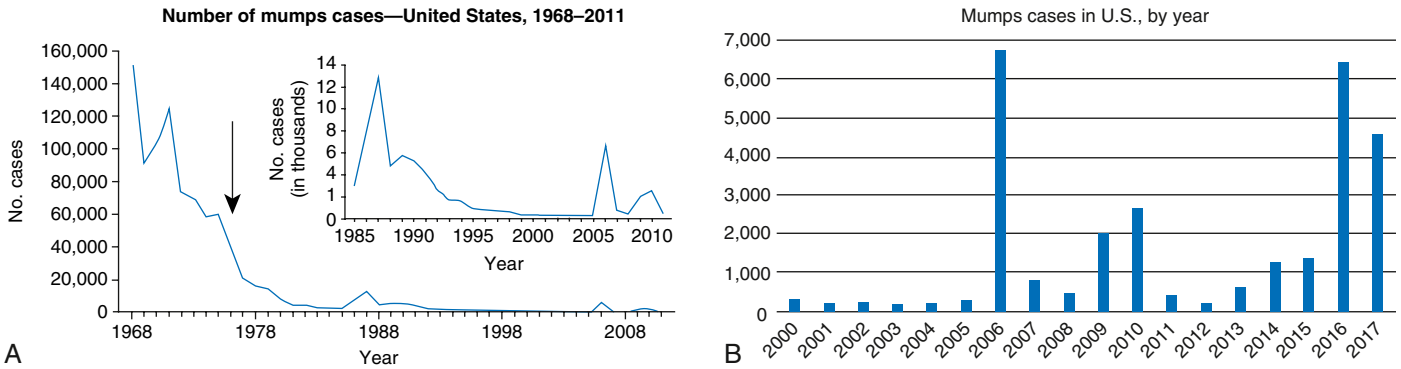

Fig. 295.1 **A,** Mumps cases in the United States from 1968, right after the live mumps vaccine was introduced in 1967, to 2011. There was a steady decline following introduction of the vaccine and recommendation for routine vaccination in 1977 *(arrow)*. Note national increases in activity in 1986–1987, 2006. Mumps data provided were reported voluntarily to the Centers for Disease Control and Prevention (CDC) from state health departments. **B,** Mumps cases in the United States from 2000–2017 showing the increased activity in 2006, 2009, 2010, and 2014–2017. Mumps data provided were reported voluntarily to CDC from state health departments. *(**A,** From McLean HQ, Fiebelkorn AP, Temte JL, et al. Prevention of measles, rubella, congenital rubella syndrome and mumps. MMWR Recomm Rep. 2013;62[RR-04]:1–34; **B,** From Morbidity and Mortality Weekly Report (MMWR): Notifiable Diseases and Mortality Tables. https://www.cdc.gov/mumps/outbreaks.html.)*

ranging from asymptomatic (in the prevaccine era 15–24% of infections were asymptomatic; accurate estimates in the postvaccination era are difficult to measure) or nonspecific symptoms to the typical illness associated with parotitis with or without complications involving several body systems. The typical patient presents with a prodrome lasting 1-2 days consisting of fever, headache, vomiting, malaise, and myalgias. Parotitis follows and may be unilateral initially but becomes bilateral in approximately 70% of cases (Fig. 295.2). The parotid gland is tender, and parotitis may be preceded or accompanied by ear pain on the ipsilateral side. Ingestion of sour or acidic foods or liquids may enhance pain in the parotid area. As swelling progresses, the angle of the jaw is obscured, and the ear lobe may be lifted upward and outward (see Figs. 295.2 and 295.3). The opening of the Stensen duct may be red and edematous. The parotid swelling peaks in approximately 3 days and then gradually subsides over 7 days. Fever and the other systemic symptoms resolve in 3-5 days. A morbilliform rash is rarely seen. Submandibular salivary glands may also be involved or may be enlarged without parotid swelling. Edema over the sternum as a result of lymphatic obstruction may also occur. Symptoms in immunized individuals are the same but tend to be less severe, and parotitis may be absent.

DIAGNOSIS

When mumps was highly prevalent, the diagnosis could be made on the basis of a history of exposure to mumps infection, an appropriate incubation period, and development of typical clinical findings. Confirmation of the presence of parotitis could be made with demonstration of an elevated serum amylase value. Leukopenia with a relative lymphocytosis was a common finding. Currently, in highly immunized populations patients with parotitis lasting longer than 2 days and of unknown cause, a specific diagnosis of mumps should be confirmed or ruled out by virologic or serologic examination. This step may be accomplished by isolation of the virus in cell culture, detection of viral antigen by direct immunofluorescence, or identification of nucleic acid by reverse transcriptase polymerase chain reaction (PCR). Virus can be isolated from upper respiratory tract secretions (buccal and oropharyngeal mucosa), CSF, or urine during the acute illness; however, PCR from the oropharyngeal secretions becomes negative quickly, especially in immunized individuals, and thus should be run within 3 days of parotid swelling. Serologic testing is usually a more convenient and available mode of diagnosis. A significant increase in serum mumps immunoglobulin G (IgG) antibody between acute and convalescent serum specimens as detected by complement fixation, neutralization hemagglutination, or enzyme immunoassay tests establishes the diagnosis. Mumps IgG antibodies may cross react with antibodies to parainfluenza virus in serologic testing. More commonly, an enzyme immunoassay for mumps IgM antibody is used to identify recent infection. All serologic tests are difficult to interpret in immunized individuals, and negative test results do not rule out mumps infection. Skin testing for mumps is neither sensitive nor specific and should not be used.

DIFFERENTIAL DIAGNOSIS

Parotid swelling may be caused by many other infectious and noninfectious conditions, especially in sporadic cases. Viruses that cause parotitis include parainfluenza 1 and parainfluenza 3 viruses, influenza A virus, cytomegalovirus, Epstein-Barr virus, enteroviruses, lymphocytic choriomeningitis virus, and HIV. Purulent parotitis, usually caused by *Staphylococcus aureus,* is unilateral, is extremely tender, is associated with an elevated white blood cell count, and may involve purulent drainage from the Stensen duct. Submandibular or anterior cervical adenitis from a variety of pathogens may also be confused with parotitis. Other noninfectious causes of parotid swelling include obstruction of the Stensen duct, collagen vascular diseases such as Sjögren syndrome, systemic lupus erythematosus, immunologic diseases, tumor, and drugs.

COMPLICATIONS

The most common complications of mumps are meningitis, with or without encephalitis, and gonadal (orchitis, oophoritis) involvement. Uncommon complications include conjunctivitis, optic neuritis, pneumonia, nephritis, pancreatitis, mastitis, and thrombocytopenia. Complications can occur in the absence of parotitis, especially in immunized individuals, and overall complication rates in immunized individuals are lower than in unimmunized and are shifted toward the adult populations.

Maternal infection with mumps during the first trimester of pregnancy results in increased fetal wastage. No fetal malformations have been associated with intrauterine mumps infection. However, perinatal mumps disease has been reported in infants born to mothers who acquired mumps late in gestation.

Meningitis and Meningoencephalitis

Mumps virus is neurotropic and is thought to enter the CNS via the choroid plexus and infect the choroidal epithelium and ependymal cells, both of which can be found in CSF along with mononuclear leukocytes. In the prevaccine era mumps represented one of the most common causes of aseptic meningitis and hearing loss among children. Symptomatic CNS involvement occurs in 10–30% of infected individuals, but CSF pleocytosis has been found in 40–60% of patients with mumps parotitis. The meningoencephalitis may occur before, along with, or following the parotitis. It most commonly manifests 5 days after the parotitis. Clinical findings vary with age. Infants and young children have fever, malaise, and lethargy, whereas older children, adolescents, and adults complain of headache and demonstrate

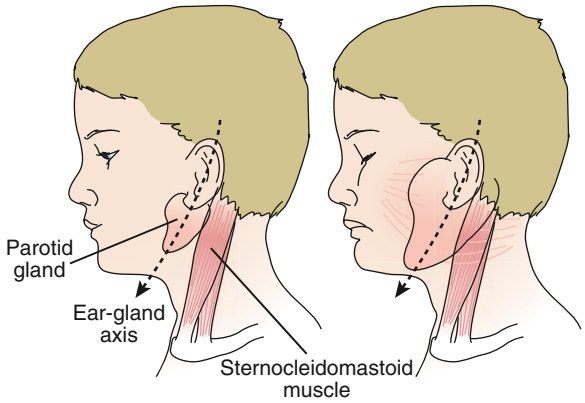

Fig. 295.2 Schematic of a parotid gland infected with mumps *(right)* compared with a normal gland *(left)*. An imaginary line bisecting the long axis of the ear divides the parotid gland into two equal parts. These anatomic relationships are not altered in the enlarged gland. An enlarged cervical lymph node is usually posterior to the imaginary line. *(From Mumps [epidemic parotitis]. In Krugman S, Ward R, Katz SL, eds. Infectious Diseases in Children, 6th ed. St. Louis: Mosby; 1977:182.)*

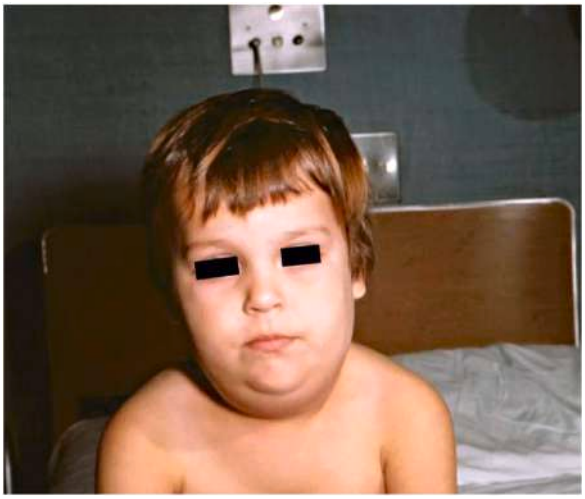

Fig. 295.3 A child with mumps showing parotid swelling. *(From the Centers for Disease Control and Prevention. Public Health Image Library [PHIL], Image 4491. https://phil.cdc.gov/Details.aspx?pid=4491.)*

meningeal signs. In a series of children with mumps and meningeal involvement, findings were fever in 94%, vomiting in 84%, headache in 47%, parotitis in 47%, neck stiffness in 71%, lethargy in 69%, and seizures in 18%. In typical cases, symptoms resolve in 7-10 days. CSF in mumps meningitis has a white blood cell pleocytosis of 200-600 μL with a predominance of lymphocytes. The CSF glucose content is normal in most patients, but a moderate hypoglycorrhachia (glucose content 20-40 mg/dL) may be seen in 10–20% of patients. The CSF protein content is normal or mildly elevated.

Less-common CNS complications of mumps include transverse myelitis, acute disseminated encephalomyelitis **(ADEM)**, aqueductal stenosis, and facial palsy. Sensorineural hearing loss is rare and has been estimated to occur in 0.5-5.0 in 100,000 cases of mumps. The hearing loss can be transient. There is some evidence that hearing loss is more likely in patients with meningoencephalitis.

Orchitis and Oophoritis

In adolescent and adult males, orchitis is second only to parotitis as a common finding in mumps. Involvement in prepubescent boys is extremely rare, but after puberty, orchitis occurs in 30–40% of males. It begins within days following onset of parotitis in most cases and is associated with moderate to high fever, chills, and exquisite pain and swelling of the testes. In 30% or less of cases, the orchitis is bilateral. Atrophy of the testes may occur, but sterility is rare even with bilateral involvement.

Oophoritis is uncommon in postpubertal females but may cause severe pain and may be confused with appendicitis when located on the right side.

Pancreatitis

Pancreatitis may occur in mumps with or without parotid involvement. Severe disease is rare, but fever, epigastric pain, and vomiting are suggestive. Epidemiologic studies have suggested that mumps may be associated with the subsequent development of diabetes mellitus, but a causal link has not been established.

Cardiac Involvement

Myocarditis has been reported in mumps, and molecular studies have identified mumps virus in heart tissue taken from patients with endocardial fibroelastosis.

Arthritis

Arthralgia, monoarthritis, and migratory polyarthritis have been reported in mumps. Arthritis is seen with or without parotitis and usually occurs within 3 weeks of onset of parotid swelling. It is generally mild and self-limited.

Thyroiditis

Thyroiditis is rare following mumps. It has not been reported without parotitis and may occur weeks after the acute infection. Most cases resolve, but some become relapsing and result in hypothyroidism.

TREATMENT

No specific antiviral therapy is available for mumps. Management should be aimed at reducing the pain associated with meningitis or orchitis and maintaining adequate hydration. Antipyretics may be given for fever.

PROGNOSIS

The outcome of mumps is nearly always excellent, even when the disease is complicated by encephalitis, although fatal cases from CNS involvement or myocarditis have been reported. No mumps deaths have occurred in the recent outbreaks in the United States.

PREVENTION

Immunization with the live mumps vaccine is the primary mode of prevention used in the United States. It is given as part of the MMR two-dose vaccine schedule, at 12-15 months of age for the first dose and 4-6 years of age for the second dose. If not given at 4-6 years, the second dose should be given before children enter puberty. In those traveling, two doses are recommended in individuals older than 12 months administered at least 28 days apart. Antibody develops in 94% (range: 89–97%) after one dose. Antibody levels achieved after vaccination are lower than after natural infection.

The median vaccine effectiveness of mumps vaccine after one dose of vaccine is 78% (range: 49–92%) and after two doses is 88% (range: 66–95%). Duration of effectiveness is ≥10 years after one dose and ≥15 years after two doses.

During outbreaks, *a third MMR dose* administered to the at-risk population was associated with improved outbreak control with significantly fewer cases in those receiving the third dose compared with those not receiving it. Despite these results, modeling supports the current two-dose schedule without a routine third booster dose because the current regimen significantly controls size of outbreaks, severity of disease, and number of hospitalizations, whereas the third dose appears to be a possible strategy during an outbreak.

As a live-virus vaccine, MMR should not be administered to pregnant women or to severely immunodeficient or immunosuppressed individuals. HIV-infected patients who are not severely immunocompromised may receive the vaccine, because the risk for severe infection with mumps outweighs the risk for serious reaction to the vaccine. Individuals with anaphylactoid reactions to egg or neomycin may be at risk for immediate-type hypersensitivity reactions to the vaccine. Persons with other types of reactions to egg or reactions to other components of the vaccine are not restricted from receiving the vaccine.

In 2006, in response to the multistate outbreak in the United States, evidence of immunity to mumps through vaccination was redefined. Acceptable presumptive evidence of immunity to mumps now consists of one of the following: (1) documentation of adequate vaccination at age 12 months or older, (2) laboratory evidence of immunity, (3) birth before 1957, and (4) documentation of physician-diagnosed mumps. Evidence of immunity through documentation of adequate vaccination is defined as one dose of a live mumps virus vaccine for preschool-age children and adults not at high risk and two doses for school-age children (i.e., grades K-12) and for adults at high risk (e.g., healthcare workers, international travelers, and students at post–high school educational institutions).

All persons who work in healthcare facilities should be immune to mumps. Adequate mumps vaccination for healthcare workers born during or after 1957 consists of two doses of a live mumps virus vaccine. Healthcare workers with no history of mumps vaccination and no other evidence of immunity should receive two doses, with >28 days between doses. Healthcare workers who have received only one dose previously should receive a second dose. Because birth before 1957 is only presumptive evidence of immunity, healthcare facilities should consider recommending one dose of a live mumps virus vaccine for unvaccinated workers born before 1957 who do not have a history of physician-diagnosed mumps or laboratory evidence of mumps immunity. During an outbreak, healthcare facilities should strongly consider recommending two doses of a live mumps virus vaccine to unvaccinated workers born before 1957 who do not have evidence of mumps immunity.

Adverse reactions to mumps virus vaccine are rare. Parotitis and orchitis have been reported rarely. There is inadequate information to make a causal relationship to other reactions, such as febrile seizures, deafness, rash, purpura, encephalitis, and meningitis with the strain of mumps vaccine virus used for immunization in the United States. Higher rates of aseptic meningitis following vaccination for mumps are associated with vaccine strains used elsewhere in the world, including the Leningrad 3 and Urabe Am 9 strains. Transient suppression of reactivity to tuberculin skin testing has been reported after mumps vaccination.

In 2005 the quadrivalent measles, mumps, rubella, and varicella (MMRV) vaccine was made available. However, in 2010, studies showed a greater risk of febrile seizures in children 12-23 months of age 5-12 days after administration of the vaccine. No increased risk of seizures was seen in children receiving the first dose of the MMRV at older than 48 months of age. As a result, the American Academy of Pediatrics currently recommends either the MMR vaccine and separate varicella vaccine or the MMRV vaccine in children 12-47 months of age. After 48 months of age, the MMRV is generally preferred.

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Chapter 296

Polioviruses

Eric A.F. Simões

ETIOLOGY

The polioviruses are nonenveloped, positive-stranded RNA viruses belonging to the Picornaviridae family, in the genus *Enterovirus,* species enterovirus C and consist of three antigenically distinct serotypes (types 1, 2, and 3). Polioviruses spread from the intestinal tract to the central nervous system (CNS), where they cause aseptic meningitis and poliomyelitis, or polio. The polioviruses are extremely hardy and can retain infectivity for several days at room temperature.

EPIDEMIOLOGY

The most devastating result of poliovirus infection is paralysis, although 90–95% of infections are inapparent. Despite the absence of symptoms, clinically inapparent infections induce protective immunity. Clinically apparent but nonparalytic illness occurs in approximately 5% of all infections, with paralytic polio occurring in approximately 1 in 1,000 infections among infants to approximately 1 in 100 infections among adolescents. In industrialized countries before universal vaccination, epidemics of paralytic poliomyelitis occurred primarily in adolescents. Conversely, in developing countries with poor sanitation, infection early in life results in infantile paralysis. Improved sanitation explains the virtual eradication of polio from the United States in the early 1960s, when only approximately 65% of the population was immunized with the Salk vaccine, which contributed to the disappearance of circulating wild-type poliovirus in the United States and Europe.

TRANSMISSION

Humans are the only known reservoir for the polioviruses, which are spread by the fecal-oral route. Poliovirus has been isolated from feces for longer than 2 weeks before paralysis to several weeks after the onset of symptoms.

PATHOGENESIS

Polioviruses infect cells by adsorbing to the genetically determined **poliovirus receptor (CD155)**. The virus penetrates the cell, is uncoated, and releases viral RNA. The RNA is translated to produce proteins responsible for replication of the RNA, shutoff of host cell protein synthesis, and synthesis of structural elements that compose the capsid. Mature virus particles are produced in 6-8 hours and are released into the environment by disruption of the cell.

In the contact host, wild-type and vaccine strains of polioviruses gain host entry via the gastrointestinal tract. Recent studies in nonhuman primates demonstrate that the primary sites of replication are in the $CD155^+$ epithelial cells lining the mucosa of the tonsil follicle and small intestine, as well as in the macrophages/dendritic cells in the tonsil follicle and Peyer patches. Regional lymph nodes are infected, and primary viremia occurs after 2-3 days. The virus seeds multiple sites, including the reticuloendothelial system, brown fat deposits, and skeletal muscle. Wild-type poliovirus probably accesses the CNS along peripheral nerves. Vaccine strains of polioviruses do not replicate in the CNS, a feature that accounts for the safety of the live-attenuated vaccine. Occasional **revertants** (by nucleotide substitution) of these vaccine strains develop a neurovirulent phenotype and cause **vaccine-associated paralytic poliomyelitis (VAPP)**. Reversion occurs in the small intestine and probably accesses the CNS via the peripheral nerves. Poliovirus has almost never been cultured from the cerebrospinal fluid (CSF) of patients with paralytic disease, and patients with aseptic meningitis caused by poliovirus never have paralytic disease. With the first appearance of non-CNS symptoms, a secondary viremia probably occurs as a result of enormous viral replication in the reticuloendothelial system.

The exact mechanism of entry into the CNS is not known. However, once entry is gained, the virus may traverse neural pathways, and multiple sites within the CNS are often affected. The effect on motor and autonomic neurons is most striking and correlates with the clinical manifestations. Perineuronal inflammation, a mixed inflammatory reaction with both polymorphonuclear leukocytes and lymphocytes, is associated with extensive neuronal destruction. Petechial hemorrhages and considerable inflammatory edema also occur in areas of poliovirus infection. The poliovirus primarily infects motor neuron cells in the spinal cord **(the anterior horn cells)** and the medulla oblongata (the cranial nerve nuclei). Because of the overlap in muscle innervation by two to three adjacent segments of the spinal cord, clinical signs of weakness in the limbs develop when more than 50% of motor neurons are destroyed. In the medulla, less-extensive lesions cause paralysis, and involvement of the reticular formation that contains the vital centers controlling respiration and circulation may have a catastrophic outcome. Involvement of the intermediate and dorsal areas of the horn and the dorsal root ganglia in the spinal cord results in hyperesthesia and myalgias that are typical of acute poliomyelitis. Other neurons affected are the nuclei in the roof and vermis of the cerebellum, the substantia nigra, and, occasionally, the red nucleus in the pons; there may be variable involvement of thalamic, hypothalamic, and pallidal nuclei and the motor cortex.

Apart from the histopathology of the CNS, inflammatory changes occur generally in the reticuloendothelial system. Inflammatory edema and sparse lymphocytic infiltration are prominently associated with hyperplastic lymphocytic follicles.

Infants acquire immunity transplacentally from their mothers. Transplacental immunity disappears at a variable rate during the first 4-6 months of life. Active immunity after natural infection is probably lifelong but protects against the infecting serotype only; infections with other serotypes are possible. Poliovirus-neutralizing antibodies develop within several days after exposure as a result of replication of the virus in the tonsils and in the intestinal tract and deep lymphatic tissues. This early production of circulating immunoglobulin (Ig) G antibodies protects against CNS invasion. Local (mucosal) immunity, conferred mainly by secretory IgA, is an important defense against subsequent reinfection of the gastrointestinal tract.

CLINICAL MANIFESTATIONS

The incubation period of poliovirus from contact to initial clinical symptoms is usually considered to be 8-12 days, with a range of 5-35 days. Poliovirus infections with wild-type virus may follow one of several courses: **inapparent infection**, which occurs in 90–95% of cases and causes no disease and no sequelae; abortive poliomyelitis; nonparalytic poliomyelitis; or paralytic poliomyelitis. Paralysis, if it occurs, appears 3-8 days after the initial symptoms. The clinical manifestations of paralytic polio caused by wild or vaccine strains are comparable, although the incidence of abortive and nonparalytic paralysis with vaccine-associated poliomyelitis is unknown.

Abortive Poliomyelitis

In approximately 5% of patients, a nonspecific influenza-like syndrome occurs 1-2 weeks after infection, which is termed *abortive poliomyelitis*. Fever, malaise, anorexia, and headache are prominent features, and there may be sore throat and abdominal or muscular pain. Vomiting occurs irregularly. The illness is short lived, lasting up to 2-3 days. The physical examination may be normal or may reveal nonspecific pharyngitis, abdominal or muscular tenderness, and weakness. Recovery is complete, and no neurologic signs or sequelae develop.

Nonparalytic Poliomyelitis

In approximately 1% of patients infected with wild-type poliovirus, signs of abortive poliomyelitis are present, as are more intense headache, nausea, and vomiting, as well as soreness and stiffness of the posterior muscles of the neck, trunk, and limbs. Fleeting paralysis of the bladder and constipation are frequent. Approximately two thirds

of these children have a short symptom-free interlude between the first phase **(minor illness)** and the second phase (CNS disease or **major illness**). Nuchal rigidity and spinal rigidity are the basis for the diagnosis of nonparalytic poliomyelitis during the second phase.

Physical examination reveals nuchal-spinal signs and changes in superficial and deep reflexes. Gentle forward flexion of the occiput and neck elicits nuchal rigidity. The examiner can demonstrate head drop by placing the hands under the patient's shoulders and raising the patient's trunk. Although normally the head follows the plane of the trunk, in poliomyelitis it often falls backward limply, but this response is not attributable to true paresis of the neck flexors. In struggling infants, it may be difficult to distinguish voluntary resistance from clinically important true nuchal rigidity. The examiner may place the infant's shoulders flush with the edge of the table, support the weight of the occiput in the hand, and then flex the head anteriorly. True nuchal rigidity persists during this maneuver. When open, the anterior fontanel may be tense or bulging.

In the early stages the reflexes are normally active and remain so unless paralysis supervenes. Changes in reflexes, either increased or decreased, may precede weakness by 12-24 hours. The superficial reflexes, the cremasteric and abdominal reflexes, and the reflexes of the spinal and gluteal muscles are usually the first to diminish. The spinal and gluteal reflexes may disappear before the abdominal and cremasteric reflexes. Changes in the deep tendon reflexes generally occur 8-24 hours after the superficial reflexes are depressed and indicate impending paresis of the extremities. Tendon reflexes are absent with paralysis. Sensory defects do not occur in poliomyelitis.

Paralytic Poliomyelitis

Paralytic poliomyelitis develops in approximately 0.1% of persons infected with poliovirus, causing 3 clinically recognizable syndromes that represent a continuum of infection differentiated only by the portions of the CNS most severely affected. These are (1) spinal paralytic poliomyelitis, (2) bulbar poliomyelitis, and (3) polioencephalitis.

Spinal paralytic poliomyelitis may occur as the second phase of a biphasic illness, the first phase of which corresponds to abortive poliomyelitis. The patient then appears to recover and feels better for 2-5 days, after which severe headache and fever occur with exacerbation of the previous systemic symptoms. Severe muscle pain is present, and sensory and motor phenomena (e.g., paresthesia, hyperesthesia, fasciculations, and spasms) may develop. On physical examination the distribution of paralysis is characteristically spotty. Single muscles, multiple muscles, or groups of muscles may be involved in any pattern. Within 1-2 days, *asymmetric flaccid paralysis or paresis occurs*. Involvement of one leg is most common, followed by involvement of one arm. The proximal areas of the extremities tend to be involved to a greater extent than the distal areas. To detect mild muscular weakness, it is often necessary to apply gentle resistance in opposition to the muscle group being tested. Examination at this point may reveal nuchal stiffness or rigidity, muscle tenderness, initially hyperactive deep tendon reflexes (for a short period) followed by absence or diminution of reflexes, and paresis or flaccid paralysis. In the spinal form, there is weakness of some of the muscles of the neck, abdomen, trunk, diaphragm, thorax, or extremities. *Sensation is intact; sensory disturbances, if present, suggest a disease other than poliomyelitis.*

The paralytic phase of poliomyelitis is extremely variable; some patients progress during observation from paresis to paralysis, whereas others recover, either slowly or rapidly. The extent of paresis or paralysis is directly related to the extent of neuronal involvement; paralysis occurs if >50% of the neurons supplying the muscles are destroyed. The extent of involvement is usually obvious within 2-3 days; only rarely does progression occur beyond this interval. Bowel and bladder dysfunction ranging from transient incontinence to paralysis with constipation and urinary retention often accompany paralysis of the lower limbs.

The onset and course of paralysis are variable in developing countries. The biphasic course is rare; typically the disease manifests in a single phase in which prodromal symptoms and paralysis occur in a continuous fashion. In developing countries, where a history of intramuscular injections precedes paralytic poliomyelitis in approximately 50–60% of patients, patients may present initially with fever and paralysis **(provocation paralysis)**. The degree and duration of muscle pain are also variable, ranging from a few days usually to a week. Occasionally, spasm and increased muscle tone with a transient increase in deep tendon reflexes occur in some patients, whereas in most patients, flaccid paralysis occurs abruptly. Once the temperature returns to normal, progression of paralytic manifestations stops. Little recovery from paralysis is noted in the first days or weeks, but, if it is to occur, it is usually evident within 6 months. The return of strength and reflexes is slow and may continue to improve for as long as 18 months after the acute disease. Lack of improvement from paralysis within the first several weeks or months after onset is usually evidence of permanent paralysis. Atrophy of the limb, failure of growth, and deformity are common and are especially evident in the growing child.

Bulbar poliomyelitis may occur as a clinical entity without apparent involvement of the spinal cord. Infection is a continuum, and designation of the disease as bulbar implies only dominance of the clinical manifestations by dysfunctions of the cranial nerves and medullary centers. The clinical findings seen with bulbar poliomyelitis with respiratory difficulty (other than paralysis of extraocular, facial, and masticatory muscles) include (1) nasal twang to the voice or cry caused by palatal and pharyngeal weakness (hard-consonant words such as cookie and candy bring this feature out best); (2) inability to swallow smoothly, resulting in accumulation of saliva in the pharynx, indicating partial immobility (holding the larynx lightly and asking the patient to swallow will confirm such immobility); (3) accumulated pharyngeal secretions, which may cause irregular respirations that appear interrupted and abnormal even to the point of falsely simulating intercostal or diaphragmatic weakness; (4) absence of effective coughing, shown by constant fatiguing efforts to clear the throat; (5) nasal regurgitation of saliva and fluids as a result of palatal paralysis, with inability to separate the oropharynx from the nasopharynx during swallowing; (6) deviation of the palate, uvula, or tongue; (7) involvement of vital centers in the medulla, which manifest as irregularities in rate, depth, and rhythm of respiration and as cardiovascular alterations, including blood pressure changes (especially increased blood pressure), alternate flushing and mottling of the skin, and cardiac arrhythmias; and as rapid changes in body temperature; (8) paralysis of one or both vocal cords, causing hoarseness, aphonia, and, ultimately, asphyxia unless the problem is recognized on laryngoscopy and managed by immediate tracheostomy; and (9) the **rope sign**, an acute angulation between the chin and larynx caused by weakness of the hyoid muscles (the hyoid bone is pulled posteriorly, narrowing the hypopharyngeal inlet).

Uncommonly, bulbar disease may culminate in an ascending paralysis (Landry type), in which there is progression cephalad from initial involvement of the lower extremities. Hypertension and other autonomic disturbances are common in bulbar involvement and may persist for a week or more or may be transient. Occasionally, hypertension is followed by hypotension and shock and is associated with irregular or failed respiratory effort, delirium, or coma. This kind of bulbar disease may be rapidly fatal.

The course of bulbar disease is variable; some patients die as a result of extensive, severe involvement of the various centers in the medulla; others recover partially but require ongoing respiratory support, and others recover completely. Cranial nerve involvement is seldom permanent. Atrophy of muscles may be evident, patients immobilized for long periods may experience pneumonia, and renal stones may form as a result of hypercalcemia and hypercalciuria secondary to bone resorption.

Polioencephalitis is a rare form of the disease in which higher centers of the brain are severely involved. Seizures, coma, and spastic paralysis with increased reflexes may be observed. Irritability, disorientation, drowsiness, and coarse tremors are often present with peripheral or cranial nerve paralysis that coexists or ensues. Hypoxia and hypercapnia caused by inadequate ventilation due to respiratory insufficiency may produce disorientation without true encephalitis. The manifestations are common to encephalitis of any cause and can be

attributed to polioviruses only with specific viral diagnosis or if accompanied by flaccid paralysis.

Paralytic poliomyelitis with ventilatory insufficiency results from several components acting together to produce ventilatory insufficiency resulting in hypoxia and hypercapnia. It may have profound effects on many other systems. Because respiratory insufficiency may develop rapidly, close continued clinical evaluation is essential. Despite weakness of the respiratory muscles, the patient may respond with so much respiratory effort associated with anxiety and fear that overventilation may occur at the outset, resulting in respiratory alkalosis. Such effort is fatiguing and contributes to respiratory failure.

There are certain characteristic patterns of disease. Pure spinal poliomyelitis with respiratory insufficiency involves tightness, weakness, or paralysis of the respiratory muscles (chiefly the diaphragm and intercostals) without discernible clinical involvement of the cranial nerves or vital centers that control respiration, circulation, and body temperature. The cervical and thoracic spinal cord segments are chiefly affected. Pure bulbar poliomyelitis involves paralysis of the motor cranial nerve nuclei with or without involvement of the vital centers. Involvement of the 9th, 10th, and 12th cranial nerves results in paralysis of the pharynx, tongue, and larynx with consequent airway obstruction. Bulbospinal poliomyelitis with respiratory insufficiency affects the respiratory muscles and results in coexisting bulbar paralysis.

The clinical findings associated with involvement of the respiratory muscles include (1) anxious expression; (2) inability to speak without frequent pauses, resulting in short, jerky, breathless sentences; (3) increased respiratory rate; (4) movement of the alae nasi and of the accessory muscles of respiration; (5) inability to cough or sniff with full depth; (6) paradoxical abdominal movements caused by diaphragmatic immobility caused by spasm or weakness of one or both leaves; and (7) relative immobility of the intercostal spaces, which may be segmental, unilateral, or bilateral. When the arms are weak, and especially when deltoid paralysis occurs, there may be impending respiratory paralysis because the phrenic nerve nuclei are in adjacent areas of the spinal cord. Observation of the patient's capacity for thoracic breathing while the abdominal muscles are splinted manually indicates minor degrees of paresis. Light manual splinting of the thoracic cage helps to assess the effectiveness of diaphragmatic movement.

DIAGNOSIS

Poliomyelitis should be considered in any unimmunized or incompletely immunized child with paralytic disease. Although this guideline is most applicable in poliomyelitis endemic countries (Afghanistan, and Pakistan in 2023), the spread of polio in 2013 from endemic countries to many nonendemic countries (Niger, Chad, Cameroon, Ethiopia, Kenya, Somalia, and Syria) and the isolation of wild poliovirus type 1 in Israel in 2014 and circulating type 1 vaccine-associated paralytic polio in Ukraine in 2015 suggest that the diagnosis of polio should be entertained in all countries. VAPP should be considered in any child with paralytic disease occurring 7-14 days after receiving the orally administered polio vaccine (OPV). VAPP can occur at later times after administration and should be considered in any child with paralytic disease in countries or regions where wild-type poliovirus has been eradicated and the OPV has been administered to the child or a contact. The combination of fever, headache, neck and back pain, asymmetric flaccid paralysis without sensory loss, and pleocytosis does not regularly occur in any other illness.

The World Health Organization (WHO) recommends that the laboratory diagnosis of poliomyelitis be confirmed by isolation and identification of poliovirus in the stool, with specific identification of wild-type and vaccine-type strains. In suspected cases of acute flaccid paralysis, two stool specimens should be collected 24-48 hours apart as soon as possible after the diagnosis of poliomyelitis is suspected. Poliovirus concentrations are high in the stool in the first week after the onset of paralysis, which is the optimal time for collection of stool specimens. Polioviruses may be isolated from 80–90% of specimens from acutely ill patients, whereas <20% of specimens from such patients may yield virus at 3-4 weeks after onset of paralysis. Because most children with spinal or bulbospinal poliomyelitis have constipation, rectal straws may be used to obtain specimens; ideally a minimum of 8-10 g of stool should be collected. In laboratories that can isolate poliovirus, isolates should be sent to either the U.S. Centers for Disease Control and Prevention (CDC) or to one of the WHO-certified poliomyelitis laboratories where DNA sequence analysis can be performed to distinguish between wild poliovirus and neurovirulent, revertant OPV strains. With the current WHO plan for global eradication of poliomyelitis, most regions of the world (the Americas, Europe, and Australia) have been certified wild-poliovirus free; in these areas, poliomyelitis is most often caused by vaccine strains. Hence it is critical to differentiate between wild-type and revertant vaccine-type strains.

The CSF is often normal during the minor illness and typically contains a pleocytosis with 20-300 cells/μL with CNS involvement. The cells in the CSF may be polymorphonuclear early during the course of the disease but shift to mononuclear cells soon afterward. By the second week of major illness, the CSF cell count falls to near-normal values. In contrast, the CSF protein content is normal or only slightly elevated at the outset of CNS disease but usually rises to 50-100 mg/dL by the second week of illness. In polioencephalitis, the CSF may remain normal or show minor changes. Serologic testing demonstrates seroconversion or a fourfold or greater increase in antibody titers from the acute phase of illness to 3-6 weeks later.

DIFFERENTIAL DIAGNOSIS

Poliomyelitis should be considered in the differential diagnosis of any case of paralysis and is only one of many causes of acute flaccid paralysis (AFP) in children and adults. There are numerous other causes of acute flaccid paralysis (Table 296.1). As evidence of this point, in 2022 of the 57,983 cases of AFP reported to WHO, there were 30 cases of WPV1, 173 of cVDPV1, and 648 cases of cVDPV2. In most conditions, the clinical features are sufficient to differentiate between these various causes, but in some cases nerve conduction studies and electromyograms, in addition to muscle biopsies, may be required.

The possibility of polio should be considered in any case of acute flaccid paralysis, even in countries where polio has been eradicated. The diagnoses most often confused with polio are VAPP, West Nile virus infection, and infections caused by other enteroviruses (including EV-A71 and EV-D68), as well as Guillain-Barré syndrome, transverse myelitis, and traumatic paralysis. In **Guillain-Barré syndrome**, which is the most difficult to distinguish from poliomyelitis, the paralysis is characteristically symmetric, and sensory changes and pyramidal tract signs are common, contrasting with poliomyelitis. Fever, headache, and meningeal signs are less notable, and the CSF has few cells but an elevated protein content. **Transverse myelitis** progresses rapidly over hours to days, causing an acute symmetric paralysis of the lower limbs with concomitant anesthesia and diminished sensory perception. Autonomic signs of hypothermia in the affected limbs are common, and there is bladder dysfunction. The CSF is usually normal. **Traumatic neuritis** occurs from a few hours to a few days after the traumatic event, is asymmetric, is acute, and affects only one limb. Muscle tone and deep tendon reflexes are reduced or absent in the affected limb with pain in the gluteus. The CSF is normal.

Conditions causing pseudoparalysis do not present with nuchal-spinal rigidity or pleocytosis. These causes include unrecognized trauma, transient (toxic) synovitis, acute osteomyelitis, acute rheumatic fever, scurvy, and congenital syphilis (pseudoparalysis of Parrot).

TREATMENT

There is no specific antiviral treatment for poliomyelitis. However, pocapavir (a capsid inhibitor) and V-7404 (an enterovirus 3C protease inhibitor) are being developed potentially for use in combination for treatment of poliovirus and other enteroviral infections. The management is supportive and aimed at limiting progression of disease, preventing ensuing skeletal deformities, and preparing the child and family for the prolonged treatment required and for permanent disability if this seems likely. Patients with the nonparalytic and mildly paralytic forms of poliomyelitis may be treated at home. All intramuscular injections and surgical procedures are contraindicated during the

Table 296.1 Differential Diagnosis of Acute Flaccid Paralysis

SITE, CONDITION, FACTOR, OR AGENT	CLINICAL FINDINGS	ONSET OF PARALYSIS	PROGRESSION OF PARALYSIS	SENSORY SIGNS AND SYMPTOMS	REDUCTION OR ABSENCE OF DEEP TENDON REFLEXES	RESIDUAL PARALYSIS	PLEOCYTOSIS
ANTERIOR HORN CELLS OF SPINAL CORD							
Poliomyelitis (wild and vaccine-associated paralytic poliomyelitis)	Paralysis	Incubation period 7-14 days (range: 4-35 days)	24-48 hr to onset of full paralysis; proximal → distal, asymmetric	No	Yes	Yes	Aseptic meningitis (moderate polymorphonuclear leukocytes at 2-3 days)
Nonpolio enteroviruses (including EV-A71, EV D68)	Hand-foot-and-mouth disease, aseptic meningitis, acute hemorrhagic conjunctivitis, possibly idiopathic epidemic flaccid paralysis	As in poliomyelitis	As in poliomyelitis	No	Yes	Yes	As in poliomyelitis
West Nile virus	Meningitis encephalitis	As in poliomyelitis	As in poliomyelitis	No	Yes	Yes	Yes
OTHER NEUROTROPIC VIRUSES							
Rabies virus		Mo to yr	Acute, symmetric, ascending	Yes	Yes	No	±
Varicella-zoster virus	Exanthematous vesicular eruptions	Incubation period 10-21 days	Acute, symmetric, ascending	Yes	±	±	Yes
Japanese encephalitis virus		Incubation period 5-15 days	Acute, proximal, asymmetric	±	±	±	Yes
GUILLAIN-BARRÉ SYNDROME							
Acute inflammatory polyradiculo-neuropathy	Preceding infection, bilateral facial weakness	Hr to 10 days	Acute, symmetric, ascending (days to 4 wk)	Yes	Yes	±	No
Acute motor axonal neuropathy	Fulminant, widespread paralysis, bilateral facial weakness, tongue involvement	Hr to 10 days	1-6 days	No	Yes	±	No

Continued

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Table 296.1 Differential Diagnosis of Acute Flaccid Paralysis—cont'd

SITE, CONDITION, FACTOR, OR AGENT	CLINICAL FINDINGS	ONSET OF PARALYSIS	PROGRESSION OF PARALYSIS	SENSORY SIGNS AND SYMPTOMS	REDUCTION OR ABSENCE OF DEEP TENDON REFLEXES	RESIDUAL PARALYSIS	PLEOCYTOSIS
ACUTE TRAUMATIC SCIATIC NEURITIS							
Intramuscular gluteal injection	Acute, asymmetric	Hr to 4 days	Complete, affected limb	Yes	Yes	±	No
Acute transverse myelitis	Preceding *Mycoplasma pneumoniae*, *Schistosoma*, other parasitic or viral infection	Acute, symmetric hypotonia of lower limbs	Hr to days	Yes	Yes, early	Yes	Yes
Epidural abscess	Headache, back pain, local spinal tenderness, meningismus	Complete		Yes	Yes	±	Yes
Spinal cord compression; trauma		Complete	Hr to days	Yes	Yes	±	±
NEUROPATHIES							
Exotoxin of *Corynebacterium diphtheriae*	In severe cases, palatal paralysis, blurred vision	Incubation period 1-8 wk (paralysis 8-12 wk after onset of illness)		Yes	Yes		±
Toxin of *Clostridium botulinum*	Abdominal pain, diplopia, loss of accommodation, mydriasis	Incubation period 18-36 hr	Rapid, descending, symmetric	±	No		No
Tick bite paralysis	Ocular symptoms	Latency period 5-10 days	Acute, symmetric, ascending	No	Yes		No
DISEASES OF THE NEUROMUSCULAR JUNCTION							
Myasthenia gravis	Weakness, fatigability, diplopia, ptosis, dysarthria		Multifocal	No	No	No	No
DISORDERS OF MUSCLE							
Polymyositis	Neoplasm, autoimmune disease	Subacute, proximal → distal	Wk to mo	No	Yes		No
Viral myositis		Pseudoparalysis	Hr to days	No	No		No
METABOLIC DISORDERS							
Hypokalemic periodic paralysis		Proximal limb, respiratory muscles	Sudden postprandial	No	Yes	±	No
INTENSIVE CARE UNIT WEAKNESS							
Critical illness polyneuropathy	Flaccid limbs and respiratory weakness	Acute, following systemic inflammatory response syndrome/sepsis	Hr to days	±	Yes	±	No

Modified from Marx A, Glass JD, Sutter RW. Differential diagnosis of acute flaccid paralysis and its role in poliomyelitis surveillance. *Epidemiol Rev*. 2000;22:298–316.

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acute phase of the illness, especially in the first week of illness, because they might result in progression of disease.

Abortive Poliomyelitis

Supportive treatment with analgesics, sedatives, an appetizing diet, and bed rest until the child's temperature is normal for several days is usually sufficient. Avoidance of exertion for the ensuing 2 weeks is desirable, and careful neurologic and musculoskeletal examinations should be performed 2 months later to detect any minor involvement.

Nonparalytic Poliomyelitis

Treatment for the nonparalytic form is similar to that for the abortive form; in particular, relief is indicated for the discomfort of muscle tightness and spasm of the neck, trunk, and extremities. Analgesics are more effective when they are combined with the application of hot packs for 15-30 minutes every 2-4 hours. Hot tub baths are sometimes useful. A firm bed is desirable and can be improvised at home by placing table leaves or a sheet of plywood beneath the mattress. A footboard or splint should be used to keep the feet at a right angle to the legs. Because muscular discomfort and spasm may continue for some weeks, even in the nonparalytic form, hot packs and gentle physical therapy may be necessary. Patients with nonparalytic poliomyelitis should also be carefully examined 2 months after apparent recovery to detect minor residual effects that might cause postural problems in later years.

Paralytic Poliomyelitis

Most patients with the paralytic form of poliomyelitis require hospitalization with complete physical rest in a calm atmosphere for the first 2-3 weeks. **Suitable body alignment** is necessary for comfort and to avoid excessive skeletal deformity. A neutral position with the feet at right angles to the legs, the knees slightly flexed, and the hips and spine straight is achieved by use of boards, sandbags, and, occasionally, light splint shells. The position should be changed every 3-6 hours. **Active and passive movements** are indicated as soon as the pain has disappeared. Moist hot packs may relieve muscle pain and spasm. Opiates and sedatives are permissible only if no impairment of ventilation is present or impending. Constipation is common, and fecal impaction should be prevented. When bladder paralysis occurs, a parasympathetic stimulant such as bethanechol may induce voiding in 15-30 minutes; some patients show no response to this agent, and others respond with nausea, vomiting, and palpitations. Bladder paresis rarely lasts more than a few days. If bethanechol fails, manual compression of the bladder and the psychologic effect of running water should be tried. If catheterization must be performed, care must be taken to prevent urinary tract infections. An appealing diet and a relatively high fluid intake should be started at once unless the patient is vomiting. Additional salt should be provided if the environmental temperature is high or if the application of hot packs induces sweating. Anorexia is common initially. Adequate dietary and fluid intake can be maintained by placement of a central venous catheter. An orthopedist and a physiatrist should see patients as early in the course of the illness as possible and should assume responsibility for their care before fixed deformities develop.

The management of pure bulbar poliomyelitis consists of maintaining the airway and avoiding all risk of inhalation of saliva, food, and vomitus. Gravity drainage of accumulated secretions is favored by using the head-low (foot of bed elevated 20-25 degrees) prone position with the face to one side. Patients with weakness of the muscles of respiration or swallowing should be nursed in a lateral or semiprone position. Aspirators with rigid or semirigid tips are preferred for direct oral and pharyngeal aspiration, and soft, flexible catheters may be used for nasopharyngeal aspiration. Fluid and electrolyte equilibrium is best maintained by intravenous infusion because tube or oral feeding in the first few days may incite vomiting. In addition to close observation for respiratory insufficiency, the blood pressure should be measured at least twice daily because hypertension is not uncommon and occasionally leads to hypertensive encephalopathy. Patients with pure bulbar poliomyelitis may require tracheostomy because of vocal cord paralysis or constriction of the hypopharynx; most patients who recover have little residual impairment, although some exhibit mild dysphagia and occasional vocal fatigue with slurring of speech.

Impaired ventilation must be recognized early; mounting anxiety, restlessness, and fatigue are early indications for preemptive intervention. Tracheostomy is indicated for some patients with pure bulbar poliomyelitis, spinal respiratory muscle paralysis, or bulbospinal paralysis because such patients are generally unable to cough, sometimes for many months. Mechanical respirators are often needed.

COMPLICATIONS

Paralytic poliomyelitis may be associated with numerous complications. Acute gastric dilation may occur abruptly during the acute or convalescent stage, causing further respiratory embarrassment; immediate gastric aspiration and external application of ice bags are indicated. Melena severe enough to require transfusion may result from single or multiple superficial intestinal erosions; perforation is rare. Mild hypertension for days or weeks is common in the acute stage and probably related to lesions of the vasoregulatory centers in the medulla and especially to underventilation. In the later stages, because of immobilization, hypertension may occur along with hypercalcemia, nephrocalcinosis, and vascular lesions. Dimness of vision, headache, and a lightheaded feeling associated with hypertension should be regarded as premonitory of a frank convulsion. Cardiac irregularities are uncommon, but electrocardiographic abnormalities suggesting myocarditis occur with some frequency. Acute pulmonary edema occurs occasionally, particularly in patients with arterial hypertension. Hypercalcemia occurs because of skeletal decalcification that begins soon after immobilization and results in hypercalciuria, which in turn predisposes the patient to urinary calculi, especially when urinary stasis and infection are present. High fluid intake is the only effective prophylactic measure.

PROGNOSIS

The outcome of inapparent, abortive poliomyelitis and aseptic meningitis syndromes is uniformly good, with death being exceedingly rare and with no long-term sequelae. The outcome of paralytic disease is determined primarily by degree and severity of CNS involvement. In severe bulbar poliomyelitis, the mortality rate may be as high as 60%, whereas in less-severe bulbar involvement and/or spinal poliomyelitis, the mortality rate varies from 5–10%, death generally occurring from causes other than the poliovirus infection.

Maximum paralysis usually occurs 2-3 days after the onset of the paralytic phase of the illness, with stabilization followed by gradual return of muscle function. The recovery phase usually lasts about 6 months, beyond which persisting paralysis is permanent. In general, paralysis is more likely to develop in male children and female adults. Mortality and the degree of disability are greater after the age of puberty. Pregnancy is associated with an increased risk for paralytic disease. Tonsillectomy and intramuscular injections may enhance the risk for acquisition of bulbar and localized disease, respectively. Increased physical activity, exercise, and fatigue during the early phase of illness have been cited as factors leading to a higher risk for paralytic disease. Finally, it has been clearly demonstrated that type 1 poliovirus has the greatest propensity for natural poliomyelitis and type 3 poliovirus has a predilection for producing VAPP.

Postpolio Syndrome

After an interval of 30-40 years, as many as 30–40% of persons who survived paralytic poliomyelitis in childhood may experience muscle pain and exacerbation of existing weakness or development of new weakness or paralysis. This entity, referred to as postpolio syndrome, has been reported only in persons who were infected in the era of wild-type poliovirus circulation. Risk factors for postpolio syndrome include increasing length of time since acute poliovirus infection, presence of permanent residual impairment after recovery from acute illness, and female sex.

PREVENTION

Vaccination is the only effective method of preventing poliomyelitis. Hygienic measures help to limit the spread of the infection among

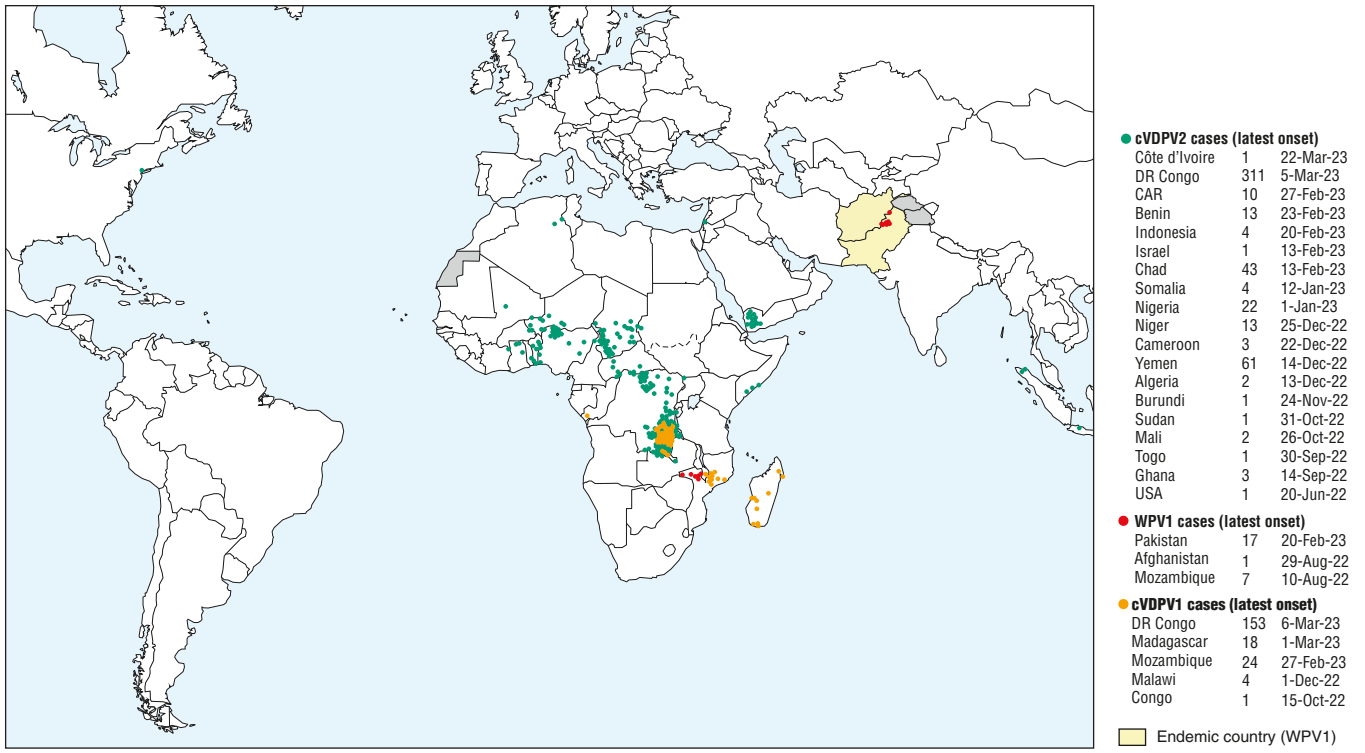

Fig. 296.1 Global WPV1 and cVDPV cases, previous 12 months. Excludes viruses detected from environmental surveillance. Onset of paralysis: 3 May 2022 to 2 May 2023; data in WHO HQ as of 2 May 2023. *(Courtesy Global Polio Eradication Initiative. https://polioeradication.org/polio-today/polio-now/. Accessed Jan 26, 2022.)*

young children, but immunization is necessary to control transmission among all age groups. Both the inactivated polio vaccine (IPV), which is currently produced using better methods than those for the original vaccine and is sometimes referred to as enhanced IPV, and the live-attenuated OPV have established efficacy in preventing poliovirus infection and paralytic poliomyelitis. Both vaccines induce production of antibodies against the three strains of poliovirus. IPV elicits higher serum IgG antibody titers, but the OPV also induces significantly greater mucosal IgA immunity in the oropharynx and gastrointestinal tract, which limits replication of the wild poliovirus at these sites. Transmission of wild poliovirus by fecal spread is limited in OPV recipients. The immunogenicity of IPV is not affected by the presence of maternal antibodies, and IPV has no adverse effects. Live vaccine may undergo reversion to neurovirulence as it multiplies in the human intestinal tract and may cause VAPP in vaccinees or in their contacts. The overall risk for recipients varies from 1 case per 750,000 immunized infants in the United States to 1 in 143,000 immunized infants in India. The risk for paralysis in the B-cell–immunodeficient recipient may be as much as 6,800 times that in normal persons. HIV infection has not been found to result in long-term excretion of virus. *As of January 2000, the IPV-only schedule is recommended for routine polio vaccination in the United States.* All children should receive four doses of IPV, at 2 months, 4 months, 6-18 months, and 4-6 years of age. Five combination vaccines (DTaP-HepB-IPV-Pediarix; DTaP-IPV/Hib—Pentacel; DTaP-IPV-Hib-HepB—Vaxelis, and DTaP-IPV—Kinrix and Quadracel) and a single antigen IPV (IPOL; distributed in 10 dose vials) are approved in the United States with different schedules and ages for use. Given the rapid spread of cVPDV (Fig. 296.1) in many countries of the world, the reader is advised to refer to CDC or WHO websites to determine the necessity for accelerated vaccination of children going to identified countries. IPV can be given at a minimum of 6, 10, or 14 weeks of age with a booster at 6 months.

In 1988 the World Health Assembly resolved to eradicate poliomyelitis globally by 2000, and remarkable progress had been made toward reaching this target. To achieve this goal, the WHO used four basic strategies: routine immunization, National Immunization Days, acute flaccid paralysis surveillance, and mop-up immunization. This strategy has resulted in a >99% decline in poliomyelitis cases; in early 2002, there were only 10 countries in the world endemic for poliomyelitis. In 2012 there were the fewest cases of poliomyelitis ever and the virus was endemic in only three countries (Afghanistan, Pakistan, and Nigeria). The last case of WPV 3 infection occurred in Nigeria in November 2012, leading to certification of global WPV3 eradication. The last case of wild poliovirus type 2 infection occurred in India in October 1999. Polioviruses remain endemic in Pakistan and Afghanistan. The rejection of poliovirus vaccine initiatives and campaign quality in security-compromised areas in parts of these countries are still the main factors interfering with efforts to eradicate polio.

In May 2013 the WHO assembly recommended the development of a *Polio Eradication and Endgame Strategic Plan*. This plan included the replacement of trivalent OPV (tOPV) with bivalent OPV (bOPV) containing only Sabin types 1 and 3 in all countries by 2016 and the introduction of initially one dose of IPV followed by the replacement of bOPV with IPV in all countries of the world by 2019. As long as the OPV is being used, there is the potential that vaccine-derived poliovirus (VDPV) will acquire the neurovirulent phenotype and transmission characteristics of the wild-type polioviruses. VDPV emerges from the OPV because of continuous replication in immunodeficient persons (iVDPV) or by circulation in populations with low vaccine coverage (cVDPVs). The risk was highest with the type 2 strain. Since the world switched from the use of tOPV to bOPV, tOPV is no longer used globally in any routine or supplemental immunization activities.

Recommendations for international travelers to certain countries were made by the WHO and endorsed by the CDC. Continuing spread due to poor herd immunity and now international spread pose a significant threat to the eradication effort. The committee recommended that for countries with WPV1, cVDPV1, or cVDPV2 with potential risk of international spread, all residents and long-term visitors (i.e., >4 weeks) of all ages receive a dose of bOPV or IPV between 4 weeks and 12 months before travel to these countries. Such travelers should

be provided with an International Certificate of Vaccination of Prophylaxis to record their polio vaccination and service proof of vaccination. These countries have been advised to restrict at the point of departure the international travel of any resident lacking documentation of full vaccination, whether by air, sea, or land. For countries infected with cVDPV2 with potential risk of international spread (see Fig. 296.1 and WHO website), visitors should be encouraged to follow these recommendations (not mandated).

The WHO has mandated that infants in all countries still using bOPV should receive a dose of IPV, to offer protection against polio virus type 2. These efforts have been stymied because of the global inability to produce IPV in a large enough volume to cover all the 128 million babies born annually in the world. This problem was a crisis during the global synchronized introduction of bOPV, when several countries (e.g., India) had to use two fractional doses of IPV (1/5 dose) administered intradermally. To enhance scale-up of IPV production in countries such as India, Brazil, and China, IPV using Sabin strains of poliovirus (sIPV) were developed in Japan and China. These mitigate the stringent requirements for wild-type poliovirus culture that are normally required for IPV production. Other strategies include developing adjuvants for IPV (approved by the Danish Medicines Agency in 2019) and other novel *E.coli*–based adjuvants that could potentially lower the antigen quantities needed for each dose.

Given the ongoing spread of cVDPVs, alternative stable novel Sabin vaccine strains that do not revert to neurovirulence (nOPVs) were developed for all three strains (Bio Farma, Indonesia) and have been shown to be immunogenic, stable, and safe.

In countries where bOPV is included in routine immunization, it is best if it follows at least one dose of IPV or two doses of fractional intradermal IPV.

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Chapter 297

Nonpolio Enteroviruses

Kevin B. Messacar and Mark J. Abzug

The genus *Enterovirus* contains a large number of viruses spread via the gastrointestinal and respiratory routes that produce a broad range of illnesses in patients of all ages. Many of the manifestations predominantly affect infants and young children.

ETIOLOGY

Enteroviruses are nonenveloped, single-stranded, positive-sense viruses in the Picornaviridae (small RNA virus) family, which also includes the rhinoviruses, hepatitis A virus, and parechoviruses. The original human enterovirus subgroups—polioviruses (see Chapter 296), coxsackieviruses, and echoviruses—were differentiated by their replication patterns in tissue culture and animals (Table 297.1). Enteroviruses have been reclassified on the basis of genetic similarity into four species, human enteroviruses A-D. Specific enterovirus types are distinguished by antigenic and genetic sequence differences, with enteroviruses discovered after 1970 classified by species and number (e.g., enterovirus D68 and A71). Although more than 100 types have been described, 10-15 account for the majority of disease. No disease is uniquely associated with any specific serotype, although certain manifestations are associated with specific serotypes. *The closely related human parechoviruses can cause clinical presentations similar to those associated with enteroviruses.*

Table 297.1 Classification of Human Enteroviruses

Family	Picornaviridae
Genus	*Enterovirus*
Subgroups*	Poliovirus serotypes 1-3 Coxsackie A virus serotypes 1-22, 24 (23 reclassified as echovirus 9) Coxsackie B virus serotypes 1-6 Echovirus serotypes 1-9, 11-27, 29-33 (echoviruses 10 and 28 reclassified as nonenteroviruses; echovirus 34 reclassified as a variant of coxsackie A virus 24; echoviruses 22 and 23 reclassified within the genus *Parechovirus*) Numbered enterovirus serotypes (enterovirus 72 reclassified as hepatitis A virus)

*The human enteroviruses have been alternatively classified on the basis of nucleotide and amino acid sequences into four species (human enteroviruses A-D).

Epidemiology

Enterovirus infections are common, with a worldwide distribution. In temperate climates, annual epidemic peaks occur in summer/fall, although some transmission occurs year-round. Enteroviruses are responsible for 33–65% of acute febrile illnesses and 55–65% of hospitalizations for suspected sepsis in infants during the summer and fall in the United States. In tropical and semitropical areas, enteroviruses typically circulate year-round. In general, only a few serotypes circulate simultaneously. Infections by different serotypes can occur within the same season. Factors associated with increased incidence and/or severity include young age, male sex, exposure to children, poor hygiene, overcrowding, and low socioeconomic status. More than 25% of symptomatic infections occur in children younger than 1 year of age. Breastfeeding reduces the risk for infection, likely via enterovirus-specific antibodies.

Humans are the only known natural reservoir for human enteroviruses. Virus is primarily spread person to person, by the fecal-oral and respiratory routes, although types causing acute hemorrhagic conjunctivitis may be spread via airborne transmission. Virus can be transmitted vertically prenatally or in the peripartum period or possibly via breastfeeding. Enteroviruses can survive on environmental surfaces, permitting transmission via fomites. Enteroviruses also can frequently be isolated from water sources, sewage, and wet soil. Although contamination of drinking water, swimming pools and ponds, and hospital water reservoirs may occasionally be responsible for transmission, such contamination is often considered the result rather than the cause of human infection. Transmission is common within families (≥50% risk of spread to nonimmune household contacts), daycare centers, playgrounds, summer camps, orphanages, and hospital nurseries; severe secondary infections may occur in nursery outbreaks. Transmission risk is increased by diaper changing and decreased by handwashing. Tickborne transmission has been suggested by some authors but is not a predominant route of transmission.

Large enterovirus outbreaks have included meningitis epidemics (echoviruses 4, 6, 9, 13, and 30 commonly); epidemics of hand-foot-and-mouth disease with severe central nervous system (CNS) and/or cardiopulmonary disease caused by enterovirus A71 in Asia and Australia; outbreaks of atypical, severe hand-foot-and-mouth disease caused by coxsackievirus A6 in the United States and United Kingdom; outbreaks of human enterovirus D68 respiratory illness associated with acute flaccid myelitis in the Americas, Europe, and Asia; outbreaks of acute hemorrhagic conjunctivitis caused by enterovirus D70, coxsackievirus A24, and coxsackievirus A24 variant in tropical and temperate regions; and community outbreaks of uveitis. Reverse transcription polymerase chain reaction (RT-PCR) and genomic sequencing help identify outbreaks and demonstrate commonality of outbreak strains, differences among epidemic strains and older prototype strains, changes in circulating viral subgroups over time, cocirculation of multiple genetic lineages, co-infections with different enterovirus serotypes, and associations between specific genogroups and/or

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genetic substitutions and epidemiologic and clinical characteristics. Genetic analyses have demonstrated recombination and genetic drift that lead to evolutionary changes in genomic sequence and antigenicity and extensive genetic diversity. For example, emergence of new subgenotypes and genetic lineages of enterovirus A71 may contribute to sequential outbreaks and increases in circulation.

The incubation period is typically 3-6 days, except for a 1-3 day incubation period for acute hemorrhagic conjunctivitis. Symptomatic and asymptomatic infected children typically shed cultivable virus from the respiratory tract for <1-3 weeks. In contrast, fecal shedding of cultivatable virus continues for as long as 7-11 weeks for acid stabile strains (e.g., poliovirus, enterovirus A71). Enterovirus RNA can be shed from mucosal sites for comparable and possibly longer periods.

PATHOGENESIS

Cell surface macromolecules, including poliovirus receptor, integrin very-late-activation antigen (VLA)-2, decay-accelerating factor/complement regulatory protein (DAF/CD55), intercellular adhesion molecule-1 (ICAM-1), ICAM-5, and coxsackievirus-adenovirus receptor, serve as viral receptors. In addition, respiratory epithelial cell sialic acids serve as receptors for enterovirus D68, enterovirus D70, and coxsackievirus A24 variants, and human scavenger receptor class B2 (SCARB2), human P-selectin glycoprotein ligand-1, and DC-SIGN are receptors for enterovirus A71. After virus attaches to a cell surface receptor, a conformational change in surface capsid proteins expels a hydrophobic pocket factor, facilitating penetration and uncoating with release of viral RNA in the cytoplasm. Translation of the positive-sense RNA produces a polyprotein that undergoes cleavage by proteases encoded in the polyprotein. Several proteins resulting from cleavage of the polyprotein guide synthesis of negative-sense RNA that serves as a template for replication of new positive-sense RNA. The genome is approximately 7,500 nucleotides long and includes a highly conserved 5′ noncoding region important for replication efficiency and a highly conserved 3′ polyA region; these regions flank a continuous region encoding viral proteins. The 5′ end is covalently linked to a small viral protein (VPg) necessary for initiation of RNA synthesis. There is significant variation within genomic regions encoding the structural proteins, leading to variability in antigenicity. Replication is followed by further cleavage of proteins and assembly into 30-nm icosahedral virions. Of the four structural proteins (VP1-VP4) in the capsid, VP1 is the most important determinant of serotype specificity. Additional regulatory proteins such as an RNA-dependent RNA polymerase and proteases are also present in the virion. Approximately 10^4-10^5 virions are released from an infected cell by lysis within 5-10 hours of infection.

Following oral or respiratory acquisition, initial replication for most enteroviruses occurs in the pharynx and intestine, possibly within mucosal M cells. The acid stability of most enteroviruses favors survival in the gastrointestinal tract. Two or more enteroviruses may invade and replicate in the gastrointestinal tract simultaneously, but interference due to replication of one type often hinders growth of the heterologous type. Initial replication of most enteroviruses in the pharynx and intestine is followed within days by multiplication in lymphoid tissue, such as tonsils, Peyer patches, and regional lymph nodes. A primary, transient viremia **(minor viremia)** results in spread to distant parts of the reticuloendothelial system, including the liver, spleen, bone marrow, and distant lymph nodes. Host immune responses may limit replication and progression beyond the reticuloendothelial system, resulting in subclinical infection. Clinical infection occurs if replication proceeds in the reticuloendothelial system and virus spreads via a secondary, sustained viremia **(major viremia)** to target organs such as the CNS, heart, and skin. *Tropism to target organs is determined in part by the infecting serotype.* Some enteroviruses, such as enterovirus D68, can be acid-labile and bind sialic acid receptors on respiratory epithelial cells in the upper and lower respiratory tract and primarily produce respiratory illness. Cytokine responses may contribute to development of respiratory disease by these viruses. Enterovirus D68 RNA has also been transiently detected by PCR in the blood of young children with enterovirus D68 pneumonia when drawn soon after illness onset.

Enteroviruses can damage a wide variety of organs and systems, including the CNS, heart, liver, lungs, pancreas, kidneys, muscle, and skin. Damage is mediated by necrosis and the inflammatory response. **CNS infections** are often associated with pleocytosis in the cerebrospinal fluid (CSF), composed of macrophages and activated T lymphocytes, and a mixed meningeal inflammatory response. Parenchymal involvement may affect the cerebral white and gray matter, cerebellum, basal ganglia, brainstem, and spinal cord with perivascular and parenchymal mixed or lymphocytic inflammation, gliosis, cellular degeneration, and neuronophagocytosis. **Encephalitis** during enterovirus A71 epidemics has been characterized by severe involvement of the brainstem, spinal cord gray matter, hypothalamus, and subthalamic and dentate nuclei, and can be complicated by pulmonary edema, pulmonary hemorrhage, and/or interstitial pneumonitis, presumed secondary to brainstem damage; sympathetic hyperactivity; myoclonus; ataxia; autonomic dysfunction; and CNS and systemic inflammatory responses (including cytokine and chemokine overexpression). Immunologic cross-reactivity with brain tissue has been postulated as one mechanism responsible for neurologic damage and sequelae following enterovirus A71 infection.

Enterovirus **myocarditis** is characterized by perivascular and interstitial mixed inflammatory infiltrates and myocyte damage, possibly mediated by viral cytolytic (e.g., cleavage of dystrophin or serum response factor) and innate and adaptive immune-mediated mechanisms. Chronic inflammation may persist after viral clearance.

The potential for enteroviruses to cause persistent infection is controversial. Persistent infection in dilated cardiomyopathy and in myocardial infarction has been suggested, but enterovirus RNA sequences and/or antigens have been demonstrated in cardiac tissues in some, but not other, series. Infections with enteroviruses such as coxsackievirus B4, during gestation or subsequently, have been implicated as a trigger for development of β-cell autoantibodies and/or type 1 diabetes in genetically susceptible hosts. Persistent infection in the pancreas, intestine, or peripheral blood mononuclear cells, with downstream immunomodulatory effects, has been suggested, but data are inconsistent. Similarly, persistent infection has been implicated in a variety of conditions, including amyotrophic lateral sclerosis, Sjögren syndrome, chronic fatigue syndrome, and gastrointestinal tumors. Early enterovirus infection was associated with reduced risk of developing lymphocytic and myeloid leukemia in a large retrospective Taiwanese cohort study.

Severe **neonatal infections** can produce hepatic necrosis, hemorrhage, inflammation, endotheliitis, and venoocclusive disease; myocardial mixed inflammatory infiltrates, edema, and necrosis; meningeal and brain inflammation, hemorrhage, gliosis, necrosis, and white matter damage; inflammation, hemorrhage, thrombosis, and necrosis in the lungs, pancreas, and adrenal glands; and disseminated intravascular coagulation. In utero infections are characterized by placentitis and infection of multiple fetal organs such as heart, lung, and brain.

Development of type-specific neutralizing antibodies appears to be the most important immune defense, mediating prevention against and recovery from infection. Immunoglobulin (Ig) M antibodies, followed by long-lasting IgA and IgG antibodies, and secretory IgA, mediating mucosal immunity, are produced. Although local reinfection of the gastrointestinal tract can occur, replication is usually limited and not associated with disease. In vitro and animal experiments suggest that heterotypic antibody may enhance disease caused by a different serotype. Evidence also suggests that subneutralizing concentrations of serotype-specific antibody may lead to antibody-dependent enhancement of enterovirus A71 infection. Innate and cellular defenses (macrophages and cytotoxic T lymphocytes) may play important roles in recovery from infection. Altered cellular responses to enterovirus A71, including T lymphocyte and natural killer cell depletion, have been associated with severe meningoencephalitis and pulmonary edema.

Hypogammaglobulinemia and *agammaglobulinemia predispose to severe, often chronic enterovirus infections.* Similarly, perinatally infected neonates lacking maternal type-specific antibody to the infecting virus are at risk for severe disease. Enterovirus A71 disease increases after 6 months of age, when maternal serotype-specific antibody levels have

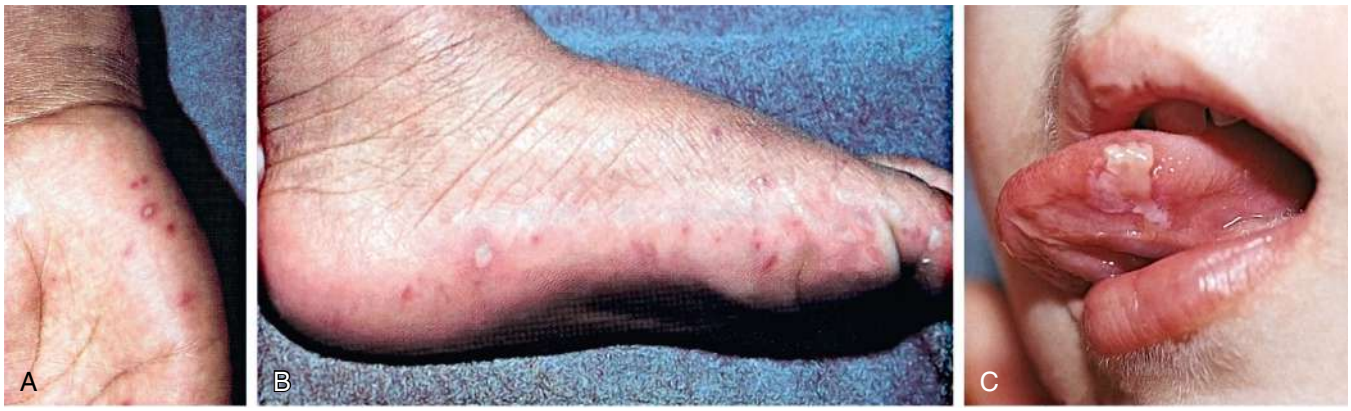

Fig. 297.1 A, Oval blisters of the palms in a child with hand-foot-and-mouth disease (coxsackievirus A16 infection). B, Oval blisters on the feet of a child with hand-foot-and-mouth disease. C, Erosion of the tongue in a child with hand-foot-and-mouth disease. *(From Weston WL, Lane AT, Morelli JG. Color Textbook of Pediatric Dermatology, 3rd ed. St. Louis: Mosby; 2002:109.)*

declined. Other risk factors for significant illness include young age, immune suppression (posttransplantation and lymphoid malignancy), and, according to animal models and/or epidemiologic observations, exercise, cold exposure, malnutrition, and pregnancy. Specific human leukocyte antigen genes, immune response gene (e.g., interleukin-10 and interferon-γ) polymorphisms, and low vitamin A levels have been linked to enterovirus A71 susceptibility and severe disease.

CLINICAL MANIFESTATIONS

Manifestations are protean, ranging from asymptomatic infection to undifferentiated febrile or respiratory illnesses, often in association with exanthems and/or enanthems, to, less frequently, severe diseases such as meningoencephalitis, myocarditis, and neonatal sepsis. A majority of individuals are asymptomatic or have very mild illness, yet may serve as important sources for spread of infection. Symptomatic disease is generally more common in young children.

Nonspecific Febrile Illness

Nonspecific febrile illnesses are the most common symptomatic manifestations, especially in infants and young children. These are difficult to differentiate clinically from serious infections such as urinary tract infection, bacteremia, and bacterial meningitis, often necessitating hospitalization with diagnostic testing and presumptive antibiotic therapy for suspected bacterial infection in young infants.

Illness usually begins abruptly with fever of 38.5–40°C (101.3–104°F), malaise, and irritability. Associated symptoms may include lethargy, anorexia, diarrhea, nausea, vomiting, abdominal discomfort, rash, sore throat, and respiratory symptoms. Older children may have headaches and myalgias. Findings are generally nonspecific and may include mild conjunctivitis, pharyngeal injection, and cervical lymphadenopathy. Meningitis may be present, but specific clinical features such as meningeal findings or bulging anterior fontanelle distinguishing those with meningitis are often lacking in infants. Fever lasts a mean of 3 days and occasionally is biphasic. Duration of illness is usually 4-7 days but can range from 1 day to >1 week. White blood cell (WBC) count, inflammatory biomarkers (e.g., C-reactive protein, erythrocyte sedimentation rate), and results of routine laboratory tests are generally normal, although transient neutropenia can be seen. Concomitant enterovirus and bacterial infection is rare but has been observed in a small number of infants, most commonly with urinary tract infections.

Enterovirus illnesses may be associated with a wide variety of skin manifestations, including macular, maculopapular, urticarial, vesicular, and petechial eruptions. Rare cases of idiopathic thrombocytopenic purpura have been reported. Enteroviruses have also been implicated in cases of pityriasis rosea. In general, the frequency of cutaneous manifestations is inversely related to age. Serotypes commonly associated with rashes are echoviruses 9, 11, 16, and 25; coxsackie A viruses 2, 4, 6, 9, and 16; coxsackie B viruses 3-5; and enterovirus A71. Virus can occasionally be recovered from vesicular skin lesions.

Hand-Foot-and-Mouth Disease

Hand-foot-and-mouth disease, one of the more distinctive rash syndromes, is most frequently caused by coxsackievirus A16, sometimes in large outbreaks, and can also be caused by enterovirus A71; coxsackie A viruses 5, 6, 7, 9, and 10; coxsackie B viruses 2 and 5; and some echoviruses. It is usually a mild illness, with or without low-grade fever. When the mouth is involved, the oropharynx is inflamed and often contains scattered, painful vesicles on the tongue, buccal mucosa, posterior pharynx, palate, gingiva, and/or lips (Fig. 297.1). These lesions may ulcerate, leaving 4-8 mm shallow lesions with surrounding erythema. Maculopapular, vesicular, and/or pustular lesions may occur on the hands and fingers, feet, and buttocks and groin (see Figs. 297.1 and 297.2). Skin lesions occur more commonly on the hands than feet and are more common on dorsal surfaces, but frequently also affect palms and soles. Hand and foot lesions are usually tender, 3-7–mm vesicles that resolve in about 1 week. Buttock lesions do not usually progress to vesiculation. Disseminated vesicular rashes described as **eczema coxsackium** may complicate preexisting eczema. Coxsackievirus A6, in particular, is responsible for relatively severe, atypical hand-foot-and-mouth disease (and herpangina) affecting adults and children that is characterized by fever, generalized rash (face, proximal extremities, and trunk, in addition to hands, feet, and buttocks), pain, dehydration, and desquamation of palms and soles (see Fig. 297.2). **Onychomadesis** (nail shedding) has been observed following coxsackievirus A6 and other coxsackievirus infections. Hand-foot-and-mouth disease caused by enterovirus A71 can be associated with neurologic and cardiopulmonary involvement, especially in young children (see "Neurologic Manifestations," later). Hand-foot-and-mouth disease caused by coxsackievirus A16 also can occasionally be associated with complications such as encephalitis, acute flaccid paralysis, myocarditis, pericarditis, and shock.

Herpangina

Herpangina is characterized by sudden onset of fever, sore throat, dysphagia, and painful lesions in the posterior pharynx. Temperatures range from normal to 41°C (105.8°F); fever tends to be higher in younger patients. Headache and backache may occur in older children, and vomiting and abdominal pain occur in 25% of cases. Characteristic lesions, present on the anterior tonsillar pillars, soft palate, uvula, tonsils, posterior pharyngeal wall, and, occasionally, the posterior buccal surfaces, are discrete 1-2–mm vesicles and ulcers that enlarge over 2-3 days to 3-4 mm and are surrounded by erythematous rings that vary in size up to 10 mm. The number of lesions can range from 1 to >15 but is most commonly around 5. The remainder of the pharynx appears normal or minimally erythematous. Most cases are mild and have no complications. However, dehydration as a result of decreased oral intake may occur with more severe illness; meningitis can also sometimes occur. Fever generally lasts 1-4 days, and resolution of symptoms occurs in 3-7 days. A variety of enteroviruses cause herpangina, including enterovirus A71, but coxsackie A viruses are implicated most often.

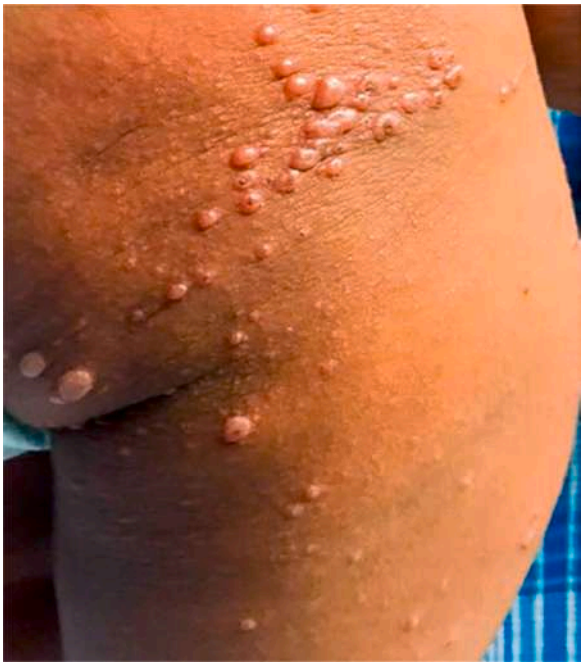

Fig. 297.2 Atypical hand-foot-and-mouth disease. Vesiculobullous rash on the right buttock and posterior thigh. *(From Waldman A, Thomas L, Thacker S, et al. Vesiculobullous eruption as an atypical hand, foot, and mouth presentation. J Pediatr. 2016;179:273. Fig. B.)*

Respiratory Manifestations

Symptoms such as sore throat and coryza frequently accompany and sometimes dominate enterovirus illnesses. Other respiratory findings may include wheezing, exacerbation of asthma, apnea, pneumonia, otitis media, bronchiolitis, croup, parotitis, and pharyngotonsillitis, which may occasionally be exudative. Lower respiratory tract infection may be significant in immunocompromised patients. Clusters and outbreaks of cases of severe respiratory disease, including pneumonia and wheezing (both in children with a history of asthma and those unaffected by asthma), have been increasingly recognized in association with multiple lineages of enterovirus D68.

Pleurodynia (Bornholm disease), caused most frequently by coxsackie B viruses 3, 5, 1, and 2 and echoviruses 1 and 6, is an epidemic or sporadic illness characterized by paroxysmal thoracic pain, as a result of myositis involving chest and abdominal wall muscles and, possibly, pleural inflammation. In epidemics, which occur every 10-20 years, children and adults are affected, but most cases occur in persons younger than age 30 years. Malaise, myalgias, and headache are followed by sudden onset of fever and spasmodic, pleuritic pain in the chest or upper abdomen aggravated by coughing, sneezing, deep breathing, or other movement. During spasms, which last from a few minutes to several hours, pain may be severe, and respirations are usually rapid, shallow, and grunting, suggesting pneumonia or pleural inflammation. A pleural friction rub is noted during pain episodes in <10% of patients. Chest radiographs are generally normal but can demonstrate pulmonary infiltrates or pleural effusions. Pain localized to the abdomen may suggest colic, intestinal obstruction, appendicitis, or peritonitis. Pain usually subsides within 3-6 days but may persist for up to weeks. Symptoms may occur in a biphasic or, rarely, recurrent pattern, with less prominent fever during recurrences. Pleurodynia may be associated with meningitis, orchitis, myocarditis, or pericarditis.

Life-threatening noncardiogenic pulmonary edema, hemorrhage, and/or interstitial pneumonitis may occur in patients with enterovirus A71 brainstem encephalitis.

Ocular Manifestations

Epidemics of **acute hemorrhagic conjunctivitis**, primarily caused by enterovirus D70 and coxsackievirus A24/A24 variant, are explosive and marked by high contagiousness, with spread mainly via eye-hand-fomite-eye transmission. School-age children, teenagers, and adults 20-50 years of age have the highest attack rates. Sudden onset of severe eye pain is associated with photophobia, blurred vision, lacrimation, conjunctival erythema and congestion, lid edema, preauricular lymphadenopathy, and, in some cases, subconjunctival hemorrhages and superficial punctate keratitis. Subconjunctival hemorrhage is the hallmark of enterovirus D70 cases (>70%) but is more rare with coxsackievirus infections. Eye discharge is initially serous but becomes mucopurulent with secondary bacterial infection. Systemic symptoms, including fever and headache, occur in up to 20% of cases; manifestations suggestive of pharyngoconjunctival fever occasionally occur. Recovery is usually complete within 1-2 weeks. Polyradiculoneuropathy or acute flaccid paralysis following enterovirus D70 infection occurs occasionally. Other enteroviruses have occasionally been implicated as causes of keratoconjunctivitis.

Epidemic and sporadic uveitis in infants caused by subtypes of enteroviruses 11 and 19 can be associated with severe complications, including destruction of the iris, cataracts, and glaucoma. Enteroviruses have been implicated in cases of chorioretinitis, uveoretinitis, optic neuritis, and unilateral acute idiopathic maculopathy.

Myocarditis and Pericarditis

Enteroviruses account for approximately 25–35% of cases of myocarditis and pericarditis of proven etiology (see Chapters 488 and 489). Coxsackie B viruses are most commonly implicated, although coxsackie A viruses and echoviruses also may be causative. Adolescents and young adults (especially physically active males) are disproportionately affected. Myopericarditis may be the dominant feature, or it may be one manifestation of disseminated disease, as in neonates. Disease ranges from relatively mild to severe. Upper respiratory tract symptoms frequently precede fatigue, dyspnea, chest pain, congestive heart failure, and dysrhythmias. Presentations may mimic myocardial infarction; sudden death may also occur (including apparent sudden infant death syndrome). A pericardial friction rub indicates pericardial involvement. Chest radiography often demonstrates cardiac enlargement, and echocardiography may confirm ventricular dilation, reduced contractility, and/or pericardial effusion. Electrocardiography frequently reveals ST segment, T wave, and/or rhythm abnormalities, and serum myocardial enzyme concentrations are often elevated. The acute mortality of enterovirus myocarditis is 0–4%. Recovery is complete without residual disability in the majority of patients. Occasionally, chronic cardiomyopathy, inflammatory ventricular microaneurysms, or constrictive pericarditis may result. The role of persistent infection in chronic dilated cardiomyopathy is controversial. Enteroviruses have also been implicated in late adverse cardiac events following heart transplantation and in acute cardiac events such as myocardial infarction, endocarditis, and peripartum cardiomyopathy. Cardiopulmonary dysfunction observed in enterovirus A71 epidemics most commonly occurs without evidence of myocarditis and may be of neurogenic origin; however, true myocarditis has also been described.

Gastrointestinal and Genitourinary Manifestations

Gastrointestinal symptoms such as emesis (especially with meningitis), diarrhea (rarely severe), and abdominal pain are frequent but generally not dominant. Diarrhea, hematochezia, pneumatosis intestinalis, and necrotizing enterocolitis have occurred in premature infants during nursery outbreaks. Enterovirus infection has been implicated in acute and chronic gastritis, intussusception, chronic intestinal inflammation in hypogammaglobulinemic patients, sporadic hepatitis in normal children, severe hepatitis in neonates, and pancreatitis, which may result in transient exocrine pancreatic insufficiency.

Coxsackie B viruses are second only to mumps as causes of orchitis, most commonly presenting in adolescents. The illness is frequently biphasic; fever and pleurodynia or meningitis are followed approximately 2 weeks later by orchitis, often with epididymitis. Enteroviruses have also been implicated in cases of nephritis and IgA nephropathy.

Neurologic Manifestations

Enteroviruses are the most common cause of viral **meningitis** in mumps-immunized populations, accounting for up to 90% or more of cases in which a cause is identified. Meningitis is particularly common in infants, especially in those younger than 3 months of age, often during community epidemics. Frequently implicated serotypes include coxsackie B viruses 2-5; echoviruses 4, 6, 7, 9, 11, 13, 16, and 30; and enteroviruses D70 and A71. Most cases in infants and young children are mild and lack specific meningeal signs, whereas nuchal rigidity is apparent in more than half of children older than 1-2 years of age. Fever is present in 50–100% and may be accompanied by irritability, malaise, headache, photophobia, nausea, emesis, anorexia, lethargy, hypotonia, rash, cough, rhinorrhea, pharyngitis, diarrhea, and/or myalgia. Some cases are biphasic, with fever and nonspecific symptoms lasting a few days and followed by return of fever with meningeal signs several days later. Fever usually resolves in 3-5 days, and other symptoms in infants and young children usually resolve within 1 week. In adults, symptoms tend to be more severe and of longer duration. CSF findings include pleocytosis (generally <500 but occasionally as high as 1,000-8,000 WBCs/μL; often predominantly polymorphonuclear cells in the first 48 hours before becoming mostly mononuclear); normal or slightly low glucose content (10% <40 mg/dL); and normal or mildly increased protein content (generally <100 mg/dL). *CSF parameters are normal in up to half of young infants despite detection of enterovirus in CSF and may also be normal in older children early after illness onset.* Acute complications occur in approximately 10% of young children, including simple and complex seizures, obtundation, increased intracranial pressure, syndrome of inappropriate antidiuretic hormone secretion, ventriculitis, transient cerebral arteriopathy, and coma. The long-term prognosis for most children, even in those with acute complications, is good.

Enteroviruses are also responsible for ≥10–20% of cases of **encephalitis** with an identified cause. Frequently implicated serotypes include echoviruses 3, 4, 6, 9, and 11; coxsackie B viruses 2, 4, and 5; coxsackie A virus 9; and enterovirus A71. After initial nonspecific symptoms, there is progression to encephalopathy characterized by confusion, weakness, lethargy, and/or irritability. Symptoms are most commonly generalized, although focal findings, including focal motor seizures, hemichorea, acute cerebellar ataxia, aphasia, extrapyramidal symptoms, and/or focal imaging abnormalities, may occur. Meningeal signs and CSF indices similar to those of enteroviral meningitis are commonly present, leading to characterization of most cases as **meningoencephalitis**. Severity ranges from mild alteration in mental status to coma and decerebrate status. Long-term sequelae, including epilepsy, weakness, cranial nerve palsy, spasticity, psychomotor retardation, and hearing loss, or death may follow severe disease. Persistent or recurrent cases have been observed rarely.

Neurologic manifestations have been prominent in epidemics in Asia and Australia of enterovirus A71, and, to a lesser extent, coxsackievirus A16 disease. Many affected children have had hand-foot-and-mouth disease, some have had herpangina, and others have had no mucocutaneous manifestations. Neurologic syndromes in a fraction of children have included meningitis, meningoencephalomyelitis, **acute flaccid paralysis**, Guillain-Barré syndrome, transverse myelitis, acute disseminated encephalomyelitis, cerebellar ataxia, opsoclonus-myoclonus syndrome, benign intracranial hypertension, and **brainstem encephalitis** (**rhombencephalitis** involving the midbrain, pons, and medulla). Enterovirus A71 rhombencephalitis is characterized by altered consciousness, myoclonus, vomiting, ataxia, nystagmus, tremor, cranial nerve abnormalities, autonomic dysfunction, and MRI demonstrating lesions in the brainstem, thalamus, and cerebellum. Although the disease has been mild and reversible in some children, others have had rapid progression to noncardiogenic (presumed neurogenic) pulmonary edema and hemorrhage, cardiopulmonary failure, shock, and coma. High mortality rates have been reported in children younger than 5 years of age, especially in those younger than 1 year of age. Deficits such as central hypoventilation, bulbar dysfunction, neurodevelopmental delay, cerebellar defects, attention deficit/hyperactivity–related symptoms, persistent limb weakness, and muscle atrophy have been observed among survivors, especially those who experienced cardiopulmonary failure or acute flaccid paralysis during their acute illness. Although the most severe cases have been associated with enterovirus A71, similar clinical pictures have been produced by other enterovirus serotypes (e.g., coxsackieviruses A16 and B5, echovirus 7).

Patients with **antibody or combined immunodeficiencies** (including human immunodeficiency virus infection, acute lymphocytic leukemia, and transplantation) and patients receiving anti-CD20 antibody therapy are at risk for acute or, more commonly, **chronic enterovirus meningoencephalitis**. The latter is characterized by persistent CSF abnormalities, viral detection in CSF or brain tissue for years, and recurrent encephalitis and/or progressive neurologic deterioration, including insidious intellectual or personality deterioration, altered mental status, seizures, motor weakness, and increased intracranial pressure. Although disease may wax and wane, deficits generally become progressive and ultimately are frequently fatal or lead to long-term sequelae. A **dermatomyositis-like syndrome**, hepatitis, arthritis, myocarditis, or disseminated infection may also occur. Chronic enterovirus meningoencephalitis has become less common with prophylactic high-dose intravenous immunoglobulin replacement in agammaglobulinemic patients.

A variety of nonpoliovirus enteroviruses, including enteroviruses D68, D70, A71, coxsackie A viruses 7 and 24, coxsackie B viruses, and several echoviruses, have been associated with acute flaccid paralysis with motor weakness as a result of spinal cord anterior horn cell involvement. **Acute flaccid myelitis** is used to designate the clinical syndrome of acute flaccid limb weakness with longitudinal MRI abnormalities in the spinal cord gray matter. Neurologic abnormalities are commonly preceded by a febrile respiratory or gastrointestinal prodromal illness around 1 week before onset. Limb involvement tends to be asymmetric and varies from one to all four limbs, with severity ranging from mild weakness to complete paralysis. Cranial nerve dysfunction, including bulbar paralysis, and respiratory failure requiring ventilator support, similar to poliovirus poliomyelitis, have been described in acute flaccid myelitis cases associated with enterovirus D68 and enterovirus A71. Sensory involvement, encephalopathy, seizures, and supratentorial imaging changes are uncommon with enterovirus D68 infection. Functional improvements may be seen over time, but muscle atrophy with limb weakness and some degree of disability persist in the vast majority of cases. A proportion of children with acute flaccid myelitis will have a need for long-term tracheostomy, ventilation, and enteral feeding tubes as a result of persistent bulbar or respiratory paralysis, and scoliosis requiring spinal fusion, limb deformity requiring orthotics and assistive devices, and low bone density predisposing to fractures are common. Nerve transfer surgical procedures that involve splitting and moving functioning nerves to completely denervated muscles have been used to improve functional outcomes in select cases.

Other neurologic syndromes include cerebellar ataxia; transverse myelitis; Guillain-Barré syndrome (including Miller Fisher variant) and axonal polyneuropathy; acute disseminated encephalomyelitis; peripheral neuritis; optic neuritis; sudden hearing loss, tinnitus, and inner ear disorders such as vestibular neuritis; and other cranial neuropathies.

Myositis and Arthritis

Although myalgia is common, direct evidence of muscle involvement, including rhabdomyolysis, muscle swelling, focal myositis, and polymyositis, has uncommonly been reported. A dermatomyositis-like syndrome and arthritis can be seen in enterovirus-infected patients with hypogammaglobulinemia. Enteroviruses are a rare cause of arthritis in normal hosts.

Neonatal Infections

Neonatal infections are relatively common, with a disease incidence comparable to or greater than that of symptomatic neonatal herpes simplex virus, cytomegalovirus, and group B streptococcus infections. Infection frequently is caused by coxsackie B viruses 2-5 and

echoviruses 6, 9, 11, and 19, although many serotypes have been implicated, including coxsackie B virus 1 and echovirus 30 in more recent years. Enteroviruses may be acquired vertically before, during, or after delivery, including possibly via breast milk; horizontally from family members; or by sporadic or epidemic transmission in nurseries. In utero infection can lead to fetal demise, nonimmune hydrops fetalis, or neonatal illness. Additionally, maternal and intrauterine infections have been speculatively linked to congenital anomalies; prematurity, low birthweight, and intrauterine growth restriction; neurodevelopmental sequelae; unexplained neonatal illness and death; and increased risk of type 1 diabetes and schizophrenia.

The majority of neonatal infections are asymptomatic, and symptomatic presentations range from benign febrile illness to severe multisystem disease. Most affected newborns are full term and previously well. Maternal history often reveals a recent viral illness preceding or immediately following delivery, which may include fever and abdominal pain. Neonatal symptoms may occur as early as day 1 of life, with onset of severe disease generally within the first 2 weeks of life. Frequent findings include fever or hypothermia, irritability, lethargy, anorexia, rash (usually maculopapular, occasionally petechial or papulovesicular), jaundice, respiratory symptoms, apnea, hepatomegaly, abdominal distention, emesis, diarrhea, and decreased perfusion. Most patients have benign courses, with resolution of fever in an average of 3 days and of other symptoms in about 1 week. A biphasic course may occur occasionally. A minority have severe disease dominated by any combination of sepsis, meningoencephalitis, myocarditis, hepatitis, coagulopathy, and/or pneumonitis. Meningoencephalitis may be manifested by focal or complex seizures, bulging fontanelle, nuchal rigidity, and/or reduced level of consciousness. Myocarditis, most often associated with coxsackie B virus infection, may be suggested by tachycardia, dyspnea, cyanosis, and cardiomegaly. Hepatitis and pneumonitis are most often associated with echovirus infection, although they may also occur with coxsackie B viruses. Gastrointestinal manifestations may be prominent in premature neonates. Laboratory and radiographic evaluation may reveal leukocytosis, thrombocytopenia, CSF pleocytosis, CNS white matter damage, elevations of serum transaminases and bilirubin, coagulopathy, pulmonary infiltrates, and electrocardiographic changes.

Complications of severe neonatal disease include CNS necrosis and generalized or focal neurologic compromise; arrhythmias, congestive heart failure, myocardial infarction, and pericarditis; hepatic necrosis and failure; coagulopathy with intracranial or other bleeding; adrenal necrosis and hemorrhage; and rapidly progressive pneumonitis and pulmonary hypertension. Myositis, arthritis, necrotizing enterocolitis, inappropriate antidiuretic hormone secretion, hemophagocytic lymphohistiocytosis-like presentation, bone marrow failure, and sudden death are rare events. Mortality with severe disease is significant and is most often associated with hepatitis and bleeding complications, myocarditis, and/or pneumonitis.

Survivors of severe neonatal disease may have gradual resolution of hepatic and cardiac dysfunction, although persistent hepatic dysfunction and residual cardiac impairment, chronic calcific myocarditis, and ventricular aneurysm may occur. Meningoencephalitis may be associated with speech and language impairment; cognitive deficits; spasticity, hypotonicity, or weakness; seizure disorders; microcephaly or hydrocephaly; and ocular abnormalities. However, many survivors appear to have no long-term sequelae. Risk factors for severe disease include illness onset in the first few days of life; maternal illness just before or after delivery; prematurity; male sex; infection by echovirus 11 or a coxsackie B virus; positive serum viral culture; absence of neutralizing antibody to the infecting virus; and evidence of severe hepatitis, myocarditis, and/or multisystem disease.

Transplant Recipients and Patients with Malignancies

Enterovirus infections in stem cell and solid organ transplant recipients may be severe and/or prolonged, causing progressive pneumonia, severe diarrhea, pericarditis, heart failure, meningoencephalitis, and disseminated disease. Enterovirus-associated hemophagocytic lymphohistiocytosis, meningitis, encephalitis, acute flaccid myelitis, and myocarditis have been reported in children with malignancies and patients treated with anti-CD20 monoclonal antibody. Infections in these groups are associated with high fatality rates.

DIAGNOSIS

Clues to enterovirus infection include characteristic findings such as hand-foot-and-mouth disease or herpangina lesions, consistent seasonality, known community outbreak, and exposure to enterovirus-compatible disease. Acute flaccid myelitis due to enterovirus should be considered in the differential diagnosis of any child presenting with acute-onset limb weakness, particularly in the summer to fall during enterovirus outbreaks and when following a febrile illness. In the neonate, history of maternal fever, malaise, and/or abdominal pain near delivery during enterovirus season is suggestive.

Traditionally, enterovirus infection has been confirmed with viral culture using a combination of cell lines. Sensitivity of culture ranges from 50% to 75% and can be increased by sampling of multiple sites (e.g., CSF plus oropharynx and rectum in children with meningitis). In neonates, yields of 30–70% are achieved when blood, urine, CSF, and mucosal swabs are cultured. A major limitation is the inability of most coxsackie A viruses to grow in culture. Yield may also be limited by neutralizing antibody in patient specimens, improper specimen handling, or insensitivity of the cell lines used. Culture is relatively slow, with 3-8 days usually required to detect growth. Although cultivation of an enterovirus from any site can generally be considered evidence of recent infection, isolation from the rectum or stool can reflect more remote shedding. Similarly, recovery from a mucosal site may suggest an association with an illness, whereas recovery from a normally sterile site (e.g., CSF, blood, or tissue) is more conclusive evidence of causation. Serotype identification by type-specific antibody staining or neutralization of a viral isolate is generally required only for investigation of an outbreak or an unusual disease manifestation, for surveillance, or to distinguish nonpoliovirus enteroviruses from vaccine or wild-type polioviruses.

Direct testing for nucleic acid has replaced culture because of increased sensitivity and more rapid turnaround. RT-PCR detection of highly conserved areas of the enterovirus genome can detect the majority of enteroviruses in CSF; serum; urine; conjunctival, nasopharyngeal, oropharyngeal, tracheal, rectal, and stool specimens; dried blood spots; and tissues such as myocardium, liver, and brain. However, the closely related parechoviruses are not detected by most enterovirus RT-PCR primers. Sensitivity and specificity of RT-PCR are high, with results available in as short as 1 hour. Real-time, quantitative PCR assays and nested PCR assays with enhanced sensitivity have been developed, as have enterovirus-containing multiplex PCR assays, nucleic acid sequence–based amplification assays, reverse transcription loop-mediated isothermal amplification, culture-enhanced PCR assays, and PCR-based microarray assays. PCR testing of CSF from children with meningitis and from hypogammaglobulinemic patients with chronic meningoencephalitis is frequently positive despite negative cultures. Routine PCR testing of CSF in infants and young children with suspected meningitis during enterovirus season decreases the number of diagnostic tests, duration of hospital stay, antibiotic use, and overall costs. Enterovirus RNA may not be detected in CSF by the time of clinical presentation with neurologic syndromes associated with certain enteroviruses (e.g., enterovirus A71 and D68), but shedding may still be detectable in nonsterile sites (stool/rectal for enterovirus A71; respiratory for enterovirus D68). PCR testing of tracheal aspirates of children with myocarditis has good concordance with testing of myocardial specimens. In ill neonates and young infants, PCR testing of serum and urine has higher yields than culture. Viral load in blood of neonates is correlated with disease severity; viral nucleic acid may persist in blood of severely ill newborns for up to 2 months.

Sequence analysis of amplified nucleic acid can be used for serotype identification and phylogenetic analysis and to establish a transmission link among cases. Serotype-specific (e.g., enterovirus A71, enterovirus D68, and coxsackievirus A16) PCR assays have been developed. For enterovirus A71, the yield of specimens other than CSF and blood (oropharyngeal, nasopharyngeal, rectal, vesicle swabs, and CNS tissue) is greater than the yield of CSF and blood, which are infrequently

positive. Enterovirus D68 is more readily detected in respiratory specimens (i.e., nasal wash or nasopharyngeal swab) compared to stool/rectal or CSF specimens. Routine collection and testing of respiratory and stool/rectal specimens, in addition to CSF, is warranted in neurologic presentations potentially associated with these viruses. Of note, commercially available multiplex respiratory PCR assays generally are unable to distinguish enteroviruses (including enterovirus D68) from rhinoviruses. Antigen detection assays that target specific serotypes such as enterovirus A71 with monoclonal antibodies have also been developed.

Enterovirus infections can be detected serologically by a rise in serum or CSF of neutralizing, complement fixation, enzyme-linked immunosorbent assay, or other type-specific antibody or by detection of serotype-specific IgM antibody. However, serologic testing requires presumptive knowledge of the infecting serotype or an assay with sufficiently broad cross-reactivity. Sensitivity and specificity may be limiting, and cross-reactivity among serotypes may occur. Except for epidemiologic studies or cases characteristic of specific serotypes (e.g., enterovirus A71 or enterovirus D68), serology is generally less useful than culture or nucleic acid detection. Enterovirus antibodies have been detected in CSF of children with acute flaccid myelitis when viral RNA was not detectable.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of enterovirus infections varies with the clinical presentation (Table 297.2).

Human parechoviruses, members of the Picornaviridae family, produce many manifestations similar to the nonpolio enteroviruses. They are small RNA viruses that were originally classified as echoviruses. Nineteen parechoviruses have been identified that infect humans; serotypes 1 and 3 are the most common causes of symptomatic infection. Parechovirus epidemics occur in the same season as enterovirus infections, with a biennial pattern of circulation noted in Europe. Outbreaks have been described in the nursery setting. In young infants, parechoviruses can cause a sepsis-like illness similar to enterovirus illness and are a common, underrecognized cause of viral meningoencephalitis. More frequently than with enteroviruses, infants with parechovirus CNS infection often have no CSF pleocytosis. There is also a higher incidence of white matter MRI abnormalities and long-term neurodevelopmental deficits with parechovirus encephalitis compared with enterovirus encephalitis. Rarely, parechoviruses have been identified in cases of hepatitis or myocarditis. Infections in older children are often unrecognized or cause acute, benign febrile, respiratory, or gastrointestinal illnesses with few specific findings.

Infants suspected of having an enterovirus infection should also be considered as possibly having a parechovirus infection, because the two may be indistinguishable. A distinctive rash involving the extremities with palm and sole erythema or peripheral leukopenia in the setting of high fever during the summer-fall season are clinical findings that should also prompt consideration of parechovirus infection. The diagnosis of parechovirus infection is confirmed by human parechovirus-specific PCR on CSF, blood, stool, and oropharyngeal or nasopharyngeal specimens.

TREATMENT

In the absence of a proven antiviral agent for enterovirus infections, supportive care is the mainstay of treatment. Newborns and young infants with nonspecific febrile illnesses and children with meningitis frequently require diagnostic evaluation and hospitalization for presumptive treatment of bacterial and herpes simplex virus infection. Neonates with severe disease and infants and children with concerning disease manifestations (e.g., myocarditis, enterovirus A71 neurologic and cardiopulmonary disease, enterovirus D68 respiratory failure, and acute flaccid myelitis) may require intensive cardiorespiratory support.

Table 297.2 Differential Diagnosis of Nonpolio Enterovirus Infections

CLINICAL MANIFESTATION	BACTERIAL PATHOGENS	VIRAL PATHOGENS	NONINFECTIOUS
Nonspecific febrile illness	*Streptococcus pneumoniae, Haemophilus influenzae* type b, *Neisseria meningitidis*	Influenza viruses, human herpesviruses 6 and 7, human parechoviruses	Rheumatologic disorders, oncologic diseases, drug reaction
Exanthems/enanthems	Group A *Streptococcus, Staphylococcus aureus, N. meningitidis, T. pallidum, M. pneumoniae*	Herpes simplex virus, adenoviruses, varicella-zoster virus, Epstein-Barr virus, measles virus, rubella virus, human herpesviruses 6 and 7, human parechoviruses	Drug reaction, Stevens Johnson syndrome, toxic epidermal necrolysis, Kawasaki syndrome, vasculitis
Respiratory illness/ conjunctivitis	*S. pneumoniae, H. influenzae* (nontypeable and type b), *N. meningitidis, Mycoplasma pneumoniae, Chlamydophila pneumoniae*	Adenoviruses, influenza viruses, respiratory syncytial virus, parainfluenza viruses, rhinoviruses, human metapneumovirus, coronaviruses	Asthma exacerbation, rheumatologic uveitis, Kawasaki syndrome
Myocarditis/pericarditis	*S. aureus, H. influenzae* type b, *M. pneumoniae*	Adenoviruses, influenza virus, parvovirus, cytomegalovirus	Drugs, Kawasaki syndrome, rheumatic fever
Meningitis/encephalitis	*S. pneumoniae, H. influenzae* type b, *N. meningitidis, Mycobacterium tuberculosis, Borrelia burgdorferi, M. pneumoniae, Bartonella henselae, Listeria monocytogenes*	Herpes simplex virus, West Nile virus, influenza viruses, adenoviruses, Epstein-Barr virus, mumps virus, lymphocytic choriomeningitis virus, arboviruses, human parechoviruses	Drugs, intravenous immunoglobulin, Kawasaki syndrome, autoimmune encephalitis (e.g., anti-NMDA receptor), acute disseminated encephalomyelitis (ADEM), demyelinating disorders
Acute flaccid myelitis	*C. botulinum*	Poliovirus, West Nile virus, Japanese encephalitis virus, rabies virus, adenovirus	Spinal cord infarction, antimyelin oligodendrocyte glycoprotein (MOG) myelitis, neuromyelitis optica (NMO), Guillain-Barré syndrome, ADEM, transverse myelitis, lupus, tick paralysis
Neonatal infections	Group B *Streptococcus*, gram-negative enteric bacilli, *L. monocytogenes, Enterococcus*	Herpes simplex virus, adenoviruses, cytomegalovirus, rubella virus, human parechoviruses	Neonatal lupus, Aicardi-Goutières syndrome

Milrinone has been suggested as a useful agent in severe enterovirus A71 cardiopulmonary disease. Liver and cardiac transplantation have been performed for neonates with progressive end-organ failure.

Immunoglobulin has been used to treat enterovirus infections based on the importance of the humoral immune response to enterovirus infection and the observation that absence of neutralizing antibody is a risk factor for symptomatic infection. Immunoglobulin products contain neutralizing antibodies to many commonly circulating serotypes, although titers vary with serotype and among products and lots. Anecdotal and retrospective, uncontrolled use of intravenous immunoglobulin or infusion of maternal convalescent plasma to treat newborns with severe disease has been associated with varying outcomes. The one randomized controlled trial was too small to demonstrate significant clinical benefits, although neonates who received immunoglobulin containing high neutralizing titers to their own isolates had shorter periods of viremia and viruria. Immunoglobulin has been administered intravenously and intraventricularly to treat hypogammaglobulinemia in patients with chronic enterovirus meningoencephalitis and intravenously in transplant and oncology patients with severe infections, with variable success. Intravenous immunoglobulin and corticosteroids have been used for patients with neurologic disease caused by enterovirus A71, enterovirus D68, and other enteroviruses. Modulation of cytokine profiles after administration of intravenous immunoglobulin for enterovirus A71–associated brainstem encephalitis has been demonstrated. High-titer enterovirus A71 immunoglobulin appeared promising in animal models, and clinical trials in regions with epidemic enterovirus A71 disease are ongoing. Anti–enterovirus A71 and D68 monoclonal antibodies have also been generated and evaluated in vitro and in animal models. A retrospective study suggested that treatment of presumed viral myocarditis with immunoglobulin was associated with improved outcome; however, virologic diagnoses were not made. Evaluation of corticosteroids and cyclosporine and other immunosuppressive therapy for myocarditis has been inconclusive. Successful treatment of enterovirus myocarditis with interferon-α has been reported anecdotally, and interferon-β treatment was associated with viral clearance, improved cardiac function, and survival in chronic cardiomyopathy associated with persistence of enterovirus (or adenovirus) genome. Activity of interferon-α against enterovirus A71 has been demonstrated with in vitro and animal models, but potency varies with interferon-α type.

Antiviral agents that act at various steps in the enterovirus life cycle—attachment, penetration, uncoating, translation, polyprotein processing, protease activity, replication, and assembly—are being evaluated. Candidates include pharmacologically active chemical compounds, small interfering RNAs and DNA-like antisense agents, purine nucleoside analogs, synthetic peptides, enzyme inhibitors of signal transduction pathways, interferon-inducers, and herbal compounds. Pleconaril, an inhibitor of attachment and uncoating, was associated with benefit in some controlled studies of enterovirus meningitis and picornavirus upper respiratory tract infections, and uncontrolled experience suggested possible benefits in high-risk infections. A randomized controlled trial of pleconaril in neonates with severe hepatitis, coagulopathy, and/or myocarditis suggested possible virologic and clinical benefits of treatment. Pocapavir, an agent with a similar mechanism of action that is in development for treatment of poliovirus infections, has been used in a small number of cases of severe neonatal enterovirus sepsis. Vapendavir is another attachment inhibitor that is in clinical trials for rhinovirus infections and has in vitro activity against enteroviruses (including enterovirus A71) but has not entered clinical trials for enterovirus infections. Pleconaril, pocapavir, and vapendavir are not currently available for clinical use.

Design and evaluation of candidate agents active against enterovirus A71 and enterovirus D68 are high priorities. Challenges for therapies of enterovirus A71 include limited cross-genotypic activity of candidate compounds and high viral mutagenicity that favors emergence of resistance. Lactoferrin and ribavirin have demonstrated activity with in vitro and/or animal models. The investigational agents rupintrivir and V-7404, which inhibit the 3C-protease conserved among many enteroviruses and essential for infectivity, have broad activity in vitro, including against both enterovirus A71 and enterovirus D68. DAS181 is an investigational, inhaled drug with sialidase activity that has in vitro activity against recently circulating strains of enterovirus D68. The antidepressant fluoxetine interacts with the enterovirus 2C protein and has in vitro activity against group B and D enteroviruses; it has been used anecdotally for chronic enterovirus encephalitis associated with agammaglobulinemia and enterovirus D68-associated acute flaccid myelitis. A retrospective study did not demonstrate a signal of efficacy in the latter condition.

COMPLICATIONS AND PROGNOSIS

The prognosis in the majority of enterovirus infections is excellent. Morbidity and mortality are associated primarily with myocarditis, neurologic disease, severe neonatal infections, and infections in immunocompromised hosts.

Prevention

The first line of defense is prevention of transmission through good hygiene, such as handwashing, avoidance of sharing utensils and drinking containers and other potential fomites, disinfection of contaminated surfaces, and avoiding community settings where exposures are likely to occur. The paucity of enterovirus circulation and associated hand-foot-mouth disease and respiratory and neurologic disease in 2020 during the COVID-19 pandemic provides indirect evidence of the efficacy of nonpharmaceutical interventions targeted to decrease SARS-CoV-2 spread (masking, distancing, school mitigation strategies) against enteroviruses. Chlorination of drinking water and swimming pools also may be an important preventative strategy. Contact precautions should be used for all patients with enterovirus infections in the hospital setting; droplet precautions should also be included for patients with respiratory syndromes and, possibly, enterovirus A71 and D68 infection. Infection control techniques such as cohorting have proven effective in limiting nursery outbreaks. Prophylactic administration of immunoglobulin or convalescent plasma has been used in nursery epidemics; simultaneous use of infection control interventions makes it difficult to determine efficacy.

Pregnant women near term should avoid contact with individuals ill with possible enterovirus infections. If a pregnant woman experiences a suggestive illness, it is advisable not to proceed with emergency delivery unless there is concern for fetal compromise or obstetric emergencies cannot be excluded. Rather, it may be advantageous to extend pregnancy, allowing the fetus to passively acquire protective antibodies. A strategy of prophylactically administering immunoglobulin (or maternal convalescent plasma) to neonates born to mothers with enterovirus infections is untested.

Maintenance antibody replacement with high-dose intravenous immunoglobulin for patients with hypogammaglobulinemia has reduced the incidence of chronic enterovirus meningoencephalitis, although breakthrough infections occur. Inactivated vaccines to prevent enterovirus A71 infections, given to children 6-35 months of age, have been demonstrated to be safe and effective (>90% against enterovirus A71 hand-foot-and-mouth disease and >80% against enterovirus A71 serious disease) in phase 3 clinical trials. Three inactivated enterovirus A71 vaccines have been licensed and approved for prevention of severe hand-foot-and-mouth disease in China and are being studied in other Asian countries. Other vaccine strategies for enterovirus A71, including VP1 capsid protein–based subunit, DNA, and vector vaccines; combined peptide vaccines; live-attenuated vaccines; virus-like particles; breast milk enriched with VP1 capsid protein or lactoferrin; and interferon-γ–expressing recombinant viral vectors, are also under investigation. Circulation of multiple enterovirus A71 types, antigenic drift, viral recombination, and potential immunologic cross-reactivity with brain tissue may pose challenges to development of enterovirus A71 vaccines. Vaccine candidates against EV-D68, including virus-like particle vaccines and inactivated whole virus vaccines, are in development, but have not progressed beyond animal studies. Most enterovirus vaccines do not provide cross-protection against other serotypes; however, the potential to create multivalent enterovirus vaccines targeting several common strains with severe manifestations is under investigation.

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Chapter 298

Parvoviruses

William C. Koch

The parvoviruses are small, single-stranded DNA viruses. They are common infectious agents of a wide variety of animal species, including mammals, birds, and insects. Parvoviruses as a group include a number of important animal pathogens. There are five different types of parvoviruses known to infect humans: the dependoviruses, also called adeno-associated viruses (AAVs), parvovirus B19 (B19V), human bocaviruses (HBoVs), parvovirus 4 (PARV4), and human bufavirus (HBuV). B19V and HBoV are the only two parvoviruses proven to be pathogenic in humans. B19V is the most well studied and clinically important of the human parvoviruses and the cause of **erythema infectiosum** or **fifth disease**. *Human bocavirus is an emerging human pathogen.*

ETIOLOGY

The five human parvoviruses are distinct enough from each other to represent five different genera within the Parvoviridae family. B19V is a member of the genus *Erythroparvovirus*, is composed of an icosahedral protein capsid without an envelope, and contains a single-stranded DNA genome of approximately 5.5 kb. It is relatively heat and solvent resistant. It is antigenically distinct from other mammalian parvoviruses and has only one known serotype, with three distinct genotypes described. The relatively short genome in parvoviruses does not encode a DNA polymerase, so all parvoviruses require either host cell factors present in late S phase or co-infection with another virus to replicate their DNA. B19V can be propagated effectively in vitro only in $CD36^+$ erythroid progenitor cells derived from human bone marrow, umbilical cord blood, or peripheral blood.

HBoV is a member of the genus *Bocaparvovirus*. HBoV was first isolated from nasopharyngeal specimens from children with respiratory tract infection in 2005. It was identified using random polymerase chain reaction (PCR) amplification and sequencing methods specifically designed to detect previously unknown viral sequences. Analysis of the gene sequences showed similarities to both *bo*vine and *ca*nine parvoviruses, and thus the virus was named human bocavirus. Later, three other HBoVs were identified in stool samples and designated as HBoV types 2, 3, and 4, with the initial respiratory isolate called HBoV1. The HBoV capsid structure and genome size are similar to those of B19V, but the genomic organization and replication are different (though not fully characterized to date). HBoVs cannot be propagated in conventional cell culture but have been grown in a pseudostratified human airway epithelial cell culture system.

The **AAVs** are members of the genus Dependoparvovirus and were the first parvoviruses to be found in humans. They were originally identified as contaminants in laboratory preparations of adenovirus, resulting in the designation "adeno-associated viruses." They were later isolated directly from human tissue samples, and now several AAV serotypes are known to commonly infect humans. AAVs have a unique life cycle that can take one of two paths: (1) a lytic infection with replication of viral DNA and production of new virus, or (2) viral integration into the host cell DNA. In the presence of a "helper" virus, usually an adenovirus or a herpesvirus, AAV can replicate its DNA, produce capsids, and release new virions by cell lysis. In the absence of a helper virus infection, the AAV genome becomes integrated into the host cell DNA. This feature has drawn interest in AAVs as potential vectors for gene therapy. Although human infection with AAVs is common, there is only one possible disease association (idiopathic hepatitis) (see Chapter 406).

PARV4 was initially identified in 2005 from the blood of an adult patient with acute viral syndrome, who was also an intravenous drug user co-infected with hepatitis C. Subsequently, this virus has been found in blood donors and donated plasma pools in many different countries. It appears to be present in approximately 3% of blood donors in the United States and 4% of plasma pools. There is currently no known disease association or clinical symptomology associated with infection. Likewise, BuV is a parvovirus that was first identified in 2012 in the feces from children <5 years of age with acute diarrhea but has an unclear role as a pathogen. PARV4 has been assigned to the genus *Tetraparvovirus*, and BuV is a member of the genus *Protoparvovirus*. The full epidemiology and clinical relevance of these viruses await further study.

EPIDEMIOLOGY

Parvovirus B19

Infections with B19V are common and occur worldwide. Clinically apparent infections, such as the rash illness of erythema infectiosum and transient aplastic crisis, are most prevalent in school-age children (70% of cases occur in patients between 5 and 15 years of age). Seasonal peaks occur in the late winter and spring, with sporadic infections throughout the year. Seroprevalence increases with age, with 40–60% of adults having evidence of prior infection.

Transmission of B19V is by the respiratory route, presumably via large-droplet spread from nasopharyngeal viral shedding. The transmission rate is 15–30% among susceptible household contacts, and mothers are more commonly infected than fathers. In outbreaks of erythema infectiosum in elementary schools, the secondary attack rates range from 10–60%. Nosocomial outbreaks also occur, with secondary attack rates of 30% among susceptible healthcare workers.

Although respiratory spread is the primary mode of transmission, B19V is also transmissible in blood and blood products, as documented among children with hemophilia receiving pooled-donor clotting factor. Given the resistance of the virus to solvents, fomite transmission could be important in childcare centers and other group settings, but this mode of transmission has not been definitively established.

Human Bocaviruses

The majority of published studies have used molecular methods to detect HBoV DNA in respiratory secretions, fecal samples, blood, and other tissues. HBoV DNA (HBoV1) can be found commonly in respiratory secretions from children hospitalized with acute lower respiratory tract infections (LRTIs). It is more prevalent in children younger than 2 years of age and seems to be associated with wheezing respiratory illness. However, it can be isolated from respiratory secretions from asymptomatic children and can often be found as a co-infection with other common respiratory pathogens of children this age, including respiratory syncytial virus, human metapneumovirus, and rhinoviruses. This has caused some confusion as to the pathogenic role of HBoV in acute LRTI, including whether it can persist in secretions long after a subclinical infection or requires a helper virus. A limited number of seroepidemiologic studies have been performed, and these suggest that infection is common in children younger than 5 years of age. The most recent studies provide evidence that the virus is in fact pathogenic, especially in children younger than 2 years with wheezing and LRTI, because HBoV1 is more likely to be the only virus isolated in these patients and more likely to have an acute antibody response when coupled with specific antibody testing. When quantitative PCR is used, the virus is found to be much higher in titer in these symptomatic cases.

HBoV DNA (HBoV2, HBoV3, and HBoV4) has also been found in fecal samples in studies from various countries, but its role as a cause of viral gastroenteritis is still undetermined.

PATHOGENESIS

Parvovirus B19

The primary target of B19V infection is the erythroid cell line, specifically erythroid precursors near the pronormoblast stage. Viral infection produces cell lysis, leading to a progressive depletion of erythroid precursors and a transient arrest of erythropoiesis. The virus has no apparent effect on the myeloid cell line. The tropism for erythroid cells is related to the erythrocyte P blood group antigen, which is the primary cell receptor for the virus and is also found on endothelial cells, placental cells, and fetal myocardial cells. Thrombocytopenia and

neutropenia are often observed clinically, but the pathogenesis of these abnormalities is not completely understood.

Experimental infection of normal volunteers with B19V revealed a biphasic illness. From 7-11 days after inoculation, subjects had viremia and nasopharyngeal viral shedding with fever, malaise, and rhinorrhea. Reticulocyte counts dropped to undetectable levels but resulted in only a mild, clinically insignificant fall in serum hemoglobin. With the appearance of specific antibodies, symptoms resolved and serum hemoglobin returned to normal. Several subjects experienced a rash associated with arthralgia 17-18 days after inoculation. Some manifestations of B19 infection, such as transient aplastic crisis, appear to be a direct result of viral infection, whereas others, including the exanthem and arthritis, appear to be *postinfectious phenomena* related to the immune response. Skin biopsy of patients with erythema infectiosum reveals edema in the epidermis and a perivascular mononuclear infiltrate compatible with an immune-mediated process.

Individuals with **chronic hemolytic anemia** and increased red blood cell (RBC) turnover are very sensitive to minor perturbations in erythropoiesis. Infection with B19V leads to a transient arrest in RBC production and a precipitous fall in serum hemoglobin, often requiring transfusion. The reticulocyte count drops to undetectable levels, reflecting the lysis of infected erythroid precursors. Humoral immunity is crucial in controlling infection. Specific immunoglobulin (Ig) M appears within 1-2 days of infection and is followed by anti-B19 IgG, which leads to control of the infection, restoration of reticulocytosis, and a rise in serum hemoglobin.

Individuals with **impaired humoral immunity** are at increased risk for more serious or persistent infection with B19V, which usually manifests as chronic RBC aplasia, although neutropenia, thrombocytopenia, and marrow failure are also described. Children undergoing chemotherapy for leukemia or other forms of cancer, transplant recipients, and patients with congenital or acquired immunodeficiency states (including AIDS) are at risk for chronic B19V infections.

Infections in the **fetus** and **neonate** are somewhat analogous to infections in immunocompromised persons. B19V is associated with nonimmune fetal hydrops and stillbirth in women experiencing a primary infection but does not appear to be teratogenic. Like most mammalian parvoviruses, B19V can cross the placenta and cause fetal infection during primary maternal infection. Parvovirus cytopathic effects are seen primarily in erythroblasts of the bone marrow and sites of extramedullary hematopoiesis in the liver and spleen. Fetal infection can presumably occur as early as 6 weeks of gestation, when erythroblasts are first found in the fetal liver; after the fourth month of gestation, hematopoiesis switches to the bone marrow. In some cases, fetal infection leads to profound fetal anemia and subsequent high-output cardiac failure (see Chapter 138). **Fetal hydrops** ensues and is often associated with fetal death. There may also be a direct effect of the virus on myocardial tissue that contributes to the cardiac failure. However, most infections during pregnancy result in normal deliveries at term. Some of the asymptomatic infants from these deliveries have been reported to have chronic postnatal infection with B19V that is of unknown significance.

Human Bocaviruses

Mechanisms of HBoV replication and pathogenesis are poorly characterized to date. Growth of HBoV1 in tissue culture is difficult, though the virus has been cultured in primary respiratory epithelial cells as noted above. The primary site of viral replication appears to be the respiratory tract, because the virus has been detected most frequently and in highest copy numbers here. HBoV1 has also been found occasionally in the serum, suggesting the potential for systemic spread. HBoV1 has also been detected in stool, but copy numbers are very low. In contrast, HBoV types 2-4 are found predominantly in the stool, but host cell types are not known.

CLINICAL MANIFESTATIONS

Parvovirus B19

Many infections are clinically inapparent (Table 298.1). Infected children characteristically demonstrate the rash illness of erythema infectiosum. Adults, especially women, frequently experience acute polyarthropathy with or without a rash.

TABLE 298.1 Clinical Associations with Parvovirus B19 Infection

Asymptomatic infection
Exanthematous disorders
Erythema infectiosum (fifth disease)
Papular-purpuric gloves-and-socks syndrome
Asymmetric periflexural exanthem
"Bathing trunk" exanthem
Petechial exanthems
Other disorders
Arthritis
Transient aplastic crises
Chronic anemia
Refractory anemia after solid organ or stem cell transplantation
Hemophagocytic lymphohistiocytosis
Myelodysplastic syndrome
Fetal hydrops
Vasculitis
Neurologic disease, including arterial ischemic stroke, encephalopathy, encephalitis
Rheumatologic disease
Liver failure
Myocarditis

From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology,* 6th ed. Philadelphia: Elsevier; 2022: Box 16.2, p. 452.

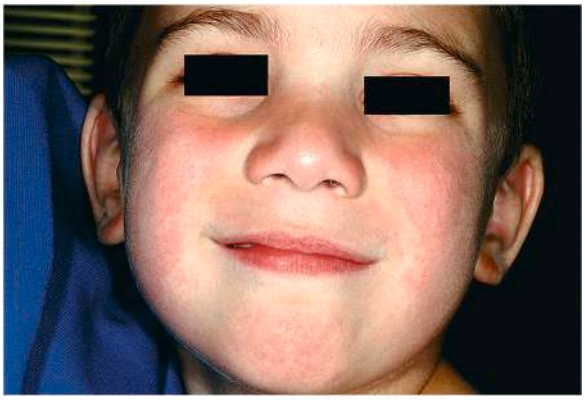

Fig. 298.1 Erythema infectiosum. Erythema of the bilateral cheeks, which has been likened to a "slapped-cheek" appearance. *(From Paller AS, Macini AJ. Hurwitz Clinical Pediatric Dermatology, 3rd ed. Philadelphia: WB Saunders; 2006:431.)*

Erythema Infectiosum (Fifth Disease)

The most common manifestation of B19V is erythema infectiosum, also known as *fifth disease*, which is a benign, self-limited exanthematous illness of childhood.

The incubation period for erythema infectiosum is 4-28 days (average: 16-17 days). The prodromal phase is mild and consists of low-grade fever in 15–30% of cases, headache, and symptoms of mild upper respiratory tract infection. The hallmark of erythema infectiosum is the characteristic rash, which occurs in three stages that are not always distinguishable. The initial stage is an erythematous facial flushing, often described as a **slapped-cheek appearance** (Fig. 298.1). The rash spreads rapidly or concurrently to the trunk and proximal extremities as a diffuse macular erythema in the second stage. Central clearing of macular lesions occurs promptly, giving the rash a **lacy**, **reticulated appearance** (Fig. 298.2). The rash tends to be more prominent on extensor surfaces, sparing the palms and soles. Affected children are afebrile and do not appear ill. Some have petechiae. Older children and adults often complain of mild pruritus. The rash resolves spontaneously without desquamation but tends to wax and wane over 1-3 weeks. It can recur with exposure to sunlight, heat, exercise, and stress.

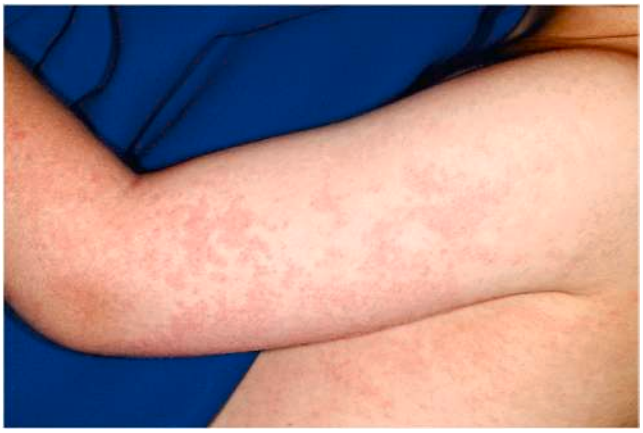

Fig. 298.2 Erythema infectiosum. Reticulate erythema on the upper arm of a patient with erythema infectiosum. *(From Paller AS, Macini AJ. Hurwitz Clinical Pediatric Dermatology, 3rd ed. Philadelphia: WB Saunders; 2006:431.)*

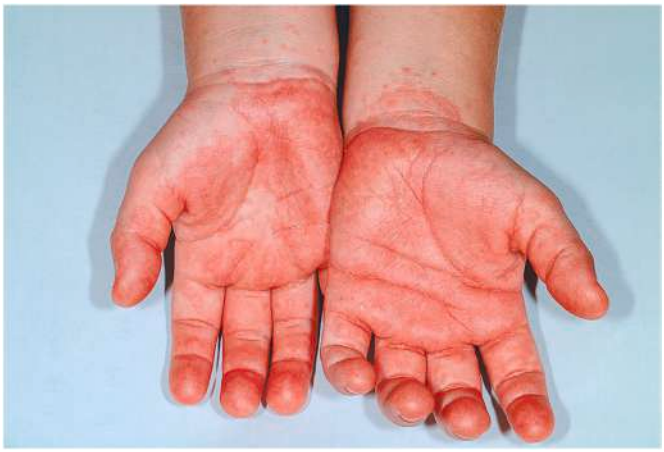

Fig. 298.3 Papular-purpuric gloves-and-socks syndrome. Petechial purpura of the palms in a patient with parvovirus B19 infection. *(From Paller AS, Mancini AJ. Hurwitz Clinical Pediatric Dermatology, 6th ed. Philadelphia: Elsevier; 2022: Fig. 16.18, p. 453.)*

Lymphadenopathy and atypical papular, purpuric and vesicular rashes are also described.

Arthropathy

Arthritis and arthralgia may occur in isolation or with other symptoms. Joint symptoms are much more common among adults and older adolescents with B19V infection. Females are affected more frequently than males. In one large outbreak of fifth disease, 60% of adults and 80% of adult women reported joint symptoms. Joint symptoms range from diffuse polyarthralgia with morning stiffness to frank arthritis. The joints most often affected are the hands, wrists, knees, and ankles, but practically any joint may be affected. The joint symptoms are self-limited and, in the majority of patients, resolve within 2-4 weeks. Some patients may have a prolonged course of many months, suggesting rheumatoid arthritis. Transient rheumatoid factor positivity is reported in some of these patients but with no joint destruction.

Transient Aplastic Crisis

The transient arrest of erythropoiesis and absolute reticulocytopenia induced by B19V infection leads to a sudden fall in serum hemoglobin in individuals with chronic hemolytic conditions. This B19V-induced RBC aplasia or transient aplastic crisis occurs in patients with all types of chronic hemolysis and/or rapid RBC turnover, including sickle cell disease, thalassemia, hereditary spherocytosis, and pyruvate kinase deficiency, among others. In contrast to children with erythema infectiosum only, patients with aplastic crisis are ill at presentation with fever, malaise, and lethargy and have signs and symptoms of profound anemia, including pallor, tachycardia, and tachypnea. Rash is rarely present. The incubation period for transient aplastic crisis is shorter than that for erythema infectiosum because the crisis occurs coincident with the viremia. Children with sickle cell hemoglobinopathies may also have a concurrent vasoocclusive pain crisis, further confusing the clinical presentation.

Immunocompromised Persons

Individuals with impaired humoral immunity are at risk for chronic B19V infection. Chronic anemia is the most common manifestation, sometimes accompanied by neutropenia, thrombocytopenia, or complete marrow suppression. Chronic infections occur in persons receiving cancer chemotherapy or immunosuppressive therapy for transplantation and persons with congenital immunodeficiencies, AIDS, and functional defects in IgG production who are thereby unable to generate neutralizing antibodies.

Fetal Infection

Primary maternal infection is associated with nonimmune fetal hydrops and intrauterine fetal demise, with the risk for fetal loss when infection occurs in pregnancy estimated at 2–5%. The mechanism of fetal disease appears to be a viral-induced RBC aplasia at a time when the fetal erythroid fraction is rapidly expanding, leading to profound anemia, high-output cardiac failure, and fetal hydrops. Viral DNA has been detected in infected abortuses. The second trimester seems to be the most sensitive period, but fetal losses are reported at every stage of gestation. If maternal B19V infection is suspected, fetal ultrasonography and measurement of the peak systolic flow velocity of the middle cerebral artery are sensitive, noninvasive procedures to diagnose fetal anemia and hydrops. Most infants infected in utero are born normal at term, including some who have had ultrasonographic evidence of hydrops. A small subset of infants infected in utero may acquire a chronic or persistent postnatal infection with B19V that is of unknown significance. Congenital anemia associated with intrauterine B19V infection has been reported in a few cases, sometimes following intrauterine hydrops. This process may mimic other forms of congenital hypoplastic anemia (e.g., Diamond-Blackfan syndrome). Fetal infection with B19V has been associated with bone lesions but has not been associated with other birth defects. B19V is only one of many causes of hydrops fetalis (see Chapter 140).

Myocarditis

B19V infection has been associated with myocarditis in fetuses, infants, children, and a limited number of adults. Diagnosis has often been based on serologic findings suggestive of a concurrent B19V infection, but in many cases B19V DNA has been demonstrated in cardiac tissue. B19-related myocarditis is plausible because fetal myocardial cells are known to express P antigen, the cell receptor for the virus. In the few cases in which histology is reported, a predominantly lymphocytic infiltrate is described. Outcomes have varied from complete recovery to chronic cardiomyopathy to fatal cardiac arrest. Although B19-associated myocarditis seems to be a rare occurrence, there appears to be enough evidence to consider B19V as a potential cause of lymphocytic myocarditis, especially in infants and immunocompromised persons.

Other Cutaneous Manifestations

A variety of atypical skin eruptions have been reported with B19V infection. Most of these are petechial or purpuric, often with evidence of vasculitis on biopsy. Among these rashes, the **papular-purpuric gloves-and-socks syndrome (PPGSS)** is well established in the dermatologic literature as distinctly associated with B19V infection (Figs. 298.3 and 298.4). PPGSS is characterized by fever, pruritus, and painful edema and erythema localized to the distal extremities in a distinct gloves-and-socks distribution, followed by acral petechiae and oral lesions. The syndrome is self-limited and resolves within a few weeks. Although PPGSS was initially described in young adults, a number of reports of the disease in

children have since been published. In those cases linked to B19V infection, the eruption is accompanied by serologic evidence of acute infection. Generalized petechial rash has also been reported.

Human Bocaviruses

Many studies have reported an association between respiratory tract infection and HBoV1 infection as detected by PCR of respiratory secretions, primarily nasopharyngeal secretions. Clinical manifestations in these studies have ranged from mild upper respiratory symptoms to pneumonia. However, the role of HBoV1 as a pathogen has been challenged by the detection of the virus in asymptomatic children and by the frequent detection of other respiratory viruses in the same samples. Nonetheless, studies that have included some combination of quantitative PCR, serum PCR, and serology have been more convincing about HBoV1 as a human pathogen. The use of a quantitative PCR method also seems to differentiate between HBoV1 infection (and wheezing) and prolonged viral shedding, because patients with higher viral titers were more likely to be symptomatic, to be viremic, and to have HBoV1 isolated without other viruses.

HBoV type 2 DNA has been found in the stool of 3–25% of children with gastroenteritis, but often with another enteric virus. DNA of HBoV types 2, 3, and 4 has also been found in the stool of healthy, asymptomatic individuals. At present, there are few data linking HBoV2, HBoV3, or HBoV4 to gastroenteritis or any clinical illness. Further studies are required to determine if any of the HBoVs are associated with some cases of childhood gastroenteritis.

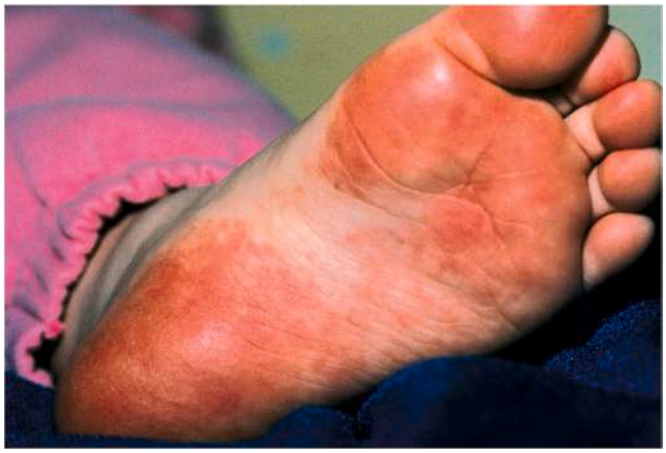

Fig. 298.4 Papular-purpuric gloves-and-socks syndrome. Erythema and petechiae of the plantar feet were accompanied by pruritus and sore throat in this young girl with parvovirus B19 infection. *(From Paller AS, Mancini AJ. Hurwitz Clinical Pediatric Dermatology, 6th ed. Philadelphia: Elsevier; 2022: Fig. 16.19, p. 454.)*

DIAGNOSIS

Parvovirus B19 Infection

The diagnosis of erythema infectiosum is usually based on clinical presentation of the typical rash and rarely requires virologic confirmation. Similarly, the diagnosis of a typical transient aplastic crisis in a child with sickle cell disease is generally made on clinical grounds without specific virologic testing.

Serologic tests for the diagnosis of B19V infection are available. B19-specific IgM develops within 2-3 days after infection and persists up to 6 months (Fig. 298.5). Anti-B19 IgG serves as a marker of current or past infection. Seroconversion of anti-B19 IgG antibodies in paired sera can also be used to confirm recent infection.

Serologic diagnosis is unreliable in immunocompromised persons; diagnosis in these patients requires methods to detect viral DNA. Because the virus cannot be isolated by standard cell culture, methods to detect viral particles or viral DNA, such as PCR are necessary to establish the diagnosis. Viral DNA may be detectable for ~1 month after infection in immunocompetent patients but longer in immune compromised patients. Some reports suggest that prolonged detection of viral DNA (months) may represent DNA but not the complete virus. Prenatal diagnosis of B19V-induced fetal hydrops can be accomplished by detection of viral DNA in fetal blood or amniotic fluid by these methods.

Human Bocavirus Infections

HBoV1 infections cannot be differentiated from other viral respiratory infections on clinical grounds. HBoV DNA can be readily detected by PCR methods and is now included in several commercially available multiplex respiratory virus PCR assays. Quantitative PCR is useful to differentiate acute infection from persistent viral shedding, because higher viral copy numbers (>10^4 HBoV1 genomes/mL) correlate with acute illness, but this test is not widely available. Likewise, serologic methods to detect specific IgM and IgG antibodies have been developed, but these too are not routinely available and there are problems with cross-reactivity among antibodies to the various HBoV types. The most reliable method to diagnose HBoV1 infection would include detection of viral DNA in serum by PCR and in respiratory tract samples by quantitative PCR, with concurrent detection of IgM or a diagnostic IgG response in paired samples.

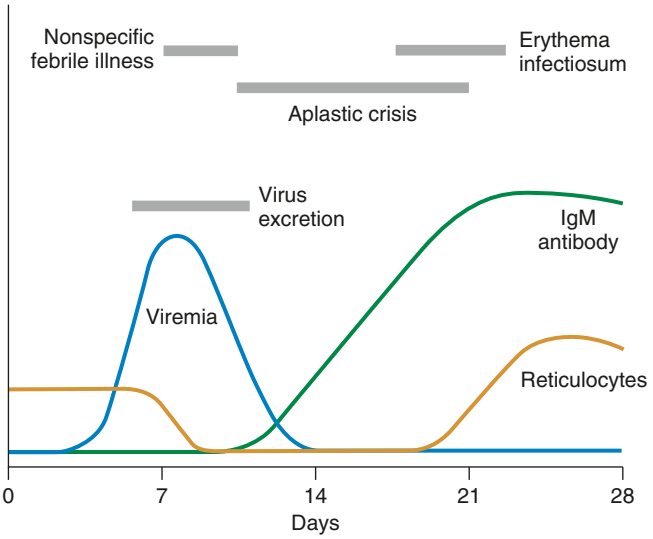

Fig. 298.5 Selected virologic, immunologic, hematologic, and clinical events in parvovirus B19 virus infection. *(From Schulte DJ. Human parvovirus B19. In Kaplan SL, Harrison GJ, Steinbach WJ, Cherry JD, Hotez PJ, eds. Feigin and Cherry's Textbook of Pediatric Infectious Diseases, 8th ed. Philadelphia: Elsevier, 2019. Fig 152.1.)*

DIFFERENTIAL DIAGNOSIS

Parvovirus B19

The rash of erythema infectiosum must be differentiated from roseola, rubella, measles, enteroviral infections, and drug reactions. Rash and arthritis in older children should prompt consideration of juvenile idiopathic arthritis, systemic lupus erythematosus, serum sickness, and other connective tissue disorders.

Human Bocavirus

Respiratory illness and wheezing caused by HBoV1 cannot be differentiated clinically from other common viral respiratory infections, especially respiratory syncytial virus, human metapneumovirus, rhinoviruses, enterovirus D68, and parainfluenza viruses. HBoV1 infection in young children seems to most closely resemble that of respiratory syncytial virus and human metapneumovirus, because the clinical symptoms and age ranges will overlap.

TREATMENT

Parvovirus B19

There is no specific antiviral therapy approved for B19V infection. The acyclic nucleoside phosphonates cidofovir and brincidofovir have been shown to inhibit B19V replication in vitro, but no clinical studies have been performed and thus antiviral therapy cannot be recommended. Commercial lots of intravenous immunoglobulin (IVIG) have been used with some success to treat B19V-related episodes of anemia and bone marrow failure in immunocompromised children. Specific antibody may facilitate clearance of the virus but is not always necessary, because cessation of cytotoxic chemotherapy with subsequent restoration of immune function often suffices. In patients whose immune function is not likely to recover, such as patients with AIDS, administration of IVIG may give only a temporary remission, and periodic reinfusions may be required. In patients with AIDS, clearance of B19V infection has been reported after initiation of highly active antiretroviral therapy (HAART) without the use of IVIG.

No controlled studies have been published regarding dosing of IVIG for B19V-induced RBC aplasia. Multiple case reports and limited clinical series have reported successful treatment of severe anemia secondary to chronic B19V infection using several different IVIG dosing regimens. Initial reports recommended a starting dose of 400 mg/kg/day for up to 5 days. Other reports have used higher doses ranging from 1-2 g/kg split into one to three infusions. The dose and duration of IVIG may be adjusted based on the response to therapy. The optimal schedule of IVIG treatment is not known.

B19V-infected fetuses with anemia and hydrops have been managed successfully with intrauterine RBC transfusions, but this procedure has significant attendant risks. Once fetal hydrops is diagnosed, regardless of the suspected cause, the mother should be referred to a fetal therapy center for further evaluation because of the high risk for serious complications (see Chapter 140).

Human Bocavirus

There is no specific antiviral therapy available. Appropriate supportive treatment for viral LRTI and pneumonia is recommended, as directed by clinical severity. For children with wheezing illness specifically caused by HBoV1 infection, there are no data examining their response to bronchodilator therapy.

COMPLICATIONS

Parvovirus B19

Erythema infectiosum is often accompanied by arthralgias or arthritis in adolescents and adults that may persist after resolution of the rash (see Table 298.1). B19V may rarely cause thrombocytopenic purpura. Neurologic conditions, including aseptic meningitis, encephalitis, and peripheral neuropathy, have been reported in both immunocompromised and healthy individuals in association with B19V infection. The incidence of stroke may be increased in children with sickle cell disease following B19V-induced transient aplastic crisis. B19V is also a cause of infection-associated hemophagocytic lymphohistiocytosis, usually in immunocompromised persons.

Human Bocavirus

There are no studies reporting on complications of HBoV1 infection. Complications of wheezing and viral pneumonia would be possible, including hypoxemia and secondary bacterial infection, among others.

PREVENTION

Parvovirus B19

Children with erythema infectiosum are not likely to be infectious at presentation because the rash and arthropathy represent immune-mediated, postinfectious phenomena. Isolation and exclusion from school or childcare are unnecessary and ineffective after diagnosis.

Children with B19V-induced RBC aplasia, including the transient aplastic crisis, are infectious upon presentation and demonstrate a more intense viremia. Most of these children require transfusions and supportive care until their hematologic status stabilizes. They should be isolated in the hospital to prevent spread to susceptible patients and staff. Isolation should continue for at least 1 week and until fever has resolved. Pregnant caregivers should not be assigned to these patients. Exclusion of pregnant women from workplaces where children with erythema infectiosum may be present (e.g., primary and secondary schools) is not recommended as a general policy because it is unlikely to reduce their risk. There are no data to support the use of IVIG for postexposure prophylaxis in pregnant caregivers or immunocompromised children. No vaccine is currently available, though this is a topic of ongoing research.

Human Bocavirus

There are no studies that have addressed the prevention of transmission of this infection. In the hospital setting, standard precautions should be observed to limit spread of the virus. Because HBoV1 causes respiratory infection and can be detected in respiratory secretions sometimes in very high titer, measures to limit contact with respiratory secretions should be considered, including contact and droplet isolation for severely symptomatic young children. No vaccine is available, and no other preventive measures have been reported.

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Chapter 299

Herpes Simplex Virus

Lawrence R. Stanberry and Philip Zachariah

The two closely related herpes simplex viruses (HSVs), HSV type 1 (HSV-1) and HSV type 2 (HSV-2), cause a variety of illnesses, depending on the anatomic site where the infection is initiated, the immune state of the host, and whether the symptoms reflect primary or recurrent infection. Common infections involve the skin, eye, oral cavity, and genital tract. Infections tend to be mild and self-limiting, except in the immunocompromised patient and newborn infants, in whom they may be severe and life-threatening.

Primary infection occurs in individuals who have not been infected previously with either HSV-1 or HSV-2. Because these individuals are HSV seronegative and have no preexisting immunity to HSV, primary infections can be severe. **Nonprimary first infection** occurs in individuals previously infected with one type of HSV (e.g., HSV-1) who

have become infected for the first time with the other type of HSV (HSV-2). Because immunity to one HSV type provides some cross-protection against disease caused by the other HSV type, nonprimary first infections tend to be less severe than true primary infections. During primary and nonprimary initial infections, HSV establishes latent infection in regional sensory ganglion neurons. Virus is maintained in this latent state for the life of the host but periodically can reactivate and cause **recurrent infection**. Symptomatic recurrent infections tend to be less severe and of shorter duration than first infections. Asymptomatic recurrent infections are extremely common and cause no physical distress, although patients with these infections are contagious and can transmit the virus to susceptible individuals. Reinfection with a new strain of either HSV-1 or HSV-2 at a previously infected anatomic site (e.g., the genital tract) can occur but is relatively uncommon, suggesting that host immunity, perhaps site-specific local immunity, resulting from the initial infection affords protection against exogenous reinfection.

ETIOLOGY

HSVs contain a double-stranded DNA genome of approximately 152 kb that encodes at least 84 proteins. The DNA is contained within an icosadeltahedral capsid, which is surrounded by an outer envelope composed of a lipid bilayer containing at least 12 viral glycoproteins. These glycoproteins are the major targets for humoral immunity, whereas other nonstructural proteins are important targets for cellular immunity. Two encoded proteins, viral DNA polymerase and thymidine kinase, are targets for antiviral drugs. HSV-1 and HSV-2 have a similar genetic composition with extensive DNA and protein homology. One important difference in the two viruses is their glycoprotein G proteins, which have been exploited to develop a new generation of commercially available, accurate, type-specific serologic tests that can be used to discriminate whether a patient has been infected with HSV-1 or HSV-2 or both.

EPIDEMIOLOGY

HSV infections are ubiquitous, and there are no seasonal variations in risk for infection. The only natural host is humans, and the mode of transmission is direct contact between mucocutaneous surfaces. There are no documented incidental transmissions from inanimate objects such as toilet seats.

All infected individuals harbor latent infection and experience recurrent infections, which may be symptomatic or may go unrecognized and thus are periodically contagious. This information helps explain the widespread prevalence of HSV.

HSV-1 and HSV-2 are equally capable of causing initial infection at any anatomic site but differ in their capacity to cause recurrent infections. HSV-1 has a greater propensity to cause recurrent oral infections, whereas HSV-2 has a greater proclivity to cause recurrent genital infections. For this reason, HSV-1 infection typically results from contact with contaminated oral secretions, whereas HSV-2 infection most commonly results from anogenital contact.

HSV seroprevalence rates are highest in developing countries and among lower socioeconomic groups, although high rates of HSV-1 and HSV-2 infections are found in developed nations and among persons of the highest socioeconomic strata. Incident HSV-1 infections are more common during childhood and adolescence but are also found throughout later life. Data on HSV-1 and HSV-2 antibody prevalence from the National Health and Nutrition Examination Survey (NHANES) among persons age 14-49 years showed the prevalence of HSV-1 and HSV-2 to be 47.8% and 11.9%, respectively. Prevalence of both HSV-1 and HSV-2 increased linearly with age and was higher among females than males.

Modifiable factors that predict HSV-2 seropositivity include less education, poverty, cocaine use, and a greater lifetime number of sexual partners. Studies show that only approximately 10–20% of HSV-2–seropositive subjects report a history of genital herpes, emphasizing the asymptomatic nature of most HSV infections.

A 3-year longitudinal study of Midwestern adolescent females 12-15 years of age found that 44% were seropositive for HSV-1 and 7% for HSV-2 at enrollment. At the end of the study, 49% were seropositive for HSV-1 and 14% for HSV-2. The attack rates, based on the number of cases per 100 person-years, were 3.2 for HSV-1 infection among all females and 4.4 for HSV-2 infection among females who reported being sexually experienced. Findings of this study indicate that sexually active young women have a high attack rate for genital herpes and suggest that genital herpes should be considered in the differential diagnosis of any young woman who reports recurrent genitourinary complaints. In this study, participants with preexisting HSV-1 antibodies had a significantly lower attack rate for HSV-2 infection, and those who became infected were less likely to have symptomatic disease than females who were HSV seronegative when they entered the study. Prior HSV-1 infection appears to afford adolescent females some protection against becoming infected with HSV-2; in adolescent females infected with HSV-2, the preexisting HSV-1 immunity appears to protect against development of symptomatic genital herpes.

Neonatal herpes is an uncommon but potentially fatal infection of the fetus or more likely the newborn. It is not a reportable disease in most states, and therefore there are no solid epidemiologic data regarding its frequency in the general population. The overall U.S. incidence of neonatal HSV was estimated to be 9.6 per 100,000 births in 2006, which is higher than reported for the reportable perinatally acquired sexually transmitted infections such as congenital syphilis and gonococcal ophthalmia neonatorum. More than 90% of the cases are the result of maternal-child transmission. The risk for transmission is greatest during a primary or nonprimary first infection (30–50%) and much lower when the exposure is during a recurrent infection (<2%). HSV viral suppression therapy in mothers does not consistently eliminate the possibility of neonatal infection. Infants born to mothers dually infected with HIV and HSV-2 are also at higher risk for acquiring HIV than infants born to HIV-positive mothers who are not HSV-2 infected. It is estimated that approximately 25% of pregnant women are HSV-2 infected and that approximately 2% of pregnant women acquire HSV-2 infection during pregnancy.

HSV is a leading cause of sporadic, fatal encephalitis in children and adults. In the United States the annual hospitalization rate for HSV encephalitis has been calculated to be 10.3 ± 2.2 cases/million in neonates, 2.4 ± 0.3 cases/million in children, and 6.4 ± 0.4 cases/million in adults.

PATHOGENESIS

In the immunocompetent host the pathogenesis of HSV infection involves viral replication in skin and mucous membranes followed by replication and spread in neural tissue. Viral infection typically begins at a cutaneous portal of entry such as the oral cavity, genital mucosa, ocular conjunctiva, or breaks in keratinized epithelia. The virus enters the cell through attachment and fusion, a multistep process mediated by interaction of viral envelope glycoproteins (e.g., gB and gH-gL) with host surface receptors (e.g., Nectin-1). Virus replicates locally, resulting in the death of the cell, and sometimes produces clinically apparent inflammatory responses that facilitate the development of characteristic herpetic vesicles and ulcers. Virus also enters nerve endings and spreads beyond the portal of entry to sensory ganglia by intraneuronal transport. Virus replicates in some sensory neurons, and the progeny virions are sent via intraneuronal transport mechanisms back to the periphery, where they are released from nerve endings and replicate further in skin or mucosal surfaces. It is virus moving through this neural arc that is primarily responsible for the development of characteristic herpetic lesions, although most HSV infections do not reach a threshold necessary to cause clinically recognizable disease. Although many sensory neurons become productively infected during the initial infection, some infected neurons do not initially support viral replication. It is in these neurons that the virus establishes a latent infection, a condition in which the viral genome persists within the neuronal nucleus in a largely metabolically inactive state. Intermittently throughout the

life of the host, undefined changes can occur in latently infected neurons that trigger the virus to begin to replicate. This replication occurs despite the host's having established a variety of humoral and cellular immune responses that successfully controlled the initial infection. With reactivation of the latent neuron, progeny virions are produced and transported within nerve fibers back to cutaneous sites somewhere in the vicinity of the initial infection, where further replication occurs and causes recurrent infections. Recurrent infections may be symptomatic (with typical or atypical herpetic lesions) or asymptomatic. In either case, virus is shed at the site where cutaneous replication occurs and can be transmitted to susceptible individuals who come in contact with the site or with contaminated secretions. Latency and reactivation are the mechanisms by which the virus is successfully maintained in the human population.

Viremia, or hematogenous spread of the virus, does not appear to play an important role in HSV infections in the immunocompetent host but can occur in neonates, individuals with eczema, and severely malnourished children. It is also seen in patients with depressed or defective cell-mediated immunity, as occurs with HIV infection, malignancy, or immunosuppressive therapies. Viremia can result in dissemination of the virus to visceral organs, including the liver and adrenals. Hematogenous dissemination of virus to the central nervous system appears to only occur in neonates.

The pathogenesis of HSV infection in newborns is complicated by their relative immunologic immaturity. The source of virus in neonatal infections is typically but not exclusively the mother. Transmission generally occurs during delivery, although it is well documented to rarely occur with cesarean delivery with intact fetal membranes. The most common portals of entry are the conjunctiva, mucosal epithelium of the nose and mouth, and breaks or abrasions in the skin that occur with scalp electrode use or forceps delivery. With prompt antiviral therapy, virus replication may be restricted to the site of inoculation (the skin, eye, or mouth). However, virus may also extend from the nose to the respiratory tract to cause pneumonia, move via intraneuronal transport to the central nervous system to cause encephalitis, or spread by hematogenous dissemination to visceral organs and the brain. Factors that may influence neonatal HSV infection include the virus type, portal of entry, inoculum of virus to which the infant is exposed, gestational age of the infant, and presence of maternally derived antibodies specific to the virus causing infection. Latent infection is established during neonatal infection, and survivors may experience recurrent cutaneous and neural infections. Persistent central nervous system infection may affect the neurodevelopment of the infant.

CLINICAL MANIFESTATIONS

The hallmarks of common HSV infections are skin vesicles and shallow ulcers. Classic infections manifest as small, 2- to 4-mm vesicles that may be surrounded by an erythematous base. These may persist for a few days before evolving into shallow, minimally erythematous ulcers. The vesicular phase tends to persist longer when keratinized epithelia is involved and is generally brief and sometimes just fleeting when moist mucous membranes are the site of infection. Because HSV infections are common, and their natural history is influenced by many factors, including portal of entry, immune status of the host, and whether it is an initial or recurrent infection, the typical manifestations are seldom classic. Most infections are asymptomatic or unrecognized, and nonclassic presentations, such as small skin fissures and small erythematous nonvesicular lesions, are common.

Acute Oropharyngeal Infections

Herpes gingivostomatitis most often affects children 6 months to 5 years of age but is seen across the age spectrum. It is an extremely painful condition with sudden onset, pain in the mouth, drooling, refusal to eat or drink, and fever of up to 40.0–40.6°C (104–105.1°F). The gums become markedly swollen, and vesicles may develop throughout the oral cavity, including the gums, lips, tongue, palate, tonsils, pharynx, and perioral skin (Fig. 299.1). The vesicles may be more extensively distributed than typically seen with enteroviral herpangina. During the initial phase of the illness there may be tonsillar exudates suggestive of bacterial pharyngitis. The vesicles are generally present only a few days before progressing to form shallow indurated ulcers that may be covered with a yellow-gray membrane. Tender submandibular, submaxillary, and cervical lymphadenopathy is common. The breath may be foul as a result of overgrowth of anaerobic oral bacteria. Untreated, the illness resolves in 7-14 days, although the lymphadenopathy may persist for several weeks.

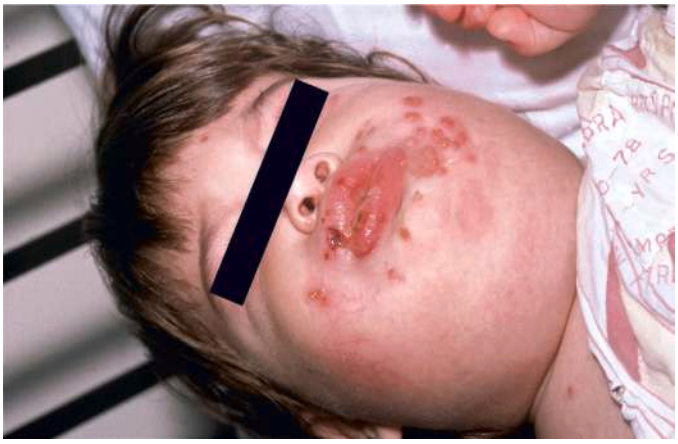

Fig. 299.1 Clustered perioral vesicles and erosions in an infant with primary herpetic gingivostomatitis. *(From Schachner LA, Hansen RC, eds. Pediatric Dermatology, 3rd ed. Philadelphia: Mosby; 1988:1078.)*

In older children, adolescents, and college students, the initial HSV oral infection may manifest as pharyngitis and tonsillitis rather than gingivostomatitis. The vesicular phase is often over by the time the patient presents to a healthcare provider, and signs and symptoms may be indistinguishable from those of streptococcal pharyngitis, consisting of fever, malaise, headache, sore throat, and white plaques on the tonsils. The course of illness is typically longer than for untreated streptococcal pharyngitis.

Herpes Labialis

Fever blisters (cold sores) are the most common manifestation of *recurrent* HSV-1 infections. The most common site of herpes labialis is the vermilion border of the lip, although lesions sometimes occur on the nose, chin, cheek, or oral mucosa. Older patients report experiencing burning, tingling, itching, or pain 3-6 hours (rarely as long as 24-48 hours) before the development of the herpes lesion. The lesion generally begins as a small grouping of erythematous papules that progress over a few hours to create a small, thin-walled vesicle. The vesicles may form shallow ulcers or become pustular. The short-lived ulcer dries and develops a crusted scab. Complete healing without scarring occurs with reepithelialization of the ulcerated skin, usually within 6-10 days. Some patients experience local lymphadenopathy but no constitutional symptoms.

Cutaneous Infections

In the healthy child or adolescent, cutaneous HSV infections are generally the result of skin trauma with macroabrasions or microabrasions and exposure to infectious secretions. This situation most often occurs in play or contact sports such as wrestling **(herpes gladiatorum)** and rugby **(scrum pox)**. An initial cutaneous infection establishes a latent infection that can subsequently result in recurrent infections at or near the site of the initial infection. Pain, burning, itching, or tingling often precedes the herpetic eruption by a few hours to a few days. Like herpes labialis, lesions begin as grouped, erythematous papules that progress to vesicles, pustules, ulcers, and crusts and then heal without scarring in 6-10 days. Although herpes labialis typically results in a single lesion, a cutaneous HSV infection results in multiple discrete lesions

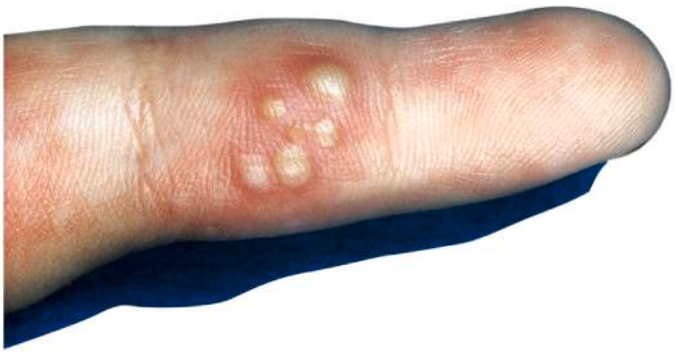

Fig. 299.2 Herpes simplex infection of finger (whitlow). *(From Schachner LA, Hansen RC, eds. Pediatric Dermatology, 3rd ed. Philadelphia: Mosby; 1988:1079.)*

and involves a larger surface area. Regional lymphadenopathy may occur, but systemic symptoms are uncommon. Recurrences are sometimes associated with local edema and lymphangitis or local neuralgia.

Herpes whitlow is a term generally applied to HSV infection of fingers or toes, although strictly speaking it refers to HSV infection of the paronychia. Among children, this condition is most commonly seen in infants and toddlers who suck the thumb or fingers and who are experiencing either a symptomatic or a subclinical oral HSV-1 infection (Fig. 299.2). An HSV-2 herpes whitlow occasionally develops in an adolescent as a result of exposure to infectious genital secretions. The onset of the infection is heralded by itching, pain, and erythema 2-7 days after exposure. The cuticle becomes erythematous and tender and may appear to contain pus, although if it is incised, little fluid is present. Incising the lesion is discouraged, because this maneuver typically prolongs recovery and increases the risk for secondary bacterial infection. Lesions and associated pain typically persist for about 10 days, followed by rapid improvement and complete recovery in 18-20 days. Regional lymphadenopathy is common, and lymphangitis and neuralgia may occur. Unlike other recurrent herpes infections, recurrent herpetic whitlows are often as painful as the primary infection but are generally shorter in duration.

Cutaneous HSV infections can be severe or life-threatening in patients with disorders of the skin such as eczema (eczema herpeticum), pemphigus, burns, and Darier disease and following laser skin resurfacing. The lesions are frequently ulcerative and nonspecific in appearance, although typical vesicles may be seen in adjacent normal skin (Fig. 299.3). If untreated, these lesions can progress to disseminated infection and death. Recurrent infections are common but generally less severe than the initial infection.

Genital Herpes

Genital HSV infection is common in sexually experienced adolescents and young adults, but up to 90% of infected individuals are *unaware* they are infected. Infection may result from genital-genital transmission (usually HSV-2) or oral-genital transmission (usually HSV-1). Symptomatic and asymptomatic individuals periodically shed virus from anogenital sites and hence can transmit the infection to sexual partners or, in the case of pregnant women, to their newborns. Classic primary genital herpes may be preceded by a short period of local burning and tenderness before vesicles develop on genital mucosal surfaces or keratinized skin and sometimes around the anus or on the buttocks and thighs. Vesicles on mucosal surfaces are short lived and rupture to produce shallow, tender ulcers covered with a yellowish gray exudate and surrounded by an erythematous border. Vesicles on keratinized epithelium persist for a few days before progressing to the pustular stage and then crusting.

Patients may experience urethritis and dysuria severe enough to cause urinary retention and bilateral, tender inguinal and pelvic lymphadenopathy. Women may experience a watery vaginal discharge,

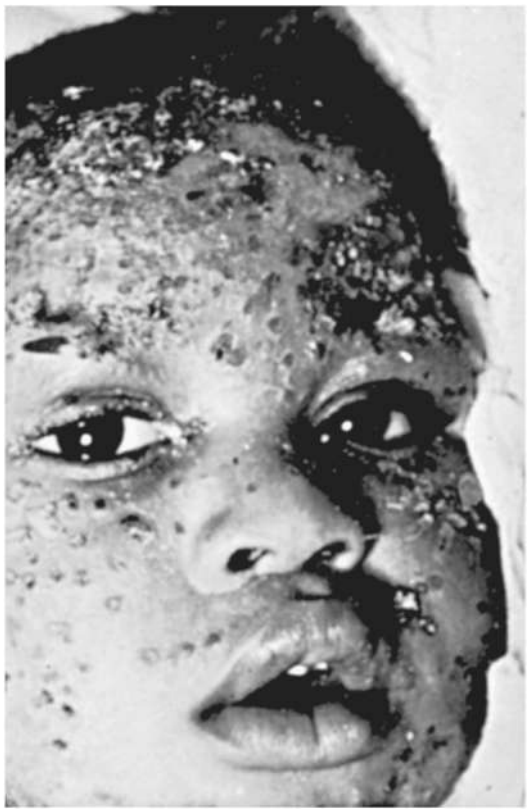

Fig. 299.3 Widespread cutaneous herpes infection in a child with underlying eczema (eczema herpeticum).

and men may have a clear mucoid urethral discharge. Significant local pain and systemic symptoms such as fever, headache, and myalgia are common. Aseptic meningitis develops in an estimated 15% of cases. The course of classic primary genital herpes from onset to complete healing is 2-3 weeks.

Most patients with symptomatic primary genital herpes experience at least one recurrent infection in the following year. Recurrent genital herpes is usually less severe and of shorter duration than the primary infection. Some patients experience a sensory prodrome with pain, burning, and tingling at the site where vesicles subsequently develop. Asymptomatic recurrent anogenital HSV infections are common, and all HSV-2–seropositive individuals appear to periodically shed virus from anogenital sites. *Most sexual transmissions and maternal-neonatal transmissions of virus result from asymptomatic shedding episodes.*

Genital infections caused by HSV-1 and HSV-2 are indistinguishable, but HSV-1 causes significantly fewer subsequent episodes of recurrent infection; hence, knowing which virus is causing the infection has important prognostic value. Genital HSV infection increases the risk for acquiring HIV infection.

Rarely, genital HSV infections are identified in young children and preadolescents. Although genital disease in children should raise concerns about possible sexual abuse, there are documented cases of autoinoculation, in which a child has inadvertently transmitted virus from contaminated oral secretions to his or her own genitalia.

Ocular Infections

HSV ocular infections may involve the conjunctiva, cornea, or retina and may be primary or recurrent. Conjunctivitis or keratoconjunctivitis is usually unilateral and is often associated with blepharitis and tender preauricular lymphadenopathy. The conjunctiva appears edematous but there is rarely purulent discharge. Vesicular lesions may be seen on the lid margins and periorbital skin. Patients typically

have fever. Untreated infection generally resolves in 2-3 weeks. Obvious corneal involvement is rare, but when it occurs it can produce ulcers that are described as appearing dendritic or geographic. Extension to the stroma is uncommon although more likely to occur in patients inadvertently treated with corticosteroids. When it occurs, it may be associated with corneal edema, scarring, and corneal perforation. Recurrent infections tend to involve the underlying stroma and can cause progressive corneal scarring and injury that can lead to blindness.

Retinal infections are rare and are more likely among infants with neonatal herpes and immunocompromised persons with disseminated HSV infections.

Central Nervous System Infections

HSV encephalitis is the leading cause of sporadic, nonepidemic encephalitis in children and adults in the United States. It is an acute necrotizing infection generally involving the frontal and/or temporal cortex and the limbic system and, beyond the neonatal period, is almost always caused by HSV-1. The infection may manifest as nonspecific findings, including fever, headache, nuchal rigidity, nausea, vomiting, generalized seizures, and alteration of consciousness. Injury to the frontal or temporal cortex or limbic system may produce findings more indicative of HSV encephalitis, including anosmia, memory loss, peculiar behavior, expressive aphasia and other changes in speech, hallucinations, and focal seizures. The untreated infection progresses to coma and death in 75% of cases. Examination of the cerebrospinal fluid (CSF) typically shows a moderate number of mononuclear cells and polymorphonuclear leukocytes, a mildly elevated protein concentration, a normal or slightly decreased glucose concentration, and often a moderate number of erythrocytes. HSV has also been associated with autoimmune (NMDA receptor) encephalitis (see Chapter 638.4). Genetic factors that increase the susceptibility to HSV encephalitis include pathogenic variants in toll-like receptor-3 *(TLR3)*-dependent interferon immunity, *DBR1*, RNA5SP141, *TRAF3*, and other genes involved in *TLR3* sensing or downstream signaling.

HSV is also a cause of aseptic meningitis and is the most common cause of recurrent aseptic meningitis **(Mollaret meningitis)**.

Infections in Immunocompromised Persons

Severe, life-threatening HSV infections can occur in patients with compromised immune functions, including neonates, the severely malnourished, those with primary or secondary immunodeficiency diseases (including AIDS), and those receiving some immunosuppressive regimens, particularly for cancer and organ transplantation. Mucocutaneous infections, including mucositis and esophagitis, are most common, although their presentations may be atypical and can result in lesions that slowly enlarge, ulcerate, become necrotic, and extend to deeper tissues. Other HSV infections include tracheobronchitis, pneumonitis, and anogenital infections. Disseminated infection can result in a sepsis-like presentation, with liver and adrenal involvement, disseminated intravascular coagulopathy, and shock.

Perinatal Infections

HSV infection may be acquired in utero, during the birth process, or during the neonatal period. Intrauterine (prenatal) and postpartum (cutaneous lesions in caretakers) infections are well described but occur infrequently. Postpartum transmission may be from the mother or another adult with a nongenital (typically HSV-1) infection such as herpes labialis. Most cases of neonatal herpes result from maternal infection and transmission, usually during passage through an infected birth canal of a mother with asymptomatic genital herpes. Transmission is well documented in infants delivered by cesarean section. *Fewer than 30% of mothers of an infant with neonatal herpes have a history of genital herpes.* The risk for infection is higher in infants born to mothers with primary genital infection (>30%) than with recurrent genital infection (<2%). Use of scalp electrodes may also increase risk. There also have been rare cases of neonatal herpes associated with Jewish ritual circumcisions, but only with ritual oral contact with the circumcision site.

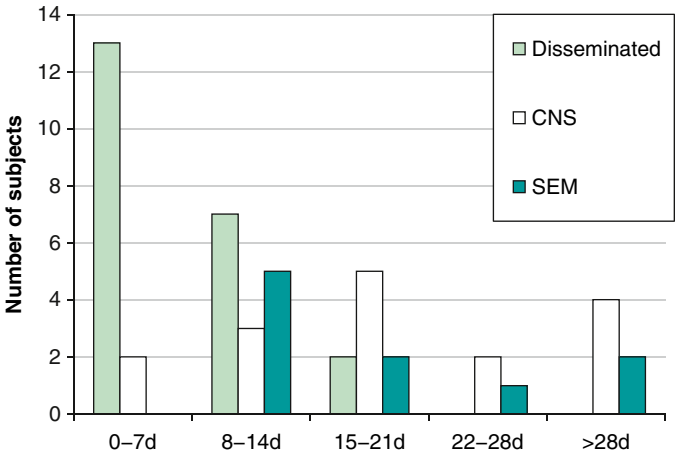

Fig. 299.4 Herpes simplex virus (HSV). Age at presentation by HSV disease type. SEM, skin, eye, mouth. *(From Curfman AL, Glissmeyer EW, Ahmad FA, et al. Initial presentation of neonatal herpes simplex virus infection. J Pediatr. 2016;172:121–126, p. 124.)*

Neonatal HSV infection is thought to never be asymptomatic. Its clinical presentation reflects timing of infection, portal of entry, and extent of spread. Infants with the rare onset of **intrauterine infection** typically have skin vesicles or scarring; eye findings, including chorioretinitis and keratoconjunctivitis; and microcephaly or hydranencephaly that are present at delivery.

Few infants survive without therapy, and those who do generally have severe sequelae. Infants infected during delivery or the postpartum period present with one of the following three patterns of disease: (1) disease localized to the skin, eyes, or mouth; (2) encephalitis with or without skin, eye, and mouth disease; and (3) disseminated infection involving multiple organs, including the brain, lungs, liver, heart, adrenals, and skin (Fig. 299.4). Most present in the first 28 days of life. Approximately 20% present between 5 and 9 weeks of age.

Infants with **skin**, **eye**, **and mouth disease** generally present at 5-11 days of life and typically demonstrate a few clustered small vesicles, particularly on the presenting part or at sites of trauma such as sites of scalp electrode placement. If untreated, skin, eye, and mouth disease in infants may progress to encephalitis or disseminated disease.

Infants with encephalitis typically present at 8-17 days of life with clinical findings suggestive of bacterial meningitis, including irritability, lethargy, poor feeding, poor tone, and seizures. Fever or hypothermia may occur but is not universal; skin vesicles occur in only approximately 60% of cases (Fig. 299.5). If untreated, 50% of infants with HSV encephalitis die and most survivors have severe neurologic sequelae.

Infants with disseminated HSV infections generally become ill at 5-11 days of life. Their clinical picture is similar to that of infants with bacterial sepsis, consisting of hyperthermia or hypothermia, irritability, poor feeding, and vomiting. They may also exhibit respiratory distress, cyanosis, apneic spells, jaundice, purpuric rash, and evidence of central nervous system infection; seizures are common. Skin vesicles are seen in approximately 75% of cases. If untreated, the infection causes shock and disseminated intravascular coagulation; approximately 90% of these infants die, and most survivors have severe neurologic sequelae.

Infants with neonatal herpes whose mothers received antiherpes antiviral drugs in the weeks before delivery may present later than their untreated counterparts; whether the natural history of the infection in these infants is different is an unanswered question.

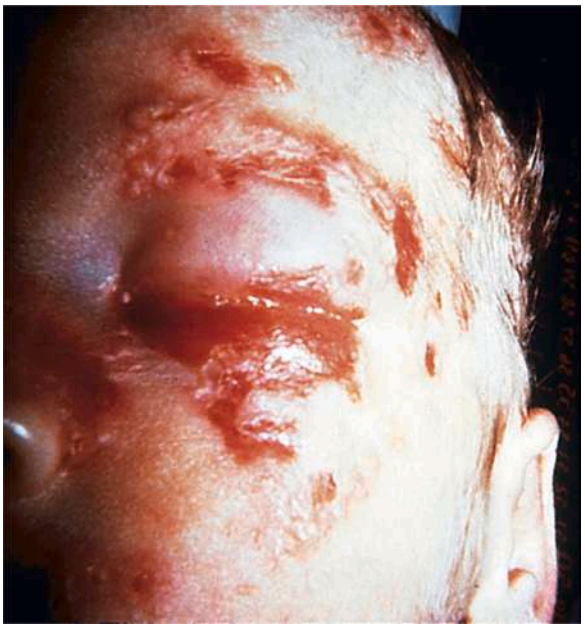

Fig. 299.5 Vesicular-pustular lesions on the face of a neonate with herpes simplex virus infection. *(From Kohl S. Neonatal herpes simplex virus infection. Clin Perinatol. 1997;24:129–150.)*

DIAGNOSIS

The clinical diagnosis of HSV infections, particularly life-threatening infections and genital herpes, should be confirmed by laboratory test, preferably isolation of virus or detection of viral DNA by polymerase chain reaction (PCR). Histologic findings or imaging studies may support the diagnosis but should not substitute for virus-specific tests. HSV immunoglobulin M tests are notoriously unreliable, and the demonstration of a fourfold or greater rise in HSV-specific immunoglobulin G titers between acute and convalescent serum samples is useful only in retrospect.

The highest yield for virus cultures comes from rupturing a suspected herpetic vesicle and vigorously rubbing the base of the lesion to collect fluid and cells. Culturing dried, crusted lesions is generally of low yield. Although not as sensitive as viral culture, direct detection of HSV antigens in clinical specimens can be done rapidly and has very good specificity. The use of DNA amplification methods such as PCR for detection of HSV DNA is highly sensitive and specific and in some instances can be performed rapidly. It is the test of choice in examining CSF in cases of suspected HSV encephalitis.

Evaluation of the neonate with suspected HSV infection should include cultures and/or PCR of suspicious lesions as well nasopharynx, mouth, conjunctivae, rectum, umbilicus, and scalp electrode site (if applicable), and PCR of *both* CSF and blood. In neonates testing for elevation of liver enzymes may provide indirect evidence of HSV dissemination to visceral organs. Efforts to develop clinical scoring systems for invasive HSV in infants have identified younger age, prematurity, seizure at home, ill appearance, abnormal triage temperature (fever or hypothermia), vesicular rash, thrombocytopenia, and CSF fluid pleocytosis as predictors.

Culture or antigen detection should be used in evaluating lesions associated with suspected acute genital herpes. HSV-2 type-specific antibody tests are useful for evaluating sexually experienced adolescents or young adults who have a history of unexplained recurrent nonspecific urogenital signs and symptoms, but these tests are less useful for general screening in populations in which HSV-2 infections are of low prevalence.

Because most HSV diagnostic tests take at least a few days to complete, treatment should not be withheld but rather initiated promptly so as to ensure the maximum therapeutic benefit.

LABORATORY FINDINGS

Most self-limited HSV infections cause few changes in routine laboratory parameters. Mucocutaneous infections may cause a moderate polymorphonuclear leukocytosis. In HSV meningoencephalitis there can be an increase in mononuclear cells and protein in CSF, the glucose content may be normal or reduced, and red blood cells may be present. The electroencephalogram and MRI of the brain may show temporal lobe abnormalities in HSV encephalitis beyond the neonatal period. Encephalitis in the neonatal period tends to be more global and not limited to the temporal lobe (Fig. 299.6). Disseminated infection may cause elevated liver enzymes, thrombocytopenia, and abnormal coagulation.

TREATMENT AND PREVENTION

See Chapter 292 for more information about principles of antiviral therapy.

Three antiviral drugs are available in the United States for the management of HSV infections, namely acyclovir, valacyclovir, and famciclovir. All three are available in oral form, but only acyclovir is available in a suspension form. Acyclovir has the poorest bioavailability and hence requires more frequent dosing. Valacyclovir, a prodrug of acyclovir, and famciclovir, a prodrug of penciclovir, both have very good oral bioavailability and are dosed once or twice daily. Acyclovir and penciclovir are also available in a topical form, but these preparations provide limited or no benefit to patients with recurrent mucocutaneous HSV infections. Only acyclovir has an intravenous formulation. Early initiation of therapy results in the maximal therapeutic benefit. All three drugs have exceptional safety profiles and are safe to use in pediatric patients. *Doses should be modified in patients with renal impairment.*

Resistance to acyclovir and penciclovir is rare in immunocompetent persons but does occur in immunocompromised persons and is usually mediated by mutations within the thymidine kinase and DNA polymerase genes. Virus isolates from immunocompromised persons whose HSV infection is not responding or is worsening with acyclovir therapy should be tested for drug sensitivities. Foscarnet and cidofovir have been used in the treatment of HSV infections caused by acyclovir-resistant mutants.

Topical trifluridine and topical ganciclovir are used in the treatment of herpes keratitis.

Patients with genital herpes also require counseling to address psychosocial issues, including possible stigma, and to help them understand the natural history and management of this chronic infection.

Acute Mucocutaneous Infections

For gingivostomatitis, limited evidence suggests that oral acyclovir (15 mg/kg/dose 5 times a day PO for 7 days; maximum: 1 g/day) started within 72 hours of onset reduces the severity and duration of the illness. Pain associated with swallowing may limit oral intake of infants and children, putting them at risk for dehydration. Intake should be encouraged through the use of cold beverages, ice cream, and yogurt.

For **herpes labialis**, oral treatment is superior to topical antiviral therapy. For treatment of a recurrence in adolescents, oral valacyclovir (2,000 mg bid PO for 1 day), acyclovir (400 mg 5 times daily PO for 5 days), or famciclovir (1,500 mg once daily PO for 1 day) shortens the duration of the episode. Long-term daily use of oral acyclovir (400 mg bid PO) or valacyclovir (500 mg once daily PO) has been used to prevent recurrences in individuals with frequent or severe recurrences.

Anecdotal reports suggest that treatment of adolescents with **herpes gladiatorum** with valacyclovir (500 mg bid PO for 7-10 days) at the

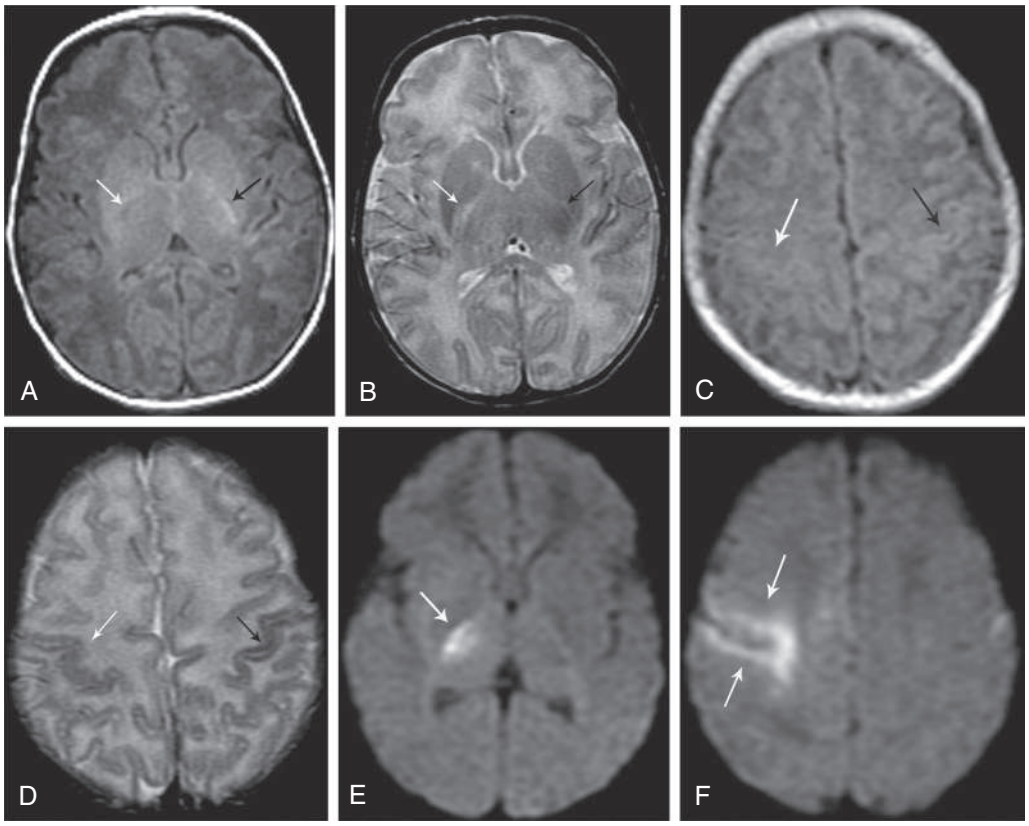

Fig. 299.6 Involvement of corticospinal tract and thalamus in a 2-wk old infant. **A,** Axial T1-weighted MRI demonstrating subtle loss of T1 hyperintensity corresponding to myelination in the posterior limb of the right internal capsule *(white arrow)*. T1 hyperintensity in the left posterior limb of the internal capsule is maintained *(black arrow)*. **B,** T2 weighted image showing findings similar to those seen on T1-weighted imaging. **C,** Axial T1- and **(D)** T2-weighted images through the vertex demonstrating subtle indistinct margins of the cortex around the right central sulcus *(white arrow)* compared to the normal appearance on the left side *(black arrow)*. **E** and **F,** Diffusion-weighted images with more extensive diffusion restriction in the posterior limb of the right internal capsule and lateral thalamus *(arrows)*, and in the right precentral and postcentral gyrus *(arrows)*. *(From Bajaj M, Mody S, Natarajan G. Clinical and neuroimaging findings in neonatal herpes simplex virus infection. J Pediatr. 2014;165:404–407. Fig. 1.)*

first signs of the outbreak can shorten the course of the recurrence with accompanying guidance on the importance of good hydration. For patients with a history of recurrent herpes gladiatorum, chronic daily prophylaxis with valacyclovir (500-1,000 mg/day) has been reported to prevent recurrences.

There are no clinical trials assessing the benefit of antiviral treatment for **herpetic whitlow**. High-dose oral acyclovir (1,600-2,000 mg/day divided in two or three doses PO for 10 days) started at the first signs of illness has been reported to abort some recurrences and reduce the duration of others in adults.

Children with mild cases of **eczema herpeticum** can be treated with oral acyclovir (10-20 mg/kg three times daily) or valacyclovir (20 mg/kg per day in three divided doses) for 7-21 days. However, serious infections should be treated with intravenous acyclovir. Oral-facial HSV infections can reactivate after cosmetic facial laser resurfacing, causing extensive disease and scarring. Treatment of adults beginning the day before the procedure with either valacyclovir (500 mg twice daily PO for 10-14 days) or famciclovir (250-500 mg bid PO for 10 days) has been reported to be effective in preventing the infections. HSV infections in **burn patients** can be severe or life-threatening and have been treated with intravenous acyclovir (10-20 mg/kg/day divided every 8 hours).

Antiviral drugs are not effective in the treatment of HSV-associated **erythema multiforme**, but their daily use as for herpes labialis prophylaxis prevents *reoccurrences* of erythema multiforme.

Genital Herpes

Pediatric patients, usually adolescents or young adults, with suspected first-episode genital herpes should be treated with antiviral therapy. Treatment of the initial infection reduces the severity and duration of the illness but has no effect on the frequency of subsequent recurrent infections. Treatment options for adolescents include acyclovir (400 mg tid PO for 7-10 days), famciclovir (250 mg tid PO for 7-10 days), or valacyclovir (1,000 mg bid PO for 7-10 days). The twice-daily valacyclovir option avoids treatment during school hours. For smaller children, acyclovir suspension can be used at a dose of 10-20 mg/kg/dose 4 times daily, not to exceed the adult dose. The first episode of genital herpes can be extremely painful, and use of analgesics is generally indicated. Intravenous acyclovir is indicated for those with severe or complicated primary infections that may require hospitalization. All patients with genital herpes should be offered counseling to help them deal with psychosocial issues and understand the chronic nature of the illness.

There are three strategic options regarding the management of recurrent infections. The choice should be guided by several factors, including the frequency and severity of the recurrent infections, the psychologic impact of the illness on the patient, and concerns regarding transmission to a susceptible sexual partner. Option 1 is no therapy; option 2 is episodic therapy; and option 3 is long-term suppressive therapy. For **episodic therapy,** treatment should be initiated at the first signs of an outbreak. Recommended choices for episodic therapy in adolescents include famciclovir (1,000 mg bid PO for 1 day), acyclovir (800 mg tid PO for 2 days), or valacyclovir (500 mg bid PO for 3 days.) Long-term suppressive therapy offers the advantage that it prevents most outbreaks, improves patient quality of life in terms of the psychosocial impact of genital herpes, and, with daily valacyclovir therapy, also reduces (but does not eliminate) the risk for sexual transmission to a susceptible sexual partner. Options for **long-term suppressive therapy** are acyclovir (400 mg bid PO), famciclovir (250 mg bid PO), and valacyclovir (500 or 1,000 mg qd PO).

Ocular Infections

HSV ocular infections can result in blindness. Management should involve consultation with an ophthalmologist.

Central Nervous System Infections

Patients older than neonates who have herpes encephalitis should be promptly treated with intravenous acyclovir (10 mg/kg every 8 hours given as a 1-hour infusion for 21 days). Treatment for increased intracranial pressure, management of seizures, and respiratory compromise may be required.

Infections in Immunocompromised Persons

Severe mucocutaneous and disseminated HSV infections in immunocompromised patients should be treated with intravenous acyclovir (30 mg/kg per day, in three divided doses for 7-14 days) until there is evidence of resolution of the infection. Oral antiviral therapy with acyclovir, famciclovir, or valacyclovir has been used for treatment of less-severe HSV infections and for suppression of recurrences during periods of significant immunosuppression. Drug resistance does occur occasionally in immunocompromised patients, and in individuals whose HSV infection does not respond to antiviral drug therapy, viral isolates should be tested to determine sensitivity. Acyclovir-resistant viruses are often also resistant to famciclovir but may be sensitive to foscarnet or cidofovir.

Perinatal Infections

All infants with proven or suspected neonatal HSV infection should be treated immediately with high-dose intravenous acyclovir (60 mg/kg/day divided every 8 hours). Treatment may be discontinued in infants shown by laboratory testing not to be infected. Infants with HSV disease limited to skin, eyes, and mouth should be treated for 14 days, whereas those with disseminated or central nervous system disease should receive a minimum of 21 days of therapy. Patients receiving high-dose therapy should be monitored for neutropenia.

Suppressive oral acyclovir therapy for 6 months after completion of the intravenous therapy has been shown to improve the neurodevelopment of infants with central nervous system infection and to prevent cutaneous recurrences in infants regardless of disease pattern. Infants surviving neonatal HSV disease of any classification should receive 300 mg/m^2 per dose 3 times daily for 6 months. The absolute neutrophil count should be measured at weeks 2 and 4 after initiation of treatment and then monthly.

PROGNOSIS

Most HSV infections are self-limiting, last from a few days (for recurrent infections) to 2-3 weeks (for primary infections) and heal without scarring. Recurrent oral-facial herpes in a patient who has undergone dermabrasion or laser resurfacing can be severe and lead to scarring. Because genital herpes is a sexually transmitted infection, it can be stigmatizing, and its psychologic consequences may be much greater than its physiologic effects. Some HSV infections can be severe and may have grave consequences without prompt antiviral therapy. Life-threatening conditions include neonatal herpes, herpes encephalitis, and HSV infections in immunocompromised patients, burn patients, and severely malnourished infants and children. Recurrent ocular herpes can lead to corneal scarring and blindness.

PREVENTION

Transmission of infection occurs through exposure to virus either as the result of skin-to-skin contact or from contact with contaminated secretions. Good handwashing and, when appropriate, the use of gloves provide healthcare workers with excellent protection against HSV infection in the workplace. Healthcare workers with active oral-facial herpes or herpetic whitlow should take precautions, particularly when caring for high-risk patients such as newborns, immunocompromised individuals, and patients with chronic skin conditions. Patients and parents should be advised about good hygienic practices, including handwashing and avoiding contact with lesions and secretions, during active herpes outbreaks. Schools and daycare centers should clean shared toys and athletic equipment such as wrestling mats at least daily after use. Athletes with active herpes infections who participate in contact sports such as wrestling and rugby should be excluded from practice or games until the lesions are completely healed. Genital herpes can be prevented by avoiding genital-genital and oral-genital contact. The risk for acquiring genital herpes can be reduced but not eliminated through the correct and consistent use of condoms. Male circumcision is associated with a reduced risk of acquiring genital HSV infection. The risk for transmitting genital HSV-2 infection to a susceptible sexual partner can be reduced but not eliminated by the daily use of oral valacyclovir by the infected partner.

For **pregnant women** with **active genital herpes** at the time of delivery, the risk for mother-to-child transmission can be reduced but not eliminated by delivering the baby via a cesarean section. The risk for recurrent genital herpes, and therefore the need for cesarean delivery, can be reduced but not eliminated in pregnant women with a history of genital herpes by the daily use of oral acyclovir, valacyclovir, or famciclovir during the last 4 weeks of gestation, which is recommended by the American College of Obstetrics and Gynecology. There are documented cases of neonatal herpes occurring in infants delivered by cesarean section, as well as in infants born to mothers who have been appropriately treated with antiherpes antiviral drugs for the last month of gestation. Therefore a history of cesarean delivery or antiviral treatment at term does not rule out consideration of neonatal herpes.

Asymptomatic infants delivered vaginally to women with *first-episode* genital herpes are at *very high risk* for acquiring HSV infection. The nasopharynx, mouth, conjunctivae, rectum, umbilicus, and scalp electrode site (if applicable) should be cultured (with PCR surface testing if available) at approximately 24 hours after birth for all infants born to mothers with primary genital herpes. Some also recommend HSV-PCR on blood and CSF. Some authorities recommend that these infants receive anticipatory acyclovir therapy for at least 10 days, and others treat such infants if signs develop or if there is evidence of HSV infection. Infants delivered to women with a history of *recurrent genital herpes* are at low risk for development of neonatal herpes. In this setting, while surface cultures and PCRs are done, empirical acyclovir is not started. Parents should be educated about the signs and symptoms of neonatal HSV infection and should be instructed to seek care without delay at the first suggestion of infection. When the situation is in doubt, infants should be evaluated and tested with surface culture (and PCR) for neonatal herpes as well as with PCR on blood *and* CSF; intravenous acyclovir is begun until culture and PCR results are negative or until another explanation can be found for the signs and symptoms.

Recurrent genital HSV infections can be prevented by the daily use of oral acyclovir, valacyclovir, or famciclovir, and these drugs have been used to prevent recurrences of oral-facial (labialis) and cutaneous (gladiatorum) herpes. Oral and intravenous acyclovir also have been used to prevent recurrent HSV infections in immunocompromised patients. Use of sun blockers is reported to be effective in preventing recurrent oral-facial herpes in patients with a history of sun-induced recurrent disease.

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Chapter 300

Varicella-Zoster Virus*

Shivang S. Shah, Mona Marin, Philip S. LaRussa, and Anne A. Gershon

Varicella-zoster virus (VZV) causes primary, latent, and reactivation infections. The primary infection manifests as varicella (chickenpox) and results in establishment of a lifelong latent infection of sensory ganglionic neurons. Reactivation of the latent infection causes herpes zoster (shingles). Although often a mild illness of childhood, varicella can cause substantial morbidity and mortality in otherwise healthy children. Morbidity and mortality are higher in immunocompetent infants, adolescents, and adults, as well as in immunocompromised persons. Varicella predisposes to severe group A streptococcus and staphylococcus infections. Primary clinical disease can be prevented by immunization with live-attenuated varicella vaccine. A clinically modified disease can occur among vaccinated persons (breakthrough varicella), usually with milder presentation. Varicella and herpes zoster can be treated with antiviral drugs. Vaccines are also available to prevent herpes zoster in older adults.

ETIOLOGY

VZV is a neurotropic human herpesvirus with similarities to herpes simplex virus. VZV enveloped viruses contain double-stranded DNA genomes that encode 71 proteins, including proteins that are targets of cellular and humoral immunity.

EPIDEMIOLOGY

Before the introduction of the varicella vaccine in 1995, varicella was an almost universal communicable infection of childhood in the United States. Annual varicella epidemics occurred in winter and spring, and there were about 4 million cases of varicella, 11,000-13,500 hospitalizations, and 100-150 deaths every year in the United States. Most children were infected by 10 years of age, with fewer than 5% of adults remaining susceptible. This pattern of infection at younger ages remains characteristic in all countries in temperate climates. By contrast, in tropical areas, children acquire varicella at older ages and a higher proportion of young adults remain susceptible, leading to a higher proportion of cases occurring among adults. Varicella is a more serious disease in young infants, adults, and immunocompromised persons, in whom there are higher rates of complications and deaths than in healthy children. Primary varicella is highly transmissible. Within households, transmission of VZV to susceptible individuals occurs at a rate of 65–86%; more casual contact, such as occurs in a school classroom, is associated with lower attack rates among susceptible children. Persons with varicella may be contagious 24-48 hours before the rash is evident and until vesicles are crusted, usually 4-7 days after onset of rash, consistent with evidence that VZV is spread by aerosolization of virus in cutaneous lesions; spread from oropharyngeal secretions may occur but to a much lesser extent. Susceptible persons may also acquire varicella after close, direct contact with adults or children who have herpes zoster, again via aerosolization of virus in skin lesions.

Since implementation of the varicella vaccination program in 1995, there have been substantial declines in varicella morbidity and mortality in the United States. By 2006, before implementation of the two-dose program, one-dose vaccination coverage had reached 90% and varicella incidence had declined 90% since 1995 in sites where active surveillance was being conducted; varicella-related hospitalizations had declined 84% from prevaccine years. Varicella-related deaths decreased by 88% from 1990–1994 to 2005–2007; in persons younger than 20 years of age there was a 97% decline in deaths. Declines in morbidity and mortality were seen in all age groups, including infants younger than 12 months of age who were not eligible for vaccination, indicating protection from exposure by indirect vaccination effects. The continued occurrence of breakthrough infections and of outbreaks in settings with high one-dose varicella vaccine coverage, together with the evidence that one dose is only 82% effective against all varicella, prompted adoption in 2007 of a routine two-dose childhood varicella vaccination program with catch-up vaccination of all individuals without evidence of immunity. Further declines in morbidity and mortality occurred during the two-dose program so that by 2019, declines reached more than 97% for incidence and 90% for hospitalizations and deaths. The greatest decline occurred in persons younger than 20 years of age, born during the varicella vaccination program, with 99%, 97%, and >99% reduction in incidence, hospitalizations, and deaths, respectively. Additionally, the two-dose program led to a reduction in the number, size, and duration of varicella outbreaks. Although the age-specific incidence has declined in all age groups, the median age at infection has increased, with cases occurring predominantly in children in ages 7-10 years rather than in the preschool years. This change in varicella epidemiology highlights the importance of offering vaccine to every susceptible child, adolescent, and adult.

Herpes zoster is caused by the reactivation of latent VZV. It is not common in childhood and shows no seasonal variation in incidence. Zoster is not caused by exposure to a patient with varicella; in fact, exposures to varicella boost the cell-mediated immune response to VZV in individuals with prior infection, decreasing the likelihood of reactivation of latent virus. The lifetime risk for herpes zoster for individuals with a history of varicella is at least 30%, with 75% of cases occurring after 45 years of age. Herpes zoster is unusual in healthy children younger than 10 years of age, with the exception of those infected with VZV in utero or in the first year of life, who have an increased risk for development of zoster in the first few years of life. Herpes zoster in otherwise healthy children tends to be milder than herpes zoster in adults, is less frequently associated with acute pain, and is generally not associated with postherpetic neuralgia. In children receiving immunosuppressive therapy for malignancy or other diseases and in those who have HIV infection, herpes zoster occurs more frequently, occasionally multiple times, and may be severe. The attenuated VZV in the varicella vaccine can establish latent infection and reactivate as herpes zoster. However, the risk for development of subsequent herpes zoster is much lower after vaccination than after natural VZV infection among both healthy and immunocompromised children. Although the Oka vaccine type VZV is attenuated, in children the severity of zoster caused by the Oka strain seems to be similar to or slightly milder than that caused by the natural or wild-type VZV. Vaccinated children who do develop zoster may have disease resulting from either vaccine or wild-type VZV, due to breakthrough varicella or subclinical infection of some vaccinees with wild-type VZV occurring at some point after immunization.

PATHOGENESIS

Primary infection (varicella) results from inoculation of the virus onto the mucosa of the upper respiratory tract and tonsillar lymphoid tissue. During the early part of the 10- to 21-day incubation period, virus replicates in the local lymphoid tissue and spreads to T lymphocytes, causing a viremia that delivers the virus to skin where innate immunity controls VZV replication for several days. After innate immunity is overcome in skin, widespread cutaneous lesions develop as the incubation period ends. Adaptive host immune responses, especially cellular immunity, limit viral replication and lead to recovery from infection. In the immunocompromised child, the failure of adaptive immunity, especially cellular immune responses, results in continued viral replication that may lead to prolonged and/or disseminated infection with resultant complications of infection in the lungs, liver, brain, and other organs.

Latent infection develops during the incubation period or the disease itself. VZV is transported in a retrograde manner through sensory axons to the dorsal root ganglia in the spinal cord and to cranial nerve ganglia. Latency may also develop from viremia, infecting spinal and cranial nerve ganglia as well as autonomic ganglia that do not project to

*The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention, U.S. Department of Health and Human Services.

the skin, including the enteric nervous system of the intestine. Latency of VZV occurs only in ganglionic neurons. Subsequent **reactivation** of latent VZV causes **herpes zoster**, usually manifested by a vesicular rash that is unilateral and dermatomal in distribution. Reactivation of VZV may also occur without a rash; examples are unilateral dermatomal pain without rash **(zoster sine herpete)**, aseptic meningitis, and gastrointestinal illness (enteric zoster). During herpes zoster, necrotic changes may be produced in the neurons and surrounding satellite cells in associated ganglia. The skin lesions of varicella and herpes zoster have identical histopathology, and infectious VZV is present in both. Varicella elicits humoral and cell-mediated immunity that is highly protective against symptomatic reinfection. Suppression of cell-mediated immunity to VZV correlates with an increased risk for VZV reactivation as herpes zoster.

CLINICAL MANIFESTATIONS

Varicella is an acute febrile rash illness that was common in children in the United States before the universal childhood vaccination program. It has variable severity but is usually self-limited. It may be associated with severe complications, including bacterial superinfection, especially with staphylococci and group A streptococci, pneumonia, encephalitis, bleeding disorders, congenital infection, and life-threatening perinatal infection. Herpes zoster is not common in children and typically causes localized cutaneous symptoms, but may disseminate in immunocompromised patients.

Varicella in Unvaccinated Individuals

The illness usually begins 14-16 days after exposure, although the incubation period can range from 10-21 days. Subclinical varicella is rare; almost all exposed, susceptible persons experience a rash, albeit so mild in some cases that it may go unnoticed. Prodromal symptoms may be present, particularly in older children and adults. Fever, malaise, anorexia, headache, and occasionally mild abdominal pain may occur 24-48 hours before the rash appears. Temperature elevation is usually 37.8–38.9°C (100–102°F) but may be as high as 41.1°C (106°F); fever and other systemic symptoms usually resolve within 2-4 days after the onset of the rash.

Varicella lesions often appear first on the scalp, face, or trunk. The initial exanthem consists of intensely pruritic erythematous macules that evolve through the papular stage to form clear, fluid-filled vesicles. Clouding and umbilication of the lesions begin in 24-48 hours. While the initial lesions are crusting, new crops form on the trunk and then the extremities; the simultaneous presence of lesions in various stages of evolution is characteristic of varicella (Fig. 300.1). The distribution of the rash is predominantly central or centripetal, with the greatest concentration on the trunk and proximally on the extremities. Ulcerative lesions involving the mucosa of the oropharynx and vagina are also common; many children have vesicular lesions on the eyelids and conjunctivae, but corneal involvement and serious ocular disease are rare. The average number of varicella lesions is about 300, but healthy children may have fewer than 10 to more than 1,500 lesions. In cases resulting from secondary household spread and in older children, more lesions usually occur, and new crops of lesions may continue to develop for more than 7 days. The exanthem may be much more extensive in children with skin disorders, such as eczema or recent sunburn. Hypopigmentation or hyperpigmentation of lesion sites persists for days to weeks in some children, but severe scarring is unusual unless the lesions were secondarily infected.

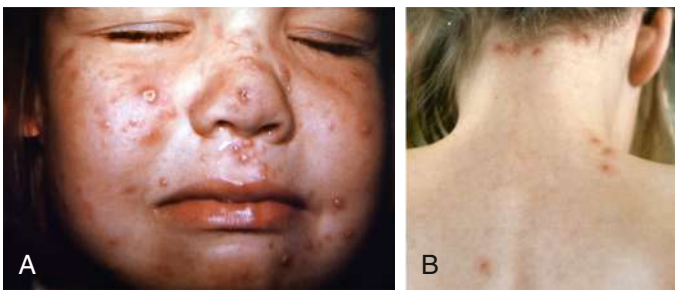

Fig. 300.1 A, Varicella lesions in unvaccinated persons display the characteristic "cropping" distribution, or manifest themselves in clusters; the simultaneous presence of lesions in various stages of evolution is characteristic. B, Breakthrough varicella lesions are predominantly maculopapular, and vesicles are less common; the illness is most commonly mild with <50 lesions. *(Courtesy Centers for Disease Control and Prevention and Dr. John Noble, Jr.)*

The differential diagnosis of varicella includes vesicular rashes caused by other infectious agents, such as herpes simplex virus, enterovirus, monkey pox (mpox), rickettsial pox, and *Staphylococcus aureus;* drug reactions; disseminated herpes zoster; contact dermatitis; and insect bites (especially for breakthrough varicella). Severe varicella was the most common illness confused with smallpox before the eradication of smallpox.

Varicelliform Rashes in Vaccinated Individuals

Varicelliform rashes that occur after vaccination could be a result of wild-type VZV, vaccine strain VZV, or other causes (e.g., insect bites, coxsackievirus). During days 0-42 after vaccination, the likelihood of rash from wild-type or vaccine strain VZV varies depending on the stage of a country's vaccination program. In the early stages of a vaccination program, rash within 1-2 weeks is still most commonly caused by wild-type VZV, reflecting exposure to varicella before vaccination could provide protection. Rash occurring 14-42 days after vaccination is a result of either wild-type or vaccine strains, reflecting exposure and infection before protection from vaccination or an adverse event of vaccination (vaccine-associated rash), respectively. As wild-type varicella continues to decline as a consequence of the vaccination program, wild-type VZV circulation will also decline and rashes in the interval 0-42 days after vaccination will be less commonly caused by wild-type VZV, as is the case in the United States. Spread of vaccine type VZV from a vaccinee with skin lesions has occurred but is rare. The resulting illness in contacts is commonly mild with only a few vesicular lesions. Clinical reversion of the vaccine virus to virulence has not been described.

Breakthrough varicella is disease caused by **wild-type** virus in a vaccinated person, occurring after 42 days past vaccination. One dose of varicella vaccine is 98% effective in preventing moderate and severe varicella and is 82% effective in preventing all disease after exposure to wild-type VZV. This means that after close exposure to VZV, as may occur in a household or an outbreak setting in a school or daycare center, about 1 of every 5 children who received one dose of vaccine may experience breakthrough varicella. Exposure to VZV may also result in asymptomatic infection in the previously immunized child. The rash in breakthrough disease is frequently atypical and predominantly maculopapular, and vesicles are seen less commonly. The illness is most commonly mild with fewer than 50 lesions, shorter duration of rash, fewer complications, and little or no fever. However, approximately 25–30% of breakthrough cases in vaccinees who received one dose are not mild, with clinical features more similar to those of wild-type infection. Breakthrough cases are overall **less contagious** than wild-type infections within household settings, but contagiousness varies proportionally with the number of lesions; typical breakthrough cases (<50 lesions) are about one-third as contagious as disease in unvaccinated cases, whereas breakthrough cases with ≥50 lesions are as contagious as wild-type cases. Consequently, children with breakthrough disease should be considered potentially infectious and excluded from school until lesions have crusted or, if there are no vesicles present, until no new lesions are occurring. Transmission has been documented to occur from breakthrough cases in household, childcare, and school settings.

Two doses of varicella vaccine provide better protection than a one-dose schedule. One clinical trial estimated the two-dose vaccine efficacy for preventing all disease at 98%; the estimate is 92% in conditions of everyday clinical practice. Institution of two doses routinely in the United States substantially reduced the school outbreaks that were occurring among children who had received only one dose.

Breakthrough cases have been reported among two-dose vaccinees; however, recipients of two doses of varicella vaccine are less likely to have breakthrough disease than those who received one dose. Additionally, data suggest that breakthrough varicella may be further attenuated among two-dose vaccine recipients.

Neonatal Varicella

Mortality is particularly high in neonates born to susceptible mothers who contract varicella around the time of delivery. Infants whose mothers demonstrate varicella in the period from 5 days before delivery to 2 days afterward are at high risk for severe varicella. These infants acquire the infection transplacentally as a result of maternal viremia, which may occur up to 48 hours before onset of maternal rash. The infant's rash usually occurs toward the end of the first week to the early part of the second week of life (although it may be as soon as 2 days). Because the mother has not yet developed a significant antibody response, the infant receives a large dose of virus without the moderating effect of maternal anti-VZV antibody. If the mother demonstrates varicella more than 5 days before delivery, she still may pass virus to the soon-to-be-born child, but infection is attenuated because of transmission of maternal VZV-specific antibody across the placenta. This moderating effect of maternal antibody is present if delivery occurs after about 30 weeks of gestation, when maternal immunoglobulin (Ig) G (IgG) is able to cross the placenta in significant amounts. *The recommendations for use of human varicella-zoster immunoglobulin (VZIG) differ based on when the infant is exposed to varicella.* Newborns whose mothers develop varicella during the period of 5 days before to 2 days after delivery should receive VZIG as soon as possible after birth. Although neonatal varicella may occur in about half of these infants despite administration of VZIG, it is milder than in the absence of VZIG administration. All premature infants born <28 weeks of gestation to a mother with active varicella at delivery (even if the maternal rash has been present for >1 week) should receive VZIG. If VZIG is not available, intravenous immunoglobulin (IVIG) may provide some protection, although varicella-specific antibody titers may vary from lot to lot. Because perinatally acquired varicella may be life threatening, the infant should usually be treated with acyclovir (10-15 mg/kg every 8 hours IV) when lesions develop. Neonatal varicella can also follow a postpartum exposure of an infant delivered to a mother who was susceptible to VZV, although the frequency of complications declines rapidly in the weeks after birth. Recommendations for VZIG administration for these infants are presented in the postexposure prophylaxis section. Neonates with community-acquired varicella who experience severe varicella, especially those who have a complication such as pneumonia, hepatitis, or encephalitis, should also receive treatment with intravenous acyclovir (10 mg/kg every 8 hours). Infants with neonatal varicella who receive prompt antiviral therapy have an excellent prognosis.

Congenital Varicella Syndrome

In utero transmission of VZV can occur; however, because most adults in temperate climates are immune, pregnancy complicated by varicella is unusual in these settings. When pregnant women do contract varicella early in pregnancy, experts estimate that as many as 25% of the fetuses may become infected. Fortunately, clinically apparent disease in the infant is uncommon: the congenital varicella syndrome occurs in approximately 0.4% of infants born to women who have varicella during pregnancy before 13 weeks of gestation and in approximately 2% of infants born to women with varicella between 13 and 20 weeks of gestation. Rarely, cases of congenital varicella syndrome have been reported in infants of women infected after 20 weeks of pregnancy, the latest occurring at 28 weeks of gestation. Before availability of varicella vaccine in the United States, 44 cases of congenital varicella syndrome were estimated to occur each year. The congenital varicella syndrome is characterized by cicatricial skin scarring in a zoster-like distribution; limb hypoplasia; and abnormalities of the neurologic system (e.g., microcephaly, cortical atrophy, seizures, and intellectual disability), eye (e.g., chorioretinitis, microphthalmia, and cataracts), renal system (e.g., hydroureter and hydronephrosis), and autonomic nervous system

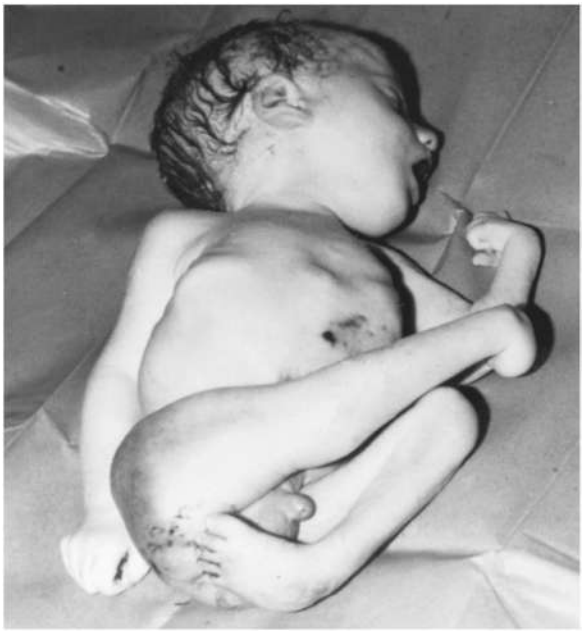

Fig. 300.2 Newborn with congenital varicella syndrome. The infant had severe malformations of both lower extremities and cicatricial scarring over his left abdomen.

(e.g., neurogenic bladder, swallowing dysfunction, and aspiration pneumonia). Low birthweight is common among infants with congenital varicella syndrome. Most of the manifestations can be attributed to virus-induced injury to the nervous system, although there is no obvious explanation why certain regions of the body are preferentially infected during fetal VZV infection. The characteristic cutaneous lesion has been called a cicatrix, a zigzag scarring, in a *dermatomal* distribution, often associated with atrophy of the affected limb (Fig. 300.2). Many infants with severe manifestations of congenital varicella syndrome (atrophy and scarring of a limb) have significant neurologic deficiencies. Alternatively, there may be neither skin nor limb abnormalities, but the infant may show cataracts or even extensive aplasia of the entire brain.

There are rare case reports of fetal abnormalities after the development of herpes zoster in the mother; whether these cases truly represent the congenital varicella syndrome is unclear. If it does occur, the congenital syndrome acquired as a result of maternal herpes zoster is exceedingly rare. Maternal herpes zoster was associated with typical congenital varicella syndrome in one case, but the mother had disseminated herpes zoster (at 12 weeks of gestation).

The diagnosis of VZV fetopathy is based mainly on the history of gestational varicella combined with the presence of characteristic abnormalities in the newborn infant. Virus cannot be cultured from the affected newborn, but viral DNA may be detected in tissue samples by polymerase chain reaction (PCR). Because many infants with congenital varicella syndrome develop zoster before a year of age, it may be possible to isolate VZV from that rash. Alternatively, use of PCR to identify VZV DNA in vesicular fluid or scabs from zoster lesions in such an infant may be diagnostic. VZV-specific IgM antibody is detectable in the cord blood sample in some infants, although the IgM titer drops quickly in the postpartum period and can be nonspecifically positive. Chorionic villus sampling and fetal blood collection for the detection of viral DNA, virus, or antibody have been used in an attempt to diagnose fetal infection and embryopathy. The usefulness of these tests for patient management and counseling has not been defined. Because these tests may not distinguish between infection and disease, their utility may primarily be that of reassurance when the result is negative. Ultrasound may be useful to try to identify limb atrophy, which is common in congenital varicella syndrome. A persistently positive VZV IgG antibody titer at 12-18 months of age is a reliable indicator of prenatal

infection in the asymptomatic child, as is the development of zoster in the first year of life without evidence of postnatal infection.

VZIG has often been administered to the susceptible mother exposed to varicella to modify maternal disease severity; it is uncertain whether this step modifies infection in the fetus, although some evidence suggests that it may be beneficial for the fetus too. Similarly, acyclovir treatment may be given to the mother with severe varicella. A prospective registry of acyclovir use in the first trimester demonstrated that the occurrence of birth defects approximates that found in the general population. Acyclovir is a class B drug for pregnancy and should be considered when the benefit to the mother outweighs the potential risk to the fetus. The efficacy of acyclovir treatment of the pregnant woman in preventing or modifying the severity of congenital varicella is not known, but its use should be considered to protect the mother from severe disease. Because the damage caused by fetal VZV infection does not progress in the postpartum period, antiviral treatment of infants with congenital VZV syndrome is not indicated.

COMPLICATIONS

The complications of VZV infection (varicella or zoster) occur more commonly in immunocompromised patients. In the otherwise healthy child, asymptomatic transient varicella hepatitis is relatively common. Mild thrombocytopenia occurs in 1–2% of children with varicella and may be associated with petechiae. Purpura, hemorrhagic vesicles, hematuria, and gastrointestinal bleeding are rare complications that may have serious consequences. Other complications of varicella, some of them rare, include acute cerebellar ataxia, encephalitis, pneumonia, nephritis, nephrotic syndrome, hemolytic-uremic syndrome, arthritis, myocarditis, pericarditis, pancreatitis, orchitis, and acute retinal necrosis. A reduction in the number and rates of varicella-related complications is seen in vaccinated populations. Reports of serious varicella-related complications in vaccinated persons (breakthrough) are rare (meningitis, pneumonia, acute transverse myelitis, encephalitis [one fatal case in an apparently immunocompetent child], and sepsis). Severe breakthrough varicella can occur among healthy persons, but cases appear to be more common among immunocompromised persons who are usually not recommended to receive varicella vaccine.

Declines in varicella-related hospitalizations and deaths in the United States since implementation of the varicella vaccination program provide supporting evidence that varicella vaccine reduces severe complications from varicella. Approximately 105 deaths (with varicella listed as the underlying cause of death) occurred in the United States annually before the introduction of the varicella vaccine; during 2017–2019 the annual average number of varicella deaths was 18. In both the pre- and postvaccine eras, the majority of deaths (>80%) have been among persons without high-risk preexisting conditions.

Bacterial Infections

Secondary bacterial infections of the skin, usually caused by group A streptococcus or *S. aureus,* may occur in children with varicella. These range from impetigo to cellulitis, lymphadenitis, and subcutaneous abscesses. An early manifestation of secondary bacterial infection is erythema of the base of a new vesicle. Recrudescence of fever 3-4 days after the initial exanthem may also herald a secondary bacterial infection. Varicella is a well-described risk factor for serious invasive infections caused by group A streptococcus, which can have a fatal outcome. The more invasive infections, such as varicella gangrenosa, bacterial sepsis, pneumonia, arthritis, osteomyelitis, cellulitis, and necrotizing fasciitis, account for much of the morbidity and mortality of varicella in otherwise healthy children. Bacterial toxin–mediated diseases (e.g., toxic shock syndrome) also may complicate varicella. A substantial decline in varicella-related invasive bacterial infections is associated with the use of the varicella vaccine.

Encephalitis and Cerebellar Ataxia

Encephalitis (1 per 50,000 cases of varicella in unvaccinated children) and acute cerebellar ataxia (1 per 4,000 cases of varicella in unvaccinated children) are well-described neurologic complications of varicella; morbidity from central nervous system complications is highest among patients younger than 5 years and older than 20 years. Nuchal rigidity, altered consciousness, and seizures characterize meningoencephalitis. Patients with cerebellar ataxia have a gradual onset of gait disturbance, nystagmus, and slurred speech. Neurologic symptoms usually begin 2-6 days after the onset of the rash but may occur during the incubation period or after resolution of the rash. Clinical recovery is typically rapid, occurring within 24-72 hours, and is usually complete. Although severe hemorrhagic encephalitis, analogous to that caused by herpes simplex virus, is very rare in children with varicella, the consequences are similar to those of herpes simplex virus encephalitis. Reye syndrome (hepatic dysfunction with hypoglycemia and encephalopathy) associated with varicella and other viral illnesses such as influenza is rare now that salicylates are no longer used as antipyretics in these situations (see Chapter 405).

Pneumonia

Varicella pneumonia (viral, due to VZV) is a severe complication that accounts for most of the increased morbidity and mortality from varicella in adults and other high-risk populations, but viral pneumonia may also complicate varicella in young children. Respiratory symptoms, which may include cough, dyspnea, cyanosis, pleuritic chest pain, and hemoptysis, usually begin within 1-6 days after the onset of the rash. Smoking has been described as a risk factor for severe pneumonia complicating varicella. The frequency of varicella pneumonia may be greater in the parturient.

Progressive Varicella

Progressive varicella, with visceral organ involvement, coagulopathy, severe hemorrhage, and continued vesicular lesion development after 7 days, is a severe complication of primary VZV infection. Severe abdominal pain, which may reflect involvement of mesenteric lymph nodes or the liver, or the appearance of hemorrhagic vesicles in otherwise healthy adolescents and adults, immunocompromised children, pregnant women, and newborns, may herald severe, and potentially fatal, disease. Although rare in healthy children, the risk for progressive varicella is highest in children with congenital cellular immune deficiency disorders and those with malignancy, particularly if chemotherapy, and especially corticosteroids, had been given during the incubation period and the absolute lymphocyte count is <500 cells/μL. The mortality rate for children who acquired varicella while undergoing treatment for malignancy and who were not treated with antiviral therapy approached 7%; varicella-related deaths usually occurred within 3 days after the diagnosis of varicella pneumonia. Children who acquire varicella after organ transplantation are also at risk for progressive VZV infection. Children undergoing long-term, low-dose systemic or inhaled corticosteroid therapy are not considered to be at higher risk for severe varicella, but progressive varicella does occur in patients receiving high-dose corticosteroids. There are case reports in patients receiving inhaled corticosteroids as well as in asthmatic patients receiving multiple short courses of systemic corticosteroid therapy. Unusual clinical findings of varicella, including lesions that develop a hyperkeratotic appearance and continued new lesion formation for weeks or months, have been described in children with untreated, late-stage HIV infection. Immunization of HIV-infected children who have a $CD4^+$ T-lymphocyte percent ≥15%, as well as children with leukemia and solid organ tumors who are in remission and whose chemotherapy can be interrupted for 2 weeks around the time of immunization or has been terminated, have reduced frequency of severe disease. Moreover, since the advent of the universal immunization program in the United States, many children who would become immunocompromised later in life because of disease or treatment are protected before the immunosuppression occurs; also, as a result of reductions in varicella incidence, immunocompromised children are less likely to be exposed to varicella.

Herpes Zoster

Herpes zoster manifests as vesicular lesions clustered within one or, less commonly, two adjacent dermatomes (Fig. 300.3). In the elderly,

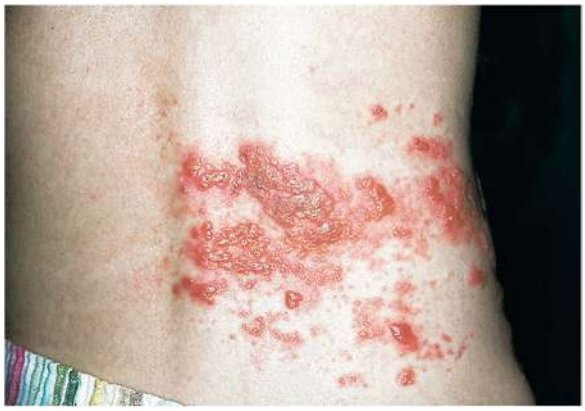

Fig. 300.3 Herpes zoster involving the lumbar dermatome. *(From Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases, 6th ed. Philadelphia: Elsevier; 2005:1783.)*

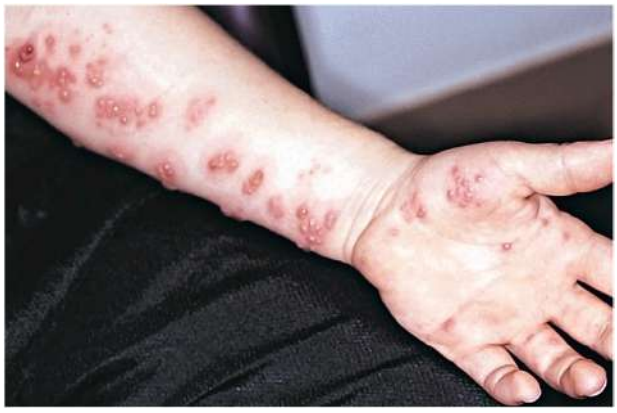

Fig. 300.4 Many groups of blisters occurring over the arm in a child with herpes zoster. *(From Weston WL, Lane AT, Morelli J. Color Textbook of Pediatric Dermatology, 3rd ed. St. Louis: Mosby; 2002: Fig. 8-28.)*

herpes zoster typically begins with burning pain or itching followed by clusters of skin lesions in a dermatomal pattern. Almost half of the elderly with herpes zoster experience complications; the most frequent complication is postherpetic neuralgia, a painful condition that affects the nerves despite resolution of the skin lesions. Approximately 4% of patients suffer a second episode of herpes zoster; three or more episodes are rare. Unlike herpes zoster in adults, zoster in children is infrequently associated with localized pain, hyperesthesia, pruritus, low-grade fever, or complications. In children, the rash is mild, with new lesions appearing for a few days (Fig. 300.4); symptoms of acute neuritis are minimal; and complete resolution usually occurs within 1-2 weeks. Unlike in adults, postherpetic neuralgia is unusual in children. An increased risk for herpes zoster early in childhood has been described in children who acquire infection with VZV in utero or in the first year of life.

Immunocompromised children may have more severe herpes zoster, similar to the situation in adults, including postherpetic neuralgia. Immunocompromised patients may also experience disseminated cutaneous disease that mimics varicella, with or without initial dermatomal rash, as well as visceral dissemination with pneumonia, hepatitis, encephalitis, and disseminated intravascular coagulopathy. Severely immunocompromised children, particularly those with advanced HIV infection, may have unusual, chronic, or relapsing cutaneous disease, retinitis, or central nervous system disease without rash. The finding of a lower risk for herpes zoster among vaccinated children with leukemia than in those who have had varicella suggested that the vaccine virus reactivates less commonly than wild-type VZV. A study of HIV-infected vaccinated children found no cases of zoster 4.4 years after immunization, which was significantly different from the rate in children who had experienced varicella. Studies to date indicate that the risk for herpes zoster in healthy children who have received one or more doses of vaccine is 78% lower than in children who had wild-type varicella, with two-dose vaccination providing 50% greater protection than one-dose. Many more years of follow-up are needed to determine whether this lower risk is maintained among older persons who are at greatest risk for herpes zoster.

DIAGNOSIS

Varicella and herpes zoster are usually diagnosed primarily by their clinical appearance. Laboratory evaluation has not been considered necessary for diagnosis or management. However, as varicella disease has declined to low levels, laboratory confirmation has become increasingly necessary. The atypical nature of breakthrough varicella, with a higher proportion of papular rather than vesicular rashes, poses both clinical and laboratory diagnostic challenges.

Rapid laboratory diagnosis of VZV is often important in high-risk patients and can be important for infection control, especially for breakthrough cases that have mild or atypical presentations. Confirmation of VZV infections can be accomplished by many referral hospital laboratories and all state health laboratories. VZV can be identified quickly by either PCR amplification testing (vesicular fluid, crusts) or direct fluorescence assay of cells from cutaneous lesions (vesicular fluid). In the absence of vesicles or scabs, scrapings of maculopapular lesions can be collected for PCR or direct fluorescence assay testing. Infectious virus may be recovered by means of tissue culture methods; such methods require specific expertise, and virus may take days to weeks to grow. Of available tests, PCR is the most sensitive and also allows for differentiation of wild-type and vaccine strains. Direct fluorescence assay is specific and less sensitive than PCR but when available allows for rapid diagnosis. Although multinucleated giant cells can be detected with nonspecific stains (Tzanck smear), they have poor sensitivity and do not differentiate VZV from herpes simplex virus infections. Strain identification (genotyping) can distinguish wild-type VZV from the vaccine strain in a vaccinated child; however, genotyping is available only at specialized reference laboratories. Laboratory tests of lesions cannot be used to distinguish between varicella and disseminated herpes zoster. VZV IgG antibodies can be detected by several methods, and a fourfold or greater rise in IgG antibodies is confirmatory of acute infection (although this requires a 2- to 3-week delay to collect a convalescent specimen). In vaccinated persons, commercially available tests are not sufficiently sensitive to always detect antibodies following immunization, and a fourfold rise in IgG antibodies may not occur. Testing for VZV IgM antibodies is not useful for routine confirmation or ruling out of varicella because commercially available methods are unreliable and the kinetics of the IgM response have not been well defined. IgM is inconsistently detected, even among patients with PCR-confirmed disease. Furthermore, IgM detection does not confirm a primary infection because specific IgM antibodies are transiently produced on each exposure to VZV, whether through primary infection, reinfection, or reactivation from latency, even subclinical. Serologic tests are not useful for the initial diagnosis of herpes zoster, but a significant rise in IgG titer in convalescent titer in the presence of an atypical zoster rash is confirmatory. As with any laboratory test, a negative varicella test should be considered in the context of the clinical presentation. Clinicians should use clinical judgment to decide on the best course of therapy. VZV IgG antibody can be useful to determine the immune status of individuals whose clinical history of varicella is unknown or equivocal. However, caution must be taken in interpreting tests for immunity to VZV, especially in immunocompromised patients after a close exposure to VZV. Due to the possibility of false-positive results, it is preferable to rely on clinical rather than laboratory information, and if in doubt, assume the individual is susceptible to varicella and proceed accordingly.

TREATMENT

Antiviral treatment with acyclovir or valacyclovir modifies the course of both varicella and herpes zoster. Antiviral drug resistance is rare for VZV but has occurred, primarily in children with HIV infection and other immunocompromising conditions in which frequent relapse of VZV infections has resulted in multiple courses of antiviral therapy. Foscarnet and cidofovir may be useful for the treatment of acyclovir-resistant VZV infections, but consultation of an infectious diseases specialist is recommended.

Varicella

Given the safety profile of acyclovir and valacyclovir, and their demonstrated efficacy in the treatment of varicella, treatment of all children, adolescents, and adults with varicella is acceptable. Oral therapy with acyclovir (20 mg/kg/dose; maximum: 800 mg/dose) given as four doses/day for 5 days can be used to treat uncomplicated varicella. Therapy is particularly important for individuals at increased risk for moderate to severe varicella: individuals older than 12 years of age; individuals older than 12 months of age with chronic cutaneous or pulmonary disorders; individuals receiving short-term, intermittent, or aerosolized corticosteroid therapy; individuals receiving long-term salicylate therapy; and possibly secondary cases among household contacts. To be most effective, treatment should be initiated as early as possible, preferably within 24 hours of the onset of the exanthem. There is less clinical benefit if treatment is initiated more than 72 hours after onset of the exanthem. Acyclovir therapy does not interfere with the induction of VZV immunity. Acyclovir has been successfully used to treat varicella in pregnant women. Valacyclovir or famciclovir may be given to older children who can swallow tablets. These drugs are highly active against VZV by the same mechanism as acyclovir and are better absorbed by the oral route than acyclovir. Valacyclovir (20 mg/kg/dose; maximum: 1,000 mg/dose, administered 3 times daily for 5 days) is licensed for treatment of varicella in children 2 to <18 years of age, and both valacyclovir and famciclovir are approved for treatment of herpes zoster in adults. Patients receiving these antivirals should be well hydrated, and for prolonged use, renal function and white blood cell counts (especially neutrophils) should be monitored frequently. Common adverse symptoms during valacyclovir treatment are neurologic (headache, agitation, dizziness) and gastrointestinal (nausea, abdominal pain).

Intravenous therapy is indicated for severe disease and for varicella in immunocompromised patients (even if begun more than 72 hours after onset of rash). Any patient who has signs of disseminated VZV, including pneumonia, severe hepatitis, thrombocytopenia, or encephalitis, should receive immediate treatment. Intravenous acyclovir therapy (10 mg/kg or 500 mg/m^2 every 8 hours) initiated within 72 hours of development of initial symptoms decreases the likelihood of progressive varicella and visceral dissemination in high-risk patients. Treatment is continued for 7-10 days or until no new lesions have appeared for 48 hours. Delaying antiviral treatment in high-risk individuals until it is obvious that prolonged new lesion formation is occurring is not recommended because visceral dissemination occurs during the same period.

Acyclovir-resistant VZV has been identified primarily in children infected with HIV. These children may be treated with intravenous foscarnet (120 mg/kg/day divided every 8 hours). The dose should be modified in the presence of renal insufficiency. Resistance to foscarnet has been reported with prolonged use. Cidofovir is also useful in this situation. Because of the increased toxicity profile of foscarnet and cidofovir, these two drugs should be initiated in collaboration with an infectious diseases specialist.

Herpes Zoster

Antiviral drugs are effective for treatment of herpes zoster. In healthy adults, acyclovir (800 mg 5 times a day PO for 5-7 days), famciclovir (500 mg tid PO for 7 days), and valacyclovir (1,000 mg tid PO for 7 days) reduce the duration of the illness but do not prevent development of postherpetic neuralgia. In otherwise healthy children, herpes zoster is a less-severe disease, and postherpetic neuralgia usually does not occur. Therefore treatment of uncomplicated herpes zoster in the child with an antiviral agent may not always be necessary, although some experts would treat with oral acyclovir (20 mg/kg/dose; maximum: 800 mg/dose) to shorten the duration of the illness. It is important to start antiviral therapy as soon as possible. Delay beyond 72 hours from onset of rash limits its effectiveness.

In contrast, herpes zoster in immunocompromised children can be severe, and disseminated disease may be life-threatening. Patients at high risk for disseminated disease should receive intravenous acyclovir (500 mg/m^2 or 10 mg/kg every 8 hours). Oral acyclovir, famciclovir, and valacyclovir are options for immunocompromised patients with uncomplicated herpes zoster, who are considered at low risk for visceral dissemination. Neuritis with herpes zoster should be managed with appropriate analgesics.

Use of corticosteroids in the treatment of herpes zoster in children is not recommended.

PROGNOSIS

Primary varicella in unvaccinated persons has a mortality rate of 2-3 per 100,000 cases, with the lowest case fatality rates among children 1-9 years of age (~1 deaths/100,000 cases). Compared with these age groups, infants have a 4 times greater risk of dying and adults have a 25 times greater risk of dying. The most common complications among people who died from varicella were pneumonia, central nervous system complications, secondary infections, and hemorrhagic conditions. The mortality rate of untreated primary infection was 7% in immunocompromised children in the 1960s. In the era of antiviral therapy and improved supportive care, the prognosis has improved with treatment administered early in the course of illness, but deaths have continued to occur. Herpes zoster among healthy children has an excellent prognosis and is usually self-limited. Severe presentation with complications and sometimes fatalities can occur in immunocompromised children.

PREVENTION

VZV transmission is difficult to prevent, especially from persons with varicella, because a person with varicella may be contagious for 24-48 hours before the rash is apparent. Herpes zoster is less infectious than varicella; nonetheless, transmission has been reported even in the absence of direct contact with the patient. Infection control practices, including caring for patients with varicella in isolation rooms with filtered air systems, are essential. All healthcare workers should have evidence of varicella immunity (Table 300.1). Unvaccinated healthcare workers without other evidence of immunity who have had a close exposure to VZV should be furloughed for days 8-21 after exposure because they are potentially infectious during this period. Routine testing for VZV antibodies after vaccination is not useful for identifying individuals who are immune to varicella because the tests are insensitive for this purpose.

Vaccine

Varicella is a vaccine-preventable disease. Varicella vaccine contains live, attenuated VZV (Oka strain) and is indicated for subcutaneous or intramuscular administration. In the United States, varicella vaccine is recommended for routine administration as a two-dose regimen to healthy children at ages 12-15 months and 4-6 years. Administration of the second dose earlier than 4-6 years of age is acceptable, but it must be at least 3 months after the first dose. Catch-up vaccination with the second dose is recommended for children and adolescents who received only one dose. Vaccination with two doses is recommended for all persons without evidence of immunity. The minimum interval between the two doses is 3 months for persons 12 years of age or younger and 4 weeks for older children, adolescents, and adults. Administration of varicella vaccine within 4 weeks of measles-mumps-rubella (MMR) vaccination is associated with a

Table 300.1 Evidence of Immunity to Varicella

Evidence of immunity to varicella consists of any of the following:

- Documentation of age-appropriate vaccination with a varicella vaccine:
  - Preschool-age children (i.e., age ≥12 mo): one dose
  - School-age children, adolescents, and adults: two doses*
- Laboratory evidence of immunity† or laboratory confirmation of disease
- Birth in the United States before 1980‡
- Diagnosis or verification of a history of varicella disease by a healthcare provider§
- Diagnosis or verification of a history of herpes zoster by a healthcare provider

*For children who received their first dose at younger than age 13 years and for whom the interval between the two doses was 28 or more days, the second dose is considered valid.

†Commercial assays can be used to assess disease-induced immunity, but they lack sensitivity to always detect vaccine-induced immunity (i.e., they might yield false-negative results).

‡For healthcare personnel, pregnant women, and immunocompromised persons, birth before 1980 should not be considered evidence of immunity.

§Verification of history or diagnosis of typical disease can be provided by any healthcare provider (e.g., school or occupational clinic nurse, nurse practitioner, physician assistant, or physician). For persons reporting a history of, or reporting with, atypical or mild cases, assessment by a physician or his/her designee is recommended, and one of the following should be sought: (1) an epidemiologic link to a typical varicella case or to a laboratory-confirmed case or (2) evidence of laboratory confirmation if it was performed at the time of acute disease. When such documentation is lacking, persons should not be considered as having a valid history of disease, because other diseases might mimic mild atypical varicella.

higher risk for breakthrough disease; therefore it is recommended that the varicella and MMR vaccines either be administered simultaneously at different sites or be given at least 4 weeks apart. Varicella vaccine can be administered as a monovalent vaccine (for all healthy persons ≥12 months of age) or as the quadrivalent measles-mumps-rubella-varicella (MMRV) vaccine (for children age 12 months through 12 years only).

Varicella vaccine is contraindicated for persons who have a history of anaphylactic reaction to any component of the vaccine; pregnant women; persons with cell-mediated immune deficiencies, including those with leukemia, lymphoma, and other malignant neoplasms affecting the bone marrow or lymphatic systems; persons receiving immunosuppressive therapy; and persons who have a family history of congenital or hereditary immunodeficiency in first-degree relatives unless the immune competence of the potential vaccine recipient is demonstrated. Children with isolated humoral immunodeficiencies may receive varicella vaccine. The monovalent varicella vaccine has been studied in clinical trial settings in children with acute lymphocytic leukemia and certain solid tumors who were in remission, but this practice is not recommended except in a research setting. Varicella vaccine can be administered to patients with leukemia, lymphoma, or other malignancies whose disease is in remission, who have restored immunocompetence, and whose chemotherapy has been terminated for at least 3 months.

The vaccine should be considered for HIV-infected children with a $CD4^+$ T-lymphocyte count ≥200 cells/mm^3 or percentage ≥15%. These children should receive two doses of the monovalent vaccine, 3 months apart. Specific guidelines for immunizing these children should be reviewed before vaccination. Data indicate that varicella vaccine is highly effective in preventing herpes zoster among children infected with HIV. MMRV should not be administered as a substitute for the component vaccines in HIV-infected children.

A recombinant subunit (non-live) adjuvanted vaccine is available in the United States for use for prevention of herpes zoster and its related complications among individuals 50 years and older and among those 19 years and older who are or will be immunodeficient or immunosuppressed because of disease or therapy. The zoster vaccine is not indicated for primary prevention of varicella, or for the treatment of zoster or postherpetic neuralgia.

Vaccine-Associated Adverse Events

Varicella vaccine is safe and well tolerated. The incidence of injection site complaints observed ≤3 days after vaccination was slightly higher after dose 2 (25%) than after dose 1 (22%). A mild vaccine-associated varicelliform rash was reported in approximately 1–5% of healthy vaccinees, consisting of 6-10 papular-vesicular, erythematous lesions with peak occurrence 8-21 days after vaccination. Serious adverse reactions confirmed to be caused by the vaccine strain are rare and include pneumonia, hepatitis, meningitis, recurrent herpes zoster, severe rash, and seven deaths (all deaths occurred in persons with immunocompromising conditions). Transmission of vaccine virus to susceptible contacts is a very rare event from healthy vaccine recipients (13 instances from 11 immunocompetent varicella vaccine recipients, all in the presence of a rash in the vaccinee, 6 varicella-like and 5 herpes zoster). MMRV vaccine is associated with a greater risk for febrile seizures 5-12 days after the first dose among children 12-23 months of age compared with simultaneous MMR and varicella vaccines (one extra febrile seizure for every 2,500 children vaccinated).

Postexposure Prophylaxis

Vaccine given to healthy children within 3 and up to 5 days after exposure (as soon as possible is preferred) is effective in preventing or modifying varicella. Varicella vaccine is recommended for postexposure use and for outbreak control. Oral acyclovir administered late in the incubation period may modify subsequent varicella in the healthy child; however, its use in this manner is not recommended until it can be further evaluated.

High-titer anti-VZV immune globulin as postexposure prophylaxis is recommended for immunocompromised children, pregnant women, and newborns exposed to varicella. Since 2012 the product licensed for use in the United States is VariZIG. VariZIG is commercially available from a broad network of specialty distributors in the United States (list available at https://www.varizig.com). The recommended dose is 1 vial (125 units) for each 10-kg increment of body weight (maximum: 625 units), except for infants weighing ≤2 kg who should receive 0.5 vial. VariZIG should be given intramuscularly as soon as possible but may be efficacious up to 10 days after exposure.

Newborns whose mothers have varicella 5 days before to 2 days after delivery should receive VariZIG (0.5 vial for those weighing ≤2 kg and 1 vial for those weighing >2 kg). VariZIG is also indicated for pregnant women and immunocompromised persons without evidence of varicella immunity; hospitalized premature infants born at <28 weeks of gestation (or weight <1,000 g) who were exposed to varicella, regardless of maternal varicella immunity; and hospitalized premature infants born at ≥28 weeks of gestation who were exposed to varicella and whose mothers have no evidence of varicella immunity. Patients given VariZIG should be monitored closely and treated with acyclovir if necessary once lesions develop.

Close contact between a susceptible high-risk patient and a patient with herpes zoster is also an indication for VariZIG prophylaxis. Passive antibody administration or treatment does not reduce the risk for herpes zoster or alter the clinical course of varicella or herpes zoster when given after the onset of symptoms.

Although licensed pooled IVIG preparations contain anti-VZV antibodies, the titer varies from lot to lot. In situations in which administration of VariZIG is not possible, IVIG can be administered (400 mg/kg administered once within 10 days of exposure). Immunocompromised patients who have received high-dose IVIG (>400 mg/kg) for other indications within 3 weeks before VZV exposure can be expected to have serum antibodies to VZV.

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Chapter 301

Epstein-Barr Virus

Terri L. Stillwell and Jason B. Weinberg

Infectious mononucleosis is the best-known clinical syndrome caused by Epstein-Barr virus (EBV). It is characterized by systemic somatic complaints consisting primarily of fatigue, malaise, fever, sore throat, and generalized lymphadenopathy. Originally described as glandular fever, it derives its name from the mononuclear lymphocytosis with atypical-appearing lymphocytes that accompany the illness.

ETIOLOGY

EBV is a double-stranded DNA virus that is a member of the gammaherpesviruses and causes >90% of cases of infectious mononucleosis. Two distinct types of EBV, type 1 and type 2 (also called type A and type B), have been characterized and have 70–85% sequence homology. EBV-1 is more prevalent worldwide, although EBV-2 is more common in Africa than in the United States and Europe. Both types lead to *persistent*, *lifelong*, *latent infection*. Dual infections with both types have been documented among immunocompromised persons. EBV-1 induces in vitro growth transformation of B lymphocytes more efficiently than does EBV-2, but no type-specific disease manifestations or clinical differences have been identified.

As many as 5–10% of infectious mononucleosis–like illnesses are caused by other types of primary infections, particularly cytomegalovirus but also pathogens such as *Toxoplasma gondii*, adenovirus, hepatitis viruses, and HIV. In the majority of EBV-negative cases of infectious mononucleosis, the exact cause remains unknown.

EPIDEMIOLOGY

EBV infects more than 95% of the world's population. It is transmitted primarily via oral secretions. Among children, transmission may occur by exchange of saliva from child to child, such as occurs between children in out-of-home childcare. EBV is shed in oral secretions consistently for more than 6 months after acute infection and then intermittently for life. As many as 20–30% of healthy EBV-infected persons shed virus at any particular time. EBV is also found in male and female genital secretions, and some studies suggest the possibility of spread through sexual contact. Nonintimate contact, environmental sources, and fomites do not contribute to transmission of EBV.

Infection with EBV in developing countries and among socioeconomically disadvantaged populations in developed countries usually occurs during infancy and early childhood. In central Africa, almost all children are infected by 3 years of age. Among more affluent populations in industrialized countries, half of the population is infected by 6-8 years of age, with approximately 30% of infections occurring during adolescence and young adulthood. In the United States, seroprevalence increases with age, from approximately 54% for children 6-8 years to 83% for patients 18-19 years. Seroprevalence at each age is substantially higher for Mexican-Americans and non-Hispanic Blacks than for non-Hispanic Whites. Large differences are seen by family income, with highest seroprevalence in children of families with lowest income.

The epidemiology of the disease manifestations of infectious mononucleosis is related to the age of acquisition of EBV infection. Primary infection with EBV during childhood is usually asymptomatic or mild and indistinguishable from other childhood infections. Primary EBV infection in adolescents and adults manifests in 30–50% of cases as the **classic triad of fatigue**, **pharyngitis**, **and generalized lymphadenopathy**, which constitute the major clinical manifestations of infectious mononucleosis. This syndrome may be seen at all ages but is rarely apparent in children younger than 4 years of age, when most EBV infections are asymptomatic, or in adults older than 40 years of age, when most individuals have already been infected by EBV. The true incidence of the syndrome of infectious mononucleosis is unknown but is estimated to occur in 20-70 per 100,000 person-years. In young adults, the incidence increases to approximately 100 per 100,000 person-years. The prevalence of serologic evidence of past EBV infection increases with age; almost all adults in the United States are seropositive.

EBV infection has been implicated in other diseases, including both nonmalignant and malignant disorders such as lymphoproliferative diseases and lymphomas (Table 301.1). In addition, various monogenic immune susceptibility defects predispose to EBV-associated hemophagocytic lymphohistiocytosis, lymphoproliferative disorders, or lymphoma (Fig. 301.1; see also Chapter 174.3).

PATHOGENESIS

After transmission by saliva to the oral cavity, EBV infects both oral epithelial cells and tonsillar B lymphocytes, although it is unclear which cells are the primary initial targets. Ongoing viral replication leads to viremia and dissemination of infected B lymphocytes into peripheral blood and the lymphoreticular system, including the liver and spleen. Clinical manifestations of infectious mononucleosis, which are due to the host immune response to EBV infection, occur after a 6-week incubation period following acute infection. The atypical lymphocytes that are frequently detected in patients with infectious mononucleosis are primarily CD8 T lymphocytes. Polyclonal CD8 T lymphocyte activation occurs early during the incubation period following infection, whereas expansion of EBV-specific CD8 T lymphocytes is detected closer to the time of symptom onset. Natural killer (NK) cells also

Table 301.1 Diseases Caused by Epstein-Barr Virus Infection

INFECTED CELL TYPE	NONMALIGNANT DISEASES	MALIGNANT DISEASES
B lymphocytes	• B-lymphoproliferations (B-LPD) • Posttransplant B-LPD • Hemophagocytic lymphohistiocytosis (HLH)	• Hodgkin lymphoma (HL) • Diffuse large B cell lymphoma (DLBCL) • Burkitt lymphoma (BL)

T/NK lymphocytes	• Systemic T/NK-cell type chronic active EBV (CAEBV)
	• Cutaneous CAEBV
	  • Hydroa vacciniforme–like lymphoproliferation (HVL)
	  • Severe mosquito bite allergy (SMBA)
	• HLH
		• Systemic EBV+ T-cell lymphoma of childhood (STLC)
		• Extranodal NK/T-cell lymphoma (ENKTL)
		• Aggressive NK cell leukemia (ANKL)

Smooth muscle cells	• Smooth muscle tumor/leiomyoma (SMT)	
Epithelial cells	• Hairy leukoplakia*	• Nasopharyngeal carcinoma (NPC) • Gastric carcinoma

*Hairy leukoplakia is a benign epithelial/mucosal disease caused by uncontrolled lytic infection that occurs in immunocompromised patients. It is characterized by white patches with hairy appearance on the tongue.

From Fournier B, Latour S. Immunity to EBV as revealed by immunodeficiencies. *Curr Opin Immunol*. 2021;72:107–115. Table 1.

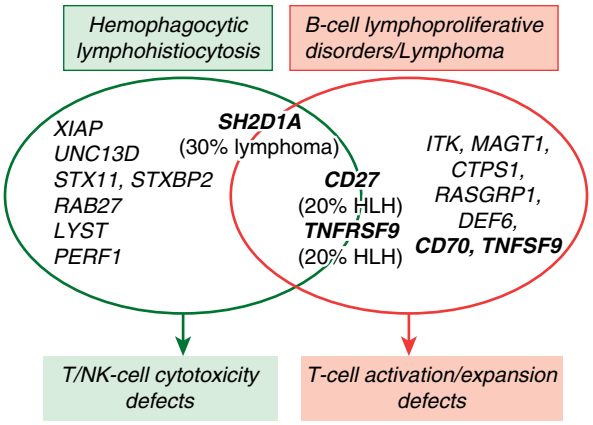

Fig. 301.1 Classification of gene defects predisposing to Epstein-Barr virus (EBV)-driven hemophagocytic lymphohistiocytosis (HLH) or B-cell lymphoproliferative disorders. *Red circle*, Gene defects associated with impaired cell-cytotoxicity causing HLH. *Green circle*, Gene defects associated with impaired T-cell activation/expansion causing B cell lymphoproliferative disorder (B-LPD)/lymphoma. Gene defects with a highly selective predisposition to EBV are in **bold**. In *parentheses* is the percentage of patients having developed HLH or B lymphoma for defects associated with both HLH and B-LPD/lymphoma. *(From Fournier B, Latour S. Immunity to EBV as revealed by immunodeficiencies. Curr Opin Immunol. 2021;72:107–115. Fig.1.)*

expand in frequency and number following infection, particularly a $CD56^{dim}$ $CD16^{-}$ NK cell subset that is more effective than other NK cell subsets at recognizing infected cells. The host immune response is effective in rapidly reducing the EBV viral load, although persistent shedding of high levels of virus can be detected in the oropharynx for up to 6 months. Intermittent shedding from the oropharynx occurs for many years following primary infection.

EBV, like the other herpesviruses, establishes lifelong latent infection after the primary infection. Latent virus persists primarily in memory B lymphocytes. The EBV genome persists as an episome in the nucleus of an infected cell and replicates with cell division. Viral integration into the cell genome is not typical. Only a few viral proteins, including the EBV-determined nuclear antigens (EBNAs), are produced during latency. These proteins are important in maintaining the viral episome during the latent state. Reactivation and new viral replication occur at a low rate in populations of latently infected cells and is responsible for intermittent viral shedding in oropharyngeal secretions of infected individuals. *Reactivation is unlikely to be accompanied by distinctive clinical symptoms*.

CLINICAL MANIFESTATIONS

The incubation period of infectious mononucleosis in adolescents is 30-50 days. In children, it may be shorter. The majority of cases of primary EBV infection in infants and young children are clinically silent. In older patients, the onset of illness is usually insidious and vague. Patients may complain of malaise, fatigue, acute or prolonged (>1 week) fever, headache, sore throat, nausea, abdominal pain, and myalgia. This prodromal period may last 1-2 weeks. The complaints of sore throat and fever gradually increase until patients seek medical care. Splenic enlargement may be rapid enough to cause left upper quadrant abdominal discomfort and tenderness, which may be the presenting complaint.

The **classic physical examination findings** are generalized lymphadenopathy (90% of cases), splenomegaly (50% of cases), and hepatomegaly (10% of cases). Lymphadenopathy occurs most commonly in the anterior and posterior cervical nodes and the submandibular nodes and less commonly in the axillary and inguinal lymph nodes. Epitrochlear lymphadenopathy is particularly suggestive of infectious mononucleosis. Although liver enzymes are usually elevated, symptomatic hepatitis or jaundice is uncommon. Splenomegaly to 2-3 cm below the costal margin is typical (15–65% of cases); massive enlargement is uncommon.

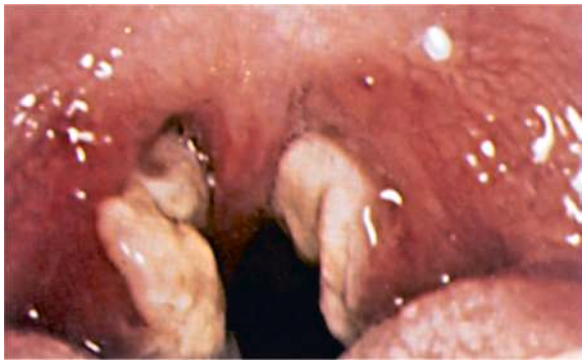

Fig. 301.2 Tonsillitis with membrane formation in infectious mononucleosis. *(Courtesy Alex J. Steigman, MD.)*

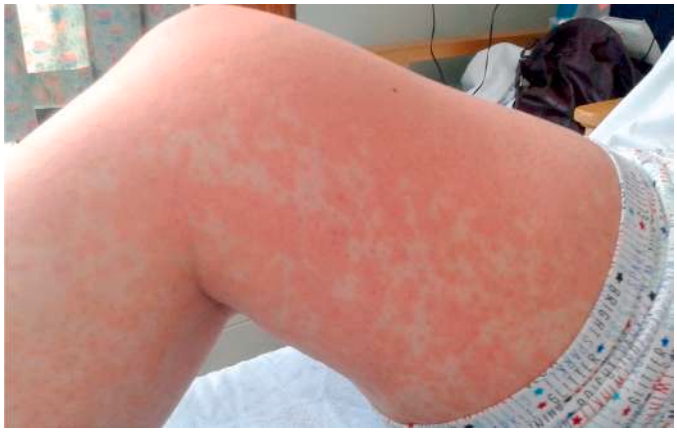

Fig. 301.3 Amoxicillin-induced rash in Epstein-Barr virus infection. Morbilliform maculopapular rash on the leg, which appeared shortly after starting amoxicillin. The rash is typical of that seen in the context of Epstein-Barr virus infection in patients treated with amoxicillin or ampicillin. *(From Norman SD, Murray IA, Shetty D, et al. Jaundice, abdominal pain, and fever in a young woman. Lancet. 2017;390:1713–1714. Fig. A.)*

The sore throat is often accompanied by moderate to severe pharyngitis with marked tonsillar enlargement, occasionally with exudates (Fig. 301.2). Palatal petechiae at the junction of the hard and soft palate are frequently seen. The pharyngitis is similar to that caused by streptococcal infection. Other clinical findings may include rashes and edema of the eyelids. Rashes are usually maculopapular and have been reported in 3–15% of patients. Patients with infectious mononucleosis who are treated with ampicillin or amoxicillin may experience an **ampicillin rash**, which may also occur with other β-lactam antibiotics (Fig. 301.3). This morbilliform, vasculitic rash is probably immune mediated and resolves without specific treatment. EBV can also be associated with Gianotti-Crosti syndrome, a symmetric rash on the cheeks with multiple erythematous papules, which may coalesce into plaques and persist for 15-50 days. The rash has the appearance of atopic dermatitis and may also appear on the extremities and buttocks.

DIAGNOSIS

A presumptive diagnosis of infectious mononucleosis may be made by the presence of classic clinical symptoms with atypical lymphocytosis in the peripheral blood. The diagnosis is usually confirmed by serologic testing, either for heterophile antibody or specific EBV antibodies.

Differential Diagnosis

EBV is the most common cause of infectious mononucleosis. Infectious mononucleosis–like illnesses may also be caused by primary infection with other pathogens, such as cytomegalovirus, *T. gondii*, adenovirus, and HIV. Streptococcal pharyngitis may cause sore throat and cervical lymphadenopathy indistinguishable from that of

infectious mononucleosis, but it is not typically associated with hepatosplenomegaly. Approximately 5% of cases of EBV-associated infectious mononucleosis have throat cultures positive for group A *Streptococcus*, representing pharyngeal streptococcal carriage. Failure of a patient with presumed streptococcal pharyngitis to improve within 48-72 hours should evoke suspicion of infectious mononucleosis. Hematologic malignancies should also be considered in a patient with an infectious mononucleosis–like illness, particularly when lymphadenopathy and hepatosplenomegaly are appreciated and the results of an initial laboratory evaluation are not consistent with an infectious etiology.

Laboratory Diagnosis

The majority of patients (>90%) have a leukocytosis of 10,000-20,000 cells/μL, of which at least two thirds are lymphocytes; atypical lymphocytes usually account for 20–40% of the total number. The atypical cells are mature T lymphocytes that have been antigenically activated. Compared with regular lymphocytes microscopically, **atypical lymphocytes** are larger overall, with larger, eccentrically placed indented and folded nuclei with a lower nuclear-to-cytoplasm ratio. Although atypical lymphocytosis may be seen with many other infections associated with lymphocytosis, the highest degree of atypical lymphocytes is classically seen with EBV infection. Mild thrombocytopenia to 50,000-200,000 platelets/μL occurs in more than 50% of patients but only rarely is associated with purpura. Mild elevation of hepatic transaminases occurs in approximately 75% of uncomplicated cases, but it is usually asymptomatic and without jaundice.

Detection of Heterophile Antibodies

Heterophile antibodies are cross-reactive immunoglobulin (Ig) M antibodies that agglutinate mammalian erythrocytes but are not EBV-specific. Heterophile antibody tests, such as the **monospot** test, are positive in 90% of cases of EBV-associated infectious mononucleosis in adolescents and adults during the second week of illness, but in only up to 50% of cases in children younger than 4 years of age. Test results can remain positive for up to 12 months. The false-positive rate is low, generally <10%. A positive heterophile antibody test in a patient with classic clinical manifestations of mononucleosis strongly supports that diagnosis. However, because of the nonspecific nature of heterophile antibody testing, EBV-specific antibody testing should be performed when a precise diagnosis is necessary.

Detection of Epstein-Barr Virus–Specific Antibodies

If the heterophile test result is negative and an EBV infection is suspected, EBV-specific antibody testing is indicated. Measurement of antibodies to EBV proteins, including viral capsid antigen (VCA), Epstein-Barr nuclear antigen (EBNA), and early antigen (EA), are used most frequently (Fig. 301.4 and Table 301.2). The acute phase of infectious mononucleosis is characterized by rapid IgM and IgG antibody responses to VCA in all cases and an IgG response to EA in most cases. The IgM response to VCA is transient but can be detected for at least 4 weeks and occasionally up to 3 months; in rare cases, anti-VCA IgM can persist even longer. The IgG response to VCA usually peaks late in the acute phase, declines slightly over the next several weeks to months, and then persists at a relatively stable level for life.

Anti-EA IgG antibodies are usually detectable for several months but may persist or be detected intermittently at low levels for many years. Antibodies to the diffuse-staining component of EA (EA-D) are found transiently in 80% of patients during the acute phase of infectious mononucleosis. Antibodies to the cytoplasmic-restricted component of EA (EA-R) emerge transiently in the convalescence from infectious mononucleosis. High levels of antibodies to EA-D or EA-R may be found also in immunocompromised patients with persistent EBV infections and active EBV replication.

Anti-EBNA IgG antibodies are the last to develop in infectious mononucleosis and gradually appear 3-4 months after the onset of illness and remain at low levels for life. Absence of anti-EBNA when other antibodies are present implies recent infection, whereas the presence of anti-EBNA implies infection occurring more than 3-4 months previously. The wide range of individual antibody responses and the various laboratory methods used can occasionally make interpretation of an antibody profile difficult. The detection of IgM antibody to VCA is generally sufficient to confirm the diagnosis of acute EBV infection, although false positive results can still occasionally occur.

Detection of Viral DNA

EBV DNA can be detected and viral genome copy number quantified in whole blood, peripheral blood mononuclear cells (PBMCs), and plasma using real-time polymerase chain reaction. EBV DNA can be detected in PBMCs and plasma of patients with infectious mononucleosis for a brief period after the onset of symptoms and in PBMCs for an extended period. However, detection of EBV DNA is usually not necessary to diagnose infectious mononucleosis in immunocompetent patients with typical manifestations of disease. In contrast, serial measurements of EBV genome copy number are often used following solid organ or hematopoietic stem cell transplantation as surveillance for posttransplant lymphoproliferative disease (PTLD). Very high or consistently increasing EBV genome copy number suggests an increased risk for PTLD, although definitive diagnosis is typically based on tissue biopsy. The frequency and duration of monitoring EBV genome copy number is determined by the time after transplant and risk factors such as the type of transplant and the degree of immunosuppression. Serial measurement of EBV genome copy number can be useful in monitoring response to therapy for PTLD. Measurement of EBV genome copy number can also be used for screening and to determine prognosis for some EBV-associated malignancies, such as nasopharyngeal carcinoma and Hodgkin lymphoma.

COMPLICATIONS

Severe complications are unusual in patients with infectious mononucleosis. Splenic rupture, either spontaneous or following mild trauma, may occur in approximately 0.1% of cases but is rarely fatal. Airway obstruction due to swelling of oropharyngeal lymphoid tissue occurs in <5% of cases. A variety of neurologic conditions have been associated with EBV infectious mononucleosis. Headache is a common symptom, but symptomatic meningitis or encephalitis is uncommon. More severe neurologic manifestations, such as seizures and ataxia, may occur in 1–5% of cases. Perceptual distortions of sizes, shapes, and spatial relationships, known as the **Alice in Wonderland syndrome (metamorphopsia)**, may be a presenting symptom. Some reports suggest an association between infectious mononucleosis and the possible development of multiple sclerosis. Hematologic abnormalities such as mild hemolytic anemia, thrombocytopenia, and neutropenia are relatively common, but aplastic anemia, severe thrombocytopenia, and severe neutropenia are rare. Other rare complications include myocarditis, interstitial pneumonia, pancreatitis, parotitis, and orchitis.

Patients with dysregulated immune responses to primary infection, such as individuals with primary or secondary **hemophagocytic lymphohistiocytosis (HLH)**, can develop severe, life-threatening complications with primary EBV infection (see Fig. 301.1). Patients with other primary immunodeficiencies that result in failure to control EBV infection and/or abnormal inflammatory responses to infection are at risk for severe manifestations of EBV infection, often with fulminant infectious mononucleosis, chronic viremia, dysgammaglobulinemia, and lymphoproliferation. Immunodeficiencies most commonly linked to severe EBV infection tend to be those affecting aspects of NK cell, T lymphocyte, and NKT lymphocyte function. Examples include X-linked lymphoproliferative (XLP) syndrome, which is caused by variants in genes encoding the signaling lymphocytic activation molecule (SLAM)-associated protein (SAP) or X-linked inhibitor of apoptosis (XIAP); X-linked immunodeficiency with magnesium defect, EBV infection, and neoplasia (XMEN), caused by mutations in *MAGT1*, which encodes a magnesium transporter protein; and deficiencies in interleukin-2–inducible T-cell kinase (ITK), CD27, or CD70 (see Fig. 301.1; Chapter 174.3).

ONCOGENESIS

Infection with EBV, the first human virus to be associated with malignancy, accounts for up to 2% of cancers worldwide (see Table 301.1).

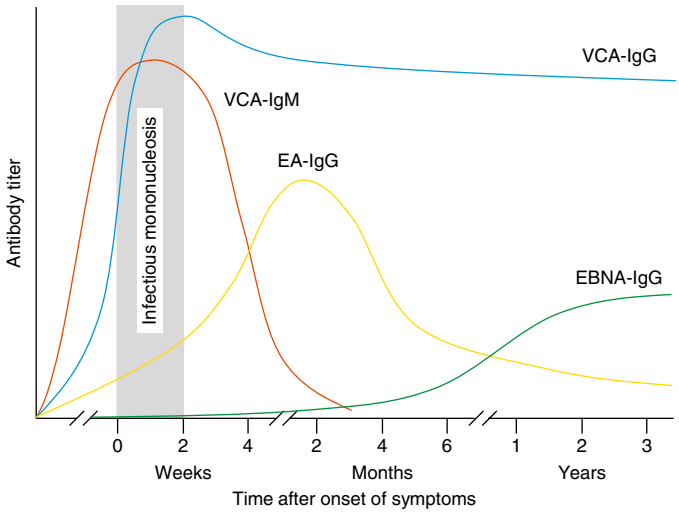

Fig. 301.4 Kinetics of antibody responses to Epstein-Barr virus (EBV) antigens in infectious mononucleosis. EA, Early antigen; EBNA, EBV-determined nuclear antigens; IgG, immunoglobulin G; IgM, immunoglobulin M; VCA, viral capsid antigen.

Table 301.2 Correlation of Clinical Status and Antibody Responses to Epstein-Barr Virus Infection

CLINICAL STATUS	VCA IgM	VCA IgG	EA IgG	EBNA IgG
Susceptible	–	–	–	–
Acute primary infection	+	+	±	–
Recent primary infection	±	+	±	±
Past infection	–	+	±	+

EA, Early antigen (typically the diffuse staining component, or EA-D); EBNA, EBV-determined nuclear antigens; EBV, Epstein-Barr virus; IgG, immunoglobulin G; IgM, immunoglobulin M; VCA, viral capsid antigen.

Manipulation of infected cells by EBV can lead to transformation and oncogenesis. EBV is associated with lymphoid malignancies, such as Burkitt lymphoma, Hodgkin lymphoma, aggressive NK cell leukemia, T- and NK-cell lymphoproliferative disorder, and epithelial cell malignancies such as nasopharyngeal carcinoma and gastric carcinoma.

Endemic Burkitt lymphoma is the most common childhood cancer in equatorial East Africa and Papua New Guinea. These regions are holoendemic for *Plasmodium falciparum* malaria and have a high rate of EBV infection early in life. Constant exposure to malaria is thought to act as a B lymphocyte mitogen that contributes to the polyclonal B-lymphocyte proliferation with EBV infection, impairs T lymphocyte surveillance of EBV-infected B lymphocytes, and increases the risk for developing Burkitt lymphoma. Approximately 98% of cases of endemic Burkitt lymphoma contain the EBV genome compared with only 20% of nonendemic (sporadic) Burkitt lymphoma cases in other areas of the world.

The incidence of **Hodgkin lymphoma** peaks in childhood in developing countries and in young adulthood in developed countries. Infection with EBV increases the risk for Hodgkin lymphoma by a factor of 2-4, with the risk of developing Hodgkin lymphoma peaking at 2.4 years following infectious mononucleosis. EBV is associated with more than half of cases of mixed-cellularity Hodgkin lymphoma and approximately one quarter of cases of the nodular sclerosing subtype, but it is rarely associated with lymphocyte-predominant Hodgkin lymphoma. Immunohistochemical studies have localized EBV to the Reed-Sternberg cells and their variants, the pathognomonic malignant cells of Hodgkin lymphoma.

Numerous congenital and acquired immunodeficiency syndromes are associated with an increased incidence of EBV-associated B-lymphocyte lymphoma, especially central nervous system lymphoma and leiomyosarcoma (see Fig. 301.1). Congenital immunodeficiencies predisposing to EBV-associated lymphoproliferation include XLP syndrome, common-variable immunodeficiency, ataxia-telangiectasia, Wiskott-Aldrich syndrome, and Chédiak-Higashi syndrome. Individuals with acquired immunodeficiencies resulting from anticancer chemotherapy, immunosuppression after solid organ or hematopoietic cell transplantation, or HIV infection have a significantly increased risk for EBV-associated lymphoproliferation. The lymphomas may be focal or diffuse and are usually histologically polyclonal but may become monoclonal. EBV-associated PTLD can occur following solid organ transplantation and, less commonly, allogeneic hematopoietic cell transplantation. The most important risk factors for PTLD are the degree of T lymphocyte immunosuppression and recipient EBV serostatus.

TREATMENT

There is no specific treatment for infectious mononucleosis. The mainstays of management are rest, adequate fluid and nutrition intake, and symptomatic treatment to manage fever, throat discomfort, and malaise. Bed rest is necessary only when the patient has debilitating fatigue. As soon as there is definite symptomatic improvement, the patient should be encouraged to resume normal activities. Because blunt abdominal trauma may predispose patients to splenic rupture, it is customary and prudent to advise against participation in contact sports and strenuous athletic activities during the first 2-3 weeks of illness or while splenomegaly is present.

Antiviral therapy is not recommended. Although nucleoside analogs such as acyclovir and ganciclovir inhibit viral replication in vitro and decrease the duration of oropharyngeal viral shedding in patients with infectious mononucleosis, they have not been shown to provide consistent clinical benefit for patients with infectious mononucleosis or EBV-associated malignancies. Short courses of corticosteroids may be helpful for selected complications of infectious mononucleosis, such as airway obstruction, but there are insufficient data to support the use of corticosteroids to control typical symptoms in patients with infectious mononucleosis. Adoptive immunotherapy involving the infusion of EBV-specific cytotoxic T lymphocytes has shown some promise in early trials for transplant recipients with PTLD and for other patients with EBV-associated malignancies.

PROGNOSIS

The prognosis for complete recovery is excellent. The major symptoms typically last 2-4 weeks, followed by gradual recovery within 2 months of symptom onset. Cervical lymphadenopathy and fatigue may resolve more slowly. Prolonged and debilitating fatigue and malaise may wax and wane for several weeks to 6 months and are common complaints even in otherwise unremarkable cases. Occasional persistence of fatigue for a few years after infectious mononucleosis is well recognized. There is no convincing evidence linking EBV infection or EBV reactivation to chronic fatigue syndrome.

PREVENTION

Vaccination against EBV would be an appealing strategy to prevent acute disease (infectious mononucleosis) and complications such as EBV-associated malignancies. Early clinical trials using strategies targeting the EBV gp350 envelope glycoprotein demonstrated some protection against symptomatic infectious mononucleosis, although vaccination did not prevent EBV infection. No EBV vaccine is currently approved for clinical use.

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Chapter 302

Cytomegalovirus

Suresh B. Boppana and William J. Britt

Human cytomegalovirus (CMV) is ubiquitous in the population, with serologic evidence of infection in >50% of adults in the United States and >96% in many populations in South America, Africa, and Asia. Individuals who become infected remain persistently infected for life and shed infectious virus intermittently from mucosal surfaces, thus serving as a source of infectious virus for transmission within populations. Although CMV infection rarely causes symptoms in immunocompetent individuals, it is an important cause of morbidity and sometimes death in immunocompromised hosts. CMV remains a well-recognized cause of disease in the newborn infant following intrauterine infection (congenital CMV) and in allograft recipients undergoing posttransplantation immunosuppression. CMV emerged as the most common opportunistic infection in HIV/AIDS patients before the advent of effective antiretroviral therapy. Invasive CMV infections can also be observed in patients treated with immunosuppressive biologics such as anti–tumor necrosis factor (TNF) antibodies. In each of these clinical settings that share some degree of immunosuppression, the association of disease with CMV infection has been linked to high levels of virus replication and end organ disease, usually associated with virus dissemination. In contrast, there is likely another group of disease states associated with chronic effects of persistent CMV infection that reflects the robust inflammatory response induced by this virus during persistent infection. Such associations have been proposed to include coronary artery disease, transplant vasculopathy and cardiac allograft loss, renal tubular sclerosis and renal allograft loss, exacerbations of inflammatory bowel disease, and possibly even some cancers such as glioblastoma. Whether definitive evidence will eventually directly link CMV to these disease states is uncertain.

THE VIRUS AND ITS HOST INTERACTIONS

CMV is the largest of the human herpesviruses, with an estimated size of 190 nm. The 230-kb double-stranded DNA genome is about 50% larger than the herpes simplex virus genome and encodes over 200 open reading frames, which conservatively estimated includes >100 unique virion proteins and an unknown number of nonstructural proteins. Viral DNA replication takes place in the nucleus of the infected cell followed by virus assembly in both the nucleus and cytoplasm. The structure of the virus is typical of herpesviruses and includes a complex envelope composed of host cell–derived membrane studded with virion glycoproteins, a less well-structured area between the envelope and the capsid called the tegument layer, and an icosahedral capsid that contains the virion DNA. The tegument layer is highly immunogenic and induces strong adaptive immune responses, including CMV specific $CD8^+$ cytotoxic T lymphocytes that are thought to play a pivotal role in controlling CMV replication in the infected host. Likewise, the protein components of the viral envelope are also immunogenic and induce antibody responses that have been correlated with virus neutralization, antibody dependent cellular cytotoxicity (ADCC), antibody dependent cellular phagocytosis (ADCP), and other potential protective effector functions. In vivo, CMV appears to replicate in nearly all tissue and cell types, whereas in vitro productive virus replication (production of infectious progeny) occurs in primary fibroblasts and cells derived from epithelial tissue. Human CMV is species specific and productively infects only cells of human origin. Each strain of CMV that is isolated from epidemiologically unrelated individuals is genetically unique, a finding that suggests an extraordinarily large and undefined number of genetically unique viruses exist in the human population. Furthermore, studies using next-generation sequencing technologies have provided evidence that CMV can exist as genetically diverse populations of viruses within an individual. This finding has argued that during replication, CMV DNA synthesis is error prone, resulting in sequence error rates in its genome that are much higher than previous studies would predict and/or a high likelihood of recombination events between viral genomes if permissive cells are infected with genetically diverse populations of viruses. Thus repeated exposures to CMV over time could result in an individual acquiring a library of CMVs as reinfection of previously infected individuals with new strains of CMV also appears commonplace. These observations have led many investigators to argue that CMV must express an armamentarium of immune evasion functions that allow it to persist even in the presence of robust host immunity. This relationship between host and virus is best illustrated by the finding that over years a persistently infected individual can maintain a stable virus load in sites of persistence, unwavering antiviral antibody responses, and, in some individuals, up to 15% of total peripheral blood $CD8^+$ cytotoxic T lymphocyte activity can be directed at CMV antigens derived from a diverse number of virus-encoded proteins. These observations have resulted in a central paradigm of CMV biology in which, following infection, a detente is established between virus replication and host innate and adaptive antiviral immunity. Thus CMV can efficiently persist in an infected host for a lifetime while inducing chronic immune activation. This latter characteristic of the biology of CMV infection has supported a linkage between CMV and chronic inflammation, a link that could provide a common mechanism for many of the chronic diseases that have been associated with this ubiquitous virus.

EPIDEMIOLOGY

CMV infections can be acquired through several settings: (1) community exposure, (2) nosocomial transmission, and (3) intrauterine infection leading to congenital infection.

Community acquisition of CMV occurs throughout life and is linked by exposure to CMV shed from mucosal surfaces such as saliva, genital secretions, and urine. Peaks in exposure to infectious virus occur during childhood and in adolescents and young adults, presumably secondary to initiation of sexual activity in the latter age group. In addition, differences in age-specific and overall rates of virus infection in the United States are observed in different racial, ethnic, and socioeconomic groups. Common routes of infection of the very young infant include perinatal exposure to infected genital secretions during birth and ingestion of CMV-containing breast milk. Breastfeeding is the most common route of CMV infection in infancy. Ingestion of breast milk from seropositive women results in a rate of infection of about 60% in infants. Infection is most common during the first several months of breastfeeding, but the risk continues for the duration of breastfeeding. Infants infected through breast milk can shed large amounts of virus in the saliva and urine for prolonged periods measured in months to years, thus serving as a reservoir of virus for transmission to other infants, children, and adults. After this period of intense exposure to CMV during the first year of life, infection in the remainder of childhood and early teenage years depends on specific exposures such as enrollment in group childcare facilities and/or exposure to infected, similarly aged siblings. Up to 50% of young infants and children attending group care facilities can be excreting CMV, a source of virus that can result in infection of children enrolled in the facility and in some cases the adult workers within the facility. Furthermore, infants and children who acquire CMV in a group care setting can then transmit virus to their parents and siblings, thus providing a mechanism for spread of CMV within the community. Throughout childhood and early adulthood, CMV is transmitted by exposure to saliva and urine. However, in adolescence and early adulthood there is a spike in infection presumably associated with sexual exposure. CMV is considered a sexually transmitted infection (STI); data have shown an increased rate of CMV infection in sexually active populations and high rates of virus transmission in CMV-discordant couples.

Nosocomial infections with CMV are well described and can be associated with exposure to blood products containing CMV or to an allograft following transplantation of an organ from a CMV-infected donor. Before improvements in blood banking that limited the number of leukocytes in red cell transfusions and that more efficiently identified

CMV infected donors, transmission of CMV by blood transfusion was not uncommon and was closely related to the volume of blood that was transfused. **Transfusion-acquired CMV** infections often resulted in symptomatic illness, with laboratory findings including hepatitis and thrombocytopenia in children and adults. Severe and sometimes fatal infections can develop following exposure to CMV-infected blood products in newborn infants who lack transplacentally transferred antibodies to CMV either as a result of being born to women without seroimmunity to CMV or secondary to extreme prematurity. Similarly, immunocompromised patients who receive CMV-containing blood can also develop severe infection, regardless of their prior exposure to CMV. Methodologies that efficiently deplete contaminating leukocytes and the use of blood products from CMV seronegative donors have greatly decreased the incidence of transfusion-associated CMV infections. CMV transmission through **infected allografts** is well described; infections arising from CMV transferred in an infected allograft are a major cause of morbidity in both the early and late period after transplantation. Severe infections and graft loss following solid organ transplantation (SOT) are more often associated with mismatches between the donor and recipient, such as that following transplantation of an organ from a donor with a history of CMV infection (donor, CMV positive) into a recipient who has not been exposed to CMV (recipient, CMV negative; D+/R− mismatch). However, clinically significant CMV infections can occur even in moderate-risk allograft recipients (D+/R+). In contrast to the risk stratification for CMV infection and disease in SOT recipients, the highest risk of posttransplant CMV infection and disease occurs follows reactivation of CMV in hematopoietic stem cell transplant (HSCT) recipients with prior CMV infection (D+/−/R+) presumably because the risk of transmission in the graft is considerably lower than reactivation of persistent infection in the previously infected recipient. Even with effective antiviral therapy to modify CMV infections in the early posttransplant period during intense immunosuppression, CMV infection is linked to long-term graft dysfunction and graft loss and in specific patient groups such as cardiac and lung transplant recipients, can represent a barrier to long-term graft survival.

Congenital CMV infection (present at birth) occurs following intrauterine transmission of CMV and infection of the fetus. Rates of congenital infection between 0.4% and 1.0% have been reported in the United States, with perhaps the best estimate being about 0.4% based on a large multicenter study of nearly 100,000 births. Rates as high as 2% in some areas in Asia and Africa have been described. CMV is thought to be transferred to the developing fetus following hematogenous spread of CMV to the placenta, infection of resident cells of the placenta followed by cell-free transfer of virus to the fetal blood system. The rate of transmission to the fetus is about 30% in nonimmune women with primary infection during pregnancy; in utero infections also occur in previously immune women (nonprimary infection), albeit at a reduced rate that has been suggested to be ~1–2%. The rate of transmission of CMV is more frequent following primary maternal infection; the absolute number of congenitally infected infants born to women with nonprimary infections in most populations outnumber those resulting from primary maternal infection by threefold to fourfold. This is particularly true in Africa, South America, and Asia, where maternal seroimmunity to CMV often exceeds 95%. Interestingly, many of these highly CMV seroimmune maternal populations also have the highest prevalence of congenital CMV infections and almost certainly account for overall burden of congenital CMV infections in most regions of the world. In fact, recent estimates based on the prevalence of congenital CMV infections in sub-Saharan Africa, Asia, and South America suggest that 90% of all cases of congenital CMV infections followed nonprimary material infections. The source of nonprimary maternal infection remains less well defined. Reinfection by genetically distinct strains of CMV is frequent in previously infected women and viruses acquired by maternal reinfection can be transmitted to the developing fetus. The reinfection rates are ~15–20%, with annualized rates as high as 25%. Thus immunity to CMV is far from protective, although it can modify the risk of transmission to the developing fetus.

In addition to the impact of maternal to fetal transmission, the type of maternal infection (primary versus nonprimary) has also been shown to be a major determinant in the outcome of the intrauterine infection. The existing paradigm is that maternal immunity can modify the severity of the intrauterine infection, thus maternal infections in women with preexisting CMV immunity (nonprimary maternal infections) that result in intrauterine transmission are less likely to result in a severe infection in the fetus. Nonetheless, severe CMV infections may occur in fetuses infected following a nonprimary maternal infection, suggesting that the characteristics of the fetal infection such as timing of infection during gestation could be as important to the outcome of a fetal infection as the maternal immune status during pregnancy. Studies have documented a higher frequency of severe infections in fetuses that were infected in the first and early second trimester of gestation, findings that parallel similar risk stratifications for other intrauterine infections, including those caused by Zika virus, rubella virus, and *Toxoplasma gondii*.

Mechanisms of Disease Associated with Cytomegalovirus Infections

The mechanism(s) of disease associated with CMV infections remains either undefined or incompletely defined for many of the clinical syndromes that follow CMV infection. Several reasons have contributed to the overall lack of understanding of the pathogenesis of CMV infections and include (1) the asymptomatic nature of infections in almost all immunocompetent individuals; (2) the complexity of the multiple disease processes in immunocompromised hosts that can confound the assignment of specific manifestations of CMV infection; (3) the species-specific tropism of human CMV; and, perhaps most importantly, (4) limitations inherent in observational studies in humans. Although CMV replicates in a limited number of cell types in vitro, CMV inclusions, antigens, and nucleic acids can be demonstrated in almost all organ systems and most cell types in individuals with severe, disseminated infections. Thus CMV does not exhibit strict cellular or organ system tropism in vivo. Hematogenous dissemination has been argued to be associated primarily with cell-associated virus, and significant levels of plasma virus are usually detected only in severely immunocompromised hosts with high levels of total-blood viral loads. Virus and viral DNA can be recovered from neutrophils, monocytes, and endothelial cells present in peripheral blood, thus providing evidence for the significance of cell-associated spread of this virus. High levels of virus replication can result in end-organ disease secondary to direct virus-mediated cellular damage. These manifestations of CMV infections are thought to result from uncontrolled virus replication, dissemination, and virus-induced cytopathology secondary to deficits in innate and adaptive immune responses to CMV. In some cases, clinical disease has also been observed in patients without significant levels of virus replication, a finding suggesting indirect mechanisms of disease such as immunopathologic responses to CMV. Such a mechanism of disease was shown to be operative in patients with immune recovery vitritis, a pathologic T-lymphocyte–mediated response to CMV in HIV/AIDS patients with CMV retinitis that developed after successful active retroviral therapy and reconstitution of their CMV-specific T lymphocyte responses. Likewise, the level of virus replication has not been closely correlated with several chronic diseases thought to be linked to CMV, an observation that is consistent with indirect mechanisms of disease such as immunopathologic responses to a persistent infection.

From early observations in allograft recipients with invasive CMV infections it was apparent that immunosuppressive therapies that resulted in altered T lymphocyte function predisposed these patients to severe infections. Definitive evidence consistent with the critical role of CMV-specific T lymphocyte immunity in protection from disease in these patients was provided by a clinical study in which in vitro expanded, CMV-specific cytotoxic T lymphocytes limited invasive infection in hematopoietic cell transplant recipients. Invasive infections associated with end-organ disease, such as retinitis and colitis in HIV/AIDS patients with very low $CD4^+$ T-lymphocyte counts, also clearly demonstrated the importance of T lymphocyte response

control of invasive CMV infections, as the risk for these manifestations of CMV infections could be predicted in models that were based on $CD4^+$ T-lymphocyte counts in these patients. However, a role of anti-CMV antibodies in limiting the early events of CMV infection was also shown in studies in SOT recipients. These early studies demonstrated the transfer of immune globulins containing high titers of anti-CMV antibodies when used in a prophylaxis protocol could provide some degree of protection from CMV infections and end-organ disease. This important finding was consistent with the proposed role of antiviral antibodies in limiting CMV dissemination and disease in animal models of invasive CMV infections. The importance of innate immune responses such as natural killer (NK) cells and γδ T lymphocytes in limiting invasive infections have been well documented in animal models. Similarly, NK cells have been associated with both control of CMV reactivation and limiting the severity of CMV end-organ disease in human HCST and SOT recipients. Effector molecules such as interferon-γ appear to contribute to the control of local CMV infections in animal models, but evidence of a similar role in humans has not been demonstrated.

Studies in immunocompromised human hosts have shown that the control of acute CMV infection depends on an effective adaptive immune response; however, even a vigorous T lymphocyte response is not sufficient to eliminate CMV from the infected host, because CMV persists for the lifetime of the host either as a low-level chronic infection and/or as a latent infection with limited transcription from multiple regions of its genome. The inability of the host to completely clear CMV remains incompletely understood, but the large array of immune evasion functions encoded by this virus likely contributes to the blunted innate and adaptive immune response. Examples of these functions include (1) inhibition of cell death functions of infected cells, including apoptosis, necroptosis, and pyroptosis, (2) inhibition of interferon-regulated responses, (3) inhibition of NK cell activation, (4) downregulation of class I major histocompatibility complex (MHC) expression and inhibition of class II MHC function, and (5) mechanisms to limit antibody recognition of envelope proteins, including carbohydrate masking of antibody recognition sites and variation in amino acid sequences in virion envelope proteins targeted by antiviral antibodies. Although each of these functions by itself could potentially have only limited effects on virus clearance, the redundancy of these viral immune evasion functions when acting in concert likely provide the virus a sufficient advantage to favor persistence.

CLINICAL MANIFESTATIONS

The clinical manifestations of CMV infection reflect two parameters of the infection that are often linked: (1) the level of virus replication and (2) the degree of end-organ involvement. The manifestations of CMV infections that have been most well described in clinical studies are those that are present in acutely infected individuals without existing immunity to the virus. Such infections are termed acute or primary infections to distinguish these infections from persistent infections that are established after an acute infection. Similar clinical findings can be observed in patients with significant underlying deficits in innate and adaptive immune responses, regardless if infection follows an acute infection or recurrence/reactivation of persistent infection and reflect loss of immune control of virus replication. In contrast, the clinical manifestations of persistent or chronic CMV infections are frequently overlaid on underlying disease syndromes such as cardiovascular disease, thus confounding the contribution of CMV to the primary disease process and clinical findings in these patients.

Normal Host

In the overwhelming majority of patients with acute CMV infections, there are no specific symptoms or clinical findings. In patients with symptomatic, acute CMV infection, clinical findings have been most commonly reported to resemble a mononucleosis-like syndrome, with fatigue and occasionally cervical adenopathy. Up to 20% of heterophile antibody-negative mononucleosis may be attributed to CMV. Laboratory findings can include mild elevation of hepatic transaminases and decreased platelet counts.

Immunocompromised Host

The clinical presentation of CMV infection in immunocompromised hosts often reflects the magnitude of the immunodeficiency. Profoundly immunocompromised hosts such as HSCT recipients can present with disseminated infection and clinical manifestations of disease in multiple organ systems, including liver, lung, gastrointestinal tract, and, less frequently, the CNS. Organ-threatening and life-threatening disease is not infrequent in these patients. In less immunocompromised patients such as the case of most SOT recipients, CMV infection can present with fever, fatigue, hematologic abnormalities, including leukopenia and thrombocytopenia, and mild hepatocellular dysfunction, a collection of laboratory findings and symptoms described as the CMV syndrome (Table 302.1). In contrast to renal and liver SOT recipients, heart-lung and lung transplant recipients are at high risk for severe manifestations from CMV infection, presumably because the transplanted organ is a site of virus replication, disease, and virus-induced life-threatening organ dysfunction (see Table 302.1). Before the widespread use of antivirals for prophylaxis of allograft recipients, clinical disease usually developed between 30 and 60 days after transplantation. Prolonged antiviral *prophylaxis* has greatly reduced the frequency of CMV disease in the early posttransplant period in most SOT and HCST recipients; late manifestations of CMV infection often become apparent after discontinuation of antiviral prophylaxis. These late manifestations are most worrisome in HSCT recipients, because they may signal deficits in graft function that in turn predispose these patients to invasive CMV infections. Long-term graft function has been reported to be influenced by CMV infection. This has been most well studied in renal allograft recipients and is thought by many investigators to represent a significant cause of chronic graft dysfunction and eventual loss of the graft. Perhaps the most dramatic impact of CMV infection late in the posttransplant period can be seen in heart transplant recipients, in whom CMV is thought to play a major role in transplant vascular sclerosis, a vasculopathy of the coronary arteries in the allograft leading to loss of the transplanted heart allograft.

Congenital Infection

Congenital infection with CMV can present with clinically apparent (symptomatic) infection (Table 302.2) in about 10% of infected newborns, whereas 90% of infected infants will have *no clinical manifestations* of infection in the newborn period (asymptomatic infection) and can be identified only by screening newborns for the presence

Table 302.1 Findings in Cytomegalovirus Infections in Solid Organ Transplant Recipients

CLINICAL FINDINGS	LABORATORY FINDINGS
CMV SYNDROME	
Fever, nonspecific findings, fatigue	Leukopenia, thrombocytopenia, reactive lymphocytosis, hepatitis, CMV DNA in blood
END-ORGAN DISEASE	
Gastrointestinal disease, including esophagitis, colitis, and hepatitis	Detection of CMV DNA in blood; detection of CMV in tissue biopsy; hepatitis, including elevated bilirubin
Lung disease; hypoxemia	Abnormalities in lung imaging CMV in bronchoalveolar lavage fluid
Encephalitis	CSF pleocytosis, elevated CSF protein Abnormalities in CNS imaging
Allograft dysfunction	Evidence of graft rejection

Table 302.2 Findings in Infants with Symptomatic Congenital Cytomegalovirus Infection

FINDINGS	% OF INFANTS
CLINICAL FINDINGS	
Prematurity (<37 wk)	24
Jaundice (direct bilirubin >2 mg/dL)	42
Petechiae	54
Hepatosplenomegaly	19
Purpura	3
Microcephaly	35
IUGR	28
1 clinical finding	41
2 clinical findings	59
LABORATORY FINDINGS	
Elevated ALT (>80 IU/mL)	71
Thrombocytopenia (<100,000 k/mm^3)	43
Direct hyperbilirubinemia (>2 mg/dL)	54
Head CT abnormalities	42

Findings in 70 infants with symptomatic congenital CMV infection identified during newborn screening program for infants with congenital CMV infection at the University of Alabama Hospitals over an approximate 20-yr interval.
CMV, Cytomegalovirus; *IUGR*, in utero growth restriction; ALT, alanine aminotransferase.

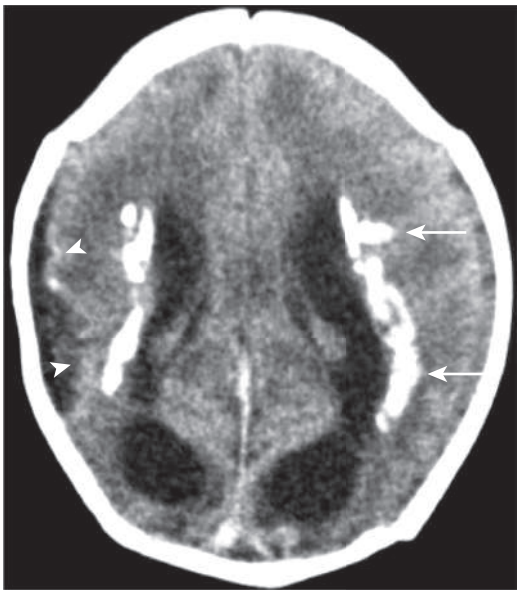

Fig. 302.1 Cytomegalovirus (CMV). One-day-old with congenital CMV infection. Noncontrast CT of the head demonstrates multiple areas of confluent calcifications within the periventricular regions bilaterally *(arrows)*, typical of the expected distribution of calcification secondary to CMV. Note the abnormal sulcal pattern of the right hemisphere, indicating associated polymicrogyria *(arrowheads)*. *(From Rothenberg Maddocks AB, Pollok AN. Infection and inflammation. In: Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 13th ed. Philadelphia: Elsevier; 2019: Fig. 34.31, p. 342.)*

of CMV in saliva, urine, or, less commonly, blood. **Severe multiorgan disease** is infrequent and occurs in approximately 30% of infants with symptomatic congenital CMV infections. The clinical findings in infants with symptomatic congenital CMV infections can include hepatosplenomegaly, petechial rashes, jaundice, and microcephaly. Intrauterine growth restriction is also a finding of symptomatic congenital CMV infection. Laboratory findings are consistent with the clinical findings and include direct hyperbilirubinemia, elevation of hepatic transaminases, thrombocytopenia, and abnormal findings on cranial ultrasonography/computed tomography/MRI (Fig. 302.1). If cerebrospinal fluid is obtained, there can be evidence of encephalitis, with elevation of mononuclear cell number and, in some cases, elevation of protein. A small number of symptomatically infected infants (<10%) will have chorioretinitis. Because **hearing loss** is the most common long-term sequela associated with congenital CMV infection, the failure of an infant to pass a newborn hearing screening exam should alert caregivers to the possibility of congenital CMV infection. Hearing loss in the older infant and young child should also alert the clinician to the possibility of congenital CMV infection, because about 50% of infants with hearing loss associated with congenital CMV infection will pass an initial hearing screening exam but will exhibit hearing loss in later infancy and early childhood. Importantly, hearing loss can be progressive in infants with congenital CMV infections and late-onset hearing loss and/or progression of hearing loss can only be identified by follow-up testing of hearing in congenitally infected infants (see later). Finally, the diagnosis of congenital CMV infection must be made within the first 2-3 weeks of life, and congenital CMV infection cannot be assumed to be the cause of hearing loss in older infants without evidence of CMV infection in the newborn period.

An organized plan for follow-up is an important component of the clinical management of infants with congenital CMV infection. Because permanent sequelae are limited to disorders of the central nervous system (CNS), long-term follow-up should include appropriate assessment of development and neuromuscular function in infected infants, with referral to specialized care if necessary. This is particularly important for infected infants who present with evidence of CNS damage such as microcephaly, seizures, or obvious motor deficits. Overall, about 11% of infected infants will exhibit some degree of hearing loss; hearing loss in some infants will progress during infancy or less frequently, develop later in infancy. Thus comprehensive audiologic testing and follow-up are mandatory in these patients. Other sequelae such as vision loss are infrequent, but vision testing and comprehensive eye examinations should be included in the care plan of infants with congenital CMV infection.

Perinatal Infection

Perinatal infections can be acquired during birth or following ingestion of CMV-containing breast milk. In almost all cases perinatal infections have not been associated with clinical manifestations of the infection and have not been associated with long-term sequelae that have been described in infants with congenital CMV infections. In rare cases such as is seen in breast milk transmission of CMV to extremely premature infants or infants born to nonimmune women, perinatal infection can result in severe, disseminated infections associated with end-organ disease and death. These more severe infections are thought to develop in infants that lack transplacentally acquired antiviral antibodies, either secondary to extreme prematurity or as the product of a mother lacking anti-CMV antibodies.

DIAGNOSIS

In the nonimmunocompromised individual, diagnosis of CMV infection has required evidence of a primary or acute infection. Serologic reactivity for CMV is lifelong following primary infection; therefore the presence of immunoglobulin (Ig) G antibody to CMV does not provide evidence of acute infection unless the absence of CMV-specific IgG reactivity in a prior serum specimen can be demonstrated, thus providing evidence of IgG seroconversion. In addition, IgM reactivity for CMV can be detected for prolonged periods after acute infection and cannot be used to reliably estimate the duration of a primary infection. Furthermore, recovery of virus from body fluids such as saliva or urine does not in itself permit diagnosis of

CMV infection, because persistently infected individuals can intermittently shed virus. In contrast, in the immunocompromised host, CMV can frequently be recovered from patients in the absence of evidence of invasive CMV infection. Thus assignment of CMV as a cause of disease in immunocompromised patients must be made carefully, and other potential causes of symptoms and clinical findings in these patients must also be considered. Serologic assays are of limited value in the transplant recipient secondary to the impact of immunosuppression on antibody responses in the allograft recipient. Moreover, IgM antibodies can be produced following a nonprimary infection in these patients. Sequential viral load measurements by nucleic acid amplification testing (NAAT) such as polymerase chain reaction (PCR) in relevant body fluids such as blood and detection of CMV DNA in biopsy tissue can be of great value in establishing CMV as a cause of disease in allograft recipients because increasing viral loads can provide evidence of the lack of host control of CMV replication (Table 302.3). Detection of CMV in urine, saliva, blood, and tissue specimens obtained at biopsy can most reliably be accomplished by NAAT, and because findings can be quantified, treatment responses can be monitored. However, conventional culture of CMV using human dermal fibroblasts often combined with immunofluorescence detection of CMV-encoded immediate early antigens also remains standard in many institutions. Histopathologic studies of tissue specimens that permit detection of CMV-infected cells containing characteristic nuclear inclusions (owl's-eye inclusions) are relatively insensitive but can aid in the diagnosis of an invasive CMV infection. The addition of immunohistochemistry for the detection of CMV-encoded proteins and/or in situ hybridization for the detection of CMV nucleic acids has greatly improved the sensitivity of histologic detection of CMV in tissue and/or biopsy specimens (see Table 302.3).

In practice, in nonimmunocompromised patients the demonstration of CMV-specific IgG seroconversion or the presence of CMV-specific IgM antibodies is considered evidence of a recently acquired CMV infection. However, in the case of pregnant women the timing of a primary infection often requires a more precise estimate of when the infection was acquired because CMV infections before conception carry significantly less risk to the developing fetus than infections acquired after conception. Furthermore, as noted in previous sections, maternal infections acquired in the first and early second trimester are more frequently associated with severe intrauterine infections and result in more significant long-term sequelae in infants with congenital CMV infections. Because IgM anti-CMV antibody reactivity can persist for months depending on the sensitivity of the particular assay, the use of IgM detection to precisely time the acquisition of CMV is of limited value. However, when combined with IgG avidity assays in which CMV-specific binding antibodies are eluted with increasing concentrations of chaotropic agents such as urea, IgG serology can provide a more accurate estimate of the duration of infection. Thus the IgG avidity assay has been used almost exclusively in the management of CMV infections during pregnancy to aid in identifying primary maternal infections in women who present at the first prenatal visits with CMV-specific IgM antibodies. The presence of CMV-specific IgG antibodies with high avidity argues for an infection that occurred in the distant past, whereas low-avidity CMV-specific IgG antibodies argues for a more proximal timing of infection. The presence of anti-CMV IgG antibodies with intermediate avidity is considered uninterpretable (see Table 302.3).

Congenital Infections

The diagnosis of congenital CMV infections requires the recovery of replicating virus and/or viral nucleic acids within the first 2-3 weeks of life. Sources of virus and viral nucleic acids include urine, saliva, and blood. Methods of detection include routine virus culture combined with immunofluorescence and NAAT. Although quantification of virus in various specimens can suggest the likelihood of long-term sequelae such as hearing loss for a population of infected newborns, the predictive value for the individual patient remains limited. A considerable amount of effort has been devoted to identifying screening assays that would be suitable for populations of newborn infants. Initial interest centered on dried blood spots, because these samples are routinely collected as a component of newborn screening programs. Unfortunately, studies have indicated that the sensitivity of detection of congenitally infected infants using dried blood spots is too low to be considered

Table 302.3 Laboratory Detection of Cytomegalovirus Infection

ASSAY	APPLICATION	CHARACTERISTICS OF ASSAY
TISSUE CULTURE		
Virus isolation	Detection of virus in clinical material	Requires prolonged culture periods; low sensitivity compared with molecular techniques; expensive
HISTOPATHOLOGY		
Histopathology	Identification of CMV infected cells (owl's eye inclusions)	Routine for most laboratories; low sensitivity is improved with IHC (see below)
Viral antigen detection (immunohistochemistry)	Sensitive and allows detection of CMV-infected cells in variety of specimens	Rapid and can be quantitative
MOLECULAR METHODOLOGIES		
Nucleic acid amplification (NAAT), including quantitative PCR, transcription-mediated amplification (TMA)	Quantitation of CMV DNA and viral RNA	Rapid, sensitive, and quantitative; can be applied to variety of clinical specimens (blood, saliva, urine, biopsy specimens, etc.)
DNA/RNA in-situ hybridization	Sensitive detection of CMV DNA or RNA transcripts in tissue specimens	Technically more difficult than NAAT, long turnaround times, can identify specific cells infected with CMV
SEROLOGIC TESTING		
CMV-specific IgM serology	Screening for recent infections	Variability in duration of response and low levels of IgM antibodies decrease sensitivity and specificity
CMV-specific IgG serology	Detection of infection with HCMV, useful for seroprevalence studies	Rapid, specific, and quantitative; gold standard for CMV infection (acute and past)
CMV-specific IgG avidity	Estimate of duration of HCMV infection	Interpretation limited to high and low values of avidity; useful for timing of recent CMV infections in pregnancy; not useful in allograft recipients

useful for screening. In contrast, newborn screening using saliva has proven sensitive and specific and is used for newborn screening in many institutions. The identification of an infected infant by screening of saliva requires confirmation, preferably by assaying urine for the presence of CMV.

TREATMENT

Treatment of *immunocompromised hosts* with invasive CMV disease limits both the morbidity and the mortality in the patient with disseminated CMV infections with end-organ disease. This has been shown in allograft transplant recipients and patients with HIV/AIDS. Similarly, antiviral prophylaxis can limit the development of clinically important CMV disease in allograft recipients and is the standard of care in most transplant centers, with the remaining centers using *preemptive* treatment in which antivirals are given once a predetermined level of CMV viremia is detected during routine monitoring in the posttransplant period. Several agents are licensed for CMV infections, including ganciclovir, foscarnet, and cidofovir; all have appreciable toxicity. Letermovir is another agent that has been licensed for use in adults; it is expected that indications for this agent will extend into pediatrics in the future. The antiviral agent, maribavir, has been licensed to treat refractory CMV infections in adult transplant recipients. In some transplant centers, high-titer CMV immunoglobulins have been included as a component of prophylaxis, most commonly in heart and lung SOT recipients. Early on, when the treatment of CMV infections with antiviral agents was in its infancy, treatment with CMV immunoglobulins was shown to alter the natural history of CMV infection in renal and liver allograft recipients. However, the efficacy of antiviral agents when used as prophylaxis in the immediate posttransplant period has resulted in less frequent use of these biologics.

Treatment of **congenitally infected infants** with ganciclovir has been studied in several clinical trials, and a significant number of infected infants with symptomatic congenital CMV infections have been treated off-label with this agent. In addition, infants with severe perinatal CMV infection following breast milk ingestion with documented end-organ disease have been successfully treated with ganciclovir. Two studies have suggested that 6 weeks of intravenously administered ganciclovir or 6 months of valganciclovir, an oral preparation of ganciclovir, could limit hearing loss and possibly improve developmental outcome of infected infants followed for approximately 2 years. In contrast to the apparent efficacy of valganciclovir treatment in congenitally CMV infected infants in these studies with relatively short-term follow-up, another study reported that valganciclovir failed to provide evidence of efficacy in altering the long-term outcomes of congenitally infected infants when followed over a longer time. Currently, there are no recommendations for the treatment of infants with congenital CMV infection.

PREVENTION

Passive Immunoprophylaxis

Passive transfer of anti-CMV antibodies has been used to limit disease but not infection in allograft recipients. A similar approach has also been considered for prevention of intrauterine transmission of CMV; disease based on studies from limited observational data suggests that antiviral antibodies could limit disease following CMV infections in the perinatal period. An uncontrolled trial of human immune globulin provided provocative evidence that passive transfer of anti-CMV antibodies to pregnant women undergoing primary CMV infection could limit intrauterine transmission and disease. A second study using the same immune globulin preparation failed to demonstrate that immune globulins provided protection from intrauterine transmission or disease. Another multicenter trial sponsored by the NIH was terminated secondary to the lack of any efficacy of the treatment. It remains to be determined if passively transferred anti-CMV antibodies can modulate infection and disease following intrauterine exposure to CMV.

Active Immunoprophylaxis

Active immunization for the prevention of congenital CMV infection (and in transplant recipients) has been a goal of biomedical research for over 3 decades. A number of different vaccine platforms have been explored, including replicating attenuated CMV vaccines, protein-based vaccines, heterologous virus-vectored CMV vaccines, DNA vaccines, and mRNA-based vaccines. In all cases, some level of immunity has been induced by each of these candidate vaccines. Larger scale trials have been carried out using replication competent, attenuated CMV vaccines and adjuvanted recombinant protein vaccines. Current approaches are directed toward development of an adequately attenuated replicating CMV strain that retains sufficient immunogenicity to induce protective responses. In contrast to programs testing candidate attenuated CMV vaccines, considerable progress has been made in the testing of adjuvanted recombinant viral proteins. An adjuvanted recombinant glycoprotein B, a major protein component of the envelope and target of neutralizing antibodies, has been shown to induce virus neutralizing antibodies and $CD4^+$ T lymphocyte proliferative responses. Moreover, this vaccine reduced virus acquisition by about 50% in a trial carried out in young women. Closer examination of this particular trial revealed that protection was very short-lived and that the effectiveness of the vaccine was not convincingly demonstrated because of the small numbers of subjects in the trial, despite attaining minimal statistical significance. A follow-up trial in adolescent women using the same vaccine preparation failed to show any statistically significant difference between vaccine and placebo recipients. A major question that will face all vaccine programs is whether existing immunity in seropositive women can be augmented to a level to prevent damaging infection in their offspring. The maternal population with existing immunity to CMV before childbearing age is responsible for the vast majority of congenitally infected infants in almost all regions of the world; thus merely recapitulating naturally acquired adaptive immunity to CMV with a vaccine may not be sufficient to prevent congenital CMV infection and/or limit disease.

Counseling

Studies of the natural history of CMV have repeatedly demonstrated that transmission requires repeated close, often direct contact with infected material such as secretions from the oral or genitourinary tract. Although limited data suggest that CMV can be transmitted on fomites, infectivity can persist for hours on surfaces such as toys. Limiting exposure to such secretions and attention to hygiene such as handwashing can drastically limit acquisition of CMV. Counseling has been shown to be very effective in the prevention of CMV infection in women of childbearing age. In fact, counseling programs have been shown to be more effective in limiting CMV infection during pregnancy than any vaccine that has been tested to date. Sexual transmission is an important route of infection, because CMV is considered to be an STI. Limiting sexual transmission through education and counseling should be considered in sexually active individuals. The acquisition of CMV by hospital workers and other healthcare providers has been shown to be less than in age-matched individuals in the general public. Importantly, these early studies in healthcare workers were carried out before universal precautions that are in place in most hospitals today. Thus patient education with an emphasis on describing the sources of infectious virus in communities and attention to general hygiene could dramatically reduce community-acquired CMV, particularly in women of childbearing age.

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Chapter 303

Roseola (Human Herpesviruses 6 and 7)

Brenda L. Tesini

Human herpesvirus 6 (HHV-6A and HHV-6B) and human herpesvirus 7 (HHV-7) cause ubiquitous infection in infancy and early childhood. HHV-6B is responsible for the majority of cases of **roseola infantum** (**exanthem subitum** or **sixth disease**) and is associated with other diseases, including encephalitis, especially in immunocompromised hosts. A small percentage of children with roseola have primary infection with HHV-7.

ETIOLOGY

HHV-6A, HHV-6B, and HHV-7 are the sole members of the Roseolovirus genus in the Betaherpesvirinae subfamily of human herpesviruses. Human cytomegalovirus, the only other β-herpesvirus, shares limited sequence homology with HHV-6 and HHV-7. Morphologically all human herpesviruses are composed of an icosahedral nucleocapsid, protein-dense tegument, and lipid envelope. Within the nucleocapsid, HHV-6 and HHV-7 both contain large, linear, double-stranded DNA genomes that encode more than 80 unique proteins.

Initially, two strain groups of HHV-6 were recognized: HHV-6 variant A and HHV-6 variant B. Despite sharing highly conserved genomes with approximately 90% sequence identity, the two variants could be distinguished by restriction fragment length polymorphisms, reactivity with monoclonal antibodies, differential cell tropism, and epidemiology. Because of these differences, the two were reclassified as separate species in the genus Roseolovirus by the International Committee on the Taxonomy of Viruses in 2012. HHV-6A detection is quite rare, and HHV-6B is the overwhelmingly predominant virus found in both immunocompetent and immunocompromised hosts. Previous reports of HHV-6A detection in children in Africa have not been substantiated in a large cohort using a more specific PCR target.

EPIDEMIOLOGY

Primary infection with HHV-6B is acquired rapidly by essentially all children after the loss of maternal antibodies in the first few months of infancy, with 95% of children being infected by 2 years of age. The peak age of primary HHV-6B infection is 6-9 months of life, with infections occurring sporadically and without seasonal predilection or contact with other ill individuals. Infection with HHV-7 is also widespread but occurs later in childhood and at a slower rate; only 50% of children have evidence of prior infection with HHV-7 by 3 years of age. Seroprevalence reaches 75% by 6 years of age. In a small study of children with primary HHV-7 infection, the mean age of the patients was 26 months, significantly older than that of children with primary HHV-6 infection.

Preliminary data suggest that the majority of children acquire primary infection with HHV-6 from the saliva or respiratory droplets of asymptomatic adults or older children. However, congenital infection with HHV-6 occurs in 1% of newborns. Two mechanisms of vertical transmission of HHV-6 have been identified: transplacental infection and chromosomal integration. HHV-6 is unique among the human herpesviruses in that it is integrated at the telomere end of human chromosomes at a frequency of 0.2–2.2% of the population and is passed from parent to child via the germline. Chromosomal integration of HHV-7 has been suggested in only a single case report thus far. Chromosomal integration has been identified as the major mechanism by which HHV-6 is vertically transmitted, accounting for 86% of congenital infections, with one third resulting from HHV-6A, a percentage much higher than in primary infection in the United States. The clinical consequences of chromosomal integration or transplacental infection with HHV-6 have yet to be determined. In one series of infants identified with HHV-6 congenital infection, no evidence of disease was present in the early neonatal period. However, reactivation of chromosomally integrated HHV-6 virus has been demonstrated following hematopoietic stem cell transplantation (HSCT). Primary infection with HHV-7 is presumed to be spread by the saliva of asymptomatic individuals. DNA of both HHV-6 and HHV-7 has been identified in the cervical secretions of pregnant women, suggesting an additional role for sexual or perinatal transmission of these viruses. Breast milk does not appear to play a role in transmission of either HHV-6 or HHV-7.

PATHOLOGY AND PATHOGENESIS

Primary HHV-6B infection causes a viremia that can be demonstrated by co-culture of the patient's peripheral blood mononuclear cells with mitogen-stimulated cord blood mononuclear cells. HHV-6 has a recognizable cytopathic effect, consisting of the appearance of large refractile mononucleated or multinucleated cells with intracytoplasmic and/or intranuclear inclusions. Infected cells exhibit a slightly prolonged life span in culture; however, lytic infection predominates. HHV-6 infection also induces apoptosis of T cells. In vitro, HHV-6 can infect a broad range of cell types, including primary T cells, monocytes, natural killer cells, dendritic cells, and astrocytes. HHV-6 has also been documented to infect B-cell, megakaryocytic, endothelial, and epithelial cell lines. Human astrocytes, oligodendrocytes, and microglia have been infected with HHV-6 ex vivo. The broad tropism of HHV-6 is consistent with the recognition that CD46, present on the surface of all nucleated cells, is a cellular receptor for HHV-6, HHV-6A in particular. CD134, a member of the TNFR superfamily, is the main entry receptor for HHV-6B and may explain some of the differences in tissue tropism noted between HHV-6A and HHV-6B. The CD4 molecule has been identified as a receptor for HHV-7. HHV-7 has been demonstrated to reactivate HHV-6 from latency in vitro, but whether this phenomenon occurs in vivo is not clear.

Primary infection with HHV-6 and HHV-7 is followed by **lifelong latency** or persistence of virus at multiple sites. HHV-6 exists in a true state of viral latency in monocytes and macrophages. The detection of replicating HHV-6 in cultures of primary $CD34^+$ hematopoietic stem cells has also been described, suggesting that cellular differentiation is a trigger of viral reactivation. This observation is clinically significant because HHV-6 may cause either primary or reactivated infection during HSCT. Additionally, HHV-6 and HHV-7 infection may be persistent in salivary glands, and DNA of both HHV-6 and HHV-7 can be routinely detected in the saliva of both adults and children. HHV-7 can also be isolated in tissue culture from saliva, but HHV-6 cannot. HHV-6 DNA has been identified in the cerebrospinal fluid (CSF) of children, both during and subsequent to primary infection, as well as in brain tissue from immunocompetent adults at autopsy, implicating the central nervous system (CNS) as an additional important site of either viral latency or persistence. HHV-7 DNA has also been found in adult brain tissue but at a significantly lower frequency.

CLINICAL MANIFESTATIONS

Roseola infantum (**exanthem subitum**, or **sixth disease**) is an acute, self-limited disease of infancy and early childhood. It is characterized by the abrupt onset of high fever, which may be accompanied by fussiness. The fever usually resolves acutely after 72 hours (crisis) but may gradually fade over a day (lysis) coincident with the appearance of a faint pink or rose-colored, nonpruritic, 2- to 3-mm morbilliform rash on the trunk (Fig. 303.1). The rash usually lasts 1-3 days but is often described as evanescent and may be visible only for hours, spreading from the trunk to the face and extremities. Because the rash is variable in appearance, location, and duration, it is not distinctive and may be missed. Associated signs are few but can include mild injection of the pharynx, palpebral conjunctivae, or tympanic membranes and

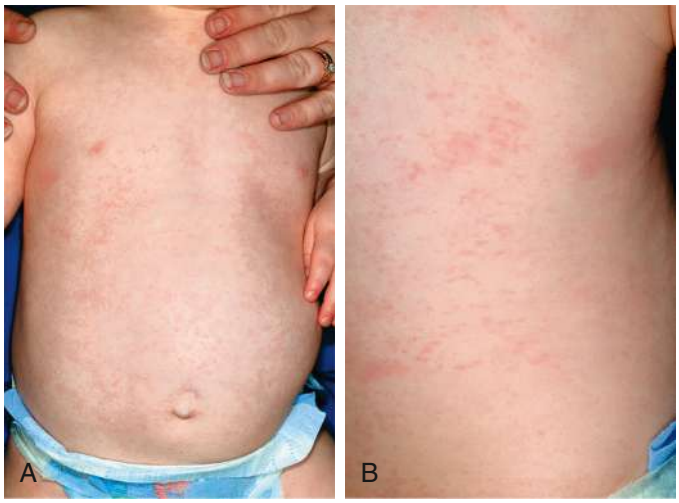

Fig. 303.1 Roseola infantum. **A,** Erythematous, blanching macules and papules in an infant who had high fever for 3 days preceding development of the rash. **B,** On closer inspection some lesions reveal a subtle peripheral halo of vasoconstriction. *(From Paller AS, Mancinin AJ, eds. Hurwitz Clinical Pediatric Dermatology, 3rd ed. Philadelphia: Elsevier; 2006: p. 434)*

enlarged suboccipital nodes. In Asian countries, ulcers at the uvulopalatoglossal junction **(Nagayama spots)** are commonly reported in infants with roseola.

High fever (mean: 39.7°C [103.5°F]) is the most consistent finding associated with primary HHV-6B infection. Rash detected either during the illness or following defervescence has been reported in approximately 20% of infected children in the United States. Additional symptoms and signs include irritability, inflamed tympanic membranes, rhinorrhea and congestion, gastrointestinal complaints, and encephalopathy. Symptoms of lower respiratory tract involvement such as cough are identified significantly less frequently in children with primary HHV-6B infection than in children with other febrile illnesses. The mean duration of illness caused by primary HHV-6B infection is 6 days, with 15% of children having fever for 6 or more days. Primary infection with HHV-6B accounts for a significant burden of illness on the healthcare system; one study found that 24% of visits to emergency departments by infants between 6 and 9 months of age were because of primary HHV-6B infection. A population-based study of primary HHV-6B infection confirmed that 93% of infants had symptoms and were more likely to visit a physician than noninfected infants. Fever was less likely to be present with HHV-6B infection in children younger than 6 months of age but was significantly more common in older infants and children.

Much less is known about the clinical manifestations of HHV-7 infection. Primary infection with HHV-7 has been identified in a small number of children with roseola in whom the illness is indistinguishable from that caused by HHV-6B. Secondary cases of roseola caused by infection with HHV-7 have also been reported. Additionally, primary infection with HHV-7 may be asymptomatic or may cause a nonspecific febrile illness lasting approximately 3 days.

LABORATORY FINDINGS

The most characteristic laboratory findings noted in children with primary HHV-6B infection are lower mean numbers of total white blood cells (8,900/μL), lymphocytes (3,400/μL), and neutrophils (4,500/μL) than in febrile children without primary HHV-6B infection. Similar hematologic findings have been reported during primary infection with HHV-7. Thrombocytopenia, elevated serum transaminase values, and atypical lymphocytes have also been noted sporadically in children with primary HHV-6B infection.

Results of CSF analyses reported in patients with encephalitis thought to be caused by HHV-6 have been normal or demonstrated only minimal CSF pleocytosis with mild elevations of protein, especially early in the course of the disease, which may progress with time. Areas of hyperintense signal on T2 weighted and fluid attenuation inversion recovery images of the hippocampus, uncus, and amygdala have been found on MRI, and increased metabolism within the hippocampus has been observed on positron emission tomography scanning.

DIAGNOSIS

Although roseola is generally a benign self-limited disease, its diagnosis can exclude other, more serious disorders that cause fever and rash. A history of 3 days of high fever in an otherwise nontoxic 10-month-old infant with a blanching maculopapular rash on the trunk suggests a diagnosis of roseola. **A specific diagnosis of HHV-6 is not usually necessary except in situations in which the manifestations of the infection are severe or unusual and might benefit from antiviral therapy.**

The diagnosis of primary infection with either HHV-6 or HHV-7 is confirmed by demonstrating the presence of actively replicating virus in the patient's blood sample coupled with seroconversion. Viral culture is the gold standard method to document active viral replication. Unfortunately, culture is expensive, time consuming, and available only in research laboratories. Two other methods used to identify active HHV-6 replication are the detection of viral DNA by PCR on acellular fluids such as plasma or reverse transcriptase PCR on peripheral blood mononuclear cell samples designed to detect viral transcription and protein production. Quantitative PCR for HHV-6 genome copy numbers on various specimens is also frequently reported and is commercially available. However, the role of this methodology is not clear, as a specific value of DNA that can discriminate between patients with viremia and those who are culture negative has not been determined. Complicating the use of molecular assays for the detection of active replication of HHV-6 is the recognition that individuals with chromosomally integrated HHV-6 have persistent HHV-6 DNA in plasma, peripheral blood mononuclear cells, and CSF in the absence of disease and replicating virus.

Serologic methods such as indirect immunofluorescence assays, enzyme-linked immunosorbent assays, neutralization assays, and immunoblot have been described for the measurement of concentrations of antibodies to HHV-6 and HHV-7 in serum or plasma and are commercially available. Although immunoglobulin M antibody is produced early in infection with HHV-6, assays designed to measure this response have not proved useful in the diagnosis of primary or reactivated infection. The absence of immunoglobulin G antibody in an infant older than 6 months of age combined with the presence of replicating virus is strong evidence of primary infection with either HHV-6 or HHV-7. Alternatively, the demonstration of seroconversion between acute and convalescent samples also confirms primary infection but is not clinically useful in the acute care setting. Unfortunately, serologic assays have not been found reliable in the detection of HHV-6 reactivation and cannot be used to differentiate between infection with HHV-6A and infection with HHV-6B. Additionally, limited antibody cross-reactivity has been demonstrated between HHV-6 and HHV-7, complicating the interpretation of serologic assays, especially if low titers are reported.

Differential Diagnosis

Primary infection with either HHV-6B or HHV-7 usually causes an undifferentiated febrile illness that may be very difficult to distinguish from other common viral infections of childhood. This difficulty also applies to the early stages of roseola, before the development of rash. Once the rash is present, roseola may be confused with other exanthematous diseases of childhood, especially measles and rubella. Children with **rubella** often have a prodrome characterized by mild illness with low-grade fever, sore throat, arthralgia,

and gastrointestinal complaints, unlike those with roseola. On physical examination, suboccipital and posterior auricular lymph nodes are prominent up to 1 week before the rash of rubella is evident and persist during the exanthematous phase. Additionally, the rash of rubella usually begins on the face and spreads to the chest, like that in measles. The associated symptoms of **measles** virus infection include cough, coryza, and conjunctivitis, with high fever coincident with the development of rash, unlike in roseola. Roseola may also be confused with scarlet fever, though the latter is rare in children younger than 2 years of age and causes a characteristic sandpaper-like rash concurrent with fever.

Roseola may be confused with illness caused by **enterovirus infections**, especially in the summer and fall months. Drug hypersensitivity reactions may also be difficult to distinguish from roseola. Antibiotics are frequently prescribed for children with fever from roseola before the appearance of rash. A child who then demonstrates rash after the resolution of fever may erroneously be labeled as being drug allergic.

COMPLICATIONS

Convulsions are the most common complication of roseola and are recognized in up to one third of patients. Seizures are also the most common complication of children with documented primary HHV-6B infection, occurring in approximately 15%, with a peak age of 12-15 months. Children with primary HHV-6B infection are also reported to have a higher frequency of partial seizures, prolonged seizures, postictal paralysis, and repeated seizures than are children with febrile seizures not associated with HHV-6. In a study limited to children with primary HHV-6B infection and seizures, 30% of patients had prolonged seizures, 29% had focal seizures, and 38% had repeated seizures. A prospective study of children 2-35 months of age with suspected encephalitis or severe febrile illness with convulsions found that 17% had primary infection with either HHV-6 or HHV-7, and status epilepticus was the most common presentation. Among children with febrile status epilepticus (FSE), primary or reactivated infection with HHV-6B or HHV-7 has been identified in approximately one third.

An association between recurrent seizures and reactivated or persistent infection of the CNS by HHV-6 has also been suggested. Studies evaluating brain tissue specimens implicate HHV-6 in as many as 60% of patients with temporal lobe epilepsy (TLE), high viral loads being found in the hippocampus or lateral temporal lobe regions. HHV-6 is postulated to induce neuroinflammation and potential injury via innate and adaptive immune system activation as a result of the broad tissue tropism of the virus. Subsequent neuronal hyperexcitability through the loss of glutamate regulatory control and increased blood-brain barrier permeability have been proposed as possible mechanisms for the development of recurrent seizures based on animal models and clinical data of patients with TLE and HHV-6 DNA detected in CNS specimens. Contrary to these findings, limited clinical data suggest that there may be a decreased risk of recurrent seizures after primary infection with HHV-6 and febrile seizures than of febrile seizures from other causes. Additionally, children with FSE associated with HHV-6B and HHV-7 had similar seizure characteristics and a similar proportion of electroencephalography and MRI hippocampal abnormalities as children with FSE not associated with HHV-6B or HHV-7, suggesting a shared pathogenesis to other etiologies of FSE.

Case reports and small-patient series have described additional complications in children with primary HHV-6B infection, including encephalitis, acute disseminated demyelination, autoimmune encephalitis, acute cerebellitis, hepatitis, and myocarditis. Late-developing long-term sequelae, including developmental disabilities and autistic-like features, are reported rarely in children who have CNS symptoms during primary HHV-6B infection.

Reactivation of HHV-6 has been reported in several different populations with and without disease with the use of various methods of detection. The best documentation of HHV-6 reactivation has been in immunocompromised hosts, especially those patients who have undergone HSCT. Such reactivation occurs in approximately 50% of patients, typically at 2-4 weeks after transplantation, and the risk of reactivation is associated with a lack of donor-derived HHV-6–specific T-cell immunity. Many of the clinical complications seen following HSCT have been associated with HHV-6B reactivation, including fever, rash, delayed engraftment of platelets or monocytes, and graft-versus-host disease, with variable degrees of support in the literature for each. HHV-6 reactivation has been associated with worse overall survival compared with HSCT recipients who did not experience reactivation.

HHV-6B reactivation has also been reported as a cause of encephalitis in both immunocompetent and immunocompromised hosts. A distinct syndrome of **posttransplant acute limbic encephalitis (PALE)** has been described primarily in patients following HSCT, especially cord blood stem cell transplantation; it is characterized by short-term memory dysfunction, confusion, and insomnia, with seizures noted either clinically or on prolonged electroencephalography monitoring. HHV-6B DNA has been identified in the CSF in the majority of these patients, with additional evidence of reactivation by detection of HHV-6B DNA in plasma. HHV-6 proteins were identified in the astrocytes of the hippocampus in one postmortem specimen, consistent with active HHV-6B infection at the time of death. The development of PALE is associated with increased mortality and long-term neurocognitive sequelae.

TREATMENT

Supportive care is usually all that is needed for infants with roseola. Parents should be advised to maintain hydration and may use antipyretics if the child is especially uncomfortable with the fever. Specific antiviral therapy is not recommended for routine cases of primary HHV-6B or HHV-7 infection. Unusual or severe manifestations of primary or presumed reactivated HHV-6B infection such as encephalitis/PALE, especially in immunocompromised patients, may benefit from treatment. Ganciclovir, foscarnet, and cidofovir all demonstrate inhibitory activity against HHV-6 in vitro, similar to their activity against cytomegalovirus. Case reports suggest that all three drugs, alone or in combination, can decrease HHV-6 viral replication, as evidenced by decreased viral loads in plasma and CSF. However, clinical data regarding efficacy are sparse and contradictory, with no randomized trials to guide use. Additionally, in vitro resistance of HHV-6 to all three drugs has been described. Despite these drawbacks, treatment with ganciclovir or foscarnet as first-line agents has been recommended for a minimum of 3 weeks in patients with PALE. Foscarnet appears to be most likely to have activity against HHV-7 on the basis of in vitro testing, but no clinical data are available.

PROGNOSIS

Roseola is generally a self-limited illness associated with complete recovery. The majority of children with primary infections with HHV-6B and HHV-7 also recover uneventfully without sequelae. Although seizures are a common complication of primary infection with HHV-6B and HHV-7, the risk of recurrent seizures does not appear to be higher than that associated with other causes of simple febrile seizures.

PREVENTION

Primary infections with HHV-6 and HHV-7 are widespread throughout the human population with no current means of interrupting transmission.

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Chapter 304

Human Herpesvirus 8

Brenda L. Tesini

Human herpesvirus 8 (HHV-8) is an oncogenic virus identified in tissue specimens from patients with Kaposi sarcoma (KS). Because of this association, it is also known as **Kaposi sarcoma–associated herpesvirus**. HHV-8 is the etiologic agent of two additional lymphoproliferative disorders: **primary effusion–based lymphoma (PEL)** and **multicentric Castleman disease (MCD)**.

ETIOLOGY

HHV-8 is a γ_2-human herpesvirus similar to Epstein-Barr virus. The virus contains a large DNA genome encoding 85-95 unique proteins. Infection is followed by both lytic and latent viral states, with different degrees of viral replication associated with distinct disease manifestations.

EPIDEMIOLOGY

The prevalence of infection with HHV-8 varies both geographically and by population and roughly matches the epidemiology of KS. HHV-8 infection is endemic in Africa and parts of South America, with infection rates of up to 30–60% by adolescence. Seroprevalence >20% has also been found in regions bordering the Mediterranean. In contrast, infection rates <5% are noted in North America, Central Europe, and Asia. However, within geographic regions, the prevalence of infection varies with risk behaviors, with rates of 30–75% being found among men who have sex with men in North America and Europe. HHV-8 DNA can be detected in saliva, blood, semen, and tissues. Based on large-scale epidemiologic studies and the high prevalence of viral shedding in oral secretions, saliva is believed to be the major mode of transmission. Other less common routes of HHV-8 transmission include blood transfusion, bone marrow transplantation, and solid organ transplantation. Vertical transmission and transmission via breast milk may occur in regions where HHV-8 is highly endemic, but the risk appears low.

PATHOLOGY AND PATHOGENESIS

HHV-8 contains multiple genes that affect cell-cycle regulation and the host immune response. Viral proteins interfere with the function of the tumor suppressor molecules, induce the expression of proangiogenesis factors, and lead to upregulation of the rapamycin pathway target, which is instrumental in the control of cell growth and metabolism. HHV-8 also encodes a homolog of human interleukin-6, which can bind and activate cytokine receptors and serve as a host cell autocrine growth factor. Additionally, viral proteins are associated with the constitutive expression of the transcription factor nuclear factor-κB. All of these proteins may be potential targets for therapeutic intervention.

CLINICAL MANIFESTATIONS

Although subclinical infection appears to be common, symptomatic primary HHV-8 infection has been described in immunocompetent children. Patients commonly have fever and a maculopapular rash or a mononucleosis-like syndrome, with full recovery the rule. In immunocompromised patients, primary infection has been associated with fever, rash, splenomegaly, pancytopenia, and lymphoid hyperplasia and may be quite severe. Additionally, preliminary data suggest that transfusion-associated primary infection with HHV-8 is associated with an increased risk of mortality.

Even in regions with high rates of seroprevalence, the development of KS is uncommon. KS has several different clinical forms; each includes multifocal, angiogenic lesions arising from vascular endothelial cells infected with HHV-8. Classic KS is an indolent disorder seen in elderly men with limited involvement of the skin of the lower extremities. Endemic KS is more aggressive, occurring in children and young people, primarily in Africa, and can include visceral involvement as well as widespread cutaneous lesions (patches, plaques, or nodules). Posttransplantation KS and AIDS-related KS are the most severe forms, with disseminated lesions, often in the gastrointestinal tract and lungs, with or without cutaneous findings.

Primary effusion–based lymphoma is a rare disease caused by HHV-8 that is seen most commonly in HIV-infected individuals. It consists of lymphomatous invasion of the serosal surfaces of the pleura, pericardium, and peritoneum. Similarly, **multicentric Castleman disease** is an unusual lymphoproliferative disorder characterized by anemia, thrombocytopenia, generalized lymphadenopathy, and constitutional symptoms and is frequently associated with HHV-8 infection and a high degree of viral replication.

DIAGNOSIS

Serologic assays, including immunofluorescence and enzyme-linked immunosorbent assays, are the primary methods of diagnosing infection with HHV-8. However, testing has limited sensitivity, specificity, and reproducibility and is primarily a research tool with no universally recognized standard assays. Additionally, the loss of antibodies over time, referred to as *seroreversion,* has been described, further complicating serodiagnosis. Immunohistochemistry and molecular methods are available for the detection of HHV-8 in tissue samples and are used in the diagnosis of KS, PEL, and MCD, alongside their disease-specific clinical manifestations. Nucleic acid testing of blood and other body fluids is also available but has a limited diagnostic role.

TREATMENT

Treatment for KS, PEL, and MCD is multifaceted and includes attempts to control malignant proliferations with traditional chemotherapeutic regimens and biologic agents as well as agents aimed at specific cellular pathways targeted by HHV-8 proteins. Combined antiretroviral therapy (ART) is a mainstay of both prevention and therapy for HHV-8–related disease in HIV-infected patients. In HIV-associated KS, treatment with ART alone is often used for the control of mild (i.e., cutaneous) disease, whereas ART plus chemotherapy is used for more severe disease. In transplantation-associated KS, the first line of treatment includes decreasing immunosuppression, often in association with a switch from calcineurin inhibitors to sirolimus (rapamycin) to block the mammalian target of rapamycin pathway. Severe disease frequently requires the use of traditional chemotherapy as well. The role of specific antiherpesvirus antiviral treatment is unclear. Valganciclovir and ganciclovir treatment have been associated with decreased viral replication and rates of development of KS in HIV-infected individuals. However, results of using antivirals in the treatment of established disease have been generally disappointing. The prognosis for PEL tends to be poor despite the use of traditional chemotherapy, whereas rituximab (anti-CD20)–based therapy has been highly successful for MCD treatment. However, relapse and the development of lymphoma after treatment can still occur. Rituximab treatment may also worsen concurrent KS without additional agents.

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Chapter 305

Influenza Viruses

Flor M. Munoz

Influenza viral infections cause a broad array of respiratory illnesses that are responsible for significant morbidity and mortality in children during **seasonal epidemics**. Influenza A viruses also have the potential to cause **global pandemics**, which can happen when a **new (novel) influenza A virus** emerges and transmits efficiently from person to person.

ETIOLOGY

Influenza viruses are large, single-stranded RNA viruses belonging to the family Orthomyxoviridae, which includes three genera (or types): A, B, and C. Influenza A and B viruses are the primary human pathogens causing seasonal epidemics, whereas influenza virus type C is a sporadic cause of predominantly mild upper respiratory tract illness. Influenza A viruses are further divided into subtypes based on two surface proteins that project as spikes from the lipid envelope, the hemagglutinin (HA) and neuraminidase (NA) proteins (Fig. 305.1). Strain variants are identified by antigenic differences in their HA and NA and are designated by the geographic area from which they were originally isolated, isolate number, and year of isolation—for example, influenza A/Victoria/361/2011(H3N2). The HA and NA antigens from influenza B and C viruses do not receive subtype designations, because there is less variation among influenza B and C antigens. However, influenza B viruses can be further broken down into lineages, with recent examples including the B/Yamagata and B/Victoria lineages.

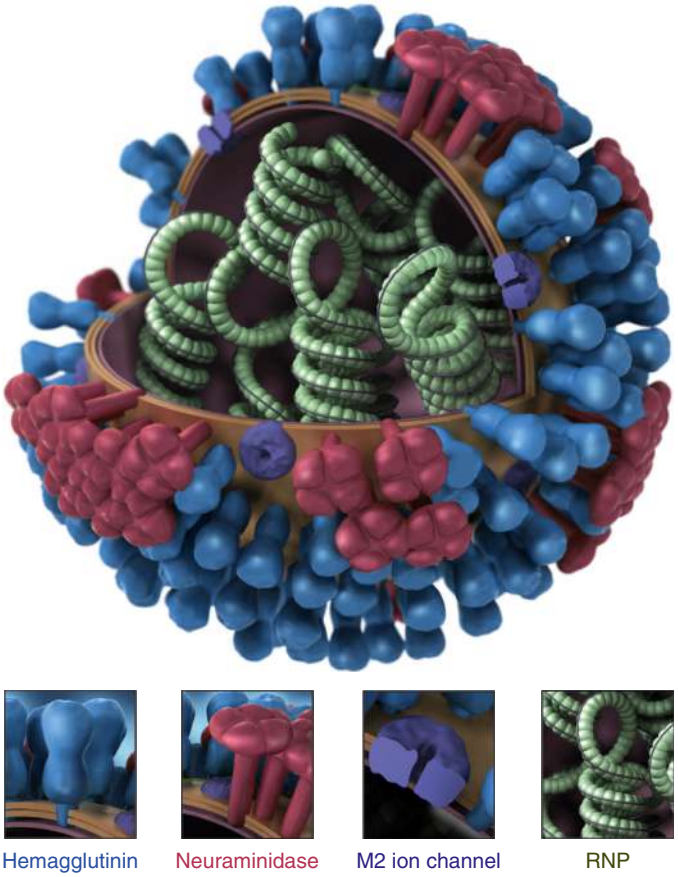

Fig. 305.1 Graphical representation of influenza virus. The key at bottom identifies the surface protein constituents: the hemagglutinin, neuraminidase, matrix protein 2 *(M2)* ion channel, and ribonucleoprotein *(RNP)*. *(From Centers for Disease Control and Prevention Public Health Image Library, Image ID#11822. https://phil.cdc.gov/Details.aspx?pid=11822; courtesy CDC/Douglas Jordan and Dan Higgins, 2009.)*

EPIDEMIOLOGY

Influenza has generally been thought to be transmitted primarily via respiratory droplets, but transmission through contact with secretions and small-particle aerosols may also occur. The typical incubation period ranges from 1 to 4 days, with an average of 2 days. Healthy adults are generally considered potentially infectious from a day before symptoms develop until 5-7 days after becoming ill. Children with primary influenza infection have higher influenza viral loads and more prolonged viral shedding than adults; therefore children may be able to infect others for a longer time. Influenza outbreaks occur commonly in schools and childcare settings. Healthcare-associated influenza infections can also occur in healthcare settings, and outbreaks in long-term care facilities and hospitals may cause significant morbidity.

In the United States, seasonal influenza viruses can be detected year-round, but circulating viruses are most common during the fall and winter. Transmission through a community is rapid, with the highest incidence of illness occurring within 2-3 weeks of introduction.

Antigenic Variation

Influenza A and B viruses contain a genome consisting of 8 single-stranded RNA segments. Minor changes within a subtype continually occur through point mutations during viral replication, particularly in the HA gene, and result in new influenza strains of the same HA type. This phenomenon, termed **antigenic drift**, occurs in both influenza A and B viruses. Variation in antigenic composition of influenza virus surface proteins occurs almost yearly, which confers a selective advantage to a new strain and contributes to annual epidemics. For this reason, the formulation of the influenza vaccine is reviewed each year and updated as needed.

Less frequent but more dramatic major changes in virus subtype can occur, resulting in a new influenza A subtype to which most people have little to no immunity. This process is called *antigenic shift* and can occur through reassortment of viral gene segments when there is simultaneous infection by more than one strain of influenza in a single host, or by direct adaptation of an animal virus to a human host. Antigenic shift occurs in influenza A viruses, which have multiple avian and mammalian hosts acting as reservoirs for diverse strains.

Through the process of **reassortment**, potentially any of 18 HA and 11 NA proteins currently known to reside in influenza A viruses of nonhuman hosts could be introduced into humans, who may have little existing immunologic cross protection to emerging viruses. A global pandemic can result if an influenza A virus with a novel HA or NA enters a nonimmune human population and acquires the capacity for sustained and efficient transmission between people. Four major **global pandemics** have occurred since 1900: in 1918 caused by an influenza A(H1N1) virus, 1957 caused by an influenza A(H2N2) virus, 1968 caused by an influenza A(H3N2) virus, and 2009 caused by an influenza A virus designated A(H1N1)pdm09. The most severe influenza pandemic in recorded history occurred in 1918, when the virus was estimated to have killed at least 50 million people. The 1918 pandemic virus was likely the result of direct adaptation of an avian influenza virus to the human host, rather than from reassortment. The 2009 pandemic virus stemmed from reassortment of genes from swine, avian, and human viruses (Fig. 305.2). This resulted in the emergence of a novel influenza A(H1N1)pdm09 virus that spread quickly from North America across the globe and replaced the previously circulating seasonal H1N1 viruses.

Several novel influenza viruses, all originating in animals, have also caused outbreaks of human infections. Avian influenza A(H5N1), a virulent avian influenza virus that was first identified in 1997, has caused more than 880 documented cases in 19 countries, with a mortality rate over 50%. A novel avian influenza A(H5N6) with a case fatality rate of >40%, emerged in China in 2014, causing infection in at least

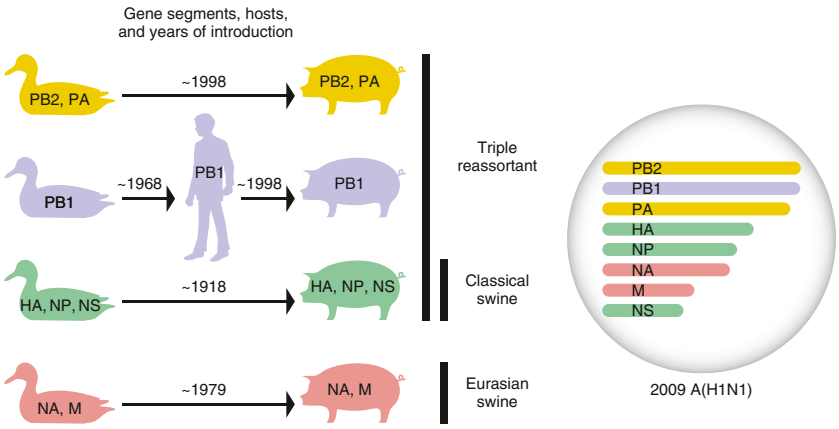

Fig. 305.2 Host and lineage origins for the gene segments of the 2009 A(H1N1) virus. HA, Hemagglutinin; M, matrix gene; NA, neuraminidase; NP, nucleoprotein; NS, nonstructural gene; PA, polymerase acidic; PB1, polymerase basic 1; PB2, polymerase basic 2. Color of gene segment in circle indicates host. *(From Garten RJ, Davis CT, Russell CA, et al. Antigenic and genetic characteristics of swine-origin 2009 A(H1N1) influenza viruses circulating in humans. Science. 2009;325[5937]:197–201.)*

Table 305.1 Subtypes of Novel Influenza A Viruses and Clinical Syndromes in Human Infections

	LPAI VIRUSES	HPAI VIRUSES	VARIANT VIRUSES*
Conjunctivitis	H7N2, H7N3, H7N7, H10N7	H7N3, H7N7	H1N1v, H3N2v
Upper respiratory tract illness	H6N1, H7N2, H7N3, H7N9, H9N2, H10N7	H5N1, H5N6, H7N7	H1N1v, H1N2v, H3N2v
Lower respiratory tract disease, pneumonia	H7N2, H7N9, H9N2, H10N8	H5N1, H5N6, H7N7, H7N9	H1N1v, H3N2v
Respiratory failure, acute respiratory distress syndrome	H7N9, H10N8	H5N1, H5N6, H7N7, H7N9	H1N1v, H3N2v
Multiorgan failure	H7N9, H10N8	H5N1, H5N6, H7N7, H7N9	—
Encephalopathy or encephalitis	H7N9	H5N1	—
Fatal outcomes†	H7N9, H9N2, H10N8	H5N1, H5N6, H7N7, H7N9	H1N1v, H3N2v

*Variant viruses of swine origin.
†High mortality in reported cases: about 40% for LPAI H7N9, about 50% for HPAI H5N1, and about 70% for HPAI H5N6.
HPAI, Highly pathogenic avian influenza; LPAI, low-pathogenic avian influenza.
From Uyeki TM, Katz JM, Jernigan DB. Novel influenza A viruses and pandemic threats. *Lancet.* 2017;389:2172–2174.

60 people. Another avian influenza, A(H7N9) virus, has caused more than 1,500 documented cases and is also highly virulent. This virus first caused an outbreak of human infections in China during the spring of 2013, with annual epidemics in China occurring in subsequent years. During the first four yearly epidemics, infection was fatal in approximately 40% of documented cases.

In addition, novel influenza A variant viruses have caused human infections (Table 305.1). These include H3N2v viruses, which caused 372 confirmed human infections in the United States from 2011 to 2016 and were primarily transmitted through swine contact at agricultural fairs. Influenza viruses that normally circulate in swine are designated variant ("v") viruses when detected in humans, and H3N2v and other variant viruses, including H1N1v and H1N2v, continue to be detected and sporadically infect humans with prolonged exposure to infected pigs. In contrast to avian influenza A(H5N1), A(H5N6), and A(H7N9) viruses, variant viruses generally cause mild illness and have been primarily detected in children. However, none of these viruses has exhibited sustained, efficient human-to-human transmission.

Seasonal Influenza

An estimated 11,000-45,000 children younger than 18 years of age are hospitalized annually in the United States as a result of seasonal influenza-associated complications, with approximately 6,000-26,000 hospitalizations in children younger than 5 years of age. Since 2004, the annual number of reported influenza-associated pediatric deaths in the United States has ranged from 37 to 199 during regular influenza seasons (358 were reported to have occurred during the 2009 H1N1 pandemic). Influenza disproportionately affects children with specific chronic conditions, such as underlying pulmonary, cardiac, or neurologic and neuromuscular disorders. Very young children, especially those younger than 2 years of age, and children with chronic medical conditions are more likely to develop severe influenza-related complications, including viral and bacterial pneumonia, hospitalization, respiratory failure, and death. However, although children with underlying medical conditions are at higher risk of complications, many healthy children are hospitalized with influenza, and nearly half of pediatric influenza-associated deaths are in children that have no known underlying medical condition.

Influenza also causes a substantial burden of disease in outpatient settings. It contributes to an estimated 600,000 to 2,500,000 outpatient medical visits annually in children younger than 5 years of age and has been identified in 10–25% of outpatient visits among all children with respiratory symptoms during influenza season. Influenza may also be underdiagnosed. Many who seek medical care for influenza do not have laboratory testing performed and do not receive a diagnosis of influenza. Every year, three or four influenza virus types or subtypes typically co-circulate, including influenza A(H3N2), influenza A(H1N1), and two types of B viruses. Although one subtype usually predominates in any given season, it is difficult to predict which will be predominant. Thus the influenza vaccine varies annually and contains three or four antigens representing the expected circulating types.

PATHOGENESIS

Influenza viruses infect the respiratory tract epithelium, primarily the ciliated columnar epithelial cells, by using the HA to attach to sialic acid residues. After viral entry into cells, virus replication occurs usually within 4-6 hours, and new virus particles are assembled and released to infect neighboring cells. With primary infection, virus replication continues for 10-14 days. Influenza virus causes a lytic infection of the respiratory epithelium with loss of ciliary function, decreased mucus

production, and desquamation of the epithelial layer. These changes permit secondary bacterial invasion, either directly through the epithelium or, in the case of the middle ear space, through obstruction of the normal drainage through the eustachian tube.

The exact immune mechanisms involved in termination of primary infection and protection against reinfection are complex. Induction of cytokines that inhibit viral replication, such as interferon and tumor necrosis factor, as well as other host defenses, such as cell-mediated immune responses and local and humoral antibody defenses, all likely play a role. Secretory immunoglobulin A antibodies produced by the respiratory mucosa are thought to be an effective and immediate response generated during influenza infection. Serum antibody levels inhibiting HA activity can usually be detected by the second week after infection. These antibodies are also generated by vaccines, and high HA inhibition antibody titers correlate with protection.

CLINICAL MANIFESTATIONS

The onset of influenza illness is *often abrupt,* with a predominance of systemic symptoms, including fever, myalgias, chills, headache, malaise, and anorexia. Coryza, pharyngitis, and dry cough are also usually present at the onset of illness but may be less prominent than systemic symptoms. Respiratory manifestations can include isolated upper respiratory tract illness, including croup, or progression to lower tract disease, such as bronchiolitis or pneumonia. More than other respiratory viruses, influenza virus typically causes systemic manifestations such as high temperature, myalgia, malaise, and headache. Less common clinical manifestations can include parotitis and rash.

Abdominal pain, vomiting, and diarrhea may also occur in children; in some studies, diarrhea was reported to be more often associated with influenza A(H1N1)pdm09 compared with influenza A(H3N2) or influenza B viruses. Influenza is a less distinct illness in younger children and infants. The infected young infant or child may be highly febrile and toxic in appearance, prompting a full diagnostic workup. The typical duration of the febrile illness is 2-4 days. Cough may persist for longer periods, and evidence of small airway dysfunction is often found weeks later. Owing to the high transmissibility of influenza, other family members or close contacts of an infected person often experience a similar illness.

COMPLICATIONS

Otitis media and pneumonia are common complications of influenza in young children. Acute otitis media may be seen in up to 25% of cases of documented influenza. Pneumonia accompanying influenza may be a primary viral process or a secondary bacterial infection (such as with *Staphylococcus aureus*) facilitated through damaged respiratory epithelium. Influenza may cause acute myositis or rhabdomyolysis marked by muscle weakness and pain, particularly in the calf muscles, and myoglobinuria. Other extrapulmonary complications include acute renal failure, myocarditis, and sepsis. Central nervous system complications, such as encephalitis, myelitis, and Guillain-Barré syndrome, can occur and are seen more commonly in children than adults. Although it has essentially disappeared in the United States, Reye syndrome can result with the use of salicylates during influenza infection (see Chapter 409). Bacterial co-infection may also exacerbate respiratory complications of influenza and lead to sepsis, bacteremia, toxic shock syndrome, and other manifestations.

Influenza is particularly severe in some children, including those with underlying cardiopulmonary disease, including congenital and acquired valvular disease, cardiomyopathy, bronchopulmonary dysplasia, asthma, cystic fibrosis, and neurologic conditions. Pregnant women and adolescent females are also at high risk for severe influenza. Children receiving cancer chemotherapy and children with immunodeficiency also have a higher risk of complications and may shed virus for longer periods than immunocompetent children.

LABORATORY FINDINGS

The clinical laboratory abnormalities associated with influenza are nonspecific. Chest radiographs may show evidence of atelectasis or infiltrate.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of influenza depends on epidemiologic, clinical, and laboratory considerations. In the context of an epidemic, the clinical diagnosis of influenza in a child who has fever, malaise, and respiratory symptoms may be made based on clinical discretion; however, clinical presentation is often indistinguishable from infection with other respiratory viruses, including SARS-CoV-2, respiratory syncytial virus, parainfluenza virus, human metapneumovirus, adenovirus, and even rhinovirus. Confirmation of influenza virus infection by diagnostic testing might be helpful in certain circumstances when other viruses are co-circulating, but it is not required for clinical decisions to prescribe antiviral medications, and prompt suspicion or diagnosis of influenza may allow for early antiviral therapy to be initiated and may reduce inappropriate use of antibiotics.

A number of diagnostic tests may be used for laboratory confirmation of influenza (Table 305.2). Although rapid influenza diagnostic tests based on antigen detection are often employed because of their ease of use and fast results, they can have suboptimal sensitivity to detect influenza virus infection, particularly for novel influenza viruses. Sensitivities of rapid antigen diagnostic tests are generally 50–70% compared to viral culture or reverse-transcription polymerase chain reaction (RT-PCR). Specificities are higher, approximately 95–100%. Therefore false-negative results occur more often than false-positive results, particularly when the prevalence of influenza is high (i.e., during peak influenza activity in the community). The interpretation of negative results should consider the clinical characteristics and the patient's risk for complications. If there is clinical suspicion for influenza in a patient at high risk for complications (Table 305.3), early empirical treatment should be given regardless of a negative rapid antigen diagnostic test result, and another type of test may be performed for confirmation. RT-PCR or other rapid molecular assays are now preferred for influenza diagnosis in both outpatients and hospitalized patients.

TREATMENT

Antiviral medications are an important adjunct to influenza vaccination. Three classes of antiviral drugs are licensed for treatment of influenza in children. The neuraminidase inhibitors (NAIs), oral oseltamivir and inhaled zanamivir, may be used for treatment of children from birth and 7 years, respectively (Table 305.4). In December 2012, the U.S. Food and Drug Administration (FDA) approved the use of oseltamivir for the treatment of influenza in infants as young as 2 wk of age, and the Centers for Disease Control and Prevention (CDC), the American Academy of Pediatrics, and the Infectious Diseases Society of America recommend its use in infants of any age. A third NAI, peramivir, is given as an intravenous infusion and is approved for treatment in persons 2 years of age and older.

The second class of drugs is represented by a new orally administered influenza antiviral called baloxavir marboxil, which was approved by the FDA in October 2018. Baloxavir is active against both influenza A and B viruses and is a cap-dependent endonuclease inhibitor that interferes with viral RNA transcription and blocks virus replication. It is approved for treatment of acute uncomplicated influenza in people 12 years and older.

The third class of drugs is the adamantanes, including oral amantadine and oral rimantadine, which are effective only against influenza A viruses. Genetic variants have conferred widespread adamantane resistance among circulating influenza A viruses, including seasonal influenza viruses and many H5N1 and H7N9 avian influenza viruses; *therefore this class of antivirals is not currently recommended for use.*

When initiated early in the course of uncomplicated influenza illness, antiviral agents can reduce the duration of symptoms and the likelihood of complications. Among hospitalized patients, observational studies suggest that early treatment reduces disease severity and mortality. Although most data regarding potential benefit are for adults, a few studies support the use of antiviral agents in children. Antiviral treatment within 2 days of illness onset has been reported to reduce illness duration, the risk of otitis media, and the likelihood of hospitalization in children. Clinical benefit is greatest when antiviral

Table 305.2 Influenza Virus Testing Methods

METHOD	ACCEPTABLE SPECIMENS	TEST TIME	COMMENTS
Rapid influenza diagnostic tests (antigen detection)	Nasopharyngeal (NP) swab, aspirate or wash, nasal swab, aspirate, or wash, throat swab	<15 min	Rapid turnaround; suboptimal sensitivity
Rapid molecular assay (influenza nucleic acid amplification)	NP swab, nasal swab	15-30 min	Rapid turnaround; high sensitivity
Immunofluorescence, direct (DFA) or indirect (IFA) fluorescent antibody staining (antigen detection)	NP swab or wash, bronchial wash, nasal or endotracheal aspirate	1-4 hr	Relatively rapid turnaround; requires laboratory expertise and experience
RT-PCR (singleplex and multiplex; real-time and other RNA-based) and other molecular assays (influenza nucleic acid amplification)	NP swab, throat swab, NP or bronchial wash, nasal or endotracheal aspirate, sputum	Varies by assay (generally 1-8 hr)	Excellent sensitivity, relatively rapid turnaround compared with conventional methods
Rapid cell culture (shell vials, cell mixtures; yields live virus)	NP swab, throat swab, NP or bronchial wash, nasal or endotracheal aspirate, sputum	1-3 day	Culture isolates important for strain information and antiviral resistance monitoring
Viral tissue cell culture (conventional; yields live virus)	NP swab, throat swab, NP or bronchial wash, nasal or endotracheal aspirate, sputum	3-10 day	Not recommended for routine patient diagnosis
Serologic tests (antibody detection)	Paired (appropriately timed) acute and convalescent serum specimens	N/A (not performed during acute infection)	Not recommended for routine patient diagnosis; useful for research studies

N/A, Not applicable; RT-PCR, reverse transcription-polymerase chain reaction.
Modified from Centers for Disease Control and Prevention (CDC): *Influenza virus testing methods*. Available at https://www.cdc.gov/flu/professionals/diagnosis/table-testing-methods.htm in Information for Health Professionals (https://www.cdc.gov/flu/professionals/index.htm); and from 2018 IDSA Clinical Practice Guidelines.

Table 305.3 Children and Adolescents Who Are at Higher Risk for Influenza Complications for Whom Antiviral Treatment is Recommended*

- Children younger than 2 yr of age†
- Persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematologic (including sickle cell disease), and metabolic disorders (including diabetes mellitus); or neurologic and neurodevelopmental conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability, moderate to severe developmental delay, muscular dystrophy, or spinal cord injury)
- Persons with immunosuppression, including that caused by medications or by HIV infection
- Adolescents who are pregnant, or postpartum (within 2 wk after delivery)
- Persons younger than 19 yr of age who are receiving long-term aspirin- or salicylate-containing medications therapy
- Indigenous/Alaska Natives
- Persons who are extremely obese (body mass index ≥40)
- Residents of long-term care facilities
- Hospitalized patients at high risk for influenza complications

*Antiviral treatment is recommended for children at high risk with confirmed or suspected influenza; antivirals are also recommended for children who are hospitalized or have severe or progressive disease.
†Although all children younger than 5 yr of age are considered at higher risk for complications from influenza, the highest risk is for those younger than 2 yr of age, with the highest hospitalization and death rates among infants younger than 6 mo of age.
Current for 2021–2022 influenza season.
Adapted from Centers for Disease Control and Prevention (CDC): Influenza antiviral medications: summary for clinicians. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm; and from American Academy of Pediatrics Policy Statement: Recommendations for Prevention and Control of Influenza in Children, 2021-2022. For current details, consult annually updated recommendations at https://www.cdc.gov/flu/professionals/index.htm.

treatment is administered early, especially within 48 hours of influenza illness onset.

The CDC recommends treatment as early as possible for (1) hospitalized patients, (2) patients with severe, complicated, or progressive illness, and (3) patients at high risk for influenza complications (see Table 305.3). Decisions about starting antiviral treatment should not wait for laboratory confirmation of influenza. Although early treatment is desired, treatment more than 48 hours from onset may be beneficial and is recommended for these three categories of patients.

The recommended treatment course for uncomplicated influenza is twice daily oral oseltamivir for 5 days, twice daily inhaled zanamivir for 5 days, or a single dose of intravenous peramivir or oral baloxavir. Currently, for hospitalized patients and patients with severe or complicated illness, treatment with oral or enterically administered oseltamivir is recommended. The optimal duration and dose are uncertain for severe or complicated influenza, and longer courses of treatment (e.g., 10 days of treatment) may be considered.

Clinical judgment considering a patient's disease severity, age, underlying medical conditions, likelihood of influenza, and time since onset of symptoms is important when making antiviral treatment decisions for outpatients at high risk for complications. Antiviral treatment can also be considered for any previously healthy, symptomatic outpatient not at high risk with confirmed or suspected influenza, if treatment can be initiated within 48 hours of illness onset.

Some influenza viruses may become resistant during antiviral treatment, an occurrence that has been reported most often for oseltamivir resistance in influenza A(H1N1) viruses. Following treatment with baloxavir, emergence of viruses with molecular markers associated with reduced susceptibility to baloxavir has been observed in clinical trials. Antiviral resistance and reduced susceptibility can also occasionally occur spontaneously with no known exposure to antiviral drugs. It is important to review annual recommendations and updates published by CDC before prescribing influenza antiviral medications (see https://www.cdc.gov/flu/professionals/antivirals/index.htm).

Table 305.4 Recommended Dosage and Schedule of Influenza Antiviral Medications for Treatment and Chemoprophylaxis in Children for the 2021–2022 Influenza Season: United States

MEDICATION	TREATMENT DOSING*	CHEMOPROPHYLAXIS DOSING*
ORAL OSELTAMIVIR†		
Adults	75 mg twice daily	75 mg once daily
Children ≥12 mo		
≤15 kg (≤33 lb)	30 mg twice daily	30 mg once daily
>15-23 kg (33-51 lb)	45 mg twice daily	45 mg once daily
>23-40 kg (>51-88 lb)	60 mg twice daily	60 mg once daily
>40 kg (>88 lb)	75 mg twice daily	75 mg once daily
Infants 9-11 mo‡	3 mg/kg per dose twice daily	3 mg/kg per dose once daily
Term infants ages 0-8 mo‡	3 mg/kg per dose twice daily	3 mg/kg per dose once daily for infants 3-8 mo old; not recommended for infants <3 mo old unless situation judged critical because of limited safety and efficacy data in this age group
Preterm infants	See details in footnote§	Not recommended
INHALED ZANAMIVIR¶		
Adults	10 mg (two 5-mg inhalations) twice daily	10 mg (two 5-mg inhalations) once daily
Children (≥7 yr old for treatment; ≥5 yr old for chemoprophylaxis)	10 mg (two 5-mg inhalations) twice daily	10 mg (two 5-mg inhalations) once daily
INTRAVENOUS PERAMIVIR		
Adults	600 mg intravenous infusion once given over 15-30 min	Not recommended
Children (2-12 yr old)	One 12 mg/kg dose, up to 600 mg maximum, once via intravenous infusion for 15-30 min	Not recommended
Children (13-17 yr old)	One 600 mg dose once via intravenous infusion for 15-30 min	Not recommended
ORAL BALOXAVIR#		
Adults		
40 to <80 kg	One 40-mg dose	One 40-mg dose
>80 kg	One 80-mg dose	One 80-mg dose
Children		
2-11 yr	Not recommended	Not recommended
12-17 yr, 40 to <80 kg	One 40-mg dose	One 40-mg dose
12-17 yr, >80 kg	One 80-mg dose	One 80-mg dose

*Antiviral treatment duration for uncomplicated influenza is 5 days for oral oseltamivir or inhaled zanamivir, and a single dose for intravenous peramivir or oral baloxavir. Recommended postexposure chemoprophylaxis with oseltamivir or zanamivir in a nonoutbreak setting is 7 days after last known exposure.

†Oseltamivir is administered orally without regard to meals, although administration with meals may improve gastrointestinal tolerability. Oseltamivir is available as Tamiflu or as a generic formulation as capsules and as a powder for oral suspension that is reconstituted to provide a final concentration of 6 mg/mL.

‡Approved by the FDA for children as young as 2 wk of age. Given preliminary pharmacokinetic data and limited safety data, oseltamivir can be used to treat influenza in both term and preterm infants from birth because benefits of therapy are likely to outweigh possible risks of treatment. CDC and U.S. Food and Drug Administration (FDA)–approved dosing is 3 mg/kg per dose twice daily for children age 9-11 mo; the American Academy of Pediatrics recommends 3.5 mg/kg per dose twice daily. The dose of 3 mg/kg provides oseltamivir exposure in children similar to that achieved by the approved dose of 75 mg orally twice daily for adults, as shown in two studies of oseltamivir pharmacokinetics in children. The AAP has recommended an oseltamivir treatment dose of 3.5 mg/kg orally twice daily for infants 9-11 mo, on the basis of data that indicated that a higher dose of 3.5 mg/kg was needed to achieve the protocol-defined targeted exposure for this cohort as defined in the CASG 114 study. It is unknown whether this higher dose will improve efficacy or prevent the development of antiviral resistance. However, there is no evidence that the 3.5-mg/kg dose is harmful or causes more adverse events to infants in this age group.

§Oseltamivir dosing for preterm infants. The weight-based dosing recommendation for preterm infants is lower than for term infants. Preterm infants may have lower clearance of oseltamivir because of immature renal function, and doses recommended for term infants may lead to high drug concentrations in this age group. Limited data from the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group provide the basis for dosing preterm infants by using their postmenstrual age (gestational age plus chronological age): 1 mg/kg per dose orally twice daily for those <38 wk postmenstrual age; 1.5 mg/kg per dose orally twice daily for those 38-40 wk postmenstrual age; and 3 mg/kg per dose orally twice daily for those >40 wk postmenstrual age. For extremely preterm infants (<28 wk), please consult a pediatric infectious diseases physician.

¶Zanamivir is administered by inhalation by using a proprietary Diskhaler device distributed together with the medication. Zanamivir is a dry powder, not an aerosol, and should not be administered by using nebulizers, ventilators, or other devices typically used for administering medications in aerosolized solutions. Zanamivir is not recommended for people with chronic respiratory diseases, such as asthma or chronic obstructive pulmonary disease, which increase the risk of bronchospasm.

#Oral baloxavir marboxil is approved by the FDA for treatment of acute uncomplicated influenza within 2 days of illness onset in people 12 yr and older. The safety and efficacy of baloxavir for the treatment of influenza have been established in pediatric patients 12 yr and older weighing at least 40 kg. Safety and efficacy in patients <12 yr of age or weighing <40 kg have not been established. Baloxavir efficacy is based on clinical trials in outpatients 12 to 64 yr of age; people with underlying medical conditions and adults >65 yr were not included in the initial published clinical trials (Hayden F et al; *Clin Infect Dis* 2018). There are no available data for baloxavir treatment of hospitalized patients with influenza.

Adapted from Centers for Disease Control and Prevention (CDC): *Influenza antiviral medications: summary for clinicians*. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. For current details, consult annually updated recommendations at https://www.cdc.gov/flu/professionals/index.htm; 2018 IDSA Clinical Practice Guidelines; and from Kimberlin DW, Acosta EP, Prichard MN, et al. National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Oseltamivir pharmacokinetics, dosing, and resistance among children aged <2 yr with influenza. *J Infect Dis*. 2013;207(5):709–720.

SUPPORTIVE CARE

Adequate fluid intake and rest are important in the management of influenza. Bacterial superinfections are relatively common and should be appropriately treated with antibiotic therapy. Bacterial superinfection should be suspected with recrudescence of fever, prolonged fever, or deterioration in clinical status. With uncomplicated influenza, people should usually start to feel better after the first 48-72 hours of symptoms.

PROGNOSIS

The prognosis for recovery from uncomplicated influenza is generally excellent, although full return to normal level of activity and freedom from cough may require weeks rather than days. Fatigue may also persist for weeks. However, severe influenza disease can be associated with hospitalizations and death, even among previously healthy children.

PREVENTION

Influenza vaccination is the best means of preventing influenza illness. In studies of children who are fully vaccinated, influenza vaccine is 40–60% effective in reducing the risk of laboratory-confirmed influenza illness. Vaccine effectiveness can vary from year to year and among different age and risk groups. Recommendations for use of the influenza vaccine have broadened as the impact of influenza is appreciated in such groups as pregnant women and young infants. Starting in the 2008–2009 influenza season, the United States Advisory Committee on Immunization Practices (ACIP) recommended that all children from 6 months to 18 years of age be vaccinated against influenza unless they have a specific contraindication to receiving the vaccine. Since the 2010–2011 season, annual flu vaccination is recommended for everyone 6 months and older, with rare exception. In 2012, the Department of Health in the United Kingdom extended their influenza vaccination program to include all children between the ages of 2 and 17 years. To protect infants younger than 6 months who are too young to receive a vaccine, pregnant women, household contacts, and out-of-home caregivers are groups for whom additional vaccination efforts should be made. Chemoprophylaxis with antiviral medications is a secondary means of prevention and is not a substitute for vaccination.

Vaccines

There are two main categories of seasonal influenza vaccines available for children: inactivated influenza vaccine (IIV) and live-attenuated influenza vaccine (LAIV). Previously referred to as the trivalent inactivated vaccine, IIV is given intramuscularly; it uses killed virus components. The LAIV vaccine uses weakened influenza virus and is administered as an intranasal spray. Neither IIV nor LAIV can cause influenza. Although in 2014–2015 ACIP and CDC recommended the use of the LAIV nasal spray vaccine for healthy children 2 through 8 years of age, this preferential recommendation was removed for the 2015–2016 season, and for the 2016–2017 and 2017–2018 seasons, ACIP and CDC made the interim recommendation that LAIV should not be used. This decision was based on concerns regarding low effectiveness against influenza A(H1N1)pdm09 in the United States noted during the 2013–2014 and 2015–2016 seasons. After review of additional data, LAIV containing an updated influenza A(H1N1)pdm09-like vaccine virus, was again recommended by CDC and ACIP as an option for vaccination for the 2018–2019 season. Since the 2018–2019 season, ACIP and CDC have recommend that LAIV4 may be used.

Special vaccination instructions for children 6 months to 8 years of age should be followed: children in this age group who have not previously received a total of at least two previous doses of trivalent or quadrivalent vaccine require two doses (at least 4 weeks apart) of the current season's influenza vaccine to optimize immune response (Fig. 305.3). Influenza vaccines have an excellent safety profile, with the most common side effects being soreness, redness, tenderness, or swelling from the injection, and nasal congestion after the nasal spray. Seasonal influenza vaccines may be co-administered with other vaccines, including SARS-CoV-2 vaccines.

Seasonal influenza vaccines become available in the late summer and early fall each year. The formulation reflects the strains of influenza viruses that are expected to circulate in the coming influenza season. Beginning in the 2013–2014 season, IIVs were available in both trivalent and quadrivalent formulations. The trivalent vaccine (IIV3) contains two influenza A strains and one influenza B strain; the quadrivalent vaccine (IIV4) contains a second influenza B strain of an antigenically distinct lineage. In addition to IIV and LAIV, a third vaccine category, recombinant HA influenza vaccine, became available in the 2013–2014 season. Since the 2020–2021 influenza season, all influenza vaccines used in the United States are quadrivalent.

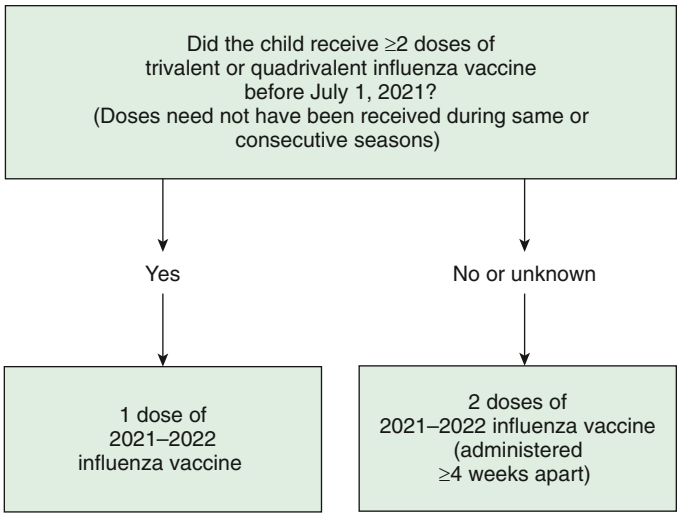

Fig. 305.3 Influenza vaccine dosing algorithm for children age 6 mo through 8 yr*—Advisory Committee on Immunization Practices, United States, 2021–2022 influenza season. *For children age 8 years who require two doses of vaccine, both dosages should be administered even if the child turns age 9 yr between receipt of dose 1 and dose 2. *(From Grohskopf LA, Alyanak E, Ferdinands JM, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the advisory committee on immunization practices—United States, 2021-22 Influenza Season. MMWR Recomm Rep. 2021;70[No. RR-5]:1–28.)*

Ideally, vaccination should be given before the onset of influenza circulation in the community, so that there is time for antibodies to reach protective levels. Healthcare providers should offer vaccination by the end of October, if possible. The ACIP publishes guidelines for vaccine use each year when the vaccines are formulated and released; these guidelines should be referred to each season. The ACIP guidelines are widely publicized but appear initially in the *Morbidity and Mortality Weekly Report* published by CDC (https://www.cdc.gov/flu/index.htm).

Chemoprophylaxis

Routine use of antiviral medications for chemoprophylaxis is not recommended. Examples for which the use of chemoprophylaxis may be considered to prevent influenza after exposure to an infectious person include (1) unvaccinated persons at high risk of influenza complications, (2) persons for whom vaccine is contraindicated or expected to have low effectiveness, and (3) residents/patients in care facilities during institutional influenza outbreaks. Oral oseltamivir or inhaled zanamivir may be used for chemoprophylaxis of influenza; baloxavir is approved for postexposure prophylaxis in persons 12 years of age and older. Peramivir is not recommended for chemoprophylaxis because of a lack of data, and adamantanes are not currently recommended because of widespread adamantane resistance. Table 305.4 shows the recommendations for dosage and duration of treatment and chemoprophylaxis for the 2021–2022 influenza season, but updated recommendations from the ACIP and CDC should be consulted every season (https://www.cdc.gov/flu/professionals/antivirals/index.htm).

In general, postexposure chemoprophylaxis for persons at high risk of influenza complications (see Table 305.3) should be started within 48 hours of exposure to an infectious person and should be continued for 7 days after the last known exposure. An alternative to chemoprophylaxis for some persons after a suspected exposure is close monitoring and early initiation of antiviral treatment if symptoms develop.

For control of influenza outbreaks among high-risk persons living in institutional settings, such as long-term care facilities, antiviral chemoprophylaxis is recommended for all vaccinated and unvaccinated residents and for unvaccinated healthcare providers. In these circumstances, CDC and the Infectious Diseases Society of America recommend antiviral chemoprophylaxis for a minimum of 2 weeks and up to 1 week after the last known case is identified, whichever is longer.

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Chapter 306

Parainfluenza Viruses

Fiona P. Havers and Angela J.P. Campbell

Human parainfluenza viruses (HPIVs) are common causes of acute respiratory illness in infants and children and are important causes of lower respiratory tract disease in young children and immunocompromised persons. These viruses cause a spectrum of upper and lower respiratory tract illnesses but are particularly associated with **croup** (laryngotracheitis or laryngotracheobronchitis), **bronchiolitis**, and **pneumonia**.

ETIOLOGY

HPIVs are members of the **Paramyxoviridae** family. Four HPIVs cause illness in humans, classified as types 1-4, with diverse manifestations of infection. Type 4 is divided into two antigenic subtypes: 4a and 4b. HPIVs have a nonsegmented, single-stranded RNA genome with a lipid-containing envelope derived from budding through the host cell membrane. The major antigenic moieties are the hemagglutinin neuraminidase (HN) and fusion (F) surface glycoproteins.

EPIDEMIOLOGY

By 5 years of age, most children have experienced primary infection with HPIV types 1, 2, and 3. HPIV-3 infections generally occur earliest, with half of infants infected by age 1 year and over 90% by age 5 years. HPIV-1 and HPIV-2 are more common after infancy, with approximately 75% infected by age 5 years. With increased use of multiplex molecular testing and more frequent addition of HPIV-4 as a panel target, HPIV-4 is more frequently recognized and appears to occur earlier in life than HPIV-1 and -2. In the United States and temperate climates, HPIV-1 has typically been reported to have biennial epidemics in the fall in odd-numbered years, whereas HPIV-2 has biennial outbreaks in the fall of even-numbered years, with peaks that are not as high as HPIV-1 or HPIV-3 (Fig. 306.1). HPIV-3 can be endemic throughout the year but typically peaks yearly in late spring or early summer. In years with less HPIV-1 activity, the HPIV-3 season has been observed to extend longer or to have a second peak in the fall (see Fig. 306.1). The epidemiology of HPIV-4 was historically less well defined, but with an increase in molecular detection, it has been found to have yearly peaks starting in the fall and peaking in winter (see Fig. 306.1).

Similar to what has been observed for other non–SARS-CoV-2 respiratory viruses, during the COVID-19 pandemic in 2020 and early 2021, HPIVs circulated at levels lower than prior years. However, HPIVs began increasing in the United States in spring of 2021 and, for HPIV types 1, 3, and 4, circulation patterns in 2022 and through fall 2023 were similar to pre-pandemic seasons; HPIV-2 continued to circulate at lower levels during that period. National HPIV trends are created from weekly laboratory test result data that are reported on a voluntary basis and are available at the Centers for Disease Control and Prevention (CDC) National Respiratory and Enteric Virus Surveillance System (NREVSS) website (https://www.cdc.gov/surveillance/nrevss).

HPIVs are spread primarily from the respiratory tract of an infected person by inhalation of large respiratory droplets or contact with infected nasopharyngeal secretions. HPIVs are notable for causing **outbreaks** of respiratory illness in hospital wards, clinics, neonatal nurseries, and other institutional settings. The incubation period from exposure to symptom onset may range from 2 to 6 days. Children are likely to excrete virus from the oropharynx for 2-3 weeks, but shedding can be more prolonged, especially in immunocompromised children, and may persist for months. Primary infection does not confer permanent immunity, and reinfections are common throughout life. Reinfections are usually mild and self-limited but can cause serious lower respiratory tract illness, particularly in children with compromised immune systems.

PATHOGENESIS

HPIVs replicate in the respiratory epithelium. The propensity to cause illness in the upper large airways is presumably related to preferential replication in the larynx, trachea, and bronchi in comparison with other viruses. Some HPIVs induce cell-to-cell fusion. During the budding process, cell membrane integrity is lost, and viruses can induce cell death through the process of apoptosis. In children, the most severe illness generally coincides with the time of maximal viral shedding. However, disease severity is likely related to the host immune response to infection as much as to direct cytopathic effects of the virus. Virus-specific immunoglobulin A antibody levels and serum antibodies to the surface HN and F glycoproteins are able to neutralize HPIV, and both likely contribute to host immunity. Cell-mediated cytotoxicity is also important for controlling and terminating HPIV infection.

CLINICAL MANIFESTATIONS

The most common type of illness caused by HPIV infection consists of some combination of low-grade fever, rhinorrhea, cough, pharyngitis, and hoarseness and may be associated with vomiting or diarrhea. Rarely, HPIV infection is associated with parotitis. HPIVs have also been associated with a variety of skin manifestations, including typical maculopapular viral exanthems, erythema multiforme, and papular acrodermatitis, or Gianotti-Crosti syndrome (see Chapter 708). Although often mild, more serious HPIV illness may result in hospitalization, with common discharge diagnoses of bronchiolitis, fever/possible sepsis, and apnea among younger children and croup, pneumonia, and asthma among older children (Fig. 306.2). HPIVs account for 50% of hospitalizations for croup and at least 15% of cases of bronchiolitis and pneumonia. HPIV-1 and HPIV-2 cause more cases of croup, whereas HPIV-3 is more likely to infect the small air passages of the lower respiratory tract and cause pneumonia, bronchiolitis, or bronchitis. HPIV-4 causes a similar range of illness as the other types, and with advancements in molecular diagnosis, there is evidence that HPIV-4 may be comparable to HPIV-3 and frequently associated with acute lower respiratory infection (ALRI).

In fact, any HPIV can cause lower respiratory tract disease, particularly during primary infection or in patients with compromised immune systems. In children and adult patients with hematologic malignancies and undergoing hematopoietic stem cell transplantation, lymphopenia has repeatedly been shown to be an independent risk factor for progression from upper to lower respiratory tract disease. Recently, the first global burden estimates of HPIV-associated and HPIV-attributable ALRI were generated, with approximately 13% of ALRI cases, 4–14% of ALRI hospital admissions, and 4% of childhood ALRI mortality attributable to HPIV.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of HPIV infection in children is often based solely on clinical and epidemiologic criteria. Croup is a clinical diagnosis and must be distinguished from other diagnoses, including foreign body aspiration, epiglottitis, retropharyngeal abscess, angioedema, and subglottic stenosis or hemangioma. Although the radiographic "**steeple sign**," consisting of progressive narrowing of the subglottic region of the trachea, is characteristic of croup, differential considerations include acute epiglottitis, thermal injury, angioedema, and bacterial tracheitis. Manifestation of HPIV lower respiratory tract disease may be similar to that of a number of other respiratory viral infections; therefore virus identification should be sought by the most sensitive diagnostic means available for certain severe illnesses, such as pneumonia in immunocompromised children.

Sensitive, specific, and rapid molecular assays such as multiplex polymerase chain reaction assays have become more widely available

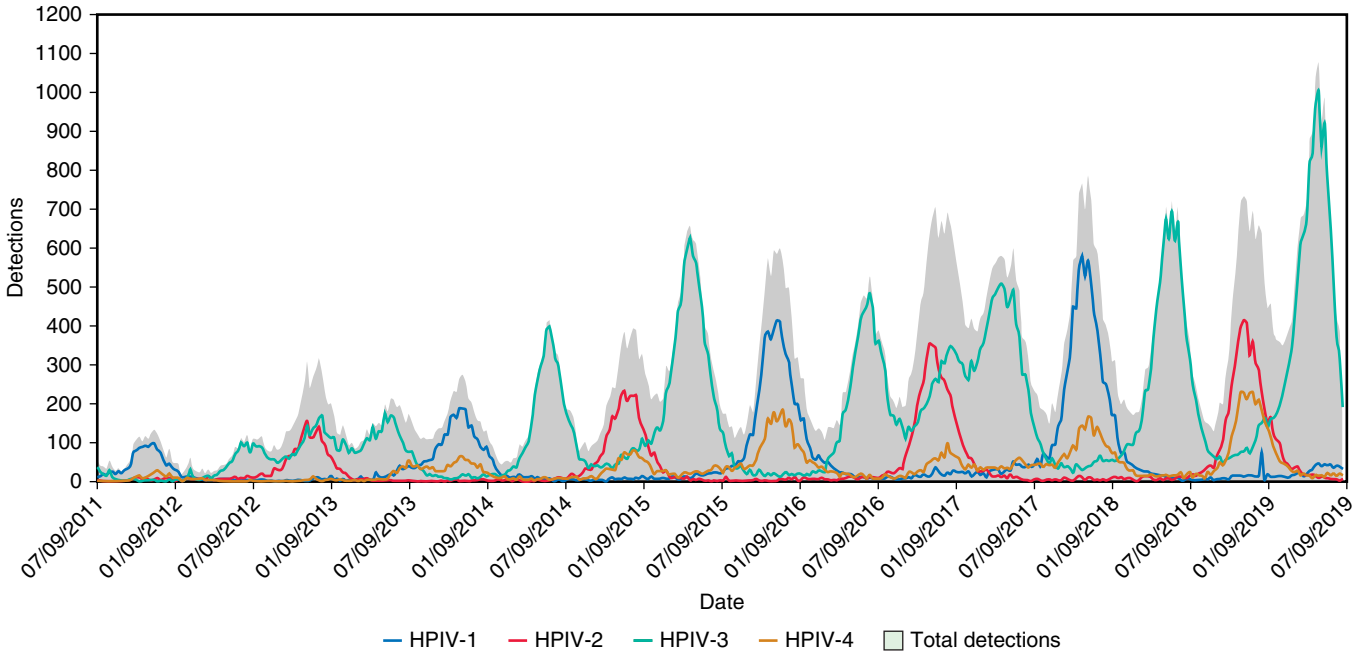

Fig. 306.1 Human parainfluenza virus (HPIV) circulation, National Enteric and Respiratory Virus Surveillance System, United States Census Regions, 2011–2019. *(From DeGroote NP, Haynes AK, Taylor C, et al. Human parainfluenza virus circulation, United States, 2011–2019. J Clin Virol. 2020;124:104261. Fig. 1.)*

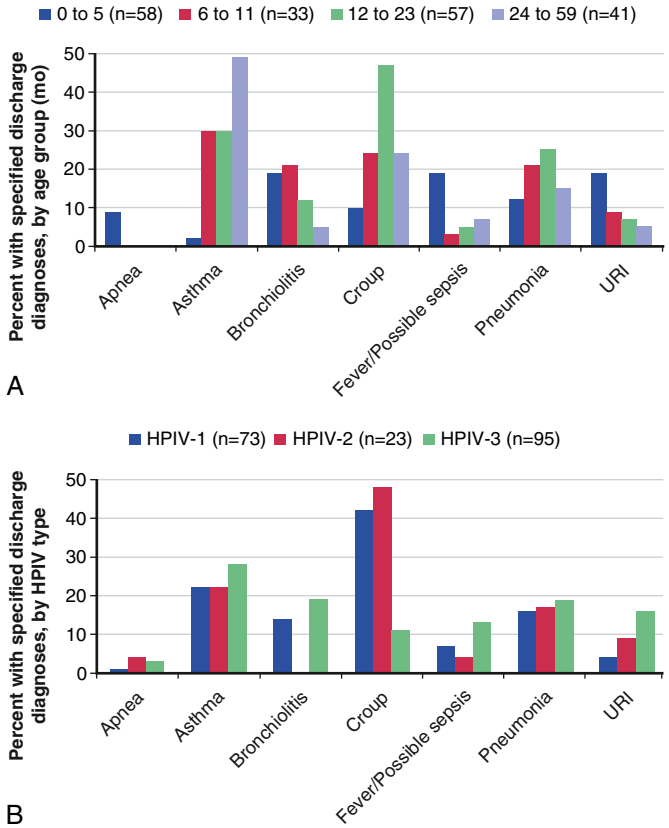

Fig. 306.2 Selected discharge diagnoses of hospitalized children with parainfluenza (HPIV) infection, by age in months (A) and virus type (B). *(Data from Weinberg GA, Hall CB, Iwane MK, et al. Parainfluenza virus infection of young children: estimates of the population-based burden of hospitalization. J Pediatr. 2009;154:694–699, Table II)*

and greatly increase sensitivity of HPIV detection. For immunocompromised patients, these highly sensitive platforms provide the critical ability to make a prompt diagnosis by detecting a wide range of viral pathogens, including HPIVs, thus allowing for early implementation of infection prevention measures and potential treatment. Other laboratory diagnosis methods are available, such as isolation in tissue culture and direct immunofluorescent staining for identification of virus antigens in respiratory secretions, but these have been used less frequently given the increasing availability of molecular assays.

TREATMENT

There are no specific antiviral medications approved for the treatment of HPIV infections. For croup, the possibility of rapid respiratory compromise should influence the level of care and treatment given (see Chapter 433). The **severity assessment** of croup generally incorporates a number of clinical features, which include the presence and degree of chest wall retractions, whether stridor is present at rest, and evaluation of the child's mental status (e.g., for agitation, anxiety, lethargy).

Humidified air has not been shown to be significantly effective in reducing symptom severity. **Glucocorticoids** improve symptoms at 2 hours after treatment, lessen the need for other medications, and shorten hospital stays. **In general, because of its safety, efficacy, and cost-effectiveness, a single dose of oral dexamethasone (0.15 to 0.6 mg/kg) is the primary treatment for mild croup in the office or emergency room setting.** Oral prednisolone (1 mg/kg) is an acceptable alternative in this setting, particularly if dexamethasone is not available; however, in a meta-analysis, dexamethasone significantly reduced the rate of return visits and/or (re)admissions.

For obstructive airway symptoms associated with moderate to severe croup, corticosteroid therapy is recommended: oral dexamethasone (0.6 mg/kg) should be given if oral intake is tolerated. A single dose of intramuscular dexamethasone or budesonide (2 mg [2 mL solution] via nebulizer) may provide an alternative to oral dexamethasone for children with severe respiratory distress or vomiting. Alternatively, intravenous (IV) dexamethasone can be administered if IV access has been established. **Nebulized epinephrine (either racemic epinephrine 2.25% solution, 0.05 mL/kg/dose [up to maximum of 0.5 mL/dose] diluted to 3 mL with normal**

saline, or L-epinephrine using parenteral 1 mg/ml [1:1000] solution, 0.5 mL/kg/dose [up to maximum 5 mL/dose]) is also recommended and may provide temporary symptomatic improvement. Children should be observed for at least 2 hours after receiving epinephrine treatment for return of obstructive symptoms. Repeated treatments may be provided, depending on the duration of symptoms. The dexamethasone dose may be repeated, but this should not be necessary on a routine basis, and there are no guidelines to compare outcomes of single- and multiple-dose treatment schedules. Moderate to severe symptoms that persist for more than a few days should prompt investigation for other causes of airway obstruction. Oxygen should be administered for hypoxia, and supportive care with analgesics and antipyretics is reasonable for fever and discomfort associated with HPIV infections. The indications for antibiotics are limited to well-documented secondary bacterial infections of the middle ear(s) or lower respiratory tract.

Ribavirin has some antiviral activity against HPIVs in vitro and in animal models. Inhaled ribavirin has been given to severely immunocompromised children with HPIV pneumonia; however, the majority of data have not shown improved outcomes, and randomized controlled studies are lacking. Some institutions use intravenous immunoglobulin for HPIV pneumonia in children with hematologic malignancies or who have undergone hematopoietic stem cell transplantation; the impact of this treatment strategy on clinical outcomes is also limited by lack of controlled studies. Use of DAS181, a novel sialidase fusion protein inhibitor, has shown clinical potential in a phase 2 clinical trial when used for treatment of HPIV lower respiratory tract disease among solid organ and hematopoietic stem cell transplant recipients, and a phase 3 trial is ongoing. Other potential strategies for drug development include hemagglutinin-neuraminidase inhibitors, transcription inhibitors, and synthetic small interfering RNAs.

COMPLICATIONS

Eustachian tube obstruction can lead to secondary bacterial invasion of the middle ear space and acute otitis media in 30–50% of HPIV infections. Similarly, obstruction of the paranasal sinuses can lead to sinusitis. The destruction of cells in the upper airways can lead to secondary bacterial invasion and resultant bacterial tracheitis, and antecedent HPIV infection of lower airways may predispose to bacterial pneumonia. Nonrespiratory complications of HPIV are rare but include aseptic meningitis, encephalitis, acute disseminated encephalomyelitis, rhabdomyolysis, myocarditis, and pericarditis.

PROGNOSIS

The prognosis for full recovery from HPIV infection in the immunocompetent child is generally excellent, with no long-term pulmonary sequelae. Deaths may rarely occur, particularly in immunocompromised children with lower respiratory tract infection.

PREVENTION

Vaccine development has focused largely on live-attenuated intranasal HPIV-3 vaccines. Candidates include a recombinant human HPIV-3 virus (rcp45) derived from complementary DNA, as well as a complementary DNA–derived chimeric bovine/human HPIV-3 virus; these candidates are well tolerated and immunogenic in infants and young children. Constructs using chimeric bovine/human HPIV-3 virus in addition to the F or both F and G proteins of respiratory syncytial virus (RSV) have been investigated. A combined messenger RNA (mRNA) vaccine against HPIV-3 and human metapneumovirus has completed phase 1 clinical trials. Live attenuated candidate HPIV-1 and HPIV-2 vaccines have also undergone phase 1 clinical studies (www.clinicaltrials.gov). The measure of protection afforded by vaccines will be difficult to assess, because symptomatic reinfection occurs and the frequency of serious infection in the general population is low. Nonetheless, it is clear that prevention of acute respiratory illness caused by HPIVs, particularly lower respiratory tract infections among infants and young children, is a worthwhile goal.

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Chapter 307

Respiratory Syncytial Virus

James E. Crowe Jr.

Respiratory syncytial virus (RSV) is the major cause of bronchiolitis (see Chapter 439) and viral pneumonia in children younger than 1 year of age and is the most important respiratory tract pathogen of early childhood.

ETIOLOGY

RSV is an enveloped RNA virus with a single-stranded negative-sense genome that replicates entirely in the cytoplasm of infected cells and matures by budding from the apical surface of the cell membrane. Because this virus has a nonsegmented genome, it cannot undergo antigenic shift by reassortment like the influenza viruses do. The virus belongs to the family Pneumoviridae, which comprises large enveloped, negative-sense RNA viruses. This taxon was formerly a subfamily within the Paramyxoviridae but was reclassified in 2016 as a family with two genera, *Orthopneumovirus* (which includes RSV) and *Metapneumovirus* (which includes human metapneumovirus; see Chapter 308). There are two antigenic subgroups of RSV (subgroups A and B), distinguished based primarily on sequence and antigenic variation in one of the two surface proteins, the G glycoprotein that is responsible for attachment to host cells. Sequence analysis of cDNAs of the full G glycoprotein ectodomain region allows clustering of sequence patterns and identification of molecular markers that can be used to assign genotypes, subgenotypes, and lineages. There is no unified classification scheme for genotypes, so reports differ in the number of genotypes in circulation. The observed genotypic variation, which also can alter antigenic properties at the protein level, is caused by point mutations from infidelity of the viral RNA polymerase and may contribute to some degree to the frequency with which RSV reinfects children and adults. However, adult human challenge experiments have shown that the same RSV strain can reinfect in the upper respiratory tract repetitively, suggesting that mucosal immunity in that site is incomplete or short-lived.

RSV replicates in a wide variety of cell line monolayer cultures in the laboratory. In HeLa and HEp-2 cell monolayers, the virus causes cell-to-cell fusion that produces characteristic cytopathology called syncytia (multinucleate enlarged cells), from which the virus derives its name. Identification of syncytia in diagnostic cultures of respiratory secretions is helpful in identifying RSV, but it is not clear whether syncytium formation occurs to any significant degree in the airway epithelium in patients.

EPIDEMIOLOGY

RSV is distributed worldwide and appears in yearly epidemics. In temperate climates, these epidemics occur each winter over a 4- to 5-month period. During the remainder of the year, infections are sporadic and much less common. In the Northern hemisphere, epidemics usually peak in January, February, or March, but peaks have been recognized as early as December and as late as June. Some areas in the United States, such as Florida, report a moderate incidence year-round. In the Southern hemisphere, outbreaks also occur during the winter months in that hemisphere. RSV outbreaks often overlap with outbreaks of influenza virus or human metapneumovirus but are generally more consistent from year to year and result in more disease overall, especially among infants younger than 6 months of age. In the tropics, the epidemic pattern is less clear. The pattern of widespread annual outbreaks and the high incidence of infection during the first 3-4 months of life are unique among human viruses. The conventional seasonality of RSV outbreaks was altered in 2020–2021 by events associated with the COVID-19 pandemic. Delayed and out-of-season RSV epidemics occurred during the COVID-19 pandemic when reopening activities

occurred after a long period of reduced transmission due to nonpharmaceutical interventions such as masking, distancing, and daycare and school closure reduced transmission.

Transplacentally acquired anti-RSV maternal immunoglobulin G (IgG) serum antibodies, if present in high concentration, appear to provide partial protection for the neonate. The age of peak incidence of severe lower respiratory tract disease and hospitalization is about 6 weeks. Maternal IgGs may account for the lower severity and incidence of RSV infections during the first 4-6 weeks of life, except among infants born prematurely, who receive less maternal immunoglobulin. Breastfeeding provides some protection against severe disease, an effect that may pertain only to female and not male infants. RSV is one of the most contagious viruses that affect humans. Infection is nearly universal among children by their second birthday. Reinfection occurs at a rate of at least 10–20% per epidemic throughout childhood, with a lower frequency among adults. In situations of high exposure, such as daycare centers, attack rates are nearly 100% among previously uninfected infants and 60–80% for second and subsequent infections.

Reinfection may occur as early as a few weeks after recovery but usually takes place during subsequent annual outbreaks. Antigenic variation is not required for reinfection, as shown by the fact that a proportion of adults inoculated repeatedly with the same experimental preparation of wild-type virus could be reinfected multiple times. The immune response of infants is poor in quality, magnitude, and durability. The severity of illness during reinfection in childhood is usually lower than that in first infection and appears to be a function of partial acquired immunity, more robust airway physiology, and increased age.

Asymptomatic RSV infection is unusual in young children. Most infants experience coryza and pharyngitis, often with fever and frequently with otitis media caused by virus in the middle ear or bacterial superinfection following eustachian tube dysfunction. The lower respiratory tract is involved to a varying degree, with bronchiolitis and bronchopneumonia in about a third of children. The hospitalization rate for RSV infection in otherwise healthy infants is typically 0.5–4%, depending on region, sex, socioeconomic status, exposure to cigarette smoke, gestational age, and family history of atopy. The admitting diagnosis is usually bronchiolitis with hypoxia, although this condition is often indistinguishable from RSV pneumonia in infants, and, indeed, the two processes frequently coexist. All RSV diseases of the lower respiratory tract (excluding croup) have their highest incidence at 6 weeks to 7 months of age and decrease in frequency thereafter. The syndrome of bronchiolitis is much less common after the first birthday. The terminology used for the diagnosis of virus-associated wheezing illnesses in toddlers can be confusing, because these illnesses are variably termed *wheezing-associated respiratory infection, wheezy bronchitis, exacerbation of reactive airways disease,* or *asthma attack*. Because many toddlers wheeze during RSV infection but do not go on to have lifelong asthma, it is best to use the diagnostic term *asthma* only later in life. It is still uncertain if RSV-associated wheezing illness in infancy causes asthma in later life. On the whole, prevention of severe RSV illness in high-risk infants using RSV monoclonal antibody prophylaxis does not seem to reduce the incidence of asthma in those populations significantly. Whether a vaccine will have such an effect in the future is still to be determined.

Acute viral pneumonia is a recurring problem throughout childhood, although RSV becomes less prominent as the etiologic agent after the first year. RSV plays a causative role in an estimated 40–75% of cases of hospitalized bronchiolitis, 15–40% of cases of childhood pneumonia, and 6–15% of cases of croup. Bronchiolitis and pneumonia resulting from RSV are more common in males than in females by a ratio of approximately 1.5:1. Other risk factors with a similar impact in the United States include one or more siblings in the home, White race, rural residence, maternal smoking, and maternal education <12 years. The medical factors in infants associated with the highest risk are chronic lung disease of prematurity, congenital heart disease, immunodeficiency, and prematurity. Still, most infants admitted to the hospital because of RSV infection do not have strong, easily identifiable risk factors. Therefore any strategy for prophylaxis focused only on individuals with strong risk factors probably could prevent only approximately 10% of hospitalizations, even if the prophylaxis was 100% effective in treated high-risk individuals.

The incubation period from exposure to first symptoms is approximately 3-5 days. The virus is excreted for variable periods, probably depending on the severity of illness and immunologic status. Most infants with lower respiratory tract illness shed infectious viruses for 1-2 weeks after hospital admission. Excretion for 3 weeks and even longer has been documented. Spread of infection occurs when large infected droplets, either airborne or conveyed on hands or other fomites, are inoculated in the nasopharynx of a susceptible subject. RSV is probably introduced into most families by young schoolchildren experiencing reinfection. Typically, in the space of a few days, 25–50% of older siblings and one or both parents acquire upper respiratory tract infections, but infants become more severely ill with fever, otitis media, or lower respiratory tract disease.

Nosocomial infection during RSV epidemics is an important concern. Virus is usually spread from child to child on the hands of caregivers or other fomites. Adults experiencing reinfection also have been implicated in the spread of the virus. Contact precautions are sufficient to prevent spread when compliance is meticulous, because the virus is not spread by small particle aerosol to an appreciable degree, and a distance of about 6 ft is likely sufficient to avoid aerosol transmission. During the COVID-19 pandemic, widespread social measures, including masking and distancing, appeared to prevent transmission of RSV on a world-wide basis. However, in normal circumstances, adherence to isolation procedures by caregivers often is not complete.

PATHOGENESIS

Bronchiolitis is caused by obstruction and collapse of the small airways during expiration. Infants are particularly apt to experience small airway obstruction because of the small size of their normal bronchioles; airway resistance is proportional to $1/\text{radius}^4$. There has been relatively little pathologic examination of RSV disease in the lower airways of otherwise healthy subjects. Airway narrowing likely is caused by virus-induced necrosis of the bronchiolar epithelium, hypersecretion of mucus, and round-cell infiltration and edema of the surrounding submucosa. These changes result in the formation of mucus plugs obstructing bronchioles, with consequent hyperinflation or collapse of the distal lung tissue. In interstitial pneumonia, the infiltration is more generalized, and epithelial shedding may extend to both the bronchi and the alveoli. In older subjects, smooth muscle hyperreactivity may contribute to airway narrowing, but the airways of young infants typically do not exhibit a high degree of reversible smooth muscle hyperreactivity during RSV infection.

Several facts suggest that elements of the host response may cause inflammation and contribute to tissue damage. The immune response required to eliminate virus-infected cells (mostly containing cytolytic T cells) is a double-edged sword, reducing the cells producing virus but also causing host cell death in the process. Many soluble factors, such as cytokines, chemokines, and leukotrienes, are released in the process, and skewing of the patterns of these responses may predispose some individuals to more severe disease. There is also evidence that genetic factors may predispose to more severe bronchiolitis.

Some studies have identified the presence of both RSV and human metapneumovirus viral RNA in airway secretions in a significant proportion of infants requiring assisted ventilation and intensive care. It may be that co-infection is associated with more severe disease. Positive results of polymerase chain reaction (PCR) analysis must be interpreted carefully because this positivity can remain for prolonged periods after infection, even when infectious virus can no longer be detected.

It is not clear how often superimposed bacterial infection plays a pathogenic role in RSV lower respiratory tract disease. RSV bronchiolitis in infants is probably exclusively a viral disease, although there is evidence that bacterial pneumonia can be triggered by respiratory viral infection, including with RSV. A large clinical study of pneumococcal vaccine showed that childhood vaccination reduced the incidence of viral pneumonia by approximately 30%, suggesting viral-bacterial interactions that we currently do not fully understand.

CLINICAL MANIFESTATIONS

Typically, the first sign of infection in infants with RSV is rhinorrhea. Cough may appear simultaneously but more often does so after an interval of 1-3 days, at which time there may also be sneezing and a low-grade fever. Soon after the cough develops, the child who experiences bronchiolitis begins to wheeze audibly. If the disease is mild, the symptoms may not progress beyond this stage. Auscultation often reveals diffuse fine inspiratory crackles and expiratory wheezes. Rhinorrhea usually persists throughout the illness, with intermittent fever. Chest radiograph findings at this stage are frequently normal.

If the illness progresses, cough and wheezing worsen and air hunger ensues, with an increased respiratory rate, intercostal and subcostal retractions, hyperexpansion of the chest, restlessness, and peripheral cyanosis. Signs of severe, life-threatening illness are central cyanosis, tachypnea of >70 breaths/min, listlessness, and apneic spells. At this stage, the chest may be significantly hyperexpanded and almost silent to auscultation because of poor air movement.

Chest radiographs of infants hospitalized with RSV bronchiolitis have normal findings in approximately 30% of cases, with the other 70% showing hyperexpansion of the chest, peribronchial thickening, and interstitial infiltrates. Segmental or lobar consolidation is unusual, and pleural effusion is rare.

In some infants, the course of the illness may resemble that of pneumonia, the prodromal rhinorrhea and cough being followed by dyspnea, poor feeding, and listlessness. Although the clinical diagnosis is pneumonia, wheezing is often present intermittently, and the chest radiographs may show air trapping.

Fever is an inconsistent sign in RSV infection. In young infants, particularly those who were born prematurely, periodic breathing and apneic spells have been distressingly frequent signs, even with relatively mild bronchiolitis. Apnea is not necessarily caused by respiratory exhaustion but rather appears to be a consequence of alterations in the central control of breathing.

RSV infections in profoundly immunocompromised hosts or those with chronic lung disease or pulmonary hypertension may be severe at any age of life. The mortality rates associated with RSV pneumonia in the first few weeks after hematopoietic stem cell or solid-organ transplantation in both children and adults are high. RSV infection does not appear to be more severe in HIV-infected patients with reasonable control of HIV disease, although these patients may shed virus in respiratory secretions for prolonged periods.

Secondary (associated) bacterial infections are uncommon in most previously healthy patients with RSV bronchiolitis. However, otitis media may be present because of either RSV or bacterial middle ear infection.

DIAGNOSIS

Bronchiolitis is a clinical diagnosis. RSV can be suspected with varying degrees of certainty based on the season of the year and the presence of the virus in the community. Other epidemiologic features that may be helpful are the presence of common colds in older household contacts and the age of the child. The other respiratory viruses that attack infants frequently during the first few months of life are human metapneumovirus, influenza viruses, parainfluenza virus type 3, rhinoviruses, enteroviruses, and coronaviruses.

Routine laboratory tests are of minimal diagnostic use in most cases of bronchiolitis or pneumonia caused by RSV. The white blood cell count is normal or elevated, and the differential cell count may be normal with either a neutrophilic or mononuclear predominance. Hypoxemia as measured by pulse oximetry or arterial blood gas analysis is frequent and tends to be more marked than anticipated from the clinical findings. A normal or elevated blood carbon dioxide value in a patient with a markedly elevated respiratory rate is a sign of respiratory failure.

The most important diagnostic concern is to differentiate viral infection from bacterial or chlamydial infection. When bronchiolitis is not accompanied by infiltrates on chest radiographs, there is little likelihood of a bacterial component. In infants 1-4 months of age, interstitial pneumonitis may be caused by *Chlamydia trachomatis* (see Chapter 272). With *C. trachomatis* pneumonia, there may be a history of conjunctivitis, and the illness tends to be of subacute onset. Coughing and inspiratory crackles may be prominent; wheezing is not. Fever is usually absent.

Lobar consolidation without other signs or with pleural effusion should be considered of bacterial etiology until proved otherwise. Other signs suggesting bacterial pneumonia are neutrophilia, neutropenia in the presence of severe disease, ileus or other abdominal signs, high temperature, and circulatory collapse. In such instances, antibiotics should be initiated.

The definitive diagnosis of RSV infection is based on the detection in respiratory secretions of live virus by cell culture. Molecular diagnostic tests are more available, however. The presence of viral RNA (detected by a molecular diagnostic test using reverse transcription PCR) or viral antigens (detected by a rapid diagnostic test, usually a membrane blotting test incorporating antibody detection of viral proteins) is strongly supportive in the right clinical setting. The antigen test is less sensitive than virus culture, whereas reverse transcription PCR analysis is more sensitive than culture. An aspirate of mucus or a nasopharyngeal wash from the child's posterior nasal cavity is the optimal specimen. Nasopharyngeal or throat swabs are less preferable but are acceptable. A tracheal aspirate is unnecessary, but endotracheal tube lavage fluid from patients intubated for mechanical ventilation can be tested. The specimen should be placed on ice, taken directly to the laboratory, and processed immediately for culture, antigen detection, or PCR analysis. RSV is thermolabile, so it degrades over relatively short periods of time unless it is frozen at a low temperature such as −80°C (−112°F) in freezers used in research settings.

TREATMENT

The treatment of uncomplicated cases of bronchiolitis is symptomatic. Many infants are slightly to moderately dehydrated, and therefore fluids should be carefully administered in amounts somewhat greater than those for maintenance. Often, intravenous or tube feeding is helpful when sucking is difficult because of tachypnea. Humidified oxygen and suctioning usually are indicated for hospitalized infants who are hypoxic. High-flow nasal cannula (HFNC) therapy is used for respiratory distress either before or after admission to an intensive care unit. HFNC is often started based on the subjective assessment of work of breathing; despite HFNC use, it remains uncertain if the outcome of RSV bronchiolitis has been improved with HFNC. Nasal continuous positive airway pressure is used in the intensive care unit for infants who have increased work of breathing, and mechanical ventilation is used for respiratory failure.

There is disagreement among experts regarding the usefulness of aerosolized saline or hypertonic saline, epinephrine, or β_2-agonists in RSV bronchiolitis. Most patients do not receive lasting benefit from prolonged therapy, which is associated with a relatively high frequency of side effects. Corticosteroid therapy is not indicated except in older children with an established diagnosis of asthma, because its use is associated with prolonged virus shedding and is of no proven clinical benefit. The 2014 American Academy of Pediatrics bronchiolitis clinical practice guideline suggests limitations on the use of α- and β-adrenergic agents and corticosteroids.

In nearly all instances of bronchiolitis, antibiotics are not useful, and their inappropriate use contributes to the development of antibiotic resistance. Interstitial pneumonia in infants 1-4 months old may be caused by *C. trachomatis,* and macrolide therapy may be indicated for that infection if identified by specific testing.

PROGNOSIS

The mortality rate of hospitalized infants with RSV infection of the lower respiratory tract is very low in the developed world. Almost all deaths occur among young, premature infants or infants with underlying disease of the neuromuscular, pulmonary, cardiovascular, or immunologic system. However, it is estimated that more than 160,000 children worldwide in resource-poor settings die each year from RSV. In addition, thousands of elderly patients die of RSV infection each year in the United States.

There is recurrent wheezing in 30–50% of children who have severe RSV bronchiolitis in infancy, and many older children who are diagnosed with asthma have a history of severe bronchiolitis in infancy. The likelihood of the recurrence of wheezing is increased in the presence

of an allergic diathesis (e.g., eczema, hay fever, or a family history of asthma). With a clinical presentation of bronchiolitis in a patient older than 1 year of age, there is an increasing probability that, although the episode may be virus-induced, the event is likely the first of multiple wheezing attacks that will later be diagnosed as hyperreactive airways disease or asthma. Asthma is difficult to diagnose in the first year of life. It is not fully clear at this time whether early, severe RSV wheezing disease causes some cases of asthma or whether persons destined to have asthma present with symptoms first when provoked by RSV infection during infancy. Results from a long-term follow-up study of infants who received palivizumab prophylaxis suggested that the prevention of severe RSV infection may reduce the incidence of reactive airways disease later in life.

PREVENTION

Prevention of Nosocomial Spread

In the hospital, the most important preventive measures are aimed at blocking nosocomial spread. During RSV season, high-risk infants should be separated from all infants with respiratory symptoms. Gowns, gloves, and careful handwashing (contact isolation) should be used for the care of all infants with suspected or established RSV infection. A high level of compliance with contact isolation is essential. Viral laboratory tests are adequate for diagnosis in the setting of acute disease when levels of virus are high, but they are not designed to detect low levels of virus. Therefore, contact precaution isolation should be observed for the duration of hospitalization for most patients admitted for acute disease. Rapid antigen tests should not be used to determine whether a patient still requires isolation, because low concentrations of virus may be present in respiratory secretions that are infectious for humans but below the lower limit of detection for such assays. Ideally, patients with RSV or metapneumovirus infections are housed separately because co-infection with the two viruses may be associated with more severe disease.

Protection of Infants Against Infection or Severe Disease

Antibodies that neutralize RSV are the principal mechanism of protection against infection or reinfection. Antibodies are induced by natural infection but can also be provided to infants prior to a first infection in several ways. *First*, all mothers pass along their own naturally occurring IgG antibodies across the placenta beginning at about 28-32 weeks' gestation. *Second*, breastfeeding may transfer maternal antibodies (including IgA antibodies) to infant mucosal surfaces, providing benefit in some infants. *Third*, antibodies manufactured as biologic drugs can be administered directly to infants after birth. *Fourth*, maternal immunization with an approved RSV vaccine can increase the level of antibodies in the mother's serum and thus also the level of antibodies transferred across the placenta. The Advisory Committee on Immunization Practices (ACIP) in the United States recommends that either antibody administration to the infant or maternal vaccination during pregnancy should be used to prevent RSV-associated lower respiratory tract illness among all infants, but *both* exogenous antibodies and maternal vaccination are not needed for most infants.

Passive Immunoprophylaxis

A neutralizing humanized murine monoclonal antibody against RSV given IM once a month (palivizumab) has been approved for protecting high-risk children against serious complications from RSV disease. A next-generation monoclonal antibody (nirsevimab, Beyfortus, Sanofi and AstraZeneca) was subsequently approved for the prevention of lower respiratory tract infection caused by RSV in the European Union, United Kingdom, United States, and Canada. Nirsevimab is an RSV fusion-protein-specific monoclonal antibody with an extended half-life because of engineered changes in the antibody Fc region. Since the antibody is long-acting (with a half-life of about 3 months instead of 3 weeks as for conventional IgG), only a single dose is necessary to protect term, preterm, and high-risk infants for an entire RSV season. In the United States, nirsevimab is indicated for the prevention of RSV lower respiratory tract disease in neonates and infants <8 months born during or entering their first RSV season and in children 8–19 months of age at increased risk for severe RSV disease entering their second RSV season.

Nirsevimab is dispensed in prefill syringes of either 50 or 100 mg; the dose is 50 mg IM for infants < 5 kg, and 100 mg IM for infants < 8 months old and ≥ 5 kg. The first dose for infants <8 months of age may be given in the first week of life. For infants 8-19 months of age entering their second RSV season and at increased risk for severe RSV infection, the dose is 200 mg.

Because of a projected shortage of the 100 mg dose, it is recommended that only infants ≥ 5kg who are at high risk for severe RSV infection receive the 100 mg dose. High risk patients are defined as:

- Infants < 6 months
- American Indian and Alaska Natives < 8 months
- Infants age 6 to < 8 months with prematurity (< 29 weeks), chronic lung disease of prematurity, hemodynamically significant congenital heart disease, severe immunocompromise, cystic fibrosis, neuromuscular disease, or congenital pulmonary abnormalities that impair the ability to clear secretions

Palivizumab should be administered only to high risk infants (8-19 months old) and to eligible infants <8 months old if nirsevimab is not available.

Administration of palivizumab (15 mg/kg intramuscularly once a month) is recommended for protecting high-risk children against serious complications from RSV disease. Palivizumab is administered from the beginning to the end of the RSV season. Palivizumab prophylaxis may be considered for the following infants and children:

- Infants born before 29 wk of gestation in the first year of life
- Infants born before 32 wk of gestation, who have chronic lung disease of prematurity (required > 21% Fio_2 [fraction of inspired oxygen] for ≥ 28 days after birth), in the first year of life and in the second RSV season if continued medical support (oxygen, diuretics, steroids) is needed
- Infants younger than 1 yr of age with hemodynamically *significant* acyanotic congenital heart disease or those with moderate to severe pulmonary hypertension and those patients following cardiac transplantation (children < 2 yr of age)
- Children 24 mo of age or younger with profound immunocompromising conditions during RSV season
- Infants in the first year of life who have either congenital abnormalities of the airway or neuromuscular disease that compromises the handling of respiratory secretions

Vaccine

There are two licensed subunit protein vaccines against RSV for older adults (Abrysvo, Pfizer; Arexvy, GSK) based on a prefusion conformation of the RSV fusion (F) protein (RSVpreF). The bivalent RSVpreF Abrysvo vaccine has subunit proteins for both the type A and type B RSV antigenic subgroups, while the Arexvy vaccine contains only subgroup A antigen combined with an adjuvant. Neither vaccine is approved for use in infants or children, but Abrysvo is used in pregnant mothers 32-36 weeks pregnant during RSV season with the goal to protect infants. The mechanism of protection is that the resulting increased serum level of RSV-neutralizing antibodies in the mother can enhance immunity in neonates following transplacental transfer of those maternal RSV antibodies to the fetus. In efficacy trials, this vaccination reduced the incidence of medically attended RSV lower respiratory tract infections and hospitalization within 90 days after birth. The Abrysvo vaccine is recommended during September through January for most of the United States. since RSV typically peaks in fall and winter. The seasonality of RSV season varies depending on location, and thus state, local, or territorial health departments may recommend different timing for administration in diverse areas. The risk of severe RSV is even greater in infants born at <32 weeks' gestation. When Abrysvo was compared to placebo in clinical trials, infants born to pregnant individuals experienced low birth weight (5.1% Abrysvo compared to 4.4% placebo, a difference that was not statistically significant). The European Medicines Agency chose to approve maternal immunization with Abrysvo between weeks 24 and 36 of gestation, while the US FDA chose to approve the vaccine between weeks 32 and 36 of gestation while awaiting additional safety information from ongoing studies.

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Chapter 308

Human Metapneumovirus

James E. Crowe Jr.

ETIOLOGY

Human metapneumovirus (HMPV) is a respiratory virus that is one of the most common causes of serious lower respiratory tract illness in children throughout the world.

ETIOLOGY

HMPV is an enveloped, single-stranded, nonsegmented, negative-sense RNA genome of the family Pneumoviridae, which comprises large enveloped negative-sense RNA viruses. This taxon was formerly a subfamily within the Paramyxoviridae but was reclassified in 2016 as a family with two genera: *Metapneumovirus* (which includes HMPV) and *Orthopneumovirus* (which includes respiratory syncytial virus [RSV]; see Chapter 307). HMPV and the avian pneumoviruses are highly related and are separated into the separate genus *Metapneumovirus* because the gene order in the nonsegmented genome is slightly altered and because avian pneumoviruses/HMPVs lack the genes for two nonstructural proteins, NS1 and NS2, which are encoded at the 3′ end of RSV genomes. These proteins are thought to counteract host type I interferons. The absence of NS1/NS2 in the metapneumoviruses (compared with RSV) may contribute to an overall slightly reduced pathogenicity relative to wild-type RSV strains.

The HMPV genome encodes nine proteins in the order 3′-N-P-M-F-M2-(orf1 and 2)-SH-G-L-5′. The genome also contains noncoding 3′ leader, 5′ trailer, and intergenic regions, consistent with the organization of most paramyxoviruses, with a viral promoter contained in the 3′ end of the genome. The F (fusion), G (glycosylated), and SH (short hydrophobic) proteins are integral membrane proteins on the surfaces of infected cells and virion particles. The F protein is a classic type I integral membrane viral fusion protein that contains two heptad repeats in the extracellular domain that facilitate membrane fusion. There is a predicted protein cleavage site near a hydrophobic fusion peptide that likely is cleaved by an extracellular protease, activating the F protein for fusion. The predicted attachment (G) protein of HMPV exhibits the basic features of a glycosylated type II mucin-like protein. The HMPV G protein differs from the RSV G protein that inhibits innate immune responses in that the HMPV G lacks a cysteine noose structure. The internal proteins of the virus appear similar in function to those of other paramyxoviruses.

EPIDEMIOLOGY

HMPV outbreaks occur in annual epidemics during late winter and early spring in temperate climates, often overlapping with the second half of the annual RSV epidemic (Fig. 308.1). Sporadic infections occur year-round. A near-total decline of HMPV infections occurred in the 2020–2021 winter associated with COVID-19 public health measures, followed by a delayed or interseasonal outbreak in 2021. The usual period of viral shedding is likely to be many days or even several weeks after primary infection in infants. The incubation period is approximately 3-5 days. Humans are the only source of the virus; there is no known animal or environmental reservoir. Transmission occurs by close or direct contact with contaminated secretions involving large-particle aerosols, droplets, or contaminated surfaces. Nosocomial infections have been reported, and contact isolation with excellent handwashing for healthcare providers is critical in medical settings. This virus also affects the elderly, immunocompromised patients, and patients with reactive airways disease more severely than otherwise healthy individuals.

PATHOLOGY

Infection is usually limited to the superficial layer of airway epithelial cells and is associated with a local inflammatory infiltrate consisting of lymphocytes and macrophages. Immunocompromised individuals have evidence of both acute and organizing injuries during prolonged infection.

PATHOGENESIS

Infection occurs via inoculation of the upper respiratory tract. Infection can spread rapidly to the lower respiratory tract, but it is not clear whether the dissemination is mediated by cell-to-cell spread or by aspiration of infected materials from the upper tract. Severe lower respiratory tract illness, especially wheezing, occurs mainly during the first year of life, at a time when the airways are of a very small diameter and thus a high resistance. Maternal serum-neutralizing antibodies that cross the placenta may afford a relative protection against severe disease for several weeks or months after birth. Once infection is established, it is likely that cytotoxic T cells recognize and eliminate virus-infected cells, thus terminating the infection but also causing some cytopathology. The virus appears to have specific mechanisms for inhibiting T-cell responses during acute infection. Individuals with an underlying predisposition for reactive airways disease (including adults) are susceptible to severe wheezing during reinfection later in life, suggesting that HMPV may cause smooth muscle hyperactivity, inflammation, or increased mucus production in such individuals. Infection in otherwise healthy individuals resolves without apparent long-term consequences in most cases. HMPV infection is associated with exacerbations of asthma later in life.

CLINICAL MANIFESTATIONS

HMPV is associated with the common cold (complicated by otitis media in approximately 30% of cases) and with lower respiratory tract illnesses such as bronchiolitis, pneumonia, croup, and exacerbation of reactive airways disease. The profile of signs and symptoms caused by HMPV is similar to that caused by RSV (Table 308.1). Approximately 5–10% of outpatient lower respiratory tract illnesses in otherwise healthy young children are associated with HMPV infection, which is second in incidence only to RSV. Children with RSV or HMPV infection require supplemental oxygen and medical intensive care at similar frequencies.

About half of the cases of HMPV lower respiratory tract illness in children occur in the first 6 months of life, suggesting that young age is a major risk factor for severe disease. Both young adults and the elderly can have HMPV infection that requires medical care, including hospitalization, but severe disease occurs at much lower frequencies in adults than in young children. Severe disease in pediatric and older subjects is most common in immunocompromised patients or those with complications of preterm birth, congenital heart disease, and neuromuscular disease and can be fatal. A significant number of both adult and pediatric patients with asthma exacerbations have HMPV infection; it is not clear whether the virus causes long-term wheezing. RSV and HMPV co-infections have been reported; co-infections may be more severe than infection with a single virus, resulting in pediatric intensive care unit admissions. It is difficult to define true co-infections because these viral RNA genomes can be detected by a reverse transcriptase polymerase chain reaction (PCR) in respiratory secretions for at least several weeks after illness, even when virus shedding has terminated.

LABORATORY FINDINGS

The virus can be visualized only with electron microscopy. The virus grows in primary monkey kidney cells or LLC-MK2 cell-line or Vero cell-line monolayer cultures in reference or research laboratories, but efficient isolation of the virus requires an experienced laboratory technician. Conventional bright-field microscopy of infected cell monolayer cultures often reveals a cytopathic effect only after multiple passages in the cell culture. The characteristics of the cytopathic effect are not sufficiently distinct to allow identification of the virus on this basis alone, even by a trained observer. The most sensitive test for identification of HMPV in clinical samples is reverse transcriptase PCR, usually performed with primers directed to conserved viral genes. Detection by this modality is also available in some multiplex PCR tests for panels of respiratory viruses. Real-time reverse transcriptase PCR tests offer enhanced sensitivity and specificity, including assays designed to detect viruses from the four known genetic lineages. Direct

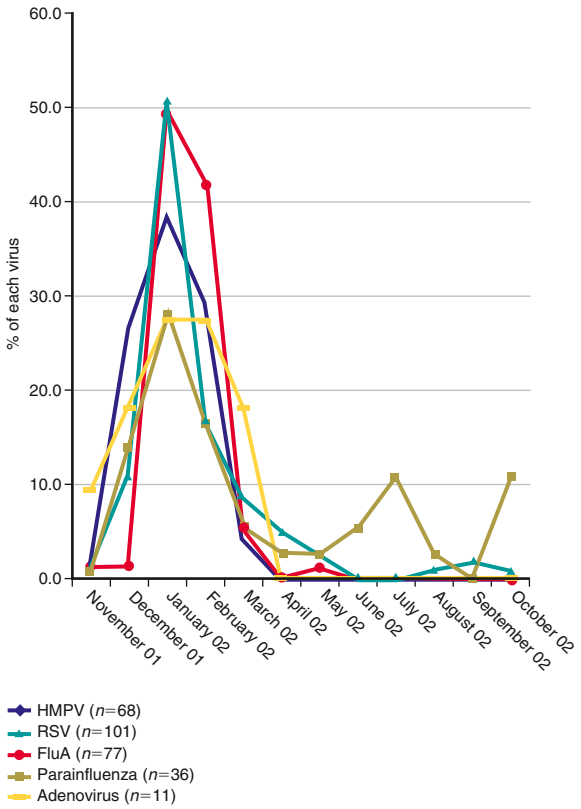

Fig. 308.1 Temporal distribution of respiratory viruses among children hospitalized with lower respiratory tract infections from November 2001 through October 2002. Data are displayed as the proportion of each virus detected monthly. FluA, influenza A; HMPV, human metapneumovirus; RSV, respiratory syncytial virus. *(From Wolf DG, Greenberg D, Kalkstein D, et al. Comparison of human metapneumovirus, respiratory syncytial virus and influenza A virus lower respiratory tract infections in hospitalized young children. Pediatr Infect Dis J. 2006;25:320–324.)*

Table 308.1 Clinical Manifestations of Human Metapneumovirus in Children

COMMON (>50%)
Fever >38°C (100.4°F)
Cough
Rhinitis, coryza
Wheezing
Tachypnea, retractions
Hypoxia (O_2 saturation <94%)
Chest radiograph demonstration of infiltrates or hyperinflation
LESS COMMON
Otitis media
Pharyngitis
Rales
RARE
Conjunctivitis
Hoarseness
Encephalitis
Fatal respiratory failure in immunocompromised children

antigen tests for identification of HMPV antigens in nasopharyngeal secretions are available but are less efficient than nucleic acid–based detection. Some laboratories have success with the use of immunofluorescence staining with monoclonal or polyclonal antibodies to detect HMPV in nasopharyngeal secretions and shell vial cultures or in monolayer cultures in which virus has been cultivated, with reported sensitivities varying from about 65% to 90%. A fourfold rise in serum antibody titer to HMPV from the acute to convalescent time point can be used in research settings to confirm infection.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

In temperate areas, the diagnosis should be suspected during the late winter in infants or young children with wheezing or pneumonia and a negative RSV diagnostic test result. The diseases caused by RSV and HMPV cannot be distinguished clinically. Many other common respiratory viruses, such as parainfluenza viruses, influenza viruses, adenoviruses, rhinoviruses, enteroviruses, and coronaviruses, can cause similar disease in young children. Some of these viruses can be identified by PCR genetic testing or conventional cell culture means. Chest radiographs are not very specific, mostly showing parahilar opacities, hyperinflation, atelectasis, and, occasionally, consolidation but not pleural effusion or pneumothorax.

COMPLICATIONS

Bacterial superinfection of the lower airways is unusual but does occur. The local complication of otitis media is common, likely a result of eustachian tube dysfunction caused by the virus.

TREATMENT

There is no specific treatment currently for HMPV infection. A single small-molecule drug inhibitor for HMPV is in clinical trials as of early 2022. Management consists of supportive care like that used for RSV (see Chapter 307). The rate of bacterial lung infection or bacteremia associated with HMPV infection is not fully defined but is suspected to be low. Antibiotics are usually not indicated in the treatment of infants hospitalized for HMPV bronchiolitis or pneumonia.

Supportive Care

Treatment is supportive and includes careful attention to hydration; monitoring of respiratory status by physical examination and measurement of oxygen saturation; the use of supplemental oxygen, high-flow nasal cannula therapy, and nasal continuous positive airway pressure in an intensive care unit for increased work of breathing; and, in the case of respiratory failure, mechanical ventilation.

PROGNOSIS

Most infants and children recover from acute HMPV infection without apparent long-term consequences. Many experts believe an association exists between severe HMPV infections in infancy and the risk for recurrent wheezing or the development of asthma; however, it is not clear whether the virus causes these conditions or precipitates their first manifestations.

PREVENTION

The only method of prevention of HMPV infection is reduction of exposure. Contact precautions are recommended for the duration of HMPV-associated illness among hospitalized infants and young children. The near-total absence of HMPV infections during the first year of the COVID-19 pandemic suggests that nonpharmacologic interventions (such as masking and distancing) are effective when compliance is high. Patients known to have HMPV infection should be housed in single rooms or with a cohort of HMPV-infected patients. When feasible, it is wise to care for patients with RSV infection in a separate cohort from HMPV-infected patients to prevent co-infection, which may be associated with more severe disease. Preventive measures include limiting exposure to contagious settings during annual epidemics (such as daycare centers) as much as possible and an emphasis on hand hygiene in all settings, including the home, especially during periods when the contacts of high-risk children have respiratory infections. However, providers should keep in mind that infection is universal in the first several years of life. Therefore reduction of exposure makes the most sense during the first 6 months of life, when infants are at the highest risk for severe disease. Experimental HMPV vaccine candidates using live attenuated viruses or a messenger RNA (mRNA)–encoded HMPV fusion protein gene are under study.

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Chapter 309

Adenoviruses

Terri L. Stillwell and Jason B. Weinberg

Human adenoviruses (HAdVs) are a common cause of human disease. Conjunctivitis is a familiar illness associated with the HAdVs, but these viruses also cause upper and lower respiratory disease, pharyngitis, gastroenteritis, and hemorrhagic cystitis. HAdVs can cause severe disease in immunocompromised hosts. Outbreaks of HAdV infection occur in communities and closed populations, notably the military. No currently approved antiviral drugs are highly effective against HAdVs. Vaccines are available for HAdV types 4 and 7 but are used only in military populations.

ETIOLOGY

Adenoviruses are nonenveloped viruses with an icosahedral protein capsid. The double-stranded DNA viral genome is contained within the particle complexed with several viral proteins. Antigenic variability in surface proteins of the virion and genomic sequencing define over 100 types, grouped into seven species. HAdV species differ in their tissue tropism and target organs, causing distinct clinical infections (Table 309.1). HAdVs can be shed from the gastrointestinal and respiratory tracts for prolonged periods and can establish persistent infection in mucosal lymphoid tissue.

EPIDEMIOLOGY

HAdVs circulate worldwide and cause endemic infections year-round in immunocompetent hosts. Asymptomatic infections are also common. Epidemics of conjunctivitis (often severe), pharyngitis, and respiratory disease can occur, especially in schools, congregate living arrangements, and military settings. Outbreaks of febrile respiratory illness caused by HAdV-4 and HAdV-7 are major sources of morbidity in military barracks, with attack rates ranging from 25% to over 90%. HAdV spread occurs by respiratory and fecal-oral routes. An important factor in HAdV transmission, especially in epidemics, is the ability of the nonenveloped particle to survive on inanimate objects in the environment. Nosocomial outbreaks have been reported.

PATHOGENESIS

HAdVs bind to cell surface receptors and trigger internalization by endocytosis. Acidification of the endosome induces conformational changes in the capsid, leading to eventual translocation of the genome to the cell nucleus. Viral messenger RNA transcription and genomic replication occur in the nucleus. Progeny virion particles assemble in the nucleus. Lysis of the cell releases new infectious particles and causes damage to epithelial mucosa, sloughing of cell debris, and inflammation. Host responses to HAdV infection include the recruitment of neutrophils, macrophages, and natural killer cells to the site of infection and the elaboration by those cells of numerous cytokines and chemokines. This host immune response is likely to contribute to the symptoms of HAdV infection, but the strict species specificity of the adenoviruses has hindered detailed studies of HAdV pathogenesis in animal models. Studies using HAdV in Syrian hamsters, which are permissive for HAdV replication, and in a humanized mouse model have provided some insight. Mouse adenoviruses have also been used to study adenovirus pathogenesis using a murine model.

CLINICAL MANIFESTATIONS

HAdVs cause a variety of common clinical syndromes in both immunocompetent and immunocompromised hosts. These syndromes are difficult to reliably distinguish from similar illnesses caused by other pathogens, such as respiratory syncytial virus, human metapneumovirus, human rhinovirus, rotavirus, group A *Streptococcus*, and other common viral and bacterial pathogens.

Acute Respiratory Disease

Respiratory tract infections are common manifestations of HAdV infections in children and adults. HAdVs cause an estimated 5–10% of all childhood respiratory diseases. Primary infections in infants may manifest as bronchiolitis or pneumonia. HAdV pneumonia may present with features more typical of bacterial disease (lobar infiltrates, high fever, parapneumonic effusions). HAdV-14 has emerged as a significant cause of severe acute respiratory disease in military and civilian populations, in some cases leading to hospitalization and death. Pharyngitis caused by HAdV infection typically includes symptoms of coryza, sore throat, and fever. The virus can be identified in 15–20% of children with isolated pharyngitis, mostly in preschool children and infants.

Ocular Infections

The common follicular conjunctivitis caused by HAdV infection is self-limiting and requires no specific treatment. A more severe form called **epidemic keratoconjunctivitis** involves the cornea and conjunctiva. **Pharyngoconjunctival fever** is a distinct syndrome that includes a high temperature, pharyngitis, nonpurulent conjunctivitis, and preauricular and cervical lymphadenopathy.

Gastrointestinal Infections

HAdV can be detected in the stools of 5–10% of children with acute diarrhea. Most cases of acute diarrhea are self-limiting, although severe disease can occur. Enteric infection with HAdV is often asymptomatic, and shedding of virus after acute infection can be prolonged, so the causative role in these episodes is frequently uncertain. HAdV infection may also cause mesenteric adenitis.

Hemorrhagic Cystitis

Hemorrhagic cystitis consists of a sudden onset of hematuria, dysuria, frequency, and urgency with negative urine bacterial culture results. Urinalysis may show sterile pyuria in addition to hematuria. This illness occurs more frequently in young males and typically resolves on its own in 1-2 weeks.

Other Complications

Less frequently, HAdVs are associated with myocarditis, hepatitis, or meningoencephalitis in immunocompetent individuals.

Adenoviruses in Immunocompromised Patients

Immunocompromised persons, particularly recipients of hematopoietic stem cell transplants (HSCTs) and solid organ transplants, are at high risk for severe and fatal disease caused by HAdV. These patients may experience primary HAdV infection, but reactivation of persistent virus in a transplant recipient or transmission of virus from a donor organ may also occur. Organ failure as a consequence of pneumonia, hepatitis, gastroenteritis, and/or disseminated infection can occur in these immunocompromised patients. HAdV infection in HSCT recipients commonly manifests as pulmonary or disseminated disease and is most likely to occur in the first 100 days after transplantation. Hemorrhagic cystitis caused by HAdV can be severe in HSCT recipients. Infections caused by HAdV in solid organ transplant recipients usually involve the transplanted organ. Immunocompromised children are at greater risk than immunocompromised adults for complicated HAdV infection, presumably because of a lack of preexisting immunity. Additional risk factors include T-cell–depleted grafts, high-level immunosuppression, and the presence of graft-versus-host disease. Some experts advocate a preemptive screening approach to detect and treat HAdV infection early in immunocompromised patients, with the intent to prevent dissemination and severe illness in this vulnerable population, though no highly effective antiviral therapy exists.

DIAGNOSIS

HAdV may be suspected as the etiology of an illness on the basis of epidemiologic or clinical features, but neither of these categories is specific enough to firmly establish the diagnosis. The **frequency of asymptomatic shedding of HAdV** makes assigning causality to this pathogen

Table 309.1 Examples of Human Adenovirus Types and Common Manifestations of Disease

SPECIES	TYPE	COMMON DISEASE ASSOCIATIONS
A	12, 18, 31, 61	Gastroenteritis
B	3, 7, 11, 14, 16, 21, 34, 35, 50, 55, 66	Pharyngitis, pharyngoconjunctival fever, acute respiratory disease, pneumonia, hemorrhagic cystitis
C	1, 2, 5, 6, 57	Pharyngitis
D	8-10, 13, 15, 17, 19, 20, 22-30, 32, 33, 36-39, 42-49, 51, 53, 54, 56, 58-60, 63-67, 69, 70-75	Epidemic keratoconjunctivitis
E	4	Acute respiratory disease
F	40, 41	Gastroenteritis
G	52	Gastroenteritis

difficult. Although most HAdV serotypes grow well in culture, culture-based identification requires several days and thus is not helpful for early identification, and most clinical microbiology laboratories no longer perform viral cultures on a routine basis. Cells from respiratory or ocular specimens can be tested using immunofluorescent staining with antibodies to detect HAdV protein. Commercially available enzyme-linked immunoassays can be used to rapidly detect HAdV in patient specimens, usually in stool. Multiplex molecular assays capable of identifying HAdV, in addition to other pathogens, are increasingly available and useful for rapid diagnosis. Specific diagnosis of HAdV infections are most clinically useful in immunocompromised hosts. In these patients, measurement of the **HAdV genome copy number (viral load)** using quantitative real-time polymerase chain reaction can facilitate diagnosis, and repeated measurements can aid in assessing a patient's response to treatment. Serology is generally useful only in epidemiologic investigations.

COMPLICATIONS

HAdV pneumonia can lead to respiratory failure requiring mechanical ventilation, especially in immunocompromised patients. Secondary bacterial pneumonia does not appear to be as common after HAdV infection as it is after influenza infection, but data that address this issue are limited. Severe HAdV pneumonia has been linked to chronic lung disease and bronchiolitis obliterans in a minority of cases. Epidemic keratoconjunctivitis is a vision-threatening form of HAdV infection. Nearly any form of HAdV infection can be fatal in an HSCT or solid organ transplant recipient. Refractory severe anemia requiring repeated blood transfusions can develop in HSCT recipients with hemorrhagic cystitis. Mortality rates of up to 60–80% have been reported in transplant recipients with disseminated HAdV or HAdV pneumonia.

TREATMENT

Supportive care is the mainstay of treatment for HAdV infections. Patients with severe HAdV conjunctivitis should be referred for ophthalmologic consultation. The nucleoside analog cidofovir has in vitro activity against most HAdV serotypes. Cidofovir is used topically to treat epidemic keratoconjunctivitis, often in conjunction with topical steroids or other immunosuppressive agents to limit the inflammatory component of the disease process. Cidofovir may be used intravenously for HAdV infections in immunocompromised patients. Cidofovir is highly nephrotoxic, but prehydration, concomitant administration of probenecid, and weekly dosing may reduce nephrotoxicity. Clinical studies suggest some benefit from cidofovir, but there are no prospective randomized controlled trials of cidofovir for HAdV infection. In addition, no formal guidelines or recommendations for treatment exist. The cidofovir derivative brincidofovir is better tolerated than cidofovir and has been evaluated as treatment of HAdV disease in immunocompromised patients, but it is not currently available for clinical use. Adoptive immunotherapy involving the infusion of HAdV-specific T cells may also provide some benefit for immunocompromised patients with life-threatening HAdV infections.

PREVENTION

Environmental and fomite transmission of HAdV occurs readily; therefore simple measures such as handwashing and cleaning are likely to reduce spread. Live-attenuated HAdV-4 and HAdV-7 vaccines were used effectively in the U.S. military from the 1970s until 1999. Cessation of their use led to widespread outbreaks in barracks, and those vaccines were subsequently reintroduced into military use. However, no HAdV-specific vaccines are available for routine use. HAdVs are highly immunogenic and have been used as gene therapy vectors and vaccine vectors for other pathogens, including malaria, HIV, and SARS-CoV-2.

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Chapter 310
Rhinoviruses

Katherine M. Richardson and Jennifer E. Schuster

Human rhinoviruses (HRVs) are the most frequent cause of the **common cold** in both adults and children. Although HRVs were once thought to cause only the common cold, it is now known that they are also associated with lower respiratory infections in adults and children. Many HRVs do not grow in culture. Recent studies using molecular diagnostic tools such as the polymerase chain reaction (PCR) have revealed that HRVs are leading causes of both mild and serious respiratory illnesses in children.

ETIOLOGY

HRVs are members of the Picornaviridae family ("pico" = small; "rna" = RNA genome). Traditional methods of virus typing using immune antiserum have identified approximately 100 serotypes, classified into HRVA, HRVB, and, recently, HRVC species based on the genetic sequence similarity. HRVCs can be detected by reverse transcriptase PCR but have been cultured only using highly specialized methods. Virus gene sequence analysis demonstrates that HRVCs are a genetically distinct and diverse species. The increased proportions of HRV reported in recent PCR-based studies are likely the result of detection of these previously unknown HRVC viruses in addition to improved detection of known HRVA and HRVB strains.

EPIDEMIOLOGY

Rhinoviruses are distributed worldwide. There is no consistent correlation between serotypes and epidemiologic or clinical characteristics. Several studies suggest that HRVCs may be more strongly associated with lower respiratory infection and asthma, and HRVC has been associated with children admitted to intensive care units with asthma exacerbations, bronchiolitis, and pneumonia. However, more studies are needed to determine severity compared with other HRVs. Multiple types circulate in a community simultaneously, and HRV strains may be isolated during consecutive epidemic seasons, suggesting persistence in a community over an extended period. In temperate climates, the incidence of HRV infection peaks in the fall, with another peak in the spring, but HRV infections occur year-round. HRVC appears to circulate with seasonal variation, exchanging dominance with HRVA. HRVs are the major infectious trigger for asthma among young children, and numerous studies have described a sharp increase in asthma attacks in this age-group when school opens in the fall. The peak HRV incidence in the tropics occurs during the rainy season, from June to October.

HRVs are present in high concentrations in nasal secretions and can be detected in the lower airways. HRV particles are nonenveloped and quite hardy, persisting for hours to days in secretions on hands or other surfaces such as telephones, light switches, doorknobs, and stethoscopes. Sneezing and coughing are inefficient methods of transfer. Transmission occurs when infected secretions carried on contaminated fingers are rubbed onto the nasal or conjunctival mucosa. HRVs are present in aerosols produced by talking, coughing, and sneezing. Children are the most important reservoir of these viruses.

PATHOGENESIS

The majority of HRVs infect respiratory epithelial cells via intercellular adhesion molecule-1, but some HRV strains utilize the low-density lipoprotein receptor. The receptor for HRVC is cadherin-related family member 3 (CDHR3); however, distinct genetic alleles encoding this protein confer different susceptibility to HRVC infection. Infection begins in the nasopharynx and spreads to the nasal mucosa and, in some cases, to bronchial epithelial cells in the lower airways. There is no direct cellular damage from the virus, and it is thought that many of the pathogenic effects are produced by the host immune response. Infected epithelial cells release a number of cytokines and chemokines, which induce an influx of neutrophils to the upper airway. Both innate and adaptive immune mechanisms are important in HRV pathogenesis and clearance. HRV-specific nasal immunoglobulin (Ig) A can be detected on day 3 after infection, followed by the production of serum IgM and IgG after 7-8 days. Neutralizing IgG to HRVs may prevent or limit the severity of illness after reinfection. However, cross protection by antibodies to different HRV serotypes is limited in breadth and duration, allowing recurrent infection. Both allergen exposure and elevated IgE values predispose patients with asthma to more severe respiratory symptoms in response to HRV infection. Abnormalities in the host cellular response to HRV infection that result in impaired apoptosis and increased viral replication may be responsible for the severe and prolonged symptoms in individuals with asthma.

CLINICAL MANIFESTATIONS

Most HRV infections produce clinical symptoms, but many are asymptomatic. Symptomatic HRV infection induces a much more robust host immune response in the blood than asymptomatic infection. After an incubation period of 1-4 days, typical symptoms of sneezing, nasal congestion, rhinorrhea, and sore throat develop. Cough and hoarseness are present in one third of cases. Fever is less common with HRV than with other common respiratory viruses, including influenza virus, respiratory syncytial virus (RSV), and human metapneumovirus. However, HRV was detected in 35% of febrile infants less than 90 days of age. Symptoms are frequently more severe and last longer in children, with 70% of children compared with 20% of adults still reporting symptoms by day 10. Virus can be shed for as long as 3 weeks. When HRV is detected >30 days from the initial illness, it is more likely to be a genotypically different strain of HRV. HRVA and HRVC are more commonly associated with symptomatic HRV infection compared with HRVB.

HRVs are the most prevalent agents associated with acute wheezing, otitis media, and hospitalization for respiratory illness in children and are an important cause of severe pneumonia and exacerbation of asthma or chronic obstructive pulmonary disease in adults. HRV-associated hospitalizations are more frequent in young infants than in older children and in children with a history of wheezing or asthma. Children hospitalized with HRV bronchiolitis are more likely to be older and have a history of wheezing than children with bronchiolitis caused by RSV. HRV infection in immunocompromised hosts may be life threatening. Certain strains or species of HRV, namely HRVC, may be more pathogenic than others.

DIAGNOSIS

Culturing HRVs is labor intensive and of relatively low yield. Sensitive and specific diagnostic methods based on reverse transcriptase PCR are commercially available. However, because commercially available reverse transcriptase PCR tests do not identify the HRV types, it can be difficult to distinguish prolonged shedding from newly acquired infection. An important caveat of HRV detection is the fact that HRV infection can be asymptomatic, and thus the presence of the virus does not prove causality in all cases. Serology is impractical because of the great number of HRV serotypes. A presumptive clinical diagnosis based on symptoms and seasonality is not specific, because many other viruses cause similar clinical illnesses. Rapid detection techniques for HRV might lessen the use of unnecessary antibiotics or procedures.

COMPLICATIONS

Possible complications of HRV infection include sinusitis, otitis media, asthma exacerbation, bronchiolitis, pneumonia, and, rarely, death. HRV-associated wheezing during infancy is a significant risk factor for the development of childhood asthma. In particular, this association has been noted with HRVA and HRVC, which have been associated with greater risk for recurrence of both wheezing and new infection with HRV. This effect appears to remain until adulthood, but the mechanisms have not been elucidated. One large study determined that genetic variants at the 17q21 locus were associated with asthma in children who had experienced HRV wheezing illnesses during infancy. A prospective study on a preterm cohort showed that a single nucleotide polymorphism on the gene coding for the vitamin D receptor was associated with development of lower respiratory infection with HRV. Further studies are required to determine the likely multiple genetic and environmental factors that contribute to HRV-related asthma.

TREATMENT

Supportive care is the mainstay of HRV treatment. The symptoms of HRV infection are commonly treated with analgesics, decongestants, antihistamines, or antitussives. Data are limited on the effectiveness of such nonprescription cold medications for children. If bacterial superinfections are highly suspected or diagnosed, antibiotics may be appropriate. Antibiotics are not indicated for uncomplicated viral upper respiratory infection. There are no licensed antivirals.

PREVENTION

Good handwashing remains the mainstay of the prevention of HRV infection and should be reinforced frequently, especially in young children, the predominant "vectors" for disease. Vaccines have not been successfully developed because of the numerous HRV serotypes and limited cross protection between serotypes. However, a polyvalent inactivated vaccine showed promise in a nonhuman primate.

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Chapter 311

Coronaviruses

Samuel R. Dominguez and Roberta L. DeBiasi

Coronaviruses are increasingly recognized as important human pathogens. Currently there are seven known coronaviruses that have been found to infect humans. Four coronaviruses are endemic in humans: human coronaviruses (HCoVs) 229E, OC43, NL63, and HKU1. These CoVs cause up to 15% of common colds and have been implicated in more serious diseases, including croup, asthma exacerbations, bronchiolitis, and pneumonia. Evidence also suggests that coronaviruses may cause enteritis and might also be agents of meningitis or encephalitis. The fifth identified HCoV, SARS-associated coronavirus (SARS-CoV), the etiologic agent of severe acute respiratory syndrome (SARS), emerged in 2003 and caused a world-wide pandemic resulting in over 8,000 cases with an estimated case fatality rate of 10% before circulation ceased because of implementation of world-wide public health measures. Similarly, Middle East respiratory syndrome coronavirus (MERS-CoV), the sixth identified HCoV, first emerged in 2012 causing significant respiratory distress with very high mortality rates. MERS-CoV continues to cause local cases and outbreaks likely as a result of continued emergent events from its animal reservoir. Likely because of their high mortality, lower transmissibility, and lack of asymptomatic or presymptomatic spread, neither SARS-CoV nor MERS-CoV became endemic viruses.

In 2019 a seventh human coronavirus, SARS-CoV-2, emerged as the etiologic agent of novel coronavirus disease 2019 (COVID-19), resulting in a multiyear and ongoing global pandemic with multiple waves of circulating variants and disease burden exceeding any prior respiratory virus pandemic, including the 1918 influenza pandemic. The ultimate trajectory of SARS-CoV-2 global circulation is unclear, but it is likely that this virus will evolve to become the fifth endemic human coronavirus. The emergence of three distinct human coronaviruses resulting in world-wide pandemics in the past 2 decades emphasizes the potential for coronaviruses to emerge from animal hosts and become important human pathogens.

ETIOLOGY

Coronaviruses are enveloped viruses of medium to large size (80-220 nm) that possess the largest known single-stranded positive-sense RNA genomes. These viruses encode the protein nsp14-ExoN, which is the first known RNA proofreading enzyme and is likely responsible for the evolution of the large and complex coronavirus genome. Coronaviruses derive their name from the characteristic surface projections of the spike protein, giving a corona or crownlike appearance on negative-stain electron microscopy. The human coronaviruses are all part of the order Nidovirales, suborder Cornidovirineae, family Coronaviridae, and subfamily Orthocoronavirinae. The subfamily Orthocoronavirinae is further subdivided into four genera based on genomic phylogenetic relationships. The genus alphacoronavirus includes HCoV-229E and HCoV-NL63. The remaining 5 HCoVs fall within the genus betacoronavirus. HCoV-OC43 and HCoV-HKU1 are in the subgenus Embecovirus, MERS-CoV is in the subgenus Merbecovirus, and SARS-CoV-1 and SARS-CoV-2 are in the subgenus Sarbecovirus (species severe acute respiratory syndrome-related coronavirus). Gammacoronaviruses and deltacoronaviruses presently include exclusively nonhuman pathogens.

Coronaviruses received international attention during the SARS outbreak, which was responsible for more than 800 deaths in 30 countries. SARS-CoV, a novel coronavirus at the time of the epidemic, was found to be the causative agent of SARS. The detection of SARS-like coronaviruses in a live animal market in the Guangdong province in Southern China, along with serologic evidence of exposure in food handlers in the same market, suggest that these markets facilitated the spread of SARS-CoV to humans from an animal reservoir. Subsequent studies identified SARS-like coronaviruses in fecal specimens from asymptomatic Chinese horseshoe bats that are very closely related to SARS-CoV and are capable of infecting human cells. Thus SARS-CoV likely originated in bats and was transmitted to humans via an intermediary animal host such as the palm civet.

Another novel coronavirus, **MERS-CoV**, was first isolated from a man with acute pneumonia and renal failure in Saudi Arabia. As of late 2023, the World Health Organization (WHO) had recorded 2,605 confirmed cases of MERS in 27 countries, with 937 deaths worldwide (~36% mortality rate). MERS-CoV differs from SARS in that it seems to be less communicable, although human-to-human transmission has been documented. MERS-CoV uses dipeptidyl peptidase 4 and carcinoembryonic antigen–like cell-adhesion molecule 5 as its cellular receptor and co-receptor, respectively, whereas SARS-CoV and SARS-CoV-2 use the angiotensin-converting enzyme-2 receptor. With this receptor specificity, MERS-CoV can infect cells from several animal lineages, including human, pig, and bat, suggesting the possibility of movement between multiple species.

EPIDEMIOLOGY

Endemic Coronaviruses

Seroprevalence studies have demonstrated that antibodies against endemic coronaviruses 229E and OC43 increase rapidly during early childhood, so that by adulthood 90–100% of persons are seropositive. Although less information is available for HKU1 and NL63, available studies demonstrate similar patterns of seroconversion to these viruses during early childhood. Seroprevalence studies have also suggested that prevalence rates may differ by geographic region. Although some degree of strain-specific protection may be afforded by recent infection, reinfections are common and occur despite the presence of strain-specific antibodies. Attack rates are similar in different age-groups. Although infections occur throughout the year, there is a peak during the winter and early spring for each of these HCoVs. In the United States, outbreaks of OC43 and 229E have occurred in 2- to 3-year alternating cycles. Independent studies of viral etiologies of upper and lower respiratory infections during the same period, but from different countries, have confirmed that all known HCoVs have a worldwide distribution. Studies using both viral culture and polymerase chain reaction (PCR) multiplex assays demonstrate that coronaviruses often appear in coinfections with other respiratory viruses. Volunteer studies demonstrated that OC43 and 229E are transmitted predominantly through the respiratory route. Droplet spread appears to be most important, although aerosol transmission may also occur.

SARS-CoV

There have been no identified natural or laboratory-acquired cases of SARS-CoV since 2004, but the mechanisms of introduction, spread, and disease remain important for potential animal-to-human transmission and disease. The primary mode of SARS-CoV transmission occurred through direct or indirect contact of mucous membranes with infectious droplets or fomites. Aerosol transmission was less common, occurring primarily in the setting of endotracheal intubation, bronchoscopy, or treatment with aerosolized medications. Fecal-oral transmission did not appear to be an efficient mode of transmission but may have occurred because of the profuse diarrhea observed in some patients. The seasonality of SARS-CoV remains unknown. SARS-CoV is not highly infectious,

with generally only two to four secondary cases resulting from a single infected adult. During the SARS epidemic, a small number of infected individuals, "superspreaders," transmitted infection to a much larger number of persons, but the mechanism for this high degree of spread remains unknown. In contrast, persons with mild disease, such as children younger than 12 years of age, rarely transmitted the infection to others. Infectivity correlated with disease stage; transmission occurred almost exclusively during symptomatic disease. During the 2003 outbreak, most individuals with SARS-CoV infection were hospitalized within 3-4 days of symptom onset. Consequently, most subsequent infections occurred within hospitals and involved either healthcare workers or other hospitalized patients.

MERS-CoV

As of late 2023, the WHO had recorded cases of MERS-CoV in 27 countries, all of which were linked to exposures in the Arabian Peninsula (~80% in Saudi Arabia). Though the route of transmission between animals and humans is not fully understood, MERS-CoV is proposed to have repeatedly entered the human population through contact with respiratory secretions of dromedary camels and possibly with raw camel products (e.g., unpasteurized milk). Antibodies to MERS-CoV are found in dromedaries throughout the Middle East, and strains identical to human MERS-CoV isolates have been found in camels in Egypt, Oman, Qatar, and Saudi Arabia. These strains do not appear to be highly pathogenic or virulent in camels and have likely circulated within dromedaries for >30 years. Despite well-documented zoonotic transmission, most reported cases occur through linked human-to-human transmission in healthcare settings, including outbreaks in Jordan, South Korea, and Saudi Arabia in 2015 and 2016. Risk factors for nosocomial MERS-CoV outbreaks include overcrowded emergency departments, delayed diagnosis or isolation, and poor infection control practices. Transmission most likely occurs through respiratory droplets and is thus a greater risk during aerosol-generating procedures. Outside of healthcare settings, human-to-human transmission has been infrequently documented and is primarily associated with close contact within households.

CLINICAL MANIFESTATIONS

Endemic Coronaviruses: Respiratory Manifestations

Even though up to 50% of respiratory tract infections with OC43 and 229E are asymptomatic, coronaviruses are still responsible for up to 15% of common colds and can cause fatal disease. Cold symptoms caused by HCoVs are indistinguishable from those caused by rhinoviruses and other respiratory viruses. The average incubation period is 2-4 days, with symptoms typically lasting 4-7 days. Rhinorrhea, cough, sore throat, malaise, and headache are the most common symptoms. Fever occurs in up to 60% of cases. Coronavirus NL63 is a cause of croup in children younger than 3 years of age. Coronavirus infections are linked to episodes of wheezing in asthmatic children, albeit at a lower frequency and severity than observed with rhinovirus and respiratory syncytial virus infections. Lower respiratory tract infections, including bronchiolitis and pneumonia, are also reported in immunocompetent and immunocompromised children and adults. As with respiratory syncytial virus or rhinovirus, coronavirus detection in upper respiratory infections is frequently associated with acute otitis media and can be isolated from middle ear fluid.

Endemic Coronaviruses: Nonrespiratory Manifestations

There is prior evidence to support a role for coronaviruses in human gastrointestinal disease, particularly in young children. Coronavirus-like particles have been detected by electron microscopy in the stools of infants with nonbacterial gastroenteritis. In addition, several outbreaks in neonatal intensive care units (ICUs) of gastrointestinal disease characterized by diarrhea, bloody stools, abdominal distention, bilious gastric aspirates, and classic necrotizing enterocolitis have also been associated with the presence of coronavirus-like particles in stools. In older children and adults, coronavirus-like viruses have been observed with similar frequency in symptomatic and asymptomatic individuals, making it difficult to discern if they are pathogenic in the gastrointestinal tract. Additionally, more recent studies using PCR assays of stool from children with gastroenteritis have infrequently found HCoVs. Coronaviruses are well-known causes of neurologic disease in animals, including demyelinating encephalitis, but their role in causing human neurologic disease remains unclear. Several studies have found an association of HCoVs, particularly HCoV-HKU1, with febrile seizures in young children. HCoVs have been detected by culture, in situ hybridization, and reverse-transcriptase PCR (RT-PCR) in brain tissue from a few patients with multiple sclerosis. HCoV-OC43 has been detected by RT-PCR in the spinal fluid, nasopharynx, or brain biopsy specimens of two children with acute encephalomyelitis. However, coronavirus RNA has also been recovered from the spinal fluid and brain tissue of adults without neurologic disease.

Severe Acute Respiratory Syndrome–Associated Coronavirus

During the 2002–2003 global outbreak of SARS, the incubation period for SARS-CoV ranged from 1-14 days, with a median of 4-6 days. SARS-CoV infections in teenagers and adults included a viral replication phase and an immunologic phase. During the viral replication phase, there was a progressive increase in viral load that reached its peak during the second week of illness. The appearance of specific antibodies coincided with peak viral replication. Clinical symptoms were nonspecific, most commonly consisting of fever, cough, malaise, coryza, chills or rigors, headache, and myalgia. Gastrointestinal symptoms, including diarrhea and nausea or vomiting, occurred in up to one third of cases. The clinical deterioration that typified the second and third week of illness was characterized by a decline in the viral load and evidence of tissue injury, likely from cytokine-mediated immunity.

Seroepidemiologic studies suggest that asymptomatic SARS-CoV infections were uncommon. The clinical course of SARS-CoV infection varied with age. Adults were most severely affected, with initial onset of fever, cough, chills, myalgia, malaise, and headache. Following an initial improvement at the end of the first week, fever recurred, and respiratory distress developed, with dyspnea, hypoxemia, and diarrhea. These symptoms progressed in 20% of patients to acute respiratory distress syndrome and respiratory failure. Adolescents manifested increasing severity in direct correlation to increasing age; respiratory distress and hypoxemia were observed in 10–20% of patients, one third of whom required ventilator support. Acute renal failure with histologic acute tubular necrosis was present in 6.9% of patients overall, likely a result of hypoxic kidney damage. Of SARS patients, 28.8% had abnormal urinalysis, with viral genome detectable by quantitative RT-PCR. The case fatality rate from SARS-CoV infection during the 2003 outbreak was 10–17%. No pediatric deaths were reported. The estimated case fatality rate according to age varied from <1% for those younger than 20 years of age to >50% for those older than 65 years of age.

In contrast, children younger than 12 years of age had a relatively mild nonspecific illness, with only a minority experiencing significant lower respiratory tract disease and illness typically lasting less than 5 days. Some young children had no respiratory symptoms. Coryza was more common in children younger than 12 years of age, whereas systemic symptoms were seen more often in teenagers. There were no deaths or cases of acute respiratory distress syndrome in children younger than 12 years of age from SARS-CoV infection.

Middle East Respiratory Syndrome Coronavirus

The incubation period of MERS-CoV is 2-14 days. The syndrome usually presents with nonspecific clinical features typical of acute febrile respiratory illnesses, including low-grade fever, rhinorrhea, sore throat, and myalgia. In mildly symptomatic cases, radiographic findings are typically normal. Severe disease is characterized by the acute respiratory distress syndrome with multilobular airspace disease, ground-glass opacities, and occasional pleural effusions on radiography. The median time between hospitalization and ICU transfer for critical illness is 2 days. Risk factors for severe disease include age >50 years and comorbidities such as obesity, diabetes, chronic obstructive pulmonary disease (COPD), end-stage renal disease, cancer, and immunosuppression. Specific host genetic risk factors have not been identified. Variation in clinical outcomes does not appear to be explained by viral strain-specific sequence variability. As with SARS, extrapulmonary manifestations are common in severe MERS disease. Gastrointestinal symptoms such as nausea, vomiting, and diarrhea occur in one third of patients, and acute kidney injury has been documented in half of critically ill patients. Encephalitis-like neurologic manifestations have been observed in three cases. Laboratory analyses typically detect leukopenia and lymphopenia, with occasional thrombocytopenia, anemia, and aminotransferase elevations. The case fatality rate remains at 35%, though the true incidence of MERS-CoV infection is likely underestimated by existing data. Most patients have been adults, although children as young as 9 months of age have been infected. It is not known whether children are less susceptible to MERS-CoV or present with a different clinical picture.

DIAGNOSIS

With the advent of commercially available, syndromic, multiplex PCR respiratory panels, respiratory infections due to the four endemic HCoVs are now easily diagnosed and widely available in most clinical settings. These panels have rapid turnaround times, excellent sensitivity and specificity, and most commonly use upper respiratory tract specimens. Virus culture of primary clinical specimens remains a challenge for HCoVs HKU1, OC43, 229E, and NL63, even though the epidemic coronaviruses can successfully be grown in culture from respiratory samples. Serodiagnosis with complement fixation, neutralization, hemagglutination inhibition, enzyme immunoassay, and Western blots have been used in the research setting. The diagnosis of SARS-CoV infection can be confirmed by serologic testing, detection of viral RNA using RT-PCR, or isolation of the virus in cell culture. Even though the serology for SARS-CoV has a sensitivity and specificity approaching 100%, antibodies are not detectable until 10 days after the onset of symptoms, and immunoglobulin (Ig) G seroconversion may be delayed for up to 4 weeks. The diagnosis of MERS-CoV should be guided by clinical features and an epidemiologic link. The mainstay for laboratory confirmation of MERS-CoV infection is real-time RT-PCR. The best diagnostic sensitivity is achieved from lower respiratory tract samples collected within the first week of infection, though MERS-CoV RNA can be detected in upper respiratory and blood samples. Alternatively, seroconversion can be documented by screening enzyme-linked immunosorbent assays followed by immunofluorescence microscopy. For all known endemic and emerging HCoVs, respiratory specimens (nasopharyngeal swabs or aspirates) are most likely to be positive, but in a setting of a possible novel coronavirus, saliva, serum, or stool may also be positive.

TREATMENT AND PREVENTION

Several antiviral agents are available for clinical use against coronaviruses targeting the conserved coronavirus protease and polymerase. Ribavirin was extensively used during the 2003 SARS-CoV outbreak but is of questionable benefit given its poor in vitro activity against SARS-CoV at clinically relevant concentrations.

Challenges for the development of effective vaccines targeted against OC43, 229E, HKU1, and NL63 include the fact that infections are rarely life-threatening and reinfection is the rule, even in the presence of natural immunity from previous infections. The durability of immunity to SARS-CoV and MERS-CoV is poorly understood. Nevertheless, effective vaccines for SARS-CoV and MERS-CoV are highly desirable but not yet available.

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311.1 COVID-19

Samuel Dominguez and Roberta L. DeBiasi

New variants may evolve: recommendations for treatment and prevention may change. See Centers for Disease Control and Prevention for updates.

SARS-CoV-2 first emerged in Wuhan China in December 2019 as the etiologic agent of a severe respiratory illness termed COVID-19. Despite measures to contain transmission, SARS-CoV-2 rapidly spread globally, resulting in declaration of a worldwide pandemic by March 2020. As of late 2023, over 770 million cases and nearly 7 million deaths have occurred globally due to SARS-CoV-2. Ongoing transmission has led to the emergence of sequential variants (e.g., Delta, Omicron, BA.2, BA.5, BQ, XBB1.5 variants) with progressively unique gene variants in the receptor binding domain of the spike protein, conferring increased transmissibility compared to the parent strain (Alpha variant). Gene changes in some variants have been associated with reduced susceptibility to monoclonal antibody therapeutics and/or reduced neutralization by convalescent and vaccine-induced antibodies, promoting immune escape and breakthrough infections in previously infected and/or immunized individuals and ongoing community transmission.

EPIDEMIOLOGY

SARS-CoV-2 transmission occurs from human to human primarily by respiratory droplet, as well as by aerosol transmission, with the highest rates of transmission occurring from 2 days prior to 2-3 days after symptom onset. Transmission is quite common among asymptomatic or presymptomatic infected patients. Close contact (conversation distance) increases the risk; normal conversation as well as coughing, sneezing, singing, or just breathing are mechanisms. Immunocompromised hosts may shed infectious virus for longer periods of time, up to 21 days or more after symptom onset. Spread within households and close communal settings is common; transmission has been confirmed from infants, toddlers, and school-age children (who may have very high viral loads in the anterior nares even with asymptomatic or mild infection) and from adolescents to adult household members as well as from adults to children. A metanalysis of household secondary transmission has identified household secondary attack rates of nearly 17%, which exceeds that for SARS-CoV (7.5%) and MERS-CoV (4.7%). Secondary attack rates within households are increased from symptomatic compared to asymptomatic index cases, in adults compared to children, in spouses compared to other household members, and in households with three or more contacts. Throughout the pandemic, it has been noted that transmission is increased in unvaccinated compared to vaccinated individuals.

Young children were initially reported to be less likely to be infected or more likely to be asymptomatic with SARS CoV-2 (alpha, delta strains) than adults and unlikely to develop severe disease. However, despite overall lower rates of hospitalization and death, children are efficiently infected and can develop severe disease (usually older children and adolescents) that results in hospitalization, ICU admission, and occasional death (mortality <0.5%); the majority of young children experience mild to moderate illness.

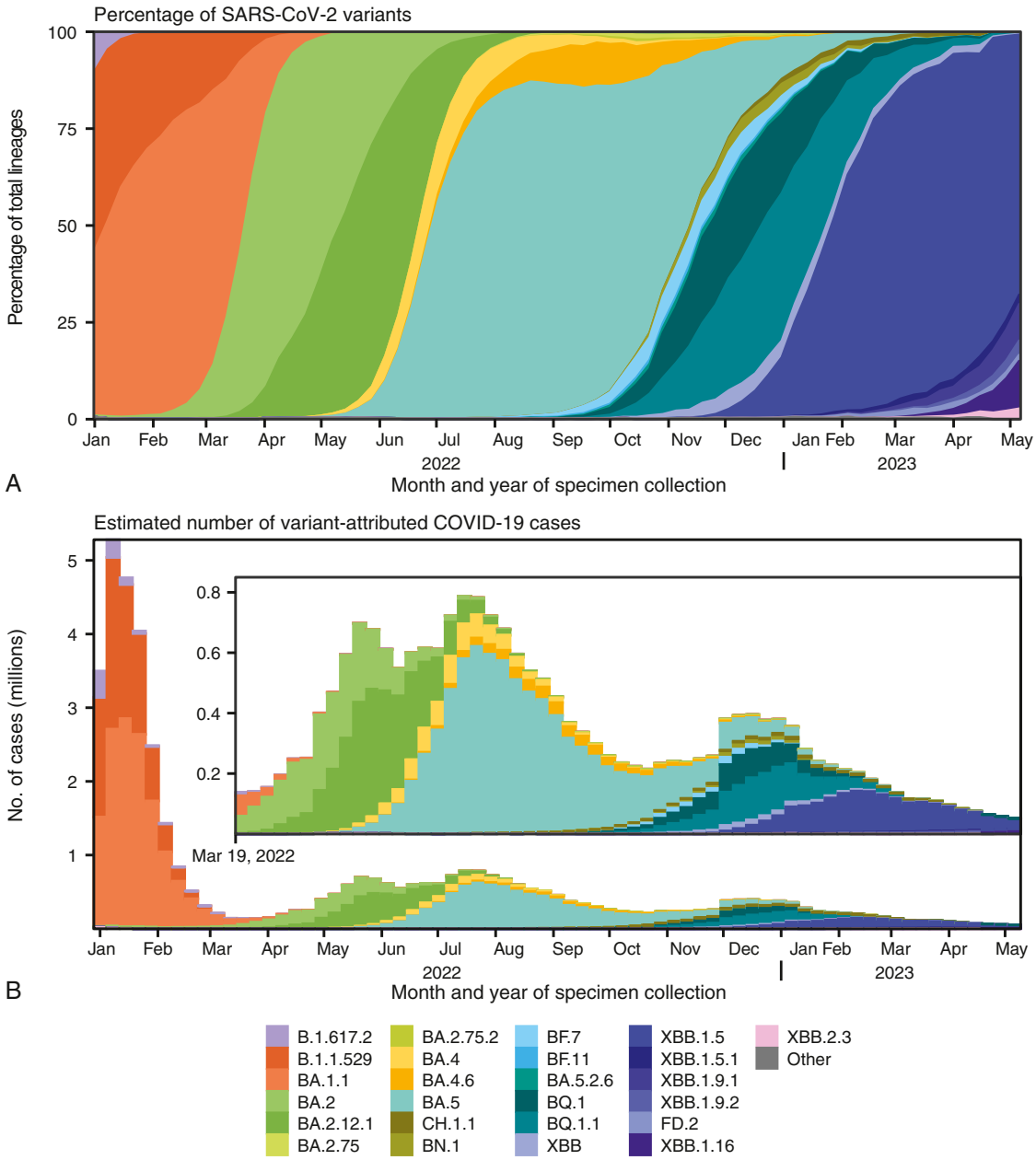

Fig. 311.1 National weekly proportion estimates* of SARS-CoV-2 variants† (A) and estimated number of variant-attributed cases‡ (B) United States, January 2, 2022–May 13, 2023. *Sequences are reported to CDC through NS3, contract laboratories, public health laboratories, and other U.S. institutions. Variant proportion estimation methods use a complex survey design and statistical weights to account for the probability that a specimen is sequenced. †Lineages reaching a prevalence of 1≥% with spike protein substitutions of potential therapeutic relevance and separated out on the COVID Data Tracker website. ‡Estimated numbers of COVID-19 cases attributable to variants were calculated by multiplying weekly numbers of reported positive nucleic acid amplification tests from CELR with estimated variant proportions. *(From Ma KC, Shirk P, Lambrou AS, et al: Genomic surveillance for SARS-CoV-2 variants: circulation of omicron lineages—United States, January 2002–May 2023. MMWR 2023;72,:651–656. Fig. 1, p. 653.)*

As of spring 2023, over 15 million laboratory-confirmed infections and nearly 40,000 hospitalizations have occurred cumulatively in U.S. children ≤18 years of age, representing ~13% of overall infections and up to 4.5% of hospitalizations in the United States. Young children under 5 years of age have made up a relatively increased proportion of cases and hospitalizations during later stages of the pandemic (late variants) presenting more with upper respiratory infection, croup, or bronchiolitis (Fig. 311.1). Milder illness may be due to less virulent variants or prior immunity from vaccination or infection; morbidity and mortality have remained low compared to adults, despite the increased transmissibility of more recent variants.

Early in the pandemic, a post-infectious hyperinflammatory complication of SARS-CoV-2 infection termed multisystem inflammatory syndrome of children (MIS-C; also referred to as pediatric inflammatory multisystem syndrome temporally associated with COVID-19, PIMS-TS) was recognized. MIS-C is associated with higher acuity in older children and initially was associated with higher rates of mortality due to hemodynamic instability, myocardial dysfunction, and cardiovascular collapse. With better recognition of this syndrome, key

Table 311.1 Case Definition for Multisystem Inflammatory Syndrome in Children (MIS-C)

Any illness in a person < 21 years that meets:
- The clinical AND the laboratory criteria (*Confirmed*), OR
- The clinical criteria AND epidemiologic linkage criteria (*Probable*), OR
- The vital records criteria (*Suspect*)

CLINICAL CRITERIA	LABORATORY CRITERIA FOR SARS-COV-2 INFECTION	EPIDEMIOLOGIC LINKAGE CRITERIA	VITAL RECORDS CRITERIA
An illness characterized by *all of the following*, in the absence of a more likely alternative diagnosis* • Subjective or documented fever (temperature ≥38.0°C) • Clinical severity requiring hospitalization or resulting in death • Evidence of systemic inflammation indicated by C-reactive protein ≥3.0 mg/dL (30 mg/L) • New-onset manifestations in *at least two* of the following categories: 1. **Cardiac** involvement indicated by: • Left ventricular ejection fraction <55% *OR* • Coronary artery dilatation, aneurysm, or ectasia, *OR* • Troponin elevated above laboratory normal range, or indicated as elevated in a clinical note 2. **Mucocutaneous** involvement indicated by: • Rash, *OR* • Inflammation of the oral mucosa (e.g., mucosal erythema or swelling, drying or fissuring of the lips, strawberry tongue), *OR* • Conjunctivitis or conjunctival injection (redness of the eyes), *OR* • Extremity findings (e.g., erythema [redness] or edema [swelling] of the hands or feet) 3. **Shock**§ 4. **Gastrointestinal** involvement indicated by: • Abdominal pain, *OR* • Vomiting, *OR* • Diarrhea 5. **Hematologic** involvement indicated by: • Platelet count <150,000 cells/μL *OR* • Absolute lymphocyte count (ALC) <1,000 cells/μL	• Detection of SARS-CoV-2 RNA in a clinical specimen† up to 60 days before or during hospitalization, or in a postmortem specimen using a diagnostic molecular amplification test (e.g., polymerase chain reaction [PCR]), OR • Detection of SARS-CoV-2– specific antigen in a clinical specimen† up to 60 days before or during hospitalization, or in a postmortem specimen, OR • Detection of SARS-CoV-2–specific antibodies‖ in serum, plasma, or whole blood associated with current illness resulting in or during hospitalization	Close contact‡ with a confirmed or probable case of COVID-19 disease in the 60 days before hospitalization	A person whose death certificate lists MIS-C or multisystem inflammatory syndrome as an underlying cause of death or a significant condition contributing to death

*If documented by the clinical treatment team, a final diagnosis of Kawasaki Disease should be considered an alternative diagnosis. These cases should not be reported to national multisystem inflammatory syndrome in children (MIS-C) surveillance.
†Positive molecular or antigen results from self-administered testing using over-the-counter test kits meet laboratory criteria.
‡Includes a positive serology test regardless of COVID-19 vaccination status. Detection of anti-nucleocapsid antibody is indicative of SARS-CoV-2 infection, and antispike protein antibody may be induced either by COVID-19 vaccination or by SARS-CoV-2 infection.
§Clinician documentation of shock meets this criterion.
‖Close contact is generally defined as being within 6 feet for at least 15 min (cumulative over a 24-hr period). However, it depends on the exposure level and setting; for example, in the setting of an aerosol-generating procedure in healthcare settings without proper personal protective equipment (PPE), this may be defined as any duration.
From Centers for Disease Control and Prevention. Information for healthcare providers about multisystem inflammatory syndrome in children (MIS-C). https://www.cdc.gov/mis/mis-c/hcp/index.html

discriminatory diagnostic criteria, and institution of rapid immunomodulatory treatment, outcomes have improved (Table 311.1; Table 208.4 in Chapter 208). As of late 2023, there have been >9500 cases and 79 deaths due to MIS-C in the United States. The incidence of MIS-C has substantially decreased with the appearance of the late pandemic viral variants.

Pathogenesis of COVID-19

Severe disease in COVID-19 likely results from both direct virologic damage and subsequent immunopathology (Fig. 311.2). Postmortem exams have demonstrated COVID-19 virus in almost all tissues (lung, blood vessels, brain, gastrointestinal tract, heart, etc.). Substantial viral loads can be detected in the upper and lower respiratory tracts, stool, and blood. Late progression to severe disease appears *independent* of the quantity and timing of viremia; excessive host immune responses likely play an important role in the progression to lower respiratory disease, acute respiratory distress syndrome, and MIS-C (see Fig. 311.2). COVID-19 is associated with massive elaboration of inflammatory cytokines and recruitment of inflammatory cells. The roles for inflammatory cells are controversial, with cytotoxic T cells and macrophages implicated in both immune protection and immunopathology.

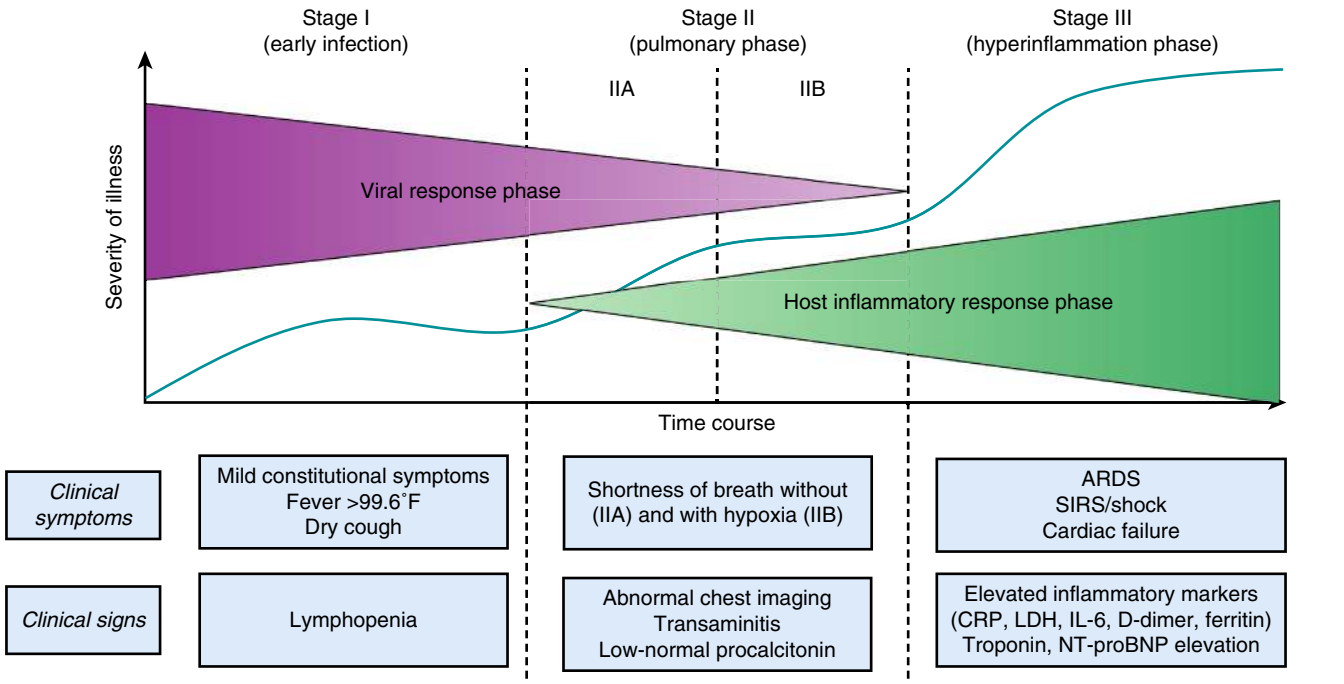

Fig. 311.2 Staging of acute COVID-19 infection. Classification of COVID-19 disease states and potential therapeutic targets. The figure illustrates three escalating phases of COVID-19 disease progression, with associated signs, symptoms. ARDS, Acute respiratory distress syndrome; JAK, Janus kinase; LDH, lactate dehydrogenase; NT-proBNP, N-terminal pro B-type natriuretic peptide; SIRS, systemic inflammatory response syndrome. *(Modified from Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. J Heart Lung Transpl. 2020;39[5]:405–407. Fig. 1.)*

Table 311.2 Clinical Spectrum of SARS-CoV-2 Infection

- *Asymptomatic or presymptomatic infection:* Individuals who test positive for SARS-CoV-2 using a virologic test (i.e., a nucleic acid amplification test [NAAT] or an antigen test) but have no symptoms consistent with COVID-19.
- *Mild illness:* Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but do not have shortness of breath, dyspnea, or abnormal chest imaging.
- *Moderate illness:* Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation measured by pulse oximetry (SpO_2) ≥94% on room air at sea level.
- *Severe illness:* Individuals who have SpO_2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (Pao_2/Fio_2) <300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50%.
- *Critical illness:* Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

Spo_2 is a key parameter for defining the listed illness categories. However, pulse oximetry has important limitations. Clinicians who use Spo_2 when assessing a patient must be aware of those limitations and conduct the assessment in the context of that patient's clinical status.

Underlying conditions associated with a higher risk of severe COVID-19 include asthma, cancer, cardiovascular disease, chronic kidney disease, chronic liver disease, chronic lung disease, diabetes, advanced or untreated HIV infection, obesity, pregnancy, cigarette smoking, and being a recipient of immunosuppressive therapy or a transplant.

The initial evaluation for patients may include chest imaging (e.g., x-ray, ultrasound or computed tomography scan) and an electrocardiogram. Laboratory testing should include a complete blood count with differential and a metabolic profile, including liver and renal function tests. Although inflammatory markers such as C-reactive protein (CRP), D-dimer, and ferritin are not routinely measured as part of standard care, results from such measurements may have prognostic value.

In children with COVID-19, radiographic abnormalities are common and, for the most part, should not be the only criteria used to determine the severity of illness. The normal values for respiratory rate also vary with age in children; therefore hypoxemia should be the primary criterion used to define severe COVID-19, especially in younger children. In a small subset of children and young adults, SARS-CoV-2 infection may be followed by the severe inflammatory condition multisystem inflammatory syndrome in children (MIS-C).

From Centers for Disease Control and Prevention. Clinical spectrum of SARS-CoV-2 infection. https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum

CLINICAL MANIFESTATIONS

In both children and adults, the spectrum of clinical manifestations of SARS-CoV-2 infection ranges from asymptomatic infection to mild, moderate, or severe, life-threatening pulmonary and extrapulmonary manifestations (Table 311.2). Children are more likely than adults to experience asymptomatic (up to 40%) or mild disease (all variants) but can also experience moderate and severe illness, including need for critical care support (MIS-C or early variants in older children or adolescents). Mild, moderate, or severe illness can include nonspecific symptoms such as fever, headache, myalgias, and fatigue (Table 311.3). Respiratory manifestations of COVID-19 in children are similar to those in adults and may include mild upper respiratory tract symptoms such as rhinorrhea, congestion, cough, and sore throat and lower respiratory symptoms such as shortness of breath and chest pain. Patients with severe or critical pulmonary and systemic features are at risk for venous thrombosis;

Table 311.3 Clinical Criteria for COVID-19

In the absence of a more likely diagnosis:

- At least two of the following symptoms:
  - Fever (measured or subjective)
  - Chills
  - Rigors
  - Myalgia
  - Headache
  - Sore throat
  - Nausea or vomiting
  - Diarrhea
  - Fatigue
  - Congestion or runny nose

OR

- Any one of the following symptoms:
  - Cough
  - Shortness of breath
  - Difficulty breathing
  - New olfactory disorder
  - New taste disorder

OR

- Severe respiratory illness with at least one of the following:
  - Clinical or radiographic evidence of pneumonia
  - Acute respiratory distress syndrome (ARDS)

LABORATORY CRITERIA (SEE TABLE 311.10)

EPIDEMIOLOGIC LINKAGE

- One or more of the following exposures in the prior 14 days:
  1. Close contact* with a confirmed or probable case of COVID-19 disease
  2. Member of a risk cohort as defined by public health authorities during an outbreak

CASE CLASSIFICATION†

Suspect

- Meets supportive laboratory evidence‡ with no prior history of being a confirmed or probable case.

Probable

- Meets clinical criteria AND epidemiologic linkage with no confirmatory laboratory testing performed for SARS-CoV-2
- Meets presumptive laboratory evidence
- Meets vital records criteria with no confirmatory laboratory evidence for SARS-CoV-2

Confirmed

- Meets confirmatory laboratory evidence

VITAL RECORDS CRITERIA

- A death certificate that lists COVID-19 disease or SARS-CoV-2 as an underlying cause of death or a significant condition contributing to death.

*Close contact is generally defined as being within 6 feet for at least 15 min. However, it depends on the exposure level and setting; for example, in the setting of an aerosol-generating procedure in healthcare settings without proper personal protective equipment (PPE), this may be defined as any duration. Data are insufficient to precisely define the duration of exposure that constitutes prolonged exposure and thus a close contact.

†The terms *confirmatory, presumptive,* and *supportive* are categorical labels used here to standardize case classifications for public health surveillance. The terms should not be used to interpret the utility or validity of any laboratory test methodology.

‡For suspect cases (positive serology only), jurisdictions may opt to place them in a registry for other epidemiologic analyses or investigate to determine probable or confirmed status.

From Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): 2020 interim case definition. Approved August 5, 2020. https://ndc.services.cdc.gov/case-definitions/coronavirus-disease-2019-covid-19/

prophylactic doses of enoxaparin are recommended. Chest imaging is essential in those with respiratory symptoms (Fig. 311.3). Croup and bronchiolitis presentations have been observed in association with the Omicron and later variants. Anosmia and ageusia have been reported in 10–15% of cases in children as well as adults. Gastrointestinal symptoms such as abdominal pain (pseudoappendicitis), diarrhea, and vomiting may be more prominent in pediatric patients (COVID-19 and/or MIS-C) compared to adults (Fig. 311.4). Although children with and without underlying medical conditions may be infected, up to 60% of hospitalized children have one or more underlying medical conditions and up to 80% of children with severe disease requiring critical care support have an underlying condition.

Cutaneous lesions have often been reported in pediatric patients with COVID-19 and pediatric patients with MIS-C (Table 311.4 and Fig. 311.5).

SARS-CoV-2 is a neurotropic virus; 10–20% of pediatric patients with COVID-19 and/or MIS-C have central or peripheral nervous system manifestations during the acute illness. The most common neurologic manifestations include seizures (including status epilepticus), headaches, behavioral changes, myalgias, and encephalopathy (~30% with reversible splenial lesions). Other identifiable syndromes include stroke, acute disseminated encephalomyelitis (ADEM) (~50% are myelin oligodendrocyte glycoprotein [MOG] antibody positive), Guillain-Barré syndrome (also reported with the vaccine), optic neuritis, psychosis, and cerebellar or brainstem lesions.

Neuroimaging findings associated with neurologic complications in children with COVID-19 are shown in Fig. 311.6. Cerebrospinal fluid (CSF) findings include a pleocytosis.

Neonates are often hospitalized because of SARS-CoV-2 infection due to febrile illness with less prominent respiratory complaints, primarily to exclude neonatal bacterial sepsis or neonatal herpes simplex virus (HSV) infection. Although nearly 15% of women presenting in labor during the early phase of the COVID-19 pandemic were found to be SARS-CoV-2 PCR positive (majority are asymptomatic), very few infants born to these women are PCR positive at birth or become infected perinatally. Preterm birth and stillbirth due to effects on the placenta, placental inflammation, and other specific abnormalities have been reported in pregnant women with symptomatic SARS-CoV-2 infection. Congenital abnormalities or intrauterine growth restriction have not been observed in live-born infants with in-utero SARS-CoV-2 exposure; potential long-term neurodevelopmental effects are not yet known.

Over the course of the pandemic, extrapulmonary manifestations and complications of SARS-CoV-2 infection have increasingly been appreciated, including new onset or exacerbation of type 1 and type 2 diabetes, intestinal inflammation (pseudo-appendicitis) and mesenteric lymphadenitis (see Fig. 311.4), and vascular complications such as thrombosis of vessels in the extremities as well as cerebral vasculature. SARS-CoV-2 infection has been associated with sickle cell vasoocclusive crises and acute chest syndrome in patients with sickle cell disease and increased seizures in children with seizure disorders.

MIS-C

The primary clinical manifestations of MIS-C occur 2-6 weeks *after* SARS-CoV-2 infection and consist of unremitting fever, involvement of two or more organ systems (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurologic), clinical severity requiring hospitalization, and laboratory evidence of inflammation (see Table 311.1). In addition, there is evidence for recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks before the onset of symptoms.

The median age for children with MIS-C is 8-10 years (range 4-14 years), but MIS-C can affect any age group, including adolescents and rarely infants. A similar syndrome, MIS-A, has been reported in adults (≥21 years). The vast majority of cases of MIS-C have occurred in children with no underlying medical conditions or immunodeficiency. Cardiac manifestations including myocardial dysfunction, coronary artery dilatation, and aneurysm formations (Fig. 311.7), valvular dysfunction, reduced left ventricular ejection fraction, shock, cardiac arrhythmias, and pericardial effusion are present in up to 50% of children at presentation. With institution of rapid

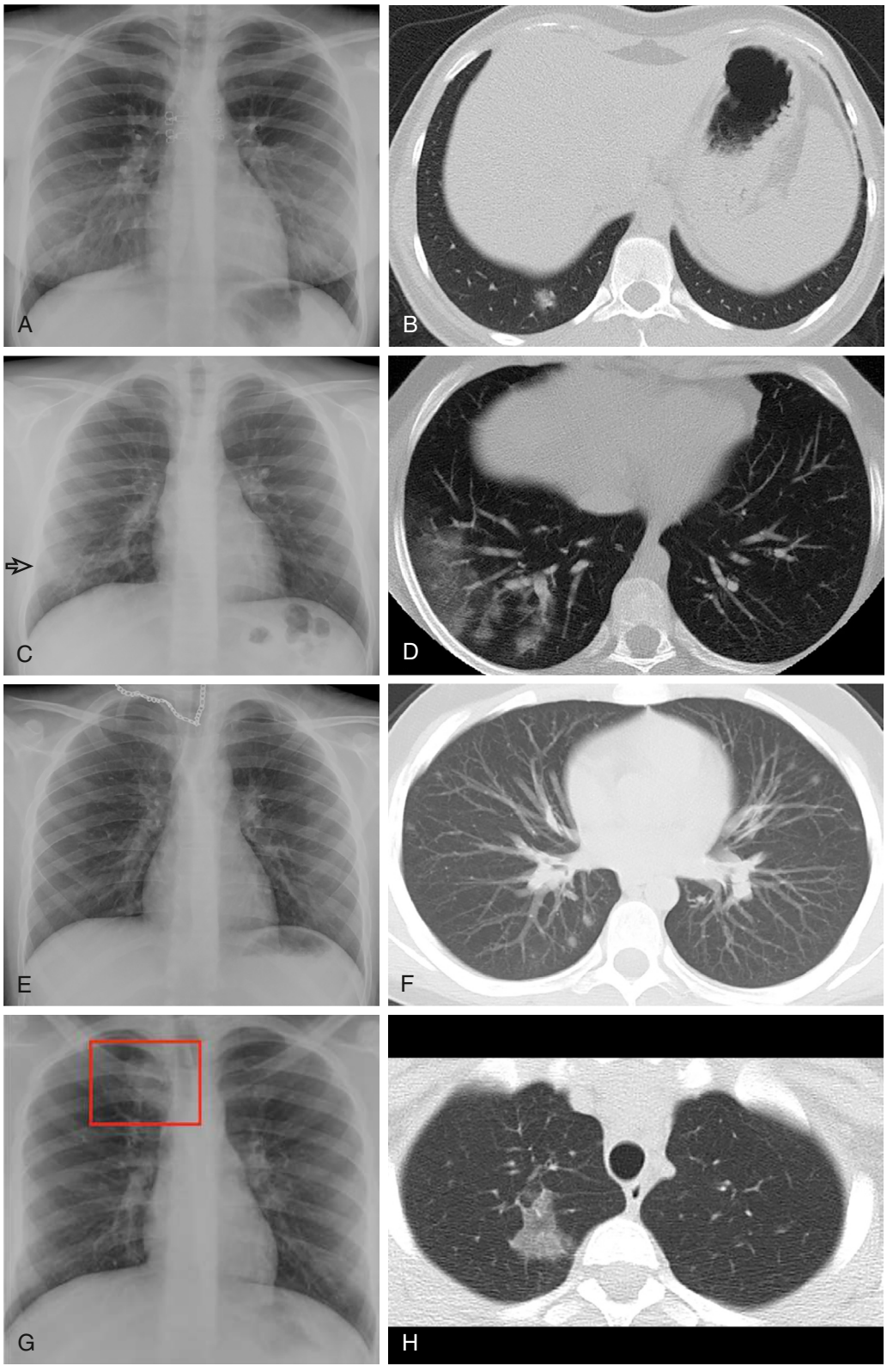

Fig. 311.3 Chest radiography and chest CT findings of children with COVID-19 in conjunction with symptom and time interval between imaging studies. **A,** Posteroanterior chest radiograph of a 13-yr-old patient who presented with fever for 2 days. Chest radiography and chest CT images were obtained on the same day. Chest radiograph was normal. **B,** Chest CT image in the axial plan revealed a single, peripheral located, ground-glass opacity (GGO) at the posterobasal segment of the right lower lobe. The opacity was obscured with the right liver lobe and diaphragm on chest radiography. **C,** Posteroanterior chest radiograph of a 10-yr-old patient who presented with cough and fever for 2 days. Chest radiography and chest CT images were obtained on the same day. Chest radiograph revealed peripheral GGO *(arrow)* at the basal segments of the right liver lobe. **D,** Axial section chest CT examination revealed bronchovascular distributed GGOs at the periphery of the basal segments of the right lower lobe. **E,** Posteroanterior chest radiograph of a 13-yr-old patient who presented with cough and fever for 2 days. Chest radiography and chest CT images were obtained on the same day. Chest radiograph was interpreted as normal. **F,** Axial chest CT image without contrast demonstrates bilateral, multifocal, peripheral, and perivascular distributed millimetric nodular-shaped GGOs. The opacities were not detected on chest radiography due to the smaller size and lower density. **G,** Posteroanterior chest radiograph of a 16-yr-old patient who presented with cough and fever for 3 days. Chest radiography and chest CT images were obtained on the same day. Chest radiograph demonstrates paramediastinal GGO at the right upper lobe *(red box)*. **H,** Axial chest CT image without contrast demonstrates peripherally distributed GGO at the right upper lobe with an interlobular interstitial thickening. *(From Bayramoglu Z, Canıpek E, Comert RG, et al. Imaging features of pediatric COVID-19 on chest radiography and chest CT: a retrospective, single-center study. Acad Radiol. 2021;28:18–27. Fig. 1.)*

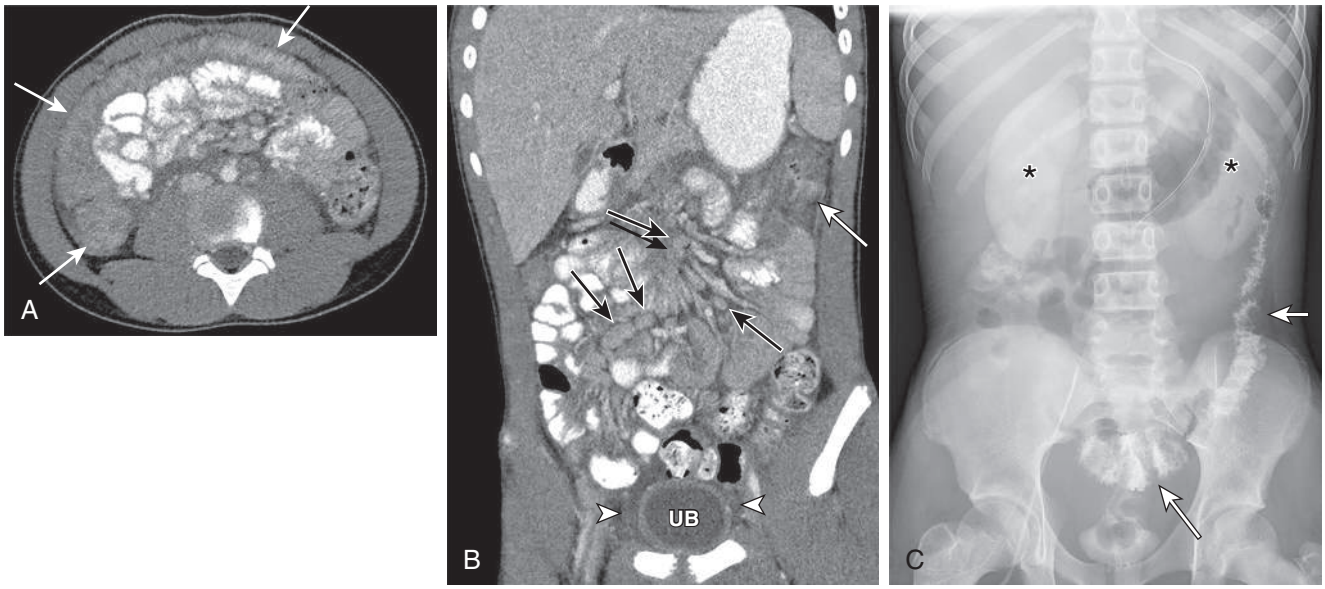

Fig. 311.4 A 14-yr-old with multisystem inflammatory syndrome in children (MIS-C). Imaging findings showed bowel wall thickening, acute kidney injury, ascites, and mesenteric adenopathy. **A,** Axial contrast-enhanced CT image shows diffuse mural thickening and mild mucosal hyperenhancement of colon *(arrows).* **B,** Coronal image from same CT examination as **A** shows mesenteric lymphadenopathy *(black arrows)* and pelvic ascites *(arrowheads).* Wall of urinary bladder *(UB)* is thickened, and thickening of colon *(white arrow)* is again noted. **C,** Supine anteroposterior abdominal radiograph obtained 15 hours after CT (**A** and **B**) shows retention of IV contrast material in kidneys *(asterisks)* (termed *delayed nephrogram*) in setting of acute kidney injury. Residual oral contrast material is present in descending colon and sigmoid *(arrows)* and shows wall thickening and irregularity. *(From Blumfield E, Levin TL, Kurian J, et al. Imaging findings in multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease (COVID-19). AJR. 2021;216:507–518. Fig. 7.)*

Table 311.4 Rashes Reported in COVID-19 Infected Patients

- Morbilliform*
- Chilblain-like/pernio*
- Urticarial
- Macular papular erythema*
- Vesicular
- Acrocyanosis
- Acral desquamation
- Papulosquamous
- Livedo reticularis–like*
- Erythema multiforme-like*
- Erythroderma
- Grover-like
- Retiform purpura*
- Petechial
- Bullous
- Palpable purpura/vasculitis (leukocytoclastic)*
- Dengue-like
- Pressure injury
- Erythema nodosum
- Livedo racemose*
- Miliaria rubra
- Acneiform
- Enanthem
- Anagen effluvium
- Erythema elevatum diutinum
- Photo-distributed

*Common.
Modified from Dinulos JE, Dinulos JG. Cutaneous coronavirus disease 2019 in children: a clinical primer for diagnosis and treatment. *Curr Opin Pediatr.* 2021;33:691–703. Table 1.

immunomodulation, short-term outcomes appear to be favorable, including resolution of coronary abnormalities in the majority of cases. Studies to evaluate the long-term prognosis for cardiac function are in progress, including studies using sensitive measures such as cardiac MRI. Patients with severe cardiac dysfunction must be followed by a pediatric cardiologist and abstain from sports for 3-6 months or until cleared by the cardiologist.

Sub-phenotypes of MIS-C include cases that appear very similar to Kawasaki disease (marked conjunctival injection, adenopathy, and/or prominent rash [Table 208.4 in Chapter 208]) and cases lacking Kawasaki disease features but with prominent abdominal symptoms mimicking an acute abdomen. Analysis of cytokine responses in children with MIS-C has identified elevation of a variety of biomarkers, confirming the hyperinflammatory nature of this illness (Table 311.5). Rapid institution of immunomodulatory therapy has been shown to be lifesaving in the setting of MIS-C and has included intravenous immunoglobulin (IGIV) with methylprednisolone and/or other biologics such as anakinra, tocilizumab, or infliximab (Table 311.6). The incidence of MIS-C has dramatically decreased with the appearance of newer variants.

Infectious complications are uncommon and are noted in Table 311.7. Another complication is rebound (recurrence) of COVID-19 symptoms after an initial episode (Table 311.8).

Post-Acute Sequelae of SARS-CoV-2 Infection (Long COVID)

An estimated 10–40% of adults and a much lower percentage of children who have recovered from recognized or unrecognized SARS-CoV-2 infection may develop long-standing and in some cases severe symptoms that are not specifically related to their original symptoms (Table 311.9). These may include ill-defined pain syndromes, headaches, abdominal pain, fatigue and postexertional malaise, shortness of breath, chronic cough, palpitations, dizziness/syncope, among others, as well as anxiety, depression, and posttraumatic stress disorder. The pathogenesis of long COVID is not yet known but may include genetic determinants related to immune dysregulation, autonomic instability, or persistent indolent viral effects. Long COVID may occur in individuals with mild symptoms, as well as those with moderate or severe infection. Affected individuals may benefit from multidisciplinary and coordinated evaluation in centers that can coordinate subspecialty evaluations

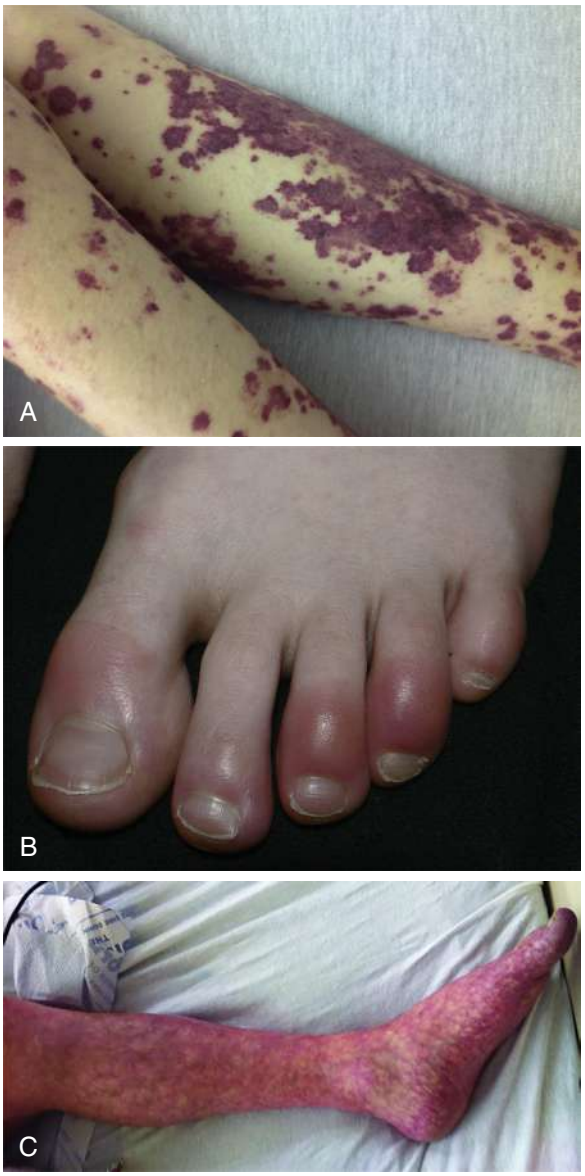

Fig. 311.5 Dermatologic manifestations of COVID-19. **A,** Petechial rash. **B,** Chilblains of the foot. **C,** Livedo reticularis of the lower extremity. *(A and B from Gottlieb M, Long B. Dermatologic manifestations and complications of COVID-19. Am J Emerg Med. 2020;38:1715–1721. Figs. 4 and 5; C from Nantsupawat T, Mankongpaisarnrung C, Soontrapa S, et al. Obscure severe infrarenal aortoiliac stenosis with severe transient lactic acidosis. J Investig Med High Impact Case Rep. 2013;1(1):2324709613479940. Fig. 2.)*

at a single visit, with focus on the symptoms that are most disruptive to quality of life and function.

DIAGNOSIS

Numerous diagnostic assays have been developed for the diagnosis of SARS-CoV-2, including laboratory-based and rapid/point-of-care nucleic acid amplification tests, rapid antigen tests, and serologic assays (Table 311.10). Multiple platforms targeting different aspects of the viral spike and nucleocapsid genes or proteins have been used for direct viral detection. Antibody to the spike protein may develop with either natural infection or vaccination, but presence of nucleocapsid antibody indicates natural infection. Virus may be detected by PCR or antigen-based methods for many days after the onset of symptoms, but immunocompetent individuals are generally not contagious after 10 days and immunocompromised patients are generally not contagious after 21 days, with late viral detection representing nonviable, replication incompetent remnants. Cycle time (Ct) in nonquantitative PCR assays cannot directly correlate with disease or likelihood of disease severity or progression but can be used as a rough estimate of viral load and shedding over time within a single patient, with lower Ct representing high viral loads and high Ct more likely representing shedding of nonviable virus.

Antibodies usually develop within 2 weeks of infection, but there is great variability in antibody responses to natural infection. Some infected individuals mount high antibody responses that are durable over many months, but others may not mount an effective or long-lived response after natural infection, highlighting the importance of vaccination for reliable immunity. Antibody responses have been documented to wane over time in both naturally infected and vaccinated individuals, leading to the recommendation for booster doses of vaccine. Vaccination has continued to be highly effective in prevention of severe disease, hospitalization, and death and in reducing the likelihood of MIS-C.

TREATMENT AND PREVENTION

Therapeutic agents for SARS-CoV-2 include antivirals that inhibit viral replication such as intravenous remdesivir, oral nirmatrelvir/ritonavir combination therapy, and oral molnupiravir. These antivirals reduce morbidity and mortality in hospitalized patients (5-10 day courses of intravenous remdesivir) as well as nonhospitalized high-risk children and adults (oral agents and shorter 3-day courses of intravenous remdesivir). High-risk conditions associated with severe disease include obesity, diabetes, chronic lung disease, neurologic disorders, cardiovascular disease, sickle cell disease, or immunosuppression because of underlying conditions or medications. Systemic corticosteroid therapy (dexamethasone) has been shown to significantly reduce morbidity and mortality in the treatment of hospitalized patients with COVID-19 pulmonary disease. Several monoclonal antibodies were developed and found to be effective during the early phase of the pandemic in preventing progression to severe disease in individuals with high-risk conditions. However, these antibodies have not retained activity against more recent variants of SARS-CoV-2. High-titer immune plasma has demonstrated variable efficacy with the original variant and is not recommended. Other biologics, such as the interleukin-6 inhibitor tocilizumab, have been used in critically ill adults unresponsive to first-line therapies but are used less commonly in children.

Multiple vaccines have been developed to combat spread of SARS-CoV-2, including novel platforms such as mRNA-based vaccines and adenovirus vector-based vaccines (see Chapter 215). For the majority of these SARS-CoV-2 vaccines, the primary target is the viral spike protein. The FDA had granted EUA approval for SARS-CoV-2 vaccines in the United States in children >6 months of age and adults.

Guidelines in late 2023 regarding isolation and precautions for people with COVID-19 are summarized in Table 311.11. However, guidelines continue to evolve and are available at the Centers for Disease Control and Prevention website (https://www.cdc.gov/coronavirus/2019-ncov/your-health/isolation.html).

Visit Elsevier eBooks+ at eBooks.Health.Elsevier.com for Bibliography.

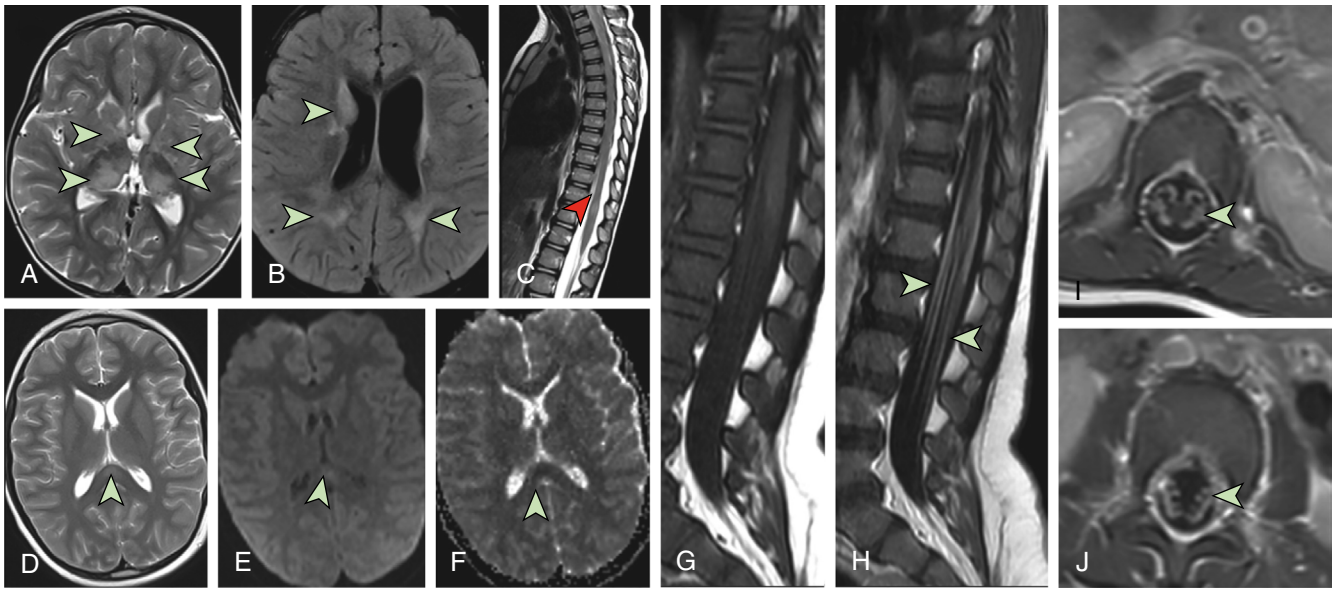

Fig. 311.6 MRI scans showing a range of neurologic complications. **A-C,** MRI brain and spine scans from 2-yr-old child with acute disseminated encephalomyelitis. Multiple hyperintense foci on axial T2-weighted (**A**) and T2 FLAIR (**B**) images involve both cerebral hemispheres, including the basal ganglia, thalami, and subcortical and periventricular white matter *(arrowheads)*. **C,** Sagittal T2-weighted image of the spine shows a focus of hyperintensity within the cord close to the conus *(arrowhead)*. **D-F,** MRI brain scans from 11-yr-old child who presented with MIS-C, encephalopathy, and MERS. **D,** Axial T2-weighted image shows a focus of hyperintensity involving the splenium of the corpus callosum along the midline *(arrowhead)*. The B1000 (**E**) and the ADC maps (**F**) from diffusion-weighted imaging show subtle diffusion restriction involving the lesion. **G-J,** MRI spine scans from a 16-mo-old infant who presented with Guillain-Barré syndrome. Sagittal T1-weighted images before (**G**) and after contrast (**H**) show enhancement of the lumbosacral nerve roots *(arrowheads)*. **I, J,** Axial T1-weighted postcontrast images show bilateral enhancement of the nerve roots. ADC, Apparent diffusion coefficient;; FLAIR, fluid-attenuated inversion recovery; MERS, mild encephalopathy with reversible splenial lesion; MIS-C, multisystem inflammatory syndrome in children. *(Modified from Ray ST, Abdel-Mannon O, Sa M, et al. Neurological manifestations of SARS-CoV-2 infection in hospitalised children and adolescents in the UK: a prospective national cohort study. Lancet Child Adolesc. 2021;5:631–641. Fig. 2.)*

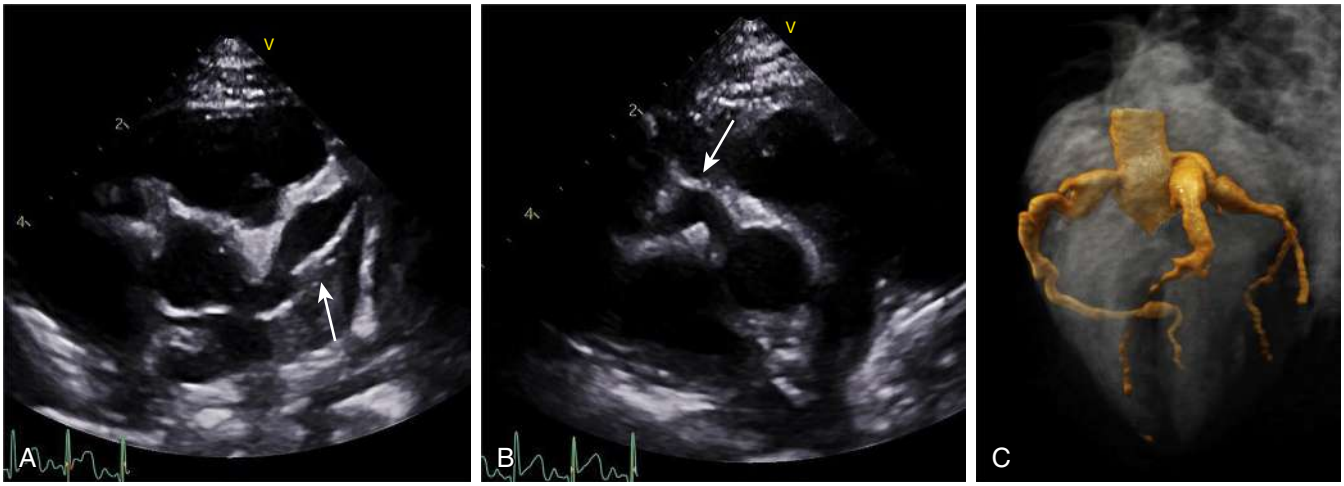

Fig. 311.7 Early cardiac imaging. Echocardiography (day 21) showing a giant (*z* score +26) left anterior descending artery aneurysm (**A**) and a large (*z* score +8.5) right coronary artery aneurysm (**B,** *arrow*). **C,** Three-dimensional reconstruction of coronary architecture. *(Modified from Villacis-Nunez DS, Hashemi S, Nelson MC, et al. Giant coronary aneurysms in multisystem inflammatory syndrome in children associated with SARS-CoV-2 infection. JACC Case Rep. 2021;3[13]:1499–1508. Fig. 2.)*

Table 311.5 Evaluation of MIS-C

LABORATORY TESTING

- A C-reactive protein ≥3.0 mg/dL (30 mg/L) is required for the CSTE/CDC MIS-C surveillance case definition; other laboratory tests may also indicate evidence of inflammation (e.g., erythrocyte sedimentation rate, fibrinogen, procalcitonin, and ferritin).
- Similarly, SARS-CoV-2 laboratory testing is indicated. Although detection of anti-nucleocapsid antibody or anti-spike protein antibody fulfill criteria for the case definition, when feasible SARS-CoV-2 anti-nucleocapsid antibody testing is recommended, particularly in children with a history of COVID-19 vaccination because anti-nucleocapsid antibody is indicative of SARS-CoV-2 infection, whereas antispike protein antibody may be induced either by COVID-19 vaccination or by SARS-CoV-2 infection. Serology testing should be obtained before administering intravenous immunoglobulin or any other exogenous antibody treatments whenever possible.

IMAGING

Given the frequent association of MIS-C with cardiac involvement, the following tests are usually performed:

- Echocardiogram
- Electrocardiogram

Other imaging should be directed by patient signs or symptoms but could include:

- Imaging to evaluate for acute appendicitis
- Imaging to evaluate for pharyngeal space infection

OTHER EVALUATIONS

It is important to evaluate children with suspected MIS-C for alternative diagnoses, particularly because MIS-C clinical manifestations overlap with those of other etiologies. Testing to evaluate for other potential diagnoses should be directed by patient signs or symptoms. Alternative diagnoses to consider include:

- Acute viral infection (e.g., SARS-CoV-2, influenza, adenovirus)
- Acute viral infection myocarditis (e.g., influenza, enteroviruses)
- Kawasaki disease
- Rickettsial disease (e.g., typhus)

CSTE/CDC, Council of State and Territorial Epidemiologists/Centers for Disease Control and Prevention; MIS-C, multisystem inflammatory syndrome in children.

From Centers for Disease Control and Prevention. Information for healthcare providers about multisystem inflammatory syndrome in children (MIS-C). https://www.cdc.gov/mis/mis-c/hcp/index.html

Table 311.6 Treatment of MIS-C

Initial treatment is tailored according to the patient's presenting signs and symptoms and may include:

- Fluid resuscitation
- Inotropic support
- Respiratory support

Antiinflammatory measures have included the frequent use of intravenous immunoglobulin and steroids. There is some evidence that multisystem inflammatory syndrome in children (MIS-C) with milder manifestations can be treated with steroid monotherapy and that prolonged duration of outpatient steroids should be avoided. The use of other antiinflammatory medications (e.g., anakinra) and the use of anticoagulation treatments have been variable. Aspirin has commonly been used because of concerns for coronary artery involvement, and antibiotics are routinely used to treat potential sepsis while awaiting bacterial cultures. Thrombotic prophylaxis is often used given the hypercoagulable state typically associated with MIS-C.

From Centers for Disease Control and Prevention. Information for healthcare providers about multisystem inflammatory syndrome in children (MIS-C). https://www.cdc.gov/mis/mis-c/hcp/index.html

Table 311.7 Infectious Complications in Patients with COVID-19

- *Co-infections at presentation:* Although most individuals present with only SARS-CoV-2 infection, concomitant viral infections, including influenza and other respiratory viruses, have been reported. Community-acquired bacterial pneumonia also has been reported, but it is uncommon, with a prevalence that ranges from 0% to 6% of people with SARS-CoV-2 infection. Antibacterial therapy is generally not recommended unless additional evidence for bacterial pneumonia is present (e.g., leukocytosis, the presence of a focal infiltrate on imaging).
- *Reactivation of latent infections:* There are case reports of underlying chronic hepatitis B virus and latent tuberculosis infections reactivating in patients with COVID-19 who receive immunomodulators as treatment, although the data are currently limited. Reactivation of herpes simplex virus and varicella zoster virus infections have also been reported. Cases of severe and disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with tocilizumab and corticosteroids. Many clinicians would initiate empirical treatment (e.g., with the antiparasitic drug ivermectin), with or without serologic testing, in patients who require immunomodulators for the treatment of COVID-19 and have come from areas where *Strongyloides* is endemic (i.e., tropical, subtropical, or warm temperate areas).
- *Nosocomial infections:* Hospitalized patients with COVID-19 may acquire common nosocomial infections, such as hospital-acquired pneumonia (including ventilator-associated pneumonia), line-related bacteremia or fungemia, catheter-associated urinary tract infection, and *Clostridioides difficile*–associated diarrhea. Early diagnosis and treatment of these infections are important for improving outcomes in these patients.
- *Opportunistic fungal infections:* Invasive fungal infections, including aspergillosis and mucormycosis, have been reported in hospitalized patients with COVID-19. Although these infections are relatively rare, they can be fatal, and they may be seen more commonly in patients who are immunocompromised or receiving mechanical ventilation. The majority of mucormycosis cases have been reported in India and are associated with diabetes mellitus or the use of corticosteroids.

From Centers for Disease Control and Prevention. Clinical spectrum of SARS-CoV-2 infection. https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum

Table 311.8 Viral or Symptom Rebound Soon After COVID-19

- Observational studies and results from clinical trials of therapeutic agents have described SARS-CoV-2 viral or COVID-19 symptom rebound in patients who have completed treatment for COVID-19.
- Viral and symptom rebounds have also occurred when anti–SARS-CoV-2 therapies were not used.
- Typically, this phenomenon has not been associated with progression to severe COVID-19.

From Centers for Disease Control and Prevention. Clinical spectrum of SARS-CoV-2 infection. https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum

Table 311.9 Adjusted Hazard Ratios of Selected Potential Post–COVID-19 Symptoms and Conditions Among Children and Adolescents Age 2-17 Years With and Without COVID-19, by Age Group: HealthVerity Medical Claims Database, United States, March 1, 2020–January 31, 2022

	ADJUSTED HAZARD RATIO (95% CI)*		
OUTCOME	**2-4 YR**	**5-11 YR**	**12-17 YR**
SYMPTOM			
Smell and taste disturbances	1.22 (0.70-2.15)	0.94 (0.83-1.07)	1.23 (1.16-1.31)†
Circulatory signs and symptoms	1.17 (1.12-1.23)†	1.11 (1.08-1.13)†	1.04 (1.02-1.06)†
Malaise and fatigue	1.13 (1.05-1.22)†	1.08 (1.05-1.12)†	1.03 (1.01-1.04)†
Musculoskeletal pain	1.16 (1.10-1.21)†	1.06 (1.04-1.07)†	1.00 (0.99-1.01)
Dizziness and syncope	1.08 (0.90-1.29)	1.03 (0.99-1.08)	1.00 (0.98-1.02)
GI and esophageal disorders	1.15 (1.10-1.20)†	1.02 (1.00-1.04)†	0.97 (0.95-0.99)†
Sleeping disorders	0.99 (0.93-1.06)	0.89 (0.86-0.92)†	0.91 (0.89-0.94)†
Respiratory signs and symptoms	1.07 (1.04-1.10)†	0.93 (0.92-0.94)†	0.88 (0.87-0.89)†
Symptoms of mental conditions	1.03 (0.97-1.10)	0.92 (0.90-0.95)†	0.89 (0.86-0.91)†
CONDITION			
Acute pulmonary embolism	—‡	—‡	2.03 (1.61-2.56)†
Myocarditis and cardiomyopathy	2.39 (1.57–3.65)†	2.84 (2.39-3.37)†	1.66 (1.48-1.88)†
Venous thromboembolic event	—‡	2.69 (1.73-4.19)†	1.52 (1.22-1.91)†
Acute and unspecified renal failure	1.52 (1.07–2.14)†	1.38 (1.16–1.63)†	1.27 (1.15–1.40)†
Type 1 diabetes	1.01 (0.57-1.78)	1.31 (1.13-1.53)†	1.20 (1.09–1.33)†
Coagulation and hemorrhagic disorders	1.47 (1.20-1.80)†	1.28 (1.15-1.43)†	1.10 (1.03–1.19)†
Type 2 diabetes	1.24 (0.85-1.81)	1.14 (1.02-1.28)†	1.18 (1.11-1.24)†
Cardiac dysrhythmias	1.44 (1.22-1.70)†	1.23 (1.14-1.32)†	1.12 (1.08-1.17)†
Cerebrovascular disease	1.66 (0.85-3.23)	1.14 (0.79-1.64)	1.18 (0.93-1.48)
Chronic kidney disease	0.86 (0.54-1.36)	1.04 (0.83-1.31)	1.12 (0.96-1.31)
Asthma	1.12 (1.07-1.18)†	1.02 (1.00-1.05)†	0.96 (0.94-0.98)†
Muscle disorders	0.87 (0.77-0.98)†	0.86 (0.82-0.91)†	0.96 (0.93-0.99)†
Neurologic conditions	0.98 (0.93-1.04)	0.96 (0.93-0.98)†	0.91 (0.89-0.93)†
Anxiety and fear-related disorders	0.91 (0.83-1.00)	0.86 (0.83-0.88)†	0.84 (0.82-0.85)†
Mood disorders	0.82 (0.62-1.08)	0.73 (0.69-0.77)†	0.80 (0.77-0.83)†

*Each adjusted hazard ratio was obtained from a single Cox proportional hazards model stratified by age group, with the specific symptom or condition as the outcome and the following covariates: presence of COVID-19, age (continuous variable), sex, race, U.S. Census Bureau region, payor type, previous medical complexity, and previous hospitalization.
†P-value < 0.05.
‡Age-stratified analyses were performed only when there were at least 10 patients with COVID-19 and at least 10 patients without COVID-19 in that age group with the specific symptom or condition.
From Kompaniyets L, Bull-Otterson L, Boehmer TK, et al. Post-COVID-19 symptoms and conditions among children and adolescents–United States, March 1, 2020-January 21, 2022. *Morb Mortal Wkly Rep*. 2022;71(31):993–998. Table 3.

Table 311.10 Laboratory Evidence for COVID-19 Infection

Laboratory evidence using a method approved or authorized by the U.S. Food and Drug Administration (FDA) or designated authority:

CONFIRMATORY* LABORATORY EVIDENCE
- Detection of SARS-CoV-2 ribonucleic acid (RNA) in a clinical or postmortem specimen using a diagnostic molecular amplification test performed by a Clinical Laboratory Improvement Amendments (CLIA)-certified provider† OR
- Detection of SARS-CoV-2 RNA in a clinical or postmortem specimen by genomic sequencing‡

PRESUMPTIVE* LABORATORY EVIDENCE
- Detection of SARS-CoV-2–specific antigen in a clinical or postmortem specimen using a diagnostic test performed by a CLIA-certified provider.†

SUPPORTIVE* LABORATORY EVIDENCE
- Detection of SARS-CoV-2 specific antigen by immunocytochemistry, OR
- Detection of SARS-CoV-2 RNA or specific antigen using a test performed without CLIA oversight.

*The terms *confirmatory, presumptive,* and *supportive* are categorical labels used here to standardize case classifications for public health surveillance. The terms should not be used to interpret the utility or validity of any laboratory test methodology.
†Includes those tests performed under a CLIA certificate of waiver.
‡Some genomic sequencing tests that have been authorized for emergency use by the FDA do not require an initial polymerase chain reaction (PCR) result to be generated. Genomic sequencing results may be all the public health agency receives.
Modified from Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19) 2023 Case Definition. https://ndc.services.cdc.gov/case-definitions/coronavirus-disease-2019-covid-19/

Table 311.11 Isolation and Precautions for People with COVID-19

WHEN TO ISOLATE

- If you test negative: You can end your isolation.
- If you test positive: Follow the full isolation recommendations below.
- When you have COVID-19, isolation is counted in days, as follows.

If You Had No Symptoms

- Day 0 is the day you were tested (not the day you received your positive test result).
- Day 1 is the first full day following the day you were tested.
- If you develop symptoms within 10 days of when you were tested, the clock restarts at day 0 on the day of symptom onset.

If You Had Symptoms

- Day 0 of isolation is the day of symptom onset, regardless of when you tested positive.
- Day 1 is the first full day after the day your symptoms started.

Isolation

- If you test positive for COVID-19, stay home for at least 5 days and isolate from others in your home.
- You are likely most infectious during these first 5 days.
- Wear a high-quality mask if you must be around others at home and in public.
- Do not go places where you are unable to wear a mask. For travel guidance, see CDC's Travel webpage.
- Do not travel.
- Stay home and separate from others as much as possible.
- Use a separate bathroom, if possible.
- Take steps to improve ventilation at home, if possible.
- Do not share personal household items, such as cups, towels, and utensils.
- Monitor your symptoms. If you have an emergency warning sign (like trouble breathing), seek emergency medical care immediately.
- Learn more about what to do if you have COVID-19.

ENDING ISOLATION

- End isolation based on how serious your COVID-19 symptoms were.
- Loss of taste and smell may persist for weeks or months after recovery and need not delay the end of isolation.

If You Had No Symptoms

- You may end isolation after day 5.

If You Had Symptoms and Your Symptoms Are Improving

- You may end isolation after day 5 if you are fever free for 24 hr (without the use of fever-reducing medication).

Your Symptoms Are Not Improving

Continue to isolate until:

- You are fever free for 24 hr (without the use of fever-reducing medication).
- Your symptoms are improving.*

If You Had Symptoms and Had Moderate illness (you experienced shortness of breath or had difficulty breathing)

- You need to isolate through day 10.

Severe Illness (You Were Hospitalized) or Have a Weakened Immune System

- You need to isolate through day 10.
- Consult your doctor before ending isolation.
- Ending isolation without a viral test may not be an option for you.
- If you are unsure if your symptoms are moderate or severe or if you have a weakened immune system, talk to a healthcare provider for further guidance.

Regardless of When You End Isolation

Until at least day 11:

- Avoid being around people who are more likely to get very sick from COVID-19.
- Remember to wear a high-quality mask when indoors around others at home and in public.
- Do not go places where you are unable to wear a mask until you are able to discontinue masking (see below).
- For travel guidance, see CDC's Travel webpage.

Removing Your Mask

After you have ended isolation, when you are feeling better (no fever without the use of fever-reducing medications and symptoms improving):

- Wear your mask through day 10.

OR

- If you have access to antigen tests, you should consider using them. With two sequential negative tests 48 hr apart, you may remove your mask sooner than day 10.

NOTE: If your antigen test results* are positive, you may still be infectious. You should continue wearing a mask and wait at least 48 hours before taking another test. Continue taking antigen tests at least 48 hr apart until you have two sequential negative results. This may mean you need to continue wearing a mask and testing beyond day 10.

After you have ended isolation, if your COVID-19 symptoms recur or worsen, restart your isolation at day 0. Talk to a healthcare provider if you have questions about your symptoms or when to end isolation.

*As noted in the U.S. Food and Drug Administration labeling for authorized over-the-counter antigen tests, negative test results do not rule out SARS-CoV-2 infection and should not be used as the sole basis for treatment or patient management decisions, including infection control decisions.

From Centers for Disease Control and Prevention. Isolation and precautions for people with COVID-19. https://www.cdc.gov/coronavirus/2019-ncov/your-health/isolation.html

Chapter 312

Rotaviruses, Caliciviruses, and Astroviruses

Dorsey M. Bass

Diarrhea is a leading cause of childhood death in the world, accounting for 5-10 million deaths per year. In early childhood, the single most important cause of severe dehydrating diarrhea is rotavirus infection. Rotavirus and other gastroenteric viruses are not only major causes of pediatric deaths but also lead to significant morbidity. Before rotavirus vaccines were available, children in the United States were estimated to have a risk of hospitalization for rotavirus diarrhea of 1:43, corresponding to 80,000 hospitalizations annually.

ETIOLOGY

Rotaviruses, astroviruses, caliciviruses such as the Norwalk agent, and enteric adenoviruses are the medically important pathogens of human viral gastroenteritis (see Chapter 387).

Rotaviruses are in the Reoviridae family and cause disease in virtually all mammals and birds. These viruses are wheel-like, triple-shelled icosahedrons containing 11 segments of double-stranded RNA. The diameter of the particles on electron microscopy is approximately 80 nm. Rotaviruses are classified by serogroup (A, B, C, D, E, F, and G) and subgroup (I or II). Rotavirus strains are species specific and do not cause disease in heterologous hosts. Group A includes the common human pathogens and a variety of animal viruses. Group B rotavirus is reported as a cause of severe disease in infants and adults in China

only. Occasional human outbreaks of group C rotavirus are reported. The other serogroups infect only nonhumans.

Subgrouping of rotaviruses is determined by the antigenic structure of the inner capsid protein, VP6. Serotyping of rotaviruses, described for group A only, is determined by classic cross-neutralization testing and depends on the outer capsid glycoproteins, VP7 and VP4. The VP7 serotype is referred to as the *G type* (for glycoprotein). There are 10 G serotypes, of which 4 cause most illness and vary in occurrence from year to year and region to region. The VP4 serotype is referred to as the P type. There are 11 P serotypes. Although both VP4 and VP7 elicit neutralizing immunoglobulin (Ig) G antibodies, the relative role of these systemic antibodies compared with mucosal IgA antibodies and cellular responses in protective immunity remains unclear.

Caliciviruses, which constitute the Caliciviridae family, are small, 27- to 35-nm viruses and are the most common cause of gastroenteritis outbreaks in older children and adults. Caliciviruses also cause a rotavirus-like illness in young infants. They are positive-sense, single-stranded RNA viruses with a single structural protein. Human caliciviruses are divided into two genera, the noroviruses and sapoviruses. Caliciviruses have been named for locations of initial outbreaks: Norwalk, Snow Mountain, Montgomery County, Sapporo, and others. Caliciviruses and astroviruses are sometimes referred to as **small, round viruses** on the basis of their appearance on electron microscopy.

Astroviruses constitute the Astroviridae family and are important agents of viral gastroenteritis in young children, with a high incidence in both the developing and developed worlds. Astroviruses are positive-sense, single-stranded RNA viruses. They are small particles, approximately 30 nm in diameter, with a characteristic central five- or six-pointed star when viewed on electron microscopy. The capsid consists of three structural proteins. There are eight known human serotypes.

Enteric adenoviruses are a common cause of viral gastroenteritis in infants and children. Although many adenovirus serotypes exist and are found in human stool, especially during and after typical upper respiratory tract infections (see Chapter 309), only serotypes 40 and 41 cause gastroenteritis. These strains are very difficult to grow in tissue culture. The virus consists of an 80-nm–diameter icosahedral particle with a relatively complex double-stranded DNA genome.

Aichi virus is a picornavirus that is associated with gastroenteritis and was initially described in Asia. Several other viruses that may cause diarrheal disease in animals have been postulated but are not well established as human gastroenteritis viruses. These include coronaviruses, toroviruses, and pestiviruses. The **picobirnaviruses** are an unclassified group of small (30-nm), single-stranded RNA viruses that have been found in 10% of patients with HIV-associated diarrhea.

EPIDEMIOLOGY

Worldwide, rotavirus is estimated to cause more than 111 million cases of diarrhea annually in children <5 years. Of these, 18 million cases are considered at least moderately severe, with approximately 200,000 deaths per year. Rotavirus caused 3 million cases of diarrhea, 80,000 hospitalizations, and 20-40 deaths annually in the United States before widespread vaccine use.

Rotavirus infection is most common in winter months in temperate climates. In the United States, the annual winter peak historically spread from west to east. Unlike the spread of other winter viruses, such as influenza, this wave of increased incidence was not caused by a single prevalent strain or serotype. Since widespread adoption of rotavirus vaccines, this geographic phenomenon has vanished and peaks have decreased. Typically, several serotypes predominate in a given community for one or two seasons, but nearby locations may harbor unrelated strains. Disease tends to be most severe in patients 3-24 months of age, although 25% of the cases of severe disease occur in children older than 2 years of age, with serologic evidence of infection developing in virtually all children by 4-5 years of age. Infants younger than 3 months are relatively protected by transplacental antibody and possibly breastfeeding. Infections in neonates and in adults in close contact with infected children are generally asymptomatic. Some rotavirus strains have stably colonized newborn nurseries for years, infecting virtually all newborns without causing any overt illness.

Rotavirus and the other gastrointestinal viruses spread efficiently by the fecal-oral route, and outbreaks are common in children's hospitals and childcare centers. The virus is shed in stool at a very high concentration before and for days after the clinical illness. Very few infectious virions are needed to cause disease in a susceptible host.

The epidemiology of **astroviruses** is not as thoroughly studied as that of rotavirus, but these viruses are a common cause of mild to moderate watery winter diarrhea in children and infants and are an uncommon pathogen in adults. Hospital outbreaks are common. **Enteric adenovirus** gastroenteritis occurs year-round, mostly in children younger than 2 years. Nosocomial outbreaks occur but are less common than with rotavirus and astrovirus. **Calicivirus** is best known for causing large, explosive outbreaks among older children and adults, particularly in settings such as schools, cruise ships, and hospitals. Often a single food, such as shellfish or water used in food preparation, is identified as a source. Like astrovirus and rotavirus, caliciviruses are also commonly found in winter infantile gastroenteritis and are now the leading cause of significant pediatric viral diarrhea in communities with high rates of rotavirus vaccination.

PATHOGENESIS

Viruses that cause human diarrhea selectively infect and destroy villus tip cells in the small intestine. Biopsies of the small intestines show variable degrees of villus blunting and round cell infiltrate in the lamina propria. Pathologic changes may not correlate with the severity of clinical symptoms and usually resolve before the clinical resolution of diarrhea. The gastric mucosa is not affected despite the commonly used term *gastroenteritis,* although delayed gastric emptying has been documented during Norwalk virus infection.

In the small intestine, the upper villus enterocytes are differentiated cells, which have both digestive functions, such as hydrolysis of disaccharides, and absorptive functions, such as the transport of water and electrolytes via glucose and amino acid cotransporters. Crypt enterocytes are undifferentiated cells that lack the brush-border hydrolytic enzymes and are net secretors of water and electrolytes. Selective viral infection of intestinal villus tip cells thus leads to (1) decreased absorption of salt and water and an imbalance in the ratio of intestinal fluid absorption to secretion and (2) diminished disaccharidase activity and malabsorption of complex carbohydrates, particularly lactose. Most evidence supports altered absorption as the more important factor in the genesis of viral diarrhea. It has been proposed that a rotavirus nonstructural protein (NSP4) functions as an enterotoxin.

Viremia may occur in severe, primary infections, but symptomatic **extraintestinal infection** is extremely rare in immunocompetent persons. In contrast, immunocompromised patients may occasionally experience central nervous system, hepatic, or renal involvement. The increased vulnerability of infants (compared with older children and adults) to severe morbidity and mortality from gastroenteritis viruses may relate to a number of factors, including decreased intestinal reserve function, lack of specific immunity, and decreased nonspecific host defense mechanisms such as gastric acid and mucus. Viral enteritis greatly enhances intestinal permeability to luminal macromolecules and has been postulated to increase the risk for food allergies and celiac disease.

CLINICAL MANIFESTATIONS

Rotavirus infection typically begins after an incubation period of <48 hours (range: 1-7 days) with mild to moderate fever as well as vomiting, followed by the onset of frequent, watery stools. All three symptoms are present in about 50–60% of cases. Vomiting and fever typically abate during the second day of illness, but diarrhea often continues for 5-7 days. The stool is without gross blood or white blood cells. Dehydration may develop and progress rapidly, particularly in infants. The most severe disease typically occurs among children 4-36 months of age. Malnourished children and children with underlying intestinal disease, such as short-bowel syndrome, are particularly likely to acquire severe rotavirus diarrhea. Rarely, immunodeficient children experience severe and prolonged illness. Rotavirus has rarely been associated with mild encephalopathy that may progress to cerebellitis and with reversible splenium lesions. Although most newborns infected with rotavirus are asymptomatic, some outbreaks of necrotizing enterocolitis have been associated with the appearance of a new rotavirus strain in the affected nurseries.

The clinical course of **astrovirus** infection appears to be similar to that of rotavirus gastroenteritis, with the notable exception that the disease tends to be milder, with less significant dehydration. **Adenovirus enteritis** tends to cause diarrhea of longer duration, often 10-14 days. The **Norwalk virus** has a short (12-hour) incubation period. Vomiting and nausea tend to predominate in an illness associated with the Norwalk virus, and the duration is brief, usually consisting of 1-3 days of symptoms. The clinical and epidemiologic picture of Norwalk virus often closely resembles so-called food poisoning from preformed toxins such as *Staphylococcus aureus* and *Bacillus cereus.*

DIAGNOSIS

In most cases, a satisfactory diagnosis of acute viral gastroenteritis can be made on the basis of the clinical and epidemiologic features. Many hospitals now offer multiplex PCR stool testing for multiple diarrheal pathogens, including a variety of bacterial and protozoan and all five common viral agents in one test. Enzyme-linked immunosorbent assays, which offer >90% specificity and sensitivity, are available for the detection of group A rotaviruses, caliciviruses, and enteric adenoviruses in stool samples. Research tools include electron microscopy of stools, RNA polymerase chain reaction analysis to identify G and P antigens, and culture. The diagnosis of viral gastroenteritis should always be questioned in patients with persistent or high fever, blood or white blood cells in the stool, or persistent severe or bilious vomiting, especially in the absence of diarrhea.

LABORATORY FINDINGS

Isotonic dehydration with acidosis is the most common finding in children with severe viral enteritis. The stools are free of blood and leukocytes. Although the white blood cell count may be moderately elevated secondary to stress, the marked left shift seen with invasive bacterial enteritis is absent.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes other infectious causes of enteritis, such as bacteria and protozoa. Occasionally, surgical conditions such as appendicitis, bowel obstruction, and intussusception may initially mimic viral gastroenteritis.

TREATMENT

Avoiding and treating dehydration are the main goals in the treatment of viral enteritis. A secondary goal is maintenance of the nutritional status of the patient (see Chapters 74 and 387).

There is no routine role for antiviral drug treatment of viral gastroenteritis. Controlled studies show limited benefits for antidiarrheal drugs, and there is a significant risk for serious side effects with these types of agents. Antibiotics are similarly of no benefit. Antiemetics such as ondansetron may help alleviate vomiting in children older than 2 years. Immunoglobulins have been administered orally to both normal and immunodeficient patients with severe rotavirus and norovirus gastroenteritis, but this treatment is currently considered experimental. Therapy with probiotic organisms such as *Lactobacillus* spp. has been shown to be helpful only in mild cases and not in dehydrating disease.

Supportive Treatment

Rehydration via the oral route can be accomplished in most patients with mild to moderate dehydration (see Chapters 74 and 387). Severe dehydration requires immediate intravenous therapy followed by oral rehydration. Modern oral rehydration solutions containing appropriate quantities of sodium and glucose promote the optimum absorption of fluid from the intestine. There is no evidence that a particular carbohydrate source (rice) or the addition of amino acids improves the efficacy of these solutions for children with viral enteritis. Other clear liquids, such as flat soda, fruit juice, and sports drinks, are inappropriate for the rehydration of young children with significant stool loss. Rehydration via the oral (or nasogastric) route should be done over 6-8 hours, and feedings should be initiated immediately thereafter. Providing the rehydration fluid at a slow, steady rate, typically 5 mL/min, reduces vomiting and improves the success of oral therapy. Rehydration solution should be continued as a supplement to make up for ongoing excessive stool loss. Initial intravenous fluids are required for the infant in shock or the occasional child with intractable vomiting.

After rehydration has been achieved, resumption of a normal diet for age has been shown to result in a more rapid recovery from viral gastroenteritis. Prolonged (>12 hours) administration of exclusive clear liquids or dilute formula is without clinical benefit and actually prolongs the duration of diarrhea. Breastfeeding should be continued even during rehydration. Selected infants may benefit from lactose-free feedings (e.g., soy formula and lactose-free cow's milk) for several days, although this step is not necessary for most children. Hypocaloric diets low in protein and fat such as BRAT (*b*ananas, *r*ice, cereal, *a*pplesauce, and *t*oast) have not been shown to be superior to a regular diet.

PROGNOSIS

Most fatalities occur in infants with poor access to medical care and are attributed to dehydration. Children may be infected with rotavirus each year during the first 5 years of life, but each subsequent infection decreases in severity. Primary infection results in a predominantly serotype-specific immune response, whereas reinfection, which is usually with a different serotype, induces a broad immune response with cross-reactive heterotypic antibody. After the initial natural infection, children have limited protection against subsequent asymptomatic infection (38%) and greater protection against mild diarrhea (73%) and moderate to severe diarrhea (87%). After the second natural infection, protection increases against subsequent asymptomatic infection (62%) and mild diarrhea (75%) and is complete (100%) against moderate to severe diarrhea. After the third natural infection, there is even more protection against subsequent asymptomatic infection (74%) and near-complete protection against even mild diarrhea (99%).

PREVENTION

Good hygiene reduces the transmission of viral gastroenteritis, but even in the most hygienic societies, virtually all children become infected as a result of the efficiency of infection of the gastroenteritis viruses. Good handwashing and isolation procedures can help control nosocomial outbreaks. The role of breastfeeding in prevention or amelioration of rotavirus infection may be slight, given the variable protection observed in a number of studies. Vaccines offer the best hope for control of these ubiquitous infections.

Vaccines

A trivalent rotavirus vaccine was licensed in the United States in 1998 and was subsequently linked to an increased risk for intussusception, especially during the 3- to 14-day period after the first dose and the 3- to 7-day period after the second dose. The vaccine was withdrawn from the market in 1999. Subsequently, two new live, oral rotavirus vaccines have been approved in the United States after extensive safety and efficacy testing.

A live, oral, pentavalent rotavirus vaccine was approved in 2006 for use in the United States. The vaccine contains five reassortant rotaviruses isolated from human and bovine hosts. Four of the reassortant rotaviruses express one serotype of the outer protein VP7 (G1, G2, G3, or G4), and the fifth expresses the protein P1A (genotype P[8]) from the human rotavirus parent strain. The pentavalent vaccine protects against rotavirus gastroenteritis when administered as a three-dose series at 2, 4, and 6 months of age. The first dose should be administered between 6 and 12 wk of age, with all three doses completed by 32 weeks of age. The vaccine provides substantial protection against rotavirus gastroenteritis, with a primary efficacy of 98% against severe rotavirus gastroenteritis caused by G1-G4 serotypes and 74% efficacy against rotavirus gastroenteritis of any severity through the first rotavirus season after vaccination. It provides a 96% reduction in hospitalizations for rotavirus gastroenteritis through the first 2 years after the third dose. In a study of more than 70,000 infants, the pentavalent vaccine did not increase the risk for intussusception, although other studies suggest a slight increased risk.

Another monovalent rotavirus vaccine was licensed in the United States and also appears to be safe and effective. It is an attenuated monovalent human rotavirus and is administered as two oral doses at 2 and 4 months of age. The vaccine has 85% efficacy against severe gastroenteritis and was found to reduce hospital admissions for all diarrhea by

42%. Despite being monovalent, the vaccine is effective in prevention of all four common serotypes of human rotavirus.

Preliminary surveillance data on the rotavirus incidence from the U.S. Centers for Disease Control and Prevention suggest that rotavirus vaccination greatly reduced the disease burden in the United States during the 2007–2008 rotavirus season and thereafter. Given the incomplete vaccine coverage during this period, the results suggest a degree of "herd immunity" from rotavirus immunization. Studies from several developed countries show greater than 90% protection against severe rotavirus disease. Studies from developing countries show 50–60% protection from severe disease. Vaccine-associated disease has been reported in vaccine recipients who have severe combined immunodeficiency disease (a contraindication). In addition, vaccine-derived virus may undergo reassortment and become more virulent, producing diarrhea in unvaccinated siblings.

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Chapter 313

Human Papillomaviruses

Kristen A. Feemster

See also Chapter 708.

Human papillomaviruses (HPVs) cause a variety of proliferative cutaneous and mucosal lesions, including common skin warts, benign and malignant anogenital tract lesions, oral pharyngeal cancers, and life-threatening respiratory papillomas. Most HPV-related infections in children and adolescents are benign (see also Chapter 708).

ETIOLOGY

The papillomaviruses are small (55 nm), DNA-containing viruses that are ubiquitous in nature, infecting most mammalian and many nonmammalian animal species. Strains are almost always species specific. Viral DNA is divided into an early region, which encodes proteins associated with viral replication and transcription, and a late region, which encodes capsid proteins necessary for virion assembly. These structural proteins are also the immunodominant antigens leading to type-specific immune responses. More than 100 different types of HPVs have been identified through the comparison of sequence homologies. The different HPV types typically cause disease in specific anatomic sites; more than 30 HPV types have been identified from genital tract specimens.

EPIDEMIOLOGY

HPV infections of the skin are common, and most individuals are probably infected with one or more HPV types at some time. There are no animal reservoirs for HPV; all transmission is presumably from person to person. There is little evidence to suggest that HPV is transmitted by fomites. Common warts, including palmar and plantar warts, are frequently seen in children and adolescents and typically infect the hands and feet, common areas of frequent minor trauma.

HPV is also the most prevalent viral sexually transmitted infection in the United States. Up to 80% of sexually active women will acquire HPV through sexual transmission; most have their first infection within 3 years of beginning sexual intercourse. Thus HPV disproportionately affects youth, with 75% of new infections occurring in 15- to 24-year-olds. The greatest risk for HPV in sexually active adolescents is exposure to new sexual partners, but HPV can still be acquired even with a history of one partner, underscoring the ease of transmission of this virus through sexual contact. It is estimated that after 11 acts of sexual intercourse, 100% of all HPV types infecting an individual will be transmitted to the other sexual partner. Couple studies show that there is high concordance in the genital area as well as between the hand and the genital area in the other partner. Whether the DNA detected in HPV on the hand is capable of transmitting infectious particles is unknown. Unlike other sexually transmitted infections, female-to-male transmission appears greater than male-to-female transmission. This may be because males in general have superficial transient infections or deposition. In turn, males do not develop an adequate immune response, so reinfections are quite common. The prevalence of HPV in women decreases with time, suggesting immune protection, whereas in men, the prevalence of HPV remains high across all ages.

As with many other genital pathogens, perinatal transmission to newborns can occur. Transmission from caregiver to child during the early childhood years has also been documented. However, both perinatal and early childhood infections appear transient. It remains unclear whether these HPV DNA detections are simply a deposition of caregiver DNA or a true infection. Detection of HPV DNA in older preadolescent children is rare. HPV DNA detection in non–sexually active adolescents has been reported, but a history of sexual activity in adolescents is not always disclosed and is therefore difficult to confirm. Although caregivers can spread HPV to young children, if lesions are detected in a child older than 3 years of age, the possibility of sexual transmission should be raised.

In adolescents, HPV DNA is most commonly detected without evidence of any lesion. Some of these detections are thought to be the result of partner deposition and hence do not represent a true infection. In older women, detection of HPV DNA is more commonly associated with a lesion. This is because the HPV DNA detected in older women reflects those HPV infections that became established persistent infections. Persistence is now the known necessary prerequisite for the development of significant precancerous lesions and cervical cancer.

Approximately 15–20% of sexually active adolescents have detectable HPV at any given time and have normal cytologic findings. The most common clinically detected lesion in adolescent women is the cervical lesion termed **low-grade squamous intraepithelial lesion (LSIL)** (Table 313.1). LSILs can be found in 25–30% of adolescents infected with HPV. External genital warts are much less common, occurring in <1% of adolescents; the incidence has decreased since introduction of HPV vaccines, but approximately 10% of individuals will develop genital warts in their lifetime. LSIL is a cytologic and histologic term to reflect the benign changes caused by an active viral infection and is likely present in most, if not all, women with HPV infection. However, the majority of women have very minute or subtle lesions not easily detected by cytology. As with HPV DNA detection, most LSILs regress spontaneously in young women and do not require any intervention or therapy. Less commonly, HPV can induce more severe cellular changes, termed **high-grade squamous intraepithelial lesions (HSILs)** (see Chapter 590).

Although HSILs are considered precancerous lesions, they rarely progress to invasive cancer. HSILs occur in approximately 0.4–3% of sexually active women, whereas invasive cervical cancer occurs in 8 cases per 100,000 adult women. In the United States, there are approximately 12,000 new cases (~7 cases/100,000) and 4,000 deaths from cervical cancer each year. Worldwide, cervical cancer is the fourth most common cause of cancer deaths among women. HPV is also associated with a range of other anogenital cancers, including an estimated 9,000 cases of anal cancer and 44,000 cases of oropharyngeal cancers in men and women.

Some infants may acquire papillomaviruses during passage through an infected birth canal, leading to recurrent **juvenile laryngeal papillomatosis** (JLP; also referred to as *respiratory papillomatosis*). Cases also have been reported after cesarean section. The incubation period for emergence of clinically apparent lesions (genital warts or laryngeal papillomas) after perinatally acquired infection is unknown but is estimated to be around 3-6 months (see Chapter 438.2). It may be that infections can also occur during hygienic care from an infected parent.

Genital warts may represent a sexually transmitted infection even in some very young children. Therefore genital warts appearing in childhood should raise suspicion for possible sexual abuse with HPV

Table 313.1 Terminology for Reporting Cervical Cytology and Histology

DESCRIPTIVE DIAGNOSIS OF EPITHELIAL CELL ABNORMALITIES	EQUIVALENT TERMINOLOGY
SQUAMOUS CELL	
Atypical squamous cells of undetermined significance (ASC-US)	Squamous atypia
Atypical squamous cells, cannot exclude HSIL (ASC-H)	
Low-grade squamous intraepithelial lesion (LSIL)	Mild dysplasia, condylomatous atypia, HPV-related changes, koilocytic atypia, cervical intraepithelial neoplasia (CIN) 1
High-grade squamous intraepithelial lesion (HSIL)	Moderate dysplasia, CIN 2, severe dysplasia, CIN 3, carcinoma in situ
GLANDULAR CELL	
Endometrial cells, cytologically benign, in a postmenopausal woman	
Atypical	
Endocervical cells, NOS	
Endometrial cells, NOS	
Glandular cells, NOS	
Endocervical cells, favor neoplastic	
Glandular cells, favor neoplastic	
ENDOCERVICAL ADENOCARCINOMA IN SITU	
Adenocarcinoma	
Endocervical	
Endometrial	
Extrauterine	
NOS	

NOS, Not otherwise specified.

transmission during the abusive contact. A child with genital warts should thus be provided with a complete evaluation for evidence of possible abuse (see Chapter 17.1), including the presence of other sexually transmitted infections (see Chapter 163). However, the presence of genital warts in a child does not confirm sexual abuse, because perinatally transmitted genital warts may go undetected until the child is older. Typing for specific genital HPV types in children is not helpful in diagnosis or to confirm sexual abuse status, because the same genital types occur in both perinatal transmission and abuse. In true virginal populations, including children who are not sexually abused, rates of clinical disease are close to zero.

PATHOGENESIS

Initial HPV infection of the cervix or other anogenital surfaces is thought to begin by viral invasion of the basal cells of the epithelium, a process that is enhanced by disruption of the epithelium caused by trauma or inflammation. It is thought that the virus initially remains relatively dormant because virus is present without any evidence of clinical disease. The life cycle of HPV depends on the differentiation program of keratinocytes. The pattern of HPV transcription varies throughout the epithelial layer and through different stages of disease (LSIL, HSIL, invasive cancer). Understanding of HPV transcription enhances understanding of its ability to behave as an oncovirus. Early region proteins, E6 and E7, function as transactivating factors that regulate cellular transformation. Complex interactions between E6- and E7-transcribed proteins and host proteins result in the perturbation of normal processes that regulate cellular DNA synthesis. The perturbations caused by E6 and E7 are primarily disruption of the anti-oncoprotein p53 and retinoblastoma protein (Rb), respectively, contributing to the development of anogenital cancers. Disruption of these proteins results in continued cell proliferation, even under the circumstances of DNA damage, which leads to basal cell proliferation, chromosomal abnormalities, and aneuploidy, hallmarks of squamous intraepithelial lesion (SIL) development.

Evidence of productive viral infection occurs in benign lesions such as external genital warts and LSILs, with the abundant expression of viral capsid proteins in the superficial keratinocytes. The appearance of the HPV-associated koilocyte is a result of the expression of E4, a structural protein that causes collapse of the cytoskeleton. Low-level expression of E6 and E7 proteins results in cell proliferation seen in the basal cell layer of LSILs. LSILs are a manifestation of active viral replication and protein expression. In HSILs, expression of E6 and E7 predominates throughout the epithelium, with little expression of the structural proteins L1 and L2. This results in the chromosomal abnormalities and aneuploidy characteristic of the higher-grade lesions. The critical events that lead to cancer have not been verified; however, several mechanisms are thought to be critical, including viral integration into the host chromosome and activation of telomerase to lengthen chromosomes and avoid physiologic cell senescence. Over 150 HPV types have been documented and are classified by extent of their DNA homology into 5 genera, with the different types having different life cycle and disease characteristics. The predominant group is α HPV types, which are associated with cutaneous and mucosal anogenital infections and cancers. β, γ, μ, and ν cause predominantly benign cutaneous lesions but can be difficult to manage in severely immunocompromised individuals. B types are commonly detected on the skin without any apparent lesions but are associated with the development of skin cancers in those with epidermodysplasia verruciformis or other forms of immunodeficiencies. Genital lesions caused by the α HPV types may be broadly grouped into those with little to no malignant potential (low risk) and those with greater malignant potential (high risk). Low-risk HPV types 6 and 11 are most commonly found in genital warts and are rarely found isolated in malignant lesions. High-risk HPV types are those types that are associated with anogenital cancers, specifically cervical cancer. HPV 16 and 18 are thought to be more oncogenic than other HPV types because they comprise 70% of cervical cancers, whereas each of the other 12 high-risk types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and 73) contribute less than 1–9%. HPV 16 appears to be even more important in anal and HPV-associated oropharyngeal cancers, comprising close to 90% of these cancers. HPV 16 is also commonly found in women without lesions or in those with LSILs, making the connection with cancer confusing. Genital warts and SIL are commonly associated with the detection of multiple HPV types, including a combination of low- and high-risk HPV types. Data show that it is likely that a single lesion arises from a single HPV type. Detection of multiple HPV types reflects the presence of cervical and anal coexisting lesions. Almost all (95%) incident low-risk and high-risk HPV DNA detections, with or without detectable SIL, will spontaneously resolve within 1-3 years. Although HPV 16 has a slower rate of regression than some of the other high-risk types, the majority of incident HPV 16 detections also will resolve. Data suggest that clearance of an HPV type results in natural immune protection against reinfection with that same type. Redetections of the same type are not common and when found are often associated with a history of a new sexual partner, suggesting that these are not reactivated infections but are due to new exposures. These redetections rarely result in high-grade disease. Persistent high-risk–type infections are associated with increased risk for development of HSILs and invasive cancer. Progression of HSIL to invasive cancer is still rare, with only 5–15% showing progression. Approximately 50% of HPV 16–associated HSILs and 80% of non–HPV 16 HSILs will spontaneously regress in young women. Genital and common warts in general also resolve without therapy but may take years to do so. Genital warts in only extremely rare conditions can become malignant.

Most infants with recognized genital warts are infected with the low-risk types. In contrast, children with a history of sexual abuse have a clinical picture more like that of adult genital warts, consisting of mixed low- and high-risk types. There are rare reports of HPV-associated genital malignancies occurring in preadolescent children and adolescents. On the other hand, precancerous HSILs do occur in sexually active adolescents. There is a concern that younger age of sexual debut has contributed to the increase in invasive cervical cancers seen in women younger than 50 years of age in the United States, specifically cervical adenocarcinomas. Persistent HPV infections are considered necessary but not sufficient for the development of invasive

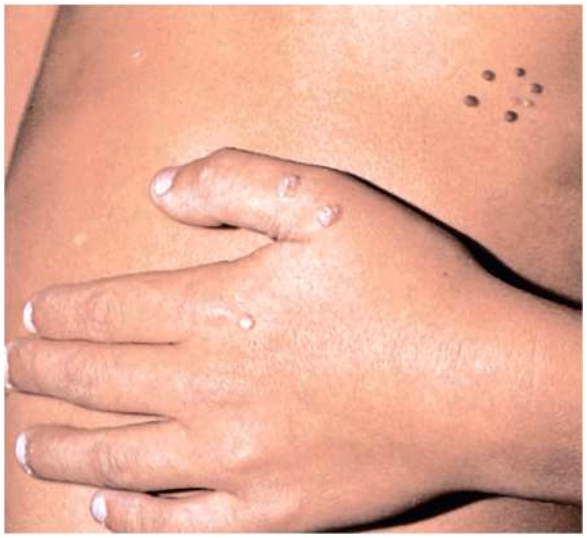

Fig. 313.1 Common warts of the left hand and the chest wall. *(From Meneghini CL, Bonifaz E. An Atlas of Pediatric Dermatology, Chicago: Year Book; 1986:45.)*

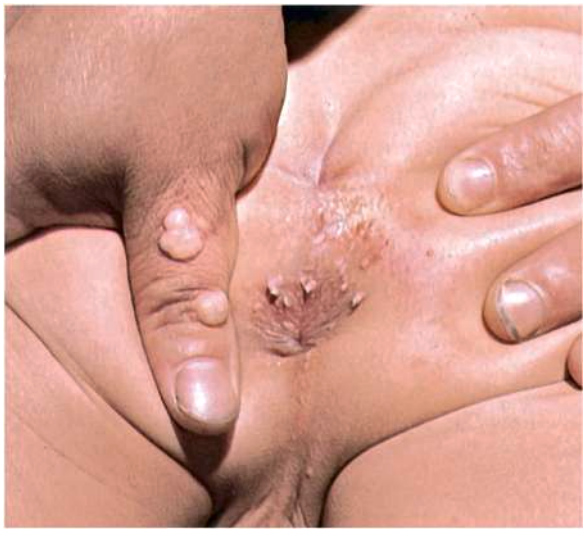

Fig. 313.2 Common warts of the hand in a mother and perianal condylomata acuminata in her son. *(From Meneghini CL, Bonifaz E. An Atlas of Pediatric Dermatology, Chicago: Year Book; 1986:44.)*

cancers. Other risk factors for which there is relatively strong suggestive evidence of association include smoking cigarettes, prolonged oral contraceptive use, greater parity, and *Chlamydia trachomatis* and herpes simplex virus infections.

CLINICAL MANIFESTATIONS

The clinical findings in HPV infection depend on the site of epithelial infection.

Skin Lesions

The typical HPV-induced lesions of the skin are proliferative, papular, and hyperkeratotic. Common warts are raised circinate lesions with a keratinized surface (Fig. 313.1). Plantar and palmar warts are practically flat. Multiple warts are common and may create a mosaic pattern. Flat warts appear as small (1- to 5-mm), flat, flesh-colored papules.

Genital Warts

Genital warts may be found throughout the perineum around the anus, vagina, and urethra, as well as in the cervical, intravaginal, and intraanal areas (Fig. 313.2). Intraanal warts occur predominantly in patients who have had receptive anal intercourse, in contrast with perianal warts, which may occur in men and women without a history of anal sex. Although rare, lesions caused by genital genotypes can also be found on other mucosal surfaces, such as the conjunctivae, tongue, gingivae, and nasal mucosa. They may be single or multiple lesions and are frequently found in multiple anatomic sites, including the cervix. External genital warts can be flat, dome shaped, keratotic, pedunculated, and cauliflower shaped and may occur singly, in clusters, or as plaques. On mucosal epithelium, the lesions are softer. Depending on the size and anatomic location, lesions may be pruritic and painful, may cause burning with urination, may be friable and bleed, or may become superinfected. Adolescents are frequently disturbed by the development of genital lesions. Other rarer lesions caused by HPV of the external genital area include Bowen disease, bowenoid papulosis, squamous cell carcinomas, Buschke-Löwenstein tumors, and vulvar intraepithelial neoplasias.

Squamous Intraepithelial Lesions and Cancers

SILs detected with cytology are usually invisible to the naked eye and require the aid of colposcopic magnification and acetic acid. With aid, the lesions appear white and show evidence of neovascularity. SILs can occur on the cervix, vagina, vulva, penis, and intraanus. HPV-associated squamous cell lesions can also be found in the oropharynx. Invasive cancers tend to be more exophytic, with aberrant-appearing vasculature. These lesions are rarely found in non–sexually active individuals.

Laryngeal Papillomatosis

The median age at diagnosis of recurrent laryngeal papillomatosis is 3 years. Children present with hoarseness, an altered cry, and sometimes stridor. Rapid growth of respiratory papillomas can occlude the upper airway, causing respiratory compromise. These lesions may recur within weeks of removal, requiring frequent surgery. The lesions do not become malignant unless treated with irradiation.

DIAGNOSIS

The diagnosis of external genital warts and common warts may be reliably determined by visual inspection of a lesion by an experienced observer and does not require additional tests for confirmation. A biopsy should be considered if the diagnosis is uncertain, the lesions do not respond to therapy, or the lesions worsen during therapy.

Screening for cervical cancer in young women begins with cytology, which is performed by either Papanicolaou smear or liquid-based cytology and may also include high-risk HPV DNA testing for women age 30-65 years. Screening guidelines were updated in 2018 by the U.S. Preventive Services Task Force (USPSTF) and recommend starting screening at age 21 years. Screening earlier is more likely to result in unnecessary referrals for colposcopy, because most lesions, including both LSILs and HSILs in this age-group, are likely to regress. Guidelines recommend screening with cytology every 3 years through 29 years of age. For women age 30-65 years of age, USPSTF recommends screening every 3 years with cervical cytology alone, or every 5 years with high-risk HPV testing alone or high-risk HPV testing with cytology (co-testing). High-risk HPV testing is not recommended earlier than age 30 years, because HPV infections are extremely common in young women, resulting in a very low positive predictive value in this age-group. These recommendations apply to all persons who have a cervix, regardless of sexual history of HPV vaccination history.

The recommended terminology used for cytologic evaluation is based on the Bethesda system (see Table 313.1). Recent updates to the terminology used for histology uses similar terms. Many clinicians still prefer the World Health Organization terminology using cervical intraepithelial neoplasia (CIN) 1, 2, and 3 (see Table 313.1). Although the purpose of screening is to identify CIN 3+ lesions, the majority of CIN lesions are found in women who were referred for **atypical squamous cells of undetermined significance (ASC-US)** or LSILs on cytology. On the other hand, few CIN 3 or cancers exist in women younger than 24 years of age. Thus, for women 21-24 years of age, ASC-US and LSILs are treated the same.

Consensus guidelines from the American Society of Colposcopy and Cervical Pathology for the management of cervical cancer screening abnormalities were updated in 2019 and used a risk-based (related to

a patient's risk of CIN 3) rather than test-based algorithm. Treatment guidelines are also dichotomized by age group, 21-24 years and 25 years or older. Women age 21-24 years with ASC-US or LSIL should have repeat cytology at 12 months and 24 months after the initial abnormal result. For persistent ASC-US or LSILs at 2 years of follow-up or for HSIL at any point, referral for colposcopy is recommended. If colposcopy results show LSIL, cytology should be repeated in 1 year. If there are two negative cytology results, routine age-based screening can be resumed. If repeat cytology shows HSIL with CIN2+, observation with repeat colposcopy every 6 months should be performed. If HSIL persists for 2 years or if CIN 3+ is identified, treatment with an excisional procedure is recommended. In women 25 years of age and older, HSIL can be treated without histologic confirmation. However, this approach should be avoided in those 21-24 years of age, because HSIL is often misdiagnosed in this group or will resolve spontaneously.

In all women age 21 years and older, high-risk HPV testing is acceptable to assist in ASC-US triage. This recommendation is based on the observations that adult women with ASC-US and a positive HPV test result for high-risk types are more likely to have CIN 2/3 than women with a negative HPV test result. However, in women with ASC-US and a positive HPV test for high-risk types, repeat cytology is recommended for confirmation. In women 21-24 years of age referred for colposcopy and found to have no lesion or biopsy-confirmed LSIL after ASC-US or LSIL cytology, repeat cytology is recommended at 12-month intervals as described previously. In women with biopsy-confirmed LSIL after atypical squamous cells of high grade (ASC-H) or HSIL, observation with cytology and colposcopy is recommended at 6-month intervals for up to 2 years. For persistent ASC-H or HSIL at 2 years or progression at any time, treatment is recommended. These guidelines and updates can be found at http://www.asccp.org.

Very sensitive tests for the presence of HPV DNA, RNA, and proteins are becoming generally available, although they are not required for the diagnosis of external genital warts or related conditions. There are no indications for HPV DNA testing in women younger than 21 years of age or children. HPV DNA testing is also not recommended in women 21-29 years of age but is acceptable for ASC-US triage. Diagnosis of JLP is made based on laryngeal examination. There are no routine screening recommendations for noncervical or oropharyngeal lesions.

DIFFERENTIAL DIAGNOSIS

A number of other conditions should be considered in the differential diagnosis of genital warts, including condyloma latum, seborrheic keratoses, dysplastic and benign nevi, molluscum contagiosum, pearly penile papules, neoplasms, Bowen disease, bowenoid papulosis, Buschke-Löwenstein tumors, and vulvar intraepithelial neoplasias.

Condyloma latum is caused by secondary syphilis and can be diagnosed with darkfield microscopy and standard serologic tests for syphilis. Seborrheic keratoses are common, localized, hyperpigmented lesions that are rarely associated with malignancy. Molluscum contagiosum is caused by a poxvirus, is highly infectious, and is often umbilicated. Pearly penile papules occur at the penile corona and are normal variants that require no treatment.

TREATMENT

Most common (plantar, palmar, skin) warts eventually resolve spontaneously (see Chapter 708). Symptomatic lesions should be removed. Removal includes a variety of self-applied therapies, including salicylic acid preparations and provider-applied therapies (cryotherapy, laser therapy, electrosurgery). Genital warts are benign and usually remit, but only over an extended period. It is recommended that genital lesions be treated if the patient or the parent requests therapy. Treatments for genital warts are categorized into self-applied and provider-applied. No one therapy has been shown to be more efficacious than any other. Recommended patient-applied treatment regimens for external genital warts include topical podofilox, imiquimod, and sinecatechins. Podofilox 0.5% solution (using a cotton swab) or gel (using a finger) is applied to visible warts in a cycle of applications twice per day for 3 days followed by 4 days of no therapy, repeated for up to a total of four cycles as needed. The total volume of podofilox used per day should not exceed 0.5 mL, and patients should wash hands before and after each application. Imiquimod 5% cream is applied at bedtime, 3 times per week, every other day, for up to 16 weeks. Imiquimod 3.75% cream is applied at bedtime every night for up to 8 weeks. For both formulations, the treated area should be washed with mild soap and water 6-10 hours after treatment. Sinecatechins (15% ointment) is a topical product from green tea extract used for external genital wart treatment that is applied 3 times daily until warts have completely resolved but no longer than 16 weeks. A 0.5-cm strand of ointment should be applied to each wart as a thin layer.

Provider-applied therapies include surgical treatments (electrosurgery, tangential scissor or shave excision, curettage, laser surgery), cryotherapy with liquid nitrogen or a cryoprobe and office-based application of bichloroacetic (BCA) or trichloroacetic acid (TCA) 80–90% solution. Surgical treatments require appropriate training and equipment but can be most beneficial for patients with large or extensive warts. Surgical removal or cryotherapy are also recommended for urethral meatus warts, while surgical removal, cryotherapy or BCA / TCA is recommended for vaginal, cervical, and intraanal warts. BCA or TCA treatment should be applied only to warts and can be repeated once per week for 3-6 weeks.

Alternative regimens include podophyllin resin, intralesional interferon, photodynamic therapy, and topical cidofovir, but there are few available data regarding their efficacy. Intralesional interferon is associated with significant adverse effects and is reserved for treatment of recalcitrant cases. Podophyllin resin is no longer recommended because of the availability of other, safer regimens but may be considered for provider-administered treatment if there can be strict adherence to recommendations to prevent complications from systemic absorption.

Many therapies are painful, and children should not undergo painful genital treatments unless adequate pain control is provided. Parents and patients should not be expected to apply painful therapies themselves. None of the patient-applied therapies are approved for use during pregnancy, and podofilox is contraindicated in pregnancy. For any of the nonsurgical treatments, prescription is contraindicated in a patient with any history of hypersensitivity to any product constituents.

If HPV exposure as a result of sexual abuse is suspected or known, the clinician should ensure that the child's safety has been achieved and is maintained.

When indicated, the most common treatments for CIN 2/3 are ablative and excisional treatments, including cryotherapy, laser, and loop electrosurgical excisional procedures. Once confirmed by histology with CIN 1, LSILs can be observed as described previously. The decision to treat a persistent CIN 1 rests between the provider and patient. Risks of treatment, including premature delivery in a future pregnancy, should be discussed before any treatment decision. Treatment in pregnancy is not recommended unless invasive cancer is present.

JLP is commonly treated with surgical removal of lesions, but laser and microdebriders are also used. However, because of the incidence of scar formation after repeat debridement procedures, medical therapies have been increasingly investigated. Adjunctive treatments have included interferon-α, antivirals such as cidofovir administered locally or systemically, photodynamic therapy, antiinflammatory drugs (celecoxib), heat shock protein, human monoclonal antibodies (bevacizumab), and HPV vaccination. However, the effectiveness of adjunctive therapies is not consistent.

COMPLICATIONS

The presence of HPV lesions in the genital area may be a cause of profound embarrassment to a child or parent. Complications of therapy are uncommon; chronic pain (vulvodynia) or hypoesthesia may occur at the treatment site. Lesions may heal with hypopigmentation or hyperpigmentation and less commonly with depressed or hypertrophic scars. Surgical therapies can lead to infection and scarring. Premature delivery and low birthweight in future pregnancies are complications of excisional therapy for CIN.

It is estimated that 5–15% of untreated CIN 3 lesions will progress to cervical cancer. Most cancer is prevented by early detection and treatment of these lesions. Despite screening, cervical cancer develops rapidly in a few adolescents and young women. The reason for the rapid

development of cancer in these rare cases remains unknown, but host genetic defects are likely underlying causes. JLPs rarely become malignant, unless they have been treated with irradiation. Vulvar condylomas rarely become cancerous. HPV-associated cancers of the vagina, vulva, anus, penis, and oral cavity are much rarer than cervical tumors, and therefore screening for noncervical lesions is not currently recommended. However, anal, vaginal, and vulvar cancers are more common in women with cervical cancer; thus it is recommended to screen women with cervical cancer for other anogenital or oropharyngeal tumors with visual and/or digital inspection

PROGNOSIS

With all forms of therapy, genital warts commonly recur, and approximately half of children and adolescents require a second or third treatment. Recurrence is also evident in patients with JLP. Patients and parents should be warned of this likelihood. Combination therapy for genital warts (imiquimod and podofilox) does not improve response and may increase complications. Prognosis of cervical disease is better, with 85–90% cure rates after a single treatment with the loop electrosurgical excision procedure. Cryotherapy has a slightly lower cure rate. Recalcitrant disease should prompt an evaluation and is common in immunocompromised individuals, specifically men and women infected with HIV.

PREVENTION

The only means of preventing all types of HPV infection is to avoid direct contact with lesions. Condoms may reduce the risk for HPV transmission; condoms also prevent other sexually transmitted infections, which are risk factors associated with SIL development. In addition, condoms appear to hasten the regression of LSILs in women. Avoiding smoking cigarettes is important in preventing cervical cancer. Prolonged oral contraceptive use and parity have been shown to be risks for cervical cancer. However, the mechanisms associated with these factors have not been identified, and consequently no change in counseling is recommended.

HPV vaccines show efficacy against type-specific persistence and development of type-specific disease, including the cervix, vagina, vulva, and anus. A quadrivalent HPV vaccine containing types 6, 11, 16, and 18 was licensed in the United States in 2006, and a bivalent HPV vaccine containing types 16 and 18 was licensed in the United States in 2009. A 9-valent vaccine containing types 6, 11, 16, 18, 31, 33, 45, 52, and 58 was approved in 2014. Initial licensure was for vaccination of persons age 9-26 years. In 2018, the FDA expanded licensure to include men and women age 27-45 years based on quadrivalent HPV vaccine clinical trial results in women age 27-45 years and bridging immunogenicity and safety data in women and men. The bivalent vaccine is indicated for the prevention of cervical precancer and cancer in females. The 4- and 9-valent HPV vaccines are indicated for the prevention of anal, cervical, vaginal, and vulvar precancers/cancers, as well as genital warts in females and anal precancer cancer and genital warts in males. The indication for the 9-valent HPV vaccine was expanded to include oropharyngeal and other head and neck cancers in 2021.

The types targeted by the nonavalent vaccine account for up to 85% of cervical cancer cases. The efficacy of these vaccines is mediated by the development of neutralizing antibodies. Prelicensure studies demonstrate 90–100% efficacy in the prevention of persistent HPV infection, CIN 2/3, adenocarcinoma in situ, anogenital warts, and precancerous vaginal and vulvar lesions. Since vaccine introduction, data from Sweden and Australia show a decrease in national rates of genital warts within 4 years of implementing vaccination programs. Data from the United States show significant reductions in the prevalence of the HPV types contained in the quadrivalent vaccine among adolescent and young adult females in the years 2009–2012 (postvaccine) compared with 2003–2006 (prevaccine). Additionally, the HPV vaccine–type prevalence was 2.1% in vaccinated compared with 16.9% in unvaccinated 14- to 24-year-old sexually active females. A systematic review of 20 studies conducted in nine high-income countries showed reductions of at least 68% in the prevalence of HPV 16 and 18 among 13- to 19-year-olds in countries with HPV vaccination rates >50%. Recent data also demonstrate significant reductions in cervical cancer rates and CIN 3 with the highest reductions among women who were vaccinated at age 12-13 years after implementation of a national HPV vaccination program in the United Kingdom. A 29% reduction in cervical cancer annual incidence rates from 2003–2006 to 2011–2014 was observed among females age 15-24 years in the United States. Additionally, an analysis of data from a population-based cancer registry showed a decline in the incidence of squamous cell carcinoma and adenocarcinoma among young women age 15-29 years, with the largest reductions in the 15- to 20-year age group. Available effectiveness data suggest that HPV vaccination confers herd immunity in addition to individual protection.

Vaccination in the United States is recommended routinely for all adolescents at 11-12 years of age and is administered intramuscularly in the deltoid region in a two-dose series at 0 and 6-12 months. A two-dose series was approved and recommended in 2016 for younger adolescents who initiate the HPV vaccine series before age 15 years based on immunogenicity data showing a comparable immune response among younger adolescents who receive a two-dose series compared with older adolescents, who receive a three-dose series. The effectiveness of one dose has also been evaluated in observational and post-hoc analyses from clinical trials.

It is important that vaccination take place in children before they become sexually active, because the rate of HPV acquisition is high shortly after the onset of sexual activity. Vaccine can be given to adolescents as young as 9 years of age, and catch-up vaccination is now recommended in all persons through 26 years of age. Vaccination is also recommended for adults 27-45 years using shared clinical decision making if they have not been previously vaccinated. For any adolescent who receives his or her first HPV vaccine dose at age 15 years or older, a three-dose series at 0, 1-2, and 6 months is recommended. The three-dose series is also recommended for adolescents and young adults 9-26 years of age who have an immunocompromising condition. Individuals who are already infected with one or more vaccine-related HPV types before vaccination are protected from clinical disease caused by the remaining vaccine HPV types. Therefore a history of prior HPV infection is not a contraindication to vaccine receipt. Currently licensed HPV vaccines are not therapeutic. However, there are therapeutic HPV vaccines under development that are primarily designed to generate a cell-mediated immune response to target infected cells.

Post-licensure vaccine safety surveillance has not identified any serious adverse events attributable to HPV vaccine receipt. Three large observational studies and safety monitoring through active and passive surveillance networks among more than 1 million individuals have not identified any association between HPV vaccination and outcomes such as autoimmune disorders, stroke, or venous thrombotic emboli. Vaccination can cause fever in approximately 1 in 60 and discomfort at the injection site in 1 in 30 vaccine recipients. Syncope has also been found to be correlated with vaccine administration in 0.1% of vaccine recipients. Therefore it is advised that adolescents remain seated for 15 minutes after vaccination.

Despite an excellent safety and efficacy profile, HPV vaccine uptake has been slow. Immunization rates have consistently lagged behind rates for the other vaccines included in the adolescent immunization platform. In 2020, 75% of 13- to 17-year-olds had received at least one HPV vaccine dose compared with 89% who received at least one dose of the quadrivalent meningococcal vaccine and 92% who received tetanus-diphtheria-acellular pertussis (Tdap) vaccine. Reasons for the slow uptake include inconsistent provider recommendation, lack of knowledge about HPV, parental belief that vaccination is not necessary for younger adolescents, and misconceptions about vaccine safety, among others. There is a growing body of literature evaluating interventions to improve HPV vaccine uptake. One important strategy is a strong, consistent recommendation in which HPV vaccines are presented in the same way as Tdap and meningococcal vaccines.

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Chapter 314

Arboviral Infections

Scott B. Halstead

The arthropod-borne viral infections are caused by a group of mosquito- or tick-transmitted viral pathogens of several taxa and manifest clinically mostly as neurologic infections, influenza-like illnesses, or acute viral exanthems. In temperate countries, arboviruses are transmitted during warmer weather; however, in tropical and subtropical countries, arboviruses may be transmitted year-round either in an urban cycle (human to mosquito to human) or by arthropods that feed on other vertebrate species and then feed on humans.

ETIOLOGY

The principal arthropod-borne viral infections in North America are West Nile encephalitis (WNE), St. Louis encephalitis (SLE), Powassan (POW) encephalitis, a complex of California encephalitis group viruses, and, less frequently, western equine encephalitis (WEE), eastern equine encephalitis (EEE), and Colorado tick fever (Fig. 314.1). In 2013, chikungunya virus (CHIK) emerged from its original African zoonosis via Asia into the tropical and subtropical Western Hemisphere, exposing indigenes and many visitors who were traveling in the region. A few cases occurred in southern United States. In 2015, Zika virus (ZIKV), a flavivirus also maintained in Africa zoonoses, was introduced into the Americas, again from endemic areas in Asia. Limited transmission occurred within the continental United States. The major source of infection among Americans for each of these viruses has been travel to tropical and subtropical countries. CHIK appears to be endemic now, whereas ZIKV illnesses have decreased dramatically.

Throughout the world outside North America, there are many arboviruses that pose major health problems (Fig. 314.2). In descending order, these are the dengue viruses (DENV; Chapter 315), transmitted in all subtropical and tropical countries; Japanese encephalitis (JE), transmitted in northern, southern, and Southeast Asia; tick-borne encephalitis (TBE), transmitted across Europe and into northern and eastern Asia; yellow fever (YF; Chapter 316), transmitted from zoonotic cycles in Africa and South America; and Venezuelan equine encephalitis (VEE), transmitted in parts of South and Central America.

The etiologic agents belong to different viral taxa: *alphaviruses* of the family Togaviridae (CHIK, EEE, VEE, WEE), *flaviviruses* of the family Flaviviridae (DENV, JE, POW, SLE, TBE, WNE, YF, ZIKV), the California complex of the family Bunyaviridae (California encephalitis), and Reoviridae (Colorado tick fever virus). *Alphaviruses* are 69-nm, enveloped, positive-sense RNA viruses. Studies suggest that this group of viruses had a marine origin (specifically the southern ocean) and has subsequently spread to both the Old and New Worlds. VEE circulates in nature in six subtypes. Virus types I and III have multiple antigenic variants. Types IAB and IC have caused epizootics and human epidemics. Flaviviruses are 40- to 50-nm, enveloped, positive-sense RNA viruses that evolved from a common ancestor. They are mosquito-borne (WNE, SLE, JE, YF, DENV, ZIKV) and tick-borne (POW, TBE) agents, globally distributed, and responsible for many important human viral diseases. The California serogroup, 1 of 16 Bunyavirus groups, are 75- to 115-nm enveloped viruses possessing a three-segment, negative-sense RNA genome. Reoviruses are 60- to 80-nm double-stranded RNA viruses.

DIAGNOSIS

For arboviral infections not described separately, the etiologic diagnosis is established by testing either an acute-phase serum to detect the virus, viral antigen, or viral RNA (influenza-like illnesses or viral exanthems) or by recovery of virus from central nervous system (CNS) tissue or cerebrospinal fluid (CSF). More commonly, the diagnosis is established serologically. Serum obtained ≥5 days after the onset of illness is tested for the presence of virus-specific immunoglobulin (Ig) M antibodies using an enzyme-linked immunosorbent assay IgM capture test, an indirect immunofluorescence test, or a precipitin test. Alternatively, acute and convalescent sera can be tested for a fourfold or greater increase in enzyme-linked immunosorbent assay, hemagglutination inhibition, or neutralizing antibody titers. Commercial serologic diagnostic kits are marketed for DENV, CHIK, JE, TBE, WNE, YF, and ZIKV viral infections. The serum and CSF should be tested for JE or WNE virus–specific IgM. However, IgM may reflect past infection, because it may be present up to 12 months after infection. For suspected flavivirus infections, including ZIKV, it may be possible to establish infection using a serologic test, calling on the specificity of neutralizing antibodies. The most common of these is the plaque or focus-reduction neutralizing antibody test. Reference laboratories offer tests for all of the pathogenic flaviviruses. The diagnosis may also be established by the isolation of virus in cell cultures, by identification of viral RNA, or by detection of viral proteins (e.g., dengue NS1) from blood, brain tissue obtained by brain biopsy, or tissues obtained at autopsy.

PREVENTION

Several vaccines for JE and TBE are licensed in endemic and nonendemic countries. An experimental vaccine for VEE is available to protect laboratory workers. Travelers who plan to be in rural areas of Asia during the expected period of seasonal transmission should receive JE vaccine. Similarly, travelers who plan to travel, camp, or picnic in rural areas of Europe and East Asia should consult local health authorities concerning the need to be vaccinated against TBE. An inactivated JE vaccine manufactured in Japan by intracerebral injection of young mice once available throughout the world was taken off the market owing to a high incidence of adverse events. In 2008–2009, tissue culture–based JE vaccine (Ixiaro) was licensed in Europe, Australia, and the United States. In the United States, this vaccine, licensed for use in children and adults, distributed by Novartis (Basel), is administered intramuscularly as two doses of 0.5 mL each, 28 days apart. The final dose should be completed at least 1 week before the patient's expected arrival in a JE endemic area. This vaccine contains alum and protamine sulfate and has exhibited only mild adverse events. Chimerivax-JE, marketed by Sanofi Pasteur and licensed in Australia and several Asian countries, is a live-attenuated two-dose vaccine composed of the structural gene of JE inserted into the YF 17D vaccine backbone. A highly efficacious live-attenuated single-dose JE vaccine, SA 14-14-2, developed in China for children is licensed and marketed in Asian countries. This vaccine can be co-administered with live-attenuated measles vaccine without altering the immune responses to either vaccine. In humans, prior DENV infection provides partial protection against clinical JE.

No TBE vaccines are licensed or available in the United States. Two inactivated cell culture–derived TBE vaccines are available in Europe, in adult and pediatric formulations: FSME-IMMUN (Baxter, Austria) and Encepur (Novartis, Germany). The adult formulation of FSME-IMMUN is also licensed in Canada. Two other inactivated TBE vaccines are available in Russia: TBE-Moscow (Chumakov Institute, Russia) and EnceVir (Microgen, Russia). Immunogenicity studies suggest that the European and Russian vaccines should provide cross-protection against all three TBE virus subtypes. For both FSME-IMMUN and Encepur, the primary vaccination series consists of three doses. The specific recommended

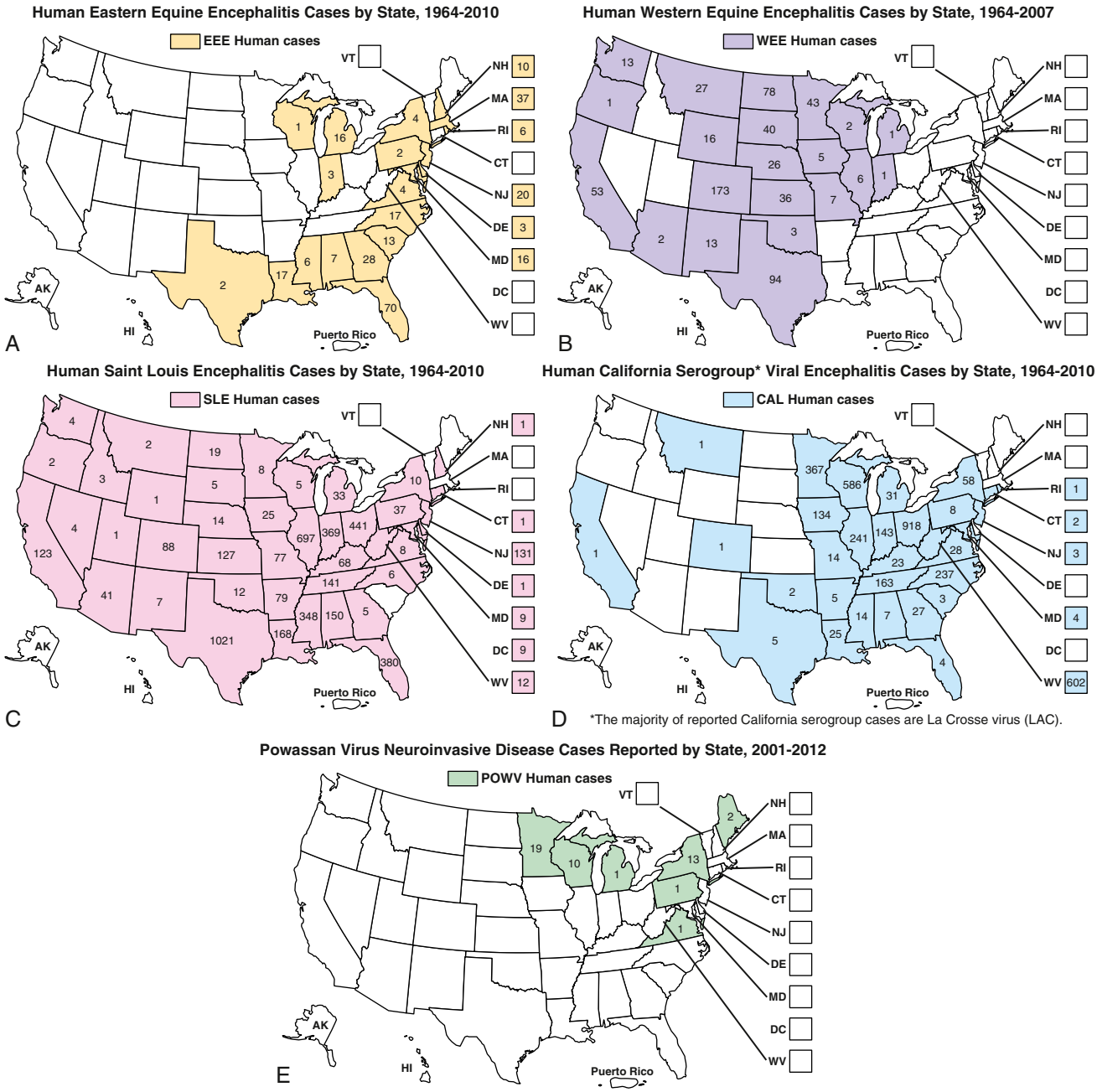

Fig. 314.1 The distribution and incidence of reported cases of eastern equine encephalitis (A), western equine encephalitis (B), St. Louis encephalitis (C), California serogroup encephalitis (D), and Powassan encephalitis; (E), reported by state to the Centers for Disease Control and Prevention, 1964 to 2010. *(From Division of Vector-Borne Diseases, Centers for Disease Control and Prevention. http://www.cdc.gov/ncidod/dvbid/arbor/arbocase/htm)*

intervals between doses vary by country and vaccine. Because the routine primary vaccination series requires ≥6 months for completion, most travelers to TBE-endemic areas will find avoiding tick bites to be more practical than vaccination.

For all viral diseases discussed in this chapter, personal measures should be taken to reduce exposure to mosquito or tick bites, especially for short-term residents in endemic areas. These measures include avoiding evening outdoor exposure, using insect repellents, covering the body with clothing, and using bed nets or house screening. Commercial pesticides, widely used by rice farmers, may be useful in reducing populations of vector mosquitoes or ticks. Fenthion, fenitrothion, and phenthoate are effectively adulticidal and larvicidal. Insecticides may be applied from portable sprayers or from helicopters or light aircraft.

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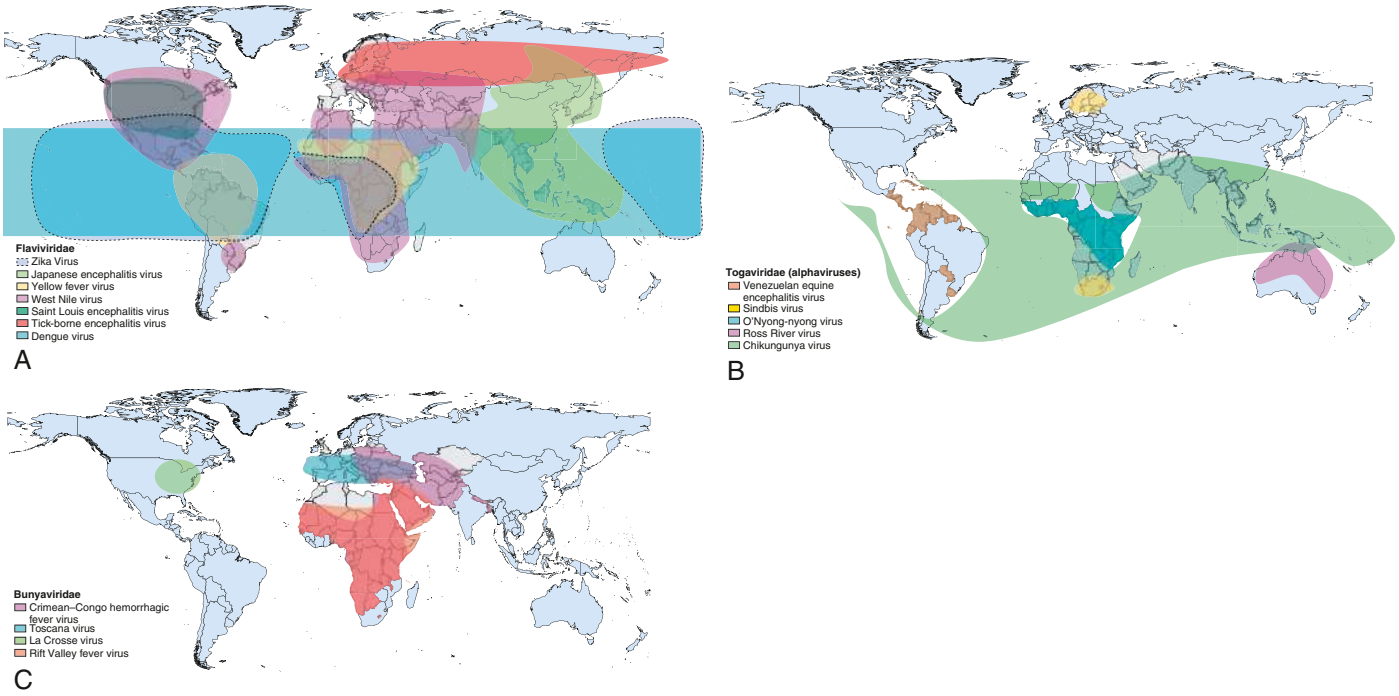

Fig. 314.2 World distribution of major arbovirus infections. *(From Charlier C, Beaudoin MC, Couderc T, et al. Arboviruses and pregnancy: maternal, fetal, and neonatal effects. Lancet Child Adolesc. 2017;1:134–146. Fig. 1.)*

314.1 Eastern Equine Encephalitis

Scott B. Halstead

In the United States, EEE is a disease with a very low incidence, with a median of eight cases occurring annually in the Atlantic and Gulf states from 1964 to 2007. A severe outbreak in 2019 resulted in 19 fatalities among 38 cases (see Fig. 314.1). Transmission occurs often in focal endemic areas of the coast of Massachusetts, the six southern counties of New Jersey, and northeastern Florida. In North America, the virus is maintained in freshwater swamps in a zoonotic cycle involving the *Culiseta melanura* mosquito and birds. Various other mosquito species obtain viremic meals from birds and transmit the virus to horses and humans. Virus activity varies markedly from year to year in response to still unknown ecologic factors. Most infections in birds are silent, but infections in pheasants are often fatal, and epizootics in these species are used as sentinels for periods of increased viral activity. Cases have been recognized on Caribbean islands. The case:infection ratio is lowest in children (1:8) and somewhat higher in adults (1:29).

EEE virus infections result in fulminant encephalitis with a rapid progression to coma and death in one third of cases. In infants and children, abrupt onset of fever, irritability, and headache are followed by lethargy, confusion, seizures, and coma. High temperature, bulging fontanel, stiff neck, and generalized flaccid or spastic paralysis are observed. There may be a brief prodrome of fever, headache, and dizziness. Unlike most other viral encephalitides, the peripheral white blood cell count usually demonstrates a marked leukocytosis and the CSF may show marked pleocytosis. Pathologic changes are found in the cortical and gray matter, with viral antigens localized to neurons. There is necrosis of neurons, neutrophilic infiltration, and perivascular cuffing by lymphocytes.

The prognosis in EEE is better for patients with a prolonged prodrome; the occurrence of convulsions conveys a poor prognosis. Patient fatality rates are 33–75% and are highest in the elderly. Residual neurologic defects are common, especially in children.

The diagnosis of encephalitis may be aided by CT or MRI and by electroencephalography. Focal seizures or focal findings on CT or MRI or electroencephalography should suggest the possibility of herpes simplex encephalitis, which should be treated with acyclovir (see Chapter 299).

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314.2 Western Equine Encephalitis

Scott B. Halstead

WEE infections occur principally in the United States and Canada west of the Mississippi River (see Fig. 314.1). Cases occur mainly in rural areas where water impoundments, irrigated farmland, and naturally flooded land provide breeding sites for the *Culex tarsalis* mosquito. The virus is transmitted in a cycle involving mosquitoes, birds, and other vertebrate hosts. Humans and horses are susceptible to encephalitis. The case:infection ratio varies by age, having been estimated at 1:58 in children younger than 4 years of age and 1:1,150 in adults. Infections are most severe at the extremes of life; one third of cases occur in children younger than 1 year of age. Recurrent human epidemics have been reported from the Yakima Valley in Washington State and the Central Valley of California; the largest outbreak on record resulted in 3,400 cases and occurred in Minnesota, North and South Dakota, Nebraska, and Montana, as well as Alberta, Manitoba, and Saskatchewan, Canada. Epizootics in horses precede human epidemics by several weeks. For the past 20 years, only three cases of WEE have been reported, presumably reflecting successful mosquito abatement.

In WEE, there may be a prodrome with symptoms of an upper respiratory tract infection. The onset is usually sudden with chills, fever, dizziness, drowsiness, increasing headache, malaise, nausea and vomiting,

stiff neck, and disorientation. Infants typically present with the sudden cessation of feeding, fussiness, fever, and protracted vomiting. Convulsions and lethargy develop rapidly. On physical examination, patients are somnolent, exhibit meningeal signs, and have generalized motor weakness and reduced deep tendon reflexes. In infants, a bulging fontanel, spastic paralysis, and generalized convulsions may be observed. On pathologic examination, disseminated small focal abscesses, small focal hemorrhages, and patchy areas of demyelination are distinctive.

Patient fatality rates in WEE are 3–9% and are highest in the elderly. Major neurologic sequelae have been reported in up to 13% of cases and may be as high as 30% in infants. Parkinsonian syndrome has been reported as a residual in adult survivors.

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314.3 St. Louis Encephalitis

Scott B. Halstead

Cases of SLE are reported from nearly all states; the highest attack rates occur in the gulf and central states (see Fig. 314.1). Epidemics frequently occur in urban and suburban areas; the largest occurred in 1975 and involved 1,800 persons living in Houston, Chicago, Memphis, and Denver. Cases often cluster in areas where there is ground water or septic systems, which support mosquito breeding. The principal vectors are *Culex pipiens* and *Culex quinquefasciatus* mosquitoes in the central gulf states, *Culex nigripalpus* in Florida, and *Culex tarsalis* in California. SLE virus is maintained in nature in a bird-mosquito cycle. Viral amplification occurs in bird species abundant in residential areas (e.g., sparrows, blue jays, and doves). Virus is transmitted in the late summer and early fall. The case:infection ratio may be as high as 1:300. Age-specific attack rates are lowest in children and highest in individuals older than 60 years. The most recent small outbreaks were in Florida in 1990 and Louisiana in 2001. For the past 15 years, there have been a mean of 18 cases annually.

Clinical manifestations of SLE vary from a mild flulike illness to fatal encephalitis. There may be a prodrome of nonspecific symptoms with subtle changes in coordination or mentation of several days to 1 week in duration. Early signs and symptoms include fever, photophobia, headache, malaise, nausea, vomiting, and neck stiffness. About half of patients exhibit an abrupt onset of weakness, incoordination, disturbed sensorium, restlessness, confusion, lethargy, and delirium or coma. The peripheral white blood cell count is modestly elevated, with 100-200 white blood cells/μL found in the CSF. On autopsy, the brain shows scattered foci of neuronal damage and perivascular inflammation.

The principal risk factor for fatal outcome of SLE is advanced age, with patient fatality rates being as high as 80% in early outbreaks. In children, mortality rates are 2–5%. In adults, underlying hypertensive cardiovascular disease has been a risk factor for fatal outcome. Recovery from SLE is usually complete, but the rate of serious neurologic sequelae has been reported to be as high as 10% in children.

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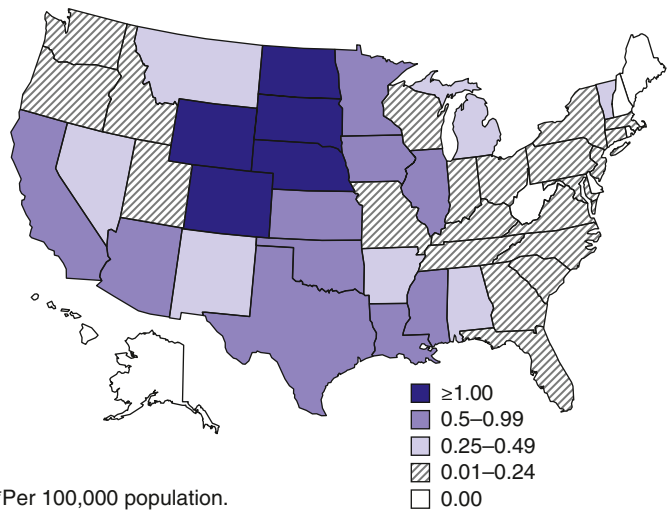

Fig. 314.3 Rate (per 100,000 population) of reported cases of West Nile virus neuroinvasive disease, United States, 2016. *(From Burakoff A, Lehman J, Fischer M, et al. West Nile virus and other nationally notifiable arboviral diseases, United States, 2016. MMWR Morb Mortal Wkly Rep. 2018;67[1]L13–17.)*

314.4 West Nile Encephalitis

Scott B. Halstead

West Nile virus (WNV) was imported into the United States in 1999 and survives in a broad enzootic cycle across the United States and Canada. Every state in the continental United States plus nine provinces in Canada have reported mosquito, bird, mammalian, or human WN virus infection, most frequently during the summer or fall months. Through the end of 2015, a total of 43,937 cases had been reported in the United States, 40–50% of which were neuroinvasive, with 1,911 deaths (Fig. 314.3). In 2020, there were 505 WNV cases, 159 of which were neuroinvasive, resulting in 52 deaths. WNV transmission cycles have come to resemble JE with large epizootics and human cases occurring every 5-10 years. WNV has entered the blood supply through asymptomatic viremic potential blood donors. Since 2003, blood banks screen for WNV RNA. During the major outbreak of 2012, 597 viremic potential blood donors were identified and the donation was rejected. WNV has also been transmitted to humans via the placenta, breast milk, and organ transplantation. Throughout its range, the virus is maintained in nature by transmission between mosquitoes of the *Culex* genus and various species of birds. In the United States, human infections are largely acquired from *C. pipiens*. Horses are the nonavian vertebrates most likely to exhibit disease with WNV infection. During the 2002 transmission season, 14,000 equine cases were reported, with a mortality rate of 30%. Disease occurs predominantly in individuals >50 years of age. WNV has been implicated as the cause of sporadic summertime cases of human encephalitis and meningitis in Israel, India, Pakistan, Romania, Russia, Canada, the United States, and parts of Central and South America. All North and South American WNVs are genetically similar and are related to a virus recovered from a goose in Israel in 1998.

West Nile encephalitis (WNE) may be asymptomatic, but when clinical features appear, they include an abrupt onset of high fever, headache, myalgias, and nonspecific signs of emesis, rash, abdominal pain, or diarrhea. Most infections manifest as a flulike febrile illness, whereas a minority of patients demonstrate meningitis or encephalitis or both. Rarely there may be cardiac dysrhythmias, myocarditis, rhabdomyolysis, optic neuritis, uveitis, retinitis, orchitis, pancreatitis, or hepatitis. WNV disease in the United States has been accompanied by prolonged lymphopenia and an acute asymmetric polio-like paralytic illness with CSF pleocytosis involving the anterior horn cells of the spinal cord. A striking but uncommon feature has been parkinsonism and movement disorders (with tremor and myoclonus). WNV infections have been shown to lead to chronic kidney disease in a small group of patients.

Cases of WNE and deaths due to the disease occur mainly in the elderly, although many serologic surveys show that persons of all ages are infected. In 2015, among a total of 2,175 human cases, 1,455 were neuroinvasive disease with 146 deaths, a 10% mortality rate (see Fig. 314.2). Paralysis may result in permanent weakness.

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314.5 Powassan Encephalitis

Scott B. Halstead

POW virus is transmitted by *Ixodes cookei* among small mammals in eastern Canada and the United States; it has been responsible for 39 deaths in the United States since 2008 (see Fig. 314.1). Other ticks may transmit the virus in a wider geographic area, and there is some concern that *Ixodes scapularis* (also called *Ixodes dammini*), a competent vector in the laboratory, may become involved as it becomes more prominent in the United States.

In a limited experience, POW encephalitis has occurred mainly in adults with vocational or recreational exposure and has a high fatality rate.

POW encephalitis has occurred mostly in adults living in enzootic areas with vocational or recreational exposure; it is associated with significant long-term morbidity and has a case fatality rate of 10–15%.

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314.6 La Crosse and California Encephalitis

Scott B. Halstead

La Crosse viral infections are endemic in the United States, occurring annually from July to September, principally in the north-central and central states (see Fig. 314.1). Infections occur in peridomestic environments as the result of bites from *Aedes triseriatus* mosquitoes, which often breed in tree holes. The virus is maintained vertically in nature by transovarial transmission and can be spread between mosquitoes by copulation and amplified in mosquito populations by viremic infections in various vertebrate hosts. Amplifying hosts include chipmunks, squirrels, foxes, and woodchucks. A case:infection ratio of 1:22-300 has been surmised. La Crosse encephalitis is principally a disease of children, who may account for up to 75% of cases. A mean of 100 cases has been reported annually for the past 10 years.

The clinical spectrum includes a mild febrile illness, aseptic meningitis, and fatal encephalitis. Children typically present with a prodrome of 2-3 days of fever, headache, malaise, and vomiting. The disease evolves with clouding of the sensorium, lethargy, and, in severe cases, focal or generalized seizures. On physical examination, children are lethargic but not disoriented. Focal neurologic signs, including weakness, aphasia, and focal or generalized seizures, have been reported in 16–25% of cases. CSF shows low to moderate leukocyte counts. On autopsy, the brain shows focal areas of neuronal degeneration, inflammation, and perivascular cuffing.

Recovery from California encephalitis is usually complete. The case fatality rate is approximately 1%.

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314.7 Colorado Tick Fever

Scott B. Halstead

Colorado tick fever virus is transmitted by the wood tick *Dermacentor andersoni,* which inhabits high-elevation areas of states extending from the central plains to the Pacific coast. The tick is infected with the virus at the larval stage and remains infected for life. Squirrels and chipmunks serve as primary reservoirs. Human infections typically occur in hikers and campers in indigenous areas during the spring and early summer.

Colorado tick fever begins with the abrupt onset of a flulike illness, including high temperature, malaise, arthralgia and myalgia, vomiting, headache, and decreased sensorium. Rash is uncommon. The symptoms rapidly disappear after 3 days of illness. However, in approximately half of patients, a second identical episode reoccurs 24-72 hours after the first one, producing the typical saddleback temperature curve of Colorado tick fever. Complications, including encephalitis, meningoencephalitis, and a bleeding diathesis, develop in 3–7% of infected persons and may be more common in children younger than 12 years of age.

Recovery from Colorado tick fever is usually complete. Three deaths have been reported, all in persons with hemorrhagic signs.

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314.8 Chikungunya Fever

Scott B. Halstead

Chikungunya virus is enzootic in several species of African subhuman primates but also is endemic in urban *Aedes aegypti* or *Aedes albopictus* transmission cycles in Africa, Asia, and the Americas. From the 18th century, chikungunya exited Africa eastward, producing Asian pandemics in 1790, 1824, 1872, 1924, 1963, and 2005. In 1827, chikungunya went the other direction via the slave trade, reaching the Western

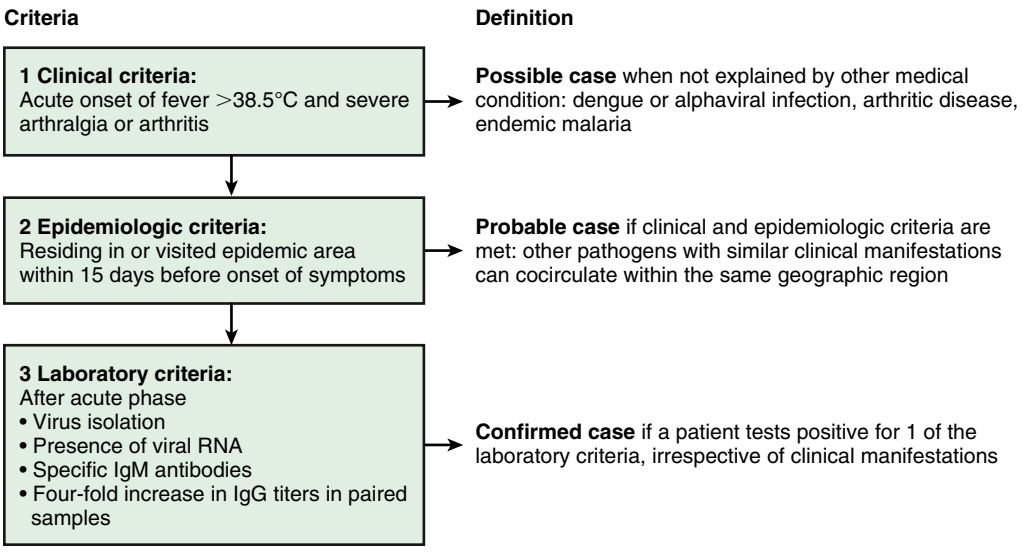

Fig. 314.4 Algorithm showing diagnostic criteria for chikungunya virus fever. *(From Burt FJ, Rolph MS, Rulli NE, et al. Chikungunya: a re-emerging virus. Lancet. 2012;379:662–668. Fig. 6.)*

Hemisphere predominantly in the Caribbean. In 2005, proceeding again in an easterly direction, virus appeared on Reunion Island and then traveled to Asia across the Indian Ocean. In 2013, chikungunya virus from this epidemic was introduced into the Americas, where it is now endemic.

Clinical manifestations begin 3-7 days after a mosquito bite; the onset is abrupt, with high fever and often severe joint symptoms (hands, feet, ankles, wrists) that include symmetric bilateral polyarthralgia or arthritis. Infections in children are often asymptomatic, but all ages are vulnerable to classic disease. There may be headache, myalgias, conjunctivitis, weakness, lymphopenia, and a maculopapular rash. Mortality is rare; some individuals develop prolonged joint symptoms (tenosynovitis, arthritis) lasting over a year. The acute episode lasts 7-10 days. The differential diagnosis includes dengue, West Nile, enterovirus diseases, leptospirosis, rickettsial disease, measles, parvovirus disease, rheumatologic diseases, and other alphavirus diseases (e.g., Ross River virus) in endemic areas. Figure 314.4 lists the diagnostic criteria.

The incidence of febrile convulsions is high in infants. The prognosis is generally good, although in large outbreaks in Africa and India, severe disease and deaths have been attributed to chikungunya infections, predominantly in adults.

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314.9 Venezuelan Equine Encephalitis

Scott B. Halstead

VEE virus was isolated from an epizootic in Venezuelan horses in 1938. Human cases were first identified in 1943. Hundreds of thousands of equine and human cases have occurred over the past 70 years. During 1971, epizootics moved through Central America and Mexico to southern Texas. After 3 decades of quiescence, epizootic disease emerged again in Venezuela and Colombia in 1995. Between December 1992 and January 1993, the Venezuelan state of Trujillo experienced an outbreak of this virus. Overall, 28 cases of the disease were reported, along with 12 deaths. A bigger outbreak occurred in June 1993, resulting in the death of 55 humans and 66 horses. A much larger outbreak in Venezuela and Colombia occurred in 1995. On May 23, 1995, equine encephalitis-like cases were reported in the northwest portion of the country. Eventually, the outbreak spread toward the north, as well as to the south. The outbreak caused about 11,390 febrile cases in humans, as well as 16 deaths. About 500 equine cases were reported with 475 deaths.

The incubation period is 2-5 days, followed by the abrupt onset of fever, chills, headache, sore throat, myalgia, malaise, prostration, photophobia, nausea, vomiting, and diarrhea. In 5–10% of cases, there is a biphasic illness; the second phase is heralded by seizures, projectile vomiting, ataxia, confusion, agitation, and mild disturbances in consciousness. There is cervical lymphadenopathy and conjunctival suffusion. Cases of meningoencephalitis may demonstrate cranial nerve palsy, motor weakness, paralysis, seizures, and coma. Microscopic examination of tissues reveals inflammatory infiltrates in lymph nodes, spleen, lung, liver, and brain. Lymph nodes show cellular depletion, necrosis of germinal centers, and lymphophagocytosis. The liver shows patchy hepatocellular degeneration, the lungs demonstrate a diffuse interstitial pneumonia with intraalveolar hemorrhages, and the brain shows patchy cellular infiltrates. Vertical transmission from mother to fetus has been documented. Ten fetal autopsies performed during an outbreak demonstrated VEE virus in the brains of aborted fetuses. https://www.ncbi.nlm.nih.gov/books/NBK559332/. Infants born to mothers with VEE may have neurologic sequelae or fatal cerebral lesions.

There is no specific treatment for VEE. The treatment is intensive supportive care (see Chapter 82), including control of seizures (see Chapter 633).

In patients with VEE meningoencephalitis, the fatality rate ranges from 10–25%. Sequelae include nervousness, forgetfulness, recurrent headache, and easy fatigability.

Several veterinary vaccines are available to protect equine animals. VEE virus is highly infectious in laboratory settings, and biosafety level 3 containment should be used. An experimental vaccine is available for use in laboratory workers. Several vaccine constructs are in the pipeline for potential use in humans.

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314.10 Japanese Encephalitis

Scott B. Halstead

JE is a mosquito-borne viral disease of humans, as well as horses, swine, and other domestic animals. The virus causes human infections and acute disease in a vast area of Asia, from Indochina through the Indian subcontinent, northern Japan, Korea, China, Taiwan, the Philippines, and the Indonesian archipelago. *Culex tritaeniorhynchus summarosus,* a night-biting mosquito that feeds preferentially on large domestic animals and birds but only infrequently on humans, is the principal vector of zoonotic and human JE in northern Asia. A more complex ecology prevails in southern Asia. From Taiwan to India, *C. tritaeniorhynchus* and members of the closely related *Culex vishnui* group are vectors. Before the introduction of JE vaccine, summer outbreaks of JE occurred regularly in Japan, Korea, China, Okinawa, and Taiwan. Over the past decade, there has been a pattern of steadily enlarging recurrent seasonal outbreaks in Vietnam, Thailand, Nepal, and India, with small outbreaks in the Philippines, Indonesia, and the northern tip of Queensland, Australia. Seasonal rains are accompanied by increases in mosquito populations and JE transmission. Pigs serve as an amplifying host.

The annual incidence in endemic areas ranges from 1-10 per 10,000 population. Children younger than 15 years of age are principally affected, with nearly universal exposure by adulthood. The case:infection ratio for JE virus has been variously estimated at 1:25 to 1:1,000. Higher ratios have been estimated for populations indigenous to enzootic areas. JE occurs in travelers visiting Asia; therefore a travel history in the diagnosis of encephalitis is critical.

After a 4- to 14-day incubation period, cases typically progress through the following four stages: prodromal illness (2-3 days), acute stage (3-4 days), subacute stage (7-10 days), and convalescence (4-7 weeks). The onset may be characterized by an abrupt onset of fever, headache, respiratory symptoms, anorexia, nausea, abdominal pain, vomiting, and sensory changes, including psychotic episodes. Grand mal seizures are seen in 10–24% of children with JE; parkinsonian-like nonintention tremor and cogwheel rigidity are seen less frequently. Particularly characteristic are rapidly changing central nervous system signs (e.g., hyperreflexia followed by hyporeflexia or plantar responses that change). The sensory status of the patient may vary from confusion through disorientation and delirium to somnolence, progressing to coma. There is usually a mild pleocytosis (100-1,000 leukocytes/μL) in the cerebrospinal fluid, initially polymorphonuclear but in a few days predominantly lymphocytic. Albuminuria is common. Fatal cases usually progress rapidly to coma, and the patient dies within 10 days.

JE should be suspected in patients reporting exposure to night-biting mosquitoes in endemic areas during the transmission season. The etiologic diagnosis of JE is established by testing acute-phase serum collected early in the illness for the presence of virus-specific IgM antibodies or, alternatively, demonstrating a fourfold or greater increase in IgG antibody titers by testing paired acute and convalescent sera. The virus can also be identified by polymerase chain reaction (PCR).

There is no specific treatment for JE. The treatment is intensive supportive care (see Chapter 82), including control of seizures (see Chapter 633).

Patient fatality rates for JE are 24–42% and are highest in children 5-9 years of age and in adults older than 65 years of age. The frequency

of sequelae is 5–70% and is directly related to the age of the patient and severity of disease. Sequelae are most common in patients younger than 10 years at the onset of disease. The more common sequelae are mental deterioration, severe emotional instability, personality changes, motor abnormalities, and speech disturbances.

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314.11 Tick-Borne Encephalitis

Scott B. Halstead

TBE refers to neurotropic tick-transmitted flaviviral infections occurring across the Eurasian land mass. In the Far East, the disease is called *Russian spring-summer encephalitis*; the milder, often biphasic form in Europe is simply called TBE. TBE is found in all countries of Europe except Portugal and the Benelux countries. The incidence is particularly high in Austria, Poland, Hungary, Czech Republic, Slovakia, former Yugoslavia, and Russia. The incidence tends to be very focal. Seroprevalence is as high as 50% in farm and forestry workers. The majority of cases occur in adults, but even young children may be infected while playing in the woods or on picnics or camping trips. The seasonal distribution of cases is midsummer in southern Europe, with a longer season in Scandinavia and the Russian Far East. TBE can be excreted in the milk of goats, sheep, or cows. Before World War II, when unpasteurized milk was consumed, milk-borne cases of TBE were common.

Viruses are transmitted principally by hard ticks, *Ixodes ricinus* in Europe and *Ixodes persulcatus* in the Far East. Viral circulation is maintained by a combination of transmission from ticks to birds, rodents, and larger mammals and transstadial transmission from larval to nymphal and adult stages. In some parts of Europe and Russia, ticks feed actively during the spring and early fall, giving rise to the name *spring-summer encephalitis.*

After an incubation period of 7-14 days, the European form begins as an acute nonspecific febrile illness that is followed in 5–30% of cases by meningoencephalitis. The Far Eastern variety more often results in encephalitis with higher case fatality and sequelae rates. The first phase of illness is characterized by fever, headache, myalgia, malaise, nausea, and vomiting for 2-7 days. Fever disappears but after 2-8 days may return, accompanied by vomiting, photophobia, and signs of meningeal irritation in children and more severe encephalitic signs in adults. This phase rarely lasts more than 1 week.

There is no specific treatment for TBE. The treatment is intensive supportive care (see Chapter 82), including control of seizures (see Chapter 633).

The main risk for a fatal outcome is advanced age; the fatality rate in adults is approximately 1%, but sequelae in children are rare. Transient unilateral paralysis of an upper extremity is a common finding in adults. Common sequelae include chronic fatigue, headache, sleep disorders, and emotional disturbances.

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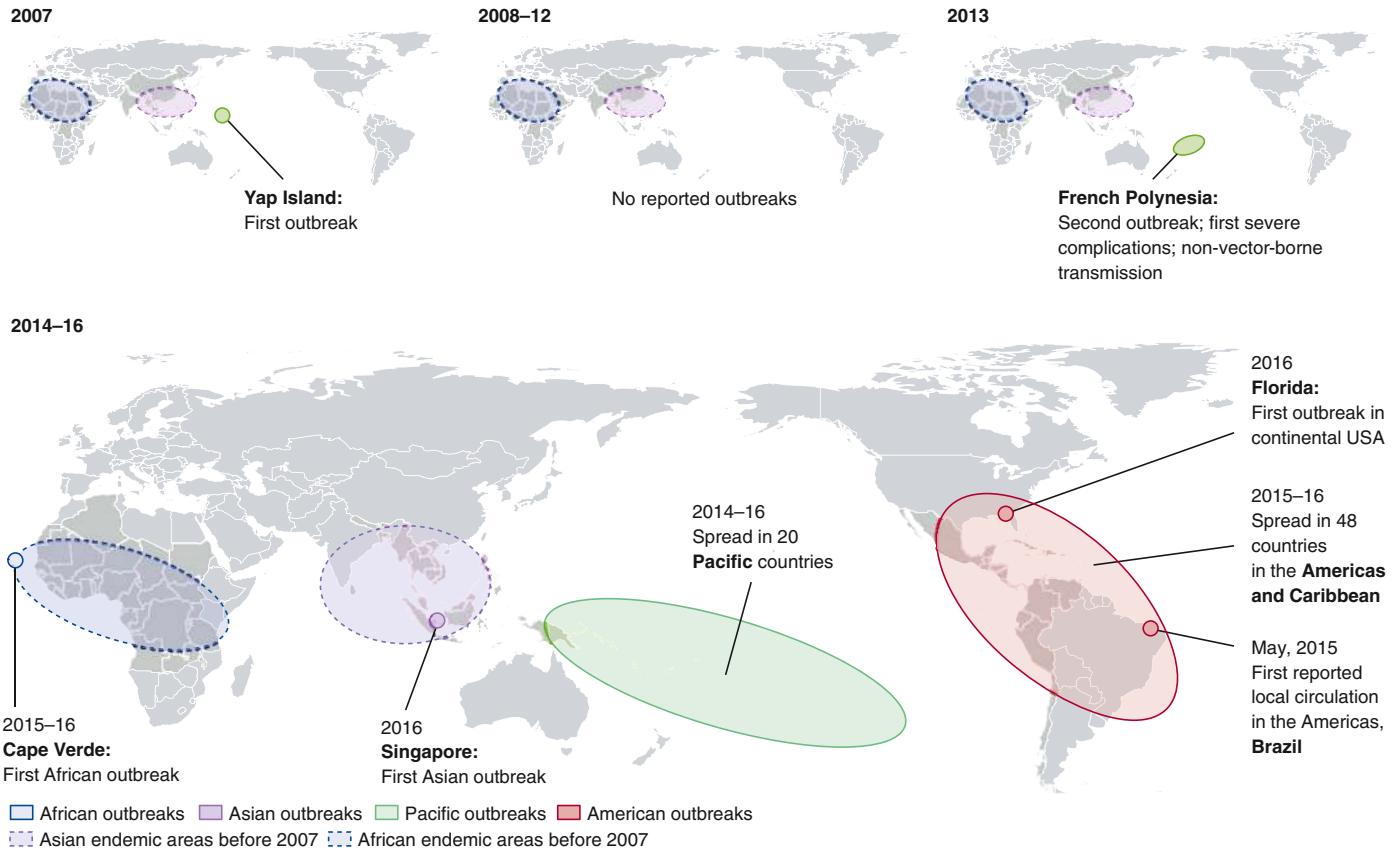

Fig. 314.5 Zika virus outbreaks from 2007 to 2016. *(From Baud D, Gubler DJ, Schaub B, et al. An update on Zika virus infection. Lancet. 2017;390:2099–2109. Fig. 2.)*

Table 314.1 Surveillance Case Classification: Children, Neonate to 2 Years of Age, Born to Mothers with Any Evidence of Zika Virus Infection During Pregnancy

ZIKA-ASSOCIATED BIRTH DEFECTS

Selected structural anomalies of the brain or eyes present at birth (congenital) and detected from birth to age 2 yr. Microcephaly at birth, with or without low birthweight, was included as a structural anomaly.

- **Selected congenital brain anomalies:** intracranial calcifications; cerebral atrophy; abnormal cortical formation (e.g., polymicrogyria, lissencephaly, pachygyria, schizencephaly, gray matter heterotopia); corpus callosum abnormalities; cerebellar abnormalities; porencephaly; hydranencephaly; ventriculomegaly/hydrocephaly.
- **Selected congenital eye anomalies:** microphthalmia or anophthalmia; coloboma; cataract; intraocular calcifications; chorioretinal anomalies involving the macula (e.g., chorioretinal atrophy and scarring, macular pallor, and gross pigmentary mottling), excluding retinopathy of prematurity; optic nerve atrophy, pallor, and other optic nerve abnormalities.
- **Microcephaly at birth:** birth head circumference <3rd percentile for infant sex and gestational age based on INTERGROWTH-21st online percentile calculator (http://intergrowth21.ndog.ox.ac.uk/).

NEURODEVELOPMENTAL ABNORMALITIES POSSIBLY ASSOCIATED WITH CONGENITAL ZIKA VIRUS INFECTION

Consequences of neurologic dysfunction detected from birth (congenital) to age 2 yr. Postnatal-onset microcephaly was included as a neurodevelopmental abnormality.

- **Hearing abnormalities:** Hearing loss or deafness documented by testing, most frequently auditory brainstem response (ABR). Includes sensorineural hearing loss, mixed hearing loss, and hearing loss not otherwise specified. Failed newborn hearing screening is not sufficient for diagnosis.
- **Congenital contractures:** Multiple contractures (arthrogryposis) and isolated clubfoot documented at birth. Brain anomalies must be documented for isolated clubfoot but not for arthrogryposis.
- **Seizures:** Documented by electroencephalogram or physician report. Includes epilepsy or seizures not otherwise specified; excludes febrile seizures.
- **Body tone abnormalities:** Hypertonia or hypotonia documented at any age in conjunction with (1) a failed screen or assessment for gross motor function; (2) suspicion or diagnosis of cerebral palsy from age 1-2 yr; or (3) assessment by a physician or other medical professional, such as a physical therapist.
- **Movement abnormalities:** Dyskinesia or dystonia at any age; suspicion or diagnosis of cerebral palsy from age 1-2 yr.
- **Swallowing abnormalities:** Documented by instrumented or noninstrumented evaluation, presence of a gastrostomy tube, or physician report.
- **Possible developmental delay:** Abnormal result from most recent developmental screening (i.e., failed screen for gross motor domain or failed screen for two or more developmental domains at the same time point or age); developmental evaluation; or assessment review by developmental pediatrician. Results from developmental evaluation are considered the gold standard if available.
- **Possible visual impairment:** Includes strabismus (esotropia or exotropia), nystagmus, failure to fix and follow at age <1 yr; diagnosis of visual impairment at age ≥1 yr.
- **Postnatal-onset microcephaly:** Two most recent head circumference measurements reported from follow-up care <3rd percentile for child's sex and age based on World Health Organization child growth standards; downward trajectory of head circumference percentiles with most recent measurement <3rd percentile. Age at measurement was adjusted for gestational age in infants born at <40 wk of gestational age through age 24 mo chronological age.

From Rice ME, Galang RR, Roth NM, et al. Vital signs: Zika-associated birth defects and neurodevelopmental abnormalities possibly associated with congenital Zika virus infection—US territories and freely associated states, 2018. *MMWR Morb Mortal Wkly Rep.* 2018;67(31):858–866.

314.12 Zika Virus

Scott B. Halstead

EPIDEMIOLOGY

ZIKV, a member of the *Flavivirus* genus, is maintained in complex African zoonotic cycles, spilling over from time to time into the *Aedes aegypti/A. albopictus* urban transmission cycles, possibly over a period of many years (Fig. 314.5). After the virus was discovered in Africa in 1947, human antibodies were found widely dispersed throughout tropical Asia. However, in all these locations, human ZIKV disease was mild and rare until 2007, when there was an outbreak of a mild febrile exanthem on the Yap Islands in the western Pacific. Soon thereafter an outbreak on Tahiti in 2013–2014 was followed in 4 weeks by a small outbreak of Guillain-Barré syndrome (GBS). In 2015 a massive epidemic in South America was accompanied by focal reports, particularly in Brazil, of ZIKV infections of pregnant women that produced infected and damaged fetuses or newborns. The epidemiology of ZIKV infections is essentially identical to that of the DENV and CHIK. Residents of urban areas, particularly those without adequate sources of piped water, are at highest risk. *A. aegypti,* the principal vector mosquito, is very abundant and widespread throughout South and Central America, Mexico, and the Caribbean region. During the North, Central, and South American pandemic, ZIKV was found to infect the male reproductive tract, be secreted in urine and saliva, and be sexually transmitted. By 2017, the ZIKV epidemic in the American tropics appeared to wane, with few cases reported since then. During 2015–2016, large numbers of imported ZIKV infections, some in pregnant women, were reported in the United States and other temperate-zone developed countries. Small outbreaks of endogenous human ZIKV infections were reported in South Florida during the summer of 2016.

From the pediatric perspective, the most important outcome of human ZIKV infection is termed the *congenital Zika syndrome (CZS),* which consists of microcephaly, facial disproportion, hypertonia/spasticity, hyperreflexia, irritability, seizures, arthrogryposis, ocular abnormalities, and sensorineural hearing loss (Table 314.1). A comprehensive understanding of the precise antecedents to CZS is not known. It appears that the earlier during pregnancy that ZIKV infections occur, the greater the likelihood of and the more severe is the CZS. Vertical transmission appears to follow viremia with ZIKV, transiting the uterus to infect the placenta and then the fetus. However, factors that affect the occurrence or severity of CZS, such as age, ethnicity, or prior immune status of the mother, are not known. In vitro studies have demonstrated that DENV antibodies can enhance ZIKV infection in vitro, in Fc-receptor–bearing cells. In Nicaraguan children, a prior DENV infection did not enhance Zika disease, and, as yet, there is no evidence that a prior DENV infection alters the chance of ZIKV crossing the placenta or increases the risk of CZS. Maternal–fetal transmission of ZIKV can occur during labor and delivery. There are no reports of ZIKV infection acquired by an infant at the time of delivery leading to microcephaly. There are no data to contraindicate breastfeeding, although the virus has been identified in breast milk. Maternal and newborn laboratory testing is indicated during the first 2 weeks of life if the mother had relevant epidemiologic exposure within 2 weeks of delivery and had clinical manifestations of ZIKV infection (e.g., rash, conjunctivitis, arthralgia, or fever). Infants and children who acquire ZIKV infection postnatally appear to have a mild course, similar to that seen in adults.

CLINICAL FEATURES

Congenital Zika syndrome may be defined in a fetus with diagnostic evidence of ZIKV infection, including (1) severe microcephaly (>3 SD below the mean), partially collapsed skull, overlapping cranial sutures, prominent occipital bone, redundant scalp skin, and neurologic impairment; (2) brain anomalies, including cerebral cortex thinning, abnormal gyral patterns, increased fluid spaces, subcortical calcifications, corpus callosum anomalies, reduced white matter, and cerebellar vermis hypoplasia; (3) ocular findings, such as macular scarring, focal pigmentary retinal mottling, structural anomalies (microphthalmia,

Table 314.2 CDC Recommendations for Preconception Counseling and Prevention of Sexual Transmission of Zika Virus Among Persons with Possible Zika Virus Exposure: United States, August 2018

EXPOSURE SCENARIO	RECOMMENDATIONS (UPDATE STATUS)
Only the male partner travels to an area with risk for ZIKV transmission and couple is planning to conceive	The couple should use condoms or abstain from sex for at least 3 mo after the male partner's symptom onset (if symptomatic) or last possible ZIKV exposure (if asymptomatic). **(Updated recommendation)**
Only the female partner travels to an area with risk for ZIKV transmission and couple is planning to conceive	The couple should use condoms or abstain from sex for at least 2 mo after the female partner's symptom onset (if symptomatic) or last possible ZIKV exposure (if asymptomatic). **(No change in recommendation)***
Both partners travel to an area with risk for ZIKV transmission and couple is planning to conceive	The couple should use condoms or abstain from sex for at least 3 mo from the male partner's symptom onset (if symptomatic) or last possible ZIKV exposure (if asymptomatic). **(Updated recommendation)**
One or both partners have ongoing exposure (i.e., live in or frequently travel to an area with risk for ZIKV transmission) and couple is planning to conceive	The couple should talk with their healthcare provider about their plans for pregnancy, their risk for ZIKV infection, the possible health effects of ZIKV infection on a baby, and ways to protect themselves from ZIKV. If either partner develops symptoms of ZIKV infection or tests positive for ZIKV infection, the couple should follow the suggested time frames listed previously before trying to conceive. **(No change in recommendation)***
Men with possible ZIKV exposure whose partner is pregnant	The couple should use condoms or abstain from sex for the duration of the pregnancy. **(No change in recommendation)***

*Petersen EE, Meaney-Delman D, Neblett-Fanfair R, et al. Update: interim guidance for preconception counseling and prevention of sexual transmission of Zika virus for persons with possible Zika virus exposure—United States, September 2016. *MMWR Morb Mortal Wkly Rep*. 2016;65:1077–1081.
From Polen KD, Gilboa SM, Hills S, et al. Update: interim guidance for preconception counseling and prevention of sexual transmission of Zika virus for men with possible Zika virus exposure: United States, August 2018. *MMWR Morb Mortal Wkly Rep*. 2018;67(31):868–870.

coloboma, cataracts, and posterior anomalies), chorioretinal atrophy, or optic nerve hypoplasia/atrophy; (4) congenital contractures, including unilateral or bilateral clubfoot and arthrogryposis multiplex congenita; and (5) neurologic impairment, such as pronounced early hypertonia/spasticity with extrapyramidal symptoms, motor disabilities, cognitive disabilities, hypotonia, irritability/excessive crying, tremors, swallowing dysfunction, vision impairment, hearing impairment, and epilepsy (see Table 314.1).

Acquired ZIKV infection may present with nonspecific viral syndrome–like features. Nonetheless, patients are at increased risk of myelitis and GBS. In addition, the virus may remain present in the blood and body fluids for months after resolution of clinical symptoms.

MANAGEMENT

For infants with confirmed ZIKV infection, close follow-up is necessary. The appropriate follow-up evaluation depends on whether the infant has clinical signs and symptoms of congenital ZIKV syndrome. All infants should have close monitoring of growth and development, repeat ophthalmologic examinations, and auditory brainstem response testing (see Table 314.1).

LABORATORY DIAGNOSIS

Laboratory testing for ZIKV infection in the neonate includes the following: serum and urine for ZIKV RNA by real-time reverse transcription polymerase chain reaction (rRT-PCR) and serum ZIKV IgM enzyme-linked immunosorbent assay. If the IgM is positive, the plaque reduction neutralization test is used to confirm the specificity of the IgM antibodies against ZIKV and to exclude a false-positive IgM result. If CSF is available, it should be tested for ZIKV RNA (via rRT-PCR), as well as ZIKV IgM. CSF specimens need not be collected for the sole purpose of ZIKV testing but may be reasonable for the evaluation of infants with microcephaly or intracranial calcifications. A definitive diagnosis of congenital ZIKV infection is confirmed by the presence of ZIKV RNA in samples of serum, urine, or CSF collected within the first 2 days of life; IgM antibodies may be positive or negative. A negative rRT-PCR result with a positive ZIKV IgM test result indicates probable congenital ZIKV infection.

Fetuses or infants born to mothers who test positive for ZIKV infection should be studied sonographically or for clinical evidence of congenital Zika syndrome; a comprehensive evaluation (including ophthalmologic examination, laboratory tests, and specialist consultation) should be performed before hospital discharge.

PROGNOSIS

The prognosis of newborns with congenital Zika syndrome is unclear. Reported acute mortality rates among live-born infants range from 4–6%. The combination of ZIKV-related microcephaly and severe cerebral abnormalities generally has a poor prognosis, but little is known about the prognosis for congenitally infected infants with less severe or no apparent abnormalities at birth.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for congenital ZIKV infection includes other congenital infections and other causes of microcephaly.

PREVENTION

The prevention of the congenital Zika syndrome includes avoidance of travel to endemic regions, if possible; if travel to endemic regions cannot be avoided, careful contraception (male and female) is essential, especially with the knowledge that ZIKV can persist in semen for months after a primary infection (Table 314.2).

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Chapter 315

Dengue Fever, Dengue Hemorrhagic Fever, and Severe Dengue

Scott B. Halstead

Dengue fever is a benign syndrome caused by several arthropod-borne viruses and is characterized by biphasic fever, myalgia or arthralgia, rash, leukopenia, and lymphadenopathy. **Dengue hemorrhagic fever** (Philippine, Thai, or Singapore hemorrhagic fever; hemorrhagic dengue; acute infectious thrombocytopenic purpura) is a severe, often fatal, febrile disease caused by one of four dengue viruses. It is characterized by capillary permeability, abnormalities of hemostasis, and, in severe cases, a protein-losing shock syndrome **(dengue shock syndrome),** which is thought to have an immunopathologic basis.

A revised case definition adopted by the World Health Organization (WHO) in 2009 includes as **severe dengue** those cases accompanied by fluid loss leading to shock, fluid loss with respiratory distress, liver damage evidenced by elevations of ALT or AST to >1000 U/L, severe bleeding, and altered consciousness or significant heart abnormalities.

ETIOLOGY

There are at least four distinct antigenic types of dengue virus (dengue 1, 2, 3, and 4), members of the family Flaviviridae. In addition, three other arthropod-borne viruses (arboviruses) cause similar dengue fever syndromes with rash (Table 315.1; see also Chapter 314).

EPIDEMIOLOGY

Dengue viruses are transmitted by mosquitoes of the Stegomyia family. *Aedes aegypti,* a daytime biting mosquito, is the principal vector, and all four virus types have been recovered from it. Transmission occurs from viremic humans by bite of the vector mosquito in which virus multiplies during an extrinsic incubation period and then by bite is passed on to a susceptible human in what is called the urban transmission cycle. In most tropical areas, *A. aegypti* is highly urbanized, breeding in water stored for drinking or bathing and in rainwater collected in any container. Dengue viruses have also been recovered from *A. albopictus,* as in the 2001 and 2015 Hawaiian epidemics, whereas outbreaks in the Pacific area have been attributed to several other *Aedes* species. These species breed in water trapped in vegetation. In Southeast Asia and West Africa, dengue virus may be maintained in a cycle involving canopy-feeding jungle monkeys and *Aedes* spp, which feed on monkeys.

In the 19th and early 20th centuries, epidemics were common in temperate areas of the Americas, Europe, Australia, and Asia. After several decades of virus control in the Americas, dengue fever and dengue-like disease are now endemic in tropical Asia, the South Pacific Islands, northern Australia, tropical Africa, the Arabian Peninsula, the Caribbean, and Central and South America (Fig. 315.1). The wide distribution of *A. aegypti* is frequently attributed to global warming, but this view is mistaken. This mosquito was widely dispersed during the "little ice age" in the 1700s, supporting yellow fever epidemics in New York and continental Europe. Mosquito breeding depends on access to stored fresh water, not temperature. Dengue fever occurs frequently among travelers to endemic areas. Locally acquired disease has been reported in Florida, Arizona, and Texas, and imported cases in the United States occur in travelers to endemic areas. More than 390 million dengue infections occur annually; approximately 96 million have clinical disease.

Dengue outbreaks in urban areas infested with *A. aegypti* may be explosive; in virgin soil epidemics, up to 70–80% of the population may be involved. Most overt disease occurs in older children and adults. Because *A. aegypti* has a limited flight range, spread of an epidemic occurs mainly through viremic human beings and follows the main lines of transportation. Sentinel cases may infect household mosquitoes; a large number of nearly simultaneous secondary infections give the appearance of a contagious disease. Where dengue is highly endemic, indigenous children and susceptible foreigners may be the only persons to acquire overt disease, because adults have become immune.

Table 315.1 Vectors and Geographic Distribution of Dengue-Like Diseases

VIRUS	GEOGRAPHIC GENUS AND DISEASE	VECTOR	DISTRIBUTION
Togavirus	Chikungunya	*Aedes aegypti* *Aedes africanus* *Aedes albopictus*	Africa, India, Southeast Asia, Latin America, United States
Togavirus	O'nyong-nyong	*Anopheles funestus*	East Africa
Flavivirus	West Nile fever	*Culex molestus* *Culex univittatus*	Europe, Africa, Middle East, India

Dengue-Like Diseases

Dengue-like diseases may occur in epidemics. Epidemiologic features depend on the vectors and their geographic distribution (see Chapter 314). Chikungunya virus is enzootic in subhuman primates throughout much of West, Central, and South Africa. Periodic introductions of virus into the urban transmission cycle have led to pandemics, resulting in widespread endemicity in the most populous areas of Asia. In Asia, *A. aegypti* is the principal vector; in Africa, other Stegomyia spp. may be important vectors. In Southeast Asia, dengue and chikungunya outbreaks occur concurrently in the urban cycle. Outbreaks of o'nyong-nyong fever usually involve villages or small towns, in contrast to the urban outbreaks of dengue and chikungunya. West Nile virus is enzootic in Africa. Chikungunya is now endemic in urban cycles in tropical countries throughout the world. Intense transmission in Caribbean and Central and South American countries beginning in 2013 results in the emergence of limited chikungunya transmission in the United States.

Dengue Hemorrhagic Fever

Dengue hemorrhagic fever occurs where multiple types of dengue virus are simultaneously or sequentially transmitted. It is endemic in tropical America, Asia, the Pacific Islands, and parts of Africa, where warm temperatures and the practices of water storage in homes plus outdoor breeding sites result in large, permanent populations of *A. aegypti.* Under these conditions, infections with dengue viruses of all types are common. A first infection, referred to as a primary infection, may be followed by infection with a different dengue virus, referred to as a secondary infection. In areas of high endemicity, secondary infections are frequent.

Secondary dengue infections are relatively mild in the majority of instances, ranging from an inapparent infection through an undifferentiated upper respiratory tract or dengue-like disease, but may also progress to dengue hemorrhagic fever. Nonimmune foreigners, both adults and children, who are exposed to dengue virus during outbreaks of hemorrhagic fever have classic dengue fever or even milder disease. The differences in clinical manifestations of dengue infections between natives and foreigners in Southeast Asia are related to immunologic status. Dengue hemorrhagic fever is unusual in patients with primary dengue infection, with the exception of infants whose mothers

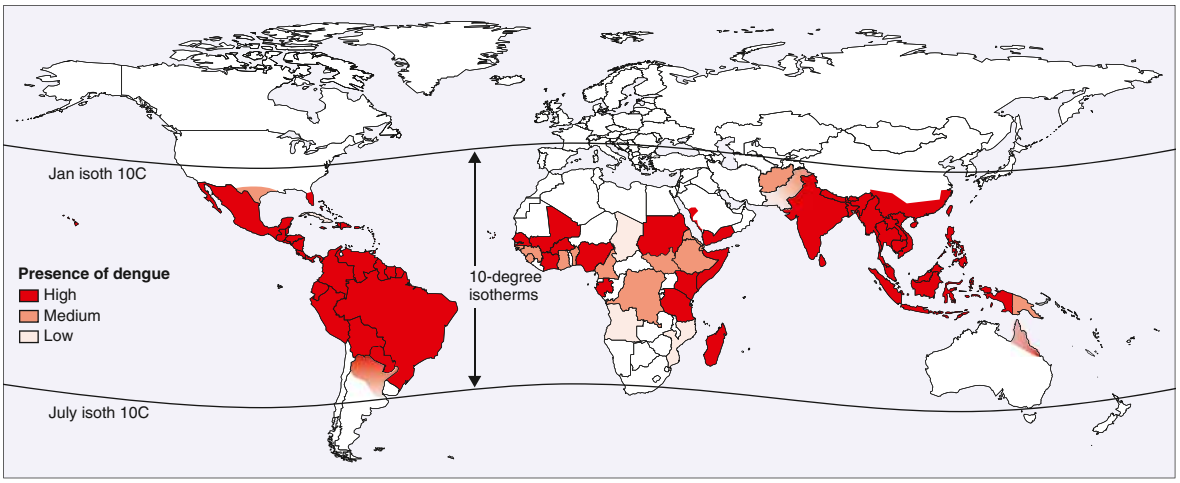

Fig. 315.1 Global dengue burden, 2014. *(From Guzman MG, Harris E. Dengue. Lancet. 2015;385:453–462. Fig. 1.)*

are immune to dengue. Dengue hemorrhagic fever or severe dengue occurs rarely in individuals of African ancestry because of an as yet incompletely described resistance gene. This gene is thought to have originated in populations with long-standing exposure to yellow fever and explains the low incidence of severe dengue throughout much of Africa and among African populations in the American tropics despite high rates of dengue infection.

PATHOGENESIS

The pathogenesis of dengue hemorrhagic fever is incompletely understood, but epidemiologic studies strongly associate this syndrome with second heterotypic infections with dengue types 1-4 or in infants born to mothers who have had two or more lifetime dengue infections. Retrospective studies of sera from human mothers whose infants acquired dengue hemorrhagic fever and prospective studies in children acquiring sequential dengue infections have shown that the circulation of infection-enhancing antibodies at the time of infection is the strongest risk factor for development of severe disease. The absence of dengue neutralizing antibodies in the presence of enhancing antibodies from passive transfer or active production is the best correlate of risk for dengue hemorrhagic fever. Monkeys that are infected sequentially or have received enhancing antibodies experience enhanced viremias. In humans studied early during the course of secondary dengue infections, viremia levels directly predicted disease severity. When dengue virus immune complexes attach to monocyte/macrophage Fc receptors, a signal is sent that suppresses innate immunity, resulting in enhanced viral production. In the Americas, dengue hemorrhagic fever and dengue shock syndrome have been associated with dengue types 1-4 strains of recent Southeast Asian origin. Outbreaks of dengue hemorrhagic fever in all areas of the world are correlated with secondary dengue infections.

Early in the acute stage of secondary dengue infections, there is rapid activation of the complement system. Shortly before or during shock, blood levels of soluble tumor necrosis factor receptor, interferon-γ, and interleukin-2 are elevated, C1q, C3, C4, C5-C8, and C3 proactivators are depressed, and C3 catabolic rates are elevated. All of these outcomes are attributed to circulating viral nonstructural protein 1 (NS1), a viral toxin that activates myeloid cells to release cytokines by attaching to toll-like receptor 4. NS1 also contributes to increased vascular permeability by activating complement and, most importantly, interacting with and damaging endothelial cells and interacting with blood clotting factors and platelets. The mechanism of bleeding in dengue hemorrhagic fever is not fully understood, but a mild degree of disseminated intravascular coagulopathy, liver damage, and thrombocytopenia may operate synergistically. NS1-mediated capillary damage allows fluid, electrolytes, small proteins, and, in some instances, red blood cells to leak into extravascular spaces. This internal redistribution of fluid, together with deficits caused by fasting, thirsting, and vomiting, results in hemoconcentration, hypovolemia, increased cardiac work, tissue hypoxia, metabolic acidosis, and hyponatremia.

Usually no pathologic lesions are found to account for death. In rare instances, death may be a result of gastrointestinal or intracranial hemorrhages. Minimal to moderate hemorrhages are seen in the upper gastrointestinal tract, and petechial hemorrhages are common in the interventricular septum of the heart, on the pericardium, and on the subserosal surfaces of major viscera. Focal hemorrhages are occasionally seen in the lungs, liver, adrenals, and subarachnoid space. The liver is usually enlarged, often with fatty changes. Yellow, watery, and at times blood-tinged effusions are present in serous cavities in approximately 75% of patients at autopsy.

Dengue virus is frequently absent in tissues at the time of death; viral antigens or RNA have been localized to hepatocytes and macrophages in the liver, spleen, lung, and lymphatic tissues.

CLINICAL MANIFESTATIONS

Dengue Fever

The incubation period is 1-7 days. The clinical manifestations are variable and are influenced by the age of the patient. In infants and young children, the disease may be undifferentiated or characterized by fever for 1-5 days, pharyngeal inflammation, rhinitis, and mild cough. A majority of infected older children and adults experience sudden onset of fever, with temperature rapidly increasing to 39.4–41.1°C (103–106°F), usually accompanied by frontal or retroorbital pain, particularly when pressure is applied to the eyes. Occasionally, severe back pain precedes the fever (back-break fever). A transient, macular, generalized rash that blanches under pressure may be seen during the first 24-48 hours of fever. The pulse rate may be slow relative to the degree of fever. Myalgia and arthralgia occur soon after the onset of fevers and increase in severity over time. From the second to sixth day of fever, nausea and vomiting are apt to occur, and generalized lymphadenopathy, cutaneous hyperesthesia or hyperalgesia, taste aberrations, and pronounced anorexia may develop.

Approximately 1-2 days after defervescence, a generalized, morbilliform, maculopapular rash appears that spares the palms and soles. It disappears in 1-5 days; desquamation may occur. Rarely there is edema of the palms and soles. About the time this second rash appears, the body temperature, which has previously decreased to normal, may become slightly elevated and demonstrate the characteristic biphasic temperature pattern.

Dengue Hemorrhagic Fever and Dengue Shock Syndrome

The differentiation between dengue fever and dengue hemorrhagic fever is difficult early in the course of illness. A relatively mild first phase with abrupt onset of fever, malaise, vomiting, headache, anorexia, and cough may be followed after 2-5 days by rapid clinical deterioration and collapse. In this second phase, the patient usually has cold, clammy extremities, a warm trunk, flushed face, diaphoresis, restlessness, irritability, mid-epigastric pain, and decreased urinary output. There may be scattered petechiae on the forehead and extremities; spontaneous ecchymoses may appear, and easy bruising and bleeding at sites of venipuncture are common. A macular or maculopapular rash may appear, and there may be circumoral and peripheral cyanosis. Respirations are rapid and often labored. The pulse is weak, rapid, and thready, and the heart sounds are faint. The liver may enlarge to 4-6 cm below the costal margin and is usually firm and somewhat tender. Approximately 20–30% of cases of dengue hemorrhagic fever are complicated by shock (dengue shock syndrome). Dengue shock can be subtle, arising in patients who are fully alert, and is accompanied by increased peripheral vascular resistance and raised diastolic blood pressure. Shock is not from congestive heart failure but from venous pooling. With increasing cardiovascular compromise, the diastolic pressure rises toward the systolic level and the pulse pressure narrows. Fewer than 10% of patients have gross ecchymosis or gastrointestinal bleeding, usually after a period of uncorrected shock. After a 24- to 36-hour period of crisis, convalescence is fairly rapid in the children who recover. The temperature may return to normal before or during the stage of shock. Bradycardia and ventricular extrasystoles are common during convalescence.

Dengue with Warning Signs and Severe Dengue

In hyperendemic areas, dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS) is the life-threatening event during a dengue infection that challenges the identifying physician. When the four dengue viruses spread to the American hemisphere and to South Asia, there were millions of primary and secondary dengue infections in individuals of all ages. Dengue disease in these areas presented a wider clinical spectrum resulting in a new diagnostic algorithm and case definitions (see later).

DIAGNOSIS

A clinical diagnosis of dengue fever derives from a high index of suspicion and knowledge of the geographic distribution and environmental cycles of causal viruses (for nondengue causes see Chapter 314). Because clinical findings vary and there are many possible causative agents, the term *dengue-like disease* should be used until a specific diagnosis is established. A case is confirmed by virologic diagnosis, which can be established by serologic tests, by detection of viral proteins or viral RNA, or by the isolation of the virus from blood leukocytes or acute-phase serum. A probable case is a typical acute febrile illness with supportive serology and occurrence at a location where there are confirmed cases.

The WHO criteria for **dengue hemorrhagic fever** are fever (2-7 days in duration or biphasic); minor or major hemorrhagic manifestations, including a positive tourniquet test, thrombocytopenia (≤100,000/μL), and objective evidence of increased capillary permeability (hematocrit increased by ≥20%); pleural effusion or ascites (by chest radiography or ultrasonography); or hypoalbuminemia. **Dengue shock syndrome** criteria include those for dengue hemorrhagic fever as well as hypotension, tachycardia, narrow pulse pressure (≤20 mm Hg), and signs of poor perfusion (cold extremities).

In 2009, the WHO promulgated guidelines for the diagnosis of probable dengue, dengue with warning signs, and a category called severe dengue (Fig. 315.2). The presence of warning signs in an individual with probable dengue alerts the physician to the possible need for hospitalization. Severe dengue is a mixture of the syndromes that are associated with dengue infection, including classic DHF/DSS, but also rare instances of encephalitis or encephalopathy, liver damage, or myocardial damage. Severe dengue also includes respiratory distress, a harbinger of pulmonary edema caused by overhydration, an all-too-common outcome of inexpert treatment (see "Treatment" and "Complications" sections).

After primary and secondary dengue infections, there is an appearance of anti-dengue (immunoglobulin [Ig] M) antibodies. These disappear after 6-12 weeks, a feature that can be used to date a dengue infection. In secondary dengue infections, most dengue antibody is of the IgG class. Serologic diagnosis depends on a fourfold or greater increase in IgG antibody titer in paired sera by hemagglutination inhibition, complement fixation, enzyme immunoassay, or neutralization test. Carefully standardized IgM and IgG capture enzyme commercial immunoassays are now widely used to identify acute-phase antibodies from patients with primary or secondary dengue infections in single-serum samples. Usually such samples should be collected not earlier than 5 days and not later than 6 weeks after onset. It may not be possible to distinguish the infecting virus by serologic methods alone, particularly when there has been prior infection with another member of the same arbovirus group. Virus can be recovered from acute-phase serum after inoculating tissue culture or living mosquitoes. Viral RNA can be

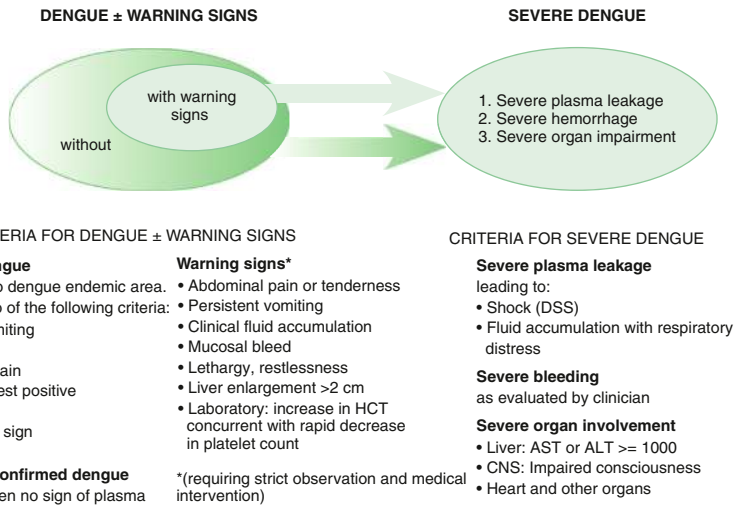

Fig. 315.2 Suggested dengue case classification and levels of severity. *(From World Health Organization [WHO] and Special Programme for Research and Training in Tropical Diseases [TDR]. Dengue: guidelines for diagnosis, treatment, prevention and control, 2009. Fig. 1.4, http://apps.who.int/iris/bitstream/handle/10665/44188/9789241547871_eng.pdf?sequence=1)*

detected in blood or tissues by specific complementary RNA probes or amplified first by polymerase chain reaction or by real-time polymerase chain reaction. A viral nonstructural protein, NS1, is released by infected cells into the circulation and can be detected in acute-stage blood samples using monoclonal or polyclonal antibodies. The detection of NS1 is the basis of commercial tests, including rapid lateral flow tests. These tests offer a reliable point-of-care diagnosis of acute dengue infection.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of dengue fever includes dengue-like diseases, viral respiratory and influenza-like diseases, including COVID-19, the early stages of malaria, mild yellow fever, scrub typhus, viral hepatitis, and leptospirosis.

Four arboviral diseases have dengue-like courses but without rash: Colorado tick fever, sandfly fever, Rift Valley fever, and Ross River fever (see Chapter 314). Colorado tick fever occurs sporadically among campers and hunters in the western United States; sandfly fever in the Mediterranean region, the Middle East, southern Russia, and parts of the Indian subcontinent; and Rift Valley fever in North, East, Central, and South Africa. Ross River fever is endemic in much of eastern Australia, with epidemic extension to Fiji. In adults, Ross River fever often produces protracted and crippling arthralgia involving weight-bearing joints.

Because meningococcemia, yellow fever (see Chapter 316), other viral hemorrhagic fevers (see Chapter 317), many rickettsial diseases, and other severe illnesses caused by a variety of agents may produce a clinical picture similar to that of dengue hemorrhagic fever, the etiologic diagnosis should be made only when epidemiologic or serologic evidence suggests the possibility of a dengue infection.

LABORATORY FINDINGS

In patients with dengue fever, pancytopenia may develop after the 3-4 days of illness. Neutropenia may persist or reappear during the latter stage of the disease and may continue into convalescence, with white blood cell counts <2,000/μL. Platelet counts rarely fall below 100,000/μL. Venous clotting, bleeding and prothrombin times, and plasma fibrinogen values are within normal ranges. The tourniquet test result may be positive. Mild acidosis, hemoconcentration, increased transaminase values, and hypoproteinemia may occur during some primary dengue virus infections. The electrocardiogram may show sinus bradycardia, ectopic ventricular foci, flattened T waves, and prolongation of the P-R interval.

In dengue hemorrhagic fever, dengue shock syndrome, and severe dengue, the most common hematologic abnormalities are hemoconcentration with an increase of >20% in the hematocrit, thrombocytopenia, a prolonged bleeding time, and a moderately decreased prothrombin time that is seldom <40% of control. Fibrinogen levels may be subnormal, and fibrin split-product values are elevated. Other abnormalities include moderate elevations of serum transaminase levels, depressed complement levels, mild metabolic acidosis with hyponatremia, occasional hypochloremia, slight elevation of blood urea nitrogen, and hypoalbuminemia. Chest x-ray reveals pleural effusions (right > left) in nearly all patients with dengue shock syndrome. Ultrasonography can be used to detect serosal effusions of the thorax or abdomen. Thickening of the gallbladder wall and the presence of perivesicular fluid, ascites, or pleural effusions are characteristic signs of increased vascular permeability.

TREATMENT

Dengue

Treatment of uncomplicated dengue fever is supportive. Bed rest is advised during the febrile period. Antipyretics should be used to keep the body temperature <40°C (104°F). Analgesics or mild sedation may be required to control pain. Aspirin is contraindicated and should not be used because of its effects on hemostasis. Fluid and electrolyte replacement is required for deficits caused by sweating, fasting, thirsting, vomiting, and diarrhea.

Dengue Hemorrhagic Fever and Dengue Shock Syndrome

Shock syndrome is a medical emergency that may occur in any child who lives in or has a recent travel history to a tropical destination. Management begins with diagnostic suspicion and the understanding that shock often accompanies defervescence. Detailed instructions for case management are available at the Centers for Disease Control and Prevention web site: https://www.cdc.gov/dengue/healthcare-providers/index.html. Management of dengue hemorrhagic fever and dengue shock syndrome includes immediate evaluation of vital signs and degrees of hemoconcentration, dehydration, and electrolyte imbalance. Close monitoring is essential for at least 48 hours because shock may occur or recur precipitously, usually several days after the onset of fever. Patients who are cyanotic or have labored breathing should be given oxygen. Rapid intravenous replacement of fluids and electrolytes can frequently sustain patients until spontaneous recovery occurs. Normal saline is more effective than the more expensive Ringer lactated saline in treating shock. When the pulse pressure is ≤10 mm Hg or when elevation of the hematocrit persists after the replacement of fluids, plasma or colloid preparations are indicated. Oral rehydration of children who are being monitored is useful. Prophylactic platelet transfusions have not been shown to reduce the risk of hemorrhaging or improve low platelet counts and may be associated with adverse effects.

Care must be taken to avoid overhydration, which may contribute to cardiac failure. Transfusions of fresh blood may be required to control bleeding but should not be given during hemoconcentration and should be administered only after evaluation of hemoglobin or hematocrit values. Salicylates are contraindicated because of their effect on blood clotting.

Sedation may be required for children who are markedly agitated. Use of vasopressors has not resulted in a significant reduction of mortality rates over that observed with simple supportive therapy. Disseminated intravascular coagulation may require treatment (see Chapter 532). Corticosteroids do not shorten the duration of disease or improve the prognosis in children receiving careful supportive therapy.

COMPLICATIONS

Hypervolemia during the fluid reabsorptive phase may be life-threatening and is heralded by a decrease in hematocrit with wide pulse pressure. Diuretics and digitalization may be necessary.

Primary infections with dengue fever and dengue-like diseases are usually self-limited and benign. Fluid and electrolyte losses, hyperpyrexia, and febrile convulsions are the most frequent complications in infants and young children. Epistaxis, petechiae, and purpuric lesions are uncommon but may occur at any stage. Blood from epistaxis that is swallowed, vomited, or passed by rectum may be erroneously interpreted as gastrointestinal bleeding. In adults and possibly in children, underlying conditions may lead to clinically significant bleeding. Convulsions may occur during a high temperature. Infrequently, after the febrile stage, prolonged asthenia, mental depression, bradycardia, and ventricular extrasystoles may occur in children.

In endemic areas, dengue hemorrhagic fever should be suspected in children with a febrile illness suggestive of dengue fever who experience hemoconcentration and thrombocytopenia.

PROGNOSIS

Dengue Fever

The prognosis for dengue fever is good. Care should be taken to avoid the use of drugs that suppress platelet activity.

Dengue Hemorrhagic Fever

The prognosis of dengue hemorrhagic fever is adversely affected by a late diagnosis and delayed or improper treatment. Death has occurred in 40–50% of patients with shock, but with adequate intensive care, deaths should occur in <1% of cases. Infrequently, there

is residual brain damage as a consequence of prolonged shock or occasionally of intracranial hemorrhage. Many fatalities are caused by overhydration.

PREVENTION

Dengue vaccines have been under development continuously since the 1970s. One such vaccine, Dengvaxia, developed by Sanofi Pasteur, is a mixture of four chimeras, dengue virus structural genes coupled with nonstructural genes of yellow fever 17D. Dengvaxia completed phase III per protocol analyses on 32,568 children, vaccinated and controls, age 2-16 years. These studies revealed poor protection and sensitization of seronegative vaccinated children to severe breakthrough dengue but moderate protection of children vaccinated when seropositive, who experienced a reduction of hospitalization and severe disease. Based on these data, the vaccine was endorsed by the WHO, United States, and European regulatory agencies for targeted use in individuals 9 years of age and older who have laboratory-based evidence of a prior dengue infection. The vaccine has been licensed for use in 20 countries. Other dengue type 1-4 vaccines are under development. The Takeda dengue 2 chimeric tetravalent vaccine has completed phase III testing with follow-up data for 2 years demonstrating strong protection against dengue 2 infection but modest protection against the other three viruses. A tetravalent dengue vaccine composed of mutagenized dengue 1, 3, and 4 and a chimeric dengue 2 virus developed by the U.S. National Institutes of Allergy and Infectious Diseases and Instituto Butantan in São Paulo, Brazil, is in the fourth year of phase III testing. Phase IIb live dengue virus human challenge data suggest this vaccine will provide solid protective immunity.

Prophylaxis in the absence of vaccine consists of avoiding daytime household-based mosquito bites through the use of insecticides, repellents, body covering with clothing, screening of houses, and destruction of *A. aegypti* breeding sites. If water storage is mandatory, a tight-fitting lid or a thin layer of oil may prevent egg laying or hatching. A larvicide, such as Abate (O,O′-[thiodi-*p*-phenylene] O,O,O,O′-tetramethyl phosphorothioate), available as a 1% sand-granule formation and effective at a concentration of 1 ppm, may be added safely to drinking water. Ultra-low-volume spray equipment effectively dispenses the adulticide malathion from trucks or airplanes for rapid intervention during an epidemic. Mosquito repellants and other personal anti-mosquito measures are effective in preventing mosquito bites in the field, forest, or jungle.

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Chapter 316

Yellow Fever

Scott B. Halstead

Yellow fever is an acute infection characterized in its most severe form by fever, jaundice, proteinuria, and hemorrhage. The virus is mosquito-borne and occurs as urban epidemic, endemic, or jungle enzootic forms in South America and Africa. Until 1900, seasonal urban epidemics occurred in cities in temperate areas of Europe and the Americas. Urban and jungle yellow fever continues to be active in West, Central, and East Africa.

ETIOLOGY

Yellow fever is the prototype of the *Flavivirus* genus of the family Flaviviridae, which are enveloped, single-stranded RNA viruses 35-50 nm in diameter.

Yellow fever circulates zoonotically as five genotypes: type IA in West Central Africa, type IB in South America, type II in West Africa, type III in East Central Africa, and type IV in East Africa. Types IA and IB are capable of urban transmission between human beings by *Aedes aegypti.* Sometime in the 1600s, *A. aegypti,* together with yellow fever virus, were brought to the American tropics through the African slave trade. Subsequently, yellow fever caused enormous coastal and riverine epidemics in the Atlantic and Caribbean basins until the 20th century, when the virus and its urban and sylvan mosquito cycles were identified, mosquito control methods were perfected, and a vaccine was developed. The East and East/Central African genotypes have not fully entered the urban cycle and have not spread to the east coast of Africa or to the countries of Asia.

EPIDEMIOLOGY

Human and nonhuman primate hosts acquire the yellow fever infection by the bite of infected mosquitoes. After an incubation period of 3-6 days, virus appears in the blood and may serve as a source of infection for other mosquitoes. The virus must replicate in the gut of the mosquito and pass to the salivary gland before the mosquito can transmit the virus. Yellow fever virus is transmitted in an urban cycle—human to *A. aegypti* to human—and a jungle cycle—monkey to jungle mosquitoes to monkey. Classic yellow fever epidemics in the United States, South America, the Caribbean, and parts of Europe were of the urban variety. Since 2000, West Africa has experienced five urban epidemics, including in the capital cities of Abidjan (Cote d'Ivoire), Conakry (Guinea), and Dakar (Senegal). In 2012–2013, large outbreaks of East and East/Central yellow fever occurred across a large, predominantly rural area of war-ravaged Darfur in southwestern Sudan and in adjacent areas of northern Uganda. Beginning in 2015 and continuing to mid-2016, there were sharp outbreaks of yellow fever in and around Rwanda, Angola, and the bordering Democratic Republic of Congo, where there were 7,000 reported cases and 500 deaths. Eleven cases were imported into China by workers in Angola. In South America, all of the approximately 200 cases reported each year are jungle yellow fever. In late 2016 and continuing through 2019, a widespread zoonosis resulted in an estimated 2,237 yellow fever cases in natives and visitors to Brazil. In colonial times, urban yellow fever attack rates in White adults were very high, suggesting that subclinical infections are uncommon in this age-group. Yellow fever may be less severe in children, with subclinical infection:clinical case ratios ≥2:1. In areas where outbreaks of urban yellow fever are common, most cases involve children because many adults are immune. Transmission in West Africa is highest during the rainy season, from July to November.

In tropical forests, yellow fever virus is maintained in a transmission cycle involving monkeys and tree hole–breeding mosquitoes (*Haemagogus* in Central and South America; the *Aedes africanus* complex in Africa). In the Americas, most cases involve tourists, campers, those who work in forested areas, and vacationers exposed to infected mosquitoes. In Africa, enzootic virus is prevalent in moist savanna and savanna transition areas, where other tree hole–breeding *Aedes* vectors transmit the virus between monkeys and humans and between humans.

PATHOGENESIS

Pathologic changes seen in the liver include (1) coagulative necrosis of hepatocytes in the midzone of the liver lobule, with sparing of cells around the portal areas and central veins, (2) eosinophilic degeneration of hepatocytes **(Councilman bodies)**, (3) microvacuolar fatty change, and (4) minimal inflammation. The kidneys show acute tubular necrosis. In the heart, myocardial fiber degeneration and fatty infiltration are seen. The brain may show edema and petechial hemorrhages. Direct viral injury to the liver results in impaired ability to perform functions of biosynthesis and detoxification; this is the central pathogenic event of yellow fever. Hemorrhage is postulated to result from decreased synthesis of vitamin K–dependent

clotting factors and, in some cases, disseminated intravascular clotting. The shock that occurs in patients with yellow fever appears similar to the shock associated with dengue shock syndrome and other viral hemorrhagic fevers and results at least in part from viral damage to endothelial cells. Death and severe disease rates are lower in susceptible sub-Saharan African Black people than in other racial groups, suggesting existence of a resistance gene.

Renal dysfunction has been attributed to hemodynamic factors (prerenal failure progressing to acute tubular necrosis).

CLINICAL MANIFESTATIONS

In Africa, inapparent, abortive, or clinically mild infections are frequent. Some studies suggest that children experience a milder disease than do adults. Abortive infections, characterized by fever and headache, may be unrecognized except during epidemics.

In its classic form, yellow fever begins with a sudden onset of fever, headache, myalgia, lumbosacral pain, anorexia, nausea, and vomiting. Physical findings during the early phase of illness, when virus is present in the blood, include prostration, conjunctival injection, flushing of the face and neck, reddening of the tongue at the tip and edges, and relative bradycardia. After 2-3 days, there may be a brief period of remission, followed in 6-24 hours by the reappearance of fever with vomiting, epigastric pain, jaundice, dehydration, gastrointestinal and other hemorrhages, albuminuria, hypotension, renal failure, delirium, convulsions, and coma. Death may occur after 7-10 days, with a fatality rate in severe cases approaching 50%. Some patients who survive the acute phase of illness later succumb to renal failure or myocardial damage. Laboratory abnormalities include leukopenia; prolonged clotting, prothrombin, and partial thromboplastin times; thrombocytopenia; hyperbilirubinemia; elevated serum transaminase values; albuminuria; and azotemia. Hypoglycemia may be present in severe cases. Electrocardiogram abnormalities such as bradycardia and ST-T changes are described.

DIAGNOSIS

Yellow fever should be suspected when fever, headache, vomiting, myalgia, and jaundice appear in residents of enzootic areas or in unimmunized visitors who have recently traveled (within 2 weeks before the onset of symptoms) to endemic areas. There are clinical similarities between yellow fever and dengue hemorrhagic fever. In contrast to the gradual onset of acute viral hepatitis resulting from hepatitis A, B, C, D, or E virus, jaundice in yellow fever appears after 3-5 days of high temperature and is often accompanied by severe prostration. Mild yellow fever is dengue-like and cannot be distinguished from a wide variety of other infections. Jaundice and fever may occur in any of several other tropical diseases, including malaria, viral hepatitis, louse-borne relapsing fever, leptospirosis, typhoid fever, rickettsial infections, certain systemic bacterial infections, sickle cell crisis, Rift Valley fever, Crimean-Congo hemorrhagic fever, and other viral hemorrhagic fevers. Outbreaks of yellow fever always include cases with severe gastrointestinal hemorrhage.

The specific diagnosis depends on the detection of the virus or viral antigen in acute-phase blood samples or antibody assays. The immunoglobulin M enzyme immunoassay is particularly useful. Sera obtained during the first 10 days after the onset of symptoms should be kept in an ultra-low-temperature freezer (−70°C [−94°F]) and shipped on dry ice for virus testing. Convalescent-phase samples for antibody tests are managed by conventional means. In handling acute-phase blood specimens, medical personnel must take care to avoid contaminating themselves or others on the evacuation trail (laboratory personnel and others). The postmortem diagnosis is based on virus isolation from liver or blood, identification of Councilman bodies in liver tissue, or detection of antigen or viral genome in liver tissue.

TREATMENT

It is customary to keep patients with yellow fever in a mosquito-free area, with use of mosquito nets if necessary. Patients are viremic during the febrile phase of the illness. Although there is no specific treatment for yellow fever, medical care is directed at maintaining the physiologic status with the following measures: (1) sponging and acetaminophen to reduce a high temperature, (2) vigorous fluid replacement of losses resulting from fasting, thirsting, vomiting, or plasma leakage, (3) correcting an acid-base imbalance, (4) maintaining nutritional intake to lessen the severity of hypoglycemia, and (5) avoiding drugs that are either metabolized by the liver or toxic to the liver, kidney, or central nervous system.

COMPLICATIONS

Complications of acute yellow fever include severe hemorrhage, liver failure, and acute renal failure. Bleeding should be managed by transfusion of fresh whole blood or fresh plasma with platelet concentrates if necessary. Renal failure may require peritoneal dialysis or hemodialysis.

PREVENTION

Yellow fever 17D is a live-attenuated vaccine with a long record of safety and efficacy. It is administered as a single 0.5-mL subcutaneous injection at least 10 days before arrival in a yellow fever–endemic area. YF-VAX, manufactured by Sanofi Pasteur, is licensed for use in the United States. With the exceptions noted later, individuals traveling to endemic areas in South America and Africa should be considered for vaccination, but the length of stay, exact locations to be visited, and environmental or occupational exposure may determine the specific risk and individual need for vaccination. Persons traveling from yellow fever–endemic to yellow fever–receptive countries may be required by national authorities to obtain a yellow fever vaccine (e.g., from South America or Africa to India). Usually, countries that require travelers to obtain a yellow fever immunization do not issue a visa without a valid immunization certificate. Vaccination is valid for 10 years for international travel certification, although immunity lasts at least 40 years and probably for life. Immunoglobulin M antibodies circulate for years after administration of yellow fever vaccine.

Since 1996, there have been a number of reports of *yellow fever vaccine–associated viscerotropic disease* with a higher risk in elderly vaccine recipients and a few cases in persons with previous thymectomies. Yellow fever vaccine should not be administered to persons who have symptomatic immunodeficiency diseases, are taking immunosuppressant drugs, have HIV, or have a history of thymectomy. A recent study has shown that individuals taking maintenance corticosteroids may be successfully vaccinated. Although the vaccine is not known to harm fetuses, its administration during pregnancy is not advised. The vaccine virus may be rarely transmitted through breastfeeding. In very young children, there is a small risk of encephalitis and death after yellow fever 17D vaccination. The 17D vaccine should not be administered to infants younger than 6 months. Residence in or travel to areas of known or anticipated yellow fever activity (e.g., forested areas in the Amazon basin), which puts an individual at high risk, warrants immunization of infants 6-8 months of age. Immunization of children 9 months of age and older is routinely recommended before entry into endemic areas. Immunization of persons older than 60 years of age should be weighed against their risk for sylvatic yellow fever in the American tropics and for urban or sylvatic yellow fever in Africa. Vaccination should be avoided in persons with a history of egg allergy. Alternatively, a skin test can be performed to determine whether a serious allergy exists that would preclude vaccination.

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Chapter 317

Ebola and Other Viral Hemorrhagic Fevers

Scott B. Halstead

Viral hemorrhagic fevers are a loosely defined group of clinical syndromes in which hemorrhagic manifestations are either common or especially notable during severe illness. Both the etiologic agents and the clinical features of the syndromes differ, but coagulopathy may be a common pathogenetic feature.

ETIOLOGY

Six of the viral hemorrhagic fevers are caused by arthropod-borne viruses (arboviruses) (Table 317.1). Four are caused by togaviruses of the family **Flaviviridae**: Kyasanur Forest disease, Omsk hemorrhagic fever, dengue (see Chapter 315), and yellow fever (see Chapter 316) viruses. Three are caused by viruses of the family **Bunyaviridae**: Congo fever, Hantaan fever, and Rift Valley fever (RVF) viruses. Four are caused by viruses of the family **Arenaviridae**: Junin fever, Machupo fever, Guanarito fever, and Lassa fever. Two are caused by viruses in the family **Filoviridae**: Ebola virus and Marburg virus, enveloped, filamentous RNA viruses that are sometimes branched, unlike any other known virus.

EPIDEMIOLOGY

With some exceptions, the viruses causing viral hemorrhagic fevers are transmitted to humans via a nonhuman entity. The specific ecosystem required for viral survival determines the geographic distribution of disease. Although it is commonly thought that all viral hemorrhagic fevers are arthropod borne, seven may be contracted from environmental contamination caused by animals or animal cells or from infected humans (see Table 317.1). Laboratory and hospital infections have occurred with many of these agents. Lassa fever and Argentine and Bolivian hemorrhagic fevers are reportedly milder in children than in adults.

Table 317.1 Viral Hemorrhagic Fevers

MODE OF TRANSMISSION	DISEASE	VIRUS
Tick-borne	Crimean-Congo hemorrhagic fever (HF)*	Congo
	Kyasanur Forest disease	Kyasanur Forest disease
	Omsk HF	Omsk
Mosquito-borne†	Dengue HF	Dengue (4 types)
	Rift Valley fever	Rift Valley fever
	Yellow fever	Yellow fever
Infected animals or materials to humans	Argentine HF	Junin
	Bolivian HF	Machupo
	Lassa fever*	Lassa
	Marburg disease*	Marburg
	Ebola HF*	Ebola
	HF with renal syndrome	Hantaan

*Patients may be contagious; nosocomial infections are common.
†Chikungunya virus is associated infrequently with petechiae and epistaxis. Severe hemorrhagic manifestations have been reported in some cases.

Crimean-Congo Hemorrhagic Fever

Sporadic human infection with Crimean-Congo hemorrhagic fever in Africa provided the original virus isolation. Natural foci are recognized in Bulgaria, western Crimea, and the Rostov-on-Don and Astrakhan regions; disease occurs in Central Asia from Kazakhstan to Pakistan. Index cases were followed by nosocomial transmission in Pakistan and Afghanistan in 1976, in the Arabian Peninsula in 1983, and in South Africa in 1984. In the Russian Federation, the vectors are ticks of the species *Hyalomma marginatum* and *Hyalomma anatolicum*, which, along with hares and birds, may serve as viral reservoirs. Disease occurs from June to September, largely among farmers and dairy workers.

Kyasanur Forest Disease

Human cases of Kyasanur Forest disease occur chiefly in adults in an area of Mysore State, India. The main vectors are two Ixodidae ticks, *Haemaphysalis turturis* and *Haemaphysalis spinigera.* Monkeys and forest rodents may be amplifying hosts. Laboratory infections are common.

Omsk Hemorrhagic Fever

Omsk hemorrhagic fever occurs throughout south-central Russia and northern Romania. Vectors may include *Dermacentor pictus* and *Dermacentor marginatus,* but direct transmission from moles and muskrats to humans seems well established. Human disease occurs in a spring–summer–autumn pattern, paralleling the activity of the vectors. This infection occurs most frequently in persons with outdoor occupational exposure. Laboratory infections are common.

Rift Valley Fever

The virus causing RVF is responsible for epizootics involving sheep, cattle, buffalo, certain antelopes, and rodents in North, Central, East, and South Africa. The virus is transmitted to domestic animals by *Culex theileri* and several *Aedes* species. Mosquitoes may serve as reservoirs by transovarial transmission. An epizootic in Egypt in 1977–1978 was accompanied by thousands of human infections, principally among veterinarians, farmers, and farm laborers. Smaller outbreaks occurred in Senegal in 1987, Madagascar in 1990, and Saudi Arabia and Yemen in 2000–2001. Humans are most often infected during the slaughter or skinning of sick or dead animals. Laboratory infection is common.

Argentine Hemorrhagic Fever

Before the introduction of vaccine, hundreds to thousands of cases of Argentine hemorrhagic fever occurred annually from April through July in the maize-producing area northwest of Buenos Aires that reaches to the eastern margin of the Province of Cordoba. Junin virus has been isolated from the rodents *Mus musculus*, *Akodon arenicola*, and *Calomys laucha*. It infects migrant laborers who harvest the maize and who inhabit rodent-contaminated shelters.

Bolivian Hemorrhagic Fever

The recognized endemic area of Bolivian hemorrhagic fever consists of the sparsely populated province of Beni in Amazonian Bolivia. Sporadic cases occur in farm families who raise maize, rice, yucca, and beans. In the town of San Joaquin, a disturbance in the domestic rodent ecosystem may have led to an outbreak of household infection caused by Machupo virus transmitted by chronically infected *Calomys callosus,* ordinarily a field rodent. Mortality rates are high in young children.

Venezuelan Hemorrhagic Fever

In 1989, an outbreak of hemorrhagic illness occurred in the farming community of Guanarito, Venezuela, 200 miles south of Caracas. Subsequently, in 1990–1991, there were 104 cases reported with 26 deaths caused by Guanarito virus. Cotton rats *(Sigmodon alstoni)* and cane rats *(Zygodontomys brevicauda)* have been implicated as likely reservoirs of Venezuelan hemorrhagic fever.

Lassa Fever

Lassa virus has an unusual potential for human-to-human spread, resulting in many small epidemics in Nigeria, Sierra Leone, and Liberia. In 2012, an outbreak of more than 1,000 cases of Lassa fever occurred in east-central Nigeria. Medical workers in Africa and the United States have also contracted the disease. Patients with acute Lassa fever have been transported by international aircraft, necessitating extensive surveillance among passengers and crews. The virus is probably maintained in nature in a species of African peridomestic rodent, *Mastomys natalensis*. Rodent-to-rodent transmission and infection of humans probably operate via mechanisms established for other arenaviruses.

Marburg Disease

Previously, the world experience of human infections caused by Marburgvirus had been limited to 26 primary and 5 secondary laboratory-based cases in Germany and Yugoslavia in 1967 and to small outbreaks in Zimbabwe in 1975, Kenya in 1980 and 1988, and South Africa in 1983. However, in 1999 a large outbreak occurred in the Republic of Congo, and in 2005 a still larger outbreak occurred in Uige Province, Angola, with 252 cases and 227 deaths. In laboratory and clinical settings, transmission occurs by direct contact with tissues of the African green monkey or with infected human blood or semen. A reservoir in the African fruit bat, *Rousettus aegyptiacus*, has been demonstrated. Fruit bats infected with Marburg virus do not show obvious signs of illness. It appears that the virus is transmitted by close contact with fructivorous bats and by aerosol from bats.

Ebola Hemorrhagic Fever

Ebola virus was isolated in 1976 from a devastating epidemic involving small villages in northern Zaire and southern Sudan; smaller outbreaks have occurred subsequently. Outbreaks have initially been nosocomial. Attack rates have been highest in children from birth to 1 year of age and in persons from 15-50 years of age. The virus is in the *Filovirus* family and closely related to viruses in the genus Marburg virus. An Ebola virus epidemic occurred in Kikwit, Zaire, in 1995, followed by scattered outbreaks in Uganda and Central and West Africa. The virus has been recovered from chimpanzees, and antibodies have been found in other subhuman primates, which apparently acquire infection from a zoonotic reservoir in bats. The natural reservoir of Ebola is thought to be fruit bats. Reston virus, related to Ebola virus, has been recovered from Philippine monkeys and pigs and has caused subclinical infections in humans working in monkey colonies in the United States.

In 2014, West Africa experienced the largest outbreak of Ebola virus disease (EVD) in history and the first transmission in a large urban area (Fig. 317.1). Countries primarily affected were Liberia, Sierra Leone, and Guinea, with imported cases reported in Nigeria, Mali, and Senegal, as well as Europe and the United States. The outbreak was caused by the Zaire Ebola virus (species of Ebola virus include the Zaire, Sudan, Bundibugyo, Reston, and Tai Forest species), which has a mortality rate of approximately 55–65%. As of 8 May 2016, the World Health Organization (WHO) and respective governments reported a total of 28,616 suspected cases and 11,310 deaths (39.5%), though the WHO thinks that this substantially understates the magnitude of the outbreak. The outbreak had largely subsided by the end of 2015. In 2018–2020, an outbreak occurred in the Democratic Republic of the Congo, affecting more than 500 people (age 8-80 years), with a case fatality of approximately 50% (Fig. 317.2). In 2021 the Ministry of Health (MOH) in the Democratic Republic of the Congo (DRC) announced that a case of EVD had been confirmed in Biena Health Zone, North Kivu Province. Sequencing of samples suggests that this outbreak was linked to the 2018–2020 outbreak, likely caused by a persistent infection in a survivor that led to either a relapse or sexual transmission of the virus.

EVD may occur after exposure to fruit bats or bushmeat but most often occurs through exposure to body fluids of infected individuals (blood, sweat, saliva, vomitus, diarrhea, and less often human milk or semen) (Table 317.2). Persistent infection after recovery from acute EVD has been well documented, with virus particles present in body fluids such as semen for many months in apparently healthy survivors. Patients are infectious once they are symptomatic; the incubation period is 2-21 days (mean: 11 days). The age range in the West African epidemic was broad, but most patients were between 15 and 44 years old.

Hemorrhagic Fever with Renal Syndrome

The endemic area of hemorrhagic fever with renal syndrome (HFRS), also known as *epidemic hemorrhagic fever* and *Korean hemorrhagic fever*, includes Japan, Korea, far eastern Siberia, north and central China, European and Asian Russia, Scandinavia, Czechoslovakia, Romania, Bulgaria, Yugoslavia, and Greece. Although the incidence and severity of hemorrhagic manifestations and the mortality rates are lower in Europe than in northeastern Asia, the renal lesions are the same. Disease in Scandinavia, **nephropathia epidemica**, is caused by a different although antigenically related virus, Puumala virus, associated with the bank vole, *Clethrionomys glareolus*. Cases occur predominantly in the spring and summer. There appears to be no age factor in susceptibility, but because of occupational hazards, young adult men are most frequently attacked. Rodent plagues and evidence of rodent infestation have accompanied endemic and epidemic occurrences. Hantaan virus has been detected in the lung tissue and excreta

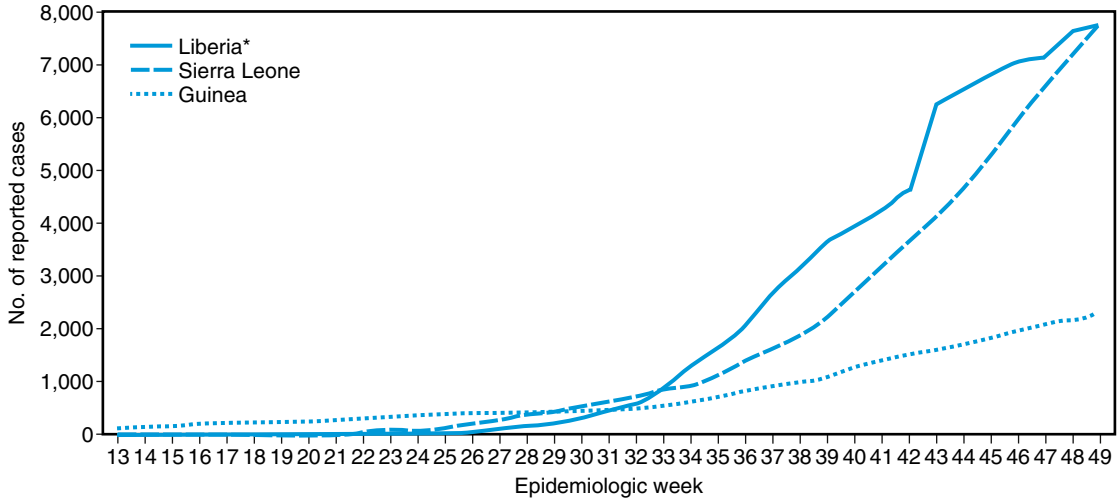

Fig. 317.1 Cumulative number of Ebola virus disease cases reported—three countries, West Africa, April 13, 2016. Reported from Sierra Leone (14,124 cases) and Liberia (10,678), followed by Guinea (3,814). *(Data from the number of cases and deaths in Guinea, Liberia, and Sierra Leone during the 2014–2016 West Africa Ebola Outbreak.* https://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/case-counts.html*)*

of *Apodemus agrarius coreae*. Antigenically related agents have been detected in laboratory rats and in urban rat populations around the world, including Prospect Hill virus in the wild rodent *Microtus pennsylvanicus* in North America and *sin nombre* virus in the deer mouse in the southern and southwestern United States; these viruses are causes of hantavirus pulmonary syndrome (see Chapter 319). Rodent-to-rodent and rodent-to-human transmission presumably occurs via the respiratory route.

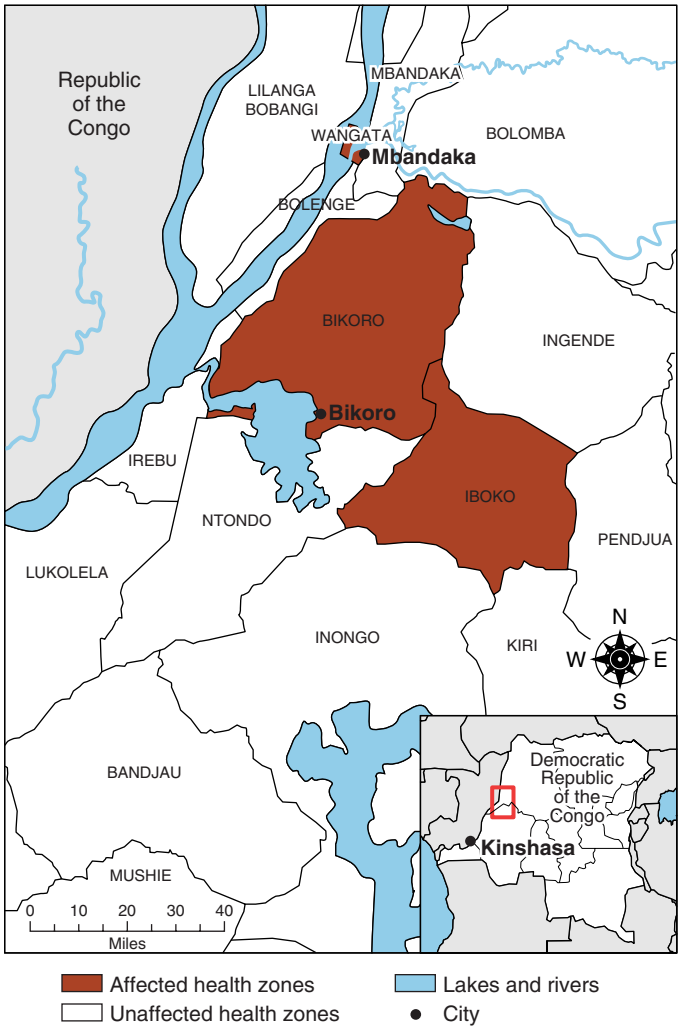

Fig. 317.2 Map of Ebola-affected health zones in the Democratic Republic of the Congo (DRC), 2018. *(Courtesy the Centers for Disease Control and Prevention, 2018.* https://www.cdc.gov/vhf/ebola/outbreaks/drc/drc-map.html*)*

CLINICAL MANIFESTATIONS

Dengue hemorrhagic fever (see Chapter 315) and yellow fever (see Chapter 316) cause similar syndromes in children in endemic areas.

Crimean-Congo Hemorrhagic Fever

The incubation period of 3-12 days is followed by a febrile period of 5-12 days and a prolonged convalescence. Illness begins suddenly with fever, severe headache, myalgia, abdominal pain, anorexia, nausea, and vomiting. After 1-2 days, the fever may subside until the patient experiences an erythematous facial or truncal flush and injected conjunctivae. A second febrile period of 2-6 days then develops, with a hemorrhagic enanthem on the soft palate and a fine petechial rash on the chest and abdomen. Less frequently, there are large areas of purpura and bleeding from the gums, nose, intestines, lungs, or uterus. Hematuria and proteinuria are relatively rare. During the hemorrhagic stage, there is usually tachycardia with diminished heart sounds and occasionally hypotension. The liver is usually enlarged, but there is no icterus. In protracted cases, central nervous system signs include delirium, somnolence, and progressive clouding of the consciousness. Early in the disease, leukopenia with relative lymphocytosis, progressively worsening thrombocytopenia, and gradually increasing anemia occur. In convalescence there may be hearing and memory loss. The mortality rate is 2–50%.

Kyasanur Forest Disease and Omsk Hemorrhagic Fever

After an incubation period of 3-8 days, both Kyasanur Forest disease and Omsk hemorrhagic fever begin with the sudden onset of fever and headache. Kyasanur Forest disease is characterized by severe myalgia, prostration, and bronchiolar involvement; it often manifests without hemorrhage but occasionally involves severe gastrointestinal bleeding. In Omsk hemorrhagic fever, there is moderate epistaxis, hematemesis, and a hemorrhagic enanthem but no profuse hemorrhage; bronchopneumonia is common. In both diseases, severe leukopenia and thrombocytopenia, vascular dilation, increased vascular permeability, gastrointestinal hemorrhages, and subserosal and interstitial petechial hemorrhages occur. Kyasanur Forest disease may be complicated by acute degeneration of the renal tubules and focal liver damage. In many patients, recurrent febrile illness may follow an

Table 317.2 Clinical Recommendations for Ebola Virus Infection

RECOMMENDATION	POPULATION	INTERVENTION
1	Patients with suspected, probable, or confirmed Ebola virus disease	Oral rehydration
2	Patients with suspected, probable, or confirmed Ebola virus disease who are unable to drink or who have inadequate oral intake	Parenteral administration of fluids
3	Patients with suspected, probable, or confirmed Ebola virus disease	Systematic monitoring and charting of vital signs and volume status
4	Patients with suspected, probable, or confirmed Ebola virus disease	Serum biochemistry
5	Patients with suspected, probable, or confirmed Ebola virus disease	Staffing ratio
6	Patients with suspected, probable, or confirmed Ebola virus disease	Communication with family and friends
7	Patients with suspected, probable, or confirmed Ebola virus disease who are in pain	Analgesic therapy
8	Patients with suspected, probable, or confirmed Ebola virus disease with high severity of illness	Antibiotics

Modified from Lamontagne F, Fowler RA, Adhikari NK, et al. Evidence-based guidelines for supportive care of patients with Ebola virus disease. *Lancet*. 2018;391:700–708. Table 2.

Table 317.3 Clinical Stages of Lassa Fever

STAGE	SYMPTOMS
1 (days 1-3)	General weakness and malaise; high fever >39°C (102.2°F), constant with peaks of 40–41°C (104–105.8°F)
2 (days 4-7)	Sore throat (with white exudative patches) very common; headache; back, chest, side, or abdominal pain; conjunctivitis; nausea and vomiting; diarrhea; productive cough; proteinuria; low blood pressure (systolic <100 mm Hg); anemia
3 (after 7 days)	Facial edema; convulsions; mucosal bleeding (mouth, nose, eyes); internal bleeding; confusion or disorientation
4 (after 14 days)	Coma and death

From Richmond JK, Baglole DJ. Lassa fever: epidemiology, clinical features, and social consequences. *BMJ*. 2003;327:1271–1275.

afebrile period of 7-15 days. This second phase takes the form of a meningoencephalitis.

Rift Valley Fever

Most RVF infections have occurred in adults with signs and symptoms resembling those of dengue fever (see Chapter 315). The onset is acute, with fever, headache, prostration, myalgia, anorexia, nausea, vomiting, conjunctivitis, and lymphadenopathy. The fever lasts 3-6 days and is often biphasic. The convalescence is often prolonged. In the 1977–1978 outbreak, many patients died after showing signs that included purpura, epistaxis, hematemesis, and melena. RVF affects the uvea and posterior chorioretina; macular scarring, vascular occlusion, and optic atrophy occur, resulting in permanent visual loss in a high proportion of patients with mild to severe RVF. At autopsy, extensive eosinophilic degeneration of the parenchymal cells of the liver has been observed.

Argentine, Venezuelan, and Bolivian Hemorrhagic Fevers and Lassa Fever

The incubation period in Argentine, Venezuelan, and Bolivian hemorrhagic fevers and Lassa fever is commonly 7-14 days; the acute illness lasts for 2-4 weeks. Clinical illnesses range from undifferentiated fever to the characteristic severe illness. **Lassa fever** is most often clinically severe in White persons. The onset is usually gradual, with increasing fever, headache, diffuse myalgia, and anorexia (Table 317.3). During the first week, signs frequently include a sore throat, dysphagia, cough, oropharyngeal ulcers, nausea, vomiting, diarrhea, and pains in the chest and abdomen. Pleuritic chest pain may persist for 2-3 weeks. In Argentine and Bolivian hemorrhagic fevers and less frequently in Lassa fever, a petechial enanthem appears on the soft palate 3-5 days after onset and at about the same time on the trunk. The tourniquet test may be positive. The clinical course of Venezuelan hemorrhagic fever has not been well described.

In 35–50% of patients, these diseases may become severe, with persistent high temperature, increasing toxicity, swelling of the face or neck, microscopic hematuria, and frank hemorrhages from the stomach, intestines, nose, gums, and uterus. A syndrome of **hypovolemic shock** is accompanied by pleural effusion and renal failure. **Respiratory distress** resulting from airway obstruction, pleural effusion, or congestive heart failure may occur. A total of 10–20% of patients experience late neurologic involvement, characterized by intention tremor of the tongue and associated speech abnormalities. In severe cases, there may be intention tremors of the extremities, seizures, and delirium. The cerebrospinal fluid is normal. In Lassa fever, nerve deafness occurs in early convalescence in 25% of cases. Prolonged convalescence is accompanied by alopecia and, in Argentine and Bolivian hemorrhagic fevers, by signs of autonomic nervous system lability, such as postural hypotension, spontaneous flushing or blanching of the skin, and intermittent diaphoresis.

Laboratory studies reveal marked leukopenia, mild to moderate thrombocytopenia, proteinuria, and, in Argentine hemorrhagic fever, moderate abnormalities in blood clotting, decreased fibrinogen, increased fibrinogen split products, and elevated serum transaminases. There is focal, often extensive eosinophilic necrosis of the liver parenchyma, focal interstitial pneumonitis, focal necrosis of the distal and collecting tubules, and partial replacement of splenic follicles by amorphous eosinophilic material. Usually, bleeding occurs by diapedesis with little inflammatory reaction. The mortality rate is 10–40%.

Marburg Disease and Ebola Hemorrhagic Fever

After an incubation period of 4-7 days, the illness begins abruptly, with severe frontal headache, malaise, drowsiness, lumbar myalgia, vomiting, nausea, and diarrhea. A **maculopapular** eruption begins 5-7 days later on the trunk and upper arms. It becomes generalized and often hemorrhagic and exfoliates during convalescence. The exanthem is accompanied by a dark red enanthem on the hard palate, conjunctivitis, and scrotal or labial edema. Gastrointestinal hemorrhage occurs as the severity of illness increases. Late in the illness, the patient may become tearfully depressed, with marked hyperalgesia to tactile stimuli. In fatal cases, patients become hypotensive, restless, and confused and lapse into coma. Convalescent patients may experience alopecia and may have paresthesias of the back and trunk. There is a marked leukopenia with necrosis of granulocytes. Dysfunction in bleeding and clotting and thrombocytopenia are universal and correlated with the severity of disease; there are moderate abnormalities in concentrations of clotting proteins and elevations of serum transaminases and amylase. Pregnant women and young children are at high risk of severe disease with a fatal outcome. The mortality rate of Marburg disease is 25–85%, and the mortality rate of Ebola hemorrhagic fever 50–90%. High viral loads in acute-phase blood samples convey a poor prognosis. Viral RNA persists in tissues long after symptoms subside, and the virus has been excreted in semen more than 1 year after recovery.

Manifestations of EVD may come in stages, but most EVD begins with the sudden onset of fever accompanied by fatigue, weakness, myalgias, headache, and sore throat. This is followed by gastrointestinal involvement, including anorexia, nausea, abdominal pain, vomiting, and diarrhea. Hemorrhage (defined by any evidence of bleeding) is seen in more than 50% and is a serious later phase, often accompanied by vascular leakage, multiorgan failure, and death. Those who survive improve on approximately days 6-11 of EVD. One late relapse producing meningoencephalitis has been reported.

Hemorrhagic Fever with Renal Syndrome

In most cases, HFRS is characterized by fever, petechiae, mild hemorrhagic phenomena, and mild proteinuria, followed by a relatively uneventful recovery. In 20% of recognized cases, the disease may progress through four distinct phases. The febrile phase is ushered in with fever, malaise, and facial and truncal flushing. It lasts 3-8 days and ends with thrombocytopenia, petechiae, and proteinuria. The hypotensive phase of 1-3 days follows defervescence. Loss of fluid from the intravascular compartment may result in marked hemoconcentration. Proteinuria and ecchymoses increase. The oliguric phase, usually 3-5 days in duration, is characterized by a low output of protein-rich urine, increasing nitrogen retention, nausea, vomiting, and dehydration. Confusion, extreme restlessness, and hypertension are common. The diuretic phase, which may last for days or weeks, usually initiates clinical improvement. The kidneys show little concentrating ability, and rapid loss of fluid may result in severe dehydration and shock. Potassium and sodium depletion may be severe. Fatal cases manifest as abundant protein-rich retroperitoneal edema and marked hemorrhagic necrosis of the renal medulla. The mortality rate is 5–10%.

DIAGNOSIS

The diagnosis of these viral hemorrhagic fevers depends on a high index of suspicion in endemic areas. In nonendemic areas, histories of recent travel, recent laboratory exposure, or exposure to an earlier case should evoke suspicion of a viral hemorrhagic fever.

In all viral hemorrhagic fevers, the viral agent circulates in the blood at least transiently during the early febrile stage. Togaviruses and bunyaviruses can be recovered from acute-phase serum samples by inoculation into a tissue culture or living mosquitoes. Argentine, Bolivian, and Venezuelan hemorrhagic fever viruses can be isolated from acute-phase blood or throat washings by intracerebral inoculation into guinea pigs, infant hamsters, or infant mice. Lassa virus may be isolated from acute-phase blood or throat washings by inoculation into tissue cultures. For Marburg disease and Ebola hemorrhagic fever, acute-phase throat washings, blood, and urine may be inoculated into a tissue culture, guinea pigs, or monkeys. The viruses are readily identified on electron microscopy, with a filamentous structure differentiating them from all other known agents. Specific complement-fixing and immunofluorescent antibodies appear during convalescence. The virus of HFRS is recovered from acute-phase serum or urine by inoculation into a tissue culture. A variety of antibody tests using viral subunits is becoming available. The serologic diagnosis depends on the demonstration of seroconversion or a fourfold or greater increase in immunoglobulin G antibody titer in acute and convalescent serum specimens collected 3-4 weeks apart. Viral RNA may also be detected in blood or tissues with the use of reverse transcriptase polymerase chain reaction analysis.

The diagnosis of EVD is confirmed by enzyme-linked immunosorbent assay immunoglobulin M and polymerase chain reaction (which may need to be repeated if initially negative) testing. Criteria to aid in the diagnosis of EVD include temperature >38.6°C (101.5°F) plus symptoms; contact with an affected patient, the patient's body fluids, or the funeral; residence in or travel to an endemic region; or a history of handling bats, rodents, or primates from an endemic area.

Handling blood and other biologic specimens is hazardous and must be performed by specially trained personnel. Blood and autopsy specimens should be placed in tightly sealed metal containers, wrapped in absorbent material inside a sealed plastic bag, and shipped on dry ice to laboratories with biocontainment safety level 4 facilities. Even routine hematologic and biochemical tests should be done with extreme caution.

Differential Diagnosis

Mild cases of hemorrhagic fever may be confused with almost any self-limited systemic bacterial or viral infection. More severe cases may suggest typhoid fever; epidemic, murine, or scrub typhus; leptospirosis; or a rickettsial spotted fever, for which effective chemotherapeutic agents are available. Many of these disorders may be acquired in geographic or ecologic locations endemic for a viral hemorrhagic fever.

The differential diagnosis of EVD includes malaria, typhoid, Lassa fever, influenza infection, and meningococcemia.

TREATMENT

Ribavirin administered intravenously is effective in reducing mortality rates in Lassa fever and HFRS. Further information and advice about the management, control measures, diagnosis, and collection of biohazardous specimens can be obtained from the Centers for Disease Control and Prevention, National Center for Infectious Diseases, Viral Special Pathogens Branch, Atlanta, Georgia 30333 (470-312-0094).

The therapeutic principle involved in all of these diseases, especially HFRS, is the reversal of dehydration, hemoconcentration, renal failure, and protein, electrolyte, or blood losses (see Table 317.2). The contribution of disseminated intravascular coagulopathy to the hemorrhagic manifestations is unknown, and the management of hemorrhage should be individualized. Transfusions of fresh blood and platelets are frequently given. Good results have been reported in a few patients after the administration of clotting factor concentrates. The efficacy of corticosteroids, ε-aminocaproic acid, pressor amines, and α-adrenergic blocking agents has not been established. Sedatives should be selected with regard to the possibility of kidney or liver damage. The successful management of HFRS may require renal dialysis.

Whole-blood transfusions from Ebola virus–immune donors and administration of Ebola monoclonal antibodies have been shown to be effective in lowering case fatality rates.

Patients suspected of having Lassa fever, Ebola fever, Marburg fever, or Congo-Crimean hemorrhagic fever should be placed in a private room on standard contact and droplet precautions. Caretakers should use barrier precautions to prevent skin or mucous membrane exposure. All persons entering the patient's room should wear gloves, gowns, and face shields. Before exiting the patient's room, caretakers should safely remove and dispose of all protective gear and should clean and disinfect shoes. Protocols require two-person clinical care teams, one observer and one caregiver (see Centers for Disease Control and Prevention [CDC] website: https://www.cdc.gov/vhf/ebola).

Treatment of EVD often requires an intensive care unit and management of multiorgan system dysfunction, including correction of hypovolemia, hyponatremia, hypokalemia, hypoalbuminemia, hypocalcemia, and hypoxia, often with renal replacement therapy as well as ventilation support (see Table 317.2). Convalescent serum and monoclonal antibodies have been employed on an experimental basis. Strict isolation and appropriate barrier protection of healthcare workers is mandatory. Several vaccines have been shown to be immunogenic, and one used late in the epidemic was protective. Epidemic control measures, isolation, and quarantine have been used to attempt to decrease the spread of the West African epidemic.

PREVENTION

A live-attenuated vaccine (Candid-I) for Argentine hemorrhagic fever (Junin virus) is highly efficacious. A form of inactivated mouse brain vaccine is reported to be effective in preventing Omsk hemorrhagic fever. Inactivated RVF vaccines are widely used to protect domestic animals and laboratory workers. HFRS inactivated vaccine is licensed in Korea, and killed and live-attenuated vaccines are widely used in China. A vaccinia-vector glycoprotein vaccine provides protection against Lassa fever in monkeys. Single doses of recombinant vesicular stomatitis virus or adenovirus type 3 vaccines containing surface glycoproteins from Ebola and Marburg viruses have been shown to protect monkeys against Ebola virus and Marburg virus disease. The vesicular stomatitis-vectored Ebola vaccine was shown to be effective in preventing Ebola cases in a ring vaccination trial in Guinea and has been used widely in outbreaks since 2018.

Prevention of mosquito-borne and tick-borne infections includes use of repellents, wearing of tight-fitting clothing that fully covers the extremities, and careful examination of the skin after exposure, with removal of any vectors found. Diseases transmitted from a rodent-infected environment can be prevented through methods of rodent control; elimination of refuse and breeding sites is particularly successful in urban and suburban areas.

Patients should be isolated until they are virus-free or for 3 weeks after illness. Patient urine, sputum, blood, clothing, and bedding should be disinfected. Disposable syringes and needles should be used. Prompt and strict enforcement of barrier nursing may be lifesaving. The mortality rate among medical workers contracting these diseases is 50%. A few entirely asymptomatic Ebola infections result in strong antibody production.

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Chapter 318

Lymphocytic Choriomeningitis Virus

Daniel J. Bonthius

Lymphocytic choriomeningitis virus (LCMV) is a prevalent human pathogen and an important cause of meningitis in children and adults. Capable of crossing the placenta and infecting the fetus, LCMV is also an important cause of neurologic birth defects and encephalopathy in the newborn.

ETIOLOGY

LCMV is a member of the family Arenaviridae, which are enveloped, negative-sense, single-stranded RNA viruses. The name of the arenaviruses is derived from *arenosus,* the Latin word for "sandy," because of the fine granularities observed within the virion on ultra-thin electron microscopic sections.

EPIDEMIOLOGY

Like all arenaviruses, LCMV uses rodents as its reservoir. The common house mouse, *Mus musculus,* is both the natural host and primary reservoir for the virus, which is transferred vertically from one generation of mice to the next via intrauterine infection. Hamsters and guinea pigs are also potential reservoirs. Although heavily infected with LCMV, rodents that acquire the virus transplacentally often remain asymptomatic because congenital infection provides rodents with immunologic tolerance for the virus. Infected rodents shed the virus in large quantities in nasal secretions, urine, feces, saliva, and milk throughout their lives.

Humans typically acquire LCMV by contacting fomites contaminated with infectious virus or by inhaling aerosolized virus. Most human infections occur during the fall and early winter, when mice move into human habitations. Humans can also acquire the virus via organ transplantation. Congenital LCMV infection occurs when a woman acquires a primary LCMV infection during pregnancy. The virus passes through the placenta to the fetus during maternal viremia. The fetus may also acquire the virus during passage through the birth canal from exposure to infected vaginal secretions. Outside of organ transplantation and vertical transmission during pregnancy, there have been no cases of human-to-human transmission of LCMV.

LCMV is prevalent in the environment, has a great geographic range, and infects large numbers of humans. The virus is found throughout the world's temperate regions and probably occurs wherever the genus *Mus* has been introduced (which is every continent but Antarctica). An epidemiologic study found that 9% of house mice are infected and that substantial clustering occurs, where the prevalence is higher. Serologic studies demonstrate that approximately 5% of adult humans possess antibodies to LCMV, indicating prior exposure and infection.

PATHOGENESIS

LCMV is not a cytolytic virus. Thus unlike many other nervous system pathogens that directly damage the brain by killing host brain cells, LCMV pathogenesis involves other underlying mechanisms. Furthermore, the pathogenic mechanisms are different in postnatal (acquired) infection compared with prenatal (congenital) infection. A critical difference in the pathogenesis of postnatal versus prenatal infection is that the virus infects brain parenchyma in the case of prenatal infection but is restricted to the meninges and choroid plexus in postnatal cases.

In postnatal infections, LCMV replicates to high titers in the choroid plexus and meninges. Viral antigen within these tissues becomes the target of an acute mononuclear cell infiltration driven by $CD8^+$ T lymphocytes. The presence of lymphocytes in large numbers within the meninges and cerebrospinal fluid (CSF) leads to the symptoms of meningitis that mark acquired LCMV infection. As the lymphocytes clear the virus from the meninges and CSF, the density of lymphocytes declines and the symptoms of meningitis resolve. Thus symptoms of acquired (postnatal) LCMV infection are immune mediated and are a result of the presence of large numbers of lymphocytes.

Prenatal infection likewise inflames the tissues surrounding the brain parenchyma, and this inflammation leads to some of the signs of congenital LCMV. In particular, within the ventricular system, congenital LCMV infection often leads to ependymal inflammation, which may block the egress of CSF at the cerebral aqueduct and lead to hydrocephalus. However, unlike postnatal cases, prenatal infection with LCMV includes infection of the substance of the brain rather than just the meninges or ependyma. This infection of brain parenchyma leads to the substantial neuropathologic changes typically accompanying congenital LCMV infection. In particular, LCMV infects the mitotically active neuroblasts, located at periventricular sites. Through an unknown mechanism, the presence of the virus kills these periventricular cells, leading to periventricular calcifications, a radiographic hallmark of this disorder. Within the fetal brain, LCMV infection of neurons and glial cells also disrupts neuronal migration, leading to abnormal gyral patterns, and interferes with neuronal mitosis, leading to microcephaly and cerebellar hypoplasia.

CLINICAL MANIFESTATIONS

The clinical manifestations of LCMV infection depend on whether the infection occurs prenatally or postnatally. Congenital infection with LCMV is unique, as it involves both the postnatal infection of a pregnant woman and the prenatal infection of a fetus.

Acquired (Postnatal) Lymphocytic Choriomeningitis Virus Infection

LCMV infection during postnatal life (during childhood or adulthood) typically consists of a brief febrile illness from which the patient fully recovers. The illness classically consists of two clinical phases. In the first phase, the symptoms are those of a nonspecific viral syndrome and include fever, myalgia, malaise, nausea, anorexia, and vomiting. These symptoms usually resolve after several days but are followed by a second phase, consisting of central nervous system disease. The symptoms of this second phase are those of aseptic meningitis, including headache, fever, nuchal rigidity, photophobia, and vomiting. The entire course of the biphasic disease is typically 1-3 weeks.

The clinical spectrum of LCMV infection is broad. One third of postnatal infections are asymptomatic. Other patients develop extraneural disease that extends beyond the usual symptoms and may include orchitis, pneumonitis, myocarditis, parotitis, dermatitis, alopecia, and pharyngitis. In others, the neurologic disease may be considerably more severe than usual and may include transverse myelitis, Guillain-Barré syndrome, hydrocephalus, and encephalitis. Recovery from acquired LCMV infection is usually complete, but fatalities occasionally occur.

LCMV infections acquired via solid organ transplantation always induce severe disease. Several weeks after the transplantation, recipients of infected organs develop fever, leukopenia, and lethargy. After these nonspecific symptoms, the course of the disease rapidly progresses to multiorgan system failure and shock. These cases are almost always fatal.

Congenital Lymphocytic Choriomeningitis Virus Infection

LCMV infection during pregnancy can kill the fetus and induce spontaneous abortion. Among surviving fetuses, the two clinical hallmarks of congenital LCMV infection are vision impairment and brain dysfunction.

The vision impairment in congenital LCMV infection is a result of **chorioretinitis** and the formation of chorioretinal scars. The scarring is usually bilateral and most commonly located in the periphery of the fundus, but involvement of the macula also occurs.

Although the retinal injuries from congenital LCMV infection are often severe, it is the *brain* effects that cause the greatest disability. Prenatal infection with LCMV commonly induces either macrocephaly or microcephaly. **Macrocephaly** after LCMV infection is almost invariably caused by noncommunicating hydrocephalus, stemming from inflammation within the ventricular system. **Microcephaly** is a result of the virus-induced failure of brain growth. In addition to disturbances of head size, periventricular calcifications are also cardinal features of congenital LCMV infection.

Although hydrocephalus, microencephaly, and periventricular calcifications are by far the most commonly observed abnormalities of the brain in congenital LCMV, other forms of neuropathology, alone or in combination, can also occur. These include periventricular cysts, porencephalic cysts, encephalomalacia, intraparenchymal calcifications, cerebellar hypoplasia, and neuronal migration disturbances.

Infants with congenital LCMV infection typically present during the newborn period with evidence of brain dysfunction. The most common signs are lethargy, seizures, irritability, and jitteriness.

Within the fetus, LCMV has a specific tropism for the brain. Thus unlike many other congenital infections, LCMV usually does not induce systemic manifestations. Birthweight is typically appropriate for gestational age. Skin rashes and thrombocytopenia, which are common in several other prominent congenital infections, are unusual in congenital LCMV infection. Hepatosplenomegaly is only rarely observed, and serum liver enzyme levels are usually normal. Auditory deficits are unusual.

LABORATORY FINDINGS

In acquired (postnatal) LCMV infection, the hallmark laboratory abnormality occurs during the second (central nervous system) phase of the disease and is CSF pleocytosis. The CSF typically contains hundreds to thousands of white blood cells, almost all of which are lymphocytes. However, CSF eosinophilia may also occur. Mild elevations of CSF protein and hypoglycorrhachia are common.

In congenital LCMV infection, laboratory findings in the newborn depend on whether the infant is still infected or not. If the infant still harbors the infection, then examination of the CSF may reveal a lymphocytic pleocytosis. Unlike many other congenital infections, LCMV does not typically induce elevations in liver enzymes, thrombocytopenia, or anemia. In many cases, the most reliably abnormal test is the head CT scan, which typically reveals a combination of microencephaly, hydrocephalus, and periventricular calcifications (Fig. 318.1).

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Acute LCMV infections can be diagnosed by isolating the virus from CSF. Polymerase chain reaction has also been used to detect LCMV RNA in patients with active infections. However, by the time of birth, a baby prenatally infected with LCMV may no longer harbor the virus. Thus congenital LCMV infection is more commonly diagnosed by serologic testing. The immunofluorescent antibody test detects both immunoglobulin (Ig) M and IgG and has greater sensitivity than the more widely available complement fixation method. The immunofluorescent antibody test is commercially available, and its specificity and sensitivity make it an acceptable diagnostic tool. A more sensitive test for detecting congenital LCMV infection is the enzyme-linked immunosorbent assay, which measures titers of LCMV IgG and IgM and is performed at the Centers for Disease Control and Prevention.

For acquired (postnatal) LCMV infection, the principal items in the differential diagnosis are the other infectious agents that can induce meningitis. These include bacteria, fungi, viruses, and some other forms of pathogens. The most common viral causes of meningitis are the enteroviruses, including coxsackieviruses and echoviruses, and the arboviruses, including La Crosse encephalitis virus and equine encephalitis virus. Unlike LCMV, which is most common in winter, the enteroviruses and arboviruses are most commonly acquired in summer and early fall.

The principal items in the differential diagnosis of congenital LCMV infection are the other infectious pathogens that can cross the placenta and damage the developing fetus. These infectious agents are linked by the acronym TORCHS and include *Toxoplasma gondii,* rubella virus, cytomegalovirus, herpes simplex virus, and syphilis. Toxoplasmosis, Zika virus infection, and cytomegalovirus infection are particularly difficult to differentiate from LCMV, because all of these infectious agents can produce microcephaly, intracerebral calcifications, and chorioretinitis. Although clinical clues may aid in distinguishing one congenital infection from another, definitive identification of the causative infectious agent usually requires laboratory data, including cultures and serologic studies.

COMPLICATIONS

Complications in children with congenital LCMV infection are nonspecific and include the medical problems that commonly arise in scenarios involving ventriculoperitoneal shunts, severe seizure disorders, and static encephalopathy. These complications include shunt failure or infection, aspiration pneumonia, injuries from falls, and joint contractures.

TREATMENT

There is no specific treatment for acquired or congenital LCMV infection. An effective antiviral therapy for LCMV infection has not yet been developed. Ribavirin is active against LCMV and other arenaviruses in vitro, but its utility in vivo is unproven. Immunosuppressive therapy, if present, should be reduced.

Supportive Care

Children with hydrocephalus from congenital LCMV infection often require placement of a ventriculoperitoneal shunt during infancy for treatment of hydrocephalus. Seizures often begin during early postnatal life, are often difficult to control, and require administration of multiple antiepileptic medications. The mental retardation induced by congenital LCMV infection is often profound. In most cases, affected children should be referred for educational intervention during early life. The spasticity accompanying congenital LCMV infection is often severe. Although physical therapy can help to maintain the range of motion and minimize painful spasms and contractures, implantation of a baclofen pump is often helpful.

PROGNOSIS

The great majority of patients with postnatally acquired LCMV infection have a full recovery with no permanent sequelae. Rarely, postnatal infections induce hydrocephalus and require shunting. Rarer yet, postnatal LCMV infection is fatal.

In contrast to the usual benign outcome of postnatal infections, prenatal infections typically lead to severe and permanent disability.

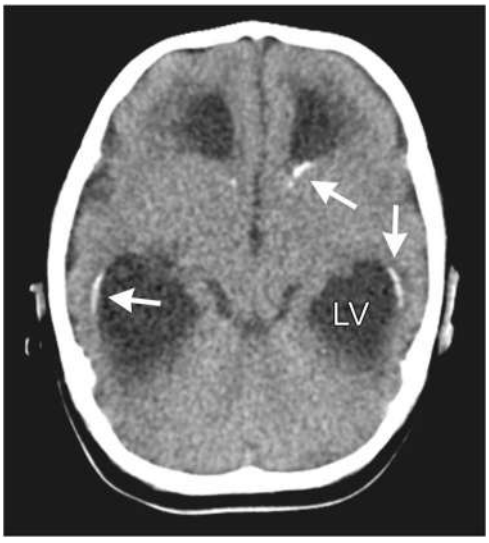

Fig. 318.1 Head CT scan from a 2-mo-old microcephalic baby with congenital lymphocytic choriomeningitis virus infection. The scan reveals enlargement of the lateral ventricles *(LV)* and periventricular calcifications *(arrows)*.

In children with congenital LCMV infection, brain function is nearly always impaired and chorioretinitis is invariably present. Mental retardation, cerebral palsy, ataxia, epilepsy, and blindness are common neurologic sequelae. However, children with congenital LCMV infection have diverse outcomes. All children with the combination of microencephaly and periventricular calcifications are profoundly neurologically impaired. Blindness, medically refractory epilepsy, spastic quadriparesis, and mental retardation are typical of this group. However, other children with congenital LCMV infection who do not have the combination of microencephaly and periventricular calcifications often have a more favorable outcome, with less severe motor, mental, and vision impairments. Children with isolated cerebellar hypoplasia may be ataxic but have only mild or moderate mental retardation and vision loss.

PREVENTION

No vaccine exists to prevent LCMV infection. However, measures can be taken to reduce the risk of infection. Because rodents, especially house mice, are the principal reservoir of LCMV, people can reduce their risk of contracting the virus by minimizing their exposure to the secretions and excretions of mice. This can be accomplished most effectively by eliminating cohabitation with mice. Congenital LCMV infection will not occur unless a woman contracts a primary infection with LCMV during pregnancy. Thus women should be especially careful to avoid contact or cohabitation with mice during pregnancy. Pregnant women should also avoid contact with pet rodents, especially mice and hamsters. These facts should be stressed during prenatal visits.

Acquisition of LCMV from solid organ transplantation represents a substantial risk to organ recipients. Prospective donors with LCMV meningitis or encephalitis pose a clear risk for transmitting a fatal infection to recipients. Healthcare providers, transplantation centers, and organ procurement organizations should be aware of the risks posed by LCMV and should consider LCMV in any potential donor with signs of aseptic meningitis but no identified infectious agent. The risks and benefits of offering and receiving organs from donors with possible LCMV infection should be carefully considered.

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Chapter 319

Hantavirus Pulmonary Syndrome

Scott B. Halstead

Hantavirus pulmonary syndrome (HPS) is caused by multiple closely related hantaviruses that have been identified from the western United States, with sporadic cases reported from the eastern United States (Fig. 319.1) and Canada and important foci of disease in several countries in South America. HPS is characterized by a febrile prodrome followed by the rapid onset of noncardiogenic pulmonary edema and hypotension or shock. Sporadic cases in the United States caused by related viruses may manifest with renal involvement. Cases in Argentina and Chile sometimes include severe gastrointestinal hemorrhaging; nosocomial transmission has been documented in this geographic region only.

ETIOLOGY

Hantaviruses are a genus in the family Bunyaviridae, which are lipid-enveloped viruses with a negative-sense RNA genome composed of three unique segments. Several pathogenic viruses that have been recognized within the genus include Hantaan virus, which causes the severe disease; hemorrhagic fever with renal syndrome (HFRS), seen primarily in mainland Asia (see Chapter 317); Dobrava virus, the cause of a form of HFRS seen primarily in the Balkans; Puumala virus, which causes a milder disease with a high proportion of subclinical infections prevalent in northern Europe; and Seoul virus, which results in moderate HFRS and is transmitted predominantly in Asia by urban rats or worldwide by laboratory rats. Prospect Hill virus, a hantavirus that is widely disseminated in meadow voles in the United States, is not known to cause human disease. There are an increasing number of case reports of European hantaviruses causing HPS.

HPS is associated with *sin nombre* virus, isolated from deer mice, *Peromyscus maniculatus,* in New Mexico. The multiple HPS-like agents in the Northern Hemisphere isolated to date belong to a single genetic group of hantaviruses and are associated with rodents of the family Muridae, subfamily Sigmodontinae. These rodent species are restricted to the Americas, suggesting that HPS may be a Western Hemisphere disease.

EPIDEMIOLOGY

Persons acquiring HPS generally have a history of recent outdoor exposure or live in an area with large populations of deer mice. Clusters of cases have occurred among individuals who have cleaned houses that were rodent infested. *P. maniculatus* is one of the most common North American mammals and, where found, is frequently the dominant member of the rodent community. About half of the average of 30+ cases seen annually occurs between the months of May and July. Patients are almost exclusively 12-70 years of age; 60% of patients are 20-39 years of age. Rare cases are reported in children younger than 12 years of age. Two thirds of patients are male, probably reflecting their greater outdoor activities. It is not known whether almost complete absence of disease in young children is a reflection of innate resistance or simply lack of exposure. Evidence of human-to-human transmission has been reported in Argentine outbreaks. As of January 2017, 728 cases of hantavirus disease have been reported in the United States since surveillance began in 1993.

Hantaviruses do not cause apparent illness in their reservoir hosts, which remain asymptomatically infected for life. Infected rodents shed virus in saliva, urine, and feces for many weeks, but the duration of shedding and the period of maximum infectivity are unknown. The presence of infectious virus in saliva, the sensitivity of these animals to parenteral inoculation with hantaviruses, and field observations of infected rodents indicate that biting is important for rodent-to-rodent transmission. Aerosols from infective saliva or excreta of rodents are implicated in the transmission of hantaviruses to humans. Persons visiting animal care areas housing infected rodents have been infected

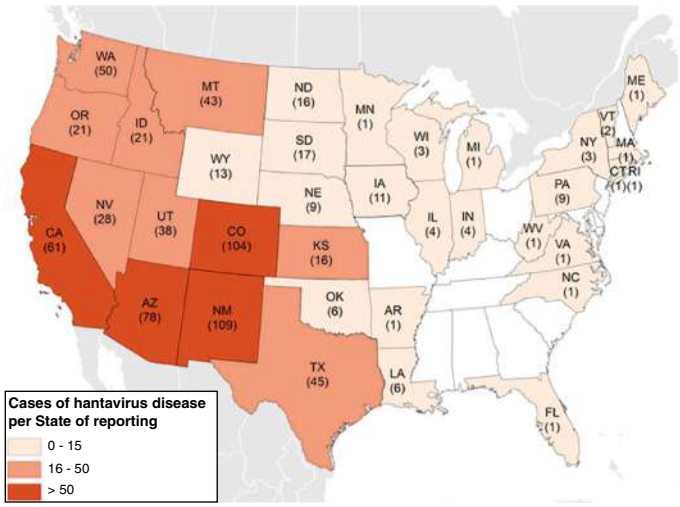

Fig. 319.1 Total number of confirmed cases of hantavirus pulmonary syndrome, by state reporting, United States, 1993-2016. N = 728 as of January 2017. *(From Viral Special Pathogens Branch, Centers for Disease Control and Prevention. http://www.cdc.gov/hantavirus/surveillance/reporting-state.html)*

after exposure for as little as 5 minutes. It is possible that hantaviruses are spread through contaminated food and breaks in skin or mucous membranes; transmission to humans has occurred by rodent bites. Person-to-person transmission is distinctly uncommon but has been documented in Argentina.

PATHOGENESIS

HPS is characterized by sudden and catastrophic pulmonary edema, resulting in anoxia and acute heart failure. The virus is detected in pulmonary capillaries, suggesting that pulmonary edema is the consequence of a T-cell attack on virus-infected capillaries. The disease severity is predicted by the level of acute-phase viremia titer. A useful hamster model of HPS is available.

CLINICAL MANIFESTATIONS

HPS is characterized by a prodrome and a cardiopulmonary phase. The mean duration after the onset of prodromal symptoms to hospitalization is 5.4 days. The mean duration of symptoms to death is 8 days (median: 7 days; range: 2-16 days). The most common **prodromal symptoms** are fever and myalgia (100%); cough or dyspnea (76%); gastrointestinal symptoms, including vomiting, diarrhea, and midabdominal pain (76%); and headache (71%). The **cardiopulmonary phase** is heralded by progressive cough and shortness of breath. The most common initial physical findings are tachypnea (100%), tachycardia (94%), and hypotension (50%). Rapidly progressive acute pulmonary edema, hypoxia, and shock develop in most severely ill patients. Pulmonary vascular permeability is complicated by cardiogenic shock associated with increased vascular resistance. The clinical course of the illness in patients who die is characterized by pulmonary edema accompanied by severe hypotension, frequently terminating in sinus bradycardia, electromechanical dissociation, ventricular tachycardia, or fibrillation. Hypotension may be progressive even with adequate oxygenation. HPS virus is excreted in the urine during the acute illness phase, and survivors may demonstrate evidence of chronic renal damage.

DIAGNOSIS

The diagnosis of HPS should be considered in a previously healthy patient presenting with a febrile prodrome, acute respiratory distress, and thrombocytopenia who has had outdoor exposure in the spring and summer months. A specific diagnosis of HPS is made by serologic tests that detect hantavirus immunoglobulin M antibodies. The early appearance of immunoglobulin G antibodies signals probable recovery. Hantavirus antigen can be detected in tissue by immunohistochemistry and amplification of hantavirus nucleotide sequences detected by reverse transcriptase polymerase chain reaction. The state health department or the Centers for Disease Control and Prevention should be consulted to assist in the diagnosis, epidemiologic investigations, and outbreak control.

Laboratory Findings

Laboratory findings include leukocytosis (median: 26,000 cells/μL), an elevated hematocrit resulting from hemoconcentration, thrombocytopenia (median: 64,000 cells/μL), prolonged prothrombin and partial thromboplastin times, elevated serum lactate dehydrogenase concentration, decreased serum protein concentrations, proteinuria, and microscopic hematuria. Patients who die often experience disseminated intravascular coagulopathy, including frank hemorrhage and exceptionally high leukocyte counts.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes adult respiratory distress syndrome, pneumonic plague, psittacosis, severe mycoplasmal pneumonia, influenza, leptospirosis, inhalation anthrax, rickettsial infections, pulmonary tularemia, atypical bacterial and viral pneumonia, legionellosis, meningococcemia, and other sepsis syndromes. The key determinant in the diagnosis of HPS is thrombocytopenia.

TREATMENT

Management of patients with hantavirus infection requires maintenance of adequate oxygenation and careful monitoring and support of cardiovascular function. The pathophysiology of HPS somewhat resembles that of dengue shock syndrome (see Chapter 315). Pressor or inotropic agents, such as dobutamine, should be administered in combination with judicious volume replacement to treat symptomatic hypotension or shock while avoiding exacerbation of the pulmonary edema. Intravenous ribavirin, which is lifesaving if given early in the course of HFRS and is effective in preventing death in the hamster model, has not yet been demonstrated to be of value in HPS.

Further information and advice about management, control measures, diagnosis, and collection of biohazardous specimens can be obtained from the Centers for Disease Control and Prevention, National Center for Infectious Diseases, Viral Special Pathogens Branch, Atlanta, Georgia 30333 (470-312-0094).

PROGNOSIS

In some geographic areas, fatality rates for HPS have been 50%. Severe abnormalities in hematocrit, white blood cell count, lactate dehydrogenase value, and partial thromboplastin time and a high viral load predict death with high specificity and sensitivity. The early appearance of immunoglobulin G antibodies may signal a hopeful prognosis.

PREVENTION

Avoiding contact with rodents is the only preventive strategy against HPS. Rodent control in and around the home is important. Barrier nursing is advised, and biosafety level 3 facilities and practices are recommended for laboratory handling of blood, body fluids, and tissues from suspect patients or rodents, because the virus may be aerosolized. However, to date, there are no cases of person-to-person transmission of HPS.

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Chapter 320

Rabies

Rodney E. Willoughby Jr.

Rabies virus is a bullet-shaped, negative-sense, single-stranded, enveloped RNA virus from the family Rhabdoviridae, genus *Lyssavirus.* There are 17 species of *Lyssavirus,* divided into three antigenic phylogroups. Rabies vaccines and immunoglobulins are active against phylogroup I viruses. The classic rabies virus (phylogroup I, genotype 1) is distributed worldwide and naturally infects a large variety of animals. The other genotypes are more geographically confined, with none found in the Americas. Six *Lyssavirus* genotypes are associated with rabies in humans, although genotype 1 accounts for the great majority of cases. Within genotype 1, different lineages are specific to animal reservoirs, although cross-species transmission can occur. Cosmopolitan dog, vampire bat, and insectivorous bat lineages in the Americas cause overlapping but distinct clinical syndromes and vary in immunogenicity, affecting survival.

EPIDEMIOLOGY

Rabies is present on all continents except Antarctica. Rabies predominantly afflicts underaged, poor, and geographically isolated populations. Approximately 59,000 cases of human rabies occur in Africa and Asia annually. Rabies virus can infect any mammal or bird, but true animal reservoirs that maintain the presence of rabies virus in the population are limited to terrestrial carnivores and bats. Worldwide, transmission from dogs accounts for >90% of human cases. In Africa and Asia, other animals serve as prominent reservoirs, such as jackals, mongooses, and raccoon dogs. In the United States, raccoons are the most infected wild animal along the eastern seaboard. Three lineages

of skunk rabies are endemic in the Midwest (north and south) and California, gray foxes harbor rabies in Arizona and Texas, red foxes and arctic foxes harbor rabies in Alaska, and mongooses carry rabies in Puerto Rico. Rabies occurs infrequently in livestock. Among American domestic pets, infected cats outnumber infected dogs, probably because cats frequently prowl unsupervised and are not uniformly subject to vaccine laws. Rabies is rare in small mammals, including mice, squirrels, and rabbits; to date, no animal-to-human transmission from these animals has been documented.

The epidemiology of human rabies in the United States is dominated by cryptogenic bat rabies. Bats are migratory in the spring and fall; rabid bats are identified in every state of the union except Hawaii. In almost all cases of bat-associated human rabies in the United States, there was no history of a bat bite. Among inhabitants of the Peruvian Amazon region who have exposure to rabies-infected vampire bats, there are some who have rabies virus–neutralizing antibodies. Antibody-positive patients remember bat bites but do not recall symptoms of rabies.

In the United States, 30,000 episodes of rabies postexposure prophylaxis (PEP) occur annually. Between one and three endemic human cases are diagnosed annually, half postmortem. There have been five outbreaks of rabies associated with solid organ and corneal transplantation.

TRANSMISSION

Rabies virus is found in large quantities in the saliva of infected animals, and transmission occurs almost exclusively through inoculation of the infected saliva through a bite or scratch from a rabid mammal. Approximately 35–50% of people who are bitten by a known rabies-infected animal and receive no PEP contract rabies. The transmission rate is increased if the victim has suffered multiple bites and if the inoculation occurs in highly innervated parts of the body such as the face and the hands. Infection does not occur after exposure of intact skin to infected secretions, but virus may enter the body through intact mucous membranes. Claims that spelunkers may experience rabies after inhaling bat excreta have come under doubt, although inhalational exposure can occur during laboratory accidents.

No case of nosocomial transmission to a healthcare worker has been documented to date, but caregivers of a patient with rabies are advised to use full barrier precautions. The virus is rapidly inactivated in the environment, and contamination of fomites is not a mechanism of spread.

PATHOGENESIS

After inoculation, rabies virus replicates slowly and at low levels in muscle or skin. This slow initial step likely accounts for the disease's long incubation period. The virus then enters the peripheral motor nerve, using the nicotinic acetylcholine receptor and possibly other receptors for entry. Once in the nerve, the virus travels by fast axonal transport, crossing synapses roughly every 12 hours. Rapid dissemination occurs throughout the brain and spinal cord before symptoms appear. Infection of the dorsal root ganglia is apparently futile but causes characteristic radiculitis. Infection concentrates in the brainstem, accounting for autonomic dysfunction and relative sparing of cognition. Despite severe neurologic dysfunction with rabies, histopathology reveals limited damage, inflammation, or apoptosis. The pathologic hallmark of rabies, the Negri body, is composed of clumped viral nucleocapsids that create cytoplasmic inclusions on routine histology. Negri bodies can be absent in documented rabies virus infection. Rabies may be a metabolic disorder of neurotransmission; tetrahydrobiopterin deficiency in human rabies causes severe deficiencies in dopamine, norepinephrine, and serotonin.

After infection of the central nervous system, the virus travels anterograde through the peripheral nervous system to virtually all innervated organs, further exacerbating dysautonomia. It is through this route that the virus infects the salivary glands. Many victims of rabies die from uncontrolled cardiac dysrhythmia in the first week of objective signs of rabies.

Deficiency of tetrahydrobiopterin, an essential cofactor for neuronal nitric oxide synthase, is predicted to lead to spasm of the basilar arteries. Onset of vasospasm has been confirmed in a few patients within 5-8 days of the first hospitalization, at about the time coma supervenes in the natural history. Metabolites in cerebrospinal fluid (CSF) consistent with ketogenesis are associated with demise. Immune response to rabies is delayed, usually evident 4-14 days after onset of clinical signs. Immune response to rabies varies by lineage; antibody responses in CSF are often inferior to those in serum. Common complications include complete heart block in dog rabies and cerebral edema in bat rabies.

CLINICAL MANIFESTATIONS

The incubation period for rabies is 1-3 months. In severe wounds to the head, symptoms may occur within 5 days after exposure, and occasionally the incubation period can extend to 8 years. Rabies has two principal clinical forms, but these overlap in practice. **Encephalitic** or **furious rabies** is extrapolated from carnivores and begins with nonspecific symptoms, including fever, sore throat, malaise, headache, nausea and vomiting, and weakness. Symptoms are often accompanied by paresthesia and pruritus at or near the site of the bite. The patient begins to demonstrate symptoms of encephalitis, with agitation, sleep disturbance, or depressed mentation. Characteristically, patients with rabies encephalitis initially have periods of lucidity alternating with periods of profound encephalopathy. Hydrophobia and aerophobia are the cardinal signs of rabies; they are unique to humans and are not universal or specific. Phobic spasms are manifested by agitation and fear created by being offered a drink or fanning of air in the face, which in turn produce choking and aspiration through spasms of the pharynx, neck, and diaphragm. Seizures are rare and should point to an alternative diagnosis; orofacial dyskinesias and myoclonus may be confused with seizures. Severe dysautonomia is common, and cardiac arrests occur in 25% of patients in the first week of hospitalization. The illness is relentlessly progressive. There is a dissociation of brain electrical activity with findings of brainstem coma caused by anterograde denervation. Death almost always occurs within 1-2 days of hospitalization in developing countries and by 18 days of hospitalization with intensive care.

Paralytic or **dumb rabies**, extrapolated from herbivores, is seen much less frequently and is characterized principally by fevers and ascending motor weakness affecting both the limbs and the cranial nerves. Most patients with paralytic rabies also have some element of encephalopathy as the disease progresses subacutely.

Case reports suggest that milder forms of rabies encephalitis may exist, and 45 rabies survivors are known. Rabies should be considered earlier and more frequently than current practice to improve outcomes.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of rabies encephalitis includes all forms of severe cerebral infections, tetanus, and some intoxications and envenomations. Rabies can be confused with autoimmune (anti–*N*-methyl-D-aspartate receptor, NMDAR) encephalitis, other infectious forms of encephalitis, psychiatric illness, drug abuse, and conversion disorders. Paralytic rabies is frequently confused with Guillain-Barré syndrome. The diagnosis of rabies is frequently delayed in Western countries because of the unfamiliarity of the medical staff with the infection. These considerations highlight the need to pursue a history of contact with an animal belonging to one of the known reservoirs for rabies or to establish a travel history to a rabies-endemic region.

DIAGNOSIS

The Centers for Disease Control and Prevention (CDC) require complementary tests to confirm a clinically suspected case of rabies. The virus can be grown both in cell culture and after animal injection, but these methods are slow. Pan-lyssavirus reverse transcription polymerase chain reaction is 90% sensitive for the diagnosis of rabies when done on skin and iteratively in saliva. Rabies antigen is detected

through immunofluorescence of saliva or biopsies of hairy skin or brain. Corneal impressions are not recommended. Rabies-specific antibody can be detected in serum or CSF samples, but most patients die while seronegative. Antirabies antibodies are present in the sera of patients who have received an incomplete course of the rabies vaccine, precluding a meaningful interpretation in this setting. Recent treatment with intravenous immunoglobulin may result in a false-positive antibody test. Antibody in CSF is rarely detected after vaccination and is considered diagnostic of rabies regardless of immunization status. CSF abnormalities in cell count, glucose, and protein content are minimal and not diagnostic. MRI findings in the brain are late.

TREATMENT AND PROGNOSIS

Rabies is generally fatal. Conventional critical care yielded 6 survivors from 79 attempts since 1990. Seventeen of 103 patients survived with use of the Milwaukee Protocol (MP) (http://www.mcw.edu/rabies); neurologic outcomes are poor in half of patients. Neither rabies immunoglobulin (RIG) nor rabies vaccine provides benefit once symptoms have appeared. Among 10 survivors of rabies after use of rabies vaccine, 7 had poor neurologic outcomes. Among seven vaccine-naïve survivors, two had poor outcomes. Antiviral treatments have not been effective; favipiravir has been administered to eight patients with modest clinical effect. Ribavirin and RIG delay the immune response and should be avoided. In contrast, appearance of the normal antibody response by 7 days is associated with clearance of salivary viral load and survival.

PREVENTION

Primary prevention of rabies infection includes vaccination of domestic animals and education to avoid wild animals, stray animals, and animals with unusual behavior.

Immunization and Fertility Control of Animal Reservoirs

The introduction of routine rabies immunization for domestic pets in the United States and Europe during the middle of the 20th century virtually eliminated infection in dogs. Dog rabies has now been almost eliminated from the Americas; residual cases concentrate in the Caribbean and Bolivia. In the 1990s, control efforts in Europe and North America shifted to immunization of wildlife reservoirs of rabies, where rabies was newly emerging. These programs employed bait laced with either an attenuated rabies vaccine or a recombinant rabies surface glycoprotein inserted into vaccinia, distributed by air or hand into areas inhabited by rabid animals. Human contact with vaccine-laden bait has been infrequent. Adverse events after such contact have been rare, but the vaccinia vector poses a threat to the same population at risk for vaccinia itself, namely, pregnant women, immunocompromised patients, and people with atopic dermatitis. Mass culling of endemic reservoirs has never worked; vaccination and fertility control stop outbreaks. Bats are ubiquitous and very important for insect control. Less than 1% of free-flying bats but >8% of downed bats and bats found in dwellings are rabid.

Postexposure Prophylaxis

Only one case of rabies has been documented in a person in the United States receiving the recommended schedule of PEP since introduction of modern cellular vaccines in the 1970s.

Given the incubation period for rabies, PEP is a medical urgency, not emergency. The relevance of rabies for most pediatricians centers on evaluating whether an animal exposure warrants PEP (Fig. 320.1). The decision to proceed ultimately depends on the local epidemiology of animal rabies as determined by active surveillance programs, information that can be obtained from local and state health departments. In general, bats, raccoons, skunks, coyotes, and foxes should be considered rabid unless proven otherwise through euthanasia and testing of brain tissue, whereas bites from small herbivorous animals (squirrels, hamsters, gerbils, chipmunks, rats, mice, and rabbits) can be discounted. The response to bites from a pet, particularly a dog, cat, or ferret, depends on local surveillance statistics and on whether the animal is vaccinated and available for observation. Areas free of canine lineage of rabies virus may still have rabid dogs and cats through wildlife transmission.

The approach to nonbite bat exposures is controversial. In response to the observation that most cases of rabies in the United States have been caused by bat variants and that most affected patients had no recollection of a bat bite, the CDC has recommended that **rabies PEP be considered after any physical contact with bats and when a bat is found in the same room as persons who may not be able to accurately report a bite**, assuming that the animal is unavailable for testing. Such people include young children, the mentally disabled, and intoxicated individuals. Other nonbite contacts (e.g., handling a carcass, exposure to an animal playing with a carcass, or coming into contact with blood or excreta from a potentially rabid animal) usually do not require PEP.

In all instances of a legitimate exposure, effort should be made to recover the animal for quarantine and observation or brain examination after euthanasia. Testing obviates the need for PEP more than half the time. In most instances, PEP can be deferred until the results of observation or brain histology are known. In dogs, cats, and ferrets, symptoms of rabies always occur within several days of viral shedding; therefore in these animals a 10-day observation period is sufficient to eliminate the possibility of rabies.

No duration of time between exposure and onset of symptoms should preclude rabies prophylaxis. Rabies PEP is most effective when applied expeditiously. Nevertheless, the series should be initiated in the asymptomatic person as soon as possible, regardless of the length of time since the bite. Rabies vaccine and RIG are contraindicated once symptoms develop.

The first step in rabies PEP is to cleanse the wound thoroughly. Soapy water is sufficient to inactivate an enveloped virus, and its effectiveness is supported by broad experience. Other commonly used disinfectants, such as iodine-containing preparations, are virucidal and should be used in addition to soap when available. Probably the most important aspect of this component is that the wound is cleansed with copious volumes of disinfectant. Primary closure is avoided; wounds may be bacterially infected as well, so cosmetic repair should follow. Antibiotics and tetanus prophylaxis (see Chapter 257) should be applied with the use of usual wound care criteria.

Schedules and indications for administration of rabies vaccine and human-derived rabies immunoglobulin (HRIG) are available at the CDC website (https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/rabies.html). These do not harmonize fully with international recommendations by the World Health Organization that seek greater efficiencies in PEP and use of RIG after dog bites.

The second component of rabies PEP consists of passive immunization with RIG. Most failures of PEP are attributed to not using RIG. HRIG, the formulation used in industrialized countries, is administered at a dose of 20 IU/kg. Globally, the World Health Organization recommends that as much of the dose is infused around the wound as possible. In the United States, where bat rabies dominates, the remainder is injected intramuscularly in a limb distant from the one injected with the killed vaccine. Like other immunoglobulin preparations, RIG interferes with the take of live viral vaccines for at least 4 months after administration of the RIG dose. A more concentrated formulation of HRIG is available, which may be more suitable for bites on the face and digits to minimize risk of compartment syndrome after injection. HRIG is not available in many parts of the developing world. Modern preparations of equine RIG are associated with fewer side effects than prior products composed of crude horse serum. Regrettably, for a large segment of the world's population, no passive immunization product is available at all, so preexposure prophylaxis (PreRP) should be considered. Monoclonal antibody products are in clinical trials and may alleviate this deficiency.

The third component of rabies PEP is immunization with inactivated vaccine. In most of the world, cell-based vaccines have replaced previous preparations. Two formulations currently are available in the United States, namely, RabAvert (Chiron Behring Vaccines, Maharashtra, India), a purified chick embryo cell–cultivated vaccine, and Imovax

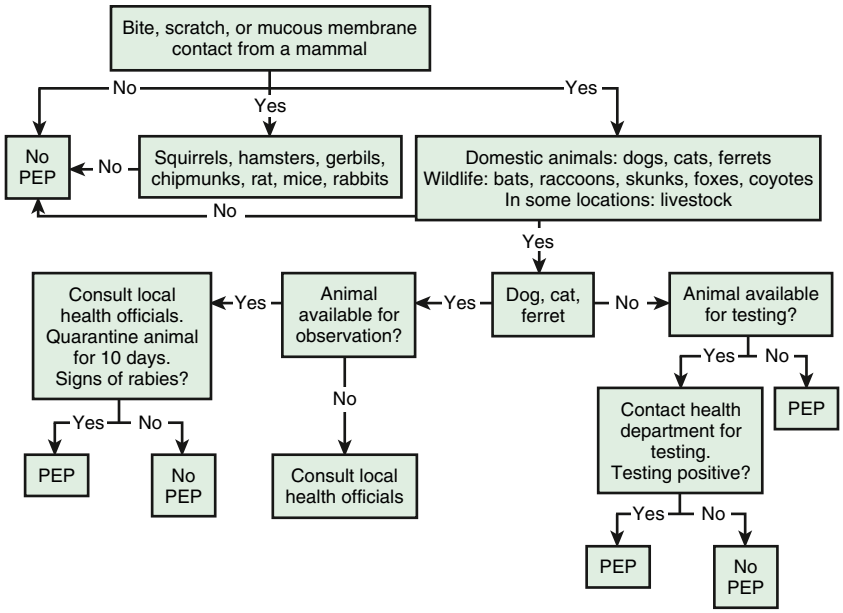

Fig. 320.1 Algorithm for evaluating a child for rabies postexposure prophylaxis. This and any other algorithm should be used in concert with local epidemiologic information regarding the incidence of animal rabies in any given location.

Rabies (Aventis Pasteur, Bridgewater, NJ), cultivated in human diploid cell cultures. In both children and adults, both vaccines are administered intramuscularly in a 1-mL volume in the deltoid or anterolateral thigh on days 0, 3, 7, and 14 after presentation. Injection into the gluteal area is associated with a blunted antibody response, so this area should not be used. The rabies vaccines can be safely administered during pregnancy. In most persons the vaccine is well tolerated; most adverse effects are related to booster doses. Pain and erythema at the injection site occur commonly, and local adenopathy, headache, and myalgias occur in 10–20% of patients. Approximately 5% of patients who receive the human diploid cell vaccine experience an immune complex–mediated allergic reaction, including rash, edema, and arthralgias, several days after a booster dose. The World Health Organization has approved schedules using smaller amounts of vaccine, administered intradermally, that are immunogenic and protective, but none is approved for use in the United States. Other cell culture–derived rabies virus vaccines are available in the developing world. A few countries still produce nerve tissue–derived vaccines; these preparations are poorly immunogenic, and cross reactivity with human nervous tissue may occur, producing severe neurologic symptoms even in the absence of rabies infection. Prompt travel to a clinic or country to obtain modern rabies vaccine is advised instead.

Preexposure Prophylaxis

The killed rabies vaccine can be given to prevent rabies in persons at high risk for exposure to wild-type virus, including laboratory personnel working with rabies virus, veterinarians, and others likely to be exposed to rabid animals as part of their occupation. PreEP should be considered for persons traveling to a rabies-endemic region where there is a credible risk for a bite or scratch from a rabies-infected animal, particularly if there is likely to be a shortage of RIG or cell culture–based vaccine. Rabies vaccine as part of the routine vaccine series is under investigation in some countries. The schedule for PreEP consists of two intramuscular injections on days 0, and 7; other schedules are available globally. PEP in the patient who has received PreEP or a prior three doses of PEP consists of two doses of vaccine (one each on days 0 and 3) and does not require RIG. Immunity from PreEP wanes after several years and requires boosting if the potential for exposure to rabid animals recurs.

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Chapter 321
Polyomaviruses

Bijal A. Parikh

Human polyomaviruses (PyV) comprise a unique group of viruses that cause disease in immunocompromised individuals but not in the healthy immune-competent host. The two best-studied human PyV, BK PyV and JC PyV, are acquired relatively early in life and generally cause no clinical disease, despite occasional bouts of asymptomatic viral shedding. PyV-associated sequelae become especially relevant in the setting of **posttransplant renal graft failure** and **hemorrhagic cystitis** in the case of BK PyV and **neurologic disease** for JC PyV reactivation. The number of human PyV has expanded dramatically, with discovery of up to 12 additional viruses. Two PyV, designated KI virus and WU virus, can be detected in respiratory samples from children; however, their disease associations are not as well established outside of a few case reports. Exceptions include **Merkel cell** or **MC PyV** and **trichodysplasia spinulosa-associated** or **TS PyV**, yet their relevance in the pediatric population is limited. Current knowledge regarding BK PyV and JC PyV epidemiology and disease associations with special emphasis on diagnostic and clinical management of pediatric populations is summarized next.

GENOMIC ORGANIZATION

PyV are nonenveloped, icosahedral virions of 40-45 nm in diameter. The genomes are circular double-stranded DNA composed of approximately 5,000 base pairs. The type member of the parent family, *Polyomaviridae*, is **simian virus 40** (SV40). Translation of proteins occurs from both early and late transcripts, transcribed in opposite directions from the noncoding control region (NCCR). The host range of PyV is very broad, having been isolated from a variety of mammals, birds, and even fish. However, PyV are strictly species specific; thus human PyV only infect humans.

PyV EPIDEMIOLOGY

Almost 90% of adults have been infected with BK PyV by their third decade; only 20% of children are seropositive for BK PyV by age 3,

climbing to 80% by age 7. Approximately 50–70% of adults are seropositive for JC PyV, and children show even lower seroprevalence rates, with less than 30% positive by age 7. Both BK PyV and JC PyV are primarily respiratory tract infections with subsequent spread to the kidneys and the central nervous system (CNS), respectively. **Tropism** for BK PyV has been demonstrated to be the bladder urothelium and renal tubular cells, where lifelong latency is likely established. In contrast, the primary tropism for JC PyV includes the CNS and lymphoid and renal tissue. MC PyV is found and shed from skin, although little is known about its acquisition.

BK PyV

BK PyV was first detected in the urine from a renal allograft recipient suffering from ureteral stenosis with the initials "BK." In the immunocompetent host, BK PyV may never result in any observable clinical disease. However, in the immunocompromised, BK PyV reactivation can lead to serious consequences. Immune suppression can either be iatrogenic after transplantation or constitutional, such as with inherited immune-deficiency syndromes. In renal transplant recipients, interstitial nephritis, renal dysfunction, and ultimately graft failure can develop. In **hematopoietic stem cell transplant** (HSCT) recipients, reactivation can lead to hemorrhagic cystitis. Although the incidence of such symptomatic complications is rare, **BK PyV must be proactively managed through careful monitoring and alteration of immunosuppressive regimens**.

Although the most common complication after pediatric kidney transplantation continues to be graft failure caused by chronic rejection, infections of the transplanted organ can also promote graft dysfunction. Common infectious complications placing pediatric recipients at risk for graft failure include EBV, CMV, BK PyV, and JC PyV. Fortunately, with current monitoring and interventions, the incidence of pediatric transplants that will fail as a result of nephropathy correlating with BK PyV infection is very low.

Nearly two thirds of pediatric renal transplant recipients show evidence of BK **viruria** (virus in the urine), with one fifth showing **viremia** (virus in the blood). **BK virus–associated nephropathy (BKVAN)** can **initially manifest as rising creatinine and is diagnosed definitively through core renal biopsies**. However, because the nephropathy can be focal, a single unaffected core specimen does not exclude disease. In the core biopsy, **BKVAN is characterized by tubular injury with cellular enlargement, epithelial necrosis, erosion of tubular basement membranes, and intranuclear inclusion bodies in epithelial cells**. If untreated, tubular necrosis and sclerosing allograft nephropathy can lead to irreversible renal impairment and rejection. Importantly, reduction of immunosuppression in viremic patients has been highly effective in limiting rejection caused by BKVAN. Rates of BKVAN in the pediatric population have been estimated at around 5%, and approximately 0.5% of renal transplant recipients will lose their graft because of BKVAN.

Laboratory evidence of BK PyV infection is best achieved through a **microscopic urine examination, followed by molecular (polymerase chain reaction [PCR]–based) quantitative analysis of urine and plasma** (Table 321.1). Depending on the method and analyte, a wide range of sensitivity and specificity has been reported. **Detection of "haufen,"** which are viral aggregates that can be detected only by electron microscopy, is nearly 100% sensitive and specific but requires special equipment. An alternative diagnostic approach includes microscopic examination for the **presence of decoy cells** (urothelial cells containing abundant viral particles) in the urine; however, sensitivity is poor, and thus examination for decoy cells is not the preferred screening method. More commonly, **PCR testing for BK genomic DNA from urine and plasma** is employed. Although highly sensitive for BK PyV, the specificity of single-time-point molecular tests for predicting renal nephropathy is low, as asymptomatic individuals can intermittently shed virus without progression to renal disease. Therefore the presence of **isolated BK viruria is not sufficient to diagnose infection** leading to renal impairment.

Accurate quantification of BK PyV in plasma and urine is essential for standardized care across transplant centers with broadly applied thresholds for intervention. The first WHO international standard for BK PyV was made available to enable interassay comparisons in 2016. In 2020, the first molecular platform to obtain FDA clearance for quantitative BK PyV testing included plasma and urine for monitoring renal transplant recipients based on the use of the WHO standard.

No single guideline exists for routine monitoring for BKVAN in either pediatric or adult populations, and thus transplant centers need to design strategies that best fit their local prevalence rates. One proposed guideline suggests **urine screening monthly in the first months after transplant, then every 3 months for 2 years, and then annually in years 3, 4, and 5. If viruria exceeds 1×10^7 copies/mL, then biopsy should be performed with a concomitant reduction in immunosuppression.** In addition, plasma levels exceeding 1×10^4 copies/mL should also prompt a biopsy and reduction in immunosuppression. Centers may include routine renal biopsies to monitor for overall graft health, and these may also be used to evaluate for BKVAN.

Although **there are no direct antiviral treatments for BK PyV**, the primary clinical parameter shown to have the greatest effect on preventing long-term kidney damage and rejection is **careful adjustment of the dose of immunosuppression**. This adjustment allows the body's natural immunity, specifically the T-cell compartment, to effectively reduce the viral burden. However, decreasing immunosuppression comes at a risk of graft rejection if not cautiously approached. A growing body of literature is beginning to emerge that reevaluates the anecdotal successes of specific treatments, including **cidofovir** (CDV) and **leflunomide**. These two drugs have shown efficacy in culture conditions, yet clinical utility remains unproven. The antibiotic class of fluoroquinolones has also demonstrated in vitro activity without a subsequent sustained clinical effect. Finally, both intravenous **immunoglobulin** (IVIG) and **cyclosporine A** have shown equally limited effects in clinical trials. In summary, **the current treatment options rely heavily on early and accurate detection of infection followed by an appropriately titered dose reduction in immunosuppressive drugs**.

In pediatric HSCT recipients, a common association between BK PyV shedding and hemorrhagic cystitis (HC) has been clinically observed. HC can occur in one fifth to one third of pediatric patients after HSCT; however, it rarely results in death. Unfortunately, the long-term sequelae of fibrosis and bladder contracture can lead to significant morbidity. After HSCT, either **early-onset (within 1 week) or late-onset (2-8 weeks) HC** may occur, with the timing providing insight into the pathogenic process. Early-onset HC appears to be a result of direct urothelial damage from conditioning agents (cyclophosphamide,

Table 321.1 Recommendations for Patients with BK PyV–Associated Nephropathy

	SCREENING	DIAGNOSIS	MONITORING
Cytology	Poor sensitivity	Decoy cells, Haufen	Poor sensitivity
Molecular	Routine BK PyV PCR after renal transplant	BK viremia >10,000 copies/mL	Follow until viral loads trend lower
Pathology	Institution specific for the frequency of kidney biopsy	Kidney allograft biopsy with characteristic changes and positive immunohistochemistry (IHC) demonstrating viral antigen	Institution specific for the frequency of kidney biopsy

busulfan, radiation) before transplant, independent of any infectious process, whereas the more commonly observed late-onset HC occurs around the time of engraftment. Although primarily associated with BK PyV, the differential diagnosis for late-onset HC also includes JC PyV, CMV, and adenovirus. **All causes of HC must be carefully considered for effective clinical management.**

Diagnosis of HC requires a triad of findings: cystitis, gross hematuria, and urine BK PyV loads >7 log10 copies/mL (Table 321.2). Current guidelines do not recommend screening for BK PyV after HSCT, citing a lack of effective prophylactic treatment. However, long-term sequelae of renal impairment greater than 2 years after transplant have been described, and therefore routine monitoring may need to eventually be considered.

The presence of BK PyV in the urine occurs in the majority of HSCT recipients and is therefore neither specific nor predictive of BK PyV-HC. Although not as sensitive, the presence of virus in plasma of >3 log10 copies/mL is seen in two thirds of recipients with BK PyV-HC, and diminution of viremia correlates strongly with resolution of HC.

For individuals with **severe HC, standard treatment includes hyperhydration and diuretics**. **Bladder irrigation may be necessary** to avoid renal damage and clotting. Less severe cases will spontaneously resolve in a few weeks. Unlike with renal transplantation, reduction of immunosuppression carries a large risk for potentially life-threatening **graft-versus-host disease (GVHD)** and so is not considered to be the initial treatment approach. Additionally, if thrombocytopenia and anemia are present**, appropriate transfusions should be initiated to maintain adequate blood counts**. The role of CDV in treating or preventing HC in the context of HSCT remains controversial, and thus professional society guidelines currently do not recommend its routine use.

JC PyV

JC PyV was first detected in the brain of a patient with Hodgkin lymphoma with the initials "JC." JC PyV can be acquired by the respiratory route and through ingestion from contaminated surfaces, food, and water and ultimately establishes latency in the kidneys, brain, and various lymphoid organs. In renal transplant recipients, JC PyV can be shed in the urine but only rarely causes nephropathy. After HSCT, HC from BK PyV is far more likely than from JC PyV. Conversely, only JC PyV infects the oligodendrocytes of the CNS and is responsible for **progressive multifocal leukoencephalopathy (PML)**. PML is a fatal demyelinating disease that results from the lysis of specific glial cells in afflicted immunocompromised individuals. In patients with hematologic malignancy, autoimmune disorders, or HIV infection leading to decreased cellular immunity, JC PyV reactivation can lead to PML. In immunocompetent adults, PML is a feared consequence of monoclonal antibody treatments for multiple sclerosis. However, the literature for JC PyV infection in the pediatric population is sparse, with the majority of studies provided as case reports. As a result, many of the clinical guidelines for screening, diagnosis, and therapy must be extended from the adult literature.

The more common clinical manifestations of PML in children are similar to what has been observed in adults and includes hemiparesis, ataxia, dysarthria, and seizures. Evaluation for PML is primarily through radiologic imaging, with primary findings consistent with characteristic asymmetric white matter lesions. The diagnosis of PML is established through molecular detection of viral DNA in the cerebrospinal fluid (CSF) or viral proteins on a brain biopsy (Table 321.3). Unlike with BK PyV, there are no quantitative thresholds because any amount of virus in the CSF is considered abnormal. Although the sensitivity for detection in pediatric cases is under 60%, the specificity is near 100%; therefore a positive PCR result can be considered diagnostic. Remarkably, the CSF cell counts and protein and glucose levels are typically normal. Cases without molecular evidence may still be termed "possible PML" based on neurologic and radiologic findings.

Treatment for PML is primarily through reversing the underlying cause of immune dysfunction. Adults with advanced HIV infection should be treated with antiretroviral therapy (ART), but the efficacy of ART for resolution of PML in children is not well-documented. It is important for the clinician to be aware of a rare but serious complication after HIV suppression promoting a paradoxical increase in JC PyV–mediated damage. This phenomenon has been termed PML-immune reconstitution inflammatory syndrome and can often be treated with steroids. Unfortunately, the prognosis for PML in children is grim, with most patients succumbing to the disease within 6 months. It remains to be seen if absolute viral load or specific radiologic and clinical findings might be used to better predict outcomes in children.

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Table 321.2 Recommendations for Patients with BK PyV–Associated Hemorrhagic Cystitis

	SCREENING	DIAGNOSIS	MONITORING
Clinical	Suspect with anemia, thrombocytopenia, dysuria, or urinary obstruction after HSCT	Cystitis/lower abdominal pain	Follow clinical resolution
Cytology	Gross hematuria	Gross hematuria	No recommendations
Molecular	No recommendations	BK viruria >10,000,000 copies/mL	

Table 321.3 Recommendations for Patients with JCV PyV/Progressive Multifocal Leukoencephalopathy

	SCREENING	DIAGNOSIS	MONITORING
Clinical	Suspect in an immunosuppressed patient with subacute neurologic findings		
Imaging	No recommendations	Characteristic MRI findings	No recommendations
Molecular	No recommendations	Positive CSF PCR for JC PyV	
Pathology	No recommendations	Brain biopsy with characteristic lesions and positive IHC demonstrating viral antigen	

Chapter 322

Human Immunodeficiency Virus and Acquired Immunodeficiency Syndrome

Ericka V. Hayes

Advances in research and major improvements in the treatment and management of HIV infection have brought about a substantial decrease in the incidence of new HIV infections and AIDS in children. Globally, from 2000–2015, there has been an estimated 70% decline in new infections in children age 0-14 years, largely the result of antiretroviral treatment (ART) of HIV-infected pregnant individuals for the prevention of vertical transmission. Of adults and children with HIV infection, 70% live in sub-Saharan Africa, where the disease continues to have a devastating impact (Fig. 322.1). Children experience more rapid disease progression than adults, with up to half of untreated children dying within the first 2 years of life. This rapid progression is correlated with a higher viral burden and faster depletion of infected CD4 lymphocytes in infants and children than in adults. Accurate diagnostic tests and the early initiation of potent drugs to inhibit HIV replication have dramatically increased the ability to prevent progression and control this disease.

ETIOLOGY

HIV-1 and HIV-2 are members of the Retroviridae family and belong to the *Lentivirus* genus, which includes cytopathic viruses causing diverse diseases in several animal species. The HIV-1 genome contains two copies of single-stranded RNA that is 9.2 kb in size. At both ends of the genome there are identical regions, called long terminal repeats, which contain the regulation and expression genes of HIV. The remainder of the genome includes three major sections: the GAG region, which encodes the viral core proteins (p24 [capsid protein: CA], p17 [matrix protein: MA], p9, and p6, which are derived from the precursor p55); the POL region, which encodes the viral enzymes (i.e., reverse transcriptase [p51], protease [p10], and integrase [p32]); and the ENV region, which encodes the viral envelope proteins (gp120 and gp41, which are derived from the precursor gp160). Other regulatory proteins, such as transactivator of transcription (tat: p14), regulator of virion (rev: p19), negative regulatory factor (nef: p27), viral protein r (vpr: p15), viral infectivity factor (vif: p23), viral protein u (vpu in HIV-1: P16), and viral protein x (vpx in HIV-2: P15), are involved in transactivation, viral messenger RNA expression, viral replication, induction of cell cycle arrest, promotion of nuclear import of viral reverse transcription complexes, downregulation of the CD4 receptors and class I major histocompatibility complex (MHC), proviral DNA synthesis, and virus release and infectivity (Fig. 322.2).

The HIV tropism to the target cell is determined by its envelope glycoprotein (Env). Env consists of two components: the surface, heavily glycosylated subunit, gp120 protein and the associated transmembrane subunit glycoprotein gp41. Both gp120 and gp41 are produced from the precursor protein gp160. The glycoprotein gp41 is very immunogenic and is used to detect HIV-1 antibodies in diagnostic assays; gp120 is a complex molecule that includes the highly variable V3 loop. This region is immunodominant for neutralizing antibodies. The heterogeneity of gp120 presents major obstacles in establishing an

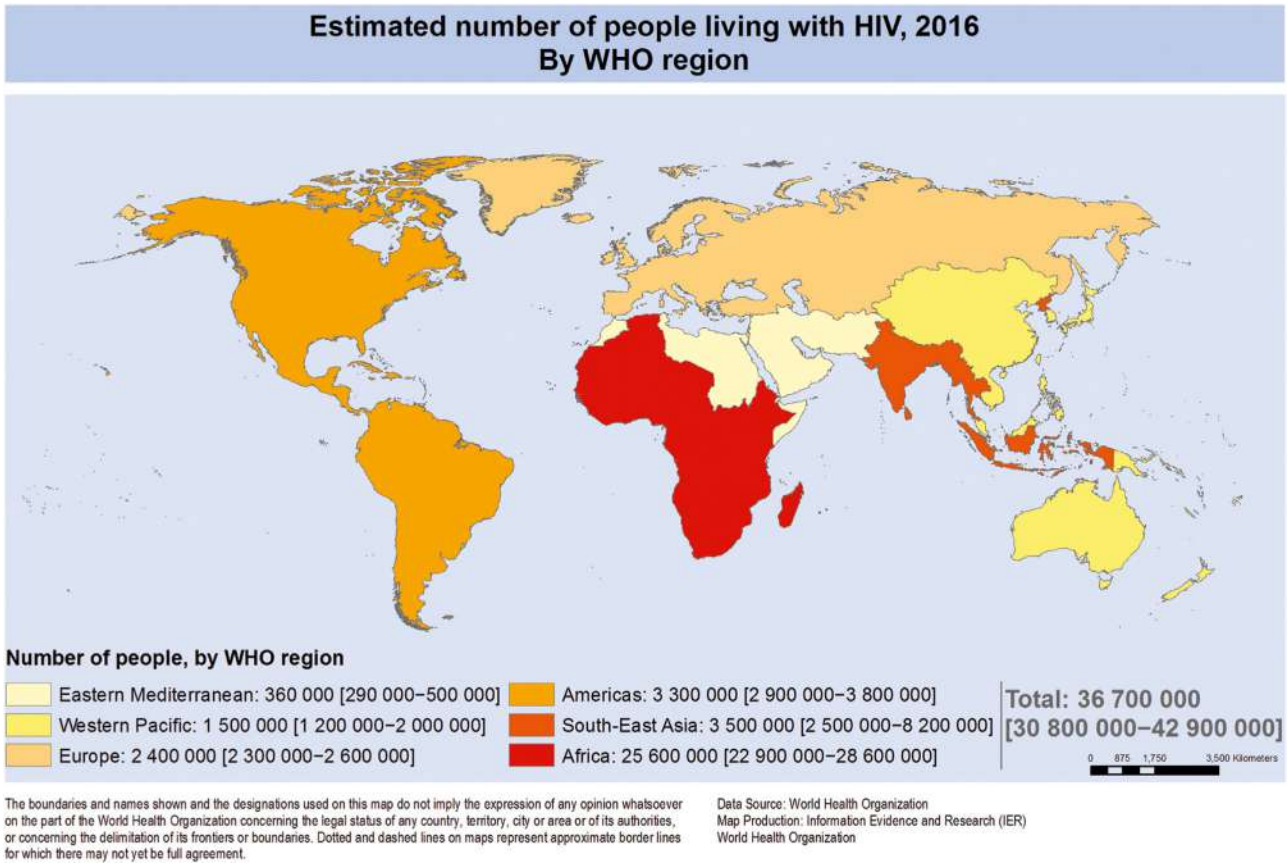

Fig. 322.1 Estimated number of people living with HIV in 2016 by WHO region. Data from WHO 2017 report. *(Courtesy World Health Organization, 2017. Global Health Observatory (GHO) data. http://www.who.int/gho/hiv/epidemic_status/cases_all/en/)*

effective HIV vaccine. The gp120 glycoprotein also carries the binding site for the CD4 molecule, the most common host cell surface receptor of T lymphocytes. This tropism for $CD4^+$ T cells is beneficial to the virus because of the resulting reduction in the effectiveness of the host immune system. Other CD4-bearing cells include macrophages and microglial cells. The observations that $CD4^-$ cells are also infected by HIV and that some $CD4^+$ T cells are resistant to such infections suggests that other cellular attachment sites are needed for the interaction between HIV and human cells. Several chemokines serve as co-receptors for the envelope glycoproteins, permitting membrane fusion and entry into the cell. Most HIV strains have a specific tropism for one of the chemokines, including the fusion-inducing molecule **CXCR-4**, which acts as a co-receptor for HIV attachment to lymphocytes, and **CCR-5**, a β chemokine receptor that facilitates HIV entry into macrophages. Several other chemokine receptors (CCR-3) have also been shown in vitro to serve as virus co-receptors. Other mechanisms of attachment of HIV to cells use nonneutralizing antiviral antibodies and complement receptors. The Fab portion of these antibodies attaches to the virus surface, and the Fc portion binds to cells that express Fc receptors (macrophages, fibroblasts), thus facilitating virus transfer into the cell. Other cell-surface receptors, such as the mannose-binding protein on macrophages or the DC-specific, C-type lectin (DC-SIGN) on dendritic cells, also bind to the HIV-1 envelope glycoprotein and increase the efficiency of viral infectivity. Cell-to-cell transfer of HIV without formation of fully formed particles is a more rapid mechanism of spreading the infection to new cells than is direct infection by the virus.

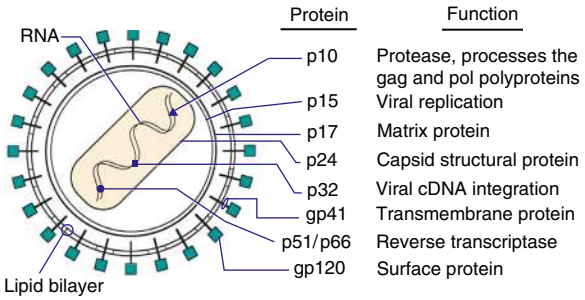

Fig. 322.2 The human immunodeficiency virus and associated proteins and their functions.

After viral attachment, gp120 and the CD4 molecule undergo conformational changes, and gp41 interacts with the fusion receptor on the cell surface (Fig. 322.3). Viral fusion with the cell membrane allows entry of viral RNA into the cell cytoplasm. This process involves accessory viral proteins (nef, vif) and binding of cyclophilin A (a host cellular protein) to the capsid protein (p24). A number of HIV drugs that target the viral fusion/cell entry of the virus have been developed. The p24 protein is involved in virus uncoating, recognition by restriction factors, and nuclear importation and integration of the newly created viral DNA. Viral DNA copies are then transcribed from the virion RNA through viral reverse transcriptase enzyme activity, which builds the first DNA strand from the viral RNA and then destroys the viral RNA and builds a second DNA strand to produce double-stranded circular DNA (see Fig. 322.3). The HIV-1 reverse transcriptase is error prone and lacks error-correcting mechanisms. Thus many mutations arise, creating a wide genetic variation in HIV-1 isolates even within an individual patient. Many of the drugs used to fight HIV infection were designed to block the reverse transcriptase action. The circular DNA is transported into the cell nucleus, using viral accessory proteins such as vpr, where it is integrated (with the help of the virus integrase) into the host chromosomal DNA and referred to as the *provirus* (see Fig. 322.3). Drugs have been developed that block this integration step. The provirus has the advantage of latency, because it can remain dormant for extended periods, making it extremely difficult to eradicate. The infected $CD4^+$ T cells that survive long enough to revert to resting memory state become the HIV latent reservoir where the virus persists

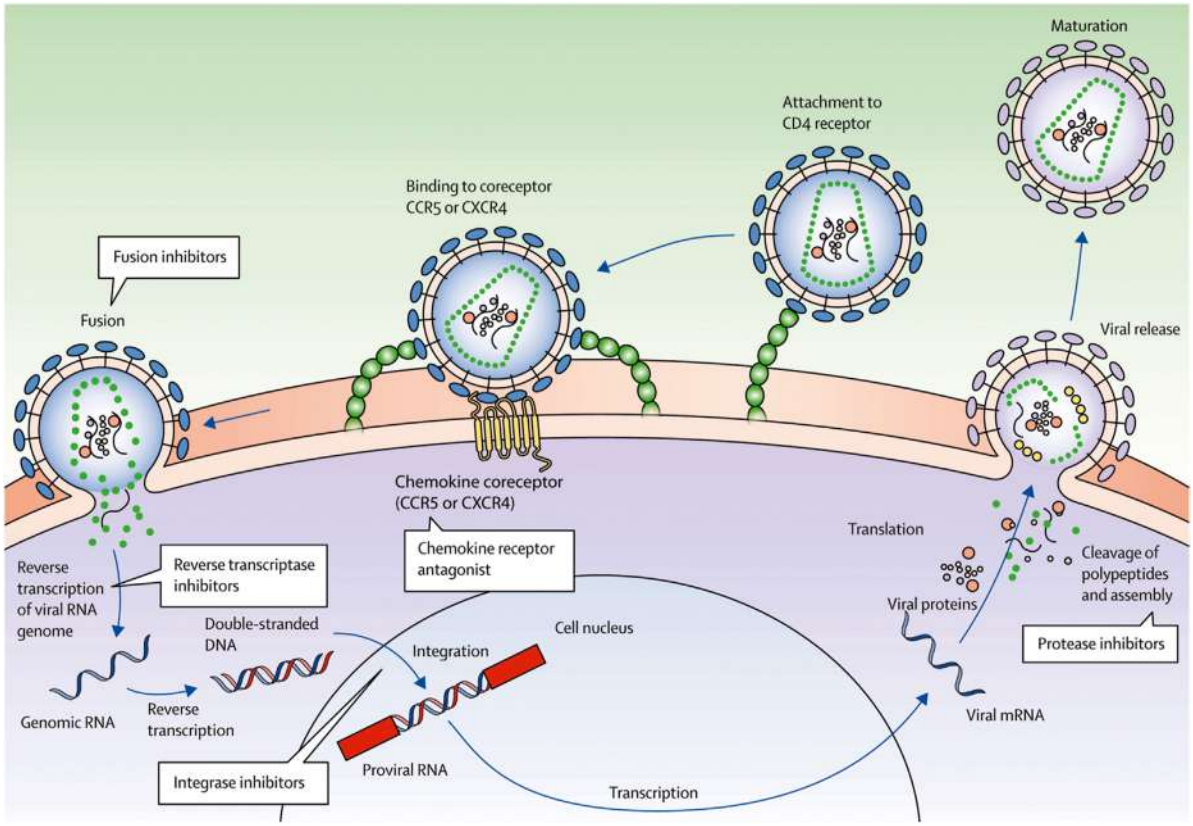

Fig. 322.3 HIV life cycle showing the sites of action and different classes of antiretroviral drugs. *(Adapted from Ralston SH, Penman ID, Strachan MWJ, Hobson R, eds. Davidson's Principles and Practice of Medicine, 23rd ed. London: Elsevier, 2018.)*

indefinitely even in patients who respond favorably to potent ART. The molecular mechanisms of this latency are complex and involve unique biologic properties of the latent provirus (e.g., absence of tat, epigenetic changes inhibiting HIV gene expression) and the nature of the cellular host (e.g., absence of transcription factors such as nuclear factor κB). Integration usually occurs near active genes, which allow a high level of viral production in response to various external factors such as an increase in inflammatory cytokines (by infection with other pathogens) and cellular activation. Depending on the relative expression of the viral regulatory genes (tat, rev, nef), the proviral DNA may encode production of the viral RNA genome, which, in turn, leads to production of viral proteins necessary for viral assembly.

HIV-1 transcription is followed by translation (see Fig. 322.3). A capsid polyprotein is cleaved to produce the virus-specific protease (p10), among other products. This enzyme is critical for HIV-1 assembly because it cleaves the long polyproteins into the proper functional pieces. Several HIV-1 antiprotease drugs have been developed, targeting the increased sensitivity of the viral protease, which differs from the cellular proteases. The regulatory protein vif is active in virus assembly and Gag processing. The RNA genome is then incorporated into the newly formed viral capsid that requires zinc finger domains (p7) and the matrix protein (MA: p17). The matrix protein forms a coat on the inner surface of the viral membrane, which is essential for the budding of the new virus from the host cell's surface. As new virus is formed, it buds through specialized membrane areas, known as lipid rafts, and is released. The virus release is facilitated by the viroporin vpu, which induces rapid degradation of newly synthesized CD4 molecules that impede viral budding. In addition, vpu counteracts host innate immunity (e.g., hampering natural killer T-cell activity).

Full-length sequencing of the HIV-1 genome demonstrated three different groups (M [main], O [outlier], and N [non-M, non-O]), probably occurring from multiple zoonotic infections from primates in different geographic regions. The same technique identified eight groups of HIV-2 isolates. Group M diversified to nine subtypes (or clades A to D, F to H, J, and K). In each region of the world, certain clades predominate, for example, clade A in Central Africa, clade B in the United States and South America, clade C in South Africa, clade E in Thailand, and clade F in Brazil. Although some subtypes were identified within group O, none was found in any of the HIV-2 groups. Clades are mixed in some patients as a result of HIV recombination, and some crossing between groups (i.e., M and O) has been reported.

HIV-2 has a similar life cycle to HIV-1 and is known to cause infection in several monkey species. Subtypes A and B are the major causes of infection in humans, but rarely cause infection in children. HIV-2 differs from HIV-1 in its accessory genes (e.g., it has no *vpu* gene but contains the *vpx* gene, which is not found in HIV-1). It is most prevalent in western Africa, but increasing numbers of cases are reported from Europe and southern Asia. The diagnosis of HIV-2 infection is more difficult because of major differences in the genetic sequences between HIV-1 and HIV-2. Thus several of the standard confirmatory assays (immunoblot), which are HIV-1 specific, may give indeterminate results with HIV-2 infection. If HIV-2 infection is suspected, a combination screening test that detects antibody to HIV-1 and HIV-2 peptides should be used. In addition, the rapid HIV detection tests have been less reliable in patients suspected to be dually infected with HIV-1 and HIV-2, because of lower antibody concentrations against HIV-2. HIV-2 viral loads also have limited availability. Notably, HIV-2 infection demonstrates a longer asymptomatic stage of infection and slower declines of $CD4^+$ T-cell counts and is less efficiently transmitted vertically than HIV-1, likely related to lower levels of viremia with HIV-2.

EPIDEMIOLOGY

In 2022, the World Health Organization (WHO) estimated that 2.6 million children younger than 19 years of age worldwide were living with HIV-1 infection, with 270,000 new infections annually. Nearly 90% of these children 0-9 years of age live in sub-Saharan Africa. From 2010-2022, there has been a 58% reduction in infection in children 0-9 years of age, reflecting steady expansion of services to prevent perinatal transmission of HIV to infants globally. Over the same period there has been a 46% reduction in new cases 10-19 years of age. Notably, there were still 100,000 deaths worldwide of children <19 years of age with HIV in 2020. As of 2022, an estimated 13.9 million children have been orphaned by AIDS (i.e., having at least one parent die from AIDS).

Globally, the vast majority of HIV infections in early childhood are the result of **vertical transmission**. In the United States, approximately 11,700 children, adolescents, or young adults were reported to be living with perinatally acquired HIV infection in 2014. The number of U.S. children with AIDS diagnosed each year increased from 1984–1992 but then declined by more than 95% to <100 cases annually by 2003, largely from the success of prenatal screening and perinatal **combination antiretroviral treatment (cART)** of HIV-infected pregnant individuals and infants. From 2014–2018, there were 507 infants born with perinatally acquired HIV in the United States and Puerto Rico, declining 54% over that interval, with 65 infants being born infected in 2018. As of 2019, the overall rate of perinatally acquired HIV infection in the United States was 0.8 per 100,000 births. Children of racial and ethnic minority groups are overrepresented, particularly non-Hispanic Blacks, who had a rate of 2.9 per 100,000 births in 2019. Race and ethnicity are not risk factors for HIV infection but more likely reflect other social determinants of health that may be predictive of an increased risk for HIV infection, such as lack of educational and economic opportunities as well as decreased access and barriers to healthcare. As of 2017, Florida, Illinois, Texas, Virginia, California, Tennessee, and Maryland are the states with the highest numbers of perinatally acquired cases of HIV in the United States.

Adolescents (13-24 years of age) constitute an important growing population of newly infected individuals; in 2018, 21% of all new HIV infections in the United States occurred in this age-group, with 81% of youth cases occurring in young males who have sex with males (MSM). It is estimated that 50% of HIV-positive youth, the highest rate of any age group, are unaware of their diagnosis. Considering the long latency period between the time of infection and the development of clinical symptoms, reliance on AIDS case definition surveillance data significantly underrepresents the impact of the disease in adolescents. Based on a median incubation period of 8-12 years, it is estimated that 15–20% of all patients with AIDS acquired HIV infection between 13 and 19 years of age.

Risk factors for HIV infection vary by sex in adolescents. Whereas 91–93% of males between the ages of 13 and 24 years with HIV acquire infection through sex with other males, 91–93% of adolescent females with HIV are infected through heterosexual contact. Adolescent racial and ethnic minority populations are overrepresented, especially among females. Another important group are **transgender** individuals. Transgender women in the United States have 49 times the odds of contracting HIV compared to the general population; transgender men have rates that are lower than in transgender women but still significantly higher than the rate in the general population. Transgender individuals unfortunately have many barriers to accessing and receiving appropriate transgender sensitive care and HIV testing and treatment that must be addressed.

Transmission

Transmission of HIV-1 occurs via sexual contact, parenteral exposure to blood, or vertical transmission from pregnant individual to child via exposure to vaginal secretions during birth or via breast milk. The primary route of infection in the pediatric population (<15 years) is vertical transmission. Rates of vertical transmission of HIV have varied in high- and low-resource countries; the United States and Europe have documented transmission rates in untreated pregnant individuals of 12–30%, whereas transmission rates in Africa and Haiti have been higher (25–52%), likely because of more advanced disease and the presence of co-infections. Perinatal treatment of HIV-infected pregnant persons with antiretroviral drugs has dramatically decreased the transmission rate to <2%.

Vertical transmission of HIV can occur before delivery **(intrauterine)**, during delivery **(intrapartum)**, or after delivery **(postpartum** through **breastfeeding)**. Although intrauterine transmission

has been suggested by identification of HIV by culture or polymerase chain reaction (PCR) in fetal tissue as early as 10 weeks, statistical modeling data suggest that the majority of in utero transmissions likely occur in late gestation, when the vascular integrity of the placenta weakens and microtransfusions across the maternal–fetal circulation occur. It is generally accepted that 20–30% of infected newborns are infected in utero, because this percentage of infants has laboratory evidence of infection (positive viral culture or PCR) within the first week of life. Some studies have found that viral detection soon after birth is also correlated with an early onset of symptoms and rapid progression to AIDS, consistent with more long-standing infection during gestation.

A higher percentage of HIV-infected children acquire the virus intrapartum, evidenced by the fact that 70–80% of infected infants do not demonstrate detectable virus until after 1 week of age. The mechanism of transmission appears to be mucosal exposure to infected blood and cervicovaginal secretions in the birth canal, and intrauterine contractions during active labor/delivery may also increase the risk of late microtransfusions. Breastfeeding is the least-common route of vertical transmission in resource-rich nations but is responsible for as much as 40% of perinatal infections in resource-limited countries. The risk of an infant acquiring HIV through breastfeeding is 15–20% over 2 years without parental cART or infant prophylaxis. Both free and cell-associated viruses have been detected in breast milk from HIV-infected individuals. The risk for transmission through breastfeeding for individuals not on suppressive cART is approximately 9–16% in individuals with established infection but is 29–53% in those who acquire HIV postnatally, suggesting that the viremia experienced by the breastfeeding individual during primary infection at least triples the risk for transmission. Where replacement feeding is readily available and safe, it is recommended that the parent substitute infant formula for breast milk if they are known to be HIV infected and not on suppressive cART or are at risk for ongoing sexual or parenteral exposure to HIV. However, the WHO recommends that in resource-limited countries where other diseases (diarrhea, pneumonia, malnutrition) substantially contribute to a high infant mortality rate, the benefit of breastfeeding outweighs the risk for HIV transmission, and HIV-infected persons in developing countries should exclusively breastfeed their infants for at least the first 6 months of life, ideally with parent on suppressive cART. Recently, infant feeding recommendations for breastfeeding (or chestfeeding) persons with HIV in resource-rich settings have evolved as well, given that the risk of transmission via breastfeeding from an individual on suppressive cART is very low (<1%) (see "Prevention" for more discussion).

Several risk factors influence the rate of vertical transmission: pregnant parent viral load at delivery, preterm delivery (<34 weeks' gestation), and low antenatal CD4 count. The most important variable is the level of viremia; the odds of transmission may be increased more than twofold for every $\log_{10}$ increase in viral load at delivery. Elective cesarean delivery has been shown to decrease transmission by 87% if used in conjunction with zidovudine therapy in the pregnant individual and infant. However, because these data predated the advent of **cART** (also called **highly active antiretroviral therapy** [**HAART**]), the additional benefit of cesarean section is negligible if the viral load is <1,000 copies/mL. It should be noted that rarely (≤0.1%), transmission may occur with viral loads <50 copies/mL.

Transfusions of infected blood or blood products have historically accounted for 3–6% of all pediatric AIDS cases. The period of highest risk was between 1978 and 1985, before the availability of HIV antibody–screened blood products. Whereas the prevalence of HIV infection in individuals with hemophilia treated before 1985 was as high as 70%, heat treatment of factor VIII concentrate and HIV antibody screening of donors has virtually eliminated HIV transmission in this population. Donor screening has dramatically reduced, but not eliminated, the risk for blood transfusion–associated HIV infection: nucleic acid amplification testing of minipools (pools of 16-24 donations) performed on antibody-nonreactive blood donations (to identify donations made during the window period before seroconversion) reduced the residual risk of transfusion-transmitted HIV-1 to approximately 1 in 2 million blood units. However, in many resource-limited countries, screening of blood is not uniform, and the risk for transmitting HIV infection via transfusion remains in these settings.

Although HIV can be isolated rarely from saliva, it is in very low titers (<1 infectious particle/mL) and saliva has not been implicated as a transmission vehicle. Studies of hundreds of household contacts of HIV-infected individuals have found that the risk for household HIV transmission is essentially nonexistent. Only a few cases have been reported in which urine or feces (possibly devoid of visible blood) have been proposed as a possible vehicle of HIV transmission, though these cases have not been fully verified.

In the pediatric population, sexual transmission is infrequent, but a small number of cases resulting from sexual abuse have been reported. Sexual contact is the major route of transmission in the adolescent population (≥13 years), accounting for the vast majority of cases. Infection via shared needles with IV drug use is seen in this population, but much less frequently.

PATHOGENESIS

HIV infection affects most of the immune system and disrupts its homeostasis (see Fig. 322.3). In most cases, the initial infection is caused by low amounts of a single founder virus. Therefore disease may be prevented by drug prophylaxis or vaccine. When the mucosa serves as the portal of entry for HIV, the first cells to be affected are the dendritic cells. These cells collect and process antigens introduced from the periphery and transport them to the lymphoid tissue. HIV does not infect the dendritic cell but binds to its DC-SIGN surface molecule, allowing the virus to survive until it reaches the lymphatic tissue. In the lymphatic tissue (e.g., lamina propria, lymph nodes), the virus selectively binds to cells expressing CD4 molecules on their surface, primarily helper T lymphocytes ($CD4^+$ T cells) and cells of the monocyte-macrophage lineage. Other cells bearing CD4, such as microglia, astrocytes, oligodendroglia, and placental tissue containing villous Hofbauer cells, may also be infected by HIV. Additional factors (co-receptors) are necessary for HIV fusion and entry into cells. These factors include the chemokines **CXCR-4** (fusion) and **CCR-5**. Other chemokines (CCR1, CCR3) may be necessary for the fusion of certain HIV strains. Several host genetic determinants affect the susceptibility to HIV infection, the progression of disease, and the response to treatment. These genetic variants vary in different populations. A deletion in the **CCR-5** gene that is protective against HIV infection (CCR-5Δ32) is relatively common in individuals of European descent but is rare in individuals of African descent. Several other genes that regulate chemokine receptors, ligands, the MHC, and cytokines also influence the outcome of HIV infection. Usually, $CD4^+$ lymphocytes migrate to the lymphatic tissue in response to viral antigens and then become activated and proliferate, making them highly susceptible to HIV infection. This antigen-driven migration and accumulation of CD4 cells within the lymphoid tissue may contribute to the generalized lymphadenopathy characteristic of acute HIV infection in adults and adolescents. HIV preferentially infects the very cells that respond to it (HIV-specific memory CD4 cells), accounting for the progressive loss of these cells and the subsequent loss of control of HIV replication. The continued destruction of memory $CD4^+$ cells in the gastrointestinal tract (in the gut-associated lymphoid tissue or GALT) leads to reduced integrity of the gastrointestinal epithelium followed by leakage of bacterial particles into the blood and increased inflammatory response, which cause further $CD4^+$ cell loss. When HIV replication reaches a threshold (usually within 3-6 weeks from the time of infection), a burst of plasma viremia occurs. This intense viremia causes **acute HIV infection**, formerly known as **acute retroviral syndrome** which can present similar to **influenza or mononucleosis** (fever, rash, pharyngitis, lymphadenopathy, malaise, arthralgia, fatigue, cytopenias, elevated liver enzymes) in 50–70% of infected adolescents and adults; this syndrome is not typically seen in infants. With establishment of a cellular and humoral immune response within 2-4 months, the viral load in the blood declines substantially, and patients enter a phase characterized by a lack of symptoms and a return of CD4 cells to only moderately decreased levels. Typically, adult patients who are not treated eventually progress to achieve a virologic set point (steady state), usually ranging from 10,000-100,000 during this clinical latency.

This is in contrast to untreated infants with vertically acquired HIV who have viral loads that are much higher, resulting in faster CD4 count declines and earlier onset of significant immunodeficiency. HIV rapidly responds to the immune system pressure by developing a genetically complex population (quasi-species) that successfully evades the immune system. In addition, inappropriate use of ART increases the ability of the virus to diverge even further by selecting for mutants with fitness or resistance advantages in the presence of subtherapeutic drug levels. Early HIV-1 replication in children has no apparent clinical manifestations. Whether tested by virus isolation or by PCR for viral nucleic acid sequences, fewer than 40% of HIV-1–infected infants demonstrate evidence of the virus at birth. The viral load increases by 1-4 months, and essentially all perinatally HIV-infected infants have detectable HIV-1 in peripheral blood by 4 months of age, except for those who may acquire infection via ongoing breastfeeding.

In adults, the long period of clinical latency (typically 8-12 years) is not indicative of viral latency. In fact, there is a very high turnover of virus and CD4 lymphocytes (more than a billion cells per day), gradually causing deterioration of the immune system, marked by depletion of CD4 cells. Several mechanisms for the depletion of CD4 cells in adults and children have been proposed, including HIV-mediated single cell killing, formation of multinucleated giant cells of infected and uninfected CD4 cells (syncytia formation), virus-specific immune responses (natural killer cells, antibody-dependent cellular cytotoxicity), superantigen-mediated activation of T cells (rendering them more susceptible to infection with HIV), autoimmunity, and programmed cell death (apoptosis). The viral burden is greater in the lymphoid organs than in the peripheral blood during the asymptomatic period. As the virions and their immune complexes migrate through the lymph nodes, they are trapped in the network of dendritic follicular cells. Because the ability of HIV to replicate in T cells depends on the state of activation of the cells, the immune activation that takes place within the microenvironment of the lymph nodes in HIV disease serves to promote infection of new CD4 cells, as well as subsequent viral replication within these cells. Monocytes and macrophages can be productively infected by HIV yet resist the cytopathic effect of the virus and, with their long lifespan, explain their role as reservoirs of HIV and as effectors of tissue damage in organs such as the brain. In addition, they reside in anatomic viral sanctuaries where current treatment agents are less effective.

The innate immune system responds almost immediately after HIV-1 infection by recognizing the viral nucleic acids, once the virus fuses to the infected cell, by the toll-like receptor 7. This engagement leads to activation of pro-inflammatory cytokines and interferon (IFN-α), which blocks virus replication and spread. The virus uses its Nef protein to downregulate the expression of MHC and non-MHC ligands to reduce the natural killer (NK) cell–mediated anti-HIV activity. It also modulates NK cell differentiation and maturation, dysregulates cytokine production, and increases apoptosis. Although the mechanism by which the innate system triggers the adaptive immune responses is not yet fully understood, cell-mediated and humoral responses occur early in the infection. CD8 T cells play an important role in containing the infection. These cells produce various ligands (macrophage inflammatory proteins 1α and 1β, RANTES), which suppress HIV replication by blocking the binding of the virus to the co-receptors (CCR-5). HIV-specific cytotoxic T lymphocytes (CTLs) develop against both the structural (ENV, POL, GAG) and regulatory (tat) viral proteins. The CTLs appear at the end of the acute infection, as viral replication is controlled by killing HIV-infected cells before new viruses are produced and by secreting potent antiviral factors that compete with the virus for its receptors (CCR-5). Neutralizing antibodies appear later in the infection and seem to help in the continued suppression of viral replication during clinical latency. There are at least two possible mechanisms that control the steady-state viral load level during the chronic clinical latency. One mechanism may be the limited availability of activated CD4 cells, which prevent a further increase in the viral load. The other mechanism is the development of an active immune response, which is influenced by the amount of viral antigen and limits viral replication at a steady state. There is no general consensus about which of these two mechanisms is more important. The CD4 cell limitation mechanism accounts for the effect of ART, whereas the immune response mechanism emphasizes the importance of immune modulation treatment (cytokines, vaccines) to increase the efficiency of immune-mediated control. A group of cytokines that includes tumor necrosis factor-α (TNF-α), TNF-β, interleukin-1 (IL-1), IL-2, IL-3, IL-6, IL-8, IL-12, IL-15, granulocyte-macrophage colony-stimulating factor, and macrophage colony-stimulating factor plays an integral role in upregulating HIV expression from a state of quiescent infection to active viral replication. Other cytokines such as IFN-γ, IFN-β, and IL-13 exert a suppressive effect on HIV replication. Certain cytokines (IL-4, IL-10, IFN-γ, transforming growth factor-β) reduce or enhance viral replication depending on the infected cell type. The interactions among these cytokines influence the concentration of viral particles in the tissues. Plasma concentrations of cytokines need not be elevated for them to exert their effect, because they are produced and act locally in the tissues. The activation of virtually all the cellular components of the immune system (i.e., T and B cells, NK cells, and monocytes) plays a significant role in the pathologic aspects of HIV infection. Further understanding of their interactions during the infection will expand our treatment options. Commonly, HIV isolated during the clinical latency period grows slowly in culture and produces low titers of reverse transcriptase. These isolates from earlier in clinical latency use CCR-5 as their co-receptor. By the late stages of clinical latency, the isolated virus is phenotypically different. It grows rapidly and to high titers in culture and uses CXCR-4 as its co-receptor. The switch from CCR-5 receptor to CXCR-4 receptor increases the capacity of the virus to replicate, to infect a broader range of target cells (CXCR-4 is more widely expressed on resting and activated immune cells), and to kill T cells more rapidly and efficiently. As a result, the clinical latency phase is over and progression toward AIDS is noted. The **progression of disease** is related temporally to the gradual disruption of lymph node architecture and degeneration of the follicular dendritic cell network with loss of its ability to trap HIV particles. The virus is freed to recirculate, producing high levels of viremia and an increased disappearance of CD4 T cells during the later stages of disease.

The clinical course of HIV infection shows substantial heterogeneity. This variation is determined by both viral and host factors. HIV viruses that use co-receptor CXCR-4 in the course of the infection are associated with an accelerated deterioration of the immune system and more rapid progression to AIDS. In addition, several known host genetic determinants (e.g., variants in the human leukocyte antigen region, polymorphisms in the CCR-5 region such as CCR-5Δ32) affect disease course. There are likely additional host and viral factors yet to be identified that contribute to the variable course of HIV infection in individuals, as well. **Three distinct patterns of disease** are described in children. Approximately 15–25% of HIV-infected newborns in high resource settings present with a **rapid progression** course, with onset of AIDS and symptoms during the first few months of life and a median survival time of 6-9 months if untreated. In resource-limited settings, the majority of HIV-infected newborns will have this rapidly progressing disease course. It has been suggested that if intrauterine infection coincides with the period of rapid expansion of CD4 cells in the fetus, the virus could effectively infect the majority of the body's immunocompetent cells. The normal migration of these cells to the marrow, spleen, and thymus would result in efficient systemic delivery of HIV, unchecked by the immature immune system of the fetus. Thus infection would be established before the normal ontogenic development of the immune system, causing more-severe impairment of immunity. Most children in this group have detectable virus in the plasma (median level: 11,000 copies/mL) in the first 48 hours of life. This early evidence of viral presence suggests that the newborn was infected in utero. The viral load rapidly increases, peaking by 2-3 months of age (median: 750,000 copies/mL) and staying high for at least the first 2 years of life.

Sixty percent to 80% of perinatally infected newborns in high-resource settings present with a **slower progression** of disease, with a median survival time of 6 years representing the second pattern of disease. Many patients in this group have a negative PCR result in the first week of life and are therefore considered to be infected intrapartum. In a typical patient, the viral load rapidly increases, peaking by 2-3 months of age (median: 100,000 copies/mL) and then slowly declines

Table 322.1 HIV Infection Stage* Based on Age-Specific CD4⁺ T-Lymphocyte Count or CD4⁺ T-Lymphocyte Percentage of Total Lymphocytes

	AGE ON DATE OF CD4⁺ T-LYMPHOCYTE TEST					
	<1 Yr		1-5 Yr		≥6 Yr	
STAGE	CELLS/μL	%	CELLS/μL	%	CELLS/μL	%
1	≥1,500	≥34	≥1,000	≥30	≥500	≥26
2	750-1,499	26-33	500-999	22-29	200-499	14-25
3	<750	<26	<500	<22	<200	<14

*Stage is based primarily on the CD4⁺ T-lymphocyte count. The CD4⁺ T-lymphocyte count takes precedence over the CD4⁺ T-lymphocyte percentage, and the percentage is considered only if the count is missing.

From Centers for Disease Control and Prevention. Revised surveillance case definition for HIV infection—United States, 2014. *MMWR Morb Mortal Wkly Rep.* 2014;63(No RR-3):1–10.

over a period of 24 months. The slow decline in viral load is in sharp contrast to the rapid decline after primary infection seen in adults. This observation can be explained only partially by the immaturity of the immune system in newborns and infants.

The third pattern of disease occurs in <5% of perinatally infected children, referred to as **long-term survivors** or **long-term nonprogressors**, who have minimal or no progression of disease with relatively normal CD4 counts and very low viral loads for longer than 8 years. Mechanisms for the delay in disease progression include effective humoral immunity and/or CTL responses, host genetic factors (e.g., human leukocyte antigen profile), and infection with an attenuated (defective-gene) virus. A subgroup of the long-term survivors called elite survivors or elite suppressors has no detectable virus in the blood and may reflect different or greater mechanisms of protection from disease progression. Note that both groups warrant long-term close follow-up because later in their course they may begin to progress with their disease.

HIV-infected children have changes in the immune system that are similar to those in HIV-infected adults. Absolute CD4 cell depletion may be less dramatic because infants normally have a relative lymphocytosis. A value of 750 CD4 cells/μL in children younger than 1 year of age is indicative of severe CD4 depletion and is comparable to <200 CD4 cells/μL in adults. Lymphopenia is relatively rare in perinatally infected children and is usually only seen in older children or those with end-stage disease. Although cutaneous anergy is common during HIV infection, it is also frequent in healthy children younger than 1 year of age, and thus its interpretation is difficult in infected infants. The depletion of CD4 cells also decreases the response to soluble antigens such as in vitro mitogens phytohemagglutinin and concanavalin A.

Polyclonal activation of B cells occurs in most children early in the infection, as evidenced by elevation of immunoglobulins IgA, IgM, IgE, and, particularly, IgG **(hypergammaglobulinemia)**, with high levels of anti–HIV-1 antibody. This response may reflect both dysregulation of the T-cell suppression of B-cell antibody synthesis and active CD4 enhancement of the B-lymphocyte humoral response. As a result, the antibody response to routine childhood vaccinations may be abnormal. The B-cell dysregulation precedes the CD4 depletion in many children and may serve as a surrogate marker of HIV infection in symptomatic children in whom specific diagnostic tests (PCR, culture) are not available or are too expensive. Despite the increased levels of immunoglobulins, some children lack specific antibodies or protective antibodies. Hypogammaglobulinemia is very rare (<1%).

Central nervous system (CNS) involvement is more common in pediatric patients than in adults. Macrophages and microglia play an important role in HIV neuropathogenesis, and data show that astrocytes may also be involved. Although the specific mechanisms for encephalopathy in children are not yet clear, the developing brain in young infants is affected by at least two mechanisms. The virus itself may directly infect various brain cells or cause indirect damage to the nervous system by the release of cytokines (IL-1α, IL-1β, TNF-α, IL-2) or reactive oxygen damage from HIV-infected lymphocytes or macrophages.

CLINICAL MANIFESTATIONS

The clinical manifestations of HIV infection vary widely among infants, children, and adolescents. In most infants, physical examination at birth is normal. Initial symptoms may be subtle, such as lymphadenopathy and hepatosplenomegaly, or nonspecific, such as failure to thrive, chronic or recurrent diarrhea, respiratory symptoms, or oral thrush, and may be distinguishable only by their persistence. Whereas systemic and pulmonary findings are common in the United States and Europe, chronic diarrhea, pneumonia, wasting, and severe malnutrition predominate in Africa. Clinical manifestations found more commonly in children than adults with HIV infection include recurrent bacterial infections, chronic parotid swelling, lymphocytic interstitial pneumonitis (LIP), and early onset of progressive neurologic deterioration; note that chronic parotid swelling and LIP are associated with a slower progression of disease.

The Centers for Disease Control and Prevention (CDC) Surveillance Case Definition for HIV infection is based on the age-specific CD4⁺ T-lymphocyte count or the CD4⁺ T-lymphocyte percentage of total lymphocytes (Table 322.1), except when a stage 3–defining opportunistic illness (Table 322.2) supersedes the CD4 data. Age adjustment of the absolute CD4 count is necessary because counts that are relatively high in normal infants decline steadily until age 6 years, when they reach adult norms. The CD4 count takes precedence over the CD4 T-lymphocyte percentage, and the percentage is considered only if the count is unavailable.

Infections

Approximately 20% of AIDS-defining illnesses in children are recurrent bacterial infections caused primarily by encapsulated organisms such as *Streptococcus pneumoniae* and *Salmonella* as a result of disturbances in humoral immunity. Other pathogens, including *Staphylococcus*, *Enterococcus*, *Pseudomonas aeruginosa*, and *Haemophilus influenzae*, and other gram-positive and gram-negative organisms may also be seen. The most common serious infections in HIV-infected children are bacteremia, sepsis, and bacterial pneumonia, accounting for more than 50% of infections in these patients. Meningitis, urinary tract infections, deep-seated abscesses, and bone/joint infections occur less frequently. Milder recurrent infections, such as otitis media, sinusitis, and skin and soft tissue infections, are very common and may be chronic with atypical presentations.

Opportunistic infections are generally seen in children with severe depression of the CD4 count. In adults, these infections often represent reactivation of a latent infection acquired early in life. In contrast, young children generally have primary infection and often have a more fulminant course of disease reflecting the lack of prior immunity. In addition, infants <1 year of age have a higher incidence of developing stage 3–defining opportunistic infections and mortality rates compared with older children and adults even at higher CD4 counts, reflecting that the CD4 count may overpredict the immune competence in young infants. This principle is best illustrated by ***Pneumocystis jirovecii* pneumonia** (formerly *Pneumocystis carinii*), the most common opportunistic infection in the pediatric population (see Chapter 290). The peak incidence of *Pneumocystis* pneumonia occurs at age 3-6

Table 322.2 Stage 3–Defining Opportunistic Illnesses in HIV Infection

- Bacterial infections, multiple or recurrent*
- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of esophagus
- Cervical cancer, invasive†
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 mo duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 mo
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy attributed to HIV‡
- Herpes simplex: chronic ulcers (>1 mo duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 mo)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 mo duration)
- Kaposi sarcoma
- Lymphoma, Burkitt (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis* of any site, pulmonary,† disseminated, or extrapulmonary
- *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis jiroveci* (previously known as *Pneumocystis carinii*) pneumonia
- Pneumonia, recurrent†
- Progressive multifocal leukoencephalopathy
- *Salmonella* septicemia, recurrent
- Toxoplasmosis of brain, onset at age >1 mo
- Wasting syndrome attributed to HIV‡

*Only among children age <6 yr.
†Only among adults, adolescents, and children age ≥6 yr.
‡Suggested diagnostic criteria for these illnesses, which might be particularly important for HIV encephalopathy and HIV wasting syndrome, are described in the following references: Centers for Disease Control and Prevention. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR Recomm Rep*. 1994;43(No. RR-12); Centers for Disease Control and Prevention. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Recomm Rep*. 1992;41(No. RR-17).
From Centers for Disease Control and Prevention. Revised surveillance case definition for HIV infection—United States, 2014. *MMWR Morb Mortal Wkly Rep*. 2014;63(No RR-3):1–10.

months in the setting of undiagnosed perinatally acquired HIV infection, with the highest mortality rate in children younger than 1 year of age regardless of CD4 count. Aggressive approaches to treatment have improved the outcome substantially. Although the overall incidence of opportunistic infections has markedly declined since the era of combination ART, opportunistic infections still occur in patients with severe immunodepletion as the result of unchecked viral replication, which often accompanies poor ART adherence.

The classic clinical presentation of *Pneumocystis* pneumonia includes an acute onset of fever, tachypnea, dyspnea, and marked hypoxemia; in some children, more indolent development of hypoxemia may precede other clinical or x-ray manifestations. In some cases, fever may be absent or low grade, particularly in more indolent cases. Chest x-ray findings most commonly consist of interstitial infiltrates or diffuse alveolar disease, which rapidly progresses. Chest x-ray in some cases can have very subtle findings and can mimic the radiologic appearance of viral bronchiolitis. Nodular lesions, streaky or lobar infiltrates, or pleural effusions may occasionally be seen. The diagnosis is established by demonstration of *P. jiroveci* with appropriate staining of induced sputum or bronchoalveolar fluid lavage; rarely, an open lung biopsy is necessary. Bronchoalveolar lavage and open lung biopsy have significantly improved sensitivity (75–95%) for *Pneumocystis* testing than induced sputum (20–40%), such that if an induced sputum is negative, it does not exclude the diagnosis. PCR testing on respiratory specimens is also available and is more sensitive than microscopy but also has less specificity; it is also not widely available.

The first-line therapy for *Pneumocystis* pneumonia is trimethoprim-sulfamethoxazole (TMP-SMX) (15-20 mg/kg/day of the TMP component divided every 6 hours intravenously) with adjunctive corticosteroids for moderate to severe disease, usually defined as if the Pao_2 is <70 mm Hg while breathing room air. After improvement, therapy with oral TMP-SMX should continue for a total of 21 days while the corticosteroids are weaned. An alternative therapy for *Pneumocystis* pneumonia includes intravenous administration of pentamidine (4 mg/kg/day). Other regimens such as TMP plus dapsone, clindamycin plus primaquine, or atovaquone are used as alternatives in adults but have not been widely used in children to date.

Nontuberculous mycobacteria (NTM), with *Mycobacterium avium-intracellulare* complex (MAC) being most common, may cause disseminated disease in HIV-infected children who are severely immunosuppressed. The incidence of MAC infection in ART–naïve children >6 years with <100 CD4 cells/μL is estimated to be as high as 10%, but effective cART that results in viral suppression makes MAC infections rare. Disseminated MAC infection is characterized by fever, malaise, weight loss, and night sweats; diarrhea, abdominal pain, and, rarely, intestinal perforation or jaundice (a result of biliary tract obstruction by lymphadenopathy) may also be present. Labs may be notable for significant anemia. The diagnosis is made by the isolation of MAC from blood, bone marrow, or tissue; the isolated presence of MAC in the stool does not confirm a diagnosis of disseminated MAC. Treatment can reduce symptoms and prolong life but is at best only capable of suppressing the infection if severe CD4 depletion persists. Therapy should include at least two drugs: clarithromycin or azithromycin and ethambutol. A third drug (rifabutin, rifampin, ciprofloxacin, levofloxacin, or amikacin) may be added to decrease the emergence of drug-resistant isolates. Careful consideration of possible drug interactions with antiretroviral agents is necessary before initiation of disseminated MAC therapy. Drug susceptibilities should be ascertained, and the treatment regimen should be adjusted accordingly in the event of an inadequate clinical response to therapy. Because of the great potential for toxicity with most of these medications, surveillance for adverse effects should be ongoing. Less commonly, NTM infections, including lymphadenitis, osteomyelitis, tenosynovitis, and pulmonary disease, can also be seen.

Oral candidiasis is the most common **fungal infection** seen in HIV-infected children. Oral nystatin suspension (2-5 mL qid) is often effective. Clotrimazole troches or fluconazole (3-6 mg/kg orally qd) are effective alternatives. Oral thrush progresses to involve the esophagus in as many as 20% of children with severe CD4 depletion, presenting with symptoms such as anorexia, dysphagia, vomiting, and fever. Treatment with oral fluconazole for 7-14 days generally results in rapid improvement in symptoms. Fungemia rarely occurs, usually in the setting of indwelling venous catheters, and up to 50% of cases may be caused by non-*albicans* species. Disseminated histoplasmosis, coccidioidomycosis, and cryptococcosis are rare in pediatric patients but may occur in endemic areas.

Parasitic infections such as intestinal cryptosporidiosis and microsporidiosis and rarely isosporiasis or giardiasis are other opportunistic infections that cause significant morbidity. Although these intestinal infections are usually self-limited in healthy hosts, they cause severe chronic diarrhea in HIV-infected children with low CD4 counts, often leading to malnutrition. Nitazoxanide therapy is partially effective at improving cryptosporidia diarrhea, but immune reconstitution with cART is the most important factor for clearance of the infection. Albendazole has been reported to be effective against most microsporidia (excluding *Enterocytozoon bieneusi* and *Vittaforma corneae*), and TMP-SMX appears to be effective for isosporiasis. Systemic fumagillin can be used to treat *Enterocytozoon* and *Vittaforma*.

Viral infections, especially with the herpesvirus group, pose significant problems for HIV-infected children. HSV causes recurrent gingivostomatitis, which may be complicated by local and distant cutaneous dissemination. Primary varicella-zoster virus infection (chickenpox) may be prolonged and complicated by bacterial superinfections or

visceral dissemination, including pneumonitis. Recurrent, atypical, or chronic episodes of herpes zoster are often debilitating and require prolonged therapy with acyclovir; in rare instances, varicella-zoster virus has developed a resistance to acyclovir, requiring the use of foscarnet. Disseminated cytomegalovirus infection occurs in the setting of severe CD4 depletion (<50 CD4 cells/μL for ≥6 years) and may involve single or multiple organs. Retinitis, pneumonitis, esophagitis, gastritis with pyloric obstruction, hepatitis, colitis, and encephalitis have been reported, but these complications are rarely seen if cART is given. Ganciclovir and foscarnet are the drugs of choice and are often given together in children with sight-threatening cytomegalovirus retinitis. Intraocular injections of foscarnet or intraocular ganciclovir implants plus oral valganciclovir have also been efficacious in adults and older children with cytomegalovirus retinitis. Measles may occur despite immunization and may present without the typical rash. It often disseminates to the lung or brain with a high mortality rate in these patients. HIV-infected children with low CD4 counts can also develop extensive cutaneous molluscum contagiosum infection. Respiratory viruses such as respiratory syncytial virus and adenovirus may present with prolonged symptoms and persistent viral shedding. In parallel with the increased prevalence of genital tract human papillomavirus infection, cervical intraepithelial neoplasia and anal intraepithelial neoplasia also occur with increased frequency among HIV-1–infected adult females compared with HIV-seronegative females. The relative risk for cervical intraepithelial neoplasia is 5-10 times higher for HIV-1 seropositive females. Multiple modalities are used to treat human papillomavirus (HPV) infection (see Chapter 313), although none is uniformly effective and the recurrence rate is high among HIV-1–infected persons. Prevention with appropriate vaccinations in patients whose CD4 counts are above threshold is recommended, including mumps-measles-rubella (MMR), varicella vaccine, and HPV vaccine (see "Supportive Care" section).

Appropriate therapy with antiretroviral agents may result in **immune reconstitution inflammatory syndrome (IRIS)**, which is characterized by an increased inflammatory response from the recovered immune system to subclinical opportunistic infections (e.g., *Mycobacterium* infection, herpes simplex virus (HSV) infection, toxoplasmosis, cytomegalovirus (CMV) infection, *Pneumocystis* infection, cryptococcal infection). This condition is more commonly observed in patients with progressive disease and severe $CD4^+$ T-lymphocyte depletion. Patients with IRIS develop fever and worsening of the clinical manifestations of the opportunistic infection or new manifestations (e.g., enlargement of lymph nodes, pulmonary infiltrates), typically within the first few weeks after initiation of ART. Determining whether the symptoms represent IRIS, worsening of a current infection, a new opportunistic infection, or drug toxicity can be challenging. If the syndrome does represent IRIS, adding nonsteroidal antiinflammatory agents or corticosteroids may alleviate the inflammatory reaction, although the use of corticosteroids is usually reserved for severe cases. The inflammation may take weeks or months to subside. In most cases, continuation of cART while treating the opportunistic infection (with or without antiinflammatory agents) is sufficient. If opportunistic infection is suspected before the initiation of ART, appropriate antimicrobial treatment should be started before starting cART, particularly in the case of cryptococcal meningitis.

Central Nervous System

The incidence of CNS involvement in perinatally infected children is as high as 50–90% in resource-limited settings but significantly lower in resource-rich settings, with a median onset at 19 months of age. Manifestations may range from subtle developmental delay to progressive encephalopathy with loss or plateau of developmental milestones, cognitive deterioration, impaired brain growth resulting in acquired microcephaly, and symmetric motor dysfunction. **Encephalopathy** may be the initial manifestation of the disease or may present much later when severe immune suppression occurs. With progression, marked apathy, spasticity, hyperreflexia, and gait disturbance may occur, as well as loss of language and oral, fine, and/or gross motor skills. The encephalopathy may progress intermittently, with periods of deterioration followed by transiently stable plateaus. Older children may exhibit behavioral problems and learning disabilities. Associated abnormalities identified by neuroimaging techniques include cerebral atrophy in up to 85% of children with neurologic symptoms, increased ventricular size, basal ganglia calcifications, and, less frequently, leukomalacia.

Fortunately, since the advent of cART, the incidence rate of encephalopathy has dramatically declined to as low as 0.08% in 2006. However, as HIV-infected children progress through adolescence and young adulthood, other subtle manifestations of CNS disease are evident, such as cognitive deficits, attention problems, and psychiatric disorders. Living with a chronic, often stigmatizing, disease; parental loss; and the requirement for lifelong pristine medication adherence compounds these issues, making it challenging for these youth as they inherit responsibility for managing their disease as adults.

Focal neurologic signs and seizures are unusual and may imply a comorbid pathologic process such as a CNS tumor, opportunistic infection, or stroke. **CNS lymphoma** may present with new-onset focal neurologic findings, headache, seizures, and mental status changes. Characteristic findings on neuroimaging studies include a hyperdense or isodense mass with variable contrast enhancement or a diffusely infiltrating contrast-enhancing mass. **CNS toxoplasmosis** is exceedingly rare in young infants but may occur in vertically HIV-infected adolescents and is typically associated with serum antitoxoplasma IgG as a marker of infection. Other opportunistic infections of the CNS are rare and include infection with CMV, JC virus **(progressive multifocal leukoencephalopathy)**, HSV, *Cryptococcus neoformans,* and *Coccidioides immitis.* Although the true incidence of cerebrovascular disorders (both hemorrhagic and nonhemorrhagic strokes) is unclear, 6–10% of children from large clinical series have been affected.

Respiratory Tract

Recurrent upper respiratory tract infections such as otitis media and sinusitis are very common. Although the typical pathogens *(S. pneumoniae*, *H. influenzae*, *Moraxella catarrhalis)* are most common, unusual pathogens such as *P. aeruginosa*, yeast, and anaerobes may be present in chronic infections and result in complications such as invasive sinusitis and mastoiditis.

LIP is the most common chronic lower respiratory tract abnormality reported to the CDC for HIV-infected children; historically this occurred in approximately 25% of HIV-infected children, although the incidence has declined in the cART era. LIP is a chronic process with nodular lymphoid hyperplasia in the bronchial and bronchiolar epithelium, often leading to progressive alveolar capillary block over months to years. It has a characteristic chronic diffuse reticulonodular pattern on chest radiography rarely accompanied by hilar lymphadenopathy, allowing a presumptive diagnosis to be made radiographically before the onset of symptoms. There is an insidious onset of tachypnea, cough, and mild to moderate hypoxemia with normal auscultatory findings or minimal rales. Progressive disease presents with symptomatic hypoxemia, which usually resolves with oral corticosteroid therapy, accompanied by digital clubbing. Several studies suggest that LIP is a lymphoproliferative response to a primary Epstein-Barr virus infection in the setting of HIV infection. It is also associated with a slower immunologic decline.

Most symptomatic HIV-infected children experience at least one episode of pneumonia during their disease. *S. pneumoniae* is the most common bacterial pathogen, but *P. aeruginosa* and other gram-negative bacterial pneumonias may occur in end-stage disease and may produce acute respiratory failure and death. Rarely, severe recurrent bacterial pneumonia results in bronchiectasis. *Pneumocystis* pneumonia is the most common opportunistic infection, but other pathogens, including CMV, *Aspergillus*, *Histoplasma*, and *Cryptococcus*, can cause pulmonary disease. Infection with common respiratory viruses, including respiratory syncytial virus, parainfluenza, influenza, and adenovirus, may occur simultaneously and have a protracted course and prolonged period of viral shedding from the respiratory tract. Infection with SARS-CoV-2 may also occur, without clear evidence of increased morbidity relative to children without HIV infection.

Pulmonary and extrapulmonary tuberculosis (TB) has been reported with increasing frequency in HIV-infected children in low-resource countries, although it is considerably more common in HIV-infected adults. Because of drug interactions between rifampin and ritonavir-based ART and poor tolerability of the combination of multiple drugs required, treatment of TB/HIV co-infection is particularly challenging in children.

Cardiovascular System

Cardiac dysfunction, including left ventricular hypertrophy, left ventricular dilation, reduced left ventricular fractional shortening, and/or heart failure occurred in 18–39% of HIV-infected children in the pre-cART era; among those affected, a lower nadir CD4 percentage and a higher viral load were associated with lower cardiac function. However, a more current evaluation of HIV-infected children taking long-term cART found that echocardiographic findings were closer to normal and none had symptomatic heart disease, suggesting that cART has a cardioprotective effect. What is still unclear is whether an increased rate of premature cardiovascular disease that has been seen in adults will be seen in children who have disease- or treatment-related hyperlipidemia, and prospective studies are needed to assess this risk. Because of this risk, regular monitoring of cholesterol and lipids, as well as education regarding a heart-healthy lifestyle and diet, is an important part of pediatric HIV care.

Gastrointestinal and Hepatobiliary Tract

Oral manifestations of HIV disease include erythematous or pseudomembranous candidiasis, periodontal disease (e.g., ulcerative gingivitis or periodontitis), salivary gland disease (i.e., swelling, xerostomia), and, rarely, ulcerations or oral hairy leukoplakia. Gastrointestinal tract involvement is common in HIV-infected children. A variety of pathogens can cause gastrointestinal disease, including bacteria (*Salmonella*, *Campylobacter*, *Shigella*, MAC), protozoa (*Giardia*, *Cryptosporidium*, *Isospora*, microsporidia), viruses (CMV, HSV, rotavirus), and fungi *(Candida)*. MAC and the protozoal infections are most severe and protracted in patients with severe CD4 cell depletion. Infections may be localized or disseminated and affect any part of the gastrointestinal tract from the oropharynx to the rectum. Oral or esophageal ulcerations, either viral in origin or idiopathic, are painful and often interfere with eating. AIDS enteropathy, a syndrome of malabsorption with partial villous atrophy not associated with a specific pathogen, has been postulated to be a result of direct HIV infection of the gut. Disaccharide intolerance is common in HIV-infected children with chronic diarrhea.

The most common symptoms of gastrointestinal disease are chronic or recurrent diarrhea with malabsorption, abdominal pain, dysphagia, and failure to thrive. Prompt recognition of weight loss or poor growth velocity in the absence of diarrhea is critical. Linear growth impairment is often correlated with the level of HIV viremia. Supplemental enteral feedings should be instituted, either by mouth or with nighttime nasogastric tube feedings in cases associated with more severe chronic growth problems; placement of a gastrostomy tube for nutritional supplementation may be necessary in severe cases. The wasting syndrome, defined as a loss of >10% of body weight, is not as common as failure to thrive in pediatric patients, but the resulting malnutrition is associated with a grave prognosis. Chronic liver inflammation evidenced by fluctuating serum levels of transaminases with or without cholestasis is relatively common, often without identification of an etiologic agent. Cryptosporidial cholecystitis is associated with abdominal pain, jaundice, and elevated γ-glutamyltransferase. In some patients, chronic hepatitis caused by CMV, hepatitis B, hepatitis C, or MAC may lead to portal hypertension and liver failure. Several of the antiretroviral drugs or other drugs such as didanosine, protease inhibitors (PIs), nevirapine, and dapsone may also cause reversible elevation of transaminases.

Pancreatitis with increased pancreatic enzymes with or without abdominal pain, vomiting, and fever may be the result of drug therapy (e.g., with pentamidine, didanosine, or stavudine) or, rarely, opportunistic infections such as MAC or CMV.

Renal Disease

Nephropathy is an unusual presenting symptom of HIV infection, more commonly occurring in older symptomatic children. A direct effect of HIV on renal epithelial cells has been suggested as the cause, but immune complexes, hyperviscosity of the blood (secondary to hyperglobulinemia), and nephrotoxic drugs are other possible factors. A wide range of histologic abnormalities has been reported, including focal glomerulosclerosis, mesangial hyperplasia, segmental necrotizing glomerulonephritis, and minimal change disease. Focal glomerulosclerosis generally progresses to renal failure within 6-12 months, but other histologic abnormalities in children may remain stable without significant renal insufficiency for prolonged periods. **Nephrotic syndrome** is the most common manifestation of pediatric renal disease, with edema, hypoalbuminemia, proteinuria, and azotemia with normal blood pressure. Cases resistant to steroid therapy may benefit from cyclosporine therapy. Polyuria, oliguria, and hematuria have also been observed in some patients.

Skin Manifestations

Many cutaneous manifestations seen in HIV-infected children are inflammatory or infectious disorders that are not unique to HIV infection. These disorders tend to be more disseminated and respond less consistently to conventional therapy than in the uninfected child. Seborrheic dermatitis or eczema that is severe and unresponsive to treatment may be an early nonspecific sign of HIV infection. Recurrent or chronic episodes of HSV, herpes zoster, molluscum contagiosum, flat warts, anogenital warts, and candidal infections are common and may be difficult to control.

Allergic drug eruptions are also common, in particular related to nonnucleoside reverse transcriptase inhibitors; they generally respond to withdrawal of the drug but also may resolve spontaneously without drug interruption; rarely, progression to Stevens-Johnson syndrome has been reported. Epidermal hyperkeratosis with dry, scaling skin is frequently observed, and sparse hair or hair loss may be seen in the later stages of the disease.

Hematologic and Malignant Diseases

Anemia occurs in 20–70% of HIV-infected children, more commonly in children with AIDS. The anemia may be a result of chronic infection, poor nutrition, autoimmune factors, virus-associated conditions (hemophagocytic syndrome, parvovirus B19 red cell aplasia), or the adverse effect of drugs (zidovudine).

Leukopenia occurs in almost 30% of untreated HIV-infected children, and neutropenia often occurs. Multiple drugs used for treatment or prophylaxis for opportunistic infections, such as *Pneumocystis* pneumonia (TMP-SMX), MAC, and CMV (ganciclovir), or antiretroviral drugs (zidovudine) may also cause leukopenia and/or neutropenia. In cases in which therapy cannot be changed, treatment with subcutaneous granulocyte colony-stimulating factor may be necessary.

Thrombocytopenia has been reported in 10–20% of patients. The etiology may be immunologic (i.e., circulating immune complexes or antiplatelet antibodies) or, less commonly, from drug toxicity, or idiopathic. cART may also reverse thrombocytopenia in ART-naïve patients. In the event of sustained severe thrombocytopenia (<10,000 platelets/μL), treatment with intravenous immunoglobulin or anti-D immune globulin offers temporary improvement in most patients already taking cART. If ineffective, a course of steroids may be an alternative, but consultation with a hematologist should be sought. Deficiency of clotting factors (factors II, VII, IX) is not rare in children with advanced HIV disease and corrects with vitamin K.

A novel disease of the thymus has been observed in a few HIV-infected children. These patients were found to have characteristic anterior mediastinal multilocular thymic cysts without clinical symptoms. Histologic examination shows focal cystic changes, follicular hyperplasia, and diffuse plasmacytosis and multinucleated giant cells. Treatment with cART may result in resolution, and spontaneous involution occurs in some cases.

Malignant diseases have been reported infrequently in HIV-infected children, representing only 2% of AIDS-defining illnesses. Non-Hodgkin lymphoma (including Burkitt lymphoma), primary CNS lymphoma, and

leiomyosarcoma are the most commonly reported neoplasms among HIV-infected children. Epstein-Barr virus is associated with most lymphomas and with all leiomyosarcomas (see Chapter 301). Kaposi sarcoma, which is caused by human herpesvirus 8, occurs frequently among HIV-infected adults but is exceedingly uncommon among HIV-infected children in resource-rich settings (see Chapter 304).

DIAGNOSIS AND TESTING

All infants born to HIV-infected individuals test antibody-positive at birth because of passive transfer of HIV antibody across the placenta during gestation; therefore antibody should not be used to establish the diagnosis of HIV in an infant. Most uninfected infants without ongoing exposure (i.e., who are not breastfed) lose antibodies against HIV between 6 and 18 months of age and are known as **seroreverters**. Because a small proportion of uninfected infants continue to test HIV antibody-positive for up to 24 months of age, positive IgG antibody tests, including the rapid tests, cannot be used to make a definitive diagnosis of HIV infection in infants younger than 24 months. The presence of IgA or IgM anti-HIV in the infant's circulation can indicate HIV infection, because these immunoglobulin classes do not cross the placenta; however, IgA and IgM anti-HIV assays have been both insensitive and nonspecific and therefore are not valuable for clinical use. In any child older than 24 months of age, demonstration of IgG antibody to HIV by a repeatedly reactive enzyme immunoassay and confirmatory HIV PCR establishes the diagnosis of HIV infection. Certain diseases (e.g., syphilis and autoimmune diseases) may cause false-positive or indeterminate results in antibody testing. In such cases, specific viral diagnostic tests must be done.

Several rapid HIV tests are currently available with sensitivity and specificity better than those of the standard enzyme immunoassay. Many of these tests require only a single step that allows test results to be reported within less than 30 minutes. Performing rapid HIV testing on individuals during delivery or immediately after birth is crucial for the care of HIV-exposed newborns whose birth parent's HIV status was unknown during pregnancy. A positive rapid test must be confirmed by a second different rapid test (testing different HIV-associated antibodies) or by HIV RNA PCR (viral load). Given the earlier detection of fourth-generation HIV enzyme-linked immunosorbent assay (ELISA) testing (p24 antigen + HIV-1, HIV-2 IgG and IgM antibodies), Western blots are not appropriate to confirm testing because the fourth-generation assays can be positive before the Western blot becomes positive (i.e., in acute infection). In acute infection, patients may have only a positive p24 antigen with negative antibodies on confirmatory testing; these patients should have HIV RNA PCR performed to confirm acute infection (or establish that the p24 antigen result was a false positive test). In infants who are at risk of exposure to HIV-2 infection (e.g., born to an HIV-infected person from West Africa or who has a partner with HIV from West Africa), a rapid test that can detect both HIV-1 and HIV-2 should be used. However, if the HIV testing is negative or the Western blot test reveals an unusual pattern, further diagnostic tests should be considered. In addition, they should be tested with an HIV-2–specific DNA PCR assay.

Viral diagnostic assays, such as HIV DNA or RNA PCR, are more useful in young infants, allowing a definitive diagnosis in most infected infants by 1-4 months of age. By 4 months of age, HIV PCR testing identifies all infected nonbreastfed infants. Historically, HIV DNA PCR testing was the preferred virologic assay over HIV RNA PCR testing in high-resource settings for young infants because of what was thought to be a modest advantage in detecting intrapartum acquired infection for DNA PCR in the first month of life. An FDA-approved HIV DNA PCR test is no longer commercially available in the United States, but other assays exist; however, the sensitivity and specificity of noncommercial HIV-1 DNA tests (using individual laboratory reagents) may differ from the sensitivity and specificity of the prior FDA-approved commercial test. HIV RNA PCR is recommended for non-subtype B viruses or group O infections, which are not common in the United States. It should be noted that PCR results can be affected by ART in both the birthing parent and the infant, serving as the rationale for the recommendation for testing 2-6 weeks after completing prophylaxis in high-risk newborns (Fig. 322.4) Almost 40% of infected newborns have positive DNA PCR test results in the first 2 days of life, with >90% testing positive by 2 weeks of age. The commercially available HIV-1 assays are not designed for quantification of HIV-2 RNA and thus should not be used to monitor patients with this infection.

Viral diagnostic testing should be performed within the first 12-24 hours of life for high-risk infants (i.e., those born to individuals without sustained virologic suppression, a late cART start, or a diagnosis with acute or primary HIV during the pregnancy); the tests can identify almost 40% of intrauterine HIV-infected children. Birth testing is optional in low-risk infants. Additional testing should be done at 2-3 weeks of age, 4-8 weeks of age, and 4-6 months of age. For higher-risk infants, additional virologic diagnostic testing should be done at 2 to 6 weeks after cessation of ARV prophylaxis (i.e., at 8-12 weeks of life) (see Fig. 322.4). Breastfed infants should have PCR testing performed per testing schedule based on their risk through 4 months of age; an additional test should be done between the 4- to 8-week test and the 4- to 6-month test if the gap between tests is more than 3 months. Breastfed infants should then be tested every 3 months while breastfeeding continues and then at 4-6 weeks, 3 months, and 6 months after cessation of breastfeeding regardless of age to identify those who may become infected at the end of lactation by the HIV-infected individual (see Fig. 322.4).

A positive virologic assay (i.e., detection of HIV by PCR) suggests HIV infection and should be confirmed by a repeat test on a second specimen as soon as possible because false-positive tests can occur. A confirmed diagnosis of HIV infection can be made with two positive virologic test results obtained from different blood samples. HIV infection can be presumptively excluded in nonbreastfed infants with two or more negative virologic tests (one at age ≥14 days and one at age ≥4 weeks), one negative virologic test (i.e., negative RNA or DNA) at age ≥8 weeks done at least 2 weeks after discontinuation of multidrug

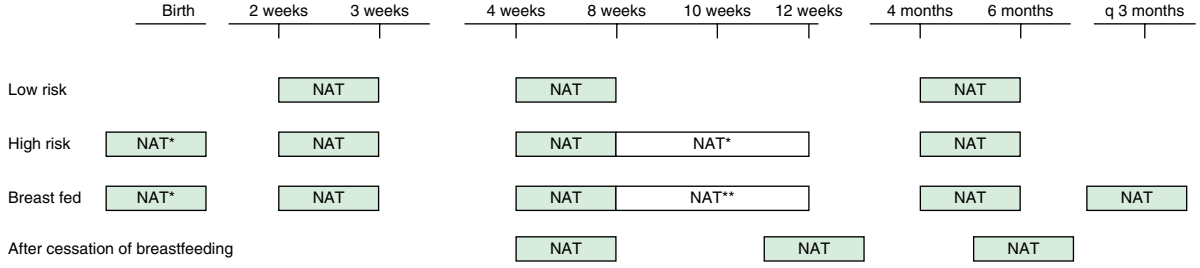

Fig. 322.4 Recommended virologic testing schedules for infants exposed to HIV by perinatal HIV transmission risk and breastfed infants. See Table 322.7 for definitions of low and high risk. *For higher-risk infants, additional virologic diagnostic testing should be done at birth and 2-6 wk after cessation of ARV prophylaxis (i.e., at 8-10 wk of life). **For breastfed infants, an additional virologic test should be performed between the 1- to 2-mo and 4- to 6-mo time points if the gap between tests is >3 mo. NAT, Nucleic acid test. *(Content adapted from Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to Reduce Perinatal HIV Transmission in the United States. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/perinatal-hiv/guidelines-perinatal.pdf)*

empirical therapy or prophylaxis, or one negative HIV antibody test at age ≥6 months. Definitive exclusion of HIV infection in nonbreastfed infants is based on two or more negative virologic tests, with one obtained at age ≥1 month (done 2-6 weeks after the cessation of multidrug empirical therapy or prophylaxis) and one at age ≥4 months, or two negative HIV antibody tests from separate specimens obtained at age ≥6 months. Documentation of seroreversion (loss of antibody) at 12-18 month of age is no longer routinely recommended for nonbreastfed infants meeting definitive exclusion criteria who have had no known or suspected postnatal HIV exposure. Infants <18 months who have postnatal HIV exposure, including new HIV infection of breastfeeding parent, premasticated feedings, sexual abuse, contaminated blood product, or percutaneous exposure, should have HIV PCR-based testing to determine infection status. Children ≥18 months of age with no HIV perinatal exposure history with these postnatal exposures should be tested with HIV antibody/antigen testing. Note that HIV antibody/antigen testing should not be used for diagnosis in the perinatally exposed child until age ≥24 months. Any child or adolescent suspected of HIV infection should be tested with age-appropriate testing with the caveat that if acute infection is suspected, additional HIV PCR testing may be required to establish the diagnosis.

TREATMENT

The currently available therapies do not eradicate the virus and cure the patient; instead they suppress the virus for extended periods and change the course of the disease to a chronic process. It is now recommended that all children be started on cART, regardless of viral load, CD4 count, or clinical status at diagnosis. Treatment should be initiated within 7 days of diagnosis, with counseling and support for adherence. Because cART therapy changes as new drugs become available, decisions regarding therapy should be made in consultation with an expert in pediatric HIV infection. The following principles form the basis for cART:

1. Uninterrupted HIV replication causes destruction of the immune system and progression to AIDS.
2. The magnitude of the viral load predicts the rate of disease progression, and the CD4 cell count reflects the risk of opportunistic infections and HIV infection complications.
3. cART, which includes at least three drugs with at least two different mechanisms of action, should be the initial treatment. Potent combination therapy that suppresses HIV replication to an undetectable level restricts the selection of ART-resistant mutants; drug-resistant strains are the major factor limiting successful viral suppression and delay of disease progression.
4. The goal of sustainable suppression of HIV replication is best achieved by the simultaneous initiation of combinations of antiretroviral drugs to which the patient has not been exposed previously and to which the patient's virus does not have cross resistance.
5. Drug-related interactions and toxicities should be minimized as much as possible.
6. Adherence to the complex drug regimens is crucial for a successful outcome.

Very rarely, treatment may need to be deferred on a case-by-case basis based on clinical or psychosocial factors that may affect adherence with the caregivers and child. In these children, virologic, immunologic, and clinical status should be closely monitored at least every 3-4 months.

Combination Therapy

As of February 2023, 21 individual ART drugs, 22 co-formulated combination tablets, one injectable long-acting combination regimen, as well as two pharmacokinetic boosters were approved by the FDA for use in HIV-infected adults and adolescents. Of the 21 individual drugs, 19 were approved for at least some portion of the pediatric population (0-12 years of age), with many but not all of them available as a liquid, powder, or small tablet/capsule (Table 322.3). ART drugs are categorized by their mechanism of action, such as preventing viral entrance into $CD4^+$ T cells, inhibiting the HIV reverse-transcriptase or protease enzymes, or inhibiting integration of the virus into the human DNA (see Fig. 322.3). Within the reverse-transcriptase inhibitors, a further subdivision can be made: **nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTIs)** and **nonnucleoside reverse transcriptase inhibitors (NNRTIs)** (see Fig. 322.3). The **NRTIs** have a structure similar to that of the building blocks of DNA (e.g., thymidine, cytosine). When incorporated into DNA, they act as chain terminators and block further incorporation of nucleosides, preventing viral DNA synthesis. Among the NRTIs, thymidine analogs (e.g., zidovudine) are found in higher concentrations in activated or dividing cells, producing >99% of the HIV virion population, and nonthymidine analogs (e.g., lamivudine and emtricitabine) have more activity in resting cells, which account for <1% of the HIV virions but may serve as a reservoir for HIV. Suppression of replication in both populations is important for long-term viral control. **NNRTIs** (i.e., nevirapine, efavirenz, etravirine, rilpivirine, doravirine) act differently than NRTIs. They attach to the reverse transcriptase and cause a conformational change, reducing the activity of the enzyme (see Fig. 322.3). The **PIs** are potent agents that act farther along the viral replicative cycle. They bind to the site where the viral long polypeptides are cut into individual, mature, and functional core proteins that produce the infectious virions before they leave the cell (see Fig. 322.3). The virus entry into the cell is a complex process that involves several cellular receptors and fusion. Several drugs have been developed to prevent this process (see Fig. 322.3). The **fusion inhibitor** enfuvirtide (T-20), which binds to viral gp41, causes conformational changes that prevent fusion of the virus with the $CD4^+$ cell and entry into the cell; with the common use of integrase inhibitors, this medication is now used very rarely. Two entry inhibiting drugs are now approved for use only in treatment-experienced adult patients with multidrug-resistant HIV infection. Fostemsavir is an **attachment inhibitor** prodrug of temsavir that works by blocking CD4 binding to gp120; ibalizumab is a humanized monoclonal antibody (mAb) that acts as a postattachment inhibitor and prevents the HIV connection to co-receptors CCR-5 or CXCR-4. Maraviroc is an example of a selective **CCR-5 co-receptor antagonist** that blocks the attachment of the virus to this chemokine (an essential process in the viral binding and fusion to the $CD4^+$ cells). **Integrase inhibitors (INSTIs)** (i.e., raltegravir, dolutegravir, elvitegravir, bictegravir) block the enzyme that catalyzes the incorporation of the viral genome into the host's DNA (see Fig. 322.3).

By targeting different points in the viral life cycle and stages of cell activation and by delivering drug to all tissue sites, maximal viral suppression is achievable. **Combinations of three drugs consisting of a two-NRTI backbone of (1) a guanosine or thymidine analog NRTI (abacavir or zidovudine) or tenofovir and (2) a nonthymidine analog NRTI (lamivudine or emtricitabine) to suppress replication in both active and resting cells added to (3) a ritonavir-boosted PI (lopinavir, atazanavir, or darunavir), an NNRTI (efavirenz, nevirapine, rilpivirine, or etravirine), or an INSTI (raltegravir, dolutegravir, elvitegravir, or bictegravir) can produce prolonged suppression of the virus.** The use of three drugs from three different classes generally should be avoided but may be necessary in children with highly resistant viruses; these regimens should be chosen only by an HIV specialist with expert pharmacist input. For adult patients with established virologic suppression, some combination therapies pare down to just two drugs. Combination treatment increases the rate of toxicities (see Table 322.3), and complex drug-drug interactions occur among many of the antiretroviral drugs, particularly with the pharmacokinetic boosters ritonavir and cobicistat. Many PIs are inducers or inhibitors of the cytochrome P450 system and are therefore likely to have serious interactions with multiple drug classes, including nonsedating antihistamines and psychotropic, vasoconstrictor, antimycobacterial, cardiovascular, anesthetic, analgesic, and gastrointestinal drugs (cisapride). Whenever new medications are added to an ART regimen, especially a PI- or cobicistat-containing regimen, a pharmacist and/or HIV specialist should be consulted to address possible drug interactions. The inhibitory effect of ritonavir (a PI) on the cytochrome P450 system is exploited, and small doses of the drug are added to several other PIs (e.g., lopinavir, atazanavir, darunavir) to slow their metabolism by the P450 system and to

Table 322.3 Summary of Antiretroviral Therapies Available in 2023

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
NUCLEOSIDE/NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS		Class adverse effects: Lactic acidosis with hepatic steatosis, particularly for older members of the class	
Abacavir (Ziagen, ABC): tablet: 300 mg; oral solution: 20 mg/mL Epzicom: combination of lamivudine, ABC (300, 600 mg) Triumeq: combination of ABC, lamivudine, dolutegravir (600, 300, 50 mg) Triumeq PD: combination of ABC, lamivudine, dolutegravir (60, 30, 5 mg)	Children: Full term <1 mo: 2 mg/kg/dose bid Full term ≥1 mo to <3 mo: 4 mg/kg/dose bid ≥3 mo to 13 yr: 8 mg/kg/dose bid (max: 300 mg bid) >25 kg: 300 mg bid Children with stable CD4 counts and undetectable viral load >6 mo while taking ABC can transition to 16 mg/kg once daily (max: 600 mg) Children ≥25 kg, adolescents and adults: 300 mg bid or 600 mg qd Epzicom (>25 kg): 1 tablet qd Triumeq: 1 tablet qd Triumeq PD (≥10 kg to <25 kg): Must be dispersed in 20 mL of water, not swallowed whole, cut, or chewed 10 kg to <14 kg: 4 tablets qd 14 kg to <20 kg: 5 tablets qd 20 kg to <25 kg: 6 tablets qd	Common: nausea, vomiting, anorexia, fever, headache, diarrhea, rash Less common: hypersensitivity reactions, which can be fatal Rare: lactic acidosis with hepatic steatosis, pancreatitis, elevated triglycerides, myocardial infarction	Genetic screening for HLAB*5701 must be done before initiation of ABC-containing treatment. If test is positive, avoid ABC. Once-daily dosing is not preferred with liquid formulations. Can be given with or without food Do not restart ABC in patients who had hypersensitivity-like symptoms (e.g., flulike symptoms). Oral solution does not require refrigeration. Abacavir should never be used for postexposure prophylaxis (PEP).
Emtricitabine (Emtriva, FTC): capsule: 200 mg; oral solution: 10 mg/mL Truvada: combination of FTC, tenofovir disoproxil fumarate (TDF) (200, 300 mg) Truvada Low Strength: combinations of FTC/TDF (100, 150 mg); (133, 200 mg); (167, 250 mg) Descovy: combinations of FTC, tenofovir alafenamide (TAF) (200, 25 mg); (120, 15 mg) Atripla: combination of FTC, TDF, efavirenz (EFV) (200, 300, 600 mg) Biktarvy: combinations of FTC, TAF, bictegravir (BIC) (200, 25, 50 mg); (120, 15, 30 mg) Complera: combination of FTC, TDF, rilpivirine (RPV) (200, 300, 25 mg) Odefsey: combination of FTC, TAF, RPV (200, 25, 25 mg) Stribild: combination of FTC, TDF, elvitegravir (EVG), cobicistat (COBI) (200, 300, 150, 150 mg) Genvoya: combination of FTC, TAF, EVG, COBI (200, 10, 150, 150 mg) Symtuza: combination of FTC, TAF, darunavir (DRV), COBI (200, 10, 800, 150 mg)	Infants: 0-<3 mo: 3 mg/kg qd Children ≥3 mo to 17 yr, oral solution: 6 mg/kg (max: 240 mg) qd >33 kg, adolescents and adults: 200 mg capsule or 240 mg solution qd ≥14 to <25 kg: Biktarvy (120, 15, 30 mg), Descovy (120, 15 mg): 1 tablet qd ≥25 kg: Biktarvy (200, 25, 50 mg), Genvoya: 1 tablet qd >25 kg to 35 kg: Descovy (200 mg, 25 mg) but cannot pair with boosted PI or COBI: 1 tablet qd ≥35 kg: Complera, Odefsey, Descovy (200, 25 mg): 1 tablet qd ≥35 kg, SMR* 4 or 5: Stribild: 1 tablet qd ≥40 kg Atripla, Symtuza: 1 tablet qd *SMR = Sexual maturity rating	Common: headache, insomnia, diarrhea, nausea, skin discoloration (hyperpigmentation of palms, soles) Less common: lactic acidosis with hepatic steatosis, neutropenia	Patient should be tested for hepatitis B virus (HBV) before starting because HBV exacerbation can occur when emtricitabine is discontinued. Some combination drugs may have food requirements. Oral solution should be refrigerated if temperature above 25°C (77°F) and for long-term storage. COBI is a pharmacokinetic enhancer (boosting agent) used to optimize drug levels; it is not interchangeable with ritonavir. It can alter renal tubular secretion of Cr, resulting in elevated Cr with normal GFR. Note FTC oral solution is less bioavailable and has a max dose of 240 mg, whereas the max dose for capsules is 200 mg.

Table 322.3 Summary of Antiretroviral Therapies Available in 2023—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
Lamivudine (Epivir, Epivir HBV, 3TC): tablet: 150 (scored), 300 mg (Epivir, generic), 100 mg (Epivir HBV); Solution: 5 mg/mL (Epivir HBV), 10 mg/mL (Epivir) Combivir: combination of ZDV, lamivudine (300, 150 mg) Cimduo: combination of 3TC, TDF (300 mg, 300 mg) Delstrigo: combination of 3TC, TDF, doravirine (DOR) (300, 300, 100 mg) Dovato: combination of 3TC, DTG (300, 50 mg) Symfi: combination of 3TC, TDF, EFV (300, 300, 600 mg) Symfi Lo: combination of 3TC, TDF, EFV (300, 300, 400 mg) Temixys: combination of 3TC, TDF (300, 300 mg) Epzicom and Triumeq, Triumeq PD combination (see abacavir)	Neonates (≥32 wk gestational age through 4 wk of age for term infants): 2 mg/kg/dose bid ≥4 wk to <3 mo: 4 mg/kg/dose bid ≥3 mo to <3 yr: 5 mg/kg/dose bid (max: 150 mg) ≥3 yr: 5 mg/kg/dose bid (max: 150 mg) or 10 mg/kg/dose qd (max: 300 mg) For ≥14 kg with scored tablet (150 mg) 14 to <20 kg: 75 mg bid or 150 mg qd (if >3 yr) ≥20 to <25 kg: 75 mg qAM and 150 mg qPM or 225 mg qd (if >3 yr) ≥25 kg: 150 mg bid or 300 mg qd Children should be switched to once-daily dosing of lamivudine (oral solution or tablets) from twice-daily dosing at ≥3 yr if clinically stable for 36 wk with an undetectable viral load and stable CD4 count Adolescents and adults: Combivir, (≥30 kg): 1 tablet bid Cimduo (>35 kg): 1 tablet qd Epzicom (≥25 kg): 1 tablet qd Triumeq (≥25 kg): 1 tablet qd Triumeq PD: see abacavir Symfi (≥40 kg), Symfi Lo (≥35 kg and SMR* 4 or 5): 1 tablet qd on empty stomach Temixys (≥35 kg): 1 tablet qd Dovato: 1 tablet qd in children who meet minimum body weight as part of a three-drug regimen Child and adolescent ≥35 kg and virologically suppressed: Delstrigo: 1 tablet qd* SMR = Sexual maturity rating	Common: headache, nausea Less common: pancreatitis, peripheral neuropathy, lactic acidosis with hepatic steatosis, lipodystrophy	No food restrictions for lamivudine alone but some restrictions with combination drugs Patient should be tested for hepatitis B virus (HBV) before starting because HBV exacerbation can occur when lamivudine is discontinued. M184V mutation for this drug decreases viral fitness and can be advantageous to maintain including inducing AZT hypersusceptibility.
Tenofovir alafenamide (Vemlidy, TAF) Descovy: combinations of TAF, FTC (25, 200 mg); (15, 120 mg) Genvoya: combination of TAF, FTC, EVG, COBI (10, 200, 150, 150 mg) Odefsey: combination of TAF, FTC, RPV (25, 200, 25 mg) Biktarvy: combinations of TAF, FTC, BIC (25, 200, 50 mg); (15, 120, 30 mg) Symtuza: combination of TAF, FTC, DRV, COBI (10, 200, 800, 150 mg)	≥ 2 yr ≥14 kg to <25 kg: Biktarvy (15, 120, 30 mg): 1 tablet qd Descovy (15, 120 mg): 1 tablet qd ≥25 kg: Biktarvy (25, 200, 50 mg), Descovy (25, 200 mg), Genvoya: 1 tablet qd ≥25 kg but <35 kg: Descovy but cannot pair with boosted PI: 1 tablet qd ≥35 kg: Descovy: 1 tablet qd ≥35 kg and ≥12 yr: Odefsey: 1 tablet qd ≥40 kg (adult dose) Symtuza: 1 tablet qd	Common: headache, diarrhea, nausea, asthenia, increased serum lipids	Newer version of TDF that has less renal and bone toxicity. Baseline serum creatinine still recommended before starting. Screen for HBV before TAF is started, because exacerbation of hepatitis may occur when TAF is discontinued. Concentrates in cells more so than TDF

Continued

Table 322.3 Summary of Antiretroviral Therapies Available in 2023—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
Tenofovir disoproxil fumarate (Viread, TDF): tablet: 150, 200, 250, 300 mg; powder: 40 mg/1 g powder Truvada: combination of FTC, TDF (200, 300 mg) Truvada Low Strength: combinations of FTC/TDF (100, 150 mg); (133, 200 mg); (167, 250 mg) Cimduo: combination of 3TC, TDF (300 mg, 300 mg) Atripla: combination of FTC, TDF, EFV (200, 300, 600 mg) Complera: combination of FTC, TDF, RPV (200, 300, 25 mg) Delstrigo: combination of 3TC, TDF, DOR (300, 300, 100 mg) Stribild: combination of FTC, TDF, EVG, COBI (200, 300, 150, 150 mg) Symfi: combination of 3TC, TDF, EFV (300, 300, 600 mg) Symfi Lo: combination of 3TC, TDF, EFV (300, 300, 400 mg) Temixys: combination of 3TC, TDF (300, 300 mg)	≥2 yr to <12 yr and ≥10 kg: 8 mg/kg/dose qd Weight probands for ≥2 yr and ≥17 kg: 17 to <22 kg: 150 mg qd 22 to <28 kg: 200 mg qd 28 to <35 kg: 250 mg qd ≥35 kg: 300 mg qd (max dose) Atripla (≥40 kg): 1 tablet qd Cimduo (≥35 kg): 1 tablet qd Complera (≥35 kg): 1 tablet qd Symfi (≥40 kg), Symfi Lo ≥ 12 yr (≥35 kg and SMR* 4 or 5): 1 tablet qd on empty stomach Stribild (≥35 kg, SMR* 4 or 5): 1 tablet qd Temixys (≥35 kg): 1 tablet qd Delstrigo: Child and adolescent ≥35 kg and virologically suppressed: 1 tablet qd *SMR = Sexual maturity rating	Common: nausea, vomiting, diarrhea, asthenia, flatulence Less common: lactic acidosis with hepatic steatosis, hepatomegaly, decreased bone density, renal toxicity (glomerular and proximal tubule dysfunction)	Baseline creatinine, urinalysis for protein and glucose should be obtained before starting. Screen for HBV before TDF is given, because exacerbation of hepatitis may occur when TDF is discontinued. Cautious use in SMR 1 and 2 patients with regard to bone mineral density.
Zidovudine (Retrovir, AZT, ZDV): capsule: 100 mg; tablet: 300 mg; syrup: 10 mg/mL; intravenous injection: 10 mg/mL (all available generic) Combivir: combination of ZDV, lamivudine (300, 150 mg)	**Low Risk Prophylaxis:** *≥35 wk gestation at birth:* *Birth to age 4 wk*: 4 mg/kg/dose PO bid (or 3 mg/kg/dose IV q12h) ≥30 to <35 wk gestation at birth: *Birth to age 2 wk*: 2 mg/kg/dose PO bid (or 1.5 mg/kg/dose IV q12h) THEN *Age 2 wk to 6 wk*: 3 mg/kg/dose PO bid (or 2.3 mg/kg/dose IV q12h) <30 wk gestation at birth *Birth to age 4 wk*: 2 mg/kg/dose PO bid (or 1.5 mg/kg/dose IV q12h) THEN *Age 4 wk to 6 wk*: 3 mg/kg/dose bid (or 2.3 mg/kg/dose IV q12h) (See text and Table 322.7 for recommended duration for low risk prophylaxis.)	Common: bone marrow suppression (e.g., anemia, neutropenia), headache, nausea, vomiting, asthenia Less common: liver toxicity, lactic acidosis with hepatic steatosis, myopathy, fat redistribution, myopathy/myositis	No food restrictions Drug interactions: should not be given with d4T or doxorubicin. Only antiretroviral with an IV formulation.
	Presumptive HIV therapy for high-risk exposed infants and treatment: *≥35 wk gestation at birth:* Birth to age 4 wk: 4 mg/kg/dose PO bid THEN Age >4 wk: 12 mg/kg/dose PO bid *≥30 to <35 wk gestation at birth:* Birth to age 2 wk: 2 mg/kg/dose PO bid THEN Age 2 wk to 6 wk: 3 mg/kg/dose PO bid THEN Age >6 wk: 12 mg/kg/dose PO bid <30 wk gestation at birth: Birth to age 4 wk: 2 mg/kg/dose PO bid THEN Age 4 wk to 8 wk: 3 mg/kg/dose PO bid THEN Age >8 wk: 12 mg/kg/dose PO bid *Infants >4 kg, ≥35 wk post conception and ≥4 wk post delivery and children:* 4 kg to <9 kg: 12 mg/kg/dose PO bid 9 kg to <30 kg: 9 mg/kg/dose PO bid >30 kg: 300 mg bid (max dose) Alternative body surface area dosing: 180-240 mg/m^2/dose PO bid Combivir (≥30 kg): 1 tablet bid IV dose is 75% of PO dose, same interval		

Table 322.3 Summary of Antiretroviral Therapies Available in 2023—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS		Class adverse effects: rash is mild to severe, usually within first 6 wk. Discontinue the drug if severe rash (with blistering, desquamation, muscle involvement, or fever)	
Doravirine (Pifeltro, DOR) Tablet: 100 mg Delstrigo: combination of 3TC, TDF, DOR (300, 300, 100 mg)	Child and adolescent ≥35 kg and virologically suppressed: Doravirine: 1 tablet qd Delstrigo: 1 tablet qd	Common: nausea, abdominal pain, diarrhea, vivid dreams, insomnia	Not approved for use in <18 yr Can have multiple drug interactions; metabolized by cytochrome P450 3A. If co-administered with rifabutin, dose DOR bid
Efavirenz (Sustiva, EFV): capsule: 50, 200 mg; tablet: 600 mg Atripla: combination of EFV, FTC, TDF (600, 200, 300 mg) Symfi Lo: combination of 3TC, TDF, EFV (300, 300, 400 mg) Symfi: combination of 3TC, TDF, EFV (300, 300, 600 mg)	Children <3 yr: Consult with expert; not recommended for children <3 yr Children ≥3 yr: 10 to <15 kg: 200 mg qd 15 to <20 kg: 250 mg qd 20 to <25 kg: 300 mg qd 25 to <32.5 kg: 350 mg qd 32.5 to <40 kg: 400 mg qd ≥40 kg: 600 mg qd or 367 mg/m^2 body surface area (max: dose 600 mg) Atripla (≥40 kg): 1 tablet qd on empty stomach Symfi Lo (≤35 kg and SMR* 4 or 5): 1 tablet qd on empty stomach *SMR = Sexual maturity rating For Symfi Lo consider use of therapeutic drug monitoring for pediatric patients ≥40 kg Symfi (≥40 kg): 1 tablet qd	Common: transient skin rashes, CNS symptoms (e.g., vivid dreams, impaired concentration, insomnia, depression, hallucinations, depression, suicidal ideation esp. in adolescents and young adults), gynecomastia Less common: increased liver enzymes; potentially teratogenic, QTc prolongation (be careful with other QT-prolonging medications), false positives on some cannabinoid and benzodiazepine tests	Capsules can be opened for mixing in food. Administer at bedtime on empty stomach to minimize CNS side effects. Taking with food, especially fatty meal, can increase absorption and worsen CNS side effects. Drug interactions: Efavirenz induces/inhibits CYP3A4 enzymes. For some individuals with certain CYP450 polymorphisms, Symfi Lo is appropriate (lower EFV dose). Increased clearance of drugs metabolized by this pathway (e.g., antihistamines, sedatives and hypnotics, cisapride, ergot derivatives, warfarin, ethinyl estradiol) and several other ARVs (i.e., protease inhibitors). Drugs that induce CYP3A4 (e.g., phenobarbital, rifampin, rifabutin) decrease efavirenz levels. Clarithromycin levels decrease with EFV, and azithromycin should be considered. Avoid using in individuals with a history of past or active psychiatric issues and use with caution in adolescents and young adults owing to possible affective side effects, including increased suicidality.
Etravirine (ETR, Intelence): tablet: 25, 100, 200 mg	Not approved for <2 yr 10 to <20 kg: 100 mg bid 20 to <25 kg: 125 mg bid 25 to <30 kg: 150 mg bid ≥30 kg: 200 mg bid	Common: nausea, rash, diarrhea Less common: hypersensitivity reactions with rash, including Stevens-Johnson syndrome, multiorgan dysfunction including hepatic failure	Always administer with a meal for absorption; taking on empty stomach decreases absorption by 50%. Tablets can be dispersed in water but swallowing is preferred because consumption of dispersed tablets results in lower levels. Inducer of CYP3A4 enzymes and inhibitor of CYP2C9 and CYP2C19, causing multiple interactions that should be checked before initiating ETR. Cobicistat-boosted PIs, nonnucleoside reverse transcriptase inhibitors, bictegravir, and elvitegravir/cobicistat should not be used with ETR. Raltegravir and dolutegravir should only be used with ETR with ritonavir (RTV)-boosted atazanavir, darunavir, or lopinavir.

Continued

Table 322.3 Summary of Antiretroviral Therapies Available in 2023—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
Nevirapine (Viramune, NVP): tablet: 200 mg; extended-release (XR) tablet: 100, 400 mg; suspension: 10 mg/mL	**Presumptive HIV therapy for high-risk exposed infants and treatment:** 32 to <34 wk gestation at birth: Birth to age 2 wk: 2 mg/kg/dose bid 2 wk to 4 wk: 4 mg/kg/dose bid 4 wk to 6 wk: 6 mg/kg bid >6 wk with confirmed infection: NVP 200 mg/m^2/dose bid 34 wk to <37 wk gestation at birth: Birth to 1 wk: 4 mg/kg/dose bid 1 wk to 4 wk: 6 mg/kg/dose bid >4 wk and confirmed infection: 200 mg/m^2/dose bid ≥37 wk gestation at birth: Birth to age 4 wk: 6 mg/kg/dose bid Age >4 wk and confirmed infection: 200 mg/m^2/dose bid ≥1 mo to <8 yr: 200 mg/m^2 once daily for 14 days; then same dose bid (max: 200 mg/dose for immediate-release tablets) ≥8 yr: 120-150 mg/m^2 once daily for 14 days; then bid (max: 200 mg/dose for immediate-release tablets) Adolescents and adults: 200 mg once daily for 14 days; then 200 mg bid Or XR 400 mg qd (after 14-day lead in) Extended-release tablets: ≥6 yr by BSA: 0.58 m^2 to 0.83 m^2: 200 mg 0.84 m^2 to 1.16 m^2: 300 mg ≥1.17 m^2: 400 mg Patients already on immediate-release formulation can transition to qd XR dosing without lead-in Note doses are never adjusted down if patient is tolerating. 3-dose series for high-risk infants (less commonly used) ≥32 wk gestation at birth: NOTE: DOSES ARE A FLAT DOSE, NOT PER KG Dosing intervals: Within 48 hr of birth, 48 hr after first dose, 96 hr after second dose Birth weight 1.5-2 kg: 8 mg/dose PO Birth weight >2 kg: 12 mg/dose PO	Common: skin rash (usually in first 6 wk of therapy), headache, fever, nausea, abnormal liver function tests Less common: hepatotoxicity (rarely life-threatening hepatic necrosis), hypersensitivity reactions, Stevens Johnson syndrome (1.4–7.1% of pediatric patients in large series) that can have multiorgan involvement	No food restrictions Drug interactions: induces hepatic CYP450A enzymes (including CYP3A and CYP2B6) activity and decreases protease inhibitor concentrations. Rifampin decreases nevirapine serum levels. Anticonvulsants and psychotropic drugs using same metabolic pathways as NVP should be monitored. Oral contraceptives also may be affected. XR formulation must be swallowed whole. For children ≤2 yr, some experts start with bid dosing without the 14 day lead-in of qd dosing. Lead-in dosing decreases occurrence of rash by allowing induction of cytochrome p450 metabolizing enzymes. If rash develops during initial 14 days of therapy, do not increase dose until rash resolves. If therapy is interrupted for >14 days, restart using lead-in dosing. Nevirapine should never be used for postexposure prophylaxis (PEP).

Table 322.3 Summary of Antiretroviral Therapies Available in 2023—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
Rilpivirine (Edurant, RPV): tablet: 25 mg Complera: combination of RPV, FTC, TDF (25, 200, 300 mg) Odefsey: combination of FTC, TAF, RPV (25, 200, 25 mg) Juluca: combination of RPV, Dolutegravir (DTG) (25, 50 mg) Co-packaged formulation (Cabenuva): combinations injectable of RPV, cabotegravir: (900, 600 mg); (600, 400 mg)	≥12 yr and ≥35 kg: 25 mg PO qd Complera or Odefsey: 1 tablet qd Juluca (>18 yr): 1 tablet qd; only for use in adults with ≥6 mo virologic suppression with no resistance to replace current regimen ≥12 years and ≥35 kg with virologic suppression and no history of treatment failure starting on last day of 28 day oral lead in therapy: Cabenuva (900, 600 mg) IM, then Cabenuva (600, 400 mg) IM monthly Alternate every 2 mo dosing also available	Headache, insomnia, rash, depression, mood changes Less common: hepatotoxicity	Given with food only, 500-kcal meal (not just liquid). Do not use with proton pump inhibitors; antacids have to be spaced from dose by 2 hr before or 4 hr after. H_2 antagonists should be administered 12 hr before or 4 hr after RPV. Should not be used if viral load >100,000 copies/μL or drugs that induce CYP3A. Injectables can give local site reaction, soreness. Administration window is ±7 days for injectable regimens. It is critical that injectable regimens are received on schedule, as prolonged subtherapeutic drug levels will lead to emergence of resistance.
PROTEASE INHIBITORS		Class adverse effects: GI side effects, hyperglycemia, hyperlipidemia (except atazanavir and darunavir), lipodystrophy, increased transaminases, increased bleeding disorders in hemophiliacs. Can induce metabolism of ethinyl estradiol; use alternative contraception (other than estrogen-containing oral contraceptives). All of these drugs undergo hepatic metabolism, mostly by CYP3A4, with many drug interactions. Treatment note: always administer with boosting agent (RTV or COBI).	
Atazanavir (Reyataz, ATV): powder packet: 50 mg/packet; capsule: 150, 200, 300 mg (*Note:* capsules and packets are *not* interchangeable) Evotaz: combination of ATV, COBI (300, 150 mg)	Infants and children ≥3 mo and ≥5 kg: 5 to <15 kg: ATV 200 mg (4 packets) + RTV 80 mg qd 15 to <25 kg: ATV 250 mg (5 packets) + RTV 80 mg qd *Note:* Capsules are not approved for <6 yr or <15 kg Children ≥6 yr and ≥15 kg capsule dosing: 15 to <35 kg: 200 mg + RTV qd 100 mg ≥35 kg: 300 mg + RTV 100 mg qd OR Evotaz: 1 tablet qd	Common: elevation of indirect bilirubin; headache, arthralgia, depression, insomnia, nausea, vomiting, diarrhea, paresthesias Less common: prolongation of PR interval on electrocardiogram (ECG); rash, rarely Stevens-Johnson syndrome, diabetes mellitus, nephrolithiasis	Administer ATV with food to increase absorption and decrease GI side effects. Do not open capsules. Review drug interactions before initiating because ATV inhibits CYP3A4, CYP1A2, CYP2C9, and UGT1A1 enzymes. Use with caution with cardiac conduction disease or liver impairment. TDF, antacids, H_2-receptor antagonists, and proton-pump inhibitors decrease ATV concentrations. PPIs should be taken 12 hr before boosted ATV and not coadministered. COBI is a pharmacokinetic enhancer (boosting agent) used to optimize drug levels; it is not interchangeable with ritonavir. It can alter renal tubular secretion of Cr, resulting in elevated Cr with normal GFR.

Continued

Table 322.3 Summary of Antiretroviral Therapies Available in 2023—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
Darunavir (Prezista, DRV): tablets: 75, 150, 600, 800 mg; suspension: 100 mg/mL Prezcobix: combination DRV, COBI (800, 150 mg) Symtuza: combination DRV, TAF, FTC, COBI (800, 10, 200, 150 mg)	<3 yr or <10 kg: Do not use 3 yr to <12 yr: 10 to <11 kg: DRV 200 mg + RTV 32 mg bid 11 to <12 kg: DRV 220 mg + RTV 32 mg bid 12 to <13 kg: DRV 240 mg + RTV 40 mg bid 13 to <14 kg: DRV 260 mg + RTV 40 mg bid 14 to <15 kg: DRV 280 mg + RTV 48 mg bid 15 to <30 kg: DRV 375 mg + RTV 48 mg bid 30 to <40 kg: DRV 450 mg + RTV 100 mg bid >12 yr and ≥30 to <40 kg: DRV 450 mg + RTV 100 mg bid ≥40 kg: DRV 600 mg + RTV 100 mg bid ≥12 yr and ≥40 kg and *no* DRV mutations: DRV 800 mg + RTV 100 mg qd OR Prezcobix: 1 tablet qd ≥40 kg *with* DRV mutation(s): DRV 600 mg + RTV 100 mg bid >40 kg with *no* DRV or TDF/TAF resistance: Symtuza: 1 tablet qd	Common: diarrhea, nausea, vomiting, abdominal pain, fatigue, headache Less common: skin rashes (including Stevens-Johnson syndrome), lipid and liver enzyme elevations and hepatotoxicity, hyperglycemia, fat maldistribution	DRV should always be given with food for absorption and to decrease GI side effects. Contraindicated for concurrent therapy with cisapride, ergot alkaloids, benzodiazepines, pimozide, or any major CYP3A4 substrates. Use with caution in patients taking strong CYP3A4 inhibitors, or moderate/strong CYP3A4 inducers. Contains sulfa moiety: potential for cross-sensitivity with sulfonamide class DRV should not be administered once daily to individuals <12 yr or <40 kg. COBI is a pharmacokinetic enhancer (boosting agent) used to optimize drug levels; it is not interchangeable with ritonavir. It can alter renal tubular secretion of Cr, resulting in elevated Cr with normal GFR.
Lopinavir/Ritonavir (Kaletra, LPV/r): tablet: 100/25 mg, 200/50 mg; solution: 80/20 mg per/mL (contains 42% alcohol, 15% propylene glycol)	<14 days: Not approved 14 days to 18 yr: LPV 300 mg/m^2/dose + RTV 75 mg/m^2/dose bid In treatment naïve children >1 yr a dose of 230 mg/m^2/dose bid can be used. >18 yr: LPV 400 mg + RTV 100 mg bid *Or* 800 mg LPV + 200 mg RTV qd >45 kg: If taken with NVP, EFV, fosamprenavir, or nelfinavir: LPV 600 mg + RTV 150 mg bid	Common: diarrhea, headache, nausea and vomiting, lipid elevation, alteration of taste, hyperlipidemia (hypertriglyceridemia) Less common: fat redistribution, hyperglycemia, diabetes mellitus, pancreatitis, hepatitis, PR interval prolongation, QT interval prolongation and torsades de pointes. Life threatening cardiotoxicity risk in neonates.	**Do not administer before postmenstrual age of 42 wk and postnatal age of 14 days due to potential severe toxicities.** If patient on concomitant NVP or EFV, dosing must be adjusted and it must be given bid. No food restrictions for tablets but has better GI tolerability when given with or after a meal. Oral solution should be administered with high-fat meal to increase absorption. Pills must be swallowed whole. Poor palatability of oral solution is difficult to mask with flavorings or foods. Once-daily dosing is poorly tolerated in most children, and plasma concentration variability makes qd dosing contraindicated in children and adolescents. Interacts with drugs using CYP3A4, which can cause multiple drug interactions.
Ritonavir (Norvir, RTV): capsule: 100 mg; tablet: 100 mg; solution: 80 mg/mL (contains 43% alcohol)	Only use is to enhance other PIs; dose varies (see information for specific PI)	Common: nausea, headache, vomiting, abdominal pain, diarrhea, taste aversion, lipid abnormalities, perioral paresthesias Less common: fat redistribution, hyperglycemia, diabetes mellitus, pancreatitis, hepatitis, PR interval prolongation, allergic reactions	Administration with food enhances bioavailability and reduces gastrointestinal symptoms. RTV solution should not be refrigerated (store at 20–25°C). RTV is potent inhibitor of CYP3A4 and CYP2D6 and inducer of CYP3A4 and CYP1A2 that leads to many drug interactions (e.g., protease inhibitors, antiarrhythmics, antidepressants, cisapride). Use cautiously with inhaled steroids (Cushing syndrome has been reported specifically with coadministration with fluticasone).

Table 322.3 Summary of Antiretroviral Therapies Available in 2023—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
ENTRY AND FUSION INHIBITORS			
Fostemsavir (Rukobia, FTR): Extended-release tablet 600 mg	Safety and efficacy data not established for <18 yr Adults >18 yr: 1 tablet twice daily	QTc prolongation with higher than recommended doses, increased transaminases in Hep B or Hep C co-infection	Reserved for treatment in experienced patients with significant resistance. Tablet must be swallowed whole. Do not co-administer with strong P450 CYP 3A4 inducers. Potential drug interactions.
Ibalizumab (Trogarzo, IBA) IV: single-dose vial 200 mg/1.33 mL	Safety and efficacy data for <18 yr olds not established Adults >18 yr: Loading dose 2000 mg IV, maintenance dose 800 mg q2 wk	Diarrhea, nausea, rash, dizziness, IRIS, possible development of anti-IBA antibodies	Reserved for treatment in experienced patients with significant resistance. Used in combination with optimized cART regimen.
Maraviroc (Selzentry, MVC): oral solution: 20 mg/mL; tablet: 25, 75, 150, 300 mg	Given with potent CYP3A inhibitors (all PIs): 2 to <10 kg: Not recommended 10 to <20 kg: 50 mg bid 20 to <30 kg: 75-80 mg bid 30 to <40 kg: 100 mg bid ≤40 kg: 150 mg bid Given with noninteracting drugs such as NRTIs, T-20, NVP, RAL, or other drugs not affecting CYP3A: 2 to <4 kg: 30 mg bid 4 to <6 kg: 40 mg bid 6 to <10 kg: 100 mg bid 10 to <14 kg: 150 mg bid 14 to <30 kg: 200 mg bid 30 to <40 kg: 300 mg bid ≥40 kg: 300 mg bid Insufficient data for all children and adolescents for dosing with potent CYP3A inducer, including EFV, ETR Adults: Given with noninteracting medications: 300 mg bid Given with potent CYP3A inhibitors (including all PIs): 150 mg bid Given with potent CYP3A inducers including EFV and ETR 600 mg bid	Common: fever, upper respiratory infection–like symptoms including cough, nausea, vomiting, rash, abdominal pain, musculoskeletal symptoms, dizziness	Testing for CCR-5-tropic virus required; virus must not have mixed tropism (i.e., CCR-5/CXC4) to have efficacy. No food restrictions. MVC is a CYP3A4 and P-glycoprotein (Pgp) substrate, which may cause many drug interactions. Caution should be used when given to patients with hepatic impairment or cardiac disease or receiving CYP3A4 or P-glycoprotein-modulating drugs.
INTEGRASE INHIBITORS (INSTI)		Class side effects: headache, mild GI symptoms, potential significant weight gain for some INSTIs	
Bictegravir (BIC) Only available as Biktarvy: combinations of BIC, TAF, FTC (50, 25, 200 mg); (30, 15, 120 mg)	≥2 y and ≥14 kg to <25 kg: 1 tablet (30, 15, 120 mg) qd ≥25 kg: 1 tablet (50, 25, 200 mg) qd	Diarrhea, nausea, headache,	No food restrictions. Metabolized by UGT1A1 and CYP450 (CYP) 3A. For children unable to swallow tablet whole, tablet can be split and all parts swallowed separately within 10 min. All patients should be screened for HBV before using FTC or TAF. Avoid in severe hepatic impairment.

Continued

Table 322.3 Summary of Antiretroviral Therapies Available in 2023—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
Cabotegravir (Vocabria, CAB): Tablet: 30 mg Single-dose vial for IM injection (Apretude): 600 mg (PrEP only) Co-packaged formulation (Cabenuva): combinations injectable of RPV, CAB: (900, 600 mg); (600, 400 mg)	**PrEP (CAB only)** Adolescents and adults ≥35 kg confirmed HIV negative who meet criteria: Optional oral lead-in for 1 mo (dosing below) then on last day oral lead-in, patient receives IM 600 mg CAB monthly for 2 mo then every 2 mo **For treatment of HIV (CAB/RPV):** ≥12 y and ≥35 kg and adults with suppressed viral load and no history of treatment failure: Optional oral lead in with oral RPV and CAB for 1 mo: CAB 30 mg, RPV 25 mg PO qd Monthly administration: Starting on last day of oral lead in IM CAB/RPV (600/900 mg) first month then CAB/RPV (400/600 mg) monthly Every 2 mo administration: Starting on last day of oral lead in IM CAB/RPV (600/900 mg) monthly for 2 mo then CAB/RPV (600/900 mg) every 2 mo.	Injection site reactions, depression, insomnia, headache, rash (can be severe with systemic symptoms), hepatotoxicity, weight gain, CPK elevation, ACTH stimulation test alteration of unclear significance	**Close monitoring and strong engagement in care needed for injectable therapies as missing doses with prolonged subtherapeutic levels can lead to emergence of resistance and for PrEP acquisition of resistant HIV infection.** There is a ±7 day dose administration window for the monthly dose. CAB and RPV are injected separately into separate ventrogluteal sites.
Dolutegravir (Tivicay, DTG): film-coated tablet: 10, 25, 50 mg Dispersible tablets for oral suspension (Tivicay PD): 5 mg Triumeq: combination of ABC, 3TC, DTG (600, 300, 50 mg) Juluca: combination of RPV, DTG (25, 50 mg) Dovato: combination of DTG, 3TC (50, 300 mg) Triumeq PD: combination of ABC, lamivudine, dolutegravir (60, 30, 5 mg)	Neonates: not approved ≥4 wk, ≥3 kg, dispersible tablets: 3 kg to <6 kg: 5 mg qd 6 kg to <10 kg: 15 mg qd 10 kg to <14 kg: 20 mg qd 14 to <20 kg: 25 mg qd ≥20 kg 30 mg qd ≥14 kg film coated tablets: 14 kg to <20 kg: 40 mg qd ≥20 kg: 50 mg qd ≥25 kg: Triumeq: 1 tablet qd Juluca: 1 tablet qd; only for use in patients with ≥6 mo virologic suppression with no resistance to replace current regimen. Can be used in adolescents meeting weight requirements for treatment simplification Dovato: 1 tablet qd; can be used in adolescents meeting weight requirements for treatment simplification Triumeq PD (≥10 kg to <25 kg): Must be dispersed, not swallowed whole, cut or chewed 10 kg to <14 kg: 4 tablets 14 kg to <20 kg: 5 tablets 20 kg to <25 kg: 6 tablets	Insomnia, headache, neuropsychiatric illness Rare: rash, hepatotoxicity, hypersensitivity reactions	**Film-coated tablets and dispersible tablets are not bioequivalent and are not interchangeable.** Film-coated tablets should not be used in <14 kg patients. Juluca and Dovato are not recommended as first-line regimens for children and adolescents but if child meets weight criteria and viral load criteria could be used to reduce pill burden).
Elvitegravir (EVG): only found in 2 co-formulated fixed-dose combination (FDC) tablets Stribild: combination of EVG, FTC, TDF, COBI (150, 200, 300, 150 mg) Genvoya: combination of FTC, TAF, EVG, COBI (200, 10, 150, 150 mg)	≥25 kg: Genvoya 1 tablet qd >35 kg and SMR* 4 or 5: Stribild 1 tablet qd *SMR = Sexual Maturity Rating	Nausea, diarrhea, headache, fatigue	Administer with food. EVG is metabolized by CYP3A4 and modestly induces CYP2D6 that can cause multiple drug interactions. Use cautiously with nephrotoxic drugs. Administer 4 hr before or after antacids, multivitamins or supplements that contain iron, calcium, aluminum, or magnesium. COBI is a pharmacokinetic enhancer (boosting agent) used to optimize drug levels; it is not interchangeable with ritonavir. It can alter renal tubular secretion of Cr, resulting in elevated Cr with normal GFR.

Table 322.3 Summary of Antiretroviral Therapies Available in 2023—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
Raltegravir (Isentress, RAL): film-coated tablet: 400 mg; film-coated high dose (HD) tablet: 600 mg; chewable tablet: 25, 100 mg (scored); granules for oral suspension: 100 mg suspended in 10 mL of water for final concentration of 10 mg/mL	**Presumptive therapy for high-risk exposed neonates and treatment:** ≥37 wk gestation at birth and ≥2 kg (oral suspension): *Birth to age 1 wk:* approximately 1.5 mg/kg/dose qd 2 to <3 kg: 4 mg qd 3 to <4 kg: 5 mg qd 4 to <5 kg: 7 mg qd If parent on raltegravir in 2-24 hr before delivery, delay first dose 24-48 hr after birth. Start other ART ASAP. *Age 1-4 wk:* approximately 3 mg/kg/dose bid 2 to <3 kg: 8 mg bid 3 to <4 kg: 10 mg bid 4 to <5 kg: 15 mg bid **Infant and Pediatrics dosing** Oral suspension: Children age ≥4 wk and ≥3 kg to <20 kg: approximately 6 mg/kg/dose bid 3 to <4 kg: 25 mg bid 4 to <6 kg: 30 mg bid 6 to <8 kg: 40 mg bid 8 to <10 kg: 60 mg bid 10 to <14 kg: 80 mg bid 14 to <20 kg: 100 mg bid Chewable tablet: 3 kg to <6 kg: 25 mg bid 6 to <10 kg: 50 mg bid 10 to <14 kg: 75 mg bid 14 to <20 kg: 100 mg bid 20 to <28 kg: 150 mg bid 28 to <40 kg: 200 mg bid ≥40 kg: 300 mg bid Film-coated tablet: ≥25 kg: 400 mg bid HD tablet: ≥40 kg HD tablet: 1200 mg qd for treatment naïve patients or patients virologically suppressed on RAL 400 mg bid	Common: nausea, headache, dizziness, diarrhea, fatigue Less common: itching, creatine phosphokinase elevation, myopathy, rhabdomyolysis, depression, hypersensitivity, insomnia, fever Rare: rash including Stevens-Johnson, TEN, hypersensitivity reaction	**Oral suspension, film-coated tablet and chewable tablet are not interchangeable; chewable tablets and suspension have better oral bioavailability than film-coated tablet; hence, higher-dose for film-coated tablets.** The chewable tablet can be crushed. Place tablet in small clean cup, add 5 mL (1 tsp) of liquid (water, breast milk, juice) and let stand for 2 min while pill absorbs liquid. Use spoon to crush remaining intact pill. Administer immediately. Add 5 mL of liquid to cup, swirl, and administer that liquid as well to ensure full dose consumed. Film-coated tablets must be swallowed whole. RAL is metabolized by UGT1A1 glucuronidation, and inducers of this system (e.g., rifampin) will reduce RAL levels, whereas inhibitors of this system (e.g., ATV) will increase RAL levels. Do not administer rifampin, ETR, or calcium carbonate with once-daily raltegravir (HD). Aluminum and magnesium containing antacids should not be taken while on RAL. UGT1A1 metabolism is low at birth and increases rapidly over first 4-6 wk of life. No data for preterm infants.

Antiretroviral drugs often have significant drug-drug interactions, with each other and with other classes of medicines, which should be reviewed before initiating any new medication.

The information in this table is not all-inclusive. Updated and additional information on dosages, drug-drug interactions, and toxicities is available and regularly updated on the AIDSinfo website at https://www.nih.gov/research-training/hiv/aids-info-center

Modified from the Guidelines for use of antiretroviral agents in pediatric HIV infection. http://aidsinfo.nih.gov/contentfiles/pediatricguidelines.pdf.

improve their pharmacokinetic profile. This strategy provides more effective drug levels with less toxicity and less-frequent dosing. Cobicistat provides an alternative to ritonavir as a pharmacokinetic booster but does not have antiviral activity against HIV. Although cobicistat is a potent inhibitor of cytochrome P450 3A, it is a weak inhibitor of CYP2D6 and other CYP isoforms (e.g., CYP1A2), making pharmacologic interactions with many drugs more predictable than for ritonavir, which is also active against these isoforms. Studies with cobicistat show a good tolerability profile and less effect on adipocytes (resulting in lesser accumulations of lipid and a milder response to insulin). The better solubility of cobicistat compared with ritonavir has helped the development of more single-tablet combination regimens with cobicistat. Cobicistat is used for boosting both PIs and INSTIs. However, cobicistat is currently approved only for children ≥25 kg; it is not recommended for use in pregnancy because of a paucity of data and concern for pharmacokinetics.

Adherence

Adherence to the medication schedules and dosages is fundamental to cART success. Therefore assessment of the likelihood of adherence to treatment is an important factor in initiating therapy and choice of regimen. Numerous studies show that compliance of <90% results in less-successful suppression of the viral load. In addition, several studies document that almost half of the pediatric patients surveyed were nonadherent to their regimen. Poor adherence to prescribed medication regimens results in subtherapeutic drug concentrations and enhances the development of resistant viruses, leading to limited treatment options. Several barriers to adherence are unique to children with HIV infection. Combination antiretroviral regimens in liquid form are often unpalatable and require extreme dedication on the part of the caregiver and child; a reluctance to disclose the child's disease to others reduces social support; there may be a tendency to skip doses if the caregiver is not around or when the child is in school. Adolescents have other issues

that reduce adherence. Denial of the diagnosis, an unstructured lifestyle, feelings of invincibility, desires for "normalcy," adherence fatigue to lifelong medications, affective disorders, and substance use are just a few of the many factors that may interfere with long-term adherence in this growing population. These and other barriers make involving the family in optimizing adherence essential when possible. Intensive education on the relationship of drug adherence to viral suppression, training on drug administration, frequent follow-up visits, peer support, ongoing support including text messaging and other platforms from medical team and case managers, and commitment of the caregiver and the patient are critical for successful antiviral treatment. Multiple methods such as the viral load response, self-reporting of missed doses during the last 3-7 days, and pharmacy/pill counting should be used to assess adherence. Assessing for emergence of resistant virus on sequencing (genotype) can also be a helpful tool in patients not achieving virologic suppression as expected. For older children and adults, long-acting injectable regimens also now exist and have the potential for enormous benefit for adherence, though currently are only FDA approved for individuals with virologic suppression and no history of treatment failure.

Initiation of Therapy

The decision of when to initiate cART has evolved significantly over the years in both adults and children. When cART was first introduced, medication regimens had significant side effects, leading to decisions to delay therapy until it was thought to be most beneficial, usually after advanced immunologic suppression had developed. The Strategic Timing of Antiretroviral Treatment (START) trial demonstrated a strong benefit in starting therapy earlier in adults, even before CD4 counts fell into an immunosuppressed range; this became more feasible with the development of safer, better-tolerated medications. In adults, it has also been found that receiving suppressive cART eliminates the risk of the sexual transmission of HIV to others. Current adult guidelines recommend the initiation of cART in all adults with HIV. **In line with the adult guidelines, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV now also recommends starting treatment for all children with HIV as soon as possible**. For children <1 year of age, the Children with HIV Early Antiretroviral Therapy (CHER) trial has clearly demonstrated the benefit of early immediate ART. Children younger than 1 year of age are at high risk for disease progression, and immunologic and virologic tests to identify those likely to develop rapidly progressive disease are less predictive than in older children. Therefore all HIV-infected infants younger than 1 year of age should be treated with cART as soon as the diagnosis of HIV infection has been confirmed, regardless of their clinical or immunologic status or viral load. Data suggest that HIV-infected infants who are treated before the age of 3 months control their HIV infection better than infants whose cART started later than 3 months of age. Among older children, mortality rates are lower and growth is more normal in children who are started on immediate cART. Initiation of cART therapy should be deferred in children with active cryptococcal meningitis, tuberculosis infection, or disseminated MAC infection in collaboration with an HIV expert.

The pediatric HIV guidelines are updated twice yearly, and care providers should check for revisions regularly at https://www.nih.gov/research-training/hiv/aids-info-center.

Dosages

Children are usually treated with higher doses (per kilogram weight) than adults because of reduced absorption or increased drug metabolism. Data on ART drug dosages for neonates, especially premature infants, are often limited. Because of the immaturity of the neonatal liver, there often must be an increase in the dosing interval of drugs primarily cleared through hepatic glucuronidation.

For some medications in older children, ART dosages/selections need to factor in sexual maturity rating (SMR) (formerly known as Tanner staging). Fortunately thanks to evolving pediatric pharmacokinetic data, many simpler regimens are now available to children ≥25 kg, including once-daily, single-pill (fixed-dose combination) regimens (see Table 322.3 for comprehensive dosing information for current HIV drugs used in children as of February 2023). Because some ART agents may alter the metabolism of some hormonal contraceptives and decrease their effectiveness, interactions should be considered when choosing contraceptive agents for adolescents. A comprehensive table of interactions of HIV medications with hormonal contraceptives can be found in the perinatal HIV guidelines that are updated twice yearly at https://www.nih.gov/research-training/hiv/aids-info-center. Medroxyprogesterone (DMPA) is a reasonable choice for most cART regimens. Alternative long-acting contraception options, such as use of an intrauterine device, should also be considered.

Changing Antiretroviral Therapy

A change in therapy should be strongly considered when the current regimen is judged ineffective as evidenced by an increase in viral load, deterioration of the CD4 cell count, or clinical progression. Development of toxicity or intolerance to drugs is another reason to consider a change in therapy. When a change is considered, the patient and family should be reassessed for adherence concerns. Because adherence is a major issue in this population, resistance testing (while the patient is taking antiretroviral medications) is important in identifying adherence issues (e.g., detectable virus sensitive to current drug regimen is consistent with a lack of adherence) or the development of resistance (e.g., evidence of resistance mutations to current drug regimen). In both situations, other contributing factors, such as poor absorption, an incorrect dose, or drug-drug interactions, should be carefully reviewed. While considering possible new drug choices, the potential for cross-resistance should be addressed. In starting a new regimen in a patient with virologic failure, the new regimen should include at least two, but preferably three, fully active antiretroviral medications, with assessment of the anticipated activity based on the treatment history and resistance testing (genotype or less commonly phenotype). The goal is to achieve and maintain virologic suppression. If virologic suppression cannot be achieved, the goals of therapy should focus on preserving immunologic function and preventing further disease progression, as well as preventing the emergence of additional drug resistance (which could limit future treatment options).

Monitoring Antiretroviral Therapy

To ensure proper monitoring, the CD4 cell count, viral load, complete blood count, chemistries, urinalysis, and serum lipids should be obtained before an initiation of or change in cART to have a baseline for comparisons during treatment. At entry into care, genotypic resistance testing should be done as well. Children must be seen within 1-4 weeks after initiation of new cART to reinforce and counsel regarding adherence and to screen for potential side effects. Ideally, telephone or text follow-up by the medical team for adherence and side effects also occurs in the interval between cART start and the follow-up visit. Virologic and immunologic surveillance (using the quantitative HIV RNA PCR and CD4 lymphocyte count), as well as clinical assessment, should be performed regularly while on cART. The initial virologic response (i.e., at least a fivefold [0.7 $\log_{10}$] reduction in viral load) should be achieved within 4-8 weeks of initiating ART. The maximum response to therapy usually occurs within 12-16 weeks but may be later (24 weeks) in very young infants. Thus HIV RNA levels should be measured at 4-8 weeks and 12-24 weeks after therapy initiation. Once an optimal response has occurred, the viral load should then be measured at least every 3-6 months. If the response is unsatisfactory, another viral load should be determined as soon as possible to verify the results before a change in therapy is considered. Virologic failure is defined as a repeated plasma viral load ≥200 copies/mL after 6 months of therapy. The CD4 cells respond more slowly to successful treatment, particularly in patients with long-standing infection and CD4 suppression. CD4 counts should be monitored every 3-4 months and potentially can be done less frequently in adolescents and adults with documented virologic suppression. Potential toxicity should be monitored closely for the first ~8 weeks (including complete blood count, serum chemistries), and if no clinical or laboratory toxicity is documented, follow-up visits are recommended every 1-2 months for children <18 months to allow increases in medication doses in

association with weight gain) and every 3-4 months for older children and adolescents. Monitoring for potential toxicity should be tailored to the patient's medication regimen. Toxicities include but are not limited to hematologic complications (e.g., zidovudine); hypersensitivity rash (e.g., efavirenz); lipodystrophy (e.g., redistribution of body fat seen with NRTIs and PIs, which can take several years to emerge); hyperlipidemia (elevation of cholesterol and triglyceride concentrations); hyperglycemia and insulin resistance (e.g., PIs); mitochondrial toxicity leading to severe lactic acidosis; electrocardiogram abnormalities (e.g., atazanavir, lopinavir); abnormal bone mineral metabolism (e.g., tenofovir disoproxil fumarate but not tenofovir alafenamide); and hepatic toxicity, including severe hepatomegaly with steatosis. After a patient is on a stable regimen, labs outside of CD4 count and viral load can be done every 6-12 months. An important part of every visit is ongoing adherence counseling given the need for excellent adherence to cART to avoid the emergence of resistance. *Detailed current guidelines for monitoring HIV-infected children during therapy can be found at* https://www.nih.gov/research-training/hiv/aids-info-center.

Resistance to Antiretroviral Therapy

Young children usually are at greater risk than adults for developing resistance because they have higher viral loads and fewer ART options than adults (reflecting the fact that only some agents are available in a liquid formulation and have pharmacokinetic dosing data for children). The high mutation rate of HIV (mainly as a result of the absence of error-correcting mechanisms in the reverse-transcriptase enzyme) results in the generation of viruses with multiple mutations every day in the absence of cART. Failure to reduce the viral load to <50 copies/mL on cART because of nonadherence resulting in subtherapeutic drug levels increases the risk for developing resistance by selecting those mutant viruses with a competitive advantage (i.e., drug resistance mutations). Even effectively treated patients do not completely suppress all viral replication, and persistence of HIV transcription and evolution of envelope sequences continues in the latent cellular reservoirs, though data show that this evolution does not appear to affect the emergence of resistance to cART in virologically suppressed patients. Accumulation of resistance mutations, particularly in nonadherent patients, progressively diminishes the potency of the cART and challenges the physician to find new regimens. For some drugs (e.g., nevirapine, lamivudine), a single mutation is associated with resistance, whereas for other drugs (e.g., zidovudine, lopinavir, darunavir, etravirine, etc.), several mutations are needed before significant resistance develops. Testing for drug resistance, especially when devising a new regimen, is standard of care. Two types of tests are available; genotype is most commonly used, but the phenotype may be helpful in select patients with complex viral resistance as a result of exposure to multiple cART regimens.

The **phenotype** measures the virus susceptibility in various concentrations of the drug. This allows calculation of the drug concentration that will inhibit the viral replication by 50% (IC_{50}). The ratio of the IC_{50} and a reference virus IC_{50} is reported as the fold resistance change. Note that this test is usually combined with a genotype when used but is largely reserved for patients with extremely complex mutations. The **genotype** predicts the virus susceptibility from mutations identified in the HIV genome isolated from the patient and is the more commonly used test. Several online sites (e.g., http://hivdb.stanford.edu) can assist in interpreting the test's results. Several studies show that the treatment success is higher in patients whose cART was guided by genotype or phenotype testing.

Neither method may detect drug resistance if the amount of the resistant virus is <10% of the circulating population or if it is present only in the latent reservoir. Note that if a patient has not been taking cART for several weeks, the absence of selective drug pressure will make the dominant population of circulating viruses revert to the wild type, and resistance mutations can be missed.

It is recommended to test for drug resistance before initiating therapy and before changing treatment because of virologic failure. When changing therapy, the resistance test results should be considered in the context of previous resistance tests results, if done, and drugs used in previous regimens.

Supportive Care

Even before cART drugs were available, a significant impact on the quality of life and survival of HIV-infected children was achieved when supportive care was given. A multidisciplinary team approach is desirable for successful management. After the initiation or change of cART, more frequent visits or contacts with the patient/caregivers for support and education will help in their acceptance and adjustment to the new regimen and will contribute to a better adherence. Close attention should be paid to the nutritional status, which is often delicately balanced and may require aggressive supplementation, especially in children with advanced disease. Painful oropharyngeal lesions and dental caries may interfere with eating, and thus routine dental evaluations and careful attention to oral hygiene are important. Paradoxically, an increasing number of adolescents with perinatally acquired or behavioral risk–acquired disease are obese. Some teens experience cART-related central lipoaccumulation (usually related to older agents), but others have poor dietary habits and inactivity as the cause of their obesity, just as others do who are obese in epidemic numbers in the United States. Their development should be evaluated regularly, with the provision of necessary physical, occupational, and/or speech therapy. Recognition of pain in the young child may be difficult, and effective nonpharmacologic and pharmacologic protocols for pain management should be instituted when indicated.

All HIV-exposed and HIV-infected children should receive standard pediatric immunizations (Table 322.4). Live oral polio vaccine should not be given because of poor immunologic response in HIV-infected children and concern for live vaccination in potentially immunocompromised children. The risk and benefits of rotavirus vaccination should be considered in HIV-exposed infants. Because <1% of these infants in resource-rich settings will develop HIV infection, the vaccine should be given in infants with negative testing at 2-3 weeks and 6-8 weeks of age. In other situations, the considerable attenuation of the vaccine's strains should be considered, and unless the infant has clinical symptoms of AIDS or a CD4 count <750, vaccination is likely appropriate; consultation with an HIV expert is recommended. Other live bacterial vaccines (e.g., bacillus Calmette-Guérin) should be avoided because of the high incidence of bacillus Calmette-Guérin–related disease in HIV-infected infants. Varicella and measles-mumps-rubella vaccines are recommended for children who are not severely immunosuppressed (i.e., CD4 cell percentage ≥15%, absolute CD4 count >500 cells/μL for ages 1-5 years), but these vaccines should not be given to severely immunocompromised children (i.e., CD4 cell percentage <15%, absolute CD4 count <500 cells/μL for age 1-5 year). Of note, prior immunizations do not always provide protection, as evidenced by outbreaks of measles and pertussis in immunized HIV-infected children. The durability of vaccine-induced titers is often short, especially if vaccines are administered when the child's CD4 cell count is low, and reimmunization when the CD4 count has increased may be indicated. It is recommended that children with HIV receive quadrivalent meningococcal conjugate vaccine at a younger age than the routine schedule. Adolescent vaccines are also important, including the Tdap booster and HPV vaccine. The current recommended annotated vaccine schedule for HIV-infected children is found here (updated annually): https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html.

Prophylactic regimens are integral for the care of HIV-infected children. All infants 4-6 weeks to 1 year of age who are proved to be HIV-infected should receive prophylaxis to prevent *P. jiroveci* pneumonia regardless of the CD4 count or percentage (Tables 322.5 and 322.6). Infants exposed to HIV-infected individuals should receive the same prophylaxis until they are proved to be noninfected; however, prophylaxis does not have to be initiated if there is strong presumptive evidence of noninfection (i.e., nonbreastfed infant with two negative HIV PCR tests at >14 days and 4 weeks of age, respectively). When the HIV-infected child is >1 year of age, prophylaxis should be given according to the CD4 lymphocyte count (see Table 322.5). The best prophylactic regimen is 150 mg/m^2/day of TMP and 750 mg/

Table 322.4 Routine Childhood Immunization Schedule for HIV-Infected Children

VACCINE	BIRTH	1 MO	2 MO	4 MO	6 MO	12-15 MO	2 YR	4-6 YR	11-12 YR
Hepatitis B	HepB		HepB			HepB			
Measles, mumps, and rubella* Varicella vaccines*						MMR* Varicella* If CD4 >500		MMR* Varicella* If CD4 >200	
Influenza†					Annual				
COVID-19‡					Regular schedule‡				
Pneumococcal conjugate vaccine§			PCV	PCV	PCV	PCV			
Pneumococcal polysaccharide vaccine							PPSV23‖		
Haemophilus influenzae B vaccine			Hib	Hib	Hib	Hib			
Diphtheria, tetanus and pertussis			DTaP	DTaP	DTaP	DTaP		DTaP	Tdap
Inactivated polio vaccine			IPV	IPV		IPV		IPV	
Hepatitis A vaccine						HepA	HepA		
Meningococcal conjugate vaccine							MCV4¶ (2-shot series)		
HPV vaccine									HPV** (3-shot series)
Rotavirus vaccine			RV†† (2- to 3-shot series)						
Dengue‡‡									Dengue‡‡ (3-shot series) If CD4 >200

Note some combination vaccines may allow for fewer doses to be administered (such as for combination vaccines containing DTaP and Hib; followed recommended schedule of product)
*MMR vaccine and varicella vaccine should only be administered to children age 1-5 yr with absolute CD4 count >500 sustained for 6 mo and children >5 yr with CD4 count >200 sustained for 6 mo (or CD4% >15% if absolute count unavailable). MMRV is contraindicated in HIV-infected children. For immune-reconstituted children can consider giving second MMR and varicella vaccines 1-3 mo after first dose as long as criteria are met.
†Inactivated influenza vaccine should be used in ages ≥6 mo.
‡COVID-19 vaccination is recommended for HIV-infected children and should be given per the pediatric recommendations, including boosters starting at 6 mo of age.
§PCV15 or PCV20 can be used.
‖PPSV23 is given and boosted at 5 years; If PCV20 is given, PPSV23 optional. PPSV23 must be given 8 weeks after PCV given.
¶MCV4 (quadrivalent conjugate vaccine) should be administered starting 24 mo with 2-dose series 8 wk apart. Must be given at least 4 wk after completion of PCV13 series. Booster recommended at 5 years. Meningococcal B conjugate vaccine also should be considered.
**HPV vaccine should be given in a 3-shot series at 0, 1-2 mo, 6 mo (minimum intervals 4 wk from dose 1 to 2, 12 wk from dose 2 to 3 with minimum of 5 mo between doses 1 and 3). HIV patients require 3 shots regardless of age series is started.
††Rotavirus vaccine has not been well studied in infants with HIV infection. It should be given to low-risk exposed infants. For infected infants, use caution particularly in those with significant immunosuppression. If given, series must be started before 15 wk of age and completed by 8 mo of age.
‡‡Dengue vaccination is recommended for children 9-16 yr living in endemic areas of dengue who have laboratory confirmed dengue at 0, 6 mo, 12 mo. It should not be given if CD4 <200. It is not recommended for children traveling to dengue-endemic areas.
Current vaccine schedule with recommendations for immunocompromised populations can be found here (updated annually): https://www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf.

m^2/day of SMX (maximum: 320/1,600 mg) given as 1-2 daily doses 3 days (consecutively or every other day) per week or daily if preferred for ease of adherence. For severe adverse reactions to TMP-SMX, alternative therapies include dapsone, atovaquone, and aerosolized pentamidine.

Prophylaxis against MAC should be offered to HIV-infected children with advanced immunosuppression (i.e., CD4 lymphocyte count <750 cells/μL in children <1 year of age, <500 cells/μL in children 1-2 year of age, <75 cells/μL in children 2-5 years of age, and <50 cells/μL in children >6 years of age) (see Table 322.6). The drugs of choice are azithromycin (20 mg/kg [maximum: 1,200 mg] once a week orally *or* 5 mg/kg [maximum: 250 mg] once daily orally) *or* clarithromycin (7.5 mg/kg twice daily orally). In rare situations, rifabutin 300 mg daily can be an alternative for children >6 years of age, though efficacy data in children is very limited.

Based on data for adults, primary prophylaxis against most opportunistic infections may be discontinued if patients have experienced sustained (>6 months' duration) immune reconstitution with cART, even if they had previous opportunistic infections such as *Pneumocystis* pneumonia or disseminated MAC. HIV-infected children are at higher risk for TB and thus should have tuberculin skin testing (5 tuberculin units purified protein derivation [PPD]) or IFN-γ release assay (IGRA) testing for TB annually; an induration of ≥5 mm should be considered positive for the PPD. IGRA is preferred in children with history of BCG

Table 322.5 Recommendations for *Pneumocystis jiroveci* Pneumonia Prophylaxis and CD4 Monitoring for HIV-Exposed Infants and HIV-Infected Children, by Age and HIV Infection Status

AGE/HIV INFECTION STATUS	PJP PROPHYLAXIS	CD4 MONITORING
Birth to 4-6 wk, HIV-exposed	No prophylaxis	None
HIV infection reasonably excluded*	No prophylaxis	None
<1 yr, HIV-infected or HIV-indeterminate	Prophylaxis regardless of CD4 count or percentage	According to local practice for initiation or follow-up of cART
1-5 yr, HIV-infected	Prophylaxis if CD4 <500 cells/μL or <15%†	According to local practice for initiation or follow-up of cART
>6 yr, HIV-infected	Prophylaxis if CD4 <200 cells/μL or <15%†,‡	According to local practice for initiation or follow-up of cART

The National Perinatal HIV Hotline (1-888-448-8765) provides consultation on all aspects of perinatal HIV care.
*See text.
†More frequent monitoring (e.g., monthly) is recommended for children whose CD4 counts or percentages are approaching the threshold at which prophylaxis is recommended.
‡Prophylaxis should be considered on a case-by-case basis for children who might otherwise be at risk for PJP, such as children with rapidly declining CD4 counts or percentages or children with category C conditions. Children who have had PJP should receive PJP prophylaxis until their CD4 count is ≥200 cells/mm^3 for patients age ≥6 yr, CD4 percentage is ≥15% or CD4 count is ≥500 cells/mm^3 for patients age 1 to <6 yr for >3 consecutive mo after receiving cART for ≥6 mo.
cART, Combined antiretroviral therapy; PJP, *Pneumocystis jiroveci* pneumonia.

Table 322.6 Prophylaxis to Prevent First Episode of Opportunistic Infections Among HIV-Exposed and HIV-Infected Infants and Children, United States*

		PREVENTIVE REGIMEN	
PATHOGEN	INDICATION	FIRST CHOICE	ALTERNATIVE
STRONGLY RECOMMENDED AS STANDARD OF CARE			
Pneumocystis pneumonia†	HIV-infected or HIV-indeterminate infants age 1-12 mo; HIV-infected children age 1-5 yr with CD4 count of <500 cells/μL or CD4 percentage of <15%; HIV-infected children age 6-12 yr with CD4 count of <200 cells/μL or CD4 percentage of <15%; >13 yr with CD4 count <200 or <15%	**TMP-SMX**, 150/750 mg/m^2 body surface area per day or 5-10 mg/kg/day (TMP)/25-50 mg/kg/day (SMX) (max: 320/1,600 mg) orally qd or bid 3 times weekly on consecutive days *Or* qd or bid orally 3 times weekly on alternate days	**Dapsone:** age ≥ 1 mo: 2 mg/kg (max: 100 mg) orally qd; or 4 mg/kg (max: 200 mg) orally once a week **Atovaquone:** age 1-3 mo and >24 mo-12 yr: 30 mg/kg orally qd with food Age 4-24 mo: 45 mg/kg orally qd with food; ≥13 yr 1,500 mg orally qd with food **Aerosolized pentamidine:** age ≥5 yr: 300 mg once a month by Respirgard II (Marquest, Englewood, CO) nebulizer
Malaria	Living or traveling to area in which malaria is endemic	Same for HIV-infected and HIV-uninfected children. Refer to http://www.cdc.gov/malaria/ for the most recent recommendations. **Mefloquine**, 5 mg/kg orally 1 time weekly (max: 250 mg) **Atovaquone/proguanil** (Malarone) qd 11-20 kg: 62.5 mg/25 mg (1 pediatric tablet) 21-30 kg: 2 pediatric tablets 31-40 kg: 3 pediatric tablets >40 kg: 1 adult tablet (250 mg/100 mg)	**Doxycycline**, 2.2 mg/kg body weight (maximum 100 mg) orally qd for children >8 yr **Chloroquine**, 5 mg/kg base (equal 7.5 mg/kg chloroquine phosphate) orally up to 300 mg weekly (only for regions where the parasite is sensitive)

Continued

Table 322.6 Prophylaxis to Prevent First Episode of Opportunistic Infections Among HIV-Exposed and HIV-Infected Infants and Children, United States*—cont'd

PATHOGEN	PREVENTIVE REGIMEN		
	INDICATION	FIRST CHOICE	ALTERNATIVE
Mycobacterium tuberculosis			
Isoniazid-sensitive	TST reaction ≥5 mm Or Prior positive TST result without treatment Or Positive interferon-γ release assay (IGRA) result Or Close contact with any person who has contagious TB. TB disease must be excluded before start of prophylaxis	Age ≥12 yr: 12 doses of weekly isoniazid (15 mg/kg rounded up to the nearest 50 or 100 mg; max 900 mg) and rifapentine: 10–14.0 kg: 300 mg 14.1–25.0 kg: 450 mg 25.1–32.0 kg: 600 mg 32.1–49.9 kg: 750 mg ≥50.0 kg: max 900 mg 12 weekly doses of isoniazid (25 mg/kg for children age 2–12 yr) and rifapentine: 10–14.0 kg: 300 mg 14.1–25.0 kg: 450 mg 25.1–32.0 kg: 600 mg 32.1–49.9 kg: 750 mg ≥50.0 kg: max 900 mg *Or* 20-30 mg/kg body weight (max: 900 mg) orally 2 times weekly for 9 mo; DOT highly recommended	**Rifampin**, 15-20 mg/kg body weight (max: 600 mg) orally daily for 4 mo Isoniazid 10–15 mg/kg (max 300 mg) daily and rifampin 10–20 mg/kg (max 300 mg/day) for 3 mo Isoniazid 10-15 mg/kg body weight (max 300 mg) daily for 6-9 mo
Isoniazid-resistant	Same as previous pathogen; increased probability of exposure to isoniazid-resistant TB	**Rifampin**, 10-20 mg/kg body weight (max: 600 mg) orally daily for 4 mo	Consult TB expert
Multidrug-resistant (isoniazid and rifampin)	Same as previous pathogen; increased probability of exposure to multidrug-resistant TB	Choice of drugs requires consultation with public health authorities and depends on susceptibility of isolate from source patient	
Mycobacterium avium complex‡	For children age ≥6 yr with CD4 count of <50 cells/μL; age 2 to <6 yr with CD4 count of <75 cells/μL; age 1 to <2 yr with CD4 count of <500 cells/μL; age <1 yr with CD4 count of <750 cells/μL	**Clarithromycin,** 7.5 mg/kg (max: 500 mg) orally bid *Or* **Azithromycin,** 20 mg/kg (max: 1,200 mg) orally once a week	**Azithromycin,** 5 mg/kg body weight (max: 250 mg) orally qd *Or* Children age ≥5 yr **Rifabutin**, 300 mg orally qd
Varicella-zoster virus§	Exposure to varicella or shingles with no history of varicella Or Zoster or seronegative status for VZV Or Lack of evidence for age-appropriate vaccination	Varicella-zoster immunoglobulin (VariZIG), 125 IU/10 kg (max: 625 IU) IM, administered ideally within 96 hr after exposure; potential benefit up to 10 days after exposure	If VariZIG is not available and <96 hr from exposure, **acyclovir** 20 mg/kg (max: 800 mg) 4 times a day for 7 days starting 7-10 days postexposure *Or* IVIG, 400 mg/kg, administered once
Vaccine-preventable pathogens	Standard recommendations for HIV-exposed and HIV-infected children	Routine vaccinations (see Table 322.4)	
USUALLY RECOMMENDED			
Toxoplasma gondii¶	Seropositive IgG to *Toxoplasma* and severe immunosuppression: age <6 yr with CD4 percentage <15%; age ≥6 yr with CD4 count <100 cells/μL	TMP-SMX, 150/750 mg/m^2 orally qd or divided bid	**Dapsone**, age ≥1 mo: 2 mg/kg or 15 mg/m^2 (max: 25 mg) orally qd Plus **Pyrimethamine**, 1 mg/kg (max: 25 mg) orally qd Plus **Leucovorin**, 5 mg orally every 3 days *Or* Atovaquone per PJP dosing
Invasive bacterial infections	Hypogammaglobulinemia (i.e., IgG <400 mg/dL)	IVIG 400 mg/kg body weight every 2-4 wk	

Table 322.6 Prophylaxis to Prevent First Episode of Opportunistic Infections Among HIV-Exposed and HIV-Infected Infants and Children, United States*—cont'd

		PREVENTIVE REGIMEN	
PATHOGEN	**INDICATION**	**FIRST CHOICE**	**ALTERNATIVE**
Cytomegalovirus	CMV antibody positivity and severe immunosuppression (CD4 count <50 cells/μL for >6 yr; CD4 percentage <5% for ≤6 yr)	**Valganciclovir**, 900 mg orally qd with food for older children who can receive adult dosing For children age 4 mo to 16 yr, valganciclovir oral solution 50 mg/mL at dose in milligrams = 7 × BSA × CrCl (up to maximum CrCl of 150 mL/min/1.73 m^2) orally qd with food (maximum dose 900 mg/day)	N/A

*Information in these guidelines might not represent FDA approval or FDA-approved labeling for products or indications. Specifically, the terms *safe* and *effective* might not be synonymous with the FDA-defined legal standards for product approval.
†Daily trimethoprim-sulfamethoxazole (TMP-SMX) reduces the frequency of certain bacterial infections. Compared with weekly dapsone, daily dapsone is associated with a lower incidence of PCP but higher hematologic toxicity and mortality rates. Patients receiving therapy for toxoplasmosis with sulfadiazine-pyrimethamine are protected against PCP and do not need TMP-SMX. TMP-SMX, dapsone-pyrimethamine, and possibly atovaquone (with or without pyrimethamine), protect against toxoplasmosis; however, data have not been prospectively collected.
‡Substantial drug interactions can occur between rifamycins (i.e., rifampin and rifabutin) and protease inhibitors and nonnucleoside reverse transcriptase inhibitors. A specialist should be consulted.
§Children routinely being administered intravenous immunoglobulin (IVIG) should receive VariZIG if the last dose of IVIG was administered more than 21 days before exposure.
¶Protection against toxoplasmosis is provided by the preferred anti-*Pneumocystis* regimens and likely by atovaquone.
CMV, Cytomegalovirus; FDA, U.S. Food and Drug Administration; HIV, human immunodeficiency virus; IgG, immunoglobulin G; IM, intramuscularly; IVIG, intravenous immunoglobulin; PCP, *Pneumocystis* pneumonia; TB, tuberculosis; TMP-SMX, trimethoprim-sulfamethoxazole; TST, tuberculin skin test; VZV, varicella-zoster virus.
From Panel on Opportunistic Infections in Children with and Exposed to HIV. Guidelines for the Prevention and Treatment of Opportunistic Infections in Children with and Exposed to HIV. Department of Health and Human Services. Available at https://clinicalinfo.hiv.gov/en/guidelines/pediatric-opportunistic-infection. Table 1: Primary Prophylaxis. Accessed 11/5/23.

vaccination. If the child is living in close contact with a person with TB, the child should be tested more frequently. Of note, the sensitivity of PPD and IGRA are reduced in severely immunocompromised patients. The Guidelines for Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children (https://www.nih.gov/research-training/hiv/aids-info-center) should be consulted for these and other opportunistic infections that may occur in these populations. To reduce the incidence of opportunistic infections, parents should be counseled about (1) the importance of good handwashing; (2) avoiding raw or undercooked food *(Salmonella)*; (3) avoiding drinking or swimming in lake or river water or being in contact with young farm animals *(Cryptosporidium)*; and (4) the risk of playing with or having certain pets (*Toxoplasma* and *Bartonella* from cats, *Salmonella* from reptiles).

PROGNOSIS

The improved understanding of the pathogenesis of HIV infection in children and the availability of more effective antiretroviral drugs has changed the prognosis considerably for children with HIV infection. The earlier cART is started, the better the prognosis. In settings with ready access to early diagnosis and ART, progression of the disease to AIDS has significantly diminished. Since the advent of cART in the mid-1990s, mortality rates in perinatally infected children have declined more than 90% and most children in high-income settings survive to adolescence and adulthood. Even with only partial reduction of the viral load, children may have significant immunologic and clinical benefits. In general, the best prognostic indicators are the sustained suppression of the plasma viral load and the restoration of a normal $CD4^+$ lymphocyte count. If determinations of the viral load and CD4 lymphocytes are available, the results can be used to evaluate prognosis. It is unusual to see rapid progression in an infant with a viral load <100,000 copies/mL. In contrast, a high viral load (>100,000 copies/mL) over time is associated with a greater risk for disease progression and death. CD4 count is also another prognostic indicator with mortality rate significantly higher in profoundly immunosuppressed individuals. To define the prognosis more accurately, the use of changes in both markers (CD4 lymphocyte percentage and plasma viral load) is recommended.

Even in resource-limited settings where cART and molecular diagnostic tests are less available, the use of cART has had a substantial benefit on the survival of HIV-infected children and has reduced the likelihood of mortality by >75%. Children with opportunistic infections (e.g., *Pneumocystis* pneumonia, MAC), encephalopathy and regressing developmental milestones, or wasting syndrome, which are all AIDS-defining conditions, have the worst prognosis, with 75% dying before 3 years of age. A higher risk of death was documented in children who did not receive TMP-SMX preventive therapy. Persistent fever and/or oral thrush, serious bacterial infections (meningitis, pneumonia, sepsis), hepatitis, persistent anemia (<8 g/dL), and/or thrombocytopenia (<100,000/μL) also suggest a poor outcome, with >30% of such children dying before 3 years of age. In contrast, lymphadenopathy, splenomegaly, hepatomegaly, lymphoid interstitial pneumonitis, and parotitis are associated with a slower progression of disease and a better prognosis. With sustained virologic suppression and maintained immunologic function, life expectancy is quite good. Unfortunately, access to cART for children in resource-limited settings lags greatly behind access for adults even today. For adults and adolescents acquiring HIV, effective cART can restore life expectancy to near normal.

PREVENTION

Parental Treatment and Infant Prophylaxis

Use of ART for interruption of perinatal transmission has been one of the greatest achievements of HIV research. cART is documented to decrease the rate of perinatal HIV-1 transmission to <2%, and to <1% if the person with HIV has a viral RNA level <1,000 copies/mL at delivery. **Therefore it is recommended that all pregnant individuals be tested for HIV, and if they are positive, be treated with a cART regimen, irrespective of the viral load or CD4 count during pregnancy. All infants born to HIV-infected individuals should receive zidovudine prophylaxis; duration is determined by risk status, with 2-4 weeks for low-risk infants and 6 weeks for high-risk infants** (Table 322.7). Additional antiretroviral drugs should be added to zidovudine if the risk of acquiring HIV by the newborn is high. High-risk scenarios include infants born to individuals who received neither antepartum nor intrapartum antiretroviral drugs or only intrapartum antiretroviral drugs, who do not achieve a suppressed viral load near delivery despite cART (defined as at least two consecutive tests with HIV RNA <50 copies/mL obtained at least 4 weeks apart), who have acute or primary HIV infection during the pregnancy, who have unknown HIV status who test positive at delivery or postpartum, or infants who have a positive

Table 322.7 Intrapartum and Neonatal Management for HIV Exposed Infants by Risk Category

RISK OF PERINATAL HIV TRANSMISSION	DEFINITION	INTRAPARTUM AND NEONATAL ART MANAGEMENT
Low risk (3 defined groups)	Infants ≥37 weeks gestation who are born to a person with HIV who meets **ALL** of the following criteria: • Is currently receiving and has received at least 10 consecutive weeks of ART during pregnancy • Has achieved and maintained or maintained viral suppression† for the remainder of the pregnancy • Has a viral load <50 copies/mL at or after 36 wk • Did not have acute HIV infection during pregnancy • Has reported good ART adherence, and adherence concerns have not been identified	No IV AZT* required in labor Vaginal delivery Prophylaxis with zidovudine × 2 wk
	Infants born to a person with HIV who do not meet the criteria above but who have a HIV RNA <50 copies/mL at or after 36 wk gestation	No IV AZT* required in labor Vaginal delivery ZDV for 4-6 wk
	Premature infants (<37 wk gestation) who are not at high risk of perinatal acquisition of HIV	No IV AZT* required in labor Vaginal delivery ZDV for 4-6 wk
High risk	Infants who are born to a person with HIV who meet **ANY** of the following criteria: • Did not receive cART antepartum or received only intrapartum therapy • Did not achieve viral suppression* within 4 wk before delivery • Had acute or primary HIV infection during the pregnancy or breastfeeding (in the case of the latter, breastfeeding should be immediately discontinued [see text])	Parent should get IV AZT in labor if viral load >1000 or unknown C-section if viral load >1000 or unknown Presumptive HIV therapy regimen × 6 wk with either • Zidovudine, lamivudine, and nevirapine* • Zidovudine, lamivudine and raltegravir* for up to 6 wk Alternate regimen: • Zidovudine × 6 wk + 3-dose nevirapine protocol In all cases, duration of zidovudine should be for 6 wk if other 2 medications are discontinued before that time point.
Presumed newborn HIV exposure	Infants born to a person with HIV who: • Have unconfirmed HIV status with at least one positive HIV test in labor or during delivery/postpartum period • Have a newborn with positive HIV antibody test at delivery	Same as for high risk If supplemental testing confirms person giving birth does not have HIV, infant ARV drugs should be discontinued immediately.

*Due to resistance of HIV-2 to NNRTIs, raltegravir regimen should be considered for high-risk infants born to individuals with HIV-2.
†See Table 322.3 for dosing.
Adapted from Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to Reduce Perinatal HIV transmission in the United States. http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf.

HIV antibody test on screening after delivery. In these scenarios, three regimen options can be considered: (1) a presumptive HIV therapy regimen of zidovudine, lamivudine, and nevirapine at treatment doses; (2) a presumptive HIV therapy regimen of zidovudine, lamivudine, and raltegravir at treatment doses; or (3) zidovudine plus the addition of three doses of nevirapine (at birth, 48 hours, and 144 hours of life) (see Table 322.7). Note that treatment doses of raltegravir for neonates are different than for older children, with an escalating dose over the 6 weeks of therapy because of evolving liver metabolism in neonates. For infants at high risk, options 1 and 2 are now preferred, though option 3 has excellent data supporting it for select patient scenarios. Enthusiasm and support for treatment regimens (particularly option 1) have been driven by a case of an apparent functional cure in an infant in 2013 who went 2 years without cART with virologic suppression before rebound of the infection occurred (the Mississippi baby), as well as a large cohort of high-risk, exposed infants in Canada. For neonates, experience is greatest with zidovudine, which can cause transient anemia or neutropenia in exposed infants. There is also a strong pool of data supporting the safety of lamivudine in neonates, including neonates born as early as 32 weeks' gestational age (GA). For the remaining drugs for treatment of infants at high risk, data are most robust for nevirapine, with dosing recommendations down to 32 weeks' GA. Data for raltegravir are more limited, supporting use only in newborns 37 weeks' GA and up. *In infants at high risk, consultation with an experienced HIV specialist is highly recommended. The National Perinatal HIV Hotline (1-888-448-8765) provides 24/7 support from experienced HIV specialists to help in managing high-risk infants. Guidelines and current recommended doses for prophylaxis in newborns are updated at least yearly and can be accessed at* https://www.nih.gov/research-training/hiv/aids-info-center. A complete blood count, differential leukocyte count, and platelet count should be performed at 4-8 weeks of age to monitor zidovudine toxicity. If the child is found to be HIV infected, baseline laboratory assessment (e.g., CD4 count, HIV RNA, complete blood count, chemistries, lipids, and genotype) should be obtained and cART should be started as soon as possible. Cesarean section as a prevention strategy was examined in a multinational meta-analysis, which showed that the combination of elective C-section and parental zidovudine treatment reduced transmission by 87%. However, these data were obtained before the advent of cART, and the additional benefit of elective C-section to the cART-treated individual whose viral load is <1,000 copies/mL is negligible. Thus elective C-section at 38 weeks of gestation should be considered only for pregnant individuals whose viral load is >1,000 copies/mL in late gestation, to further reduce the risk of vertical transmission.

Because perinatal transmission can be reduced dramatically by treating pregnant individuals, prenatal testing and identification of HIV-1 infection as early as possible is extremely important. The benefit of therapy both for the individual's health and to prevent transmission

to the infant cannot be overemphasized. The recommended universal prenatal HIV counseling and testing for all pregnant individuals has reduced the number of new infections dramatically in many areas of the United States and Europe. For those not tested during pregnancy, the use of rapid HIV antibody testing during labor or shortly after the infant's birth is a way to provide perinatal prophylaxis to an additional group of at-risk infants. Perinatal recommendations also now endorse the testing of pregnant individuals' partners to identify partners with HIV who may transmit HIV infection to them, leading to acute HIV infection, which carries an extremely high risk of vertical transmission both intrapartum and postpartum if the individual is breastfeeding and seroconverts.

Feeding of the HIV-Exposed Infant: Breastfeeding Recommendations and Prophylaxis

It is universally recommended that all pregnant individuals receive a cART regimen appropriate for their own health, which should be continued for the remainder of their lives. This approach improves parental survival, lowers the transmission risk to sexual partners, promotes simplified universal treatment regimens, and reduces transmission during breastfeeding and future pregnancies.

Breastfeeding has been recommended for infants born to individuals with HIV in resource-limited settings by the WHO and other authorities for nearly 2 decades. This recommendation was based on strong evidence that early weaning is not safe in resource-limited settings because of the high risk of death from malnutrition and diarrhea in formula-fed infants without a consistent source of clean water and formula. Furthermore, exclusive breastfeeding (no additional solids or fluids other than water) resulted in less transmission than mixed feeding. Guidelines evolved to recommend that HIV-infected persons living in resource-limited settings should breastfeed their infants until at least 12 months of age, with exclusive breastfeeding for the first 6 months, and cART should continue to be provided to the breastfeeding parent. **Data from multiple large studies of this practice in low- and middle-income countries have shown suppressive parental cART is extremely effective in preventing transmission of HIV via breastfeeding to <1%. Additionally, there have been a series of smaller case series in resource-rich settings with individuals on suppressive cART breastfeeding with no transmission documented. However, it is important to stress that the rate of transmission even for fully suppressed HIV-infected breastfeeding individuals is not zero.** Because of this data, in January 2023, the guidelines in the U.S. for recommended infant feeding have significantly changed for feeding of the HIV-exposed infant. These recommendations were made for several reasons:

- Recognition of the very low risk of transmission from virologically suppressed individuals.
- Recognition of the benefits of breastfeeding to both the infant (improved immune status, lower risk of developing asthma, obesity, type 1 diabetes, severe lower respiratory disease, otitis media, sudden infant death syndrome, gastrointestinal infections, and necrotizing enterocolitis) and breastfeeding parent (decreased risk of hypertension; type 2 diabetes; breast, endometrial, and ovarian cancers; bonding with infant; decreased monetary costs of feeding).
- Recognition that pregnant individuals living with HIV in the United States are disproportionately Black, a group that has significantly higher prevalence of many of these negative health outcomes as well and that prohibiting breastfeeding in this group denies them potential benefit.
- Recognition of important cultural pressures that may affect the desire to breastfeed and fear that by not breastfeeding, HIV status may be inadvertently disclosed to family and friends.
- Recognition that some individuals living with HIV in the past who were prohibited from breastfeeding did so surreptitiously without support that could have decreased risk to infant.

It is now recommended that expectant individuals with HIV should receive evidence-based, patient-centered counseling regarding infant feeding starting early, ideally before conception or in early pregnancy. The provider should engage in open-minded shared decision making in discussing the decision to breastfeed or formula feed the infant throughout the pregnancy. Key points of counseling should include:

- Achieving and maintaining viral suppression through ART during pregnancy and postpartum decreases breastfeeding transmission risk to less than 1%, but not zero.
- Replacement feeding with properly prepared formula or pasteurized donor human milk from a milk bank eliminates the risk of postnatal HIV transmission to the infant. This is the recommended feeding choice for individuals living with HIV who do not have suppressed viral load through the third trimester and at delivery given the significantly increased risk of HIV transmission to the infant.
- Individuals with HIV who are on cART with a sustained undetectable viral load and who choose to breastfeed will be supported in this decision.
- Individuals with HIV who choose to formula feed should also be supported in their decision, and potential barriers should be addressed.

It is important to stress that engaging Child Protective Services or similar agencies is not an appropriate response to infant feeding choices of an individual living with HIV. This puts an important therapeutic relationship at risk for both the individual and the infant, can result in harm to families, and can further exacerbate the stigma and discrimination that individuals living with HIV face.

The risk of HIV transmission via breastmilk for individuals on suppressive cART (<50) is <1%. There are ways to make risk of transmission as low as possible in this scenario, including providing excellent parental support such as addressing resource needs, mental health, and helping promote cART adherence. The postpartum period is a time of high risk for developing nonadherence to cART because of the stress of child-raising, lack of sleep, potential postpartum depression (PPD) and other factors. Individuals living with HIV who give birth have significantly higher rates of PPD that is associated with significant rise in cART nonadherence, so early screening and treatment of PPD is critical. Support of a lactation specialist is also important to help establish and maintain good milk supply so that mixed feeding can be minimized and to promote good breast health and avoidance of milk stasis, bleeding nipples, and mastitis. In the pre cART era, mixed feeding (i.e., introduction of breast milk plus other liquid or solid foods, including formula) was associated with increased risk of transmission of HIV, particularly in the first 2 months of life; no data are available in this area (including just formula supplementation) in the context of cART and virologic suppression. Because of this historical data, the goal is exclusive breastfeeding for 6 months to minimize risk.

It is recommended that individuals with HIV who are breastfeeding/chestfeeding have HIV RNA testing every 1-2 months to monitor virologic suppression closely. For the breastfed infant, the initial testing schedule is dictated by risk of infant at birth. Additionally, the breastfed infant should receive testing at 1-2 months and 4-6 months to avoid an interval of >3 months between tests, and every 3 months after the 4- to 6-month test for as long as breastfeeding continues. It is recommended to avoid rapid weaning, with a goal of weaning over 2-4 weeks because of pre-cART data associating rapid weaning with increased risk of HIV transmission to the infant. Infants should be tested 4-6 weeks, 3 months, and 6 months after weaning is complete (see Fig. 322.4).

Several studies demonstrate the efficacy of ART prophylaxis of the breastfed infant in preventing transmission of HIV during breastfeeding in the era before cART being recommended for all pregnant individuals and in some studies in which pregnant individuals received cART but did not have viral load routinely monitored. Successful regimens have included daily single-dose nevirapine (NVP), lamivudine (3TC), lopinavir/ritonavir (LPV/r), and a combined NVP + ADV regimen. For infants at low risk, it is not clear whether additional prophylaxis during breastfeeding after the initial prophylaxis of 2-6 weeks adds additional benefit; that said, some experts choose to provide prophylaxis for infants at low risk. In the scenario in which an individual with HIV who is not virologically suppressed elects to breastfeed after counseling despite recommendations not to do so because of increased risk, it is recommended that the infant receive 6 weeks of three-drug presumptive HIV therapy (high risk), and then daily NVP throughout

Table 322.8 Infant Antiretroviral Prophylaxis for Newborns of Individuals Who Breastfeed

NEWBORNS AT LOW RISK OF HIV ACQUISITION DURING BREASTFEEDING*	
RECOMMENDED REGIMEN	**DURATION**
ZDV	2 wk
EXTENDED POSTNATAL PROPHYLAXIS FOR NEWBORNS AT HIGH RISK OF HIV TRANSMISSION DURING BREASTFEEDING*	
RECOMMENDED REGIMEN	**DURATION**
ZDV	4-6 wk*
NVP†	SIMPLIFIED AGE-BASED DOSING FOR NEWBORNS ≥32 WK GESTATION RECEIVING EXTENDED NVP PROPHYLAXIS DURING BREASTFEEDING‡
AGE	**VOLUME NVP MG/ML ORAL SYRUP DAILY**
6 wk to 6 mo	2 mL
6 mo to 9 mo	3 mL
9 mo to 1-4 wk post weaning	4 mL

*This extended neonatal prophylaxis regimen is optional for low-risk infants, though recommended by some experts. For high-risk breastfed infants (parent not virologically suppressed), 6 wk of ZDV (plus additional agents as recommended in Table 322.7) followed by extended neonatal NVP prophylaxis is recommended.

†For breastfeeding parents with viral resistance to NVP, alternative regimens for infant prophylaxis after completion of the 4-6 wk of presumptive HIV therapy include daily 3TC or LPV/r; see Table 322.3 Antiretroviral Drug Dosing Recommendations for Newborns for dosing information.

‡Extended NVP prophylaxis during breastfeeding recommendations are adapted from the Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring: Recommendations for a Public Health Approach. If prescribed, these simplified doses should start following confirmation of a negative infant NAT test and completion of a presumptive HIV therapy regimen in infants at high risk of HIV acquisition. For infants at low risk of transmission, these doses can be given from birth. World Health Organization. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. Geneva: World Health Organization, 2021. Table A1.7. Available at https://www.who.int/publications/i/item/9789240031593. (Accessed 5 Nov 2023)

breastfeeding and for 1-4 weeks after weaning to further mitigate risk of HIV transmission (Table 322.8).

HIV-negative breastfeeding individuals with a sexual partner with HIV should also be monitored closely for developing HIV infection, because acute infection during breastfeeding carries a high risk of transmission to the infant (29–53%). It is recommended that these individuals consider preexposure prevention (PrEP) (see later) and practice barrier protection consistently to decrease risk of acute HIV infection during the breastfeeding period and educated on the signs and symptoms of acute HIV infection. They should also be tested every 1-2 months for seroconversion; if they become positive, breastfeeding should cease, and the infant should be placed on a high-risk three-drug presumptive HIV therapy regimen for 28 days and tested per the high-risk schedule with start point at time of cessation of breastfeeding.

Risk of transmission of HIV goes up considerably if virologic suppression in the breastfeeding parent is compromised. Therefore frequent HIV RNA (viral load) monitoring is recommended so that if there is virologic rebound, risk can be mitigated. In the scenario that viral load becomes detectable in the breastfeeding parent, it is recommended that the parent stop breastfeeding the infant immediately; milk can be pumped and discarded to maintain supply. The individual should be provided counseling regarding adherence, support, and resources, and discussion of whether to cease breastfeeding altogether or continue given the risk of HIV transmission to the infant should occur. Other scenarios that would require either modifying or stopping breastfeeding (in some cases temporarily) include cracked or bleeding nipples and mastitis. In these conditions, breastfeeding can continue on the unaffected side, and milk from the affected side should be pumped and discarded until the breast is fully healed and recovered. Again, having an experienced lactation consultant involved in the care of these individuals is critical. *Clinicians are strongly encouraged to consult the national Perinatal HIV/AIDS hotline (1-888-448-8765) with questions about infant feeding by individuals with HIV; the hotline provides 24/7 support from experienced HIV specialists to help in managing infants at high risk. U.S. guidelines for prevention of vertical transmission are regularly updated at https://www.nih.gov/research-training/hiv/aids-info-center/ and the international guidelines are regularly updated at the WHO website (https://www.who.int/health-topics/hiv-aids#tab=tab_1).*

Prevention of Sexual Transmission: Preexposure Prophylaxis and Postexposure Prevention

Prevention of sexual transmission involves avoiding the exchange of bodily fluids. In sexually active adolescents, barrier protection (male and female condoms) should be an integral part of programs to reduce sexually transmitted diseases, including HIV-1. Unprotected sex with older partners, multiple partners, transactional sex, and the use of recreational drugs can be associated with acquisition of HIV-1 infection in adolescents and young adults. Educational efforts about avoidance of risk factors and safer sex practices are essential for older school-age children and adolescents and should begin well before the onset of sexual activity. In addition, promising research for sexually active adults may translate to increased prevention for adolescents. Three African trials demonstrated that male circumcision was associated with a 50–60% reduction in the risk of HIV acquisition in young men. For females, use of a 1% vaginal gel formulation of tenofovir during intercourse was found to reduce HIV acquisition by nearly 40% in one study, though subsequent trials have had variable efficacy; other topical microbicides are being investigated. An increasingly important tool for HIV prevention is **PrEP** using once-daily dosing of co-formulated tenofovir and emtricitabine, approved for adolescents and adults weighing at least 35 kg (77 lb). The efficacy of PrEP in preventing sexual acquisition of HIV in MSM, heterosexual couples, and individuals in noncommitted relationships ranges from 70–92%. A depo injectable PrEP option (cabotegravir) dosed every 8 weeks is now approved for adults and adolescents ≥12 years weighing at least 35 kg (77 lb). large randomized multinational clinical trials of HIV serodiscordant adults have demonstrated that effective cART therapy in the HIV-infected partner essentially eliminates secondary sexual transmission to an uninfected sexual partner, creating the catchphrase "U = U" or "undetectable = untransmittable." The data from these trials can likely be extrapolated for youth with long-standing virologic suppression.

Postexposure prevention (PEP) is another important tool in HIV prevention and has been used in healthcare workers after needlesticks and body substance exposures. It can also be effective after a single high-risk event (including unprotected sexual activity, high-risk sexual assault, and intravenous drug use/needle sharing). PEP should be given as soon as possible after the high-risk exposure, ideally within 24 hours and at the latest within 72 hours of the exposure to have efficacy. Efficacy is higher the sooner it is given. Baseline testing should be performed at the time PEP is started, but initial doses should not be delayed for laboratory test results. Baseline testing includes HIV antigen/antibody testing (fourth-generation HIV ELISA), hepatitis B and C testing (because most high-risk exposures have risk of transmission of these as well), serum creatinine, and alanine aminotransferase (ALT). If a patient is hepatitis B immune (including having completed a full hepatitis B vaccine series), hepatitis B testing does not need to be performed. For sexual exposures, gonorrhea, chlamydia, and syphilis, testing should be done. After completion of a PEP course, follow-up testing should be done at 4-6 weeks and 3 months after exposure. If hepatitis C was transmitted, HIV testing should be repeated at 6 months as well, because HIV seroconversion can be delayed in patients with co-infection with hepatitis C. PEP regimens are three-drug treatment regimens for 28 days. For

individuals ≥12 years old, generally the preferred regimen consists of tenofovir DF + emtricitabine with either dolutegravir or raltegravir (note that dolutegravir allows for a once-daily regimen). For individuals 2 years old to <12 years old, the preferred regimen is tenofovir DF + emtricitabine + raltegravir. For those <2 years old the preferred regimen is zidovudine + lamivudine + raltegravir. In the rare cases in which the source patient is known to have HIV infection and is in care, selection can be guided by the source patient's genotype and/or treatment history. Abacavir and nevirapine are both contraindicated for use in PEP.

SUMMARY

The course and prognosis of HIV infection has improved dramatically as a consequence of cART for all ages, particularly with newer agents with fewer side effects. With good adherence, patients can achieve prolonged virologic suppression and immune function can be preserved or reconstituted. However, lifelong adherence and side effects of medications are important challenges to recognize that can prevent patients from achieving good outcomes. Globally, great strides have been made in preventing vertical transmission and increasing access to cART for children and adults, which is important for maintaining health as well as driving down sexual and vertical transmission with virologic suppression. However, there is still much work to be done to ensure the end of the global HIV epidemic, including continued advancement of our understanding of the immunology of HIV latency and reservoirs, HIV vaccines, and continued increases in access to cART worldwide, particularly in children.

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Chapter 323

Human T-Cell Leukemia Viruses (1 and 2)

Paul Spearman and Lee Ratner

ETIOLOGY

Human T-cell leukemia viruses 1 (HTLV-1) and 2 (HTLV-2) are members of the *Deltaretrovirus* genus of the Retroviridae family, which are single-stranded RNA viruses that encode reverse transcriptase, an RNA-dependent DNA polymerase that transcribes the single-stranded viral RNA into a double-stranded DNA copy. HTLV-1 was the first human retrovirus discovered, isolated in 1979 from a cutaneous T-cell lymphoma. The closely related virus HTLV-2 was subsequently identified in 1981. HTLV-1 is associated with adult T-cell leukemia/lymphoma (ATL) and HTLV-1–associated myelopathy/tropical spastic paraparesis (HAM/TSP), whereas HTLV-2 is less pathogenic and rarely is associated with neurologic diseases.

HTLV-1 and -2 share a genome homology of approximately 65%. The genome contains *gag, pr, pol,* and *env* genes and several nonstructural genes. The nonstructural proteins include the Tax and Rex regulatory proteins, the novel proteins essential for virus spread (p30, p12, and p13), and the antisense-encoded HTLV-1 basic leucine zipper factor, HBZ. HTLV-1 and -2 infect cells via the ubiquitous glucose transporter type or via neuropilin-1, both of which serve as virus receptors. HTLV-1 and -2 can infect a variety of cells, with HTLV-1 most often found in $CD4^+$ T cells and HTLV-2 showing preference for $CD8^+$ T cells. After viral entry, reverse transcription produces a double-stranded DNA copy of the RNA genome that is transported into the nucleus and integrated into chromosomal DNA (the provirus), evading the typical mechanisms of immune surveillance and facilitating lifelong infection.

EPIDEMIOLOGY AND MODES OF TRANSMISSION

HTLV-1 has infected 15-20 million persons globally. It is endemic in southwestern Japan (where >10% of adults are seropositive); areas of the Caribbean, including Jamaica and Trinidad (up to 6%); and in parts of sub-Saharan Africa (up to 5%). Lower seroprevalence rates are found in South America (up to 2%) and Taiwan (0.1–1%). There is microclustering with marked variability within geographic regions.

The seroprevalence of HTLV-1 and HTLV-2 in the general population in the United States is 0.01–0.03% for each virus, with higher rates with increasing age. The prevalence of HTLV-1 infection is highest in babies born in endemic areas or in persons who have had sexual contact with persons from endemic areas. The prevalence of HTLV-2 infection is highest in intravenous drug users, with a seroprevalence of 8.8–17.6% in this population.

HTLV-1 and -2 are transmitted as cell-associated viruses from mother to child and **transmission** through genital secretions, contaminated blood products, and intravenous drug use. Mother-to-child transmission during the intrauterine period or peripartum period is estimated to occur in less than 5% of cases but increases to approximately 20% with breastfeeding. Higher maternal HTLV-1 proviral load and prolonged breastfeeding are associated with greater risk of mother-to-child transmission. In Japan, approximately 20–25% of children born to HTLV-1–infected mothers became infected before recommendations that seropositive mothers should avoid breastfeeding, with a marked reduction to 2.5% transmission after restriction of breastfeeding. HTLV-2 may also be transmitted via breastfeeding, but it has a slightly lower reported transmission rate via breast milk of approximately 14%.

DIAGNOSIS

HTLV-1 and HTLV-2 infections are diagnosed by screening using a second-generation enzyme immunoassay with confirmation by immunoblot, indirect immunofluorescence, or line immunoassays. Polymerase chain reaction can also be used to distinguish HTLV-1 from HTLV-2 infection.

CLINICAL MANIFESTATIONS

The lifetime risk of disease associated with HTLV-1 infection is estimated at 5–10% and is highest after vertical transmission. HTLV-1 is associated with ATL and several nonmalignant conditions, including the neurodegenerative disorder HAM, also known as tropical spastic paraparesis (TSP) and sometimes termed HAM/TSP. The geographic epidemiologic characteristics of ATL and HAM are similar. **HTLV-1–associated arthropathy** mimics rheumatoid arthritis, including a positive rheumatoid factor. Treatment is with antiinflammatory agents. **HTLV-1–associated uveitis** may be unilateral or bilateral, is more common among women, and resolves spontaneously, although it often recurs within 1-3 years. Topical corticosteroids hasten recovery. **HTLV-1–associated infective dermatitis** is a chronic and recurrent eczematous disease occurring during childhood and adolescence that predisposes to staphylococcal infection. HTLV-1 infection predisposes to disseminated and recurrent *Strongyloides stercoralis* infection, increased risk of developing tuberculosis disease after latent infection, and severe scabies.

ADULT T-CELL LEUKEMIA/LYMPHOMA

The age distribution of ATL peaks at approximately 50 years, underscoring the long latent period of HTLV-1 infection. HTLV-1–infected persons remain at risk for ATL even if they move to an area of low HTLV-1 prevalence, with a lifetime risk for ATL of 2–4%. Most cases of ATL are associated with monoclonal integration of HTLV-1 provirus into the cellular genome of $CD4^+$ T lymphocytes, resulting in unchecked proliferation of CD4 T cells. There is a spectrum of disease that is categorized into different forms: acute, lymphomatous, chronic, primary cutaneous smoldering, and primary cutaneous tumoral. The acute form of ATL comprises 55–75% of all cases. Smoldering subclinical lymphoproliferation may spontaneously resolve in approximately

half of cases or progress to chronic leukemia or lymphomatous, or even acute ATL. **Chronic, low-grade, HTLV-1–associated lymphoproliferation (pre-ATL)** may persist for years with abnormal lymphocytes with or without peripheral lymphadenopathy before progressing to the acute form. Acute ATL is characterized by hypercalcemia, lytic bone lesions, lymphadenopathy that spares the mediastinum, hepatomegaly, splenomegaly, cutaneous lymphomas, and opportunistic infections. Leukemia may develop with circulating polylobulated malignant lymphocytes, called **flower cells**, possessing mature T-cell markers. Antiviral therapy with zidovudine and interferon-α is the standard therapy for leukemic-type ATL in the United States and Europe. In lymphoma-type ATL, **response rates may be improved using the anti-CCR4 monoclonal antibody mogamulizumab with chemotherapy**. Allogeneic hematopoietic stem cell transplantation is sometimes employed.

HUMAN T-CELL LYMPHOTROPIC VIRUS-1–ASSOCIATED MYELOPATHY

HAM is more common in women than in men and has a relatively short incubation period of 1-4 years after HTLV-1 infection, compared with 40-60 years for ATL. HAM occurs in up to 4% of persons with HTLV-1 infection, usually developing during middle age. It is characterized by infiltration of mononuclear cells into the gray and white matter of the thoracic spinal cord, leading to severe white matter degeneration and fibrosis. HTLV-1 is found near but not directly within the lesions, suggesting that reactive inflammation is a major mechanism of disease. The cerebrospinal fluid typically shows a mildly elevated protein and a modest monocytic pleocytosis, along with anti–HTLV-1 antibodies. Neuroimaging studies are normal or show periventricular lesions in the white matter. Clinical manifestations include gradual onset of slowly progressive, symmetric neurologic degeneration of the corticospinal tracts and, to a lesser extent, the sensory system that leads to lower-extremity spasticity or weakness, lower back pain, and hyperreflexia of the lower extremities with an extensor plantar response. The bladder and intestines may become dysfunctional, and men may become impotent. Some patients develop dysesthesias of the lower extremities with diminished sensation to vibration and pain. Upper-extremity function and sensation, cranial nerves, and cognitive function are usually preserved. **Treatment regimens have included corticosteroids, danazol, interferon, plasmapheresis, high-dose vitamin C, and antivirals, all with minimal effects.** Recent studies examined the effects of mogamulizumab (anti-CCR4 antibody) on HAM, but results are not yet conclusive.

HUMAN T-CELL LYMPHOTROPIC VIRUS-2

HTLV-2 was originally identified in patients with hairy cell leukemia, although most patients with hairy cell leukemia are seronegative for HTLV-2 infection. HTLV-2 has been rarely isolated from patients with leukemias or with myelopathies resembling HAM, and there is limited evidence of disease specifically associated with HTLV-2 infection.

PREVENTION

Routine antibody testing of all blood products for HTLV-1 and -2 is performed in many developed countries and is effective in preventing blood transfusion–associated infections. Unfortunately, this testing is not always available in low- and middle-income countries with higher endemicity. Prenatal screening and avoidance of breastfeeding by HTLV-1–infected mothers is an effective means of reducing mother-to-child transmission of HTLV-1. Safe sexual practices to avoid sexually transmitted infections, such as condom use and avoiding multiple sexual partners, may reduce transmission of both HTLV-I and HTLV-2. No vaccine is available.

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Chapter 324

Transmissible Spongiform Encephalopathies

David M. Asher and Brian S. Appleby

The transmissible spongiform encephalopathies (**TSEs, prion diseases**) are slow infections of the human nervous system, consisting of at least four diseases of humans (Table 324.1): kuru; **Creutzfeldt-Jakob disease (CJD)** with its variants—sporadic CJD (sCJD), familial CJD (fCJD—some authorities prefer "genetic" CJD), iatrogenic CJD (iCJD), and new-variant or **variant CJD** (vCJD); Gerstmann-Sträussler-Scheinker syndrome (GSS); and fatal familial insomnia (FFI), or the even more rare sporadic fatal insomnia syndrome. sCJD can also be further subdivided based on clinical features—e.g., Heidenhain variant in which early onset of occipital blindness is prominent—or differences in characteristics of abnormal prion protein—e.g., variably protease-sensitive prionopathy (VPSPr). TSEs also affect animals. The most common and best-known TSEs of animals are scrapie in sheep, bovine spongiform encephalopathy (BSE or mad cow disease) in cattle, and a chronic wasting disease (CWD) of deer, elk, reindeer, and moose found in parts of the United States, Canada and, more recently, in Norway, Sweden, and Finland. A TSE of camels has recently been described in North Africa, and others might be anticipated. So far, of all the TSEs of animals, only BSE has proven zoonotic (i.e., transmissible to humans).

All TSEs have similar clinical manifestations and histopathology, and all are "slow" infections with very long asymptomatic incubation periods (often years), durations of several months or more, and overt disease affecting only the nervous system. TSEs are relentlessly progressive after illness begins and invariably fatal. The most striking neuropathologic change that occurs in each TSE, to a greater or lesser extent, is vacuolation, sometimes leading to spongy degeneration of the cerebral cortical gray matter.

ETIOLOGY

The TSEs are transmissible to susceptible animals by inoculation of suspensions of brain and some other tissues from affected subjects. Although the infectious agents replicate in a few cell cultures, they do not achieve the high titers of infectivity found in brain tissues or cause recognizable cytopathic effects in cultures. Most studies of TSE agents, before discovery of the prion proteins, used in vivo bioassays, relying on the transmission of typical neurologic disease to animals as evidence that the agent was present. Inoculation of susceptible recipient animals with small amounts of infectious TSE agents results, months or years later, in the accumulation in tissues of large amounts of agent having the same physical and biologic properties as the original agent. The TSE agents display a spectrum of extreme resistance to inactivation by a variety of chemical and physical treatments that is unknown among conventional pathogens. This characteristic, as well as their partial resistance to protein-disrupting treatments and their consistent association with abnormal isoforms of the normal host-encoded "prion" protein (PrP), stimulated the hypothesis that the TSE agents are probably subviral in size, composed of protein, and devoid of nucleic acid.

The term **prion** (for proteinaceous infectious agent), coined by S. B. Prusiner, is now widely used for such agents. The prion hypothesis proposes that the molecular mechanism by which the pathogen-specific information of TSE agents is propagated involves a self-replicating change in the folding of host-encoded PrP associated with a transition

Table 324.1 Clinical and Epidemiologic Features of Human Transmissible Spongiform Encephalopathies (Prion Diseases)

DISEASE	CLINICAL FEATURES	SOURCE OF INFECTION	GEOGRAPHIC DISTRIBUTION AND PREVALENCE	USEFUL ANCILLARY TESTS	DURATION OF ILLNESS
sCJD	Dementia, myoclonus, ataxia	Unknown	Worldwide; ~1-2/1 million/yr; 85–95% of all CJD cases in the United States	EEG-PSWCs; CSF 14-3-3; RT-QuIC, MRI/DWI	1-24 mo (mean: 4-6 mo)
fCJD	Dementia, myoclonus, ataxia	Genetic association (*PRNP* pathogenic variants)	Worldwide; geographic clusters; >100 known families; 5–15% of CJD cases	Gene testing; EEG-PSWC; CSF 14-3-3, RT-QuIC, MRI/DWI	Mean ~15 mo
iCJD	Incoordination, dementia (late)	Cadaveric dural grafts, human pituitary hormones, corneal transplantation, neurosurgical instruments, EEG depth electrodes	~1% of CJD cases in toto (cadaveric dural grafts); human pituitary hormones, >100 cases; corneal transplantation, three cases; neurosurgical instruments, six cases, including two from cortical depth electrodes; RBC transfusions, four cases of vCJD infection, three clinical, one preclinical (United Kingdom); human plasma–derived factor VIII, one preclinical case of vCJD (United Kingdom)	EEG-PSCW, CSF 14-3-3, RT-QuIC, MRI/DWI	18 mo - >30 yr
vCJD	Mood and behavioral abnormalities, paresthesias, dementia	Linked to BSE in cattle, transfusion plasma products	>230 clinical cases (see iatrogenic vCJD): none living, May 2017	Tonsil biopsy may show PrP^{TSE} MRI/FLAIR	8-36 mo (mean 14 mo)
Kuru	Incoordination, ataxia, tremors, dementia (late)	Linked to cannibalism	Fore tribe of Papua New Guinea (~2,600 known cases)	EEG-no PSWCs; CSF 14-3-3 often negative; MRI (?)	3-24 mo
GSS	Incoordination, chronic progressive ataxia, corticospinal tract signs, dementia (late), myoclonus (rare)	90% genetic (*PRNP* pathogenic variants)	Worldwide; >50 families; ~1-10/100 million/yr	*PRNP* gene sequencing	2-12 yr (mean ~ 57 mo)
FFI	Disrupted sleep, intractable insomnia; autonomic hyperactivation; myoclonus, ataxia; corticospinal tract signs; dementia	*PRNP* gene pathogenic variant (D 178L); very rare sporadic cases	~27 families in Europe, United Kingdom, United States, Finland, Australia, China, Japan	PRNP testing; EEG-PSWCs only rarely positive; MRI-no DWI abnormalities; CSF 14-3-3 positive in ~50%	8 mo to 6 yr (mean: *PRNP* 129 MM 12 ± 4 mo 129 MV 21 ± 15 mo)

BSE, Bovine spongiform encephalopathy; CSF, cerebrospinal fluid; CJD, Creutzfeldt-Jakob disease; DWI, diffusion-weighted image; fCJD, familial Creutzfeldt-Jakob disease; FFI, fatal familial insomnia; FLAIR, fluid attenuation inversion recovery MRI; GSS, Gerstmann-Sträussler-Scheinker syndrome; iCJD, iatrogenic Creutzfeldt-Jakob disease; *PRNP*, prion protein–encoding gene; PrP^{TSE}, abnormal prion protein; PSWCs, periodic sharp wave complexes; RBC, red blood cell; RT-QuIC, real-time quaking-induced conversion; sCJD, sporadic Creutzfeldt-Jakob disease; vCJD, variant Creutzfeldt-Jakob disease.

NOTE: PRNP 129 MM, homozygous, encoding the amino acid methionine at both codons 129 of the prion protein–encoding (*PRNP*) gene on chromosome 20; 129 MV, heterozygous at PRNP codon 129, encoding methionine on one chromosome 20 and valine on the other.

Modified from Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Diseases*. 6th ed. Philadelphia: Elsevier; 2005: p. 2222; Love S, Louis DN, Ellison DW, eds. *Greenfield's Neuropathology*. 8th ed. London: Hodder Arnold; 2008: p. 1239.

from an α-helix-rich structure in the native protease-sensitive conformation ("cellular" PrP or PrP^{C}) to a β-sheet-rich structure in the protease-resistant conformation associated with infectivity. The existence of a second host-encoded protein—termed *protein X*—that participates in the transformation was once postulated to explain certain otherwise puzzling findings but was never identified.

The prion hypothesis is still not universally accepted; it relies on the postulated existence of a genome-like coding mechanism based on differences in protein folding that have not yet been satisfactorily elucidated at a molecular level. In addition, it has yet to account convincingly for the many biologic strains of TSE agent that have been observed, although strain-specific differences in glycosylation patterns

of abnormal PrP have been proposed as providing a plausible molecular basis for the coding. It fails to explain why pure PrP uncontaminated with nucleic acid from an infected host has not consistently transmitted a typical spongiform encephalopathy associated with a serially self-propagating agent. Also troubling is the fact that abnormal PrP and infectivity were not consistently associated in several experimental models and human illnesses. Particularly problematic is the finding that some illnesses associated with pathogenic variants in the *PRNP* gene and accompanied by abnormal PrP failed to transmit infection to animals. If the TSE agents ultimately prove to consist of protein and only protein, with no obligatory nucleic acid component, then proponents of the prion hypothesis will have been prescient. If the agents are ultimately found to contain small nucleic acid genomes, then they might better be considered atypical viruses, for which the term *virino* was once suggested. Until the actual molecular structure of the infectious TSE pathogens and the presence or absence of a nucleic acid genome are rigorously established, it seems acceptable to continue calling them TSE agents (a term that remains popular among some European authorities). Most U.S. authorities now prefer the term *prion* (sometimes referring to the infectious agents of TSEs and sometimes to abnormal PrP, even when not transmissible).

The earliest evidence that abnormal proteins are associated with the TSE was morphologic: scrapie-associated fibrils (SAFs) were found by negative-stain electron microscopy in detergent-treated extracts of brain tissues from patients and animals with TSEs but not in brain tissues of unaffected persons. SAFs resemble but are distinguishable from the amyloid fibrils that accumulate in the brains of patients with Alzheimer disease. Antigenically related protease-resistant PrPs (PrP-res) proved to be components of SAFs and to be present in the amyloid plaques found in the brains of patients and animals with TSEs. The abnormal forms of PrP have been variously designated PrP^{Sc} (scrapie-type PrP), PrP-res, PrP^{TSE} (TSE-associated PrP), or PrP^{D} (also PrP^{Dis}, for "disease-associated" PrP) by different authorities.

It remains unclear whether abnormal PrP constitutes the complete infectious particle of spongiform encephalopathies, is a component of those particles, or is a pathologic host protein not usually separated from the actual infectious entity by current techniques. The demonstration that PrP is encoded by a normal host gene seemed to favor the last possibility. (A possible model for mammalian prions was provided by several studies. The model suggested that agent-specific pathogenic information can be transmitted and replicated by different conformations of fungal proteins having the same primary amino acid sequence without participation of any agent-specific nucleic acids, although those transmissions required microinjections and misfolded proteins were apparently not naturally transmitted to recipient fungi as infectious elements.)

Whatever its relationship to the actual infectious TSE particles, PrP clearly plays a central role in susceptibility to infection, because the normal PrP must be expressed in mice and cattle to infect them. Furthermore, inherited normal variations (genetic polymorphisms) in PrP genotype are associated with increased susceptibility to vCJD and, to a lesser extent, to sCJD and with occurrence of two familial TSEs (fCJD and GSS). PrPs are glycoproteins that have the physical properties of amyloid proteins when misfolded and aggregated into protease-resistant PrP^{TSE}. The PrPs of different species of animals are very similar in their amino acid sequences and antigenicity but are not identical in structure. The primary structure of PrP is encoded by the host and is not altered by the source of the infectious agent provoking its formation. The function of the normal ubiquitous protease-sensitive PrP precursor (designated either PrP^{C} or PrP-sen, for protease-sensitive PrP, by different authorities) in normal cells is unknown; it binds copper and may play some role in normal synaptic transmission but is not required to sustain life or for relatively normal cerebral function in mice and cattle. As noted, animals must express PrP to develop overt TSE as well as to support replication of the TSE agents. The degree of homology between amino acid sequences of PrPs in different animal species may correlate with a "species barrier" that affects susceptibility of animals of one species to infection with a TSE agent adapted to grow in another species, although the degree of sequence homology does not always predict susceptibility to the same TSE agent.

Attempts to find particles resembling those of known viruses or virus-like agents in brain tissues of humans or animals with spongiform encephalopathies have been unsuccessful. Peculiar tubulovesicular structures reminiscent of some viruses have been seen repeatedly in thin sections of TSE-infected brain tissues and cultured cells but not in normal brain cells; it has never been established that those structures are associated with infectivity.

EPIDEMIOLOGY

Kuru once affected many children of both sexes ≥4 years of age, adolescents, and young adults (mainly women) living only in a limited area of Papua New Guinea. The complete disappearance of kuru among people born after 1957 suggests that the practice of ritual cannibalism (thought to have ended that year) was probably the only mechanism by which the infection spread in Papua New Guinea. The probable incubation periods of some cases of kuru have exceeded 50 years. Kuru has not been diagnosed since 2005.

sCJD is the most common human spongiform encephalopathy. Most countries with surveillance for CJD have identified between one and two cases of sCJD per million total population per year (0.25-2 cases per million population, not age-adjusted). That figure is somewhat misleading in that the Centers for Disease Control and Prevention (CDC) has estimated the lifetime risk of sCJD in the United States to be as many as 1 in 6,000 persons, taking into account the number of recognized iCJD cases attributed to use of cadaveric pituitary hormones, typical advanced age of CJD cases at onset, and probable incubation periods of decades. sCJD was formerly thought to occur only in older adults; however, sCJD and sporadic fatal insomnia have also affected a few young people (to date, seven cases reported in adolescents, one in a 14-year-old girl). vCJD, however, has a peculiar predilection for younger people. Of 174 cases of vCJD reported through 2010 in the United Kingdom, all except 23 were in people younger than 40 years of age and 22 were younger than 20 years of age; the youngest age at onset was 12 years.

Proponents of the prion hypothesis are convinced that PrP can spontaneously misfold, becoming self-replicating and causing sCJD; skeptics favor the hypothesis of infection with some ubiquitous TSE agent that, fortunately, has a very low attack rate except in persons with certain pathogenic variants in the *PRNP* gene or possibly non-*PRNP* genetic risk factors. Neither possible etiology has been proven. fCJD, the second most common human TSE, accounts for only 10% or 15% of total cases of CJD. fCJD occurs in a foci of considerably higher incidence in Israel (among Libyan Jews), in isolated villages of Slovakia, and in other limited areas.

sCJD has not been convincingly linked to any prior exposure to other cases and the source of infection remains unknown. Person-to-person spread has been confirmed only for iatrogenic cases. Spouses and household contacts of patients are not at increased risk of acquiring CJD, although two instances of conjugal CJD have been reported. However, medical personnel exposed to brains of patients with CJD may be at some increased risk; at least 20 healthcare workers have been recognized with the disease. In 2019 a young laboratory worker in France died after a 2-year illness confirmed at autopsy to be vCJD; her infection was plausibly attributed to an accidental penetrating wound 7.5 years before onset by a forceps contaminated with brain tissue from a mouse experimentally infected with BSE agent.

The striking resemblance of CJD to scrapie prompted a concern that infected sheep tissues might be a source of spongiform encephalopathy in humans. No reliable epidemiologic evidence suggests that exposure to potentially scrapie-contaminated animals, meat, meat

products, or experimental preparations of the scrapie agent have transmitted a TSE to humans. The potential of the CWD agent to infect human beings has also not been demonstrated but remains under investigation by the CDC and Canadian authorities. Consumption of contaminated venison from animals infected with the CWD agent has not been implicated as a risk factor for human TSE by epidemiologic studies. However, a Canadian study reported that CWD had been experimentally transmitted to monkeys fed venison from overtly healthy infected deer, prompting a health advisory from Canadian authorities (https://www.thetyee.ca/Documents/2017/06/24/Risk-Advisory-Opinion-CWD-2017.pdf).

The same thing is not true for vCJD, which is clearly a zoonosis acquired by humans after dietary exposure to the BSE agent. The outbreak of BSE among cattle (possibly infected by eating scrapie agent–contaminated meat-and-bone meal and later bovine-contaminated meal added to feed) was first recognized in the United Kingdom in 1986 and later reported in cattle of 27 other countries, including Canada and the United States. More than 190,000 cases of BSE have been reported to the World Organization for Animal Health (OIE), almost 97% of those from the United Kingdom. Cases of BSE progressively declined in the United Kingdom after 1992 and somewhat later in other countries; in 2016 only two cases worldwide were reported to the OIE (from France and Spain) and none from the United Kingdom. A single case of BSE was recognized in the United States in 2018. Rare sporadic cases of BSE in old cows, associated with an "atypical" PrP^{TSE} having somewhat different electrophoretic properties from those of the PrP^{TSE} in younger cattle with "classic" cases of BSE during the epidemic, stimulated the hypothesis that atypical BSE was caused by spontaneous generation of a PrP^{TSE} rather than by a feed-borne infection; that hypothesis, however intriguing and appealing to some agricultural authorities, remains unconfirmed though little investigated.

The finding of a new TSE in ungulate and feline animals in British zoos and later in domestic cats first raised a fear that the BSE agent might have acquired a range of susceptible hosts broader than that of scrapie, posing a potential danger for humans. A broadening of the host range of BSE agent remains the most plausible explanation for the later appearance of human vCJD, first described in adolescents in Britain in 1996 and, as of August 2021, eventually affecting at least 178 people potentially exposed to a BSE agent in the United Kingdom (not counting a disturbing number of people with evidence of possible asymptomatic or "preclinical" vCJD infection) and more than 50 in 11 other countries (total 231 cases worldwide): 28 in France, 5 in Spain, 4 in Ireland, 3 in the Netherlands, 3 in Italy, 2 in Portugal, and single cases in Japan and Saudi Arabia. vCJD has also occurred in former residents in the United Kingdom (for more than 6 months) later living in Ireland (two cases), France (one case), Canada (one case), Taiwan (one case), and the United States (two cases). Two cases of vCJD, one in the United States and one in Canada, have been reported in former long-time residents of the Kingdom of Saudi Arabia, a country that has not recognized BSE but might have imported infected cattle or contaminated halal beef products from Britain. A third case of vCJD was previously confirmed in a Saudi citizen residing in the Kingdom of Saudi Arabia. The most recent case of vCJD diagnosed in the United States occurred in an immigrant deemed by the CDC to have been infected during years spent in Kuwait or, less likely, Russia.

No case of vCJD has been confirmed in anyone born in the United Kingdom after 1989. However, examination by immunohistochemistry of resected appendices in the United Kingdom for evidence of subclinical vCJD infection suggested that about 1 in 2,000 tissues tested had detectable accumulations of PrP^{TSE} in lymphoid follicles. It remains controversial whether those accumulations result from subclinical vCJD or other TSE (https://app.box.com/s/hhhhg857fjpu2bnxhv6e/1/2936396377/91796156506/1); none of the PrP^{TSE}-positive subjects to date has been reported with overt TSE.

Iatrogenic transmissions of CJD (iCJD) have been recognized for more than 30 years (Table 324.2). Such accidental medical transmissions of CJD have been attributed to use of contaminated neurosurgical instruments (no case reported since 1980), cortical electrodes contaminated during epilepsy surgery, injections of human cadaveric pituitary growth hormone and gonadotropin (neither currently marketed in the United States), transplantation of human dura mater allografts formerly used as a surgical patching material (especially in Japan), and, rarely, contaminated corneal transplants. Pharmaceuticals and tissue grafts derived from or contaminated with human neural tissues, particularly if obtained from unselected donors and large pools of donors, pose special risks.

Studies of animals experimentally infected with TSE agents first suggested that blood and blood components from humans with preclinical CJD infections might pose a risk of transmitting disease to recipients. Since the 1980s such blood components have been withdrawn as a precaution in the United States when a donor was later found to have CJD and blood products were still in-date. A surveillance program in the United Kingdom reported vCJD in three recipients of nonleukoreduced red blood cells from donors later diagnosed with vCJD; there was autopsy evidence of a preclinical vCJD infection in a fourth red cell recipient who died of another disease. (vCJD has not occurred in anyone exclusively transfused with leukoreduced red blood cells from a donor who later developed vCJD.) A study initiated more than 20 years ago by the American Red Cross and CDC found no recipient of blood components obtained from donors later diagnosed with sCJD (and from one donor with fCJD) had ever developed a TSE.

Evidence of a preclinical vCJD infection was found at autopsy in a British patient with hemophilia A treated with a human plasma–derived coagulation factor VIII to which at least one vCJD-infected donor contributed; the coagulation factor involved was never licensed or marketed in the United States. Authorities in the United Kingdom described two recipients of plasma-derived coagulation factors (both having history of transfusion with blood components as well) who later developed sCJD, concluding that the finding, while of concern, might be coincidental.

PATHOGENESIS AND PATHOLOGY

The probable portal of entry for the TSE agent in kuru is thought to have been either through the gastrointestinal tract or lesions in the mouth or integument incidentally exposed to the agent during cannibalism. Patients with vCJD (and animals with BSE and BSE-related TSEs) are thought to have been similarly infected with the BSE agent by consuming contaminated beef products. Except after direct introduction into the nervous system, the first site of replication of TSE agents appears to be in tissues of the reticuloendothelial system. TSE agents have been detected in low titers in blood of experimentally infected animals (mice, hamsters, cervids, sheep, and monkeys) and in the blood of persons with vCJD; infectivity was mainly associated with nucleated cells, although plasma contained a substantial portion of total infectivity in blood. Mice must have circulating lymphoid cells to be infected by peripheral routes. Limited evidence suggests that TSE agents can also spread to the central nervous system (CNS) by ascending peripheral nerves.

In kuru, it seems probable that the only portal of exit of the agent from the body, at least in quantities sufficient to infect others, was through infected tissues exposed during cannibalism. In iatrogenically transmitted CJD, the brains and eyes of patients with sCJD have been the probable sources of contamination. Experimental transmission of the agent to animals from kidney, liver, lung, lymph node, and spleen sampled at autopsies of patients with sCJD showed that those tissues as well as cerebrospinal fluid (CSF) sometimes contained the CJD agent; none of those sources has been implicated in accidental transmissions of CJD to humans. At no time during the course of any TSE have antibodies or cell-mediated immunity

Table 324.2 Iatrogenic Transmission of Creutzfeldt-Jakob Disease by Products of Human Origin

PRODUCT	PATIENTS (NO.)	INCUBATION TIME	
		MEAN	RANGE
Cornea	3	17 mo	16-18 mo
Dura mater allograft	>100	7.4 yr	1.3-16 yr
Pituitary extracts			
Growth hormone	>100*	12 yr	5-38.5 yr
Gonadotropin	4	13 yr	12-16 yr
Red blood cells	4	? 6 yr	6.3-8.5 yr†
Plasma-derived coagulation factor VIII	1	? >11 yr‡	

*There have been 28 cases reported among approximately 8,000 recipients of human cadaveric growth hormone in the United States; the remaining cases have been reported in other countries.

†The second transfusion-transmitted case of vCJD (Peden AH, Head MW, Ritchie DL, et al. Preclinical vCJD after blood transfusion in a *PRNP* codon 129 heterozygous patient. *Lancet.* 2004;364:527–529) died of unrelated causes about 5 years after transfusion but was found to have accumulations of abnormal PrP in spleen and cervical lymph node, a finding unique to vCJD and interpreted as probable preclinical infection.

‡The diagnosis of vCJD infection attributed to treatment with human plasma–derived coagulation factor VIII (UK Health Protection Agency vCJD abnormal prion protein found in a patient with haemophilia at post mortem. Press release 17 February 2009. http://webarchive.nationalarchives.gov.uk/20140714084352/http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C-/1234859690542?p=1231252394302) was also supported by immunohistochemical testing for abnormal PrP in the spleen of a person who died of other causes. Both patients with "preclinical" infections are thought to have died during the asymptomatic incubation period of vCJD.

to the infectious agents been convincingly demonstrated in either patients or animals. However, mice must be immunologically competent to be infected with the scrapie agent by peripheral routes of inoculation.

Typical changes in TSE include vacuolation and loss of neurons with hypertrophy and proliferation of glial cells, most pronounced in the cerebral cortex in patients with CJD and in the cerebellum in those with kuru. The lesions are usually most severe in or even confined to gray matter, at least early in the disease. Loss of myelin appears to be secondary to degeneration of neurons. There generally is no inflammation, but a marked increase in the number and size of astrocytes is usual. Spongiform changes are not a striking autopsy finding in patients with FFI, and neuronal degeneration and gliosis are largely restricted to thalamic nuclei.

Amyloid plaques are found in the brains of all patients with GSS and in at least 70% of those with kuru. These plaques are less common in patients with CJD. Amyloid plaques are most common in the cerebellum but occur elsewhere in the brain as well. In brains of patients with vCJD, plaques surrounded by halos of vacuoles (described as flower-like or "florid" plaques) have been a consistent finding. TSE amyloid plaques react with antiserum prepared against PrP. Even in the absence of plaques, extracellular PrP^{TSE} can be detected in the brain parenchyma by immunostaining, Western blotting, and enzyme-linked immunosorbent assay (ELISA).

CLINICAL MANIFESTATIONS

Kuru was a progressive degenerative disease of the cerebellum and brainstem with less obvious involvement of the cerebral cortex. The first sign of kuru was usually cerebellar ataxia followed by progressive incoordination. Coarse, shivering tremors were characteristic. Variable abnormalities in cranial nerve function appeared, frequently with impairment in conjugate gaze and swallowing. Patients died of inanition and pneumonia or of burns from cooking fires, usually within 1 year after onset. Although changes in mentation were common, there was no frank dementia or progression to coma, as seen in CJD. There were also no signs of acute encephalitis such as fever, headaches, and convulsions.

Patients with sCJD initially have either sensory disturbances (most often visual) or confusion and inappropriate behavior, progressing over weeks or months to frank dementia, akinetic mutism, and ultimately coma. Some patients have cerebellar ataxia early in disease, and most patients experience myoclonic jerking movements. Mean survival of patients with sCJD has been 4-6 months from the earliest signs of illness, although approximately 10% live for 2 years. vCJD (Table 324.3) differs from the more common sCJD: patients with vCJD are much younger at onset (as young as 12 years) and more often present with complaints of dysesthesia and subtle behavioral changes, often mistaken for psychiatric illness. Severe mental deterioration occurs later in the course of vCJD. Patients with vCJD have survived substantially longer than those with sCJD. (Attempts have been made to subclassify cases of CJD based on electrophoretic differences in PrP^{TSE} and variation in its sensitivity to digestion with the proteolytic enzyme proteinase [PK]; the different variants are said to have somewhat different clinical features, including duration of illness, though all are ultimately fatal.)

GSS is a familial disease somewhat resembling CJD but with more prominent cerebellar ataxia or parkinsonian syndrome and amyloid plaques. Dementia may appear only late in the course of GSS, and the average duration of illness is longer than that of typical sCJD (~5 years). Progressively severe insomnia and dysautonomia as well as ataxia, myoclonus, and other signs resembling those of CJD and GSS characterize FFI and sporadic fatal insomnia. GSS has not been diagnosed in children or adolescents. A case of sporadic fatal insomnia has been described in a young adolescent.

DIAGNOSIS

Diagnosis of spongiform encephalopathies is most often determined on clinical grounds after excluding other diseases. The presence of the 14-3-3 protein (see the section "Laboratory Findings") in CSF may aid in distinguishing between CJD and Alzheimer disease, which is not a consideration in children. Elevations of 14-3-3 protein levels in CSF are not specific to TSEs and are common in viral encephalitis and other conditions causing rapid necrosis of brain tissue. A research-use PrP peptide amplification test (real-time quaking-induced conversion [RT-QuIC]) appears to be sensitive and specific for antemortem diagnosis of sCJD when applied to CSF or nasal brushings but may be less sensitive in younger patients compared with older individuals with TSEs. Brain MRI has proven clinically useful (see later). Brain biopsy may be diagnostic for all forms of CJD but can be recommended only if a potentially treatable disease remains to be excluded or some other reason compels an antemortem diagnosis and may result in a false negative result depending on tissue quality, type, and TSE. Definitive diagnosis usually requires microscopic examination of brain tissue obtained at autopsy. The demonstration of PrP^{TSE} in brain extracts augments histopathologic diagnosis. Accumulation of the abnormal PrP in lymphoid tissues, even before the onset of neurologic signs, is typical of vCJD. Tonsil biopsy may avoid the need for brain biopsy when antemortem histologic diagnosis of vCJD is indicated. To date no blood-based test has been validated for antemortem testing of either humans or animals, though one cumbersome PrP^{TSE} research-use test (protein misfolding cyclic amplification [PMCA]) shows promise. Transmission of disease to susceptible animals by inoculation of brain suspension, while sensitive, specific, and reliable, must be reserved for cases of special research interest. Diagnosis usually rests on recognizing the typical constellation of clinical findings, course of illness, and

Table 324.3 Clinical and Histopathologic Features of Patients with Variant and Typical Sporadic Creutzfeldt-Jakob Disease

FEATURE	VARIANT CJD (FIRST 10 PATIENTS)	SPORADIC CJD (185 PATIENTS)
Years of age at death* (range)	29 (19-74)	65
Duration of illness, mo (range)	12 (8-23)	4-6
Presenting signs	Abnormal behavior, dysesthesia	Dementia, ataxia
Later signs	Dementia, ataxia, myoclonus	Ataxia, myoclonus
Periodic complexes on EEG	Rare	Most
PRNP 129 Met/Met	All tested (except one transfusion-transmitted case, one plasma-derivative transmitted case; one possible clinical case in United Kingdom where no tissue was available to confirm)	83%
Histopathologic changes	Vacuolation, neuronal loss, astrocytosis, plaques (100%)	Vacuolation, neuronal loss, astrocytosis, plaques (≤15%)
Florid PrP plaques†	100%	0
PrP^{TSE} glycosylation pattern	BSE-like‡	Not BSE-like

*Median age and duration for variant CJD; averages for typical sporadic CJD.
†Dense plaques with a pale periphery of surrounding vacuolated cells.
‡Characterized by an excess of high molecular mass band (diglycosylated) and 19-kDa nonglycosylated band glycoform of PrP-res (Collinge J, Sidle KC, Meads J, et al. Molecular analysis of prion strain variation and the aetiology of "new variant" CJD. *Nature.* 1996;383:685–690).
BSE, Bovine spongiform encephalopathy; CJD, Creutzfeldt-Jakob disease; Met, codon 129 of one *PRNP* gene encoding for methionine; *PRNP*, prion protein–encoding gene; PrP, prion protein.
Modified from Will RG, Ironside JW, Zeidler M, et al. A new variant of Creutzfeldt-Jakob disease in the UK. *Lancet.* 1996;347:921–925.

testing (CSF examination, MRI, EEG), confirmed by histopathology and detection of PrP^{TSE} in brain tissues at autopsy (or, less often, by tonsil or brain biopsy).

LABORATORY FINDINGS

Virtually all patients with typical sporadic, iatrogenic, and familial forms of CJD have abnormal EEGs as the disease progresses; the background becomes slow and irregular with diminished amplitude. A variety of paroxysmal discharges such as slow waves, sharp waves, and spike-and-wave complexes may also appear, and these may be unilateral or focal or bilaterally synchronous. Paroxysmal discharges may be precipitated by loud noise. Many patients have typical periodic suppression-burst complexes of high-voltage slow activity on EEG at some time during the illness. Patients with vCJD have only generalized slowing, without periodic bursts of high-voltage discharges on EEG. CT or MRI may show cortical atrophy and large ventricles late in the course of CJD. Most cases of sCJD and many cases of familial TSE demonstrate hyperintensity in cortex or basal ganglia diffusion by weighted imaging (DWI). Many patients with vCJD have an increase in density of the pulvinar on fluid attenuated inversion recovery (FLAIR) MRI sequences. Reliable interpretation of the images is best left to experienced radiologists.

There may be modest elevation of CSF protein content in patients with TSE. Unusual protein spots were observed in CSF specimens from sCJD patients separated by two-dimensional gel electrophoresis and silver staining; the spots were later identified as 14-3-3 proteins, normal proteins not related to PrP that are abundant in neurons but not ordinarily detected in CSF. However, 14-3-3 protein, as noted previously, has also been detected in CSF specimens from some patients with acute viral encephalitides and recent cerebral infarctions, and is not specific to CJD. Finding the 14-3-3 protein in CSF is neither sensitive nor specific but can help confirm the diagnosis of sCJD, especially when accompanied by increases in other cellular proteins. Tests for 14-3-3 in CSF are often negative in patients with vCJD.

TREATMENT

No treatment has proven effective for any TSE, and it seems unlikely that treatment can reverse the severe brain damage found in late disease. Studies of cell cultures and rodents experimentally infected with TSE agents suggested that treatments with chlorpromazine, quinacrine, and tetracyclines might be of benefit, especially during the incubation period; however, results of clinical trials based on those studies have been discouraging. Infusions with pentosan polysulfate directly into the cerebral ventricles may have delayed the progression of vCJD in at least one patient but did not reverse earlier brain damage. On the basis of experimental studies in animals, several prophylactic postexposure treatment regimens have been suggested, but none has been validated or widely accepted. Results of some preliminary studies suggested that treatments with antisense oligonucleotides or other molecular genetic therapies might impair translation of the prion protein gene, potentially ameliorating the degenerative process of TSE if initiated before CNS damage has appeared; such early treatment would have to be directed to otherwise healthy persons bearing a pathogenic variant known to occur in familial TSE, because those destined to develop the more common sCJD cannot be identified before brain damage appears. Appropriate compassionate supportive care should be provided to all CJD patients as for those with other progressive fatal neurologic diseases.

GENETIC COUNSELING

TSEs occur in some families in a pattern consistent with an autosomal dominant mode of inheritance. In patients with a family history of CJD, the clinical and histopathologic findings are similar to those seen in sporadic cases. In the United States, only approximately 10% of cases of CJD are familial. GSS and FFI are always familial. In some affected families, approximately 50% of siblings and children of a patient with a familial TSE eventually acquire the disease; in other families, the "penetrance" of illness is lower.

The gene encoding PrP is closely linked if not identical to that controlling the incubation periods of scrapie in sheep and both scrapie and CJD in mice. The same gene in humans is designated the *PRNP*

gene, located on the short arm of chromosome 20. It has an open reading frame of about 759 nucleotides (253 codons), in which more than 20 different point pathogenic variants and a variety of inserted sequences encoding extra tandem-repeated octapeptides have been linked to the occurrence of spongiform encephalopathy in families, a disease expressed in a pattern consistent with autosomal dominance of variable penetrance. The E200K point pathogenic variant has been the most common worldwide.

The same nucleotide substitution at codon 178 of the *PRNP* gene (D178N) associated with CJD in some families has also been found in all patients with FFI but associated with linkage to a different polymorphic amino acid at codon 129 of the *PRNP* gene on the same chromosome (fCJD with 129V and FFI with 129M). Homozygosity for valine (V) and especially for methionine (M) at codon 129 seems to increase susceptibility to both iCJD and sCJD. All but three patients with vCJD to be genotyped have been homozygous for methionine at codon 129 of the *PRNP* gene. A few probable preclinical vCJD infections and two clinically typical cases of vCJD (one confirmed and another not completely evaluated) occurred in persons with the 129 MV heterozygous genotype. It is of interest that when the *PRNP* genes from appendices containing accumulations of what appears to be PrP^{TSE} in the United Kingdom were sequenced, a surprising number were homozygous for 129V—the genotype of only approximately 10% of British subjects—and never found in a case of overt vCJD. The significance of this finding is not clear. Authorities in the United Kingdom adopted the precautionary assumption that some persons with PrP^{TSE} in lymphoid tissues may have latent infections; as time goes by without detecting any overt cases of vCJD in those persons, that assumption becomes less likely. Whether the blood or tissues of such persons are infectious remains unknown.

Although the interpretation of these findings in regard to the prion hypothesis remains controversial, persons from families with CJD or GSS who have the associated pathogenic variants in the *PRNP* gene clearly have a high probability of eventually developing TSE. Bearers of TSE-associated pathogenic variants have successfully employed preimplantation genetic diagnosis and in vitro selection of embryos to avoid passing the mutant gene to offspring. The significance of pathogenic variants in the *PRNP* genes of individuals from families with no history of spongiform encephalopathy is not known. It seems wise to avoid alarming those from unaffected families who have miscellaneous pathogenic variants in the *PRNP* gene, because the implications are not yet clear. In the United States, persons are currently deferred from donating blood if a blood relative has been diagnosed with a familial TSE unless the donor (the relative or implicated parent) has no TSE-related mutation.

PROGNOSIS

The prognosis of all spongiform encephalopathies is uniformly poor. Approximately 10% of patients may survive for longer than 2 years but the quality of life is poor.

FAMILY SUPPORT

The CJD Foundation (http://www.cjdfoundation.org), organized and maintained by family members and friends of patients with CJD and related disorders, working closely with the CDC (www.cdc.gov/prions/index.html) and with the National Prion Disease Pathology Surveillance Center, Case Western Reserve University, Cleveland, Ohio (http://www.cjdsurveillance.com), is a support and educational group and a useful source of information regarding available resources for those dealing with the diseases.

PREVENTION

Exposure to the BSE agent in meat products clearly poses a special danger, which is now greatly reduced. Authorities in Canada, the United States, and other countries responded by implementing progressively more stringent agricultural and public health measures during the past 25 years, with prohibition of most bovine-derived materials from feeds for ruminants probably the most effective measure. Three cases of BSE in native cattle were recognized in the United States from 2004 through 2012; a case was also found in a Canadian cow imported into the United States in 2003. Canada found 20 native cattle with BSE between 2003 and 2015 (and imported a case from the United Kingdom in 1993). In spite of encouraging epidemiologic studies that failed to implicate exposure to scrapie or CWD agents in human TSEs, it seems prudent to avoid exposing children to meat and other products likely to be contaminated with any TSE agent.

The safety of human blood, blood components, and plasma derivatives in the United States and Canada is protected by deferring, as a precaution, some donors with histories suggesting an increased risk of exposure to TSE agents: persons treated with human cadaveric pituitary hormones or dura mater allografts (neither currently marketed in the United States) and donors who voluntarily disclose history of familial TSE (fCJD, GSS, FFI) unless sequencing shows that the TSE-affected relative or the donor has no TSE-related mutation in either *PRNP* gene (https://www.fda.gov/vaccines-blood-biologics/guidancecompliance-regulatory-information-biologics/biologicsguidances).

In principle, it would be better to identify the very few blood and tissue donors actually infected with a TSE rather than deferring all those at increased risk of exposure, because most of them are unlikely to have been infected. Antemortem screening tests that might eventually identify donors with preclinical TSE infections are currently under development though not clinically validated. It seems unlikely that any test would be adopted to screen blood donors without simultaneously implementing a highly specific validated confirmatory test to avoid the serious adverse implications resulting from the inevitable false-positive screening results. In any case, the current risk of transfusion-transmitted TSE in the United States appears to be extremely low. Postmortem testing of brain tissue from cadaveric tissue donors would be feasible and more justifiable in view of the surprisingly high lifetime risk of sCJD; tissue transplantation–associated TSE has not been recognized since donors with history of dementia and other neurologic disease have been excluded.

Standard universal precautions should be used to handle all human tissues, blood, and body fluids. Materials and surfaces contaminated with tissues and CSF from patients suspected of having CJD must be treated with great care, paying special attention to preventing injuries with needles and other sharp instruments. Whenever possible, discard contaminated instruments as "medical-pathological waste" by careful packaging and incineration. Contaminated tissues and biologic products probably cannot be completely freed of infectivity without destroying their structural integrity and biologic activity; therefore the medical and family histories of individual tissue donors should be carefully reviewed to exclude a diagnosis of TSE or other neurologic disease. Histopathologic examination of brain tissues of cadaveric donors and rapid testing for abnormal PrP might eventually be performed where feasible (no rapid diagnostic test is currently marketed for use with human tissues, though commercial animal TSE tests detect PrP^{TSE} in human CJD brains) to provide some additional assurance of safety. Although no method of sterilization can be relied on to remove all infectivity from contaminated surfaces, exposures to moist heat, sodium hydroxide, chlorine bleach, concentrated formic acid, acidified detergent, and guanidine salts markedly reduced infectivity in experimental studies.

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Section 14

Antiparasitic Therapy

Chapter 325

Principles of Antiparasitic Therapy

Beth K. Thielen

Parasites are divided into three main groups taxonomically: **protozoans,** which are unicellular, and **helminths** and **ectoparasites,** which are multicellular. Chemotherapeutic agents appropriate for one group may not be appropriate for the others, and not all drugs are readily available (Table 325.1). Some drugs are not available in the United States, and some are available only from the manufacturer, specialized compounding pharmacies, or the Centers for Disease Control and Prevention (CDC). Information on the availability of drugs and expert guidance in management can be obtained by contacting the CDC Parasitic Diseases Branch (1-404-718-4745; e-mail parasites@cdc.gov (M-F, 8 AM-4 PM, Eastern time). For assistance in the management of malaria, healthcare providers should call the CDC Malaria Hotline: 1-770-488-7788 or 1-855-856-4713 toll-free, e-mail malaria@cdc.gov (M-F, 9 AM-5 PM, Eastern time). For all emergency consultations after hours, clinicians can contact the CDC Emergency Operations Center at 1-770-488-7100 and request to speak with a CDC Malaria Branch clinician or on-call parasitic diseases physician. Some antiparasitic drugs are not licensed for use in the United States but can be obtained as investigational new drugs (INDs) from the CDC; providers should call the CDC Drug Service, Division of Scientific Resources and Division of Global Migration and Quarantine, at 1-404-639-3670.

SELECTED ANTIPARASITIC DRUGS FOR PROTOZOANS

Nitazoxanide (Alinia)

Nitazoxanide is a nitrothiazole benzamide, initially developed as a veterinary anthelmintic. Nitazoxanide inhibits pyruvate: ferredoxin oxidoreductase, which is an enzyme necessary for anaerobic energy metabolism. In humans, nitazoxanide is effective against many **protozoans** and **helminths.** Nitazoxanide is approved for the treatment of diarrhea caused by *Cryptosporidium parvum* and *Giardia intestinalis* in patients ≥1 year of age.

Nitazoxanide is available as a tablet (500 mg) and an oral suspension (100 mg/5 mL), which has a pink color and strawberry flavor. The bioavailability of the suspension is ~70% compared with the tablet. The drug is well absorbed from the gastrointestinal tract but should be taken with food due to approximately twofold higher absorption. One third is excreted in urine, and two thirds is excreted in feces as the active metabolite, tizoxanide. Although in vitro metabolism studies have not demonstrated cytochrome P450 enzyme effects, no pharmacokinetic studies have been performed in patients with compromised renal or hepatic function. In addition, limited studies have been performed in pregnant or lactating women; nevertheless, CDC Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV recommend nitazoxanide for the treatment of severe cryptosporidiosis after the first trimester. Tizoxanide is known to be excreted in breast milk, but decisions to breastfeed during therapy can be individualized. Common adverse effects include abdominal pain, diarrhea, nausea, and urine discoloration. Rare side effects include anorexia, flatulence, increased appetite, fever, pruritus, and dizziness. Intriguingly, nitazoxanide has in vitro activity against multiple other pathogens, including influenza virus, rotavirus, hepatitis C virus, and SARS-CoV-2, although the clinical use of the agent against these viruses remains investigational.

Tinidazole (Tindamax)

Tinidazole is a synthetic nitroimidazole with a chemical structure similar to metronidazole. It is approved by the Food and Drug Administration (FDA) for patients 3 years of age and older and for treatment of trichomoniasis, giardiasis, and amebiasis. In the treatment of giardiasis, it has the advantages of very few side effects and only requiring a single dose. It is available as a tablet, which can be crushed and administered with food. Its mechanism of action against *Trichomonas* may be secondary to the generation of free nitro radicals by the **protozoan.** The mechanism of action against *Giardia lamblia* and *Entamoeba histolytica* is unknown. Like metronidazole, it can cause a disulfiram-like reaction if combined with alcohol. After oral administration, tinidazole is rapidly and completely absorbed and is distributed into almost all tissues and body fluids; it can cross the blood-brain barrier and placental barrier. It is excreted via urine and feces. Hemodialysis increases clearance of the drug. No studies have been performed for patients undergoing peritoneal dialysis or for patients with compromised hepatic function. Tinidazole is known to cross the placenta and enter fetal circulation; the safety in pregnancy has not been well evaluated, and alternative agents are preferred. It can also be detected in breast milk, and breastfeeding should be interrupted during treatment and for 3 days after treatment.

Atovaquone/Proguanil (Malarone)

Atovaquone is a hydroxynaphthoquinone and has been used in the past predominantly against *Pneumocystis* pneumonia in AIDS patients. Its mechanism of action is via disruption of the mitochondria membrane potential through interaction with cytochrome b. However, atovaquone can also effectively inhibit liver stages of all *Plasmodium* species, and in 2000 the FDA approved atovaquone/proguanil for the prevention and treatment of acute, uncomplicated *Plasmodium falciparum* malaria in adults and children ≥11 kg. Atovaquone alone and in combination with proguanil is the only drug to completely inhibit the liver stage, providing the advantage of only needing to use the drug for 7 days after departing a malaria-endemic area (compared with several weeks).

Proguanil inhibits the parasite dihydrofolate reductase enzyme by the active form, cycloguanil. When used alone, it has poor efficacy for prophylaxis, but when administered with atovaquone, it acts in synergy on the cytochrome b enzyme in *Plasmodia* mitochondria, though the exact mechanism of synergy is unknown.

Two double-blind, randomized clinical trials assessing malaria prophylaxis demonstrated that atovaquone/proguanil was at least comparable to (and perhaps better than) chloroquine plus proguanil, and that atovaquone/proguanil was comparable to mefloquine. Atovaquone/proguanil was better tolerated than chloroquine plus proguanil and mefloquine. Atovaquone/proguanil treatment of acute uncomplicated *P. falciparum* infection has demonstrated higher or comparable cure rates when compared with other *P. falciparum* treatment drugs. Compared with other antimalarial therapies, atovaquone/proguanil has the highest cost. There are limited data on use during pregnancy, and pharmacokinetics may be altered during pregnancy so alternative regimens are preferred for malaria in pregnancy if available.

ARTEMISININ DERIVATIVES (ARTEMETHER, ARTESUNATE) AND COMBINATION THERAPIES (ARTEMETHER/LUMEFANTRINE OR COARTEM)

Artemisinin is a sesquiterpene lactone isolated from the weed *Artemisia annua.* It was developed in China, where it is known as qinghaosu. Artemisinin and its derivatives act very rapidly against *Plasmodium vivax* as well as chloroquine-sensitive and chloroquine-resistant *P. falciparum.* Artemisinins are also rapidly eliminated. Resistance to artemisinins has been documented in Cambodia, Laos, Myanmar, Thailand, and Vietnam. Coartem is the first artemisinin-containing

Table 325.1 Drugs for Parasitic Infections

Parasitic infections are found throughout the world. With increasing travel, immigration, use of immunosuppressive drugs, and the spread of HIV, physicians anywhere may see infections caused by previously unfamiliar parasites. This table lists first-choice and alternative drugs for most parasitic infections.

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
ACANTHAMOEBA KERATITIS			
Drug of choice:	See footnote[1]		
AMEBIASIS (ENTAMOEBA HISTOLYTICA)			
Asymptomatic			
Drug of choice:	Iodoquinol (Yodoxin)[2]	650 mg PO tid × 20 days	30-40 mg/kg/day (max 1950 mg) in 3 doses PO × 20 days
or	Paromomycin	25-35 mg/kg/day PO in 3 doses × 5-10 days	25-35 mg/kg/day PO in 3 doses × 5-10 days
Alternative:	Diloxanide furoate[3]	500 mg tid PO × 10 days	20 mg/kg/day PO in 3 doses × 10 days
Mild to moderate intestinal disease			
Drug of choice:	Metronidazole	500-750 mg tid PO × 7-10 days	35-50 mg/kg/day PO in 3 doses × 7-10 days
or	Tinidazole[4]	2 g PO once daily × 3 days	50 mg/kg/day PO (max 2 g) in 1 dose × 3 days
Either followed by:	Iodoquinol[2]	650 mg PO tid × 20 days	30-40 mg/kg/day PO in 3 doses × 20 days (max 2 g)
or	Paromomycin	25-35 mg/kg/day PO in 3 doses × 7 days	25-35 mg/kg/day PO in 3 doses × 5-10 days
Alternative:	Nitazoxanide[5]	500 mg bid × 3 days	1-3 yr: 100 mg bid × 3 days 4-11 yr: 200 mg bid × 3 days ≥12 yr: use adult dosing
Severe intestinal and extraintestinal disease			
Drug of choice:	Metronidazole	750 mg PO tid × 7-10 days	35-50 mg/kg/day PO in 3 doses × 7-10 days
or	Tinidazole[4]	2 g PO once daily × 5 days	50 mg/kg/day PO (max 2 g) × 5 days
Either followed by:	Iodoquinol[2]	650 mg PO tid × 20 days	30-40 mg/kg/day PO in 3 doses × 20 days (max 2 g)
or	Paromomycin	25-35 mg/kg/day PO in 3 doses × 5-10 days	25-35 mg/kg/day PO in 3 doses × 7 days
Amebic meningoencephalitis, primary and granulomatous			
NAEGLERIA FOWLERI			
Drug of choice:	Amphotericin B deoxycholate[6,7]	1.5 mg/kg/day IV in 2 divided doses × 3 days, then 1 mg/kg daily IV × 11 days	1.5 mg/kg/day IV in 2 divided doses × 3 days, then 1 mg/kg daily IV × 11 days
	plus Amphotericin B deoxycholate[6,7]	1.5 mg/kg intrathecally daily × 2 days, then 1 mg/kg intrathecally every other day × 8 days	1.5 mg/kg intrathecally daily × 2 days, then 1 mg/kg intrathecally every other day × 8 days
	plus Rifampin[7]	10 mg/kg (max 600 mg) IV or PO daily × 28 days	10 mg/kg (max 600 mg) IV or PO daily × 28 days
	plus Fluconazole[7]	10 mg/kg (max 600 mg) IV or PO daily × 28 days	10 mg/kg (max 600 mg) IV or PO daily × 28 days
	plus Azithromycin[7]	500 mg IV or PO daily × 28 days	10 mg/kg (max 500 mg) IV or PO daily × 28 days

[1]For treatment of keratitis caused by *Acanthamoeba*, 0.02% topical polyhexamethylene biguanide (PHMB) and 0.02% chlorhexidine have been successfully used individually and in combination in a large number of patients (Tabin G, et al. *Cornea.* 2001;20:757; Wysenbeek YS, et al. *Cornea.* 2000;19:464). The expected treatment course is 6-12 mo. PHMB is no longer available from Leiter's Park Avenue Pharmacy but is available from the O'Brien Pharmacy (1-800-627-4360; distributes in many states) and the Greenpark Pharmacy (1-713-432-9855; Texas only). Combinations with either 0.1% propamidine isethionate (Brolene) or hexamidine (Desomedine) have been used (Seal DV. *Eye.* 2003;17:893) successfully, but these are not available in the United States. Neomycin is not recommended due to high levels of resistance (*Acanthamoeba* keratitis: Treatment guidelines from *The Medical Letter,* 143, 8/1/2013). In addition, the combination of chlorhexidine, natamycin (pimaricin), and debridement also has been successful (Kitagawa K, et al. *Jpn J Ophthalmol.* 2003;47:616).

[2]The drug is not available commercially but can be compounded by Expert Compounding Pharmacy, 6744 Balboa Blvd, Lake Balboa, CA 91406 (1-800-247-9767 or 1-818-988-7979 or info@expertpharmacy.org).

[3]This drug is not available commercially in the United States.

[4]A nitroimidazole similar to metronidazole, tinidazole was approved by the FDA in 2004 and appears to be as effective and better tolerated than metronidazole. It should be taken with food to minimize GI adverse effects. For children and patients unable to take tablets, a pharmacist may crush the tablets and mix them with cherry syrup (HUMCO, and others). The syrup suspension is good for 7 days at room temperature and must be shaken before use. Ornidazole, a similar drug, is also used outside the United States.

[5]Nitazoxanide is FDA approved as a pediatric oral suspension for treatment of *Cryptosporidium* in immunocompetent children ≥1 yr of age. It has also been used in some small studies for *Balantidium coli* infection. It may also be effective for mild to moderate amebiasis (Diaz E, et al. *Am J Trop Med Hyg.* 2003;68:384; Rossignol JF, et al. *Trans R Soc Trop Med Hyg.* 2007;101:1025) and as an alternative therapy for microsporidiosis (published dosing for microsporidiosis: Bicart-See A, et al. *Antimicrob Agents Chemother.* 2000;44:167), 2020 CDC Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV). Nitazoxanide is available in 500 mg tablets and an oral suspension; it should be taken with food.

[6]*Naegleria* infection has been treated successfully with IV and intrathecal use of both amphotericin B and miconazole plus rifampin and with amphotericin B, rifampin, and ornidazole (Seidel J, et al. *N Engl J Med.* 1982;306:346; Jain R, et al. *Neurol India.* 2002;50:470). Other reports of successful therapy are less well documented.

[7]An approved drug, but usage is considered off-label for this condition by the FDA.

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
	plus Miltefosine[6–8]	50 mg PO tid × 28 days	<45 kg: 50 mg bid (max 2.5 mg/kg) × 28 days
			≥45 kg: use adult dosing
	plus dexamethasone	0.6 mg/kg/day IV in 4 divided doses × 4 days	0.6 mg/kg/day IV in 4 divided doses × 4 days
ACANTHAMOEBA			
Drug of choice:	See footnote[7,8]		
BALAMUTHIA MANDRILLARIS			
Drug of choice:	See footnote[7,9,10]		
SAPPINIA DIPLOIDEA			
Drug of choice:	See footnote[11]		
ANCYLOSTOMA CANINUM (EOSINOPHILIC ENTEROCOLITIS)			
Drug of choice:	Albendazole[7]	400 mg PO once	<10 kg/2 yr[12]
			≥2 yr: see adult dosing
or	Mebendazole	100 mg PO bid × 3 days	100 mg PO bid × 3 days[13]
or	Pyrantel pamoate (OTC)[7]	11 mg/kg PO (max 1 g) × 3 days	11 mg/kg PO (max 1 g) × 3 days
or	Endoscopic removal		
ANCYLOSTOMA DUODENALE, (see Hookworm infection)			
ANGIOSTRONGYLIASIS (*ANGIOSTRONGYLUS CANTONENSIS, ANGIOSTRONGYLUS COSTARICENSIS*)			
Drug of choice:	See footnote[14]		
ANISAKIASIS (*ANISAKIS* SPP.)			
Treatment of choice:	Surgical or endoscopic removal		
Alternative:	Albendazole[7,15]	400 mg PO bid × 6-21 days	<10 kg/2 yr[12]
			≥2 yr: see adult dosing
ASCARIASIS (*ASCARIS LUMBRICOIDES*, ROUNDWORM)			
Drug of choice:	Albendazole[7]	400 mg PO once	<10 kg/2 yr: see adult dosing[12]
			≥2 yr: see adult dosing
or	Mebendazole	100 mg PO bid × 3 days or 500 mg PO once	100 mg PO bid × 3 days or 500 mg PO once[13]
or	Ivermectin[7]	150-200 µg/kg PO once	<15 kg: not indicated
			≥15 kg: see adult dosing

[8]If you have a patient with suspected free-living amoeba infection, please contact the CDC Emergency Operations Center at 1-800-CDC-INFO to consult with a CDC expert regarding the use of this drug. Miltefosine has been reported to successfully treat primary amebic meningoencephalitis due to *Naegleria fowleri,* although controlled trials have not been conducted (Linam WM, et al. *Pediatrics.* 2015;135:e744).

[9]Strains of *Acanthamoeba* isolated from fatal granulomatous amebic encephalitis are usually susceptible in vitro to pentamidine, ketoconazole, flucytosine, and (less so) amphotericin B. Chronic *Acanthamoeba* meningitis has been successfully treated in two children with a combination of oral trimethoprim-sulfamethoxazole, rifampin, and ketoconazole (Singhal T, et al. *Pediatr Infect Dis.* 2001;*J* 20:623), and in an AIDS patient with fluconazole, sulfadiazine, and pyrimethamine combined with surgical resection of the CNS lesion (Seijo Martinez M, et al. *J Clin Microbiol.* 2000;38:3892). Disseminated cutaneous infection in an immunocompromised patient has been treated successfully with IV pentamidine isethionate, topical chlorhexidine, and 2% ketoconazole cream, followed by oral itraconazole (Slater CA, et al. *N Engl J Med.* 1994;331:85).

[10]A free-living leptomyxid ameba that causes subacute to fatal granulomatous CNS disease. Several cases of *Balamuthia* encephalitis have been successfully treated with flucytosine, pentamidine, fluconazole, and sulfadiazine plus either azithromycin or clarithromycin (phenothiazines were also used) combined with surgical resection of the CNS lesion (Deetz TR, et al. *Clin Infect Dis.* 2003;37:1304; Jung S, et al. *Arch Pathol Lab Med.* 2004;128:466). Case reports and in vitro data suggest miltefosine may have some antiamebic activity (Aichelburg AC, et al. *Emerg Infect Dis.* 2008;14:1743; Martínez DY, et al. *Clin Infect Dis.* 2010;51:e7; Schuster FL, et al. *J Eukaryot Microbiol.* 2006;53:121). Miltefosine (Impavido) is now commercially available. Contact the Centers for Disease Control/Agency for Toxic Substances Disease Registry at 1-770-488-7100 or 1-800-232-4636 (main number) for guidance on treatment.

[11]A free-living ameba not previously known to be pathogenic to humans. It has been successfully treated with azithromycin, IV pentamidine, itraconazole, and flucytosine combined with surgical resection of the CNS lesion (Gelman BB, et al. *J Neuropathol Exp Neurol.* 2003;62:990).

[12]Limited data in children <2 yr but has been used successfully for treatment of cutaneous larva migrans in children as young as 8 mo at a dose of 200 mg daily × 3 days (Black MD, et al. *Australas J Dermatol.* 2010;51:281). The WHO also recommends albendazole in children <2 yr for treatment of taeniasis, strongyloidiasis, filariasis, hookworms, roundworms, pinworms, and threadworms.

[13]Limited safety data in children <2 yr of age.

[14]Most patients have a self-limited course and recover completely. Analgesics, corticosteroids, and careful removal of CSF at frequent intervals can relieve symptoms from increased intracranial pressure (Lo Re V III, Gluckman SJ. *Am J Med.* 2003;114:217). No anthelmintic drug is proven to be effective, and some patients have worsened with therapy (Slom TJ, et al. *N Engl J Med.* 2002;346:668). Mebendazole or albendazole and a corticosteroid appeared to shorten the course of infection (Sawanyawisuth K, et al. *Trans R Soc Trop Med Hyg.* 2008;102:990; Chotmongkol V, et al. *Am J Trop Med Hyg.* 2009;81:443).

[15](Repiso Ortega A, et al. *Gastroenterol Hepatol.* 2003;26:341.) Successful treatment of a patient with anisakiasis with albendazole has been reported (Moore DA, et al. *Lancet.* 2002;360:54).

Continued

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
BABESIOSIS (*BABESIA MICROTI*)			
Drugs of choice:[16]	Atovaquone[7]	750 mg PO bid × 7-10 days	20 mg/kg (max 750 mg) PO bid × 7-10 days
	plus azithromycin[7]	500-1,000 mg once, then 250 mg daily × 7-10 days. Higher doses (600-1,000 mg) and/or prolonged therapy (6 wk or longer) may be required for immunocompromised patients	10 mg/kg PO on day 1 (max 500 mg/dose), then 5 mg/kg/day (max 250 mg/dose) PO days 2-10
or	Clindamycin[7]	300-600 mg IV qid or 600 mg tid PO × 7-10 days	20-40 mg/kg/day IV or PO in 3 or 4 doses × 7-10 days (max 600 mg/dose)
	plus quinine[7]	542 mg base (650 mg salt) tid PO × 7-10 days	6 mg base/kg (8 mg salt/kg) (max 542 mg base or 650 mg salt/ dose), PO tid × 7-10 days
Balamuthia mandrillaris, *see Amebic meningoencephalitis, primary*			
BALANTIDIASIS (*BALANTIDIUM COLI*)			
Drug of choice:	Tetracycline[7,17]	500 mg PO qid × 10 days	<8 yr: not indicated
			≥8 yr: 10 mg/kg (max 500 mg) PO qid × 10 days
Alternatives:	Metronidazole[7]	750 mg PO tid × 5 days	35-50 mg/kg/day PO in 3 divided doses × 5 days
or	Iodoquinol[2,7]	650 mg PO tid × 20 days	30-40 mg/kg/day (max 2 g) PO in 3 divided doses × 20 days
or	Nitazoxanide[5,7]	500 mg PO bid × 3 days	1-3 yr: 100 mg PO bid × 3 days
			4-11 yr: 200 mg PO bid × 3 days
			≥12 yr: see adult dosing
BAYLISASCARIASIS (*BAYLISASCARIS PROCYONIS*)			
Drug of choice:	Albendazole[7,18]	400 mg PO bid × 10-20 days	<10 kg/2 yr: 25-50 mg/kg/day PO in 1-2 divided doses × 10-20 days[12]
			≥2 yr: 25-50 mg/kg/day PO in 1-2 divided doses × 10-20 days
BLASTOCYSTIS HOMINIS INFECTION			
Drug of choice:	See footnote[19]		
CAPILLARIASIS (*CAPILLARIA PHILIPPINENSIS*)			
Drug of choice:	Mebendazole[7]	200 mg PO bid × 20 days	200 mg PO bid × 20 days[13]
Alternative:	Albendazole[7]	400 mg PO daily × 10 days	<10 kg/2 yr [12]
			≥15 kg/2 yr: see adult dosing
CHAGAS DISEASE, SEE TRYPANOSOMIASIS			
CLONORCHIS SINENSIS, SEE FLUKE INFECTION			
CRYPTOSPORIDIOSIS (*CRYPTOSPORIDIUM PARVUM*)			
Immunocompetent			
Drug of choice:	Nitazoxanide[5]	500 mg PO bid × 3 days	1-3 yr: 100 mg PO bid × 3 days
			4-11 yr: 200 mg PO bid × 3 days
			≥12 yr: see adult dosing

[16]Exchange transfusion has been used in severely ill patients and those with high (>10%) parasitemia (Hatcher JC, et al. *Clin Infect Dis.* 2001;32:1117). Clindamycin and quinine is the preferred therapy for severely ill patients. In patients who were not severely ill, combination therapy with atovaquone and azithromycin was as effective as clindamycin and quinine and may have been better tolerated (Krause PJ, et al. *N Engl J Med.* 2000;343:1454). Highly immunosuppressed patients should be treated for a minimum of 6 wk and at least 2 wk past the last positive smear (Krause PJ, et al. *Clin Infect Dis.* 2008;46:370). High doses of azithromycin (600-1,000 mg) have been used in combination with atovaquone for the treatment of immunocompromised patients (Weiss LM, et al. *N Engl J Med.* 2001;344:773). Resistance to atovaquone plus azithromycin has been reported in immunocompromised patients treated with a single subcurative course of this regimen (Wormser GP, et al. *Clin Infect Dis.* 2010;50:381). Most asymptomatic patients do not require treatment unless parasitemia persists >3 mo (Wormser GP, et al. *Clin Infect Dis.* 2006;43:1089).

[17]Use of tetracyclines has historically been contraindicated in pregnancy and in children younger than 8 yr. The American Academy of Pediatrics now recommends that doxycycline can be administered for short durations (i.e., 21 days or less) without regard to the patient's age (Kimberlin DW, et al. *Red Book: 2021-2024 Report of the Committee on Infectious Diseases.* 32nd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2021. p 866).

[18]No drugs have been consistently demonstrated to be effective. The combination of albendazole 37 mg/kg/day PO and high-dose steroids has been used successfully (Peters JM, et al. *Pediatrics.* 2012;129:e806; Haider S. *Emerg Infect Dis.* 2012;18:347). Albendazole 25 mg/kg/day PO × 20 days started as soon as possible (up to 3 days after possible infection) might prevent clinical disease and is recommended for children with known exposure, as in the setting of ingestion of raccoon stool or contaminated soil (Murray WJ, et al. *Clin Infect Dis.* 2004;39:1484). Mebendazole, levamisole, or ivermectin could be tried if albendazole is not available. Ocular baylisascariasis has been treated successfully using laser photocoagulation therapy to destroy the intraretinal larvae.

[19]Clinical significance of these organisms is controversial; metronidazole 750 mg tid × 10 days, iodoquinol 650 mg tid × 20 days, or trimethoprim-sulfamethoxazole 1 DS tablet bid × 7 days has been reported to be effective (Stenzel DJ, et al. *Clin Microbiol Rev.* 1996;9:563; Ok UZ, et al. *Am J Gastroenterol.* 1999;94:3245). Metronidazole resistance may be common (Haresh K, et al. *Trop Med Int Health.* 1999;4:274). Nitazoxanide has been effective in children (Diaz E, et al. *Am J Trop Med Hyg.* 2003;68:384).

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
HIV infected			
Drug of choice:	See footnote[20]		
CUTANEOUS LARVA MIGRANS (*ANCYLOSTOMA BRAZILIENSE, ANCYLOSTOMA CANINUM*, DOG AND CAT HOOKWORM, CREEPING ERUPTION)			
Drug of choice:	Albendazole[7,21]	400 mg PO daily × 3-7 days	<10 kg/2 yr: 200 mg PO daily × 3 days[12]
			≥2 yr: see adult dosing
or	Ivermectin[7]	200 µg/kg PO daily × 1-2 days	<15 kg: not indicated
			≥15 kg: see adult dosing
Alternative:	Thiabendazole	Apply topically tid × 7 days	Apply topically tid × 7 days
CYCLOSPORIASIS (*CYCLOSPORA CAYETANENSIS*)			
Drug of choice:	Trimethoprim-sulfamethoxazole (TMP-SMX)[7,22]	TMP 160 mg/SMX 800 mg (1 DS tab) PO bid × 7-10 days	4-5 mg/kg TMP component (max 160 mg) PO bid × 7-10 days
CYSTICERCOSIS, SEE TAPEWORM INFECTION			
CYSTOISOSPORIASIS (*CYSTOISOSPORA BELLI*, FORMERLY KNOWN AS *ISOSPORA BELLI*)			
Drug of choice:	TMP-SMX[7]	TMP 160 mg/SMX 800 mg (1 DS tab) PO bid × 10 days	4-5 mg/kg TMP component (max 160 mg) PO bid × 10 days
Alternative:	Pyrimethamine	50-75 mg PO divided bid x 10 days	—
	plus leucovorin	10-25 mg PO daily × 10 days	—
or	Ciprofloxacin[7]	500 mg PO bid × 7-10 days	—
Dientamoeba fragilis infection[23]			
	Paromomycin[7]	25-35 mg/kg/day PO in 3 doses × 7 days	25-35 mg/kg/day PO in 3 divided doses × 7 days
or	Iodoquinol[2]	650 mg PO tid × 20 days	30-40 mg/kg/day PO (max 2 g) in 3 divided doses × 20 days
or	Metronidazole[7]	500-750 mg tid × 10 days	35-50 mg/kg/day in 3 divided doses × 10 days
DIPHYLLOBOTHRIUM LATUM, SEE TAPEWORM INFECTION			
DRACUNCULUS MEDINENSIS (GUINEA WORM) INFECTION			
Treatment of choice:	Slow mechanical extraction of worm[24]		
ECHINOCOCCUS, SEE TAPEWORM INFECTION			
ENTAMOEBA HISTOLYTICA, SEE AMEBIASIS			
ENTEROBIUS VERMICULARIS (PINWORM) INFECTION[25]			
Drug of choice:	Albendazole[7]	400 mg PO once; repeat in 2 wk	<10 kg/2 yr: 200 mg PO once; repeat in 2 wk[12]
			≥2 yr: see adult dosing
or	Mebendazole	100 mg PO once; repeat in 3 wk	100 mg PO once; repeat in 3 wk[13]
or	Pyrantel pamoate (OTC)	11 mg/kg base PO once (max 1 g); repeat in 2 wk	11 mg/kg base PO once (max 1 g); repeat in 2 wk

[20]Nitazoxanide has not consistently been shown to be superior to placebo in HIV-infected patients (Amadi B, et al. *Lancet*. 2002;360;1375). For HIV-infected patients, potent antiretroviral therapy (ART) is the mainstay of treatment. Nitazoxanide 500-1,000 mg for 14 days, paromomycin 500 mg 4 times daily × 14-21 days, or a combination of paromomycin and azithromycin may be tried to decrease diarrhea and recalcitrant malabsorption of antimicrobial drugs, which can occur with chronic cryptosporidiosis (Pantenburg B, et al. *Expert Rev Anti Infect Ther*. 2009;7:385).

[21]Albanese G, et al. *Int J Dermatol*. 2001;40:67.

[22]HIV-infected patients may need a higher dosage and long-term maintenance (Kansouzidou A, et al. *J Trav Med*. 2004;11:61).

[23]Norberg A, et al. *Clin Microbiol Infect*. 2003;9:65.

[24]Treatment of choice is slow extraction of worm combined with wound care (*MMWR Morbid Mortal Wkly Rep*. 2011;60:1450). Instructions for this can be found at https://www.cdc.gov/parasites/guineaworm/treatment.html. Ten days of treatment with metronidazole 250 mg tid in adults and 25 mg/kg/day in 3 doses in children is not curative, but it decreases inflammation and facilitates removal of the worm. Mebendazole 400-800 mg/day × 6 days has been reported to kill the worm directly.

[25]Because all family members are usually infected, treatment of the entire household is recommended.

Continued

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
FASCIOLA HEPATICA, SEE FLUKE INFECTION			
FILARIASIS[26]			
Lymphatic filariasis (Wuchereria bancrofti, Brugia malayi, Brugia timori)			
Drug of choice:[27]	Diethylcarbamazine[28,29]	6 mg/kg once or 6 mg/kg PO in 3 divided doses × 12 days[30]	<18 mo: no indication
			≥18 mo: see adult dosing
LOA LOA			
<8,000 microfilaria/mL[29]			
Drug of choice:	Diethylcarbamazine[28,29]	9 mg/kg PO in 3 doses × 14 days[30]	<18 mo: no indication
			≥18 mo: see adult dosing
Alternatives:	Albendazole[28]	200 mg PO bid × 21 days	<10 kg/2 yr[12]
			≥2 yr: see adult dosing
8,000 microfilaria/mL[29,31]			
Treatment of choice:	Apheresis		
or	Albendazole[28]	200 mg PO bid × 21 days	<10 kg/2 yr[12]
			≥2 yr: see adult dosing
Either followed by:	Diethylcarbamazine[28,29]	8-10 mg/kg PO in 3 doses × 21 days[30]	<18 mo: no indication
			≥18 mo: see adult dosing
MANSONELLA OZZARDI			
Drug of choice:	See footnote[32]		
MANSONELLA PERSTANS			
Drug of choice:	Doxycycline[7,17,33]	100 mg bid PO × 6 wk	4 mg/kg/day in 2 doses PO × 6 wk
MANSONELLA STREPTOCERCA[34]			
Drug of choice:	Diethylcarbamazine[28]	6 mg/kg/day PO × 14 days	6 mg/kg/day PO × 14 days
or	Ivermectin[7]	150 µg/kg PO once	<15 kg: not indicated
			≥15 kg: see adult dosing
TROPICAL PULMONARY EOSINOPHILIA (TPE)[35]			
Drug of choice:	Diethylcarbamazine[28]	6 mg/kg once or 6 mg/kg PO in 3 divided doses × 14-21 days[27]	<18 mo: no indication
			≥18 mo: see adult dosing

[26]Antihistamines or corticosteroids may be required to decrease allergic reactions due to disintegration of microfilariae from treatment of filarial infections, especially those caused by *Loa loa*. Endosymbiotic *Wolbachia* bacteria may have a role in filarial development and host response and may represent a new target for therapy. Treatment with doxycycline 100 or 200 mg/day × 4-6 wk in lymphatic filariasis and onchocerciasis has resulted in substantial loss of *Wolbachia* with subsequent blocking of microfilariae production and absence of microfilaria when followed for 24 mo after treatment (Hoerauf A, et al. *Med Microbiol Immunol*. 2003;192:211; Hoerauf A, et al. *BMJ*. 2003;326:207).

[27]Most symptoms caused by adult worm. Single-dose combination of albendazole (400 mg) with either ivermectin (200 µg/kg) or diethylcarbamazine (6 mg/kg) is effective for reduction or suppression of *Wuchereria bancrofti* microfilaria but does not kill the adult forms (Addiss D, et al. *Cochrane Database Syst Rev*. 2004;(1):CD003753).

[28]This drug is not FDA approved and not commercially available but is available under IND application through the CDC Drug Service (CDC Drug Service, Division of Scientific Resources, telephone at 1-404-639-3670).

[29]Diethylcarbamazine is contraindicated in patients co-infected with *Onchocerca volvulus* due to risk of a life-threatening Mazzotti reaction and in patients with *Loa loa* infection and microfilaria levels ≥8,000 mm^3 due to risk of encephalopathy and renal failure. Some experts use a cutoff of ≥2,500 mm^3.

[30]For patients with microfilaria in the blood, *Medical Letter* consultants would start with a lower dosage and scale up: day 1, 50 mg; day 2, 50 mg tid; day 3, 100 mg tid; day 4-14, 6 mg/kg in 3 doses (for *Loa loa*, day 4-14, 9 mg/kg in 3 doses). Multidose regimens have been shown to provide more rapid reduction in microfilaria than single-dose diethylcarbamazine, but microfilaria levels are similar 6-12 mo after treatment (Andrade LD, et al. *Trans R Soc Trop Med Hyg*. 1995;89:319; Simonsen PE, et al. *Am J Trop Med Hyg*. 1995;53:267). A single dose of 6 mg/kg is used in endemic areas for mass treatment (Figueredo-Silva J, et al. *Trans R Soc Trop Med Hyg*. 1996;90:192; Noroes J, et al. *Trans R Soc Trop Med Hyg*. 1997;91:78).

[31]In heavy infections with *Loa loa*, rapid killing of microfilariae can provoke encephalopathy. Apheresis has been reported to be effective in lowering microfilarial counts in patients heavily infected with *Loa loa* (Ottesen EA. *Infect Dis Clin North Am*. 1993;7:619). Albendazole or ivermectin has also been used to reduce microfilaremia; albendazole is preferred because of its slower onset of action and lower risk for encephalopathy (Klion AD, et al. *J Infect Dis*. 1993;168:202; Kombila M, et al. *Am J Trop Med Hyg*. 1998;58:458). Albendazole may be useful for treatment of loiasis when diethylcarbamazine is ineffective or cannot be used, but repeated courses may be necessary (Klion AD, et al. *Clin Infect Dis*. 1999;29:680). Diethylcarbamazine, 300 mg once a week, has been recommended for prevention of loiasis (Nutman TB, et al. *N Engl J Med*. 1988;319:752).

[32]Diethylcarbamazine has no effect. Ivermectin 200 µg/kg once has been effective.

[33]Doxycycline is preferred for strains that carry *Wolbachia* bacteria. Combination therapy with diethylcarbamazine and mebendazole and monotherapy with mebendazole have been used successfully in strains that do not carry *Wolbachia*. Evidence is limited, and optimal therapy is uncertain. Ivermectin and albendazole appear to be ineffective.

[34]Diethylcarbamazine is potentially curative because of activity against both adult worms and microfilariae. Ivermectin is only active against microfilariae. (*The Medical Letter:* Drugs for parasitic infections, vol 11, 2013.)

[35]Relapse occurs and can be treated with diethylcarbamazine.

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
ONCHOCERCA VOLVULUS (RIVER BLINDNESS)			
Drug of choice:	Ivermectin[36]	150 µg/kg PO once, repeated every 6-12 mo until asymptomatic	<15 kg: not indicated
			≥15 kg: see adult dosing
FLUKE, HERMAPHRODITIC, INFECTION			
Clonorchis sinensis (Chinese liver fluke)			
Drug of choice:	Praziquantel	25 mg/kg PO tid × 2 day	25 mg/kg PO tid × 2 day[37]
or	Albendazole[7]	10 mg/kg PO × 7 days	<10 kg/2 yr[12]
			≥2 yr: see adult dosing
Fasciola hepatica (sheep liver fluke)			
Drug of choice:	Triclabendazole[7,38,39]	10 mg/kg PO once or twice	10 mg/kg PO once or twice
Alternative:	Nitazoxanide[7]	500 mg PO bid × 7 days	1-3 yr: 100 mg PO bid
			4-11 yr: 200 mg PO bid
			≥2 yr: see adult dosing
or	Bithionol[3,7]	30-50 mg/kg PO on alternate days × 10-15 doses	30-50 mg/kg PO on alternate days × 10-15 doses
Fasciolopsis buski, Heterophyes heterophyes, Metagonimus yokogawai (intestinal flukes)			
Drug of choice:	Praziquantel[7]	25 mg/kg PO tid × 1 day	25 mg/kg PO tid × 1 day[37]
Metorchis conjunctus (North American liver fluke)[40]			
Drug of choice:	Praziquantel[7]	25 mg/kg PO tid × 1 day	25 mg/kg PO tid × 1 day[37]
Nanophyetus salmincola			
Drug of choice:	Praziquantel[7]	20 mg/kg PO tid × 1 day	20 mg/kg PO tid × 1 day[37]
Opisthorchis viverrini (Southeast Asian liver fluke), Opisthorchis felineus (cat liver fluke)			
Drug of choice:	Praziquantel	25 mg/kg PO tid × 2 days	25 mg/kg PO tid × 2 days[37]
or	Albendazole[7]	10 mg/kg PO × 7 days	<10 kg/2 yr[12]
			≥2 yr: see adult dosing
Paragonimus westermani (lung fluke)			
Drug of choice:	Praziquantel[7]	25 mg/kg PO tid × 2 days	25 mg/kg PO tid × 2 days[37]
or	Triclabendazole[7,41]	10 mg/kg PO bid × 1 day or 5 mg/kg daily × 3 days	10 mg/kg PO bid × 1 day or 5 mg/kg daily × 3 days
or	Bithionol[3,7]	30-50 mg/kg PO on alternate days × 10-15 doses	30-50 mg/kg PO on alternate days × 10-15 doses
GIARDIASIS (*GIARDIA INTESTINALIS*, ALSO KNOWN AS *GIARDIA DUODENALIS* OR *GIARDIA LAMBLIA*)			
Drugs of choice:	Metronidazole[7]	250 mg PO tid × 5 days	5 mg/kg (max 250 mg) PO tid × 5 days
or	Nitazoxanide[5]	500 mg PO bid × 3 days	1-3 yr: 100 mg PO every 12 hr × 3 days
			4-11 yr: 200 mg PO every 12 hr × 3 days
			≥12 yr: see adult dosing

[36]Annual treatment with ivermectin, 150 µg/kg, can prevent blindness from ocular onchocerciasis (Mabey D, et al. *Ophthalmology.* 1996;103:1001). Ivermectin kills only the microfilaria but not the adult worms; emerging evidence suggests doxycycline is effective in killing adult worms and sterilizing females. The recommended regimen from the CDC is doxycycline 100-200 mg PO daily for 6 wk begun 1 wk after a dose of ivermectin is given to reduce the microfilaria burden. Diethylcarbamazine and suramin were formerly used for treatment of this disease but should no longer be used because of the availability of less toxic therapies.

[37]Limited safety data in children <4 yr of age but has been used in mass prevention campaigns with no reported adverse effects.

[38]Unlike infections with other flukes, *Fasciola hepatica* infections do not respond to praziquantel. Triclabendazole may be safe and effective, but data are limited (Graham CS, et al. *Clin Infect Dis.* 2001;33:1). In the United States, the drug is not approved by the FDA and is not yet commercially available. However, it is available to physicians licensed in the United States through the CDC Drug Service, under a special protocol, which requires that both the CDC and FDA agree that the drug is indicated for treatment of a particular patient. Providers should contact the CDC Drug Service, Division of Scientific Resources, at 1-404-639-3670. It is available from Victoria Pharmacy, Zurich, Switzerland (www.pharmaworld.com). The drug should be given with food for better absorption. A single study has found that nitazoxanide has limited efficacy for treating fascioliasis in adults and children (Favennec L, et al. *Aliment Pharmacol Ther.* 2003;17:265).

[39]Richter J, et al. *Curr Treat Options Infect Dis.* 2002;4:313.

[40]MacLean JD, et al. *Lancet.* 1996;347:154.

[41]Triclabendazole may be effective in a dosage of 5 mg/kg once a day × 3 days or 10 mg/kg bid × 1 day (Calvopiña M, et al. *Trans R Soc Trop Med Hyg.* 1998;92:566). In the United States, it is not approved by the FDA and is not yet commercially available. However, it is available to physicians licensed in the United States through the CDC Drug Service, under a special protocol, which requires both the CDC and FDA to agree that the drug is indicated for treatment of a particular patient. Providers should contact the CDC Drug Service, Division of Scientific Resources, at 1-404-639-3670. The drug is available from Victoria Pharmacy, Zurich, Switzerland; Phone, 41 43 344 60 60; FAX, 41 43 344 60 69; http://www.pharmaworld.com; e-mail, info@pharmaworld.com.

Continued

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
GIARDIASIS (*GIARDIA INTESTINALIS*, ALSO KNOWN AS *GIARDIA DUODENALIS* OR *GIARDIA LAMBLIA*)			
Drugs of choice:	Metronidazole[7]	250 mg PO tid × 5 days	5 mg/kg (max 250 mg) PO tid × 5 days
or	Tinidazole[4]	2 g PO once	50 mg/kg PO once (max 2 g)
Alternatives[42]	Paromomycin[7,43]	25-35 mg/kg/day PO in 3 doses × 7 days	25-35 mg/kg/day PO in 3 doses × 7 days
or	Furazolidone[3]	100 mg PO qid × 7-10 days	6 mg/kg/day PO in 4 doses × 7-10 days
or	Quinacrine[2]	100 mg PO tid × 5 days	2 mg/kg tid PO × 5 days (max 300 mg/day)
GNATHOSTOMIASIS (*GNATHOSTOMA SPINIGERUM*)			
Treatment of choice:[44]	Albendazole[7]	400 mg PO bid × 21 days	<10 kg/2 yr[12]
			≥2 yr: see adult dosing
or	Ivermectin[7]	200 µg/kg/day PO × 2 days	<15 kg: not indicated
			≥15 kg: see adult dosing
±	Surgical removal		
GONGYLONEMIASIS (*GONGYLONEMA* SP.)[45]			
Treatment of choice:	Surgical removal		
or	Albendazole[7]	400 mg PO daily × 3 days	10 mg/kg/day PO × 3 days
HOOKWORM INFECTION (*ANCYLOSTOMA DUODENALE, NECATOR AMERICANUS*)			
Drug of choice:	Albendazole[7]	400 mg PO once	<10 kg/2 yr[12]
			≥2 yr: see adult dosing
or	Mebendazole	100 mg PO bid × 3 days or 500 mg once	100 mg PO bid × 3 days or 500 mg once[13]
or	Pyrantel pamoate (OTC)[7]	11 mg/kg (max 1 g) PO × 3 days	11 mg/kg (max 1 g) PO × 3 days
HYDATID CYST, SEE TAPEWORM INFECTION			
HYMENOLEPIS NANA, SEE TAPEWORM INFECTION			
LEISHMANIA INFECTION[46]			
Visceral[47]			
Drugs of choice:	Liposomal amphotericin B (AmBisome)[48,49]	3 mg/kg/day IV on days 1-5, 14, and 21 (total dose 21 mg/kg)	3 mg/kg/day IV on days 1-5, 14, and 21 (total dose 21 mg/kg)
or	Miltefosine[50]	30-44 kg: 50 mg PO bid × 28 days	<12 yr: 2.5mg/kg daily × 28 days[7]
		45 kg: 50 mg PO tid × 28 days	≥12 yr: see adult dosing
or	Sodium stibogluconate (Pentostam)[28,51]	20 mg Sb/kg/day IV or IM × 28 days	20 mg Sb/kg/day IV or IM × 28 days
or	Amphotericin B deoxycholate[7]	1 mg/kg IV daily or every 2 days for 15-20 doses	1 mg/kg IV daily or every 2 days for 15-20 doses

[42]Albendazole 400 mg daily × 5 days alone or in combination with metronidazole may also be effective (Hall A, et al. *Trans R Soc Trop Med Hyg*. 1993;87:84; Dutta AK, et al. *Indian J Pediatr*. 1994;61:689; Cacopardo B, et al. *Clin Ter*. 1995;146:761). Combination treatment with standard doses of metronidazole and quinacrine given for 3 wk has been effective for a small number of refractory infections (Nash TE, et al. *Clin Infect Dis*. 2001;33:22). In one study, nitazoxanide was used successfully in high doses to treat a case of *Giardia* infection resistant to metronidazole and albendazole (Abboud P, et al. *Clin Infect Dis*. 2001;32:1792).

[43]Not absorbed; may be useful for treatment of giardiasis in pregnancy.

[44]de Gorgolas M, et al. *J Travel Med*. 2003;10:358. All patients should be treated with a medication regardless of whether surgery is attempted.

[45]Eberhard ML, et al. *Am J Trop Med Hyg*. 1999;61:51; Wilson ME, et al. *Clin Infect Dis*. 2001;32:1378.

[46]Consultation with physicians experienced in management of this disease is recommended. To maximize effectiveness and minimize toxicity, the choice of drug, dosage, and duration of therapy should be individualized based on the region of disease acquisition, likely infecting species, number, significance and location of lesions, and host factors such as immune status (Murray HW. *Lancet*. 2005;366:1561; Aronson N, et al. *Clin Infect Dis*. 2016;63:e202). Some of the listed drugs and regimens are effective only against certain *Leishmania* species/strains and only in certain areas of the world (Sundar S, et al. *Expert Opin Pharmacother*. 2013;14:53).

[47]Visceral infection is most commonly caused by the Old World species *Leishmania donovani* (kala-azar) and *Leishmania infantum* and the New World species *Leishmania chagasi*. Treatment duration may vary based on symptoms, host immune status, species, and area of the world in which the infection was acquired. Liposomal amphotericin B is the treatment of choice in the IDSA leishmaniasis guidelines (Aronson N, et al. *Clin Infect Dis*. 2016;63:e202).

[48]Three lipid formulations of amphotericin B have been used for treatment of visceral leishmaniasis. Largely based on clinical trials in patients infected with *Leishmania infantum*, the FDA approved liposomal amphotericin B (AmBisome) for treatment of visceral leishmaniasis (Meyerhoff A. *Clin Infect Dis*. 1999;28:42). Amphotericin B lipid complex (Abelcet) and amphotericin B cholesteryl sulfate (Amphotec) have also been used with good results but are considered investigational for this condition by the FDA.

[49]The FDA-approved dosage regimen for immunocompromised patients (e.g., HIV infected) is 4 mg/kg/day on days 1-5 and 4 mg/kg/day on days 10, 17, 24, 31, and 38. The relapse rate is high; maintenance therapy may be indicated, but there is no consensus as to dosage or duration. (Russo R, et al. *J Infect*. 1996;32:133).

[50]For treatment of kala-azar in adults in India, oral miltefosine 100 mg/day (~205 mg/kg/day) for 3-4 wk was 97% effective after 6 mo (Jha TK, et al. *N Engl J Med*. 1999;341:1795; Sangraula H, et al. *J Assoc Physicians India*. 2003;51:686). GI adverse effects are common, and the drug is contraindicated in pregnancy. The dose of miltefosine in an open-label trial in children in India was 2.5 mg/kg/day × 28 days (Bhattacharya SK, et al. *Clin Infect Dis*. 2004;38:217). Miltefosine (Impavido) has been approved by the FDA for treatment of leishmaniasis due to *Leishmania donovani;* cutaneous leishmaniasis due to *L. braziliensis*, *Leishmania guyanensis*, and *Leishmania panamensis*, and mucosal leishmaniasis due to *L. braziliensis* since 2014 and is now commercially available.

[51]May be repeated or continued; a longer duration may be needed for some patients (Herwaldt BL. *Lancet*. 1999;354:1191).

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Alternative:	Meglumine antimonate[3,51]	20 mg pentavalent antimony/kg/day IV or IM × 28 days	20 mg pentavalent antimony/kg/day IV or IM × 28 days
or	Pentamidine[7]	4 mg/kg IV or IM daily or every 2 days for 15-30 doses	4 mg/kg IV or IM daily or every 2 days for 15-30 doses
Cutaneous[52,53]			
Drugs of choice:	Sodium stibogluconate[28,51]	20 mg Sb/kg/day IV or IM × 20 days	20 mg Sb/kg/day IV or IM × 20 days
or	Liposomal amphotericin B (AmBisome)[7]	3 mg/kg/day IV on days 1-5 and 10 or 1-7 (total dose 18-21 mg/kg)	3 mg/kg/day IV on days 1-5 and 10 or 1-7 (total dose 18-21 mg/kg)
or	Amphotericin B deoxycholate[7]	0.5-1 mg/kg IV daily or every 2 days (total dose 15-30 mg/kg)	0.5-1 mg/kg IV daily or every 2 days (total dose 15-30 mg/kg)
or	Miltefosine[50]	30-44 kg: 50 mg PO bid × 28 days	<12 yr: 2.5mg/kg daily × 28 days[7]
		³ 45 kg: 50 mg PO tid x 28 days	≥12 yr: see adult dosing
Alternatives:	Meglumine antimonate[3,51]	20 mg pentavalent antimony/kg/day IV or IM × 20 days	20 mg pentavalent antimony/kg/day IV or IM × 20 days
or	Pentamidine[7,54]	3-4 mg/kg IV or IM every 2 days × 3-4 doses	2-3 mg/kg IV or IM daily or every 2 days × 4-7 doses
or	Paromomycin[7,55]	Topically 2×/day × 10-20 days	Topically 2×/day × 10-20 days
or	Ketoconazole[7]	600 mg daily × 28 days	
or	Fluconazole[7]	200 mg daily × 6 wk	
or	Local therapy including cryotherapy, thermotherapy, intralesional Sb^V, topical paromomycin, photodynamic or laser therapy		
Mucosal[56]			
Drugs of choice:	Sodium stibogluconate[28,51]	20 mg Sb/kg/day IV or IM × 28 days	20 mg Sb/kg/day IV or IM × 28 days
or	Liposomal amphotericin B (AmBisome)[7]	3 mg/kg/day IV × 10 days or 4 mg/kg days 1-5, 10, 17, 24, 31, and 38 (total dose 20-60 mg/kg)	2-4 mg/kg/day IV × 10 days or 4 mg/kg days 1-5, 10, 17, 24, 31, and 38 (total dose 20-60 mg/kg)
or	Amphotericin B deoxycholate[7]	0.5-1 mg/kg IV daily or every 2 days (total dose 20-45 mg/kg)	0.5-1 mg/kg IV daily or every 2 days (total dose 20-45 mg/kg)
or	Miltefosine[50]	30-44 kg: 50 mg PO bid × 28 days	<12 yr: 2.5 mg/kg daily × 28 days[7]
		45 kg: 50 mg PO tid × 28 days	≥12 yr: see adult dosing
Alternative:	Meglumine antimonate[3,51]	20 mg pentavalent antimony/kg/day IV or IM × 28 days	20 mg pentavalent antimony/kg/day IV or IM × 28 days
LICE (HEAD AND BODY) INFESTATION (*PEDICULUS HUMANUS CAPITIS, PEDICULUS HUMANUS HUMANUS*)			
Drugs of choice:	0.5% Malathion (Ovide)[57]	Topically 2×, 1 wk apart	Topically 2×, 1 wk apart, approved for 6 yr
or	1% Permethrin (Nix) (OTC)[57]	Topically 2×, 1 wk apart	Topically 2×, 1 wk apart, approved for 2 mo
or	Pyrethrins with piperonyl butoxide (A-200, Proto, R&C, Rid, Triple X) (OTC)[58]	Topically 2×, 1 wk apart	Topically 2×, 1 wk, approved for ≥2 yr

[52]Cutaneous infection is most commonly caused by the Old World species *Leishmania major* and *Leishmania tropica* and the New World species *Leishmania mexicana, Leishmania (Viannia) braziliensis,* and others. Treatment duration may vary based on symptoms, host immune status, species, and area of the world where infection was acquired.

[53]In a placebo-controlled trial in patients 12 yr old and older, oral miltefosine was effective for the treatment of cutaneous leishmaniasis caused by *Leishmania (Viannia) panamensis* in Colombia but not *Leishmania (Viannia) braziliensis* in Guatemala at a dosage of about 2.5 mg/kg/day for 28 days. "Motion sickness," nausea, headache, and increased creatinine were the most frequent adverse effects (Soto J, et al. *Clin Infect Dis.* 2004;38:1266). For treatment of *Leishmania major* cutaneous lesions, a study in Saudi Arabia found that oral fluconazole, 200 mg once/day × 6 wk, appeared to speed healing (Alrajhi AA, et al. *N Engl J Med.* 2002;346:891).

[54]At this dosage, pentamidine has been effective against leishmaniasis in Colombia, where the likely organism was *Leishmania (Viannia) panamensis* (Soto-Mancipe J, et al. *Clin Infect Dis.* 1993;16:417; Soto J, et al. *Am J Trop Med Hyg.* 1994;50:107); its effect against other species is not well established. Updated based on *Leishmania* practice guidelines (Aronson N, et al. *Clin Infect Dis.* 2016;63:e202).

[55]Topical paromomycin should be used only in geographic regions where cutaneous leishmaniasis species have low potential for mucosal spread. A formulation of 15% paromomycin/12% methylbenzethonium chloride (Leshcutan) in soft white paraffin for topical use has been reported to be partially effective in some patients against cutaneous leishmaniasis due to *Leishmania major* in Israel and against *Leishmania mexicana* and *Leishmania (Viannia) braziliensis* in Guatemala, where mucosal spread is very rare (Arana BA, et al. *Am J Trop Med Hyg.* 2001;65:466). Methylbenzethonium is irritating to the skin; lesions may worsen before they improve.

[56]Mucosal infection is most commonly due to the New World species *Leishmania (Viannia) braziliensis, Leishmania (Viannia) panamensis,* or *Leishmania (Viannia) guyanensis.* Treatment duration may vary based on symptoms, host immune status, species, and area of the world where infection was acquired.

[57]Yoon KS, et al. *Arch Dermatol.* 2003;139:994.

Continued

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
or	0.5% Ivermectin lotion (Sklice)	Topically, once	Topically once, approved for ≥6 mo
or	0.9% Spinosad suspension (Natroba)	Topically once, second dose in 1 wk if live adult lice seen	Topically once, second dose in 1 wk if live adult lice seen, approved for ≥6 mo
or	Ivermectin[7,59]	200-400 µg/kg PO 2×, 1 wk apart	<15 kg: not indicated
			15 kg: see adult dosing
or	5% Benzyl alcohol lotion (Ulesfia)	Topically 2×, 1 wk apart	Topically 2×, 1 wk apart
LICE (PUBIC) INFESTATION *(PHTHIRUS PUBIS)*[60]			
Drugs of choice:	1% Permethrin (Nix) (OTC)[57]	Topically 2×, 1 wk apart	Topically 2×, 1 wk apart, approved for ≥2 mo
or	Pyrethrins with piperonyl butoxide (A-200, Proto, R&C, Rid, Triple X) (OTC)[53]	Topically 2×, 1 wk apart	Topically 2×, 1 wk apart, approved for ≥2 yr
or	0.5% Malathion (Ovide)[57]	Topically 2×, 1 wk apart	Topically 2×, 1 wk apart, approved for ≥6 yr
or	0.5% Ivermectin lotion (Sklice)	Topically, once	Topically once, approved for ≥6 mo
or	Ivermectin[7,59]	200-400 µg/kg PO 2×, 1 wk apart	<15 kg: not indicated
			≥15 kg: see adult dosing
LOA LOA, SEE FILARIASIS			
MALARIA (*PLASMODIUM FALCIPARUM, PLASMODIUM OVALE, PLASMODIUM VIVAX*, AND *PLASMODIUM MALARIAE*) – TREATMENT			
Uncomplicated infection due to P. falciparum or species not identified acquired in areas of chloroquine resistance or unknown resistance[61]			
Drugs of choice:[62]	Atovaquone/proguanil (Malarone) Adult tabs: 50 mg atovaquone/100 mg proguanil Pediatric tabs 62.5 mg atovaquone/25 mg proguanil)[63]	4 adult tabs PO once daily or 2 adult tabs PO bid × 3 days[64]	<5 kg: not indicated
			5-8 kg: 2 pediatric tabs PO daily × 3 days
			9-10 kg: 3 pediatric tabs PO daily × 3 days
			11-20 kg: 1 adult tab PO daily × 3 days
			21-30 kg: 2 adult tabs PO daily × 3 days
			31-40 kg: 3 adult tabs PO daily × 3 days
			>40 kg: 4 adult tabs PO daily × 3 days
or	Coartem (artemether/lumefantrine) Fixed dose of 20 mg artemether and 120 mg lumefantrine per tablet	4 tablets per dose. A 3-day treatment schedule with a total of 6 oral doses is recommended for both adult and pediatric patients based on weight. These 6 doses should be administered over 3 days at 0, 8, 24, 36, 48, and 60 hr	5 to <15 kg: 1 tablet PO per dose
			15 to <25 kg: 2 tablets PO per dose
			25 to <35 kg: 3 tablets per dose
			≥35 kg: 4 tablets PO per dose

[58]A second application is recommended 1 wk later to kill hatching progeny. Lice are increasingly demonstrating resistance to pyrethrins and permethrin (Meinking TL, et al. *Arch Dermatol.* 2002;138:220). Ivermectin lotion 0.5% was approved by the FDA in 2012 for treatment of head lice in persons 6 mo of age and older. It is not ovicidal, but it appears to prevent nymphs from surviving. It is effective in most patients when given as a single application on dry hair without nit combing (www.cdc.gov/parasites/lice/head/treatment.html).

[59]Ivermectin is effective against adult lice but has no effect on nits (Jones KN, et al. *Clin Infect Dis.* 2003;36:1355).

[60]For infestation of eyelashes with *Phthirus pubis* lice, use petrolatum; Trimethoprim-sulfamethoxazole (TMP-SMX) has also been used (Meinking TL. *Curr Probl Dermatol.* 1996;24:157). For pubic lice, treat with 5% permethrin or ivermectin as for scabies. TMP-SMX has also been effective, together with permethrin for head lice (Hipolito RB, et al. *Pediatrics.* 2001;107:E30).

[61]Chloroquine-resistant *Plasmodium falciparum* occurs in all malarious areas except Central America west of the Panama Canal Zone, Mexico, Haiti, the Dominican Republic, and most of the Middle East (chloroquine resistance has been reported in Yemen, Oman, Saudi Arabia, and Iran). For treatment of multidrug-resistant *P. falciparum* in Southeast Asia, especially Thailand, where resistance to mefloquine is frequent, atovaquone/proguanil, artesunate plus mefloquine, or artemether plus mefloquine may be used (Luxemburger C, et al. *Trans R Soc Trop Med Hyg.* 1994;88:213; Karbwang J, et al. *Trans R Soc Trop Med Hyg.* 1995;89:296).

[62]Uncomplicated or mild malaria may be treated with oral drugs.

[63]To enhance absorption and reduce nausea and vomiting, it should be taken with food or a milky drink. Safety in pregnancy is unknown, and use is generally not recommended. In a few small studies, outcomes were normal in women treated with the combination in the second and third trimesters (Paternak B, et al. *Arch Intern Med.* 2011;171:259; Boggild AK, et al. *Am J Trop Med Hyg.* 2007;76:208). The drug should not be given to patients with severe renal impairment (creatinine clearance <30 mL/min). There have been isolated case reports of resistance in *Plasmodium falciparum* in Africa, but *Medical Letter* consultants do not believe there is a high risk for acquisition of Malarone-resistant disease (Schwartz E, et al. *Clin Infect Dis.* 2003;37:450; Farnert A, et al. *BMJ.* 2003;326:628; Kuhn S, et al. *Am J Trop Med Hyg.* 2005;72:407; Happi C, et al. *Malar J.* 2006;5:82).

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
or	Quinine sulfate	542 mg base (650 mg salt) PO tid × 3-7 days[64]	8.3 mg base/kg (10 mg salt/kg) PO tid × 3-7 days[65]
	plus doxycycline[7,17]	100 mg PO bid × 7 days	4 mg/kg/day PO in 2 doses × 7 days
	or plus tetracycline[7,17]	250 mg PO qid × 7 days	6.25 mg/kg PO qid × 7 days
	or plus clindamycin[7,66]	20 mg/kg/day PO in 3 divided doses × 7 days[67]	20 mg/kg/day PO in 3 doses × 7 days
Alternative:	Mefloquine[68,69]	750 mg PO followed 12 hr later by 500 mg	15 mg/kg PO followed 12 hr later by 10 mg/kg
Uncomplicated infection due to P. falciparum or species not identified acquired in areas of chloroquine sensitivity or uncomplicated P. malariae or P. knowlesi			
Drug of choice:	Chloroquine phosphate (Aralen)	600 mg base (1,000 mg salt) PO, then 300 mg base (500 mg salt) PO at 6, 24, and 48 hr	10 mg base/kg (16.7 mg salt/kg) PO, then 5 mg base/kg (8.3 mg salt/kg) PO at 6, 24, and 48 hr
or	Hydroxychloroquine (Plaquenil)[70]	620 mg base (800 mg salt) PO, then 310 mg base (400 mg salt) PO at 6, 24, and 48 hr	10 mg base/kg (12.9 mg salt/kg) PO, then 5 5 mg base/kg (6.5 mg salt/kg) PO at 6, 24, and 48 hr
or	Artemether-lumefantrine (Coartem)10 (1 tab: 20 mg artemether / 120 mg lumefantrine)	Adults: 4 tabs PO per dose Three-day course: day 1: initial dose and second dose 8 hr later; days 2 and 3: 1 dose bid	5 to <15 kg: 1 tab PO per dose 15 to <25 kg: 2 tabs PO per dose 25 to <35 kg: 3 tabs PO per dose ≥35 kg: 4 tabs PO per dose Three-day course: day 1: initial dose and second dose 8 hr later; days 2 and 3: 1 dose bid
Uncomplicated infection with P. vivax acquired in areas of chloroquine resistance[71]			
Drugs of choice:	Atovaquone/proguanil (Malarone) Adult tabs: 50 mg atovaquone/100 mg proguanil Pediatric tabs 62.5 mg atovaquone/25 mg proguanil)[63]	4 adult tabs PO once daily × 3 days	<5 kg: not indicated
			5-8 kg: 2 pediatric tabs PO daily × 3 days
			9-10 kg: 3 pediatric tabs PO daily × 3 days
			11-20 kg: 1 adult tab PO daily × 3 days
			21-30 kg: 2 adult tabs PO daily × 3 days
			31-40 kg: 3 adult tabs PO daily × 3 days
			>40 kg: 4 adult tabs PO daily × 3 days
	plus primaquine[72]	30 mg base PO daily × 14 days	0.5 mg/kg/day PO × 14 days
or	Quinine sulfate	542 mg base (650 mg salt) PO tid × 3-7 days[64]	8.3 mg base/kg (10 mg salt/kg) PO tid × 3-7 days[58]
	plus doxycycline[7,17]	100 mg PO bid × 7 days	4 mg/kg/day PO in 2 doses × 7 days
	or plus tetracycline[7,17]	250 mg PO qid × 7 days	6.25 mg/kg PO qid × 7 days
	or plus clindamycin[7,66]	20 mg/kg/day PO in 3 divided doses × 7 days[67]	20 mg/kg/day PO in 3 doses × 7 days
	plus primaquine[72]	30 mg base PO daily × 14 days	0.5 mg/kg/day PO × 14 days

[64]Although approved for once-daily dosing, *Medical Letter* consultants usually divide the dose into 2 doses to decrease nausea and vomiting.

[65]In Southeast Asia, relative resistance to quinine has increased and treatment should be continued for 7 days.

[66]For use in pregnancy.

[67]Lell B, et al. *Antimicrob Agents Chemother*. 2002;46:2315.

[68]At this dosage, adverse effects, including nausea, vomiting, diarrhea, dizziness, a disturbed sense of balance, toxic psychosis, and seizures can occur. Mefloquine should not be used for treatment of malaria in pregnancy unless there is no other treatment option, because of an increased risk for stillbirth (Nosten F, et al. *Clin Infect Dis*. 1999;28:808). It should be avoided for treatment of malaria in persons with active depression or with a history of psychosis or seizures and should be used with caution in persons with psychiatric illness. Mefloquine can be given to patients taking β-blockers if they do not have an underlying arrhythmia; it should not be used in patients with conduction abnormalities. Mefloquine should not be given together with quinine, quinidine, or halofantrine, and caution is required in using quinine, quinidine, or halofantrine to treat patients with malaria who have taken mefloquine for prophylaxis. Resistance to mefloquine has been reported in some areas, such as the Thailand-Myanmar and Thailand-Cambodia borders and in the Amazon basin, where 25 mg/kg should be used. In the United States, a 250 mg tablet of mefloquine contains 228 mg mefloquine base. Outside the United States, each 275 mg tablet contains 250 mg base.

[69]*Plasmodium falciparum* with resistance to mefloquine is a significant problem in the malarious areas of Thailand and in areas of Myanmar and Cambodia that border on Thailand. It has also been reported on the borders between Myanmar and China, Laos and Myanmar, and in Southern Vietnam. In the United States, a 250 mg tablet of mefloquine contains 228 mg mefloquine base. Outside the United States, each 275 mg tablet contains 250 mg base.

[70]If chloroquine phosphate is not available, hydroxychloroquine sulfate is as effective; 400 mg of hydroxychloroquine sulfate is equivalent to 500 mg of chloroquine phosphate.

[71]*Plasmodium vivax* with decreased susceptibility to chloroquine is a significant problem in Papua New Guinea and Indonesia. There are also a few reports of resistance from Myanmar, India, the Solomon Islands, Vanuatu, Guyana, Brazil, Colombia, and Peru.

[72]Primaquine phosphate can cause hemolytic anemia, especially in patients whose red cells are deficient in glucose-6-phosphate dehydrogenase (G6PD). This deficiency is most common in African, Asian, and Mediterranean peoples. Patients should be screened for G6PD deficiency before treatment. Primaquine should not be used during pregnancy. For those with intermediate G6PD deficiency, weekly primaquine may be used (45 mg/wk) for 8 wk with close monitoring for hemolysis. Those with G6PD deficiency may be given chloroquine 300 mg (base) PO weekly for 1 yr for acute infection to prevent relapses.

Continued

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
or	Artemether-lumefantrine (1 tab: 20 mg artemether/120 mg lumefantrine) Weight-based treatment schedule for both adult and pediatric patients. Patients take initial dose, followed by a second dose 8 hr later, then 1 dose twice a day for the next 2 days (total of 6 oral doses over 3 days)		5 kg to <15 kg: 1 tablet per dose 15 kg to <25 kg: 2 tablets per dose 25 kg to <35 kg: 3 tablets per dose ≥35 kg: 4 tablets per dose Not recommended for people taking mefloquine prophylaxis or for children weighing <5 kg, or people breastfeeding infants weighing <5 kg
or	Mefloquine[68]	750 mg PO followed 12 hr later by 500 mg PO	15 mg/kg PO followed 12 hr later by 10 mg/kg PO
	plus primaquine[72]	30 mg base PO daily × 14 days	0.5 mg/kg/day PO × 14 days
Uncomplicated infection with P. ovale and P. vivax acquired in areas without chloroquine resistance[71]			
Drug of choice:	Chloroquine phosphate (Aralen)	600 mg base (1,000 mg salt) PO, then 300 mg base (500 mg salt) PO at 6, 24, and 48 hr	10 mg base/kg (16.7 mg salt/kg) PO, then 5 mg base/kg (8.3 mg salt/kg) PO at 6, 24, and 48 hr
	plus primaquine[72]	30 mg base PO daily × 14 days	0.5 mg/kg/day PO × 14 days
or	Hydroxychloroquine (Plaquenil)[70]	620 mg base PO, then 310 mg base PO at 6, 24, and 48 hr	10 mg/kg base PO, then 5 mg/kg base PO at 6, 24, and 48 hr
	plus primaquine[72]	30 mg base PO daily × 14 days	0.5 mg/kg/day PO × 14 days
or	Tafenoquine (Krintafel)[73]	300 mg PO × 1 dose	>16 yr: see adult dosing
Severe malaria due to all Plasmodium spp.			
Drugs of choice:[74]	Artesunate[28,75]	2.4 mg/kg/dose IV × 3 days, at 0, 12, and 24 hr	2.4 mg/kg/dose IV × 3 days, at 0, 12, and 24 hr
	Followed by: • Artemether/lumefantrine (preferred), *or* • Atovaquone-proguanil, *or* • Quinine *plus* doxycycline *or* clindamycin, *or* • Mefloquine (only if no other options available)	Dosing as above	Dosing as above
Alternative:	Coartem (Artemether/lumefantrine) Fixed dose of 20 mg artemether and 120 mg lumefantrine per tablet (preferred)	4 tablets per dose. A 3-day treatment schedule with a total of 6 oral doses is recommended for both adult and pediatric patients based on weight. These 6 doses should be administered over 3 days at 0, 8, 24, 36, 48, and 60 hr	5 to <15 kg: 1 tablet PO per dose 15 to <25 kg: 2 tablets PO per dose 25 to <35 kg: 3 tablets per dose ≥35 kg: 4 tablets PO per dose
or	Atovaquone/proguanil (Malarone) Adult tabs: 50 mg atovaquone/100 mg proguanil Pediatric tabs 62.5 mg atovaquone/25 mg proguanil)[63]	4 adult tabs PO once daily × 3 days	<5 kg: not indicated 5-8 kg: 2 pediatric tabs PO daily × 3 days 9-10 kg: 3 pediatric tabs PO daily × 3 days 11-20 kg: 1 adult tab PO daily × 3 days 21-30 kg: 2 adult tabs PO daily × 3 days 31-40 kg: 3 adult tabs PO daily × 3 days >40 kg: 4 adult tabs PO daily × 3 days

[73]Tafenoquine received regulatory approval in the United States in 2018 for prophylaxis of malaria and radical cure of *Plasmodium vivax*. Tafenoquine is associated with hemolytic anemia in those with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Prior to use, quantitative G6PD testing is needed to confirm normal activity.

[74]Exchange transfusion has been helpful for some patients with high-density (>10%) parasitemia, altered mental status, pulmonary edema, or renal complications (Miller KD, et al. *N Engl J Med*. 1989;321:65).

[75]Artesnuate is considered first-line therapy for severe malaria. If not available within 24 hours, contact CDC's Malaria Hotline. To avoid the development of resistance, adults treated with artesunate must also receive oral treatment doses of either atovaquone/proguanil, doxycycline, clindamycin, or mefloquine; children should take either atovaquone/proguanil, clindamycin, or mefloquine (Nosten F, et al. *Lancet*. 2000;356:297; van Vugt M. *Clin Infect Dis*. 2002;35:1498; Smithuis F, et al. *Trans R Soc Trop Med Hyg*. 2004;98:182). If artesunate is given IV, oral medication should be started when the patient is able to tolerate it (SEAQUAMAT group. *Lancet*. 2005;366:717; Duffy PE, et al. *Lancet*. 2005;366:1908). If oral therapy is not tolerated, consider administration via nasogastric (NG) tube or after an antiemetic. If parasitemia >1%, continue IV artesunate at the same dose daily up to 6 more days until parasite density ≤1%. When parasite density ≤1%, give complete follow-up on oral regimen as listed earlier. Reduced susceptibility to artesunate characterized by slow parasitic clearance has been reported in Cambodia (Rogers WO, et al. *Malar J*. 2009;8:10; Dundorp AM, et al. *N Engl J Med*. 2009;361:455).

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
or	Quinine sulfate	648 mg salt PO tid × 3-7 days[64]	10 mg salt/kg PO tid × 3-7 days[58]
	plus doxycycline[7,17]	100 mg PO bid × 7 days	4 mg/kg/day PO in 2 doses × 7 days
	or plus tetracycline[7,17]	250 mg PO qid × 7 days	6.25 mg/kg PO qid × 7 days
	or plus clindamycin[7,66]	20 mg/kg/day PO in 3 divided doses × 7 days[67]	20 mg/kg/day PO in 3 doses × 7 days
or	Artemether-lumefantrine (1 tab: 20 mg artemether/120 mg lumefantrine) Weight-based treatment schedule for both adult and pediatric patients. Patients take initial dose, followed by a second dose 8 hr later, then 1 dose twice a day for the next 2 days (total of 6 oral doses over 3 days)		5 kg to <15 kg: 1 tablet per dose 15 kg to <25 kg: 2 tablets per dose 25 kg to <35 kg: 3 tablets per dose ≥35 kg: 4 tablets per dose Not recommended for people taking mefloquine prophylaxis or for children weighing <5 kg, or people breastfeeding infants weighing <5 kg
or	Mefloquine[68]	750 mg PO followed 12 hr later by 500 mg PO	15 mg/kg PO followed 12 hr later by 10 mg/kg PO
Prevention of relapses: P. vivax and P. ovale only			
Drug of choice:	Primaquine phosphate[72]	30 mg base/day PO × 14 days	0.6 mg base/kg/day PO × 14 days
or	Tafenoquine (Krintafel)[73]	300 mg PO × 1 dose	>16 yr: see adult dosing
MALARIA – PREVENTION[76]			
Chloroquine-sensitive areas[61]			
Drug of choice	Chloroquine phosphate[77–79]	500 mg salt (300 mg base), PO once/wk beginning 1-2 wk before travel to malarious area and 4 wk after leaving	5 mg/kg base once/wk, up to adult dose of 300 mg base beginning 1-2 wk before travel to malarious area and 4 wk after leaving
or	Hydroxychloroquine (Plaquenil)[70]	400 mg (310 mg base) PO once/wk beginning 1-2 wk before travel to malarious area and 4 wk after leaving	5 mg/kg base once/wk, up to adult dose of 310 mg base beginning 1-2 wk before travel to malarious area and 4 wk after leaving
Chloroquine-resistant areas[61]			
Drug of choice:	Atovaquone/ proguanil[63,78,80]	1 adult tab PO per day beginning 1-2 days before travel to malarious area and 7 days after leaving	11-20 kg: 1 pediatric tab PO/day
			21-30 kg: 2 pediatric tabs PO/day
			31-40 kg: 3 pediatric tabs PO/day
			>40 kg: 1 adult tab PO/day
or	Mefloquine[48,78,79,81]	1 adult tab PO per day beginning 1-2 wk before travel to malarious area and 4 wk after leaving	<9 kg: 5 mg/kg salt once/wk
			9-19 kg: 1/4 tab once/wk
			19-30 kg: 1/2 tab once/wk
			31-45 kg: 3/4 tab once/wk
			>45 kg: 1 tab once/wk

[76]No drug regimen guarantees protection against malaria. If fever develops within a year (particularly within the first 2 mo) after travel to malarious areas, travelers should be advised to seek medical attention. Insect repellents, insecticide-impregnated bed nets, and proper clothing are important adjuncts for malaria prophylaxis (*Med Lett.* 2003;45:41). Malaria in pregnancy is particularly serious for both the pregnant individual and the fetus; therefore, prophylaxis is indicated if exposure cannot be avoided.

[77]In pregnancy, chloroquine prophylaxis has been used extensively and safely.

[78]For prevention of attack after departure from areas where *Plasmodium vivax* and *Plasmodium ovale* are endemic, which includes almost all areas where malaria is found (except Haiti), some experts prescribe in addition primaquine phosphate 30 mg base/day or, for children, 0.6 mg base/kg/day during the last 2 wk of prophylaxis. Others prefer to avoid the toxicity of primaquine and rely on surveillance to detect cases when they occur, particularly when exposure was limited or doubtful. See also footnote[71].

[79]Beginning 1-2 wk before travel and continuing weekly for the duration of stay and for 4 wk after leaving malarious zone. Most adverse events occur within three doses. Some *Medical Letter* consultants favor starting mefloquine 3 wk before travel and monitoring the patient for adverse events; this allows time to change to an alternative regimen if mefloquine is not tolerated. Mefloquine should not be taken on an empty stomach; it should be taken with at least 8 oz of water. For pediatric doses less than ½ tablet, it is advisable to have a pharmacist crush the tablet, estimate doses by weighing, and package them in gelatin capsules. There are no data for use in children weighing <5 kg, but based on dosages in other weight groups, a dose of 5 mg/kg can be used.

[80]Beginning 1-2 days before travel and continuing for the duration of stay and for 1 wk after leaving malarious zone. In one study of malaria prophylaxis, atovaquone/proguanil was better tolerated than mefloquine in nonimmune travelers (Overbosch D, et al. *Clin Infect Dis.* 2001;33:1015). The protective efficacy of Malarone against *Plasmodium vivax* is variable, ranging from 84% in Indonesian New Guinea (Ling J, et al. *Clin Infect Dis.* 2002;35:825) to 100% in Colombia (Soto J, et al. *Am J Trop Med Hyg.* 2006;75:430). Some *Medical Letter* consultants prefer alternate drugs if traveling to areas where *P. vivax* predominates.

[81]Mefloquine has not been approved for use during pregnancy. However, it has been reported to be safe for prophylactic use during the second or third trimester of pregnancy and possibly during early pregnancy, as well. Mefloquine is not recommended for patients with cardiac conduction abnormalities, and patients with a history of depression, seizures, psychosis, or psychiatric disorders should avoid mefloquine prophylaxis. Resistance to mefloquine has been reported in some areas, such as the Thailand-Myanmar and Thailand-Cambodia borders; in these areas, atovaquone/proguanil or doxycycline should be used for prophylaxis.

Continued

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
or	Doxycycline[7,82]	100 mg PO daily	≥8 yr: 2 mg/kg/day, up to 100 mg/day
or	Tafenoquine (Arakoda)	200 mg once daily for 3 days before travel to a malarious area, then 200 mg weekly while in the malarious area, then 200 mg as a single dose, 7 days after leaving malarious area	No dosing data for children
Alternatives for areas with primarily *P. vivax:*	Primaquine[7,83]	30 mg base PO daily beginning 1-2 days before travel to malarious area and 7-14 days after leaving	0.5 mg/kg base (max 30 mg) daily beginning 1-2 days before travel to malarious area and 7-14 days after leaving
MALARIA – PRESUMPTIVE SELF-TREATMENT[84]			
Drugs of choice:	Atovaquone/proguanil (Malarone) Adult tabs: 50 mg atovaquone/100 mg proguanil Pediatric tabs 62.5 mg atovaquone/25 mg proguanil)[63]	4 adult tabs PO once daily × 3 days	<5 kg: not indicated
			5-8 kg: 2 pediatric tabs PO daily × 3 days
			9-10 kg: 3 pediatric tabs PO daily × 3 days
			11-20 kg: 1 adult tab PO daily × 3 days
			21-30 kg: 2 adult tabs PO daily × 3 days
			31-40 kg: 3 adult tabs PO daily × 3 days
			>40 kg: 4 adult tabs PO daily × 3 days
or	Quinine sulfate[64]	648 mg salt PO tid × 3-7 days	10 mg salt/kg PO tid × 3-7 days
	plus doxycycline[7,17]	100 mg PO bid × 7 days	4 mg/kg/day PO in 2 divided doses × 7 days
or	Mefloquine[68,69]	750 mg PO followed 12 hr later by 500 mg	15 mg/kg PO followed 12 hr later by 10 mg/kg
MICROSPORIDIOSIS			
Ocular (Encephalitozoon hellem, Encephalitozoon cuniculi, Vittaforma corneae [Nosema corneum])			
Drug of choice:	Albendazole[7,85]	400 mg PO bid	<10 kg/2 yr: 15 mg/kg/day in 2 doses[12] ≥2 yr: see adult dosing
	plus fumagillin[86]	Topical Fumidil B (fumagillin bicyclohexylammonium) in saline (to achieve concentration of 70 mg/mL of fumagillin) 2 drops per eye every 2 hr for 4 days, then 2 drops qid	
Intestinal (Enterocytozoon bieneusi, Encephalitozoon [Septata] intestinalis)			
E. bieneusi[87]			
Drug of choice:	Fumagillin	60 mg/day PO × 14 days in 3 divided doses	
Alternatives:	Nitazoxanide[5,7]	1000 mg PO bid × 3 days	
E. intestinalis			
Drug of choice	Albendazole[7,85]	400 mg PO bid × 21 days	<10 kg/2 yr 15 mg/kg/day in 2 doses:[12]
			≥2 yr: see adult dosing
Disseminated (E. hellem, E. cuniculi, E. intestinalis, Pleistophora sp., Trachipleistophora sp., and Brachiola vesicularum)			
Drug of choice[88]	Albendazole[7,85]	400 mg PO bid	<10 kg/2 yr[12]
			≥2 yr: see adult dosing

[82]Beginning 1-2 days before travel and continuing for the duration of stay and for 4 wk after leaving. Use of tetracyclines is contraindicated in pregnancy and in children younger than 8 yr old. Doxycycline can cause GI disturbances, vaginal moniliasis, and photosensitivity reactions.

[83]Studies have shown that daily primaquine beginning 1 day before departure and continued until 3-7 days after leaving the malarious area provides effective prophylaxis against chloroquine-resistant *Plasmodium falciparum* (Baird JK, et al. *Clin Infect Dis.* 2003;37:1659). Some studies have shown less efficacy against *Plasmodium vivax.* Nausea and abdominal pain can be diminished by taking with food.

[84]A traveler can be given a course of atovaquone/proguanil, mefloquine, or quinine plus doxycycline for presumptive self-treatment of febrile illness. The drug given for self-treatment should be different from that used for prophylaxis. This approach should be used only in very rare circumstances when a traveler cannot promptly get to medical care.

[85]For HIV-infected patients, continue until resolution of ocular symptoms and until CD4 count >200 cells/μL for >6 mo after initiation of antiretroviral therapy.

[86]Ocular lesions caused by *Encephalitozoon hellem* in HIV-infected patients have responded to fumagillin eyedrops prepared from Fumidil-B (bicyclohexyl ammonium fumagillin) used to control a microsporidial disease of honey bees (Diesenhouse MC. *Am J Ophthalmol.* 1993;115:293), available from Leiter's Park Avenue Pharmacy (San Jose, CA; 1-800-292-6773; www.leiterrx.com). For lesions caused by *Vittaforma corneae,* topical therapy is generally not effective and keratoplasty may be required (Davis RM, et al. *Ophthalmology.* 1990;97:953).

[87]Oral fumagillin (Sanofi Recherche, Gentilly, France) has been effective in treating *Enterocytozoon. bieneusi* (Molina J-M, et al. *N Engl J Med.* 2002;346:1963), but it has been associated with thrombocytopenia. HAART may lead to microbiologic and clinical response in HIV-infected patients with microsporidial diarrhea (Benson CA, et al. *MMWR Recomm Rep.* 2004;53([RR-15]:1). Octreotide (Sandostatin) has provided symptomatic relief in some patients with large-volume diarrhea.

[88]Molina J-M, et al. *J Infect Dis.* 1995;171:245. There is no established treatment for *Pleistophora.* For disseminated disease caused by *Trachipleistophora* or *Brachiola,* itraconazole 400 mg PO once/day plus albendazole may also be tried (Coyle CM, et al. *N Engl J Med.* 2004;351:42).

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
MITES, SEE SCABIES			
MONILIFORMIS MONILIFORMIS INFECTION			
Drug of choice:	Pyrantel pamoate (OTC)[7]	11 mg/kg PO once, repeat twice, 2 wk apart	11 mg/kg PO once, repeat twice, 2 wk apart
NAEGLERIA SPECIES, SEE AMEBIC MENINGOENCEPHALITIS, PRIMARY			
NECATOR AMERICANUS, SEE HOOKWORM INFECTION			
OESOPHAGOSTOMUM BIFURCUM			
Drug of choice:	See footnote[89]		
ONCHOCERCA VOLVULUS, SEE FILARIASIS			
OPISTHORCHIS VIVERRINI, SEE FLUKE INFECTION			
PARAGONIMUS WESTERMANI, SEE FLUKE INFECTION			
PEDICULUS CAPITIS, PEDICULUS HUMANUS, PHTHIRUS PUBIS, SEE LICE			
PINWORM, SEE ENTEROBIUS			
PNEUMOCYSTIS JIROVECII (FORMERLY *PNEUMOCYSTIS CARINII*) PNEUMONIA (PCP)[90]			
Moderate to severe disease			
Drug of choice:	TMP-SMX	15-20 mg/kg/day TMP component IV in 3-4 divided doses × 21 days (change to PO after clinical improvement)	15-20 mg/kg/day TMP component IV in 3-4 divided doses × 21 days (change to PO after clinical improvement)
Alternatives:	Pentamidine	3-4 mg IV daily × 21 days	3-4 mg IV daily × 21 days
or	Primaquine	30 mg base PO daily × 21 days	0.3 mg/kg base PO (max 30 mg) daily × 21 days
	plus clindamycin[7]	600-900 mg IV tid or qid × 21 days, or 300-450 mg PO tid or qid × 21 days (change to PO after clinical improvement)	15-25 mg/kg IV tid or qid × 21 days, or 10 mg/kg PO tid or qid (max 300-450 mg/dose) × 21 days (change to PO after clinical improvement)
Mild to moderate disease			
Drug of choice:	TMP-SMX	320 mg/1600 mg (2 DS tablets) PO tid × 21 days	TMP 15-20 mg/kg/day PO in 3 or 4 doses × 21 days
Alternative:	Dapsone	100 mg PO daily × 21 days	2 mg/kg/day (max 100 mg) PO × 21 days
	plus trimethoprim	15 mg/kg/day PO in 3 doses	15 mg/kg/day PO in 3 doses
or	primaquine	30 mg base PO daily × 21 days	0.3 mg/kg base PO daily (max 30 mg) × 21 days
	plus clindamycin	300-450 mg PO tid or qid × 21 days	10 mg/kg PO tid or qid (max 300-450 mg/dose) × 21 days
or	atovaquone	750 mg PO bid × 21 days	1-3 mo: 30 mg/kg/day PO in 2 doses × 21 days
Primary and secondary prophylaxis[91]			
Drug of choice:	TMP-SMX	1 tab (single strength or greater) PO daily or 1 DS tab PO 3 days/wk	TMP 150 mg/m^2 in 1-2 doses daily or on 3 consecutive days/wk
Alternatives:[91]	Dapsone[7]	50 mg PO bid, or 100 mg PO daily	2 mg/kg/day (max 100 mg) PO or 4 mg/kg (max 200 mg) PO each wk
or	Dapsone[7]	50 mg PO daily or 200 mg PO each wk	
	plus pyrimethamine[92]	50 mg PO or 75 mg PO each wk	
or	Pentamidine aerosol	300 mg inhaled monthly via Respirgard II nebulizer	≥5 yr: 300 mg inhaled monthly via Respirgard II nebulizer
or	Atovaquone[7]	1,500 mg/day PO in 1 or 2 doses	1-3 mo: 30 mg/kg/day PO
			4-24 mo: 45 mg/kg/day PO in 2 doses × 21 days
			>24 mo: 30 mg/kg/day PO in 2 doses × 21 days

[89]Albendazole or pyrantel pamoate may be effective (Ziem JB, et al. *Ann Trop Med Parasitol*. 2004;98:385).
[90]*Pneumocystis* has been reclassified as a fungus. In severe disease with room air P_{O_2} ≤70 mm Hg or A-a O_2 gradient ≥35 mm Hg, prednisone should also be used (Gagnon S, et al. *N Engl J Med*. 1990;323:1444; Caumes E, et al. *Clin Infect Dis*. 1994;18:319).
[91]Primary/secondary prophylaxis in patients with HIV can be discontinued after the CD4 count increases to >200 × 10^6/L for longer than 3 mo.
[92]Plus leucovorin 25 mg with each dose of pyrimethamine.

Continued

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
ROUNDWORM, SEE ASCARIASIS			
SAPPINIA DIPLOIDEA, SEE AMEBIC MENINGOENCEPHALITIS, PRIMARY			
SCABIES (*SARCOPTES SCABIEI*)			
Drug of choice:	5% Permethrin[93]	Topically, 2× at least 1 wk apart	Topically 2×, 1 wk apart, approved for ≥ 2 mo
Alternatives:[93]	Ivermectin[7,93,94]	200 µg/kg PO × 2 at least 1 wk apart	<15 kg: not indicated
			≥15 kg: see adult dosing
	10% Crotamiton	Topically overnight on days 1, 2, 3, and 8	Topically overnight on days 1, 2, 3, and 8
SCHISTOSOMIASIS (BILHARZIASIS)			
Schistosoma haematobium or Schistosoma intercalatum			
Drug of choice:	Praziquantel	40 mg/kg/day PO in 1 or 2 doses × 1 day	40 mg/kg/day PO in 1 or 2 doses × 1 day[37]
Schistosoma japonicum or Schistosoma mekongi			
Drug of choice:	Praziquantel	60 mg/kg/day PO in 2 or 3 doses × 1 day	60 mg/kg/day PO in 3 doses × 1 day[37]
Schistosoma mansoni			
Drug of choice:	Praziquantel	40 mg/kg/day PO in 1 or 2 doses × 1 day	40 mg/kg/day PO in 1 or 2 doses × 1 day[37]
Alternative:	Oxamniquine[95,96]	15 mg/kg PO once	20 mg/kg/day PO in 2 doses × 1 day
Sleeping sickness, see Trypanosomiasis			
Strongyloidiasis (Strongyloides stercoralis)			
Drug of choice:[97]	Ivermectin	200 µg/kg/day PO × 2 days	<15 kg: not indicated
			≥15 kg: see adult dosing
Alternative:	Albendazole[7,98]	400 mg PO bid × 7 days	<10 kg/2 yr[12]
			≥2 yr: see adult dosing
TAPEWORM INFECTION			
Adult (intestinal stage)			
Diphyllobothrium latum (fish), *Taenia saginata* (beef), *Taenia solium* (pork), *Dipylidium caninum* (dog)			
Drug of choice:	Praziquantel[7]	5-10 mg/kg PO once	5-10 mg/kg PO once[37]
Alternative:	Niclosamide	2 g PO once	50 mg/kg PO once
Hymenolepis nana (dwarf tapeworm)			
Drug of choice:	Praziquantel[7]	25 mg/kg PO once	25 mg/kg PO once[37]
Alternative:	Niclosamide[99]	2 g PO daily × 7 days	11-34 kg: 1 g PO on day 1 then 500 mg/day PO × 6 days
			>34 kg: 1.5 g PO on day 1 then 1 g/day PO × 6 days
Larval (tissue stage)			
Echinococcus granulosus (hydatid disease cystic echinococcosis)			
Drug of choice:[100]	Albendazole[7]	400 mg PO bid × 1-6 mo	<10 kg/2 yr: 10-15 mg/kg/day (max 800 mg/day) PO, in 2 doses[12]
			≥2 yr: 15 mg/kg/day PO (max 400 mg) × 1-6 mo

[93]In some cases, treatment may need to be repeated in 10-14 days (Currie BJ, et al. *N Engl J Med*. 2010;362:717). A second ivermectin dose taken 2 wk later increased the cure rate to 95%, which is equivalent to that of 5% permethrin (Usha V, et al. *J Am Acad Dermatol*. 2000;42:236). Ivermectin, either alone or in combination with a topical scabicide, is the drug of choice for crusted scabies in immunocompromised patients (del Giudice P. *Curr Opin Infect Dis*. 2004;15:123).

[94]Ivermectin, either alone or in combination with a topical scabicide, is the drug of choice for crusted scabies in immunocompromised patients (del Giudice P. *Curr Opin Infect Dis*. 2004;15:123). The safety of oral ivermectin in pregnancy and young children has not been well studied. Ivermectin is included on the KIDS list (Meyers RS, et al. *J Pediatr Pharmacol Ther*. 2020;25:175) due to concerns about encephalopathy, but more recent studies suggest that it may be used safely (Levy M, et al. *Br J Dermatol*. 2020;182:1003).

[95]Oxamniquine has been effective in some areas in which praziquantel is less effective (Stelma FF, et al. *J Infect Dis*. 1997;176:304). Oxamniquine is contraindicated in pregnancy.

[96]In East Africa, the dose should be increased to 30 mg/kg, and in Egypt and South Africa to 30 mg/kg/day × 2 days. Some experts recommend 40-60 mg/kg over 2-3 days in all of Africa (Shekhar KC. *Drugs*. 1991;42:379).

[97]In immunocompromised patients or disseminated disease, it may be necessary to prolong or repeat therapy or to use other agents. Veterinary parenteral and enema formulations of ivermectin have been used in severely ill patients unable to take oral medications (Chiodini PL, et al. *Lancet*. 2000;355:43; Orem J, et al. *Clin Infect Dis*. 2003;37:152; Tarr PE. *Am J Trop Med Hyg*. 2003;68:453).

[98]Albendazole must be taken with food; a fatty meal increases oral bioavailability.

[99]Niclosamide must be thoroughly chewed or crushed and swallowed with a small amount of water. Nitazoxanide may be an alternative (Juan JO, et al. *Trans R Soc Trop Med Hyg*. 2002;96:193; Chero JC, et al. *Trans R Soc Trop Med Hyg*. 2007;101:203; Diaz E, et al. *Am J Trop Med Hyg*. 2003;68:384).

[100]Optimal treatment depends on multiple factors, including size, location, and number of cysts and presence of complications. In some patients, medical therapy alone is preferred, but some patients may benefit from surgical resection or percutaneous drainage of cysts. Praziquantel is useful preoperatively or in case of spillage of cyst contents during surgery. Puncture aspiration-injection-reaspiration (PAIR) with ultrasound guidance plus albendazole therapy has been effective for management of hepatic hydatid cyst disease (Smego RA Jr, et al. *Clin Infect Dis*. 2003;37:1073).

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Echinococcus multilocularis (alveolar echinococcosis)			
Treatment of choice:	See footnote[101]		
Neurocysticerosis			
Taenia solium (pork)			
		1-2 viable parenchymal cysticerci[115]	
Treatment of choice:[102,115]	Albendazole	400 mg bid PO × 8-30 days; can be repeated as necessary	<10 kg/2 yr: 15 mg/kg/day PO in 2 doses (max dose 1200 mg/day) for 10-14 days with food
			≥2 yr: 15 mg/kg/day PO in 2 doses (max 1200 mg/day) for 10-14 days with food
		>2 viable parenchymal cysticerci[115]	
	Albendazole plus praziquantel	—	15 mg/kg/day for 10-14 days 50 mg/kg/day for 10-14 days
		Single enhancing lesions (SELs) from cysticercosis[115]	
	Albendazole	—	15 mg/kg/day bid with meals for 1–2 weeks
		Single enhancing lesions (SELs) from cysticercosis[115]	
	Albendazole	—	15 mg/kg/day bid with meals for 1–2 weeks
		Calcified parenchymal lesions[115]	
		Symptomatic therapy alone	
	plus steroids		
or	Surgical removal		

[101]Surgical excision is the only reliable means of cure. Reports have suggested that in nonresectable cases, the use of albendazole or mebendazole can stabilize and sometimes cure infection (Craig P. *Curr Opin Infect Dis.* 2003;16:437). Medical treatment is prolonged up to 2 yr or more.

[102]Initial therapy for patients with inflamed parenchymal cysticercosis should focus on symptomatic treatment with antiseizure medication. Treatment of parenchymal cysticerci with albendazole or praziquantel is controversial (Maguire JH. *N Engl J Med.* 2004;350:215). Patients with live parenchymal cysts who have seizures should be treated with albendazole together with steroids (6 mg dexamethasone or 40-60 mg prednisone daily) and an antiseizure medication (Garcia HH, et al. *N Engl J Med.* 2004;350:249). Some recent studies have shown improved outcomes with combination albendazole and praziquantel (Garcia HH, et al. *Lancet Infect Dis.* 2014;14:687). Patients with subarachnoid cysts or giant cysts in the fissures should be treated for at least 30 days (Proaño JV, et al. *N Engl J Med.* 2001;345:879). Surgical intervention or CSF diversion is indicated for obstructive hydrocephalus; prednisone 40 mg/day may be given with surgery. Arachnoiditis, vasculitis, or cerebral edema is treated with prednisone 60 mg/day or dexamethasone 4-6 mg/day together with albendazole or praziquantel (White AC Jr. *Annu Rev Med.* 2000;51:187). Any cysticercocidal drug may cause irreparable damage when used to treat ocular or spinal cysts, even when corticosteroids are used. An ophthalmic exam should always precede treatment to rule out intraocular cysts.

[115]For patients with *1-2 viable parenchymal cysticerci*, albendazole monotherapy for 10-14 days compared to either no antiparasitic therapy (strong, high) or combination antiparasitic therapy (weak, moderate). We recommend albendazole (15 mg/kg/day) combined with praziquantel (50 mg/kg/day) for 10–14 days rather than albendazole monotherapy for patients with *>2 viable parenchymal cysticerci* (strong, moderate). We suggest retreatment with antiparasitic therapy for parenchymal cystic lesions persisting for 6 months after the end of the initial course of therapy (weak, low). We suggest albendazole therapy rather than no antiparasitic therapy for all patients with SELs (weak, moderate). Remarks: albendazole (15 mg/kg/day in twice-daily doses up for 1–2 weeks) should be given with meals. We recommend symptomatic therapy alone instead of antiparasitic drugs in patients with calcified parenchymal lesions (strong, moderate). (Infectious Diseases Society of America [IDSA] and the American Society of Tropical Medicine and Hygiene [ASTMH]. Diagnosis and treatment of neurocysticercosis: 2017 Clinical Practice Guidelines by the CID. Published 2/22/2018. *Clin Infect Dis* 2018;66(8):e49–e75.)

Continued

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
TOXOCARIASIS, SEE VISCERAL LARVA MIGRANS			
TOXOPLASMOSIS (*TOXOPLASMA GONDII*)[103] (ACQUIRED OR OCULAR INFECTION)			
Drugs of choice:[104,105]	Pyrimethamine[106]	Dosage is adjusted for weight, but 50 mg PO bid on days 1 and 2, then 50 mg qd is maximum. Duration depends on clinical response, treating at least 1-2 wk beyond complete resolution and end of any immune compromise or immaturity. Please see Chapter 336	1 mg/kg (max 50 mg) bid × 2 days, then 1 mg/kg qd (max 50 mg). Duration depends on clinical response, treating at least 1-2 wk beyond complete resolution and end of any immune compromise or immaturity. Please see Chapter 336[107] Calcium leucovorin is always given with pyrimethamine and in the week after discontinuing Please see formulation and instructions for infants in Chapter 336 In the United States pyrimethamine serum levels can be measured at NMS Laboratories in Philadelphia Pyrimethamine cannot be given in the first trimester of pregnancy
	plus sulfadiazine	1.5 g PO bid is a standard dose for a 100-lb person, maximum 2 g PO bid. Duration depends on clinical response, treating at least 1-2 wk beyond complete resolution and end of any immune compromise or immaturity. Please see Chapter 336.	1.5 g PO bid is a standard dose for a 100-lb person, maximum 2 g PO bid. Duration depends on clinical response, treating at least 1-2 wk beyond complete resolution and end of any immune compromise or immaturity. Please see Chapter 336 This is used with pyrimethamine for synergy
Alternative for sulfadiazine or for suppression/ prophylaxis	Trimethoprim-sulfamethoxazole (TMP-SMX)	1 double-strength tablet daily. *Alternative dosing*: one double-strength tablet 3 times weekly. *Adult alternative regimen:* Trimethoprim-sulfamethoxazole (TMP-SMX) – 5 mg/kg trimethoprim and 25 mg/kg sulfamethoxazole given PO or IV bid Clindamycin (600 mg IV or PO 4 times daily) plus oral pyrimethamine (200 mg loading dose followed by 50 mg daily among patients <60 kg or 75 mg daily among patients ≥60 kg) plus oral leucovorin (10 to 25 mg daily).	TMP-SMX 150/750 mg/m^2 body surface area once daily PO
TRICHINELLOSIS (*TRICHINELLA SPIRALIS*)			
Drugs of choice:	Steroids for severe symptoms	Prednisone 30-60 mg PO daily × 10-15 days	
	plus Albendazole[7]	400 mg PO bid × 8-14 days	<10 kg/2 yr[12]
			≥2 yr: see adult dosing
Alternative:	Mebendazole[7]	200-400 mg PO tid × 3 days, then 400-500 mg PO tid × 10 days	200-400 mg PO tid × 3 days, then 400-500 mg PO tid × 10 days[13]
TRICHOMONIASIS (*TRICHOMONAS VAGINALIS*)			
Drug of choice:[108]	Metronidazole	2 g PO once or 500 mg PO bid × 7 days	15 mg/kg/day PO in 3 doses × 7 days
or	Tinidazole[4]	2 g PO once	50 mg/kg PO once (max 2 g)
TRICHOSTRONGYLUS INFECTION			
Drug of choice:	Pyrantel pamoate[7]	11 mg/kg base PO once (max 1 g)	11 mg/kg PO once (max 1 g)
Alternative:	Mebendazole[7]	100 mg PO bid × 3 days	100 mg PO bid × 3 days[13]
or	Albendazole[7]	400 mg PO once	<10 kg/2 yr[12]
			≥2 yr: 15 mg/kg/day PO (max 800 mg) × 1-6 mo

[103]In ocular toxoplasmosis with macular involvement, corticosteroids are recommended in addition to antiparasitic therapy for an antiinflammatory effect.

[104]To treat CNS toxoplasmosis in HIV-infected patients, some clinicians have used pyrimethamine 50-100 mg/day (after a loading dose of 200 mg) with sulfadiazine and, when sulfonamide sensitivity developed, have given clindamycin 1.8-2.4 g/day in divided doses instead of the sulfonamide. Atovaquone plus pyrimethamine appears to be an effective alternative in sulfa-intolerant patients (Chirgwin K, et al. *Clin Infect Dis.* 2002;34:1243). Treatment is followed by chronic suppression with lower-dosage regimens of the same drugs. For primary prophylaxis in HIV patients with <100 × 10^6/L CD4 cells, either trimethoprim-sulfamethoxazole, pyrimethamine with dapsone, or atovaquone with or without pyrimethamine can be used. Primary or secondary prophylaxis may be discontinued when the CD4 count increases to >200 × 10^6/L for more than 3 mo (Benson CA, et al. *MMWR Recomm Rep.* 2004;53([RR-15]:1).

[105]Women who develop toxoplasmosis during the first trimester of pregnancy can be treated with spiramycin (3-4 g/day). After the first trimester, if there is no documented transmission to the fetus, spiramycin can be continued until term. If transmission has occurred in utero, therapy with pyrimethamine and sulfadiazine should be started (Montoya JG, et al. *Lancet.* 2004;363:1965). Pyrimethamine is a potential teratogen and should be used only after the first trimester.

[106]Plus leucovorin 10-25 mg with each dose of pyrimethamine.

[107]Congenitally infected newborns should be treated with pyrimethamine every 2 or 3 days and a sulfonamide daily for about 1 yr (Remington JS, et al., eds. *Infectious Disease of the Fetus and Newborn Infant.* 5th ed. Philadelphia: WB Saunders; 2001: p. 290).

[108]Sexual partners should be treated simultaneously. Metronidazole-resistant strains have been reported and can be treated with higher doses of metronidazole (2-4 g/day × 7-14 days) or with tinidazole (Hager WD. *Sex Transm Dis.* 2004;31:343).

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
TRICHURIASIS (*TRICHURIS TRICHIURA*, WHIPWORM)			
Drug of choice:	Mebendazole	100 mg PO bid × 3 days	100 mg PO bid × 3 days[13]
Alternative:	Albendazole[7]	400 mg PO × 3 days	<10 kg/2 yr[12]
			≥2 yr: see adult dosing
or	Ivermectin[7]	200 µg/kg PO daily × 3 days	<15 kg: not indicated
			≥15 kg: see adult dosing
TRYPANOSOMIASIS[109]			
Trypanosoma cruzi (American trypanosomiasis, Chagas disease)			
Drug of choice:	Benznidazole[28]	5-7 mg/kg/day PO in 2 divided doses × 60 days	≤12 yr: 5-7.5 mg/kg/day PO in 2 divided doses × 60 days
			>12 yr: see adult dosing
Alternative:	Nifurtimox[28,110]	8-10 mg/kg/day PO in 3-4 doses × 90 days	≤10 yr: 15-20 mg/kg/day PO in 3-4 doses × 90 days
			11-16 yr: 12.5-15 mg/kg/day in 3-4 doses × 90 days
			>16 yr: see adult dosing
Trypanosoma brucei gambiense (West African trypanosomiasis, sleeping sickness)			
Hemolymphatic stage			
Drug of choice[111]	Pentamidine isethionate[7]	4 mg/kg/day IM × 7-10 days	4 mg/kg/day IM or IV × 7-10 days
Alternative:	Suramin[28]	100 mg (test dose) IV, then 1 g IV on days 1, 3, 7, 14, and 21	2 mg/kg (test dose) IV, then 20 mg/kg IV on days 1, 3, 7, 14, and 21
Late disease with CNS involvement			
Drug of choice:	Eflornithine[28,112]	100 mg/kg IV qid × 14 days	100 mg/kg IV qid × 14 days
Alternative:	Melarsoprol[28,113]	2-3.6 mg/kg (max 200 mg) daily IV (progressively increased during series) × 3 days After 7 days, 3.6 mg/kg daily × 3 days After 7 days, give a third series of 3.6 mg/kg daily × 3 days.	2-3.6 mg/kg (max 200 mg) daily IV (progressively increased during series) × 3 days After 7 days, 3.6 mg/kg daily × 3 days After 7 days, give a third series of 3.6 mg/kg daily × 3 days
Trypanosoma brucei rhodesiense (East African trypanosomiasis, sleeping sickness)			
Hemolymphatic stage			
Drug of choice:	Suramin[28]	100 mg (test dose) IV, then 1 g IV on days 1, 3, 7, 14, and 21	2 mg/kg (test dose), then 20 mg/kg IV on days 1, 3, 7, 14, and 21
Late disease with CNS involvement			

[109]Barrett MP, et al. *Lancet*. 2003;362:1469.

[110]The addition of γ-interferon to nifurtimox for 20 days in experimental animals and in a limited number of patients appears to shorten the acute phase of Chagas disease (McCabe RE, et al. *J Infect Dis*. 1991;163:912).

[111]For treatment of *Trypanosoma brucei gambiense*, pentamidine and suramin have equal efficacy but pentamidine is better tolerated.

[112]Eflornithine is highly effective in *Trypanosoma brucei gambiense* but not against *Trypanosoma brucei rhodesiense* infections. It is available in limited supply only from the WHO and the CDC. Eflornithine dose may be reduced to 400 mg/kg IV in 2 doses for 7 days when used in conjunction with nifurtimox at a dose of 5 mg/kg PO tid × 10 days (Priotto G, et al. *Lancet*. 2009;374:56).

[113]In frail patients, begin with as little as 18 mg and increase the dose progressively. Pretreatment with suramin has been advocated for debilitated patients. Corticosteroids have been used to prevent arsenical encephalopathy (Pépin J, et al. *Trans R Soc Trop Med Hyg*. 1995;89:92). Up to 20% of patients with *Trypanosoma brucei gambiense* fail to respond to melarsoprol (Barrett MP. *Lancet*. 1999;353:1113). Consultation with experts at the CDC is recommended.

Continued

Table 325.1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Drug of choice:	Melarsoprol[28,112]	2-3.6 mg/kg (max 200 mg) daily IV (progressively increased during series) × 3 days After 7 days, 3.6 mg/kg daily × 3 days After 7 days, give a third series of 3.6 mg/kg daily × 3 days	2-3.6 mg/kg (max 200 mg) daily IV (progressively increased during series) × 3 days After 7 days, 3.6 mg/kg daily × 3 days After 7 days, give a third series of 3.6 mg/kg daily × 3 days
VISCERAL LARVA MIGRANS (TOXOCARIASIS)[114]			
Drugs of choice:	Albendazole[7]	400 mg PO bid × 5 days	<10 kg/2 yr[12]
			≥2 yr: see adult dosing
or	Mebendazole[7]	100-200 mg PO bid × 5 days	100-200 mg PO bid × 5 days[13]
WHIPWORM, SEE TRICHURIASIS			
WUCHERERIA BANCROFTI, SEE FILARIASIS			

[114]Optimum duration of therapy is not known; some consultants would treat for 20 days. For severe symptoms or eye involvement, corticosteroids can be used in addition.
bid, Twice a day; CDC, Centers for Disease Control and Prevention; CNS, central nervous system; CSF, cerebrospinal fluid; DEC, diethylcarbamazine; DS, double strength; FDA, U.S. Food and Drug Administration; GI, gastrointestinal; HAART, highly active antiretroviral therapy; IDSA, Infectious Disease Society of America; IM, intramuscularly; IND, investigational new drugs; IV, intravenously; OTC, over the counter; PO, by mouth; qd, once a day; qid, four times a day; tid, three times a day; WHO, World Health Organization.
Adapted from Drugs for parasitic infection. *Med Lett.* 2013;11(Suppl):e1–e23. Available at http://www.medicalletter.org

drug approved for use by the FDA for patients ≥5 kg. It is a fixed-dose combination of two novel antimalarials, artemether (20 mg) and lumefantrine (120 mg). It is a highly effective 3-day malaria treatment, with cure rates of >96%, even in areas of multidrug resistance. It can be used to treat chloroquine-resistant uncomplicated malaria during the second and third trimesters of pregnancy and as an alternative agent in the first trimester. Artesunate was approved by the FDA for intravenous (IV) treatment for severe malaria in 2020.

SELECTED ANTIPARASITIC DRUGS FOR HELMINTHS AND ECTOPARASITES

Albendazole (Albenza)

Albendazole is a benzimidazole carbamate structurally related to mebendazole and has similar anthelmintic activity. Its absorption from the gastrointestinal tract is poor but improved with a concomitant high-fat meal. Albendazole sulfoxide, the principal metabolite with anthelmintic activity, has a plasma half-life of 8.5 hours. It is widely distributed in the body, including the bile and cerebrospinal fluid. It is eliminated in bile. Albendazole is FDA approved for treatment of two cestode (tapeworm) infections: neurocysticercosis and hydatid diseases *(Echinococcus granulosus).* It is used off-label for numerous other **helminth** infections, including cutaneous larva migrans *(Ancylostoma caninum* and *Ancylostoma braziliense),* ascariasis *(Ascaris lumbricoides),* liver flukes *(Clonorchis sinensis* and *Opisthorchis viverrini),* pinworm *(Enterobius vermicularis),* lymphatic filariasis *(Wuchereria bancrofti, Brugia malayi, Brugia timori),* gnathostomiasis (*Gnathostoma* spp.), hookworms *(Ancylostoma duodenale* and *Necator americanus),* microsporidiosis, trichinellosis *(Trichinella spiralis),* and visceral larva migrans *(Toxocara canis* and *Toxocara cati).* Albendazole is generally well tolerated. Common adverse effects include headache, nausea, vomiting, and abdominal pain. Serious adverse effects include elevated liver enzymes and leukopenia, which have occurred in a few patients with treatment of hydatid disease. Rare adverse effects include acute renal failure, pancytopenia, granulocytopenia, and thrombocytopenia. Despite the fact that albendazole and other antiparasitic drugs, including mebendazole, praziquantel, and pyrimethamine, have been in use for decades, the number of manufacturers is small and costs have risen in recent years. Data are limited in pregnancy, and treatment during pregnancy generally deferred if possible. Albendazole is excreted in breast milk but is generally considered compatible with breastfeeding by the WHO.

Ivermectin (Stromectol, Mectizan)

Ivermectin is a semisynthetic derivative of one of the avermectins, which is a group of macrocyclic lactones produced by *Streptomyces avermitilis.* After oral administration, ivermectin has peak plasma concentrations after approximately 4 hours and a plasma elimination half-life of approximately 12 hours. It is excreted as metabolites over a 2-week period via feces. It is FDA approved for treatment of two nematode (roundworm) infections: onchocerciasis (*Onchocerca volvulus)* and strongyloidiasis *(Strongyloides stercoralis).* It may have some effect in treating a broad range of other **helminths** and **ectoparasites,** including cutaneous larva migrans *(Ancylostoma braziliense),* ascariasis *(Ascaris lumbricoides),* loiasis, pinworm *(Enterobius vermicularis),* whipworm *(Trichuris trichiura),* gnathostomiasis *(Gnathostoma spinigerum), Mansonella* infections, lice *(Pediculus humanus* and *Phthirus pubis),* mites (*Demodex* spp.), and scabies *(Sarcoptes scabiei).* Combination therapies of ivermectin with albendazole or diethylcarbamazine are being used to treat lymphatic filariasis. Combination therapy with albendazole and the off-label use of veterinary injectable formulations have been used to treat complicated *Strongyloides* infections, including disseminated disease and hyperinfection syndrome. Though there has been significant public interest in ivermectin as a treatment for SARS-CoV-2, clinical studies have not shown efficacy. Common adverse events include dizziness, headache, pruritus, and gastrointestinal effects. Serious adverse events include encephalopathy due to pathogenic variants in the *ABCB1* transporter and **Mazzotti reactions** in patients with onchocerciasis, including arthralgia, synovitis, enlarged lymph nodes, rash, and fever secondary to microfilaria death. A topical formulation is available for treatment of head lice, which are increasingly becoming very resistant to over-the-counter medications such as permethrins. Data are limited in pregnancy, and other agents are preferred if available for a given condition. Ivermectin is excreted in breast milk, and decisions to use this medication while breastfeeding should consider the risks and benefits of therapy based on the specific indication.

Praziquantel (Biltricide)

Praziquantel achieves its antiparasitic activity via the pyrazino isoquinoline ring system and was originally synthesized as a potential tranquilizer. After oral administration, praziquantel is rapidly absorbed, with peak levels in 1-2 hours and a plasma half-life of about 1-3 hours. Elimination via the urine and feces is >80% complete after 24 hours. Praziquantel is metabolized in the liver by the microsomal cytochrome P450 (especially 2B1 and 3A). Bioavailability of praziquantel is increased with concomitant administration of agents that inhibit cytochrome P450. Praziquantel is FDA approved for treatment of several species of trematodes (flatworms) including the Chinese liver fluke *(Clonorchis sinensis),* Southeast Asian liver fluke *(Opisthorchis viverrini),* and schistosomiasis (*Schistosoma* spp.). It is used off-label for treatment of additional trematode pathogens, including the North American liver fluke *(Metorchis conjunctus), Nanophyetus salmincola,* intestinal flukes *(Fasciolopsis buski, Heterophyes heterophyes, Metagonimus yokogawai),* and lung flukes *(Paragonimus westermani, Paragonimus kellicotti).* It is also used off-label for multiple cestode (tapeworm) infections. Adverse effects can be seen in 30–60% of patients, although most are mild and disappear within 24 hours. Common adverse effects include headache, abdominal pain, dizziness, and malaise. Serious but rare adverse effects include arrhythmias, heart block, and convulsions.

Section 15

Protozoan Diseases

Chapter 326

Primary Amebic Meningoencephalitis

Matthew D. Eberly

Naegleria, Acanthamoeba, Balamuthia, and *Sappinia* are small, free-living amebae that cause human amebic meningoencephalitis, which has two distinct clinical presentations. The more common is an acute, fulminant, and usually fatal **primary amebic meningoencephalitis** caused by *Naegleria fowleri* that occurs in previously healthy children and young adults. **Granulomatous amebic meningoencephalitis,** which is caused by *Acanthamoeba, Balamuthia,* and *Sappinia,* is a more indolent infection that typically occurs in immunocompromised hosts and may also present with a disseminated form of the disease.

ETIOLOGY

Naegleria is an ameboflagellate that can exist as cyst, trophozoite, and transient flagellate forms. Temperature and environmental nutrient and ion concentrations are the major factors that determine the stage of the ameba. Trophozoites are the only stages that are invasive, although cysts are potentially infective because they can convert to the vegetative form very quickly under the proper environmental stimuli. Although there are over 40 species of *Naegleria,* only *Naegleria fowleri* has been shown to be pathogenic for humans.

Acanthamoeba exists in cyst and motile trophozoite forms; only the trophozoite form is invasive. Cases of *Acanthamoeba* **keratitis** usually follow incidents of trivial corneal trauma followed by flushing with contaminated tap water. Infections can also occur among contact lens wearers who come into contact with contaminated water during swimming or use contact lenses cleaned or stored in contaminated tap water. Granulomatous amebic encephalitis from *Acanthamoeba* occurs worldwide and is associated with an immunocompromising condition such as HIV infection, diabetes mellitus, chronic liver disease, renal failure, immunosuppressive therapy, or radiation therapy.

Balamuthia mandrillaris has been implicated as an etiology of granulomatous amebic encephalitis. Although the clinical presentation is similar to infection with *Acanthamoeba,* most patients are not immunocompromised.

Other free-living amebae can also cause infection, as illustrated by a case report of *Sappinia pedata* granulomatous encephalitis.

EPIDEMIOLOGY

The free-living amebae have a worldwide distribution. *Naegleria* species have been isolated from a variety of freshwater sources, including ponds and lakes, domestic water supplies, hot springs and spas, thermal discharge of power plants, groundwater, and, occasionally, from the nasal passages of healthy children. *Acanthamoeba* species have been isolated from soil, mushrooms, vegetables, brackish water, and seawater, as well as most of the freshwater sources for *Naegleria.* It can also be found in tap water because chlorination does not kill *Acanthamoeba. Balamuthia* is present in soil and may be transmitted by inhalation or contamination of preexisting skin lesions.

Naegleria meningoencephalitis has been reported from every continent except Antarctica. Most of the cases occur during the summer months in previously healthy individuals who have a history of swimming in or contact with freshwater lakes and rivers before their illness. Between 1962 and 2022, 157 cases of primary amebic meningoencephalitis (PAM) were reported in the United States. Most of the reports have come from the southern and southwestern states, particularly Florida and Texas, but infections have occurred in Kansas, Indiana, and Minnesota. Of note, cases have been linked to sinus irrigation with neti pots containing contaminated tap water; exposure to a lawn water slide, which derived its tap water from a treated public drinking water system; a chlorinated recreational splash pad; a swimming pool supplied by an overland water pipe; and rafting on an artificial whitewater river.

PATHOGENESIS

The free-living amebae enter the nasal cavity by inhalation or aspiration of dust or water contaminated with trophozoites or cysts. *Naegleria* gains access to the central nervous system through the olfactory epithelium and migrates via the olfactory nerve to the olfactory bulbs located in the subarachnoid space and bathed by the cerebrospinal fluid (CSF). This space is richly vascularized and is the route of spread to other areas of the central nervous system. Grossly, there is widespread cerebral edema and hyperemia of the meninges. The olfactory bulbs are necrotic, hemorrhagic, and surrounded by a purulent exudate. Microscopically, the gray matter is the most severely affected, with severe involvement in all cases. Fibrinopurulent exudate may be found throughout the cerebral hemispheres, brainstem, cerebellum, and upper portions of the spinal cord. Pockets of trophozoites may be seen in necrotic neural tissue, usually in the perivascular spaces of arteries and arterioles.

The route of invasion and penetration in cases of granulomatous amebic meningoencephalitis caused by *Acanthamoeba* and *Balamuthia* may be by direct spread through olfactory epithelium or hematogenous spread from a primary focus in the skin or lungs. Pathologic examination reveals granulomatous encephalitis, with multinucleated giant cells mainly in the posterior fossa structures, basal ganglia, bases of the cerebral hemispheres, and cerebellum. Both trophozoites and cysts may be found in the central nervous system lesions, primarily located in the perivascular spaces and invading blood vessel walls. The olfactory bulbs and spinal cord are usually spared. The single case of *Sappinia* encephalitis followed a sinus infection, and evaluation revealed a solitary 2 cm temporal lobe mass with mild ring enhancement.

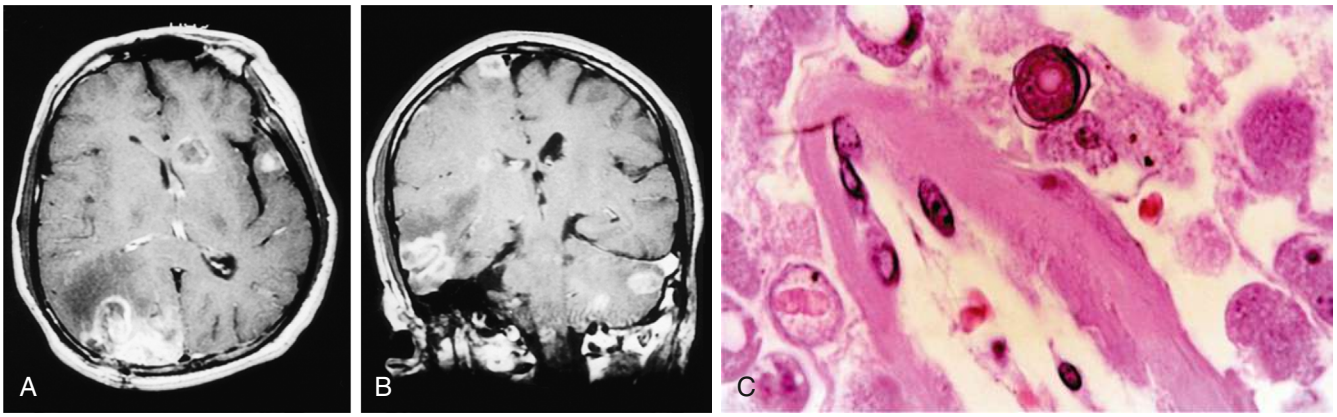

Fig. 326.1 A and B, MRIs of the brain of a patient with *Balamuthia mandrillaris* granulomatous amebic encephalitis. Multiple enhancing lesions are seen in the right hemisphere, left cerebellum, midbrain, and brainstem. C, Photomicrograph of the brain lesion from the same patient showing perivascular amebic trophozoites. A round amebic cyst with a characteristic double wall is seen in the top center (hematoxylin and eosin, original magnification ×100). *(From Deol I, Robledo L, Meza A, et al. Encephalitis due to a free-living amoeba [Balamuthia mandrillaris]: case report with literature review. Surg Neurol. 2000;53:611–616.)*

CLINICAL MANIFESTATIONS

The incubation period of ***Naegleria* infection** may be as short as 2 days or as long as 15 days. Symptoms have an acute onset and progress rapidly. Infection is characterized by a sudden onset of severe headache, fever, pharyngitis, nasal congestion or discharge, and nausea and vomiting, followed by altered mental status, nuchal rigidity, photophobia, confusion, somnolence, seizures, and ultimately coma. Most cases end in death within 3-10 days after onset of symptoms.

Granulomatous amebic meningoencephalitis may occur weeks to months after the initial infection. The presenting signs and symptoms are often those of single or multiple central nervous system space-occupying lesions and include hemiparesis, ataxia, personality changes, seizures, and drowsiness. Altered mental status is often a prominent symptom. Headache and fever occur only sporadically, but stiff neck is seen in a majority of cases. Cranial nerve palsies, especially of cranial nerves III and VI, may be present. There is also one report of acute hydrocephalus and fever with *Balamuthia.* Granulomatous amebic meningoencephalitis is usually fatal after 4-6 weeks of illness. Results of neuroimaging studies of the brain usually demonstrate multiple low-density lesions resembling infarcts or enhancing lesions of granulomas (Fig. 326.1).

DIAGNOSIS

The CSF in *Naegleria* infection may mimic that of herpes simplex encephalitis early in the disease and that of acute bacterial meningitis later in the disease, with a neutrophilic pleocytosis, elevated protein level, and hypoglycorrhachia. *Motile amebae may be visualized on a wet mount of freshly drawn CSF using Wright or Giemsa stains*, but they are often mistaken for lymphocytes or macrophages. Because *Naegleria* are the only amebae that differentiate into the flagellate state in a hypotonic environment, placing a drop of fresh CSF in 1 mL of distilled water and watching for the development of swimming flagellates after 1-2 hours can confirm the diagnosis of *Naegleria. Naegleria* can also be grown on a non-nutrient agar plate coated with *Escherichia coli,* on which they feed. Polymerase chain reaction (PCR) and immunofluorescence assays for *Naegleria* performed on CSF and biopsy material are available through the U.S. Centers for Disease Control and Prevention (CDC).

The diagnosis of granulomatous amebic meningoencephalitis relies on the isolation or histologic identification of *Acanthamoeba* trophozoites or cysts from brain tissue specimens. The CSF findings of granulomatous meningoencephalitis reveal lymphocytic pleocytosis, moderately elevated protein, and low glucose concentrations. However, motile trophozoites of *Acanthamoeba* are more difficult to isolate than *Naegleria,* and the CSF is typically sterile. *Acanthamoeba* may be cultured from the same agar used for growing *Naegleria,* but *Balamuthia* must be grown on mammalian cell cultures. Pediatric cases of *Balamuthia* meningoencephalitis have been diagnosed antemortem by brain biopsy as well as postmortem. PCR and immunofluorescence assays can be used on specimens to identify *Acanthamoeba* and *Balamuthia* species, and are also available from the CDC.

TREATMENT

Naegleria infection is nearly always fatal, but early recognition and treatment are crucial to survival. Until 2013, there had been only two known survivors in North America, with treatment regimens of amphotericin B, either alone or in combination with other agents such as rifampin, chloramphenicol, fluconazole, ketoconazole, and dexamethasone. In 2013, however, the CDC made available the antileishmanial drug **miltefosine** for the treatment of primary amebic meningoencephalitis. That summer, two children who contracted *Naegleria* both survived; both patients received oral miltefosine as part of their treatment, and one underwent external ventricular drain placement and therapeutic hypothermia. Miltefosine is now commercially available in the United States (www.impavido.com). **The recommended drug treatment for primary amebic meningoencephalitis by the CDC includes intravenous and intrathecal amphotericin B, oral miltefosine, along with azithromycin, fluconazole, rifampin, and dexamethasone**. Early identification, early initiation of combination therapy, and aggressive management of increased intracranial pressure remain key elements for a successful outcome. For suspected cases, clinicians should contact the CDC Emergency Operations Center at (770) 488-7100 for assistance.

The optimal therapy for granulomatous amebic meningoencephalitis is uncertain. However, miltefosine has likewise been used to successfully treat patients with *Balamuthia* and disseminated *Acanthamoeba* infections. Strains of *Acanthamoeba* isolated from fatal cases are usually susceptible in vitro to pentamidine, ketoconazole, and flucytosine and less so to amphotericin B. One patient was successfully treated with sulfadiazine and fluconazole, and another was successfully treated with intravenous pentamidine followed by oral itraconazole. *Acanthamoeba* keratitis responds to long courses of topical propamidine–polymyxin B sulfate or topical polyhexamethylene biguanide or chlorhexidine gluconate, and antifungal azoles plus topical steroids. Limited success has been demonstrated in *Balamuthia* infection with systemic azole therapy combined with flucytosine. More recently, the combination of flucytosine, pentamidine, fluconazole, sulfadiazine, azithromycin, and phenothiazines resulted in the survival of two patients with *Balamuthia* meningoencephalitis, although both were left with mild neuromotor and cognitive impairment. Corticosteroids before initiating effective therapy appear to have a detrimental effect, contributing to rapid progression of disease.

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Chapter 327

Amebiasis

Edsel Maurice T. Salvana and Robert A. Salata

Entamoeba species infect or colonize up to 10% of the world's population, with a disproportionate burden of illness in resource-limited settings. In most infected individuals, *Entamoeba histolytica* or a related species infects the lumen of the gastrointestinal tract and causes few symptoms or sequelae. Although *E. histolytica* is the only confirmed invasive species, other *Entamoeba* species have been implicated in human disease. Molecular epidemiology is helping detail the role that these diverse protozoans play in human health. Invasive *E. histolytica* infection can lead to **amebic colitis, amebic liver abscess,** and, less commonly, abscesses in other extraintestinal sites.

ETIOLOGY

Four morphologically identical but genetically distinct species of *Entamoeba* are known to infect humans. *Entamoeba histolytica*, the main pathogenic species, causes a spectrum of disease and can become invasive in 4–10% of infected patients. *Entamoeba dispar,* the most prevalent species, does not cause symptomatic disease. *Entamoeba moshkovskii,* can cause diarrhea in infants and children, and asymptomatic infection with *E. moshkovskii* may be as common as *E. dispar* infection in some communities. Patients previously described as asymptomatic carriers of *E. histolytica* based on microscopy findings were likely harboring *E. dispar* or *E. moshkovskii.* A fourth species, *E. bangladeshi,* was discovered in Bangladesh in 2012 and has recently been found in South Africa. The potential for *E. bangladeshi* to cause human disease remains unclear. Four other species of nonpathogenic *Entamoeba* are known to colonize the human gastrointestinal tract: *Entamoeba coli, E. hartmanni, E. gingivalis,* and *E. polecki.* A fifth species, *E. nuttalli,* typically infects nonhuman primates such as macaques, but a case of asymptomatic infection has been described in a zookeeper.

Infection is usually acquired through the ingestion of parasite cysts, which measure 10-18 μm in diameter and contain four nuclei. Cysts are resistant to harsh environmental conditions, including chlorine concentrations commonly used in water purification, but can be killed by heating them to 55°C (131°F). Cysts are resistant to gastric acidity and digestive enzymes and germinate in the small intestine to form trophozoites. These large, actively motile organisms colonize the lumen of the large intestine and may invade the mucosal lining. Some eventually transform to cysts and are passed out in the stool to infect other hosts anew.

EPIDEMIOLOGY

The prevalence of infection with *E. histolytica* varies greatly by region and socioeconomic status. Early prevalence studies did not distinguish between *E. histolytica* and *E. dispar,* but more recent estimates show that infection with *E. histolytica* causes 100 million cases of symptomatic disease and 2,000 to 17,000 deaths annually. Molecular studies have put the global prevalence of *E. histolytica* at 3.55%, ranging from 1.72% to 21.58% in different regions of the world.

Prospective studies have shown that 4–10% of individuals infected with *E. histolytica* develop amebic colitis and that <1% of infected individuals develop disseminated disease, including amebic liver abscess. These numbers vary by region; for example, in South Africa and Vietnam, liver abscesses form a disproportionately large number of the cases of invasive disease due to *E. histolytica.* Amebic liver abscesses occur equally in male and female children but are generally rare in childhood. Peak abscess formation occurs in individuals between 30-60 years old and is 10-12 times more prevalent in adult males than females.

Amebiasis causes its largest burden of disease in Africa, Southeast Asia, and the Eastern Mediterranean. In the United States, amebiasis is seen most frequently in travelers to and immigrants from developing countries. Residents of mental health institutions and men who have sex with men are at increased risk for invasive amebiasis. Food or drink contaminated with *Entamoeba* cysts and oral-anogenital sex are the most common means of infection. Untreated water and night soil (human feces used as fertilizer) are important sources of infection in resource-limited settings. Food handlers shedding amebic cysts play a role in spreading infection.

PATHOGENESIS

Trophozoites are responsible for tissue invasion and destruction. *E. histolytica* secretes many proteases, the best described of which is amebic cysteine protease 5 (EhCP5). EhCP5 cleaves MUC2 mucin, degrading the intestinal mucus layer and exposing colonic epithelial cells. MUC2 is also involved in regulating antimicrobial peptide production by Paneth cells during *E. histolytica* infection. Amebae then attach using a galactose and *N*-acetyl-D-galactosamine–specific lectin. This lectin also provides resistance to complement-mediated lysis, and its intermediate subunit has been found to have hemagglutinating, hemolytic, and cytolytic activity.

Once attached to the colonic mucosa, trophozoites penetrate the epithelial layer, destroying host cells by cytolysis and induction of apoptosis. Cytolysis is mediated by trophozoite release of amebapores (pore-forming proteins), phospholipases, and hemolysins. Once host cells are partially digested by amebic proteases, the degraded material is internalized through phagocytosis. Trogocytosis is another mechanism that amebae use to kill host cells. This involves ingesting pieces of living cells, inducing intracellular calcium elevation leading to apoptosis.

Early invasive amebiasis produces significant inflammation, owing in part to parasite-mediated activation of nuclear factor-κB. Once *E. histolytica* trophozoites invade the intestinal mucosa, the organisms multiply and spread laterally underneath the intestinal epithelium to produce the characteristic *flask-shaped ulcers.* Amebae produce similar lytic lesions if they reach the liver. These lesions are commonly called *abscesses,* although they contain no granulocytes. Well-established ulcers and amebic liver abscesses demonstrate little local inflammatory response.

Immunity to infection is associated with a mucosal secretory IgA response against the galactose/*N*-acetyl-D-galactosamine lectin.

Macrophages are among the earliest responders, mediating phagocytosis and secreting cytokines to recruit other inflammatory cells. Eosinophilia is common in parasitic infections and may play a role in IgA regulation. Neutrophils are generally protective and exert amebicidal activity by phagocytosis, degranulation, and formation of neutrophil extracellular traps (NETs). The disparity between the extent of tissue destruction by amebae and the absence of a local host inflammatory response in the presence of systemic humoral and cell-mediated responses may reflect both parasite-mediated apoptosis and the ability of the trophozoite to kill not only epithelial cells but also neutrophils, monocytes, and macrophages.

The *E. histolytica* genome is functionally tetraploid, and there is evidence of lateral gene transfer from bacteria. The amebapore-A *(Ap-A)* gene, along with other important genes, can be epigenetically silenced using plasmids with specifically engineered sequences or short hairpin RNAs. Transcriptional profiling using proteomics and microarrays has identified multiple virulence factors, including cysteine proteases, which modulate lysosome and phagosome function, as well as excretory-secretory proteins. Many calcium-binding proteins are encoded and are involved in motility, adhesion, cytolysis, and phagocytosis. Some of these proteins bind directly to actin to modulate pseudopod formation and phagocytosis. The bacterial microbiome has also been shown to influence *E. histolytica* pathogenicity by affecting lectin expression, with increased *Prevotella copri* populations associated with higher rates of diarrhea in infected children. Enteropathogenic *Escherichia coli* have been linked to increased *E. histolytica* virulence through upregulation of amebic proteolytic activity. Enteric bacteria improve survival of these anaerobic amebae during times of oxidative stress. Decreased bacterial diversity has been linked to an increase in symptomatic amebic infections in children.

CLINICAL MANIFESTATIONS

Clinical presentations range from asymptomatic cyst passage to amebic colitis, amebic dysentery, ameboma, and extraintestinal disease. Up to 10% of infected persons develop invasive disease within a year, and asymptomatic carriers should be treated. Severe disease is more common in young children, pregnant women, malnourished individuals, and persons taking corticosteroids. Invasive disease is more common in men. Extraintestinal disease usually involves the liver, but less common extraintestinal manifestations include amebic brain abscess, pleuropulmonary disease, skin ulcers, and genitourinary lesions.

Amebic Colitis

Amebic colitis may occur within 2 weeks of infection or may be delayed for months. The onset is usually gradual, with colicky abdominal pain and frequent bowel movements (6-8/day). Diarrhea is frequently associated with tenesmus. Almost all stool is heme-positive, but most patients do not present with grossly bloody stools. Generalized constitutional symptoms and signs are characteristically absent, with fever documented in only one third of patients. Amebic colitis affects all age groups but is strikingly common in children 1-5 years of age. Severe amebic colitis in infants and young children tends to be rapidly progressive, with more frequent extraintestinal involvement and high mortality rates, particularly in tropical countries. Amebic dysentery can result in dehydration and electrolyte disturbances.

Amebic Liver Abscess

Amebic liver abscess, a serious manifestation of disseminated infection, is uncommon in children. Although diffuse liver enlargement has been associated with intestinal amebiasis, liver abscesses occur in <1% of infected individuals and may appear in patients with no clear history of intestinal disease. Amebic liver abscess may occur months to years after exposure, so obtaining a careful travel history is critical. In children, fever is the hallmark of amebic liver abscess and is frequently associated with abdominal pain, abdominal distention, and enlargement and tenderness of the liver. Changes at the base of the right lung may also occur, including elevation of the diaphragm and atelectasis or effusion.

LABORATORY FINDINGS

Laboratory examination findings are often unremarkable in uncomplicated amebic colitis. Laboratory findings in amebic liver abscess are a slight leukocytosis, moderate anemia, high erythrocyte sedimentation rate, and elevations of hepatic enzyme (particularly alkaline phosphatase) levels. Stool examination for amebae is negative in more than half of patients with documented amebic liver abscess. Ultrasonography, CT, or MRI can localize and delineate the size of the abscess cavity (Fig. 327.1). The most common finding is a single abscess in the right hepatic lobe.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

A diagnosis of amebic colitis is made in the presence of compatible symptoms with detection of *E. histolytica* either by stool antigen testing or PCR. This approach has a greater than 95% sensitivity and specificity, and when it is coupled with a positive serology test, it is the most accurate means of diagnosis in developed countries. Several approved stool antigen kits are commercially available in the United States, but most cannot distinguish between *E. histolytica* and *E. dispar.* Microscopic examination of stool samples has a sensitivity of 60%. Sensitivity can be increased to 85–95% by examining three stools. Microscopy cannot differentiate between *E. histolytica*, *E. dispar*, *E. moshkovskii,* and *E. bangladeshi* unless phagocytosed erythrocytes (specific for *E. histolytica*) are seen. Endoscopy and biopsies of suspicious areas should be performed when stool sample results are negative and suspicion remains high. Various serum antibody tests are available. Serologic results are positive in 70–80% of patients with invasive disease (colitis or liver abscess) at presentation and in >90% of patients after 7 days. Indirect hemagglutination is the most sensitive serologic test and yields a positive result even years after invasive infection. Therefore many uninfected adults and children in highly endemic areas demonstrate antibodies to *E. histolytica.*

Conventional and real-time multiplex PCR performed on stool is the most sensitive and preferred method for distinguishing *E. histolytica* from nonpathogenic *E. dispar*, *E. moshkovskii,* and *E. bangladeshi.*

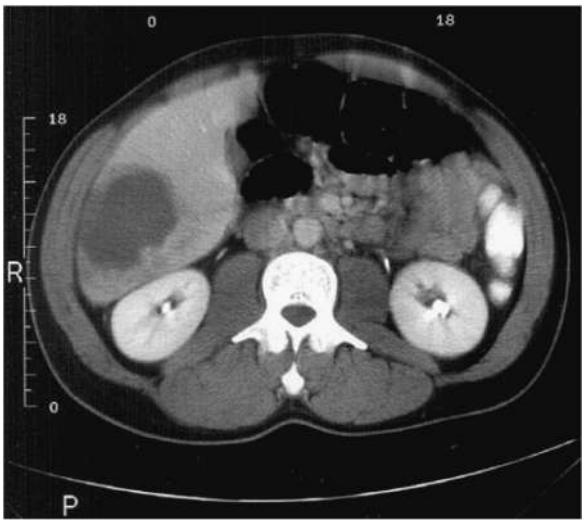

Fig. 327.1 Abdominal CT scan of a patient with an amebic liver abscess. *(From Miller Q, Kenney JM, Cotlar AM. Amebic abscess of the liver presenting as acute cholecystitis. Curr Surg. 2000;57:476–479. Fig. 1.)*

Different multiplex formats have also been developed, including enteric pathogen panels with varying sensitivities and specificities. Tetraplex assays that can distinguish between all four morphologically identical isolates have also been developed. Isothermal nucleic acid methods using recombinase and loop-mediated amplification (LAMP) in point-of-care diagnostics are promising and will greatly facilitate treatment, especially in developing countries. A small study using quantitative PCR detected *E. histolytica* DNA in the serum of patients with amebic liver abscess with a sensitivity of 89.5% and a specificity of 100%.

The **differential diagnosis** for amebic colitis includes colitis due to bacterial, mycobacterial, and viral pathogens, as well as noninfectious causes such as inflammatory bowel disease. Pyogenic liver abscess due to bacterial infection, hepatoma, and echinococcal cysts are in the differential diagnosis for amebic liver abscess. However, echinococcal cysts are rarely associated with systemic symptoms such as fever, unless there is cyst rupture or leakage.

COMPLICATIONS

Complications of amebic colitis include acute necrotizing colitis, ameboma, toxic megacolon, extraintestinal extension, and local perforation and peritonitis. Less commonly, a chronic form of amebic colitis develops, often recurring over several years. Amebomas are nodular foci of proliferative inflammation that sometimes develop in the wall of the colon. Amebiasis should be excluded before initiating corticosteroid treatment for inflammatory bowel disease because steroid treatment of *E. histolytica* is associated with high mortality rates.

An amebic liver abscess may rupture into the peritoneum, pleural cavity, skin, and pericardium. Cases of amebic abscesses in extrahepatic sites, including the lung and brain, have been reported.

TREATMENT

Invasive amebiasis is treated with a nitroimidazole such as **metronidazole** or **tinidazole** and then a luminal amebicide (Table 327.1). Tinidazole may have better clinical efficacy than metronidazole, with shorter and simpler dosing, and is better tolerated. Adverse effects include nausea, abdominal discomfort, and a metallic taste that disappears after completion of therapy. Therapy with a nitroimidazole should be followed by treatment with a luminal agent, such as paromomycin (which is preferred) or iodoquinol. Diloxanide furoate can also be used in children >2 years of age but is no longer available in the United States. Paromomycin should not be given concurrently with metronidazole or tinidazole because diarrhea is a common side effect of paromomycin and may confuse the clinical picture. Asymptomatic intestinal infection with *E. histolytica* should be treated, preferably with paromomycin or alternatively with either iodoquinol or diloxanide furoate. For fulminant cases of amebic colitis, some experts suggest adding dehydroemetine (1 mg/kg/

Table 327.1 Drug Treatment for Amebiasis

MEDICATION	ADULT DOSAGE (ORAL)	PEDIATRIC DOSAGE (ORAL)*
INVASIVE DISEASE		
Metronidazole	Colitis or liver abscess: 500 mg tid for 7-10 days	Colitis or liver abscess: 35-50 mg/kg/day in 3 divided doses for 7-10 days
Or		
Tinidazole	Colitis: 2 g once daily for 3 days Liver abscess: 2 g once daily for 3-5 days	Colitis: 50 mg/kg/day once daily for 3 days Liver abscess: 50 mg/kg/day once daily for 3-5 days
Followed by:		
Paromomycin (preferred)	500 mg tid for 7 days	25-35 mg/kg/day in 3 divided doses for 7 days
Or		
Diloxanide furoate†	500 mg tid for 10 days	20 mg/kg/day in 3 divided doses for 7 days
Or		
Iodoquinol	650 mg tid for 20 days	30-40 mg/kg/day in 3 divided doses for 20 days
ASYMPTOMATIC INTESTINAL COLONIZATION		
Paromomycin (preferred) *Or* Diloxanide furoate† *Or* Iodoquinol	As for invasive disease	As for invasive disease

*All pediatric dosages are up to a maximum of the adult dose.
†Not available in the United States.

day subcutaneously or intramuscularly, never intravenously), available only through the Centers for Disease Control and Prevention (CDC). Patients should be hospitalized for monitoring if dehydroemetine is administered. Dehydroemetine should be discontinued if tachycardia, T-wave depression, arrhythmia, or proteinuria develops. Nitazoxanide has been shown to be amebicidal in several clinical trials, but more studies are needed to define optimal dosing and duration of treatment.

Broad-spectrum antibiotic therapy may be indicated in fulminant colitis to cover possible spillage of intestinal bacteria into the peritoneum and translocation into the bloodstream. Intestinal perforation and toxic megacolon are indications for surgery. In amebic liver abscess, image-guided aspiration of large lesions or left lobe abscesses may be necessary if rupture is imminent or if the patient shows a poor clinical response 4-6 days after administration of amebicidal drugs. A Cochrane meta-analysis comparing metronidazole and metronidazole plus aspiration in uncomplicated amebic liver abscess showed that there is insufficient evidence to make any recommendation for or against this approach. Chloroquine, which concentrates in the liver, may also be a useful adjunct to nitroimidazoles in the treatment of amebic liver abscess or in cases of treatment failure or intolerance. To confirm cure, stool examination should be repeated every 2 weeks after completion of therapy until clear.

PROGNOSIS

Most infections evolve to either an asymptomatic carrier state or eradication. Extraintestinal infection carries about a 5% mortality rate.

PREVENTION

Control of amebiasis can be achieved by exercising proper sanitation and hygiene. Regular examination of food handlers and thorough investigation of diarrheal episodes may help identify the source of infection. No prophylactic drug or vaccine is available.

Immunization with different *E. histolytica* antigens has shown promising protective responses in animal models. Amebic surface protein LecA, galactose/*N*-acetyl-D-galactosamine lectin, serine-rich *E. histolytica* protein (SREHP), heparan sulfate binding proteins, and other antigens have elicited protective immune responses, especially in combination with different adjuvants. Acquired immune response can be protective as evidenced by anti-lectin IgA in stool among Bangladeshi children.

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Chapter 328 Giardiasis and Balantidiasis

328.1 *Giardia duodenalis*

Chandy C. John

Giardia duodenalis is a flagellated protozoan that infects the duodenum and jejunum. Infection results in clinical manifestations that range from asymptomatic colonization to acute or chronic diarrhea and malabsorption. Infection is more prevalent in children than in adults. *Giardia* is endemic in areas of the world with poor levels of sanitation. It is also an important cause of morbidity in developed countries, where it is associated with urban childcare centers, residential institutions for the developmentally delayed, and waterborne and foodborne outbreaks. *Giardia* is a particularly significant pathogen in children with malnutrition and certain immunodeficiencies (IgA deficiency, common variable immunodeficiency, X-linked hypogammaglobulinemia).

ETIOLOGY

The life cycle of *G. duodenalis* (also known as *Giardia lamblia* or *Giardia intestinalis*) is composed of two stages: trophozoites and cysts. *Giardia* infects humans after ingestion of as few as 10-100 cysts, which measure 8-10 μm in diameter. Each ingested cyst produces two trophozoites in the duodenum. After excystation, trophozoites colonize the lumen of the duodenum and proximal jejunum, where they attach to the brush border of the intestinal epithelial cells and multiply by binary fission. The body of the trophozoite is teardrop shaped, measuring 10-20 μm in length and 5-15 μm in width. *Giardia* trophozoites contain two oval nuclei anteriorly, a large ventral disk, a curved median body posteriorly, and four pairs of flagella. As detached trophozoites pass down the intestinal tract, they encyst to form oval cysts that contain four nuclei. Cysts are passed in stools of infected individuals and may remain viable in water for as long as 2 months. Their viability often is not affected by the usual concentrations of chlorine used to purify water for drinking.

Giardia strains that infect humans are diverse biologically, as shown by differences in antigens, restriction endonuclease patterns, DNA fingerprinting, isoenzyme patterns, and pulsed-field gel electrophoresis. Studies suggest that different *Giardia* genotypes may cause unique clinical manifestations, but these findings appear to vary according to the geographic region tested.

EPIDEMIOLOGY

Giardia occurs worldwide and is the most common intestinal parasite identified in public health laboratories in the United States, where it is estimated that up to 2 million cases of giardiasis occur annually. *Giardia* infection usually occurs sporadically, but *Giardia* is a frequently identified etiologic agent of outbreaks associated with drinking water. The age-specific prevalence of giardiasis is high during childhood and begins to decline after adolescence. The asymptomatic carrier rate of *G.*

lamblia in the United States is as high as 20–30% in children younger than 36 months of age attending childcare centers. Asymptomatic carriage may persist for several months.

Risk of acquiring and transmitting *Giardia* is increased in children and employees in childcare centers, individuals who drink contaminated water, international travelers, men who have sex with men, immunodeficient individuals, and individuals exposed to farm animals. Children visiting friends and relatives are at increased risk for *Giardia* infections during international travel. The major reservoir and vehicle for spread of *Giardia* appears to be water contaminated with *Giardia* cysts, but foodborne transmission also occurs. The seasonal peak in age-specific case reports coincides with the summer recreational water season and may be a result of the extensive use of communal swimming venues by young children, the low infectious dose, and the extended periods of cyst shedding that can occur. In addition, *Giardia* cysts are relatively resistant to chlorination and to ultraviolet light irradiation. Boiling is effective for inactivating cysts.

Person-to-person spread also occurs, particularly in areas of low hygiene standards, frequent fecal-oral contact, and crowding. Individual susceptibility, lack of toilet training, crowding, and fecal contamination of the environment all predispose to transmission of enteropathogens, including *Giardia,* in childcare centers. Childcare centers play an important role in transmission of urban giardiasis, with secondary attack rates in families as high as 17–30%. Children in childcare centers may pass cysts for several months. Campers who drink untreated stream or river water, particularly in the western United States, and residents of institutions for the developmentally delayed are also at increased risk for infection.

Humoral immunodeficiencies, including common variable immunodeficiency and X-linked agammaglobulinemia, predispose humans to chronic symptomatic *Giardia* infection, suggesting the importance of humoral immunity in controlling giardiasis. Selective immunoglobulin A deficiency is also associated with *Giardia* infection. Although many individuals with AIDS have relatively mild *Giardia* infections, *Giardia* infection refractory to treatment may occur in a subset of individuals with AIDS. Human milk contains glycoconjugates and secretory immunoglobulin A antibodies that may provide protection to nursing infants against *Giardia*.

CLINICAL MANIFESTATIONS

The incubation period of *Giardia* infection usually is 1-2 weeks but may be longer. A broad spectrum of clinical manifestations occurs, depending on the interaction between *G. lamblia* and the host. Children who are exposed to *G. lamblia* may experience asymptomatic excretion of the organism, acute infectious diarrhea, or chronic diarrhea with persistent gastrointestinal tract signs and symptoms, including failure to thrive and abdominal pain or cramping. *Giardia* was the cause of 15% of nondysenteric diarrheal illnesses in children examined in U.S. outpatient clinics in one study. Most infections in children and adults are asymptomatic. There is usually no extraintestinal spread, but occasionally trophozoites may migrate into bile or pancreatic ducts.

Symptomatic infections occur more frequently in children than in adults. Most symptomatic patients usually have a limited period of acute diarrheal disease with or without low-grade fever, nausea, and anorexia; in a small proportion of patients, an intermittent or more protracted course characterized by diarrhea, abdominal distention and cramps, bloating, malaise, flatulence, nausea, anorexia, and weight loss develops (Table 328.1). Stools initially may be profuse and watery and later become greasy and foul smelling and may float. Stools do not contain blood, mucus, or fecal leukocytes. Varying degrees of malabsorption may occur. Abnormal stool patterns may alternate with periods of constipation and normal bowel movements. Malabsorption of sugars, fats, and fat-soluble vitamins is well documented and may be responsible for substantial weight loss. *Giardia* has been associated with iron deficiency in internationally adopted children. Extraintestinal manifestations of *Giardia* appear to be more common in adults than children and include arthritis and, in one report after an outbreak, chronic fatigue syndrome. Giardiasis in children has been associated with growth stunting, and repeated *Giardia* infections correlate with a decrease in cognitive function in children in endemic areas.

Table 328.1 Clinical Signs and Symptoms of Giardiasis

SYMPTOM	FREQUENCY (%)
Diarrhea	64–100
Malaise, weakness	72–97
Abdominal distention	42–97
Flatulence	35–97
Abdominal cramps	44–81
Nausea	14–79
Foul-smelling, greasy stools	15–79
Anorexia	41–73
Weight loss	53–73
Vomiting	14–35
Fever	0–28
Constipation	0–27

DIAGNOSIS

Giardiasis should be considered in children who have acute nondysenteric diarrhea, persistent diarrhea, intermittent diarrhea and constipation, malabsorption, chronic crampy abdominal pain and bloating, failure to thrive, or weight loss. It should be particularly high in the differential diagnosis of children in childcare centers, children in contact with an index case, children with a history of recent travel to an endemic area, and children with humoral immunodeficiencies. Testing for giardiasis should be standard for internationally adopted children from *Giardia*-endemic areas, and screening for iron deficiency should be considered in internationally adopted children with giardiasis.

Stool enzyme immunoassay (EIA) or direct fluorescent antibody tests for *Giardia* antigens are the tests of choice for giardiasis. EIA is less reader dependent and more sensitive for detection of *Giardia* than microscopy. Some studies report that a single stool is sufficiently sensitive for detection of *Giardia* by EIA, whereas others suggest that sensitivity is increased with testing of two samples. A diagnosis of giardiasis was traditionally established by microscopy documentation of trophozoites or cysts in stool specimens, but three stool specimens are required to achieve a sensitivity of >90% using this approach. In patients in whom other parasitic intestinal infections are in the differential diagnosis, microscopy examination of stool allows evaluation for these infections in addition to *Giardia.*

Polymerase chain reaction and gene probe–based detection systems specific for *Giardia* have been used in environmental monitoring and clinical testing. Multiplex polymerase chain reaction testing for multiple parasitic pathogens is a viable option for testing.

In patients with chronic symptoms in whom giardiasis is suspected but in whom testing of stool specimens for *Giardia* yields a negative result, aspiration or biopsy of the duodenum or upper jejunum should be considered. In a fresh specimen, trophozoites usually can be visualized by direct wet mount. An alternate method of directly obtaining duodenal fluid is the commercially available Entero-Test (Hedeco Corp, Mountain View, CA), but this method is less sensitive than aspiration or biopsy. The biopsy can be used to make touch preparations and tissue sections for identification of *Giardia* and other enteric pathogens and also to visualize changes in histology. Biopsy of the small intestine should be considered in patients with characteristic clinical symptoms, negative stool and duodenal fluid specimen findings, and one or more of the following: abnormal radiographic findings (such as edema and segmentation in the small intestine); an abnormal lactose tolerance test result; an absent secretory immunoglobulin A level; hypogammaglobulinemia; or achlorhydria. Duodenal biopsy may show findings consistent with chronic inflammation, including eosinophilic infiltration of the lamina propria.

Radiographic contrast studies of the small intestine may show nonspecific findings such as irregular thickening of the mucosal folds. Blood cell counts usually are normal. Giardiasis is not tissue invasive and is not associated with peripheral blood eosinophilia.

TREATMENT

Children with acute diarrhea in whom *Giardia* organisms are identified should receive therapy. In addition, children who manifest failure to thrive or exhibit malabsorption or gastrointestinal tract symptoms such as chronic diarrhea should be treated.

Asymptomatic excreters generally are not treated, except in specific instances such as outbreak control, prevention of household transmission by toddlers to pregnant women and patients with hypogammaglobulinemia or cystic fibrosis, and situations requiring oral antibiotic treatment where *Giardia* may produce malabsorption of the antibiotic.

The FDA has approved tinidazole and nitazoxanide for the treatment of *Giardia* in the United States. Both medications have been used to treat *Giardia* in thousands of patients in other countries and have excellent safety and efficacy records against *Giardia* (Table 328.2). Tinidazole has the advantage of single-dose treatment and very high efficacy (>90%), while nitazoxanide has the advantage of a suspension form, high efficacy (80–90%), and very few adverse effects. Metronidazole, although never approved by the FDA for treatment of *Giardia,* is also highly effective (80–90% cure rate), and the generic form is considerably less expensive than tinidazole or nitazoxanide. For children ≥3 year of age, tinidazole is the preferred treatment, with nitazoxanide as alternative, while for children 1-2 years, nitazoxanide is the preferred treatment, since tinidazole is approved only for children ≥3 years of age. Metronidazole is the drug of choice for children <12 months and an alternative to tinidazole and nitazoxanide for children ≥12 months. Recent reports on travelers to South Asia document resistance rates as high as 30% to metronidazole, so nitazoxanide or tinidazole may be preferred for children who have traveled to or are from this area. Frequent adverse effects are seen with metronidazole therapy, and it requires 3-times-a-day dosing for 5-7 days. Suspension forms of tinidazole and metronidazole must be compounded by a pharmacy; neither drug is sold in suspension form.

Second-line alternatives for the treatment of patients with giardiasis include albendazole, paromomycin, and quinacrine (see Table 328.2). Albendazole may be of similar efficacy to metronidazole. Albendazole has few adverse effects and is effective against many helminths, making it useful for treatment when multiple intestinal parasites are identified or suspected. Paromomycin is a nonabsorbable aminoglycoside and is less effective than other agents but is recommended for treatment of pregnant women with giardiasis because of the potential teratogenic effects of other agents. Quinacrine is effective and inexpensive but is not available commercially and must be obtained from compounding pharmacies (see Table 328.2). Quinacrine can also rarely have serious side effects, including hallucinations and psychosis. Refractory cases of giardiasis have been successfully treated with a number of regimens, including nitazoxanide, prolonged courses of tinidazole, or combination therapy, most commonly a 3-week course of metronidazole and quinacrine.

Table 328.2 Drug Treatment for Giardiasis

MEDICATION	ADULT DOSAGE (ORAL)	PEDIATRIC DOSAGE (ORAL)*
RECOMMENDED		
Tinidazole	2 g once	>3 yr: 50 mg/kg once
Nitazoxanide	500 mg bid for 3 days	1-3 yr: 100 mg (5 mL) bid for 3 days 4-11 yr: 200 mg (10 mL) bid for 3 days >12 yr: 500 mg bid for 3 days
Metronidazole	250 mg tid for 5-7 days	15 mg/kg/day in 3 divided doses for 5-7 days
ALTERNATIVE		
Albendazole	400 mg once a day for 5 days	>6 yr: 400 mg once a day for 5 days
Paromomycin	500 mg tid for 5-10 days	Not recommended
Quinacrine†	100 mg tid for 5-7 days	6 mg/kg/day in 3 divided doses for 5 days

*All pediatric dosages are up to a maximum of the adult dose.
†Not commercially available. Can be compounded by Medical Center Pharmacy in New Haven, CT (203-688-8970) or Panorama Compounding Pharmacy in Van Nuys, CA (818-988-7979).

PROGNOSIS

Symptoms recur in some patients in whom reinfection cannot be documented and in whom an immune deficiency such as an immunoglobulin abnormality is not present, despite use of appropriate therapy. Several studies have demonstrated that variability in antimicrobial susceptibility exists among strains of *Giardia,* and in some instances resistant strains have been demonstrated. Combined therapy may be useful for infection that persists after single-drug therapy, assuming reinfection has not occurred and the medication was taken as prescribed.

PREVENTION

Infected persons and persons at risk should practice strict handwashing after any contact with feces. This point is especially important for caregivers of diapered infants in childcare centers, where diarrhea is common and *Giardia* organism carriage rates are high.

Methods to purify public water supplies adequately include chlorination, sedimentation, and filtration. Inactivation of *Giardia* cysts by chlorine requires the coordination of multiple variables such as chlorine concentration, water pH, turbidity, temperature, and contact time. These variables cannot be appropriately controlled in all municipalities and are difficult to control in swimming pools. Individuals, especially children in diapers, should avoid swimming if they have diarrhea. Individuals should also avoid swallowing recreational water and drinking untreated water from shallow wells, lakes, springs, ponds, streams, and rivers.

Travelers to endemic areas are advised to avoid uncooked foods that might have been grown, washed, or prepared with water that was potentially contaminated. Purification of drinking water can be achieved by a filter with a pore size of <1 μm or that has been rated by the National Sanitation Foundation for cyst removal, or by brisk boiling of water for at least 1 minute. Treatment of water with chlorine or iodine is less effective but may be used as an alternate method when boiling or filtration is not possible.

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328.2 Balantidiasis

Chandy C. John

Balantidium coli is a ciliated protozoan and is the largest protozoan that parasitizes humans. Both trophozoites and cysts may be identified in feces. Disease caused by this organism is uncommon in the United States and generally is reported where there is a close association of humans with pigs, which are the natural hosts of *B. coli.* Because the organism infects the large intestine, symptoms are consistent with large bowel disease, similar to those associated with amebiasis and trichuriasis, and include nausea, vomiting, lower abdominal pain, tenesmus, and bloody diarrhea. Symptoms associated with chronic infection include abdominal cramps, watery diarrhea with mucus, occasionally bloody diarrhea, and colonic ulcers similar to those associated with *Entamoeba histolytica.* Extraintestinal spread of *B. coli* is rare and usually occurs only in immunocompromised patients. Most infections are asymptomatic.

Diagnosis using direct saline mounts is established by identification of trophozoites (50-100 μm long) or spherical or oval cysts (50-70 μm in diameter) in stool specimens. Trophozoites usually are more numerous than cysts.

The recommended treatment regimen is metronidazole (25-50 mg/kg/day divided tid PO; maximum: 750 mg/dose) for 5 days, or tetracycline (40 mg/kg/day divided qid PO; maximum: 500 mg/dose) for 10 days for persons older than 8 years of age. An alternative is iodoquinol (40 mg/kg/day divided tid PO; maximum: 650 mg/dose) for 20 days.

Prevention of contamination of the environment by pig feces is the most important means for control.

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Chapter 329

Cryptosporidium, Cystoisospora, Cyclospora, and *Microsporidia*

Sarah M. Heston and Patricia M. Flynn

The spore-forming intestinal protozoa *Cryptosporidium, Cystoisospora* (formerly *Isospora*), and *Cyclospora* are important intestinal pathogens in both immunocompetent and immunocompromised hosts. *Cryptosporidium, Cystoisospora,* and *Cyclospora* are coccidian parasites that predominantly infect the epithelial cells lining the digestive tract, and all are transmitted by the fecal-oral route. Microsporidia were formerly considered spore-forming protozoa but have been reclassified as fungi. Microsporidia are ubiquitous, obligate intracellular organisms that infect many other organ systems in addition to the gastrointestinal tract and cause a broader spectrum of disease.

CRYPTOSPORIDIUM

Cryptosporidium is recognized as a leading protozoal cause of diarrhea in children worldwide and is a **common cause of outbreaks in childcare centers**; it is also a significant pathogen in immunocompromised patients.

Etiology

Cryptosporidium hominis and *Cryptosporidium parvum* cause most cases of cryptosporidiosis in humans. Disease is initiated by ingestion of infectious oocysts that were excreted in the feces of infected humans and animals. The oocysts are immediately infectious to other hosts or can reinfect the same host. The ingested oocysts release sporozoites that attach to and invade the intestinal epithelial cells.

Epidemiology

Cryptosporidiosis is associated with diarrheal illness worldwide and is more prevalent in developing countries and among children younger than 2 years of age. It has been implicated as an etiologic agent of persistent diarrhea in the developing world and as a cause of significant morbidity and mortality from malnutrition, including permanent effects on growth. Risk factors for infection include animal contact, diarrhea in a household member, open defecation/lack of toilet facilities, and poor drinking water quality.

Transmission of *Cryptosporidium* to humans can occur by close association with infected animals, via person-to-person transmission, or from environmentally contaminated water and food. Although zoonotic transmission, especially from cows, occurs in persons in close association with animals, person-to-person transmission is probably responsible for cryptosporidiosis outbreaks within hospitals and childcare centers, where transmission rates as high as 67% have been reported. Recommendations to prevent outbreaks in childcare centers include exclusion of children with diarrhea from attending, strict handwashing, elimination of water play or swimming activities, use of protective clothes or diapers capable of retaining liquid diarrhea, and separation of diapering and food-handling areas and responsibilities.

Outbreaks of cryptosporidial infection are associated with contaminated community water supplies and recreational waters, including lakes and chlorinated swimming pools. Wastewater in the form of raw sewage and runoff from dairies and grazing lands can contaminate both drinking and recreational water sources. It is estimated that *Cryptosporidium* oocysts are present in 65–97% of the surface water in the United States. The organism's small size (4-6 μm in diameter), resistance to chlorination, and ability to survive for long periods outside a host create problems in public water supplies.

Clinical Manifestations

The **incubation period is 2-10 days** (average, 7 days) after infection. *Cryptosporidium* infection is associated with **profuse, watery, nonbloody diarrhea** that can be accompanied by diffuse crampy abdominal pain, nausea, vomiting, and anorexia. Although less common in adults, vomiting occurs in more than 80% of children with cryptosporidiosis. Nonspecific symptoms such as myalgia, weakness, and headache also may occur. Fever occurs in 30–50% of cases. Malabsorption, lactose intolerance, dehydration, weight loss, and malnutrition often occur in severe cases. The clinical spectrum and disease severity have been linked with both the infecting species and host human leukocyte antigen class I and class II alleles.

In **immunocompetent persons, the disease is usually self-limiting**, typically 5-10 days, although diarrhea may persist for several weeks and oocyst shedding may persist for many weeks after symptoms resolve. Chronic diarrhea is common in young infants and individuals with immunodeficiency, such as congenital hypogammaglobulinemia or HIV infection. Symptoms and oocyst shedding can continue indefinitely and may lead to severe malnutrition, wasting, anorexia, and even death.

Cryptosporidiosis in immunocompromised hosts is often associated with biliary tract disease, characterized by fever, right upper quadrant pain, nausea, vomiting, and diarrhea. It also is associated with pancreatitis. Respiratory tract disease is rare.

Diagnosis

Infection can be diagnosed by microscopy using modified acid-fast stain or polymerase chain reaction (PCR), but immunodetection of antigens on the surface of the organism in stool samples using monoclonal antibody–based assays is the current diagnostic method of choice because of the high sensitivity and specificity. Multiplex molecular test panels for gastrointestinal pathogens that include *Cryptosporidium* are available and are a standard test.

In stool, oocysts appear as small, spherical bodies (2-6 μm) and stain red with modified acid-fast staining. Because *Cryptosporidium* does not invade below the epithelial layer of the mucosa, fecal leukocytes are not found in stool specimens. Oocyst shedding in feces can be intermittent, and several fecal specimens (at least three for an immunocompetent host) should be collected for microscopic examination. Serologic diagnosis is not helpful in acute cryptosporidiosis.

In tissue sections, *Cryptosporidium* organisms can be found along the microvillus region of the epithelia that line the gastrointestinal tract. The highest concentration usually is detected in the jejunum. Histologic section results reveal villus atrophy and blunting, epithelial flattening, and inflammation of the lamina propria.

Treatment

Often the diarrheal illness attributable to cryptosporidiosis is self-limited in *immunocompetent* patients and requires no specific antimicrobial therapy. Treatment should focus on supportive care, including rehydration orally or, if fluid losses are severe, intravenously. A 3-day course of nitazoxanide (100 mg bid PO for 3 days for children 1-3 years of age; 200 mg bid PO for children 4-11 years of age; 500 mg bid PO for children ≥12 years of age) is approved for treatment of diarrhea caused by *Cryptosporidium.* A recent meta-analysis revealed a favorable clinical response to treatment with nitazoxanide compared with placebo, although the parasitologic response was no different than the response to placebo. Clinical studies have not definitively demonstrated that nitazoxanide is superior to placebo in trials of HIV-infected (with low CD4 counts) or immunocompromised patients. However, given the severity of the infection in these populations, nitazoxanide treatment

is usually initiated. Immune function should be optimized in immunocompromised patients, with combination antiretroviral therapy in patients living with HIV and decreased immunosuppression in transplant recipients, if possible. Other agents that have been suggested for treatment in clinical reports or small studies include orally administered human serum immunoglobulin or bovine colostrum, paromomycin, spiramycin, azithromycin, and roxithromycin or a combination of antibiotics. Clofazimine was recently investigated as a potential therapy among adults living with HIV; however, it failed to show efficacy based on clinical and parasitologic outcomes. Prevention measures include adequate hand hygiene, avoiding untreated ice or water, especially in areas with poor sanitation, and exclusion of children with diarrhea from public pools.

CYSTOISOSPORA

Like *Cryptosporidium, Cystoisospora belli* is implicated as a cause of diarrhea in institutional outbreaks and in travelers and has also been linked with **contaminated water and food**. *Cystoisospora* appears to be more common in tropical and subtropical climates and in developing areas, including South America, Africa, and Southeast Asia. *Cystoisospora* has not been associated with animal contact. It is also an infrequent cause of diarrhea in patients with AIDS in the United States but may infect up to 15% of AIDS patients in Haiti.

The life cycle and pathogenesis of infection with *Cystoisospora* species are similar to those of *Cryptosporidium* organisms except that oocysts excreted in the stool are not immediately infectious and must undergo further maturation at temperatures below 37°C (98.6°F). Thus **direct person-to-person transmission is unlikely**. The **incubation period averages approximately one week.** The most common clinical manifestation is **watery, nonbloody diarrhea**. Symptoms of infection are indistinguishable from those of cryptosporidiosis, although fever may be a more common finding. Eosinophilia may be present in up to 50% of cases, contrasting with other enteric protozoan infections. The diagnosis is established by detecting the oval, 22- to 33-μm long by 10- to 19-μm wide oocysts by using modified acid-fast staining of the stool. Fecal leukocytes are not detected. Oocysts are shed in low numbers, underscoring the need for repeated stool examinations. The presence of oocysts in the gastrointestinal tract is almost always associated with clinical symptoms. The histologic appearance of the gastrointestinal epithelium reveals blunting and atrophy of the villi, acute and chronic inflammation, and crypt hyperplasia.

Cystoisosporiasis responds promptly to treatment with oral **trimethoprim-sulfamethoxazole** (TMP-SMX: 5 mg TMP and 25 mg SMX/kg/dose [maximum: 160 mg TMP and 800 mg SMX/dose] bid for 10 days). In patients with AIDS, relapses are common and often necessitate higher doses of TMP/SMX and/or maintenance therapy. Combination antiretroviral therapy associated with immune recovery may also result in improved symptoms. **Ciprofloxacin** or a regimen of **pyrimethamine** alone or with **folinic acid** is effective in patients intolerant of sulfonamide drugs. In endemic areas, *Cystoisospora* can be avoided by ensuring water used for drinking, food preparation, and washing fresh produce has been filtered or boiled.

CYCLOSPORA

Cyclospora cayetanensis is a coccidian parasite similar to but larger than *Cryptosporidium.* The organism infects both immunocompromised and immunocompetent individuals and is more common in children younger than 18 months of age. The pathogenesis and pathologic findings of cyclosporiasis are similar to those of cystoisosporiasis. Asymptomatic carriage of the organism has been found, but travelers who harbor the organism almost always have diarrhea. Most cases of cyclosporiasis in the United States are domestically acquired. Outbreaks of cyclosporiasis are linked with **contaminated food and water** and occur most frequently during spring and summer months. Implicated foods include raspberries, lettuce, snow peas, basil, cilantro, and other fresh food items. After fecal excretion, the oocysts must sporulate outside the host to become infectious. This finding explains the lack of person-to-person transmission.

The clinical manifestations of cyclosporiasis are similar to those of cryptosporidiosis and cystoisosporiasis and follow an **incubation period of approximately 7 days**. Moderate *Cyclospora* illness is characterized by a median of 6 stools/day with a median duration of 10 days (range: 3-25 days). The duration of diarrhea in immunocompetent persons is characteristically longer in cyclosporiasis than in the other intestinal protozoan illnesses. Associated symptoms frequently include anorexia; fatigue; abdominal bloating or gas; abdominal cramps or pain; nausea; muscle, joint, or body aches; low-grade fever; chills; headache; and weight loss. Vomiting may occur. Bloody stools are uncommon. Biliary disease has been reported. Intestinal pathology includes inflammation with villus blunting.

The diagnosis is established by identification of oocysts in the stool or molecular diagnostic testing. Oocysts are wrinkled spheres, measure 8-10 μm in diameter, and resemble large *Cryptosporidium* organisms. The organisms can be seen by using modified acid-fast, auramine-phenol, or modified trichrome staining, but stain less consistently than *Cryptosporidium.* They can also be detected with phenosafranin stain and by autofluorescence using strong green or intense blue under ultraviolet epifluorescence. Multiple stool samples enhance identification of the pathogen. Fecal leukocytes are not present. Commercially available multiplex molecular test panels for gastrointestinal pathogens that include *Cyclospora* are now available and may become the new standard. The sensitivity of molecular testing and the inclusion of *Cyclospora* on multiplex molecular testing may be partly responsible for the increased number of reported cases in the United States in recent years.

The treatment of choice for cyclosporiasis is **TMP-SMX** (5 mg TMP and 25 mg SMX/kg/dose bid [maximum 160 mg TMP and 800 mg SMX/dose] for 10 days.) **Ciprofloxacin** or **nitazoxanide** is effective in patients intolerant of sulfonamide drugs.

MICROSPORIDIA

Microsporidia are ubiquitous and infect most animal groups, including humans. They are classified as fungi, and multiple species of the phylum Microsporidia have been linked with human disease in both immunocompetent and immunocompromised hosts. The species most commonly associated with gastrointestinal disease are *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis.* The global prevalence of microsporidial infections among children is 7.5%, although prevalence is likely higher among pediatric patients living with HIV, oncology patients, and transplant recipients.

Although still not definitive, the source of human infections is likely zoonotic. Like *Cryptosporidium,* there is concern for waterborne transmission through occupational and recreational contact with contaminated water sources. There is also the potential for foodborne outbreaks; the organisms have been identified on vegetables as a consequence of contaminated irrigation water. Vector-borne transmission is hypothesized because one species, *Brachiola algerae,* typically infects mosquitoes. Finally, transplacental transmission has been reported in animals but not in humans. Once infected, intracellular division produces new spores that can spread to nearby cells, disseminate to other host tissues, or be passed into the environment via feces. Spores also have been detected in urine and respiratory epithelium, suggesting that some body fluids may also be infectious. Once in the environment, microsporidial spores remain infectious for up to 4 months.

Initially, microsporidial intestinal infection had been almost exclusively reported in patients with AIDS, but there are increasing reports of microsporidial infections in transplant recipients, including donor-derived infections in solid organ transplant recipients. There is increasing evidence that immunocompetent individuals are also commonly infected. Microsporidia-associated **diarrhea is intermittent, watery, copious, and nonbloody**. Abdominal cramping and weight loss may be present; fever is unusual. Stromal keratitis and encephalitis may

also be associated with microsporidia infections. Disseminated disease involving most organs, including liver, heart, kidney, bladder, biliary tract, lung, bone, skeletal muscle, central nervous system, skin, and sinuses, has been reported.

Microsporidia stain with modified trichrome, hematoxylin-eosin, Giemsa, Gram, periodic acid–Schiff, and acid-fast stains but are often overlooked because of their small size (1-5 μm) and the absence of associated inflammation in surrounding tissues. Electron microscopy remains the reference method of detection. An immunofluorescence assay is available. The Centers for Disease Control and Prevention (CDC) offer a molecular identification of *Enterocytozoon bieneusi, Encephalitozoon intestinalis, Encephalitozoon hellem,* and *Encephalitozoon cuniculi* using species-specific PCR assays.

There is no proven therapy for microsporidial intestinal infections. **Albendazole** (adult dose 400 mg bid PO for 3 weeks; for children, 7.5 mg/kg body weight [maximum 400 mg/dose] bid PO) is usually effective against *E. intestinalis* infection but is ineffective against infection caused by some microsporidial species. Fumagillin (adult dose 20 mg tid PO for 2 weeks) was effective in a small controlled study of adults with *E. bieneusi* infection, and topical therapy with this agent was also demonstrated to be effective in HIV-infected adults with keratoconjunctivitis. Fumagillin is not currently available in the United States. Supportive care with hydration, correction of electrolyte imbalances, and nutrition should be used in gastrointestinal infection when clinically indicated. Improvement in underlying HIV infection with combination antiretroviral therapy also improves microsporidiosis symptoms.

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Chapter 330

Trichomoniasis (*Trichomonas vaginalis*)

Edsel Maurice T. Salvana and Robert A. Salata

Trichomoniasis is caused by the protozoan *Trichomonas vaginalis*. It is the second most common sexually transmitted infection worldwide. Vulvovaginitis is the symptomatic disease form, but *T. vaginalis* has been implicated in pelvic inflammatory disease, pregnancy loss, chronic prostatitis, and an increased risk of HIV transmission.

EPIDEMIOLOGY

Over 156 million new cases of trichomoniasis occur annually around the world. Most men and up to 30% of women are asymptomatic. Although the disease is easily treated, sequelae of untreated infection remain a significant cause of morbidity because of high reinfection rates from untreated partners, underrecognition of asymptomatic cases, and insensitive diagnostics.

Trichomoniasis is the most common parasitic infection in the United States, with a prevalence of 2.6 million cases and 6.9 million incident infections per year. Among the factors associated with a higher prevalence of infection are female sex, belonging to underrepresented minorities, poverty, lower educational attainment, younger age at first sex, multiple sexual partners, and a recent *Chlamydia* infection. Vaginal trichomoniasis is rare until menarche, and its presence in a younger child should raise the possibility of **sexual abuse.**

Trichomoniasis may be transmitted to neonates during passage through an infected birth canal. Infection in this setting is usually self-limited, but rare cases of neonatal vaginitis and respiratory infection have been reported.

PATHOGENESIS

T. vaginalis is an anaerobic, flagellated protozoan parasite. Infected vaginal secretions contain 10^1 to 10^5 or more protozoa/mL. *T. vaginalis* is pear shaped and exhibits characteristic twitching motility in wet mount (Fig. 330.1). Reproduction is by binary fission. It exists only as vegetative cells; cyst forms have not been described. *T. vaginalis* has hydrogenosomes, which are organelles that produce energy in anaerobic environments and have hydrogen as a waste product. Hydrogenosomes are derived from mitochondria, suggesting that *T. vaginalis* may have had an aerobic ancestor.

Many types of adhesion molecules allow attachment of *T. vaginalis* to host cells. Tv lipoglycan is a surface glycoconjugate that binds human galectin-1 and galectin-3 and plays a major role in adhesion, pathogenicity, and immune modulation. In addition, hundreds of putative membrane proteins, BspA proteins, and tetraspanins are involved in cellular attachment. Adhesion is a prerequisite for cytolysis and, once attached, the parasite secretes hydrolases, proteases, and cytotoxic molecules that destroy or impair the integrity of host cells.

Trichomonas is highly dependent on iron for its growth and metabolism. Cysteine proteinase mRNAs have been shown to interact with other parasite proteins for posttranscriptional regulation in the absence of iron-regulatory proteins. The *T. vaginalis* genome is very large at 160 Mbps, with multiple repetitive sequences and transposable elements making up over 60,000 genes and with apparently nonfunctional but transcribed pseudogenes.

Macrophage migration and cytokine production have been shown to be downregulated by the parasite in successful infection. Parasite-specific antibodies and lymphocyte priming occur in response to infection, but durable protective immunity does not occur, possibly also owing to degradation of antibodies by parasitic cysteine proteases. *Trichomonas* infection has been linked to dysregulation of the vagina microbiota and is frequently associated with concomitant bacterial vaginosis. *Trichomonas* can host *Mycoplasma genitalium* as a symbiont, and the presence of both microorganisms can significantly increase the risk of bacterial vaginosis, pelvic inflammatory disease, and adverse pregnancy outcomes.

CLINICAL MANIFESTATIONS

The incubation period in females is 5-28 days. Symptoms may begin or worsen with menses. Most infected women eventually develop symptoms, although up to one third remain asymptomatic. Common signs and symptoms include a copious malodorous gray, frothy vaginal discharge, vulvovaginal irritation, dysuria, and dyspareunia. Physical examination may reveal a frothy discharge with vaginal erythema and

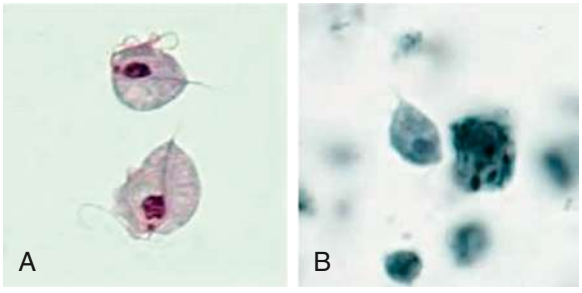

Fig. 330.1 *Trichomonas vaginalis* trophozoites stained with Giemsa (A) and iron hematoxylin (B). *(From the Centers for Disease Control and Prevention: Laboratory identification of parasites of public health concern. Trichomoniasis [website].* https://www.cdc.gov/dpdx/trichomoniasis/index.html*)*

cervical hemorrhages (strawberry cervix). The discharge usually has a pH of >4.5. Abdominal discomfort is unusual and should prompt evaluation for pelvic inflammatory disease (see Chapter 163).

Most infections in males are asymptomatic. Symptomatic males usually have dysuria and scant urethral discharge. Trichomonads occasionally cause epididymitis, prostatic involvement, and superficial penile ulceration. Infection is often self-limited, spontaneously resolving in about one third of men. *Trichomonas* has been implicated as a cause of recurrent or relapsing urethritis and can be isolated in 3–20% of men with nongonococcal urethritis. Treatment failures with standard therapy for gonorrhea and *Chlamydia* are frequently treated with antitrichomonal therapy.

DIAGNOSIS

Trichomonads may be recognized in vaginal secretions by wet mount microscopy, which has a sensitivity of 51–65% in vaginal specimens and a lower sensitivity in specimens from men. Although *Trichomonas* is sometimes seen on Pap smears and urine microscopy, these methods are not considered reliable tests for disease. Culture of the organism used to be the gold standard for detection, but this is increasingly being replaced by nucleic acid amplification tests, which are more sensitive. The APTIMA TV (Hologic/Gen-Probe, Inc., Marlborough, MA) assay and the BD Probe Tec TV Q^x Amplified DNA Assay (Becton Dickinson, Franklin Lakes, NJ) are U.S. Food and Drug Administration (FDA) cleared commercial NAATs for testing of samples from women. Xpert TV (Cepheid Inc., Sunnyvale, CA) is a cartridge-based near-point-of-care nucleic acid test that is FDA-cleared for men and women, with a sensitivity of 95% for self-collected vaginal swabs and up to 100% for symptomatic endocervical swabs. Three point-of-care kits for rapid testing, Affirm VP III (BD Diagnostic Systems, Sparks, MD), OSOM Trichomonas Rapid Test (Sekisui Diagnostics, Lexington, MA), and Solana Trichomonas Assay (Quidel, San Diego, CA) are FDA cleared for women and can yield results in 45 minutes or less. Patients with *T. vaginalis* should be screened for other sexually transmitted infections.

COMPLICATIONS

Untreated trichomoniasis has been associated with pelvic inflammatory disease, premature delivery, low birthweight, endometritis, salpingitis, and vaginal cuff cellulitis. The association between trichomoniasis and infertility is relatively weak, but there is some evidence that coinfection with other sexually transmitted infections increases the overall risk of pelvic inflammatory disease. *T. vaginalis* infection increases the risk of acquisition and transmission of HIV. In HIV-infected individuals, trichomoniasis is associated with higher viral loads in cervical secretions and semen, as well as higher levels of infected lymphocytes in urogenital fluids.

TREATMENT

In the United States, metronidazole and tinidazole are used; in other countries, secnidazole, azanidazole, and ornidazole are also used. Both **metronidazole** (single-dose regimen of 2 g orally as a single dose for adolescents and adults; alternative regimen, 500 mg orally bid for 7 days) and **tinidazole** (single 2 g dose orally in adolescents and adults) are used as first-line treatments. For children infected before adolescence, the recommended regimen is metronidazole 15 mg/kg/day divided in three doses orally for 7 days; tinidazole is not approved for dosing in younger children. For HIV-infected patients, the 7-day course of metronidazole is superior to and recommended over the single-dose regimen. Sexual partners should be treated simultaneously to prevent reinfection. Recent studies have shown that single-dose metronidazole is less effective than a multidose regimen in women. A small number of patients with severe nitroimidazole hypersensitivity have been treated with intravaginal suppositories of boric acid, nitazoxanide, and paromomycin with varying degrees of success. Desensitization to metronidazole with a validated protocol under an allergy specialist is recommended if possible.

Treatment failures have been reported with metronidazole and tinidazole. Metronidazole resistance in *Trichomonas* is estimated to be 4.3–9.6%, and tinidazole resistance is about 1%. Second-line treatment is a 7-day course of metronidazole 500 mg twice daily. If this approach fails, either metronidazole or tinidazole at 2 g daily for 7 days is recommended. Further treatment failure should be referred to an infectious diseases specialist. Susceptibility testing is available from the Centers for Disease Control and Prevention (CDC). Higher dose tinidazole (2-3 g for 14 days) in combination with intravaginal tinidazole or paromomycin have been used in nitroimidazole-resistant infections. Metronidazole has not been shown to be teratogenic but is currently classified as a category C drug. Treatment of trichomoniasis in pregnancy should always be considered, especially in symptomatic patients, and may decrease the risk of perinatal transmission.

PREVENTION

Prevention of *T. vaginalis* infection is best accomplished by treatment of all sexual partners of an infected person, and by programs aimed at prevention of all sexually transmitted infections (see Chapter 163). No vaccine is available, and drug prophylaxis is not recommended. A recent randomized controlled trial showed that *T. vaginalis* infection with concurrent bacterial vaginosis responded better to metronidazole treatment when intravaginal probiotics were co-administered, consistent with findings that altered vaginal microflora plays a significant role in *T. vaginalis* pathogenesis.

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Chapter 331

Leishmaniasis *(Leishmania)*

Peter C. Melby

The leishmaniases are a diverse group of diseases caused by intracellular protozoan parasites of the genus *Leishmania,* which are transmitted by phlebotomine sand flies. Multiple species of *Leishmania* are known to cause human disease involving the skin and mucosal surfaces and the visceral reticuloendothelial organs (Table 331.1). Cutaneous disease is usually localized and mild but may cause cosmetic disfigurement. Rarely, cutaneous infection can disseminate or involve the skin diffusely. Mucosal and visceral forms of leishmaniasis are associated with significant morbidity and mortality.

ETIOLOGY

Leishmania organisms are members of the Trypanosomatidae family and include two subgenera, *Leishmania (Leishmania)* and *Leishmania (Viannia)*. The parasite is dimorphic, existing as a flagellate promastigote in the insect vector and as an aflagellate amastigote that resides and replicates within mononuclear phagocytes of the vertebrate host. Within the **sand fly** vector, the promastigote changes from a noninfective procyclic form to an infective metacyclic stage (Fig. 331.1). Amplification of the number of metacyclic promastigotes in the infected sand fly occurs following a second blood meal. Fundamental to metacyclogenesis are changes that take place in the terminal polysaccharides of the surface **lipophosphoglycan,** which allow forward migration of the infective parasites to be inoculated in the host skin during a blood meal. Metacyclic lipophosphoglycan also plays an important role in the entry and survival of *Leishmania* in the vertebrate host cells. Once within the macrophage, the promastigote transforms to an amastigote and resides and replicates within a phagolysosome. The parasite is resistant to the acidic, hostile environment of the macrophage and eventually ruptures the cell and goes on to infect other macrophages. Infected macrophages have a diminished capacity to initiate and respond to an inflammatory response, thus providing a safe haven for the intracellular parasite.

Table 331.1 Clinical and Epidemiologic Characteristics of Main *Leishmania* Species

	SUBGENUS	CLINICAL FORM	MAIN CLINICAL FEATURES	NATURAL PROGRESSION	RISK GROUPS	MAIN RESERVOIR	HIGH-BURDEN COUNTRIES OR REGIONS	ESTIMATED ANNUAL WORLDWIDE INCIDENCE
*Leishmania donovani**	*Leishmania*	VL, PKDL	Persistent fever, splenomegaly, weight loss, and anemia in VL; multiple painless macular, papular, or nodular lesions in PKDL	VL is fatal within 2 yr; PKDL lesions self-heal in up to 85% of cases in Africa but rarely in Asia	Predominantly adolescents and young adults for VL; young children in Sudan and no clearly established risk factors for PKDL	Humans	India, Bangladesh, Ethiopia, Sudan, and South Sudan	50,000-90,000 VL cases; unknown number of PKDL cases
*Leishmania tropica**	Leishmania	CL, LR, rarely VL	Ulcerating dry lesions, painless, and frequently multiple	CL lesions often self-heal within 1 yr	No well-defined risk groups	Humans, but zoonotic foci exist	Eastern Mediterranean, Middle East, northeastern and southern Africa	200,000-400,000 CL
*Leishmania aethiopica**	*Leishmania*	CL, DCL, DsCL, oronasal CL	Localized cutaneous nodular lesions; occasionally oronasal; rarely ulcerates	Self-healing, except for DCL, within 2-5 yr	Limited evidence; adolescents	Hyraxes	Ethiopia, Kenya	20,000-40,000 CL
*Leishmania major**	*Leishmania*	CL	Rapid necrosis, multiple wet sores, severe inflammation	Self-healing in >50% of cases within 2-8 mo; multiple lesions slow to heal, and severe scarring	No well-defined risk groups	Rodents	Iran, Saudi Arabia, North Africa, Middle East, Central Asia, West Africa	230,000-430,000 CL
*Leishmania infantum**	*Leishmania*	VL, CL	Persistent fever and splenomegaly in VL; typically single nodules and minimal inflammation in CL	VL is fatal within 2 yr; CL lesions self-heal within 1 yr and confers individual immunity	Children <5 yr old and immunocompromised adults for VL; older children and young adults for CL	Dogs, hares, humans	China, Southern Europe, Brazil, and South America for VL and CL; Central America for CL	6,200-12,000 cases of Old World VL and 4,500-6,800 cases of New World VL; unknown number of CL cases
Leishmania mexicana†	*Leishmania*	CL, DCL, DsCL	Ulcerating lesions, single or multiple	Often self-healing in 3-4 mo	No well-defined risk groups	Rodents, marsupials	South America	Limited number of cases, included in the 187, 200-300,000 total cases of New World CL‡
Leishmania amazonensis†	*Leishmania*	CL, DCL, DsCL	Ulcerating lesions, single or multiple	Not well described	No well-defined risk groups	Possums, rodents	South America	Limited number of cases, included in the 187, 200-300,000 total cases of New World CL‡
Leishmania braziliensis†	*Viannia*	CL, MCL, DCL, LR	Ulcerating lesions can progress to mucocutaneous form; local lymph nodes are palpable before and early on in the onset of the lesions	Might self-heal in 6 mo; 2.5% of cases progress to MCL	No well-defined risk groups	Dogs, humans, rodents, horses	South America	Majority of the 187, 200-300,000 total cases of New World CL‡
Leishmania guyanensis†	*Viannia*	CL, DsCL, MCL	Ulcerating lesions, single or multiple that can progress to mucocutaneous form; palpable lymph nodes	Might self-heal within 6 mo	No well-defined risk groups	Possums, sloths, anteaters	South America	Limited number of cases, included in the 187, 200-300,000 total cases of New World CL‡

*Old World leishmaniasis.
†New World leishmaniasis.
‡Estimates are of all New World leishmaniases, with *Leishmania braziliensis* comprising the vast majority of these cases.
CL, Cutaneous leishmaniasis; DCL, diffuse cutaneous leishmaniasis; DsCL, disseminated cutaneous leishmaniasis; LR, leishmaniasis recidivans; MCL, mucocutaneous leishmaniasis; PKDL, post–kala-azar dermal leishmaniasis; VL, visceral leishmaniasis.
Adapted from Burza S, Croft SL, Boelaert ML. Leishmaniasis. *Lancet*. 2018;392:951–966. Table 1.

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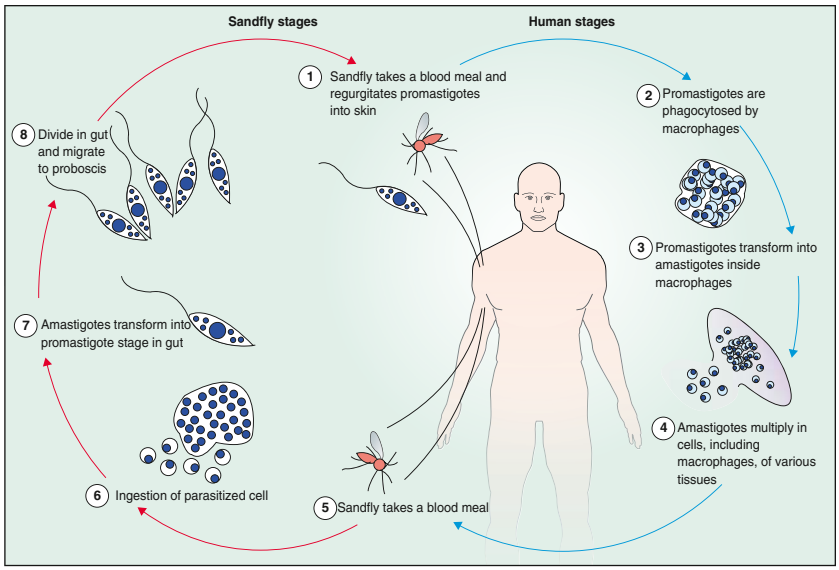

Fig. 331.1 *Leishmania* life cycle. *(From Reithinger R, Dujardin JC, Louzir H, et al. Cutaneous leishmaniasis. Lancet Infect Dis. 2007;7:581–596. Fig. 5.)*

EPIDEMIOLOGY

The leishmaniases are estimated to affect 10-20 million people in endemic tropical and subtropical regions on all continents except Australia and Antarctica (Fig. 331.2). The different forms of the disease are distinct in their causes, epidemiologic characteristics, transmission, and geographic distribution. The leishmaniases may occur sporadically throughout an endemic region or may occur in epidemic waves. With only rare exceptions, the *Leishmania* organisms that primarily cause cutaneous disease do not cause visceral disease.

Localized cutaneous leishmaniasis (LCL) in the Old World is caused by *L. (Leishmania) major* and *L. (L.) tropica* in North Africa, the Middle East, Central Asia, and the Indian subcontinent. *L. (L.) aethiopica* is a cause of LCL and **diffuse cutaneous leishmaniasis (DCL)** in Kenya and Ethiopia. In the New World, *L. (L.) mexicana* causes LCL in a region stretching from Texas through Central America. *L. (L.) amazonensis, L. (L.) pifanoi, L. (L.) garnhami,* and *L. (L.) venezuelensis* cause LCL in South America, the Amazon basin, and northward. These parasites can also cause DCL. Members of the *Viannia* subgenus (*L. [Viannia] braziliensis, L. [V.] panamensis, L. [V.] guyanensis,* and *L. [V.] peruviana*) cause LCL and **mucosal leishmaniasis (ML)** from the northern highlands of Argentina northward to Central America. Some species, particularly *L. (V.) braziliensis,* rarely cause **disseminated leishmaniasis (DL)**. **Visceral leishmaniasis (VL)** in the Old World is caused by *L. (L.) donovani* in Kenya, Sudan, India, Pakistan, and China and by *L. (L.) infantum* in the Mediterranean basin, Middle East, and central Asia. *L. tropica* also has been recognized as an uncommon cause of visceral disease in the Middle East and India. VL in the New World is caused by *L. (L.) infantum* (formerly also called *L. chagasi*), which is distributed from Mexico (rare) through Central and South America. *L. infantum* can also cause LCL in the absence of visceral disease in this same geographic distribution.

The maintenance of *Leishmania* in most endemic areas is through a **zoonotic** transmission cycle. In general, the dermotropic strains in both the Old and the New World are maintained in rodent reservoirs, and the domestic dog is the usual reservoir for *L. infantum*. The transmission between reservoir and sand fly is highly adapted to the specific ecologic characteristics of the endemic region. Human infections occur when activities bring them in contact with the zoonotic cycle. **Anthroponotic** transmission, in which humans are the presumed reservoir for vector-borne transmission, occurs with *L. tropica* in some urban areas of the Middle East and Central Asia, and with *L. donovani* in India and Sudan. Congenital transmission of *L. donovani* or *L. infantum* has been reported.

There is a resurgence of leishmaniasis in long-standing endemic areas as well as in new foci. Tens of thousands of cases of LCL occurred in outbreaks in Syria and Kabul, Afghanistan; severe epidemics with >100,000 deaths from VL have occurred in India and Sudan. VL is most prevalent among the poorest of the poor, with substandard housing contributing to the vector-borne transmission and undernutrition leading to increased host susceptibility. The emergence of the leishmaniases in new areas is the result of (1) movement of a susceptible population into existing endemic areas, usually because of agricultural or industrial development or timber harvesting; (2) increase in vector and/or reservoir populations as a result of agriculture development projects and/or climate change; (3) increase in anthroponotic transmission resulting from rapid urbanization in some focuses; and (4) increase in sand fly density resulting from a reduction in vector control programs.

PATHOLOGY

Histopathologic analysis of the skin lesions of LCL and DL show intense chronic granulomatous inflammation involving the epidermis and dermis with relatively few amastigotes. Occasionally, neutrophils and even microabscesses can be seen. The lesions of DCL are characterized by dense infiltration with vacuolated macrophages containing abundant amastigotes. ML is characterized by an intense granulomatous reaction with prominent tissue necrosis, which may include adjacent cartilage or bone. In VL there is prominent reticuloendothelial cell hyperplasia in the liver, spleen, bone marrow, and lymph nodes. Amastigotes are abundant in the histiocytes and Kupffer cells. Late in the course of disease, splenic infarcts are common, centrilobular necrosis and fatty infiltration of the liver occur, the normal marrow elements are replaced by parasitized histiocytes, and erythrophagocytosis is present.

PATHOGENESIS

Cellular immune mechanisms determine resistance or susceptibility to infection with *Leishmania*. Resistance is mediated by interleukin (IL)-12–driven generation of a T helper 1 (Th1) cell response, with interferon (IFN)-γ inducing classic macrophage (M1) activation and parasite killing. Susceptibility is associated with expansion of IL-4–producing Th2 cells and/or the production of IL-10 and transforming growth factor (TGF)-β, which are inhibitors of macrophage-mediated parasite killing, and the generation of regulatory T cells and arginase-producing (M2) macrophages. An exuberant innate inflammatory response involving inflammasome activation and IL-1β production in lesions is associated with greater local pathology and delayed healing. Patients with ML exhibit a hyperresponsive cellular immune reaction that contributes to the prominent tissue destruction seen in this form of the disease. Patients with DCL or active VL demonstrate reduced or altered *Leishmania*-specific cellular immune responses, with prominent generation of IL-10, but these responses recover after successful therapy.

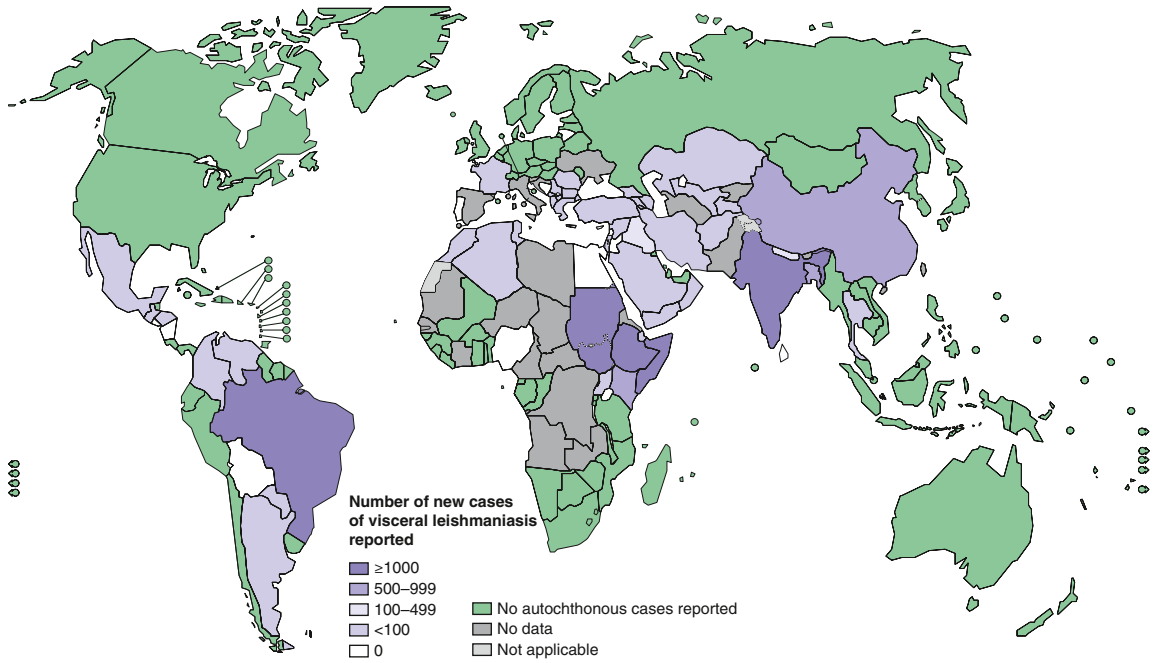

Fig. 331.2 Status of endemicity of visceral leishmaniasis worldwide in 2016. *(From World Health Organization. Recognizing Neglected Tropical Diseases Through Changes on the Skin: A Training Guide for Front-Line Health Workers. Geneva: WHO; 2018.)*

Within endemic areas, people who have had a subclinical infection can be identified by a positive delayed-type hypersensitivity skin response to leishmanial antigens (**Montenegro skin test**) or by antigen-induced production of IFN-γ in a whole blood assay. Subclinical infection occurs considerably more frequently than does active cutaneous or visceral disease. **Host** factors (genetic background, concomitant disease, nutritional status), **parasite** factors (virulence, size of the inoculum), and possibly **vector**-specific factors (vector genotype, immunomodulatory salivary constituents) influence the expression as either subclinical infection or active disease. Within endemic areas, the prevalence of skin test positivity increases with age, and the incidence of clinical disease decreases with age, indicating that immunity is acquired in the population over time. Individuals with prior active disease or subclinical infection are usually immune to a subsequent clinical infection; however, latent infection can lead to active disease if the patient is immunosuppressed.

CLINICAL MANIFESTATIONS

The different forms of the disease are distinct in their causes, epidemiologic features, transmission, and geographic distribution.

Localized Cutaneous Leishmaniasis

LCL (**Oriental sore**) can affect individuals of any age, but children are the primary victims in many endemic regions. It may present as one or a few papular, nodular, plaque-like, or ulcerative lesions that are usually located on exposed skin, such as the face and extremities (Fig. 331.3). Rarely, >100 lesions have been recorded. The lesions typically begin as a small papule at the site of the sand fly bite, which enlarges to 1-3 cm in diameter and may ulcerate over the course of several weeks to months. The shallow ulcer is usually nontender and surrounded by a sharp, indurated, erythematous margin. There is no drainage unless a bacterial superinfection develops. Lesions caused by *L. major* and *L. mexicana* usually heal spontaneously after 3-6 months, leaving a depressed scar. Lesions on the ear pinna caused by *L. mexicana,* called **chiclero ulcer** because they were common in chicle harvesters in Mexico and Central America, often follow a chronic, destructive course. In general, lesions caused by *L. (Viannia)* species tend to be larger and more chronic. Regional lymphadenopathy and palpable subcutaneous nodules or lymphatic cords, the so-called sporotrichoid appearance, are also more common when the patient is infected with organisms of the *Viannia* subgenus. If lesions do not become secondarily infected, there are usually no complications aside from the residual cutaneous scar.

Diffuse Cutaneous Leishmaniasis

DCL is a rare form of leishmaniasis caused by organisms of the *L. mexicana* complex in the New World and *L. aethiopica* in the Old World. DCL manifests as large, non-ulcerating macules, papules, nodules, or plaques that often involve large areas of skin and may resemble lepromatous leprosy. The face and extremities are most often involved. Dissemination from the initial lesion usually takes place over several years. These patients are anergic to the Montenegro skin test, and it is thought that an immunologic defect underlies this severe form of cutaneous leishmaniasis.

Disseminated Leishmaniasis

In rare cases, parasites can spread (likely by the hematogenous route) in an immunocompetent host from a primary lesion to cause DL. This is defined as >10 lesions (usually in the hundreds) involving at least two noncontiguous areas of the skin. DL has been most often attributed to *L. (V.) braziliensis*. The lesions are typically inflammatory papules or ulcers, in contrast to the nodular and plaque-like lesions of DCL, and about one-third of patients have mucosal involvement.

Mucosal Leishmaniasis

ML (**espundia**) is an uncommon but serious manifestation of leishmanial infection resulting from hematogenous spread of parasites to the nasal or oropharyngeal mucosa from a cutaneous infection. It is usually caused by parasites in the *L. (Viannia)* complex. Approximately half of the patients with mucosal lesions have had active cutaneous lesions within the preceding 2 years, but ML may not develop until many years after resolution of the primary lesion. ML occurs in <5% of individuals who have, or have had, LCL caused by *L. (V.) braziliensis.* Patients with ML typically have nasal mucosal involvement and present with nasal congestion, discharge, and recurrent epistaxis. Oropharyngeal and laryngeal involvement is less common but associated with severe morbidity. Marked soft tissue, cartilage, and even bone destruction occurs late in the course of disease and may lead to visible

deformity of the nose or mouth, nasal septal perforation, and tracheal narrowing with airway obstruction.

Visceral Leishmaniasis

VL **(kala-azar)** typically affects children <5 years old in the New World and Mediterranean region *(L. infantum)* and older children and young adults in Africa and Asia *(L. donovani)*. After inoculation of the organism into the skin by the sand fly, the child may have a completely asymptomatic infection or an oligosymptomatic illness that either resolves spontaneously or evolves into active kala-azar. Children with **asymptomatic** infection are transiently seropositive but show no clinical evidence of disease. Children who are **oligosymptomatic** have mild constitutional symptoms (malaise, intermittent diarrhea, poor activity tolerance) and intermittent fever; most will have a mildly enlarged liver. In most of these children the illness will resolve without therapy, but in approximately 25% it will evolve to active kala-azar within 2-8 months. Extreme incubation periods of several years have rarely been described. During the first few weeks to months of disease evolution, the fever is intermittent, there is weakness and loss of energy, and the spleen begins to enlarge. The classic clinical features of high fever, marked splenomegaly, hepatomegaly, and severe cachexia typically develop 3-6 months after the onset of the illness, but a rapid clinical course over 1 month has been noted in up to 20% of patients in some series (Fig. 331.4). At the terminal stages of kala-azar, the hepatosplenomegaly is massive, there is gross wasting, the pancytopenia is profound, and jaundice, edema, and ascites may be present. Anemia may be severe enough to precipitate heart failure. Bleeding episodes, especially epistaxis, are frequent. The late stage of the illness is often complicated by secondary bacterial infections, which frequently are a cause of death. A younger age at the time of infection, HIV coinfection, and underlying malnutrition are risk factors for the development, rapid evolution, and severe disease of active VL. Death occurs in >90% of patients without specific antileishmanial treatment and in 4–10% of treated patients. VL is a known cause of **hemophagocytic lymphohistiocytosis** in endemic areas.

VL is an opportunistic infection associated with **HIV infection**. Most cases have occurred in southern Europe and Brazil, often as a result of needle sharing associated with illicit drug use, with the potential for many more cases as the endemic regions for HIV and VL converge. Leishmaniasis may also result from reactivation of a long-standing subclinical infection. Frequently there is an atypical clinical presentation of VL in HIV-infected individuals with prominent involvement of the gastrointestinal tract and absence of the typical hepatosplenomegaly.

A small percentage of patients previously treated for VL develop diffuse skin lesions, a condition known as **post–kala-azar dermal leishmaniasis.** These lesions may appear during or shortly after therapy (Africa) or up to several years later (India). The lesions of post–kala-azar dermal leishmaniasis are hypopigmented, erythematous, or nodular and usually involve the face and torso. They may persist for several months or for many years.

LABORATORY FINDINGS

Patients with cutaneous leishmaniasis or ML generally do not have abnormal laboratory results unless the lesions are secondarily infected with bacteria. Laboratory findings associated with classic kala-azar include anemia (hemoglobin, 5-8 mg/dL), thrombocytopenia, leukopenia (2,000-3,000 cells/μL), elevated hepatic transaminase levels, and hyperglobulinemia (>5 g/dL) that is mostly immunoglobulin G.

DIFFERENTIAL DIAGNOSIS

Diseases that should be considered in the differential diagnosis of LCL include sporotrichosis, blastomycosis, chromomycosis, lobomycosis, cutaneous tuberculosis, atypical mycobacterial infection, leprosy, ecthyma, syphilis, yaws, and neoplasms. Infections such as syphilis, tertiary yaws, histoplasmosis, and paracoccidioidomycosis, as well as sarcoidosis, granulomatosis with polyangiitis, midline granuloma, and carcinoma, may have clinical features similar to those of ML. VL should be strongly suspected in the patient with prolonged fever, weakness, cachexia, marked splenomegaly, hepatomegaly, cytopenias, and hypergammaglobulinemia who has had potential exposure in an endemic area. The clinical picture may also be consistent with that of malaria, typhoid fever, miliary tuberculosis, schistosomiasis, brucellosis, amebic liver abscess, infectious mononucleosis, lymphoma, and leukemia.

DIAGNOSIS

The development of one or several slowly progressive, nontender, nodular, or ulcerative lesions in a patient who had potential exposure in an endemic area should raise suspicion of LCL.

Serologic tests for diagnosis of cutaneous or mucosal disease generally have low sensitivity and specificity and offer little for diagnosis. Serologic testing by enzyme immunoassay, indirect fluorescence assay, or direct agglutination is very useful in VL because of the very high level of antileishmanial antibodies. An immunochromatographic strip test using a recombinant antigen (K39) has a diagnostic sensitivity and specificity for VL of 80–90% and 95%, respectively. Serodiagnostic tests have positive findings in only about half the patients co-infected with HIV.

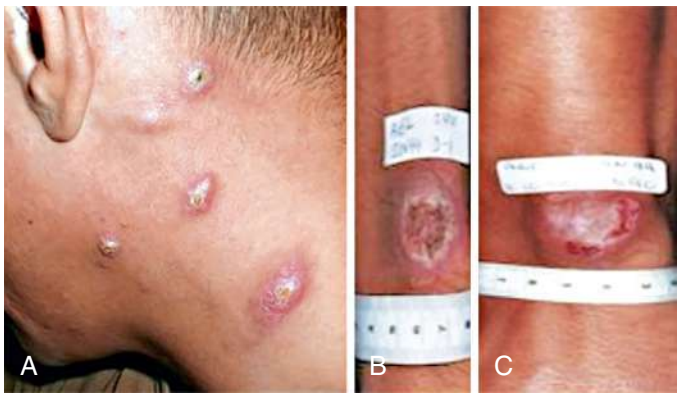

Fig. 331.3 Cutaneous disease. **A**, Old World infection *(Leishmania major)* acquired in Iraq; note five papular and nodular lesions on neck. **B**, New World infection *(Leishmania panamensis)* in Colombia; purely ulcerative lesion is characteristic of New World disease. **C**, Healed infection in patient shown in **B** 70 days after 20 days of meglumine antimonate treatment; note paper-thin scar tissue over flat reepithelialized skin. *(**A**, Courtesy P. Weina; **B**, Courtesy J. Soto. **A-C**, Modified from Murray HW, Berman JD, Davies CR, et al. Advances in leishmaniasis. Lancet. 2005;366:1561–1577.)*

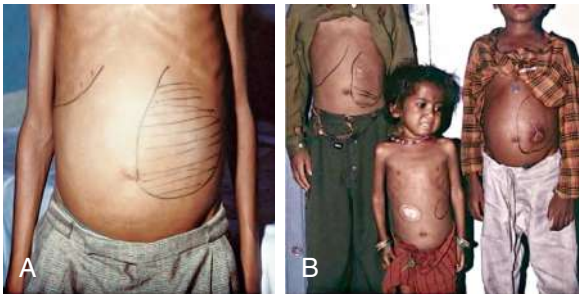

Fig. 331.4 Visceral leishmaniasis *(Leishmania donovani)* in Bihar State, India. **A**, Hepatosplenomegaly and wasting in a young man. **B**, Children with burn marks over enlarged spleen or liver evidence of a local shaman's unsuccessful remedy. *(**A**, Courtesy D. Sacks; **B**, Courtesy R. Kenney; **A** and **B**, Adapted from Murray HW, Berman JD, Davies CR, et al. Advances in leishmaniasis. Lancet. 2005;366:1561–1577.)*

Definitive diagnosis of leishmaniasis is established by the demonstration of amastigotes in tissue specimens or isolation of the organism by culture. **Amastigotes** can be identified in Giemsa-stained tissue sections, aspirates, or impression smears in about half the cases of LCL but only rarely in the lesions of ML. **Culture** of a tissue biopsy or aspirate, best performed by using Novy-MacNeal-Nicolle biphasic blood agar medium, yields a positive finding in only approximately 65% of cases of cutaneous leishmaniasis. Identification of parasites in impression smears, histopathologic sections, or culture medium is more readily accomplished in DCL than in LCL. In patients with VL, smears or cultures of material from splenic, bone marrow, or lymph node aspirations are usually diagnostic. In experienced hands, **splenic aspiration** has a higher diagnostic sensitivity, but it is rarely performed in the United States because of the risk for bleeding complications. A positive culture result allows speciation of the parasite, usually by isoenzyme analysis by a reference laboratory, which may have therapeutic and prognostic significance.

TREATMENT

Specific antileishmanial therapy should be individualized for each patient. It is not routinely indicated for immunocompetent persons having uncomplicated simple LCL (single or few lesions, lesion diameter <1 cm, no mucosal involvement) caused by strains that have a high rate of spontaneous resolution and self-healing *(L. major, L. mexicana).* Lesions that are extensive, severely inflamed, or located where a scar would result in disability (near a joint) or cosmetic disfigurement (face or ear), that involve the lymphatics, or that do not begin healing within 3-4 months should be treated. Cutaneous lesions suspected or known to be caused by members of the *Viannia* subgenus (New World) should be treated because of the low rate of spontaneous healing and the potential risk for development of mucosal or disseminated disease. Similarly, patients with lesions caused by *L. tropica* (Old World), which are typically chronic and nonhealing, should be treated. All patients with VL or ML should receive therapy.

The pentavalent **antimony compounds** (sodium stibogluconate [Pentostam, GlaxoSmithKline, Uxbridge, UK] and **meglumine antimoniate** [Glucantime, Aventis, Strasbourg, France]) have been the mainstay of antileishmanial chemotherapy for >40 years. These drugs have similar efficacies, toxicities, and treatment regimens. Currently, for **sodium stibogluconate** (available in the United States from the Centers for Disease Control and Prevention, Atlanta, GA), the recommended regimen is 20 mg/kg/day intravenously (IV) or intramuscularly (IM) for 20 days (for LCL and DCL) or 28 days (for ML and VL). Repeated courses of therapy may be necessary in patients with severe cutaneous lesions, ML, DCL, DL, or VL. An initial clinical response to therapy usually occurs in the first week of therapy, but complete clinical healing (reepithelialization and scarring for LCL and ML, and regression of splenomegaly and normalization of cytopenias for VL) is usually not evident for weeks to a few months after completion of therapy. Cure rates with this regimen of 90–100% for LCL, 50–70% for ML, and 80–100% for VL were common in the 1990s, but treatment failures, especially in children, have become common in parts of India, East Africa, and Latin America.

Relapses are common in patients who do not have an effective antileishmanial cellular immune response (DCL or HIV co-infection). Adverse effects of antimony therapy are dose and duration dependent and include fatigue, arthralgias, and myalgias (50%), abdominal discomfort (30%), elevated hepatic transaminase level (30–80%), elevated amylase and lipase levels (almost 100%), mild hematologic changes (slightly decreased leukocyte count, hemoglobin level, and platelet count) (10–30%), and nonspecific T-wave changes on electrocardiography (30%). Sudden death from cardiac toxicity has rarely been reported with use of very high doses of pentavalent antimony.

Amphotericin B desoxycholate and **liposomal amphotericin B** are very useful in the treatment of VL, ML, or DL, and in some regions have replaced antimony as first-line therapy, especially in HIV-infected patients. However, the prohibitively high cost of these drugs precludes their use in many resource-poor regions of the world. Amphotericin B desoxycholate at doses of 0.5-1.0 mg/kg every day or every other day for 14-20 doses achieved a cure rate for VL of close to 100%, but renal toxicity associated with amphotericin B was common. **Liposomal amphotericin B** (AmBisome, Gilead Sciences, Foster City, CA) is especially attractive for treatment of leishmaniasis because the drug is concentrated in the reticuloendothelial system and is less nephrotoxic. It is approved by the U.S. Food and Drug Administration (FDA) for treatment of VL at a recommended dose for *immunocompetent patients* of 3 mg/kg on days 1-5, 14, and 21 (total dose 21 mg/kg) and should be considered for first-line therapy in the United States. It is highly effective, with a 90–100% cure rate for VL in immunocompetent children, including those who were refractory to antimony therapy. Therapy for *immunocompromised patients* should be prolonged (recommended total dose 40 mg/kg). A single high dose of liposomal amphotericin B (10 mg/kg) was found to be effective in India (approximately 95% efficacy) but was less effective in East Africa (58% efficacy).

Parenteral treatment of VL with the aminoglycoside **paromomycin** (aminosidine) has efficacy (95%) similar to that of amphotericin B in India. A dose-sparing regimen of the combination of sodium stibogluconate and paromomycin is effective and used in East Africa. **Miltefosine**, a membrane-activating alkyl phospholipid, has been approved as the first oral treatment for VL and has a cure rate of 80–90% in Indian patients with VL when administered orally at 50-100 mg/day (or 2.5 mg/kg for children <12 years old) for 28 days. Miltefosine is indicated for cutaneous infection caused by *L. braziliensis*, *L. guyanensis,* and *L. panamensis*; ML caused by *L. braziliensis*; and VL caused by *L. donovani*. Gastrointestinal adverse effects were frequent but did not require discontinuation of the drug. An increased rate of relapse (up to 20%) has been seen in children treated with miltefosine. Dose-sparing combination regimens are being actively investigated for treatment of VL. Treatment of LCL with oral drugs has had only modest success. Ketoconazole has been effective in treating adults with LCL caused by *L. major, L. mexicana,* and *L. panamensis,* but not *L. tropica* or *L. braziliensis*. Fluconazole in high doses (up to 8 mg/kg/day) for 4-8 weeks was demonstrated to be effective in treating LCL in studies in both the Old and New World; however, the experience in young children is limited. Miltefosine, 2.5 mg/kg/day orally for 20-28 days, was effective in 70–90% of patients with LCL in the Americas. Local therapy, including heat, cryotherapy, and topical 15% paromomycin ointment has been effective treatment for LCL in selected areas in both the Old and the New World. Enhanced drug development efforts and clinical trials of new drugs are clearly needed, especially in children.

PREVENTION

Personal protective measures should include avoidance of exposure to the nocturnal sand flies and, when necessary, the use of insect repellent and permethrin-impregnated mosquito netting. Where peridomiciliary transmission is present, community-based residual insecticide spraying has had some success in reducing the prevalence of leishmaniasis, but long-term effects are difficult to maintain. Control or elimination of infected reservoir hosts (e.g., seropositive domestic dogs) has had limited success. Where anthroponotic transmission is thought to occur, as in south Asia, early recognition, diagnosis, and treatment of cases and vector control measures are essential for progress toward elimination. Several vaccines have been demonstrated to have efficacy in experimental models, and vaccination of humans or domestic dogs may have a role in the control of the leishmaniases in the future.

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Chapter 332

African Trypanosomiasis (Sleeping Sickness; *Trypanosoma brucei* Complex)

Edsel Maurice T. Salvana and Robert A. Salata

Sixty-five million people in 36 countries are at risk for infection with *Trypanosoma brucei* complex, the causative agent of sleeping sickness. Also known as **human African trypanosomiasis (HAT)**, this disease is restricted to sub-Saharan Africa, the range of the tsetse fly vector. It is a disease of extreme poverty, with the highest disease burden observed in remote rural areas. HAT comes in two geographically and clinically distinct forms. *Trypanosoma brucei gambiense* causes a chronic infection and affects people who live in western and central Africa **(West African sleeping sickness, Gambian trypanosomiasis)**. *Trypanosoma brucei rhodesiense* is a zoonosis that presents as an acute illness lasting several weeks and usually occurs in residents or travelers from eastern and southern Africa **(East African sleeping sickness, Rhodesian trypanosomiasis)**.

ETIOLOGY

HAT is a vector-borne disease caused by parasitic, extracellular, flagellated kinetoplastid protozoans of two subspecies of *T. brucei*. It is transmitted to humans through the bite of *Glossina,* commonly known as the **tsetse fly**.

Humans usually contract East African HAT when they venture from towns to rural areas to visit woodlands or livestock, highlighting the importance of zoonotic reservoirs in this disease. West African HAT is contracted closer to settlements and only requires a small vector population, making it difficult to eradicate. Animal reservoirs occur, but the main source of infection remains chronically infected human hosts.

LIFE CYCLE

T. brucei undergoes several stages of development in the insect and mammalian host. On ingestion with a blood meal, nonproliferative **short stumpy (SS)** forms of the parasite transform into procyclic forms in the insect's midgut. These procyclic forms proliferate and undergo further development into epimastigotes, which then become infective metacyclic forms that migrate to the insect's salivary glands. The life cycle within the tsetse fly takes 15-35 days. On inoculation into the mammalian host, the metacyclic stage transforms into proliferative **long slender (LS)** forms in the bloodstream and the lymphatics, eventually penetrating the central nervous system (CNS). LS forms appear in waves in the peripheral blood, with each wave followed by a febrile crisis and heralding the formation of a new antigenic variant. Once a critical density of LS forms is reached, a quorum-sensing mechanism causes most of these to transform into nonproliferative SS forms that are ingested by *Glossina* and start the cycle anew. Quorum sensing controls peak parasitemia to ensure that the host survives infection long enough for the parasite to complete its life cycle.

Direct transmission to humans has been reported, either vertically to infants or mechanically through contact with tsetse flies with viable LS forms on their mouthparts from a recent blood meal from an infected host.

EPIDEMIOLOGY

HAT occurs mainly in sub-Saharan Africa between latitudes 14 degrees north and 29 degrees south, where the annual rainfall creates optimal climatic conditions for *Glossina*. In 2009, new HAT cases annually fell below 10,000 as a result of intensive control efforts. In 2018, new cases fell to 977, the lowest level in 80 years since the start of systematic data collection. In the last 10 years, 70% of cases were reported from the Democratic Republic of Congo. Gambian trypanosomiasis is targeted for sustainable elimination as a public health problem by 2030.

T. brucei rhodesiense infection is restricted to the eastern third of the endemic area in tropical Africa, stretching from Ethiopia to the northern boundaries of South Africa. *T. brucei gambiense,* which accounts for 95% of HAT cases, occurs mainly in the western half of the continent's endemic region. Rhodesian HAT, which has an acute and often fatal course, greatly reduces chances of transmission to tsetse flies. The ability of *T. brucei rhodesiense* to multiply rapidly in the bloodstream and infect other species of mammals helps maintain its life cycle. HAT is infrequently reported in non-endemic countries, usually in returning travelers or migrants.

PATHOGENESIS

At the site of the *Glossina* bite, tsetse fly salivary antigens, peptides, and proteins promote an immune-tolerant microenvironment that facilitates parasite invasion. Injected metacyclic parasites transform into LS forms, which rapidly divide by binary fission. The parasites, along with the attendant inflammation, cellular debris, and metabolic products, may give rise to a hard, painful, red nodule known as a **trypanosomal chancre** within 5-15 days postinoculation. Parasites directionally migrate from the skin to the lymphatics via an unknown mechanism and pass into the draining lymph node and onward into the main lymphatic ducts. Dissemination into the blood and lymphatic systems follows, with subsequent localization to the CNS. Histopathologic findings in the brain are consistent with meningoencephalitis. The appearance of **morula** cells of Mott (large, strawberry-like cells, supposedly derived from plasma cells) is a characteristic finding in chronic disease.

Mechanisms underlying virulence in HAT are still incompletely understood but seem to be mediated by a complex interplay of trypanosomal, human, and *Glossina* factors. *T. brucei gambiense* utilizes at least three mechanisms to evade lysis by human sera. These include reduced binding to trypanolytic factor 1 (TLF1) via reduced expression and mutation of a haptoglobin-hemoglobin receptor; expression of a specific glycoprotein TgsGP, which reduces trypanosomal membrane fluidity; and a cysteine protease-mediated reduction of sensitivity to apolipoprotein L-1 (APOL1). *T. brucei rhodesiense,* on the other hand, expresses a protein known as serum resistance–associated protein (SRA), which counteracts trypanolytic APOL1 in human serum. APOL1 and the hemoglobin binding protein haptoglobin-related protein (HPR) are major components of two high-density lipoprotein complexes called TLF1 and TLF2, which protect humans against non-human trypanosomes. Trypanosomes also secrete a host of biologically active molecules that can dampen immune responses.

Antigenic variation of **variant surface glycoprotein (VSG)** on the trypanosome surface has long been recognized as a major factor in evading acquired immunity during infection. This antigenic diversity is generated by a tightly controlled system of DNA double-stranded breaks with associated homologous recombination. VSG also inhibits complement activation and antibody-mediated aggregation, facilitating establishment and maintenance of infection. Soluble VSG is hypersecreted, especially at the peak of parasitemia, and may serve as a decoy for antibodies and complement factor, diverting immune responses away from trypanosomes.

CLINICAL MANIFESTATIONS

Clinical presentations vary not only because of the two subspecies of organisms but also because of differences in host response in the

indigenous population of endemic areas and in newcomers or visitors. Visitors usually suffer more from the acute symptoms, but if untreated, death usually follows for natives and visitors alike. Symptoms usually occur within 2-3 weeks of infection. The clinical syndromes of HAT are trypanosomal chancre, hemolymphatic stage, and meningoencephalitic stage.

Trypanosomal Chancre

The site of the tsetse fly bite may be the first presenting feature. A nodule or chancre (3-4 cm) develops in 2-3 days and becomes a painful, hard, red nodule surrounded by an area of erythema and swelling within 1 week. Nodules are typically seen on the lower limbs and sometimes also on the head. They subside spontaneously in about 2 weeks, leaving no permanent scar.

Hemolymphatic Stage (Stage 1)

The most common presenting features of acute HAT occur at the time of invasion of the bloodstream by the parasites, 2-3 weeks after infection. Patients usually present with irregular episodes of fever, each lasting up to 7 days, accompanied by headache, sweating, and generalized lymphadenopathy. Attacks may be separated by symptom-free intervals of days or even weeks. Painless, nonmatted **lymphadenopathy**, most often of the posterior cervical and supraclavicular nodes, is one of the most constant signs, particularly in the Gambian form. A common feature of trypanosomiasis is the presence of blotchy, irregular, nonpruritic, erythematous **macules**, which may appear any time after the first febrile episode, usually within 6-8 weeks. The majority of macules have a normal central area, giving the rash a circinate outline. This **rash** is seen mainly on the trunk and is evanescent, fading in one place only to appear at another site. Examination of the blood during this stage may show anemia, leukopenia with relative monocytosis, and elevated levels of immunoglobulin M (IgM). Cardiac manifestations of HAT have also been reported but are generally limited to nonspecific ST-T wave electrocardiographic abnormalities. Histopathologic characterization shows a lymphomonohistiocytic infiltrate in the interstitium, with no penetration of the myocardial cells, unlike that for American trypanosomiasis (see Chapter 333). The perimyocarditis is usually self-limited and does not typically progress to congestive heart failure.

Meningoencephalitic Stage (Stage 2)

Neurologic symptoms and signs are nonspecific, including irritability, insomnia, and irrational and inexplicable anxieties with frequent changes in mood and personality. Neurologic symptoms may precede invasion of the CNS by the organisms. In untreated *T. brucei rhodesiense* infections, CNS invasion occurs within 3-6 weeks and is associated with recurrent bouts of headache, fever, weakness, and signs of acute toxemia. Death occurs in 6-9 months as a result of secondary infection or cardiac failure.

In Gambian HAT, cerebral symptoms appear within 2 years after the acute symptoms. An increase in drowsiness during the day and insomnia at night reflect the continuous progression of infection and may be accompanied by anemia, leukopenia, and muscle wasting. The chronic, diffuse meningoencephalitis without localizing symptoms is the form referred to as **sleeping sickness**. Drowsiness and an uncontrollable urge to sleep are the major features of this stage and become almost continuous in the terminal stages. Tremor or rigidity with stiff and ataxic gait suggest involvement of the basal ganglia. Psychotic changes occur in one third of untreated patients. Although most untreated disease is fatal, in rare cases, individuals remain asymptomatic, clear parasitemia, and become seronegative.

DIAGNOSIS

Definitive diagnosis can be established during the early stages by examination of a fresh, thick blood smear, which permits visualization of the motile active forms (Fig. 332.1). HAT can also be detected from blood using a variety of sensitive techniques, such as quantitative buffy coat smears and mini anion exchange resins. Dried, Giemsa-stained smears should be examined for the detailed morphologic features of the organisms. If a thick blood or buffy coat smear is negative, concentration techniques may help. Aspiration of an enlarged lymph node can also be used to obtain material for parasitologic examination. If positive, cerebrospinal fluid (CSF) should also be examined for the organisms. The presence of trypanosomes, or ≥5 white blood cells (WBCs)/μL, or both, is indicative of stage 2 disease. If trypanosomes are absent in the CSF, some authorities use a count of 10-20 WBCs/μL as a cutoff for diagnosing late-stage disease.

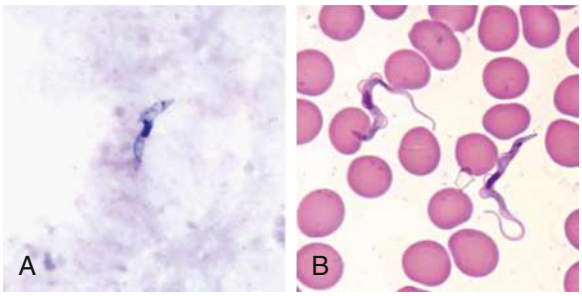

Fig. 332.1 *Trypanosoma brucei* sp. trypomastigotes in thick blood smear stained with Giemsa (A) and thin blood smear stained with Wright-Giemsa (B). *(From Centers for Disease Control and Prevention: Laboratory identification of parasites of public health concern. Trypanosomiasis, African [website], 2018. https://www.cdc.gov/dpdx/trypanosomiasisafrican/index.html)*

The card agglutination trypanosomiasis test (CATT) is of value for epidemiologic purposes and for screening for *T. brucei gambiense*. Lateral flow formats of CATT have enabled point-of-care testing. Because CATT detects antibodies against particular VSG molecules, it cannot distinguish present from past infection.

Polymerase chain reaction–based tests have been shown to be highly sensitive and specific, but these tests require laboratory facilities. Field-based loop-mediated isothermal amplification tests have been developed and validated. Other areas of active research for diagnostics include new biomarkers, cytokine profiles, proteomics, and polysomnography, which are being used not only to identify disease but to differentiate disease stages.

TREATMENT

The choice of chemotherapeutic agents for treatment depends on the stage of the infection and the causative organisms.

Stage 1 Treatment

Hematogenous forms of both Rhodesian and Gambian HAT have been traditionally treated with either suramin or pentamidine. **Suramin** is a polysulfonated symmetric naphthalene derivative given as a 10% solution for intravenous (IV) administration. A **test dose** (10 mg for children; 100-200 mg for adults) is initially administered to detect rare idiosyncratic reactions of shock and collapse. The dose for subsequent IV injections is 20 mg/kg (maximum 1 g) administered on days 1, 3, 7, 14, and 21. Suramin is nephrotoxic; thus a urinalysis should be performed before each dose. Marked proteinuria, blood, or casts is a contraindication to continuation of suramin. Resistance is rare but has been reported.

Pentamidine isethionate (4 mg/kg/day intramuscularly [IM] daily or on alternate days for 7-10 days) concentrates to high levels in trypanosomes and is highly trypanocidal. It is better tolerated than suramin but carries significant risk of hypoglycemia, nephrotoxicity, hypotension, leukopenia, and liver enzyme elevation. Because of its

potency, long half-life, and toxicity, short-course treatment is desirable and is being investigated.

Fexinidazole has recently been approved for oral treatment of stage 1 and 2 Gambian HAT in 6 years of age and older and weighing at least 20 kg. Dosing is weight based over 10 days. For 35 kg and above, a loading dose of 1,800 mg for 4 days followed by a maintenance dose of 1,200 mg over 6 days is recommended. For 20 kg to <35 kg, the loading dose is 1,200 mg over 4 days and 600 mg maintenance over 6 days. Common side effects include gastrointestinal upset, asthenia, headache, tremors, and dizziness. Some patients may develop neutropenia.

Stage 2 Treatment

Combination **eflornithine and nifurtimox** (NECT) is the current treatment of choice for *T. brucei gambiense* CNS infection. Eflornithine is given at 400 mg/kg/day IV divided every 12 hours for 7 days, along with nifurtimox, 15 mg/kg/day orally divided every 8 hour for 10 days. If nifurtimox is unavailable, eflornithine monotherapy can be given at 400 mg/kg/day IV divided every 6 hours for 14 days. Adverse reactions to these regimens include fever, hypertension, and seizures, with NECT having less frequent events.

Fexinidazole is a safe and effective, all oral alternative to NECT for stage 2 Gambian HAT. However, it is associated with lower efficacy in severe disease (86.9% with fexinidazole vs 98.7% for NECT). Dosing and duration are the same as for stage 1 disease.

Melarsoprol is an arsenical compound and is the only effective treatment for late *T. brucei rhodesiense* disease. Treatment of children is initiated at 0.36 mg/kg IV once daily, with gradually escalating doses every 1-5 days to 3.6 mg/kg once daily; treatment is usually 10 doses (18-25 mg/kg total dose). Treatment of adults is with melarsoprol 2-3.6 mg/kg IV once daily for 3 days; and after 1 week, 3.6 mg/kg once daily for 3 days, which is repeated after 10-21 days. An alternative regimen is 2.2 mg/kg once daily for 10 days. Guidelines recommend 18-25 mg/kg total over 1 month. Reactions such as fever, abdominal pain, and chest pain are rare but may occur during or shortly after administration. Serious toxic effects include encephalopathy and exfoliative dermatitis.

Following on the success of fexinidazole, other candidate oral drugs for HAT are being studied. This includes acoziborole, which is currently in clinical trials as a single-dose oral treatment for stage 2 HAT.

PREVENTION

A vaccine or consistently effective prophylactic therapy is not available and is particularly challenging because of the antigenic variation caused by VSGs. Virus-like particles are being explored as an adjuvant to hurdle the complexities of the immunologic response. A single injection of pentamidine (3-4 mg/kg IM) provides protection against Gambian trypanosomiasis for at least 6 months, but the effectiveness against the Rhodesian form is uncertain.

Vector control programs against *Glossina* have been essential in controlling disease, coupled with the use of screens, traps, insecticides, and sanitary measures. Neutral-colored clothing may reduce tsetse fly bites. Control of infection in animal reservoirs with mass administration of trypanocidal drugs in cattle has met with some success.

The full genome of *T. brucei* with about 9,000 genes has been sequenced. Approximately 10% of these genes encode VSGs. CRISPR-Cas9-based gene editing has helped identify genes relevant to the disease and its possible prevention, as well as the design of new antitrypanosomal drugs, including those that target specific metabolic pathways.

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Chapter 333

American Trypanosomiasis (Chagas Disease; *Trypanosoma cruzi*)

Edsel Maurice T. Salvana and Robert A. Salata

American trypanosomiasis or Chagas disease is caused by the protozoan *Trypanosoma cruzi*. Its natural vectors are the reduviid insects, specifically **triatomines**, variably known as wild bedbugs, assassin bugs, or kissing bugs. It can also be transmitted orally from contaminated food, vertically from mother to child, and through blood transfusion or organ transplantation. Signs and symptoms of acute Chagas disease are usually nonspecific, whereas chronic disease may manifest as cardiomyopathy or severe gastrointestinal (GI) dilation and dysfunction.

ETIOLOGY

American trypanosomiasis is caused by *T. cruzi*, a parasitic, flagellated kinetoplastid protozoan. The main vectors for *T. cruzi* are insects of the family Reduviidae, subfamily Triatominae, which includes *Triatoma infestans, Rhodnius prolixus,* and *Panstrongylus megistus.*

LIFE CYCLE

T. cruzi has three recognizable morphogenetic phases: amastigotes, trypomastigotes, and epimastigotes (Figs. 333.1 and 333.2). **Amastigotes** are intracellular forms found in mammalian tissues that are spherical and have a short flagellum but form clusters of oval shapes (pseudocysts) within infected tissues. **Trypomastigotes** are spindle-shaped, extracellular, nondividing forms that are found in blood and are responsible for both transmission of infection to the insect vector and cell-to-cell spread of infection. **Epimastigotes** are found in the midgut of the vector insect and multiply in the midgut and rectum of arthropods, differentiating into metacyclic forms. **Metacyclic trypomastigotes** are the infectious form for humans and are released onto the skin of a human when the insect defecates close to the site of a bite, entering through the damaged skin or mucous membranes. Once in the host, these multiply intracellularly as amastigotes, which then differentiate into bloodstream trypomastigotes and are released into the circulation when the host cell ruptures. Blood-borne trypomastigotes circulate until they enter another host cell or are taken up by the bite of another insect, completing the life cycle. There is some variability in these stages. Reverse transitions can occur; epimastigote-like forms have been found in the mammalian hosts, and trypomastigotes have been observed to replicate. Amastigotes can also quickly transform into quiescent forms upon drug exposure and can maintain persistent infection despite treatment.

EPIDEMIOLOGY

Natural transmission of Chagas disease occurs in North and South America, most frequently in continental Latin America. The disease may arise elsewhere because of migration and transmission through contaminated blood. World Health Organization (WHO) and Pan-American Health Organization–led efforts in large-scale vector control, blood donor screening to prevent transmission through transfusion and case finding, and treatment of chronically infected

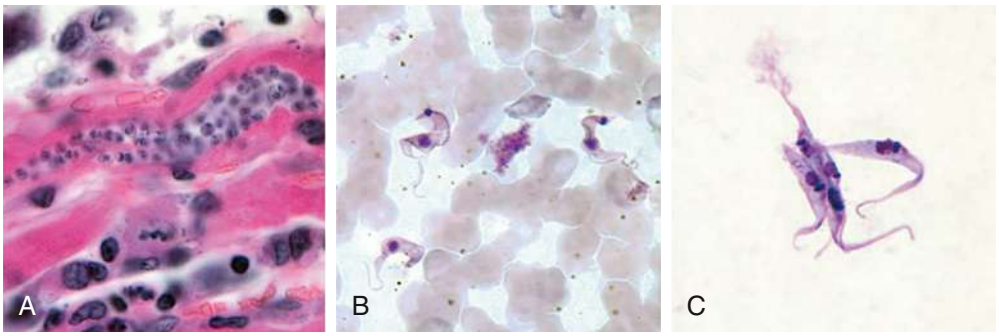

Fig. 333.1 Stages of *Trypanosoma cruzi*. **A,** Amastigote. **B,** Trypomastigote. **C,** Epimastigotes. *(From Centers for Disease Control and Prevention. Laboratory identification of parasites of public health concern. Trypanosomiasis, American [website], 2018. https://www.cdc.gov/dpdx/trypanosomiasisamerican/index.html)*

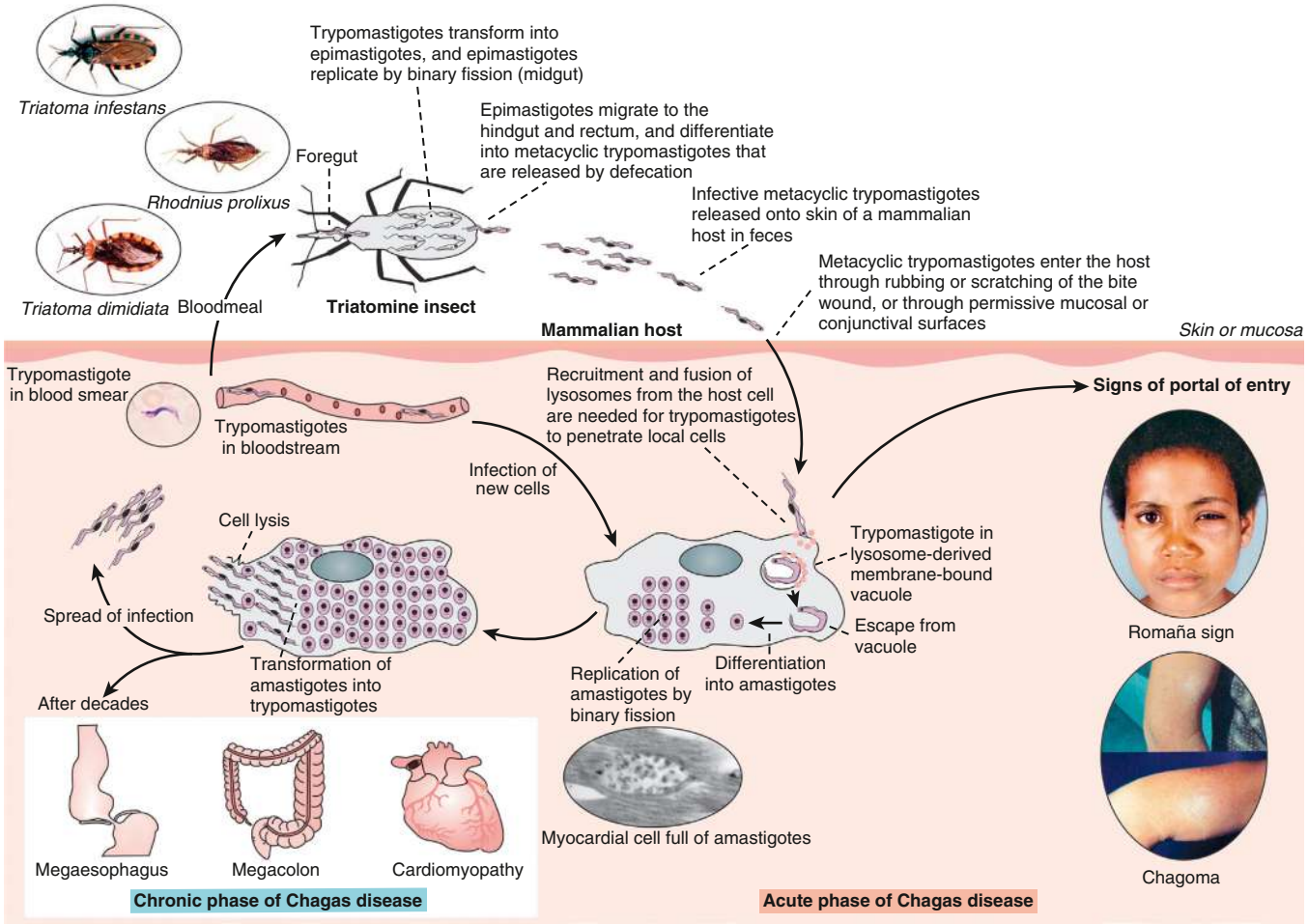

Fig. 333.2 Vector-borne transmission and life cycle of *Trypanosoma cruzi*. *(From Rassi A Jr, Rassi A, Marin-Neto JA. Chagas disease. Lancet. 2010;375:1388–1400. Fig. 1.)*

mothers and newborn infants have effectively halted transmission in a number of areas of South America. The number of cases has dropped from a peak of 24 million in 1984 to a current estimate of 6-7 million. Incident cases are estimated at 30,000 infections per year, including 8,000 newborns from vertical transmission. Chagas disease causes 10,000-12,000 deaths annually. This is likely an underestimate as long-term complications of Chagas disease as a cause of death may not be properly attributed to undiagnosed, chronically infected persons.

Infection is divided into two main phases: acute and chronic (Table 333.1). **Acute infection** can manifest as fever, lymphadenopathy, organomegaly, myocarditis, and meningoencephalitis but is otherwise asymptomatic in up to 95% of infected individuals. **Chronic infection** in 60–70% of patients is *indeterminate,* meaning the patient is asymptomatic but has a positive antibody titer. Approximately 30% of infected persons proceed to chronic determinate or symptomatic *T. cruzi* infection.

The *T. cruzi* genome has been fully sequenced and contains 12,000 genes, the most widely expanded among trypanosomatids, and may reflect its ability to invade virtually any nucleated cell type within reach. Significant variability is present, along with extensive epigenetic modification of surface proteins, which may contribute to immune evasion. Seven genetic lineages, known as *discrete typing units* (DTUs) are recognized. These are referred to as TcI through TcVI, and Tcbat for

Table 333.1 Clinical Features and Diagnosis of Chagas Disease

	GEOGRAPHIC DISTRIBUTION	CLINICAL SIGNS/SYMPTOMS	DIAGNOSIS
ACUTE FORMS*			
Vectorial	Endemic countries	• Incubation period: 1-2 wk • Signs of portal of entry: indurated cutaneous lesion (chagoma) or palpebral edema (Romaña sign) • Most cases are mild disease (95–99%) and unrecognized • Persistent fever, fatigue, lymphadenopathy, hepatomegaly, splenomegaly, morbilliform rash, edema • In rare cases, myocarditis or meningoencephalitis • Anemia, lymphocytosis, elevated AST/ALT concentrations • Risk of mortality: 0.2–0.5%	• Direct parasitologic methods: patent parasitemia up to 90 days • Microscopic examination of fresh blood, Giemsa-stained thin and thick blood films, or buffy coat • Concentration methods: microhematocrit and Strout method PCR techniques • Serology is not useful
Congenital	Endemic and nonendemic countries	• Incubation period: birth to several weeks • Most are asymptomatic or have mild disease • Prematurity, low birthweight, abortion, neonatal death • Fever, jaundice, edema, hepatomegaly, splenomegaly, respiratory distress syndrome, myocarditis, meningoencephalitis • Anemia and thrombocytopenia • Risk of mortality: <2%	• Direct parasitologic methods • Concentration methods: microhematocrit, Strout method • Direct microscopy also useful • PCR: most sensitive technique • Serology: after 9 mo or later
Oral	Restricted areas of endemic countries (Amazon basin) and local outbreaks	• Incubation period: 3-22 days • Fever, vomiting, periocular edema, dyspnea, fever, myalgia, prostration, cough, splenomegaly, hepatomegaly, chest pain, abdominal pain, digestive hemorrhage • Risk of mortality: 1–35%	Same as for vectorial
Transfusion and transplant	Endemic and nonendemic countries	• Incubation period: 8-160 days; persistent fever • Clinical characteristics similar to those of vectorial cases (excluding portal of entry signs) • Risk of mortality is variable and depends on the severity of baseline disease	• Same as for vectorial • PCR techniques usually yield positive results days to weeks before trypomastigotes are detectable in blood • Tissue samples are needed in some circumstances
Reactivation in HIV-infected patients	Endemic and nonendemic countries	• Behaves as other opportunistic infections • Reactivation with <200 CD4 cells/μL (mostly with <100) • Affects CNS (75–90%) as single or multiple space-occupying lesions or as severe necrohemorrhagic meningoencephalitis • Cardiac involvement (10–55%): myocarditis, pericardial effusion or worsening of previous cardiomyopathy • Risk of mortality: 20%	• Direct parasitologic methods, as in vectorial cases • Parasite can be found in CSF, other body fluids, and tissue samples • PCR: not useful for diagnosis of reactivation • Serology: indicative of chronic infection and helpful in cases of suspected disease
Reactivation in other immunosuppressed patients	Endemic and nonendemic countries	• Reactivation after transplantation or in patients with hematologic malignancies • Clinical characteristics similar to those of patients who undergo transfusion and those with panniculitis and other skin disorders • Risk of mortality is variable and depends on severity of baseline disease and prompt diagnosis	• Direct parasitologic methods, as in vectorial cases • Parasite can be found in tissue samples • PCR: increasing parasite load detected with real-time PCR in serial specimens could be indicative of a high risk of reactivation
CHRONIC FORMS			
Indeterminate	Endemic and nonendemic countries	• Asymptomatic • Normal chest radiograph and 12-lead ECG	• Serology: detection of IgG • PCR: low sensitivity

Table 333.1 Clinical Features and Diagnosis of Chagas Disease—cont'd

	GEOGRAPHIC DISTRIBUTION	CLINICAL SIGNS/SYMPTOMS	DIAGNOSIS
Cardiac and gastrointestinal	Endemic and nonendemic countries	• Cardiac manifestations: fatigue, syncope, palpitations, dizziness, stroke; late manifestations: chest pain (atypical), dyspnea, edema, left ventricular dysfunction, congestive heart failure; alterations in 12-lead ECG, echocardiography, or other heart function tests • Gastrointestinal: dysphagia, regurgitation, severe constipation (dilated esophagus or colon); alterations in esophageal manometry, barium swallow, or barium enema	• Serology: detection of IgG • PCR: low sensitivity

*Including reactivation in immunosuppressed patients.
ALT, Alanine transaminase; AST, aspartate transaminase; CNS, central nervous system; CSF, cerebrospinal fluid; PCR, polymerase chain reaction.
From Pérez-Molina J, Molina I. Chagas disease. *Lancet*. 2018;391:82–92. Table 2.

the seventh DTU. DTUs may differ in geographic distribution and predominant vector and hosts and may also vary in disease manifestations and response to treatment. A recent meta-analysis showed that TcI, the most widespread DTU, may be less susceptible to benznidazole.

T. cruzi infection is primarily a zoonosis, and humans are incidental hosts. *T. cruzi* has a large sylvan reservoir and has been isolated from numerous animal species. The presence of reservoirs and vectors of *T. cruzi* and the socioeconomic and educational levels of the population are the most important risk factors for vector-borne transmission to humans. Insect vectors are found in rural, wooded areas and acquire infection through ingestion of blood from humans or animals with circulating trypomastigotes.

Housing conditions are very important in the transmission chain. Incidence and prevalence of infection depend on the adaptation of the triatomines to human dwellings, as well as the vector capacity of the species. Animal reservoirs of reduviid bugs include dogs, cats, rats, opossum, guinea pigs, monkeys, bats, and raccoons. Humans often become infected when land in enzootic areas is developed for agricultural or commercial purposes. An estimated 240,000 to 350,000 immigrants from endemic countries living in the United States are likely infected with *T. cruzi*. Seventy-six cases of **autochthonous** transmission in the United States have also been reported from 2000 to 2018; more than half of the cases were described in Texas.

The risk of congenital Chagas disease transmission is 1–5%. Heavy parasite loads are associated with higher risk of vertical transmission. Transplacental infection is associated with premature birth, fetal wastage, hepatomegaly, and anemia. Infected infants are mostly asymptomatic at birth, although 10–40% may have signs suggestive of congenital infection. Untreated infected infants are at risk for developing Chagas cardiomyopathy later in life.

Disease transmission can occur through blood transfusions in endemic areas from asymptomatic blood donors. The risk for transmission through a single blood transfusion from a chagasic donor is 13–23%. Blood screening for Chagas disease in the United States has detected 2,462 confirmed cases between 2007 and 2019 (www.aabb.org).

Percutaneous injection from laboratory accidents is a documented mode of transmission. Oral transmission through **contaminated food** can occur. Although transmission from breastfeeding is uncommon, women with acute infections should not nurse until they have been treated.

PATHOGENESIS

Acute Disease

At the site of entry or puncture site, neutrophils, lymphocytes, macrophages, and monocytes infiltrate. *T. cruzi* organisms are engulfed by macrophages and are sequestered in membrane-bound vacuoles. Trypanosomes lyse the phagosomal membrane, escape into the cytoplasm, and replicate. A local tissue reaction, the **chagoma**, develops and the process extends to a local lymph node (see Fig. 333.2). Blood forms appear, and the process disseminates. A multitude of innate response mechanisms are deployed at the beginning of infection but are largely ineffective for controlling invasion. However, this initial response is essential for setting up the more potent subsequent adaptive response. Peak parasite numbers are seen after 2-3 weeks and drop quickly when the adaptive immune response comes into play. This response, while efficient at clearing up to 95% of the parasites, is not sterilizing and parasites can persist in more susceptible tissues such as muscle and ganglion cells.

Chronic Disease

The pathophysiology of chronic Chagas disease involves several mechanisms and most significantly affects two main target organs: the heart and the GI tract. Development of pathology in these organs is linked to parasite tropism and persistence in susceptible tissue types against the background of an otherwise effective *T. cruzi*–specific systemic immune response.

In the case of cardiac pathology, parasite-dependent myocardial damage plays some role because of invasion of myocardial cells. The extent of injury seems to be less severe compared to acute disease, and its actual proportional contribution to overall tissue destruction is unclear. Additional damage comes from chronic immune-mediated myocardial injury as a result of delayed type IV hypersensitivity to parasite persistence in myocardial cells. This causes mononuclear myocarditis and myocytolysis, leading to fibrosis and contributing to the development of cardiomyopathy. Dysautonomia due to direct damage to ganglion cells and antineuronal autoimmune reactions leads to the development of cardiomyopathy as an effect of excess catecholamine stimulation. This phenomenon in turn increases myocardial irritability resulting in a higher risk of malignant arrhythmias and sudden cardiac death. Microvascular disturbances also further exacerbate cardiac damage from intimal proliferation and fibrosis due to parasite-induced perivascular inflammation and cell necrosis.

In patients with GI tract involvement, myenteric plexus destruction leads to pathologic organ dilation. There is a diminution in the Auerbach and the Meissner plexus, as well as preganglionic lesions and a reduction in the number of dorsal motor nuclear cells of the vagus nerve. Loss of ganglia in the esophagus results in abnormal dilation.

Antibodies involved in resistance to *T. cruzi* invasion are related to the phase of infection. IgG antibodies to several major surface antigens mediate immunophagocytosis of *T. cruzi* by macrophages. Activation

of autoreactive T- and B-cell clones (with B-cell clones resulting in the production of autoantibodies) is a well-described phenomenon during *T. cruzi* infection. However, the contribution of this activation to pathology seems to be dependent on persistence of infection. Conditions that depress cell-mediated immunity increase the severity of *T. cruzi* infection. There is evidence that host genetic factors play a significant role in progression and severity of chronic disease.

CLINICAL MANIFESTATIONS

Acute Chagas disease in children is usually asymptomatic or is associated with mild febrile illness characterized by malaise, facial edema, and lymphadenopathy (see Table 333.1). Infants often demonstrate local signs of inflammation at the site of parasite entry, which is then referred to as a **chagoma**. Approximately 50% of children come to medical attention with the **Romaña sign** (unilateral, painless eye swelling), conjunctivitis, and preauricular lymphadenitis. Patients complain of fatigue and headache. Fever can persist for 4-5 weeks. More severe systemic presentations can occur in children <2 years old and may include lymphadenopathy, hepatosplenomegaly, and meningoencephalitis. A cutaneous morbilliform eruption can accompany the acute syndrome. Anemia, lymphocytosis, hepatitis, and thrombocytopenia have also been described.

The heart, central nervous system (CNS), peripheral nerve ganglia, and reticuloendothelial system are often heavily parasitized. The heart is the primary target organ. The intense parasitism can result in acute inflammation and in four-chamber cardiac dilation.

Intrauterine infection in pregnant women can cause spontaneous abortion or premature birth. In children with congenital infection, severe anemia, hepatosplenomegaly, jaundice, and seizures can mimic congenital cytomegalovirus infection, toxoplasmosis, and erythroblastosis fetalis. *T. cruzi* can be visualized in the cerebrospinal fluid in cases of meningoencephalitis. Children usually undergo spontaneous remission in 8-12 weeks and enter the indeterminate chronic phase with lifelong low-grade parasitemia and development of antibodies to many *T. cruzi* cell surface antigens. In acute disease, mortality is 5–10%, with deaths caused by acute myocarditis, with resultant heart failure, or meningoencephalitis. Acute Chagas disease should be differentiated from malaria, schistosomiasis, visceral leishmaniasis, brucellosis, typhoid fever, and infectious mononucleosis.

Autonomic dysfunction and peripheral neuropathy can occur. CNS involvement in Chagas disease is uncommon. If granulomatous encephalitis occurs during acute infection, it is usually fatal.

Chronic Chagas disease may be asymptomatic or symptomatic. The most common presentation of chronic *T. cruzi* infection is **cardiomyopathy,** manifested by congestive heart failure, arrhythmia, and thromboembolic events. ECG abnormalities include partial or complete atrioventricular block and right bundle branch block. Left bundle branch block is unusual. Myocardial infarction has been reported and may be secondary to left apical aneurysm embolization or necrotizing arteriolitis of the microvasculature. Left ventricular apical aneurysms are pathognomonic of chronic chagasic cardiomyopathy.

GI manifestations of chronic Chagas disease occur in 8–10% of patients. Characteristically, this involvement presents clinically as megaesophagus and megacolon. Sigmoid dilation, volvulus, and fecalomas are often found in **megacolon**. **Megaesophagus** presents as dysphagia, odynophagia, and cough. The esophagus can reach up to 26 times its normal weight and hold up to 2 L of excess fluid. Esophageal body abnormalities occur independently of lower esophageal dysfunction. Megaesophagus can lead to esophagitis and cancer of the esophagus. Aspiration pneumonia and pulmonary tuberculosis are also more common in patients with megaesophagus.

Immunocompromised Persons

T. cruzi infections in immunocompromised persons may be caused by **transmission** from an asymptomatic donor of blood products or **reactivation** of prior infection. Organ donation to allograft recipients can result in a devastating form of the illness. Cardiac transplantation for Chagas cardiomyopathy has resulted in reactivation, despite prophylaxis and postoperative treatment with benznidazole. HIV infection also leads to reactivation in about 20% of cases; cerebral lesions are more common in these patients and can mimic *Toxoplasma* encephalitis. Myocarditis is also frequently observed, and secondary prophylaxis may be of benefit in some HIV–co-infected patients. In immunocompromised patients at risk for reactivation, serologic testing and close monitoring are necessary.

DIAGNOSIS

A careful history with attention to geographic origin and travel is important. A peripheral blood smear or a Giemsa-stained smear during the acute phase of illness may show motile trypanosomes, which is diagnostic for Chagas disease (see Fig. 333.1). These are only seen in the first 6-12 weeks of illness. Buffy coat smears may improve yield.

Most persons seek medical attention during the chronic phase of the disease, when parasites are not found in the bloodstream and clinical symptoms are not diagnostic. Serologic testing is used for diagnosis, most commonly enzyme-linked immunosorbent assay (ELISA), indirect hemagglutination, and indirect fluorescent antibody testing. No single serology test is sufficiently reliable to make the diagnosis, so repeat or parallel testing using a different method or antigen is required to confirm the result of an initial positive serologic test, and in the case of discordant results, a third test may be employed. Two tests, the Ortho *T. cruzi* ELISA Test System and the Abbott Prism Chagas Assay, are approved by the U.S. Food and Drug Administration (FDA) for screening of blood donors but not for clinical samples. For clinical samples in suspected Chagas cases in the United States, contact the Centers for Disease Control and Prevention (CDC) for further guidance. Confirmatory tests include the radiologic immunoprecipitation assay (Chagas RIPA, currently for research or limited clinical testing only) and Western blot assays based on trypomastigote excreted-secreted antigens (TESA-WB). The Abbott Enzyme Strip Assay Chagas (ESA-Chagas) using recombinant *T. cruzi* antigens is the only FDA-approved confirmatory test in the United States.

Nonimmunologic methods of diagnosis are available. Mouse inoculation and **xenodiagnosis** (allowing uninfected reduviid bugs to feed on a patient's blood and examining the intestinal contents of those bugs 30 days after the meal) are cumbersome and not routinely performed. Parasites can be cultured in Novy-MacNeal-Nicolle (NNN) media. Polymerase chain reaction (PCR) tests of nuclear and kinetoplast DNA sequences have been developed and can be highly sensitive in acute disease but are less reliable in chronic disease. PCR has been used as an early indicator of treatment failure in therapeutic clinical trials, and to detect reactivation in chronically infected patients at risk because of immunosuppression. PCR is not sufficiently sensitive for blood screening. Moreover, there is significant variability among methods and parasite strains. Diagnosis of congenital transmission in newborns cannot be made at birth with serology because of the presence of maternal antibodies in the first 6 months of life. Microscopic examination, parasite culture, or PCR can be used. However, a serologic test at 6-12 months is recommended to exclude infection definitively.

TREATMENT

Biochemical differences between the metabolism of American trypanosomes and that of mammalian hosts have been exploited for chemotherapy. Trypanosomes are very sensitive to oxidative radicals and do not possess catalase or glutathione reductase/glutathione peroxidase, which are key enzymes in scavenging free radicals. All trypanosomes also have an unusual, reduced nicotinamide adenine dinucleotide phosphate (NADPH)–dependent disulfide reductase. Drugs that stimulate hydrogen peroxide (H_2O_2) generation or prevent its utilization are potential trypanosomicidal agents. Other biochemical pathways

that have been targeted include ergosterol synthesis using azole compounds and the hypoxanthine-guanine phosphoribosyltransferase pathway using allopurinol.

Drug treatment for *T. cruzi* infection is currently limited to nifurtimox and benznidazole. Both are effective against trypomastigotes and amastigotes and have been used to eradicate parasites in the acute stages of infection. Treatment responses vary according to the phase of Chagas disease, duration of treatment, dose, age of the patient, and geographic origin of the patient. For acute disease, the average cure rate is about 60–80%. Cure of chronic disease is difficult to assess due to the different definitions of cure, whether with a negative serology or quantitative PCR. Other drugs that have been tried include posaconazole, ravuconazole, and fexinidazole but have not been as successful as traditional treatment.

Benznidazole, a nitroimidazole derivative, is the most effective treatment for Chagas disease. Benznidazole's primary mechanism of action involves covalent binding with trypanosomal protein thiols and low molecular weight thiols, resulting in depletion of these molecules and disruption of the parasite metabolism. The recommended treatment regimen for children 2-12 years old is 5-8 mg/kg/day orally (PO), which can be divided twice daily (bid) for 60 days. For those >12 years old, 5-7 mg/kg/day for 60 days is recommended. The tablets can be administered as a slurry for children who have difficulty swallowing. A recent meta-analysis suggests a 30-day regimen may be noninferior to a 60-day regimen. Cure rates for chronic disease as assessed by PCR is 66–91% at the end of treatment, but this drops to 82% at 1 year, 55% at 2 years, and 47% at 5 years. This drug is associated with significant toxicity, including rash, photosensitivity, peripheral neuritis, granulocytopenia, and thrombocytopenia.

Nifurtimox generates highly toxic oxygen metabolites through the action of nitroreductases, which produce unstable nitroanion radicals, which in turn react with oxygen to produce peroxide and superoxide free radicals. The FDA recently approved nifurtimox for the treatment of Chagas disease in pediatric patients from birth to <18 years of age and weighing at least 2.5 kg. The recommended total daily dose in pediatric patients is 10-20 mg/kg/day orally divided into three doses for 60 days for children <40 kg, and 8-10 mg/kg/day orally divided into three doses for children >40 kg. Nifurtimox has been associated with weakness, anorexia, GI disturbances, toxic hepatitis, tremors, seizures, and hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency.

With the adoption by WHO of control and elimination strategies for Chagas disease, both acute and chronic disease should be treated. Serologic conversion is seen as an appropriate treatment response for chronic disease, although some patients who achieve this still eventually develop symptoms. One study reported cure rates as high as 97% for chronic disease in patients <16 years old and supports early and aggressive case findings and treatment. Infants suspected of congenitally acquired Chagas disease should be properly evaluated and treated immediately upon confirmation of the diagnosis. Women who give birth to infants with congenital Chagas disease should be offered treatment to prevent congenital transmission in subsequent pregnancies. Continuing efforts for elimination will necessitate development of more accurate diagnostics and more effective drugs, particularly for chronic disease.

Treatment of congestive heart failure is generally in line with recommendations for management of dilated cardiomyopathy from other causes. β-Adrenergic blockers have been validated in the management of these patients. Digitalis toxicity occurs frequently in patients with Chagas cardiomyopathy. Pacemakers may be necessary in cases of severe heart block. Although cardiac transplantation has been used successfully in chagasic patients, it is reserved for those with the most severe disease manifestations. Plasmapheresis to remove antibodies with adrenergic activity has been proposed for refractory patients; this approach has worked in patients with dilated cardiomyopathy from other causes, but its application to Chagas disease is unproved.

A light, balanced diet is recommended for **megaesophagus**. Surgery or dilation of the lower esophageal sphincter treats megaesophagus; pneumatic dilation is the superior mode of therapy. Nitrates and nifedipine have been used to reduce lower esophageal sphincter pressure in patients with megaesophagus. Treatment of **megacolon** is surgical and symptomatic.

In accidental infection when parasitic penetration is certain, treatment should be immediately initiated and continued for 10-15 days. Blood is usually collected and serologic samples tested for seroconversion at 15, 30, and 60 days.

PREVENTION

Massive coordinated vector control programs under the auspices of WHO and the Pan-American Health Organization and the institution of widespread blood donor screening and targeted surveillance of chronically infected mothers and infants at risk have effectively eliminated or at least drastically reduced transmission in most endemic countries. Chagas disease remains linked to poverty; thus improvement of living conditions is likewise essential to successful control and eradication. Education of residents in endemic areas, use of bed nets, use of insecticides, and destruction of adobe houses that harbor reduviid bugs are effective methods to control the bug population. Synthetic pyrethroid insecticides help keep houses free of vectors for up to 2 years and have low toxicity for humans. Paints incorporating insecticides have also been used.

Because immigrants can carry this disease to nonendemic areas, serologic testing should be performed in blood and organ donors from endemic areas. Potential seropositive donors can be identified by determining whether they have been or have spent extensive time in an endemic area. Questionnaire-based screening of potentially infected blood and organ donors from areas endemic for infection can reduce the risk for transmission. Seropositivity should be considered a contraindication to organ donation, particularly for heart transplantation.

Prophylactic and therapeutic vaccine development is being pursued but is hampered by the ability of the parasite to evade immune mechanisms and persist in different body compartments. Nucleic acid–based techniques and viral vectors are being explored, along with novel adjuvants and strategies for addressing significant genetic variability among the DTUs.

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Chapter 334

Malaria *(Plasmodium)*

Chandy C. John and Robert O. Opoka

Malaria is a vector-borne disease caused by intraerythrocytic protozoa of the genus *Plasmodium* and transmitted by an infective female *Anopheles* mosquito. Malaria is an acute illness characterized by paroxysms of fever, chills, sweats, fatigue, anemia, and splenomegaly. It has played a major role in human history, causing harm to more people than perhaps any other infectious disease. Although substantial progress has been made in combating malaria in endemic areas, with a 22% reduction in malaria incidence since 2010, malaria remains one of the leading causes of morbidity and mortality worldwide, with an estimated 229 million cases and 409,000 deaths in 2019. Malarial deaths in areas of high malaria transmission occur primarily in children <5 years of age, but in areas of low transmission, a large percentage of

deaths may occur in older children and adults. Although malaria is not endemic in the United States, 1,500-2,000 imported cases are seen in the United States each year. Physicians practicing in non-endemic areas should consider the diagnosis of malaria in any febrile child who has returned from a malaria-endemic area within the previous year, because delay in diagnosis and treatment can result in severe illness or death.

ETIOLOGY

Malaria is caused by intracellular *Plasmodium* protozoa transmitted to humans by female *Anopheles* mosquitoes. Before 2004, only four species of *Plasmodium* were known to cause malaria in humans: *P. falciparum, P. malariae, P. ovale,* and *P. vivax*. In 2004, *P. knowlesi* (a primate malaria species) was also shown to cause human malaria, and cases of *P. knowlesi* infection have been documented in Malaysia, Indonesia, Singapore, and the Philippines. Malaria also can be transmitted through blood transfusion and use of contaminated needles and transplacentally from a pregnant woman to her fetus. The risk for blood transmission is low in the United States, but may occur through transfusion of whole blood, packed red blood cells (RBCs), platelets, and leukocytes and through organ transplantation.

EPIDEMIOLOGY

Malaria is a major worldwide problem, occurring in 87 countries that comprise approximately half the world's population (Fig. 334.1). Worldwide malaria cases decreased from an estimated 238 million cases in 2010 to 229 million cases of in 2019. The principal areas of transmission are Africa, Asia, and South America. *P. falciparum* and *P. malariae* are found in most malarious areas. *P. falciparum* is the predominant species in Africa, Haiti, and New Guinea. *P. vivax* predominates in Bangladesh, Central America, India, Pakistan, and Sri Lanka. *P. vivax* and *P. falciparum* predominate in Southeast Asia, South America, and Oceania. *P. ovale* is the least common species and is transmitted primarily in Africa. Transmission of malaria has been eliminated in most of North America (including the United States), Europe, and most of the Caribbean, as well as Australia, Chile, Israel, Japan, Lebanon, and Taiwan. In 2021, the World Health Organization (WHO) certified that China had eliminated malaria, a landmark achievement for this area of >1 billion people.

P. falciparum is the parasite most commonly associated with severe illness and death, typically among young children. *P. falciparum* is the predominant species in Africa, Haiti, and New Guinea. Over 99% of cases in Africa are caused by *P. falciparum*, and 94% of all malaria deaths occur in Africa. Previously malarial deaths were predominantly in children under 5 years of age but over the years more older children are being affected, with the percentage of total malaria deaths among children age under 5 years dropping from 84% in 2000 to 67% in 2019. *P. vivax,* contributes to about 3.3% of global malaria. *P. vivax* is responsible for 75% of malaria cases in central America and 50% of cases in Southeast Asia (World Malaria Report 2019).

Most cases of malaria in the United States occur among previously infected visitors to the United States from endemic areas and among U.S. citizens who travel to endemic areas without appropriate chemoprophylaxis. Due to the increase in global travel, the number of imported malaria cases has been increasing over the last 40 years, with 2,161 cases reported in 2017. Most cases were acquired in Africa (87%), with Asia (8%), South America (1.9%), and Central America (1.5%) contributing most remaining cases. Among all cases, *P. falciparum* accounted for the majority of infections (1,523; 70.5%), followed by *P. vivax* (216; 10.0%), *P. ovale* (119; 5.5%), and *P. malariae* (55; 2.6%). Among all reported cases of malaria in 2017, a total of 312 (14.4%) were classified as severe malaria, and 6 of these 312 persons (1.9%) died. Cases peak during the summer travel months. Children comprised 18% of all malaria cases in the United States in 2017, and 39% of pediatric cases occurred in U.S. resident children, 70% of whom were visiting friends or relatives. Severe malaria was more slightly common in children (18.4%) than adults (13.6%).

Local transmission of malaria can rarely occur in the United States, as demonstrated in 2003, when eight cases were diagnosed among non-travelers in Palm Beach, Florida, and as demonstrated again in 2023 in Florida, Texas, and Maryland. These cases may result from transmission from untreated and often asymptomatic infected individuals from malaria-endemic countries who travel to the United States and infect local mosquitoes or from infected mosquitoes from malaria-endemic areas that are transported to the United States on airplanes. Transfusion-transmitted malaria can also occur in the United States.

PATHOGENESIS

Plasmodium species exist in a variety of forms and have a complex life cycle that enables them to survive in different cellular environments in the human host (asexual phase) and the mosquito (sexual phase) (Fig. 334.2). A marked amplification of *Plasmodium,* from approximately 10^2 to as many as 10^{14} organisms, occurs during a two-step process in humans, with the first phase in hepatic cells (pre-erythrocytic phase) and the second phase in the RBCs (erythrocytic phase). The **pre-erythrocytic phase** begins with inoculation of sporozoites into the bloodstream by a female *Anopheles* mosquito. Within minutes the

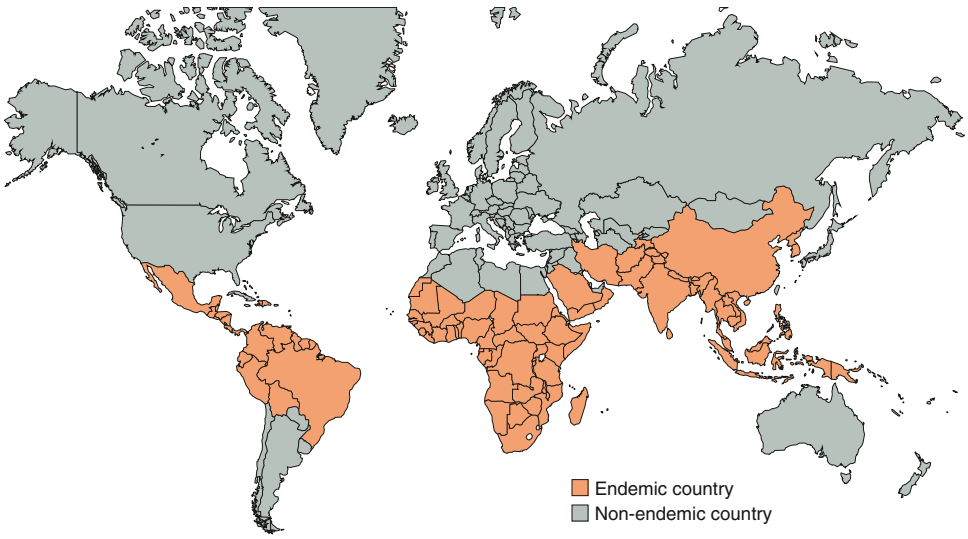


Fig. 334.1 Spatial distribution of malaria in the Eastern and Western hemispheres. In this map, countries with areas endemic for malaria are shaded completely even if transmission occurs only in a small part of the country. For more specific within-country malaria transmission information, see the Yellow Fever & Malaria Information, by Country section in in the Centers for Disease Control and Prevention (CDC) link in this caption. *(From Tan RK, Arguin PM. Malaria. In Centers for Disease Control and Prevention. CDC Yellow Book 2020: Health Information for International Travel. New York: Oxford University Press; 2017. Maps 4.8 and 9* https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-related-infectious-diseases/malaria#5217*)*

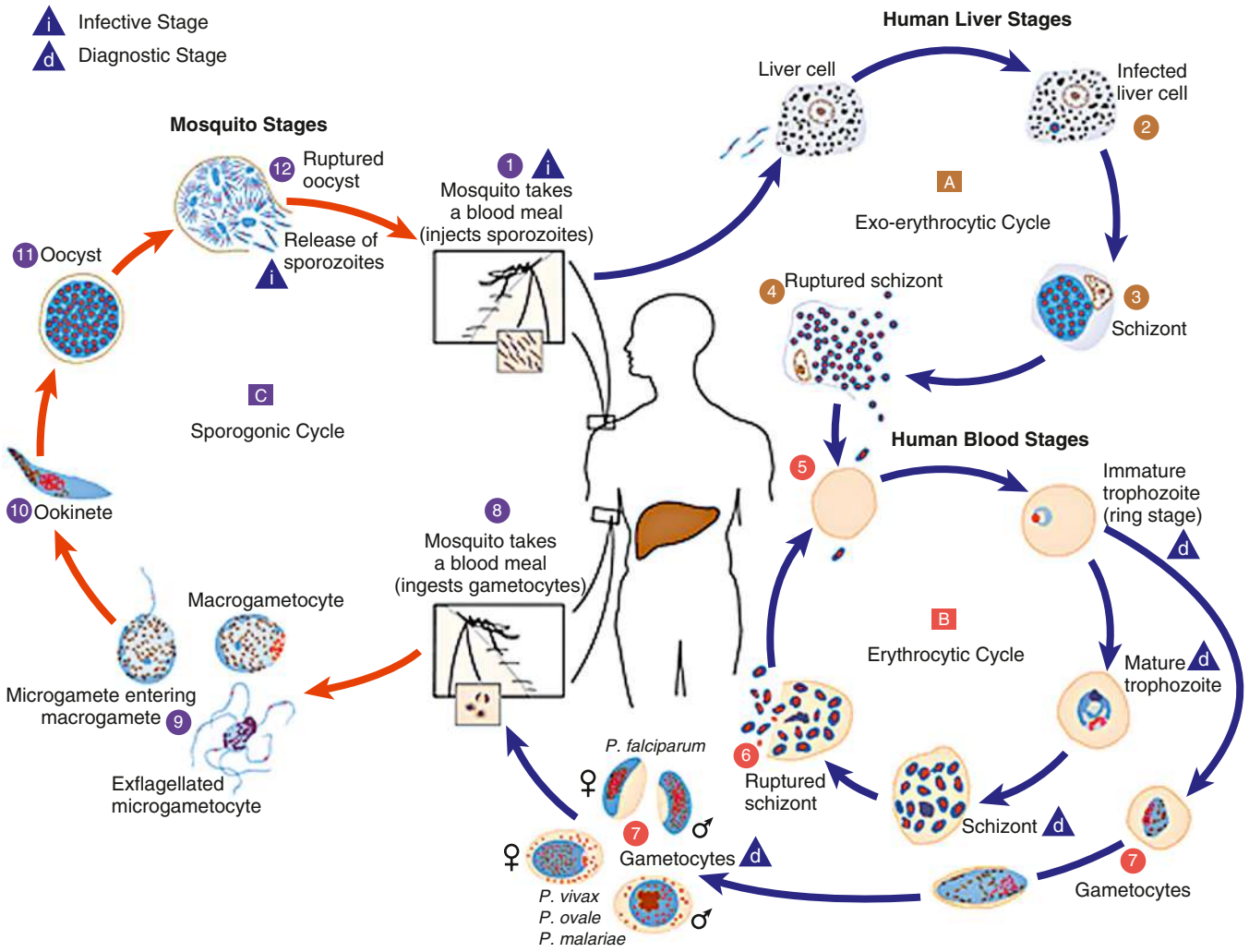


Fig. 334.2 Life cycle of *Plasmodium* spp. *(From Centers for Disease Control and Prevention. Laboratory diagnosis of malaria: Plasmodium spp. https://www.cdc.gov/dpdx/malaria/index.html)*

sporozoites enter the hepatocytes of the liver, where they develop and multiply asexually as a **schizont.** After 1-2 weeks, the hepatocytes rupture and release thousands of merozoites into the circulation. The tissue schizonts of *P. falciparum, P. malariae,* and apparently *P. knowlesi* rupture once and do not persist in the liver. There are two types of tissue schizonts for *P. ovale* and *P. vivax.* The primary type ruptures in 6-9 days, and the secondary type remains dormant in the liver cell for weeks, months, or as long as 5 years before releasing merozoites and causing relapse of infection. The **erythrocytic phase** of *Plasmodium* asexual development begins when the merozoites from the liver penetrate erythrocytes. Once inside the erythrocyte, the parasite transforms into the **ring form**, which then enlarges to become a **trophozoite.** These latter two forms can be identified with Giemsa stain on blood smear, the primary means of confirming the diagnosis of malaria (Fig. 334.3). The trophozoite multiplies asexually to produce a number of small erythrocytic **merozoites** that are released into the bloodstream when the erythrocyte membrane ruptures, which is associated with fever. Over time, some of the merozoites develop into male and female gametocytes that complete the *Plasmodium* life cycle when they are ingested during a blood meal by the female anopheline mosquito. The male and female gametocytes fuse to form a **zygote** in the stomach cavity of the mosquito. After a series of further transformations, sporozoites enter the salivary gland of the mosquito and are inoculated into a new host with the next blood meal.

Pathophysiology and pathogenesis in malaria differ according to species. Infection with all species leads to **fever,** caused by the host immune response when erythrocytes rupture and release merozoites into the circulation, and **anemia,** caused by hemolysis and bone marrow suppression. Severe malaria is more common in *P. falciparum* because of several processes, including higher-density parasitemia, which may lead to excessive production of proinflammatory cytokines; cytoadherence of *P. falciparum*-infected erythrocytes to the vascular endothelium; and polyclonal activation, resulting in both hypergammaglobulinemia and the formation of immune complexes. **Cytoadherence** of infected erythrocytes to vascular endothelium can lead to obstruction of blood flow and capillary damage, with resultant vascular leakage of blood, protein, and fluid and tissue anoxia. Parasite anaerobic metabolism may also lead to hypoglycemia and metabolic acidosis. The cumulative effects of these pathologic processes may lead to cerebral, cardiac, pulmonary, renal, and hepatic failure.

Immunity after *Plasmodium* sp. infection is incomplete, preventing severe disease but still allowing future infection. In some cases, parasites circulate in small numbers for a long time but are prevented from rapidly multiplying and causing severe illness. Repeated episodes

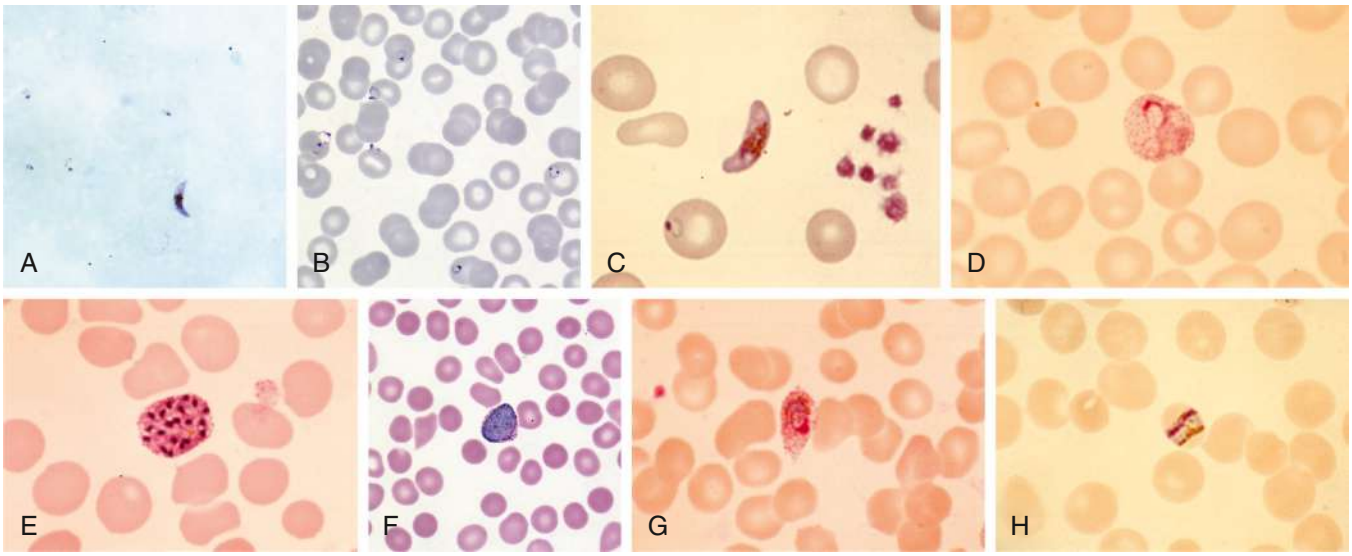


Fig. 334.3 Giemsa-stained thick (A) and thin (B-H) smears used for the diagnosis of malaria and the speciation of *Plasmodium* parasites. A, Multiple signet-ring *Plasmodium falciparum* trophozoites that are visualized outside erythrocytes. B, A multiply infected erythrocyte containing signet-ring *P. falciparum* trophozoites, including an accolade form positioned up against the inner surface of the erythrocyte membrane. C, Banana-shaped gametocyte unique to *P. falciparum*. D, Ameboid trophozoite characteristic of *P. vivax*. Both *P. vivax*– and *P. ovale*–infected erythrocytes exhibit Schüffner dots and tend to be enlarged compared with uninfected erythrocytes. E, *P. vivax* schizont. Mature *P. falciparum* parasites, by contrast, are rarely seen on blood smears because they sequester in the systemic microvasculature. F, *P. vivax* spherical gametocyte. G, *P. ovale* trophozoite. Note Schüffner dots and ovoid shapes of the infected erythrocyte. H, Characteristic band-form trophozoite of *P. malariae*, containing intracellular pigment hemozoin. *(A, B, and F, from Centers for Disease Control and Prevention. DPDx: Laboratory identification of parasites of public health concern.* https://www.cdc.gov/dpdx/malaria/index.html*; C, D, E, G, and H, courtesy David Wyler, Newton Centre, MA.)*

of infection occur because the parasite has developed a number of immune-evasive strategies, such as intracellular replication, vascular cytoadherence that prevents infected erythrocytes from circulating through the spleen, rapid antigenic variation, and alteration of the host immune system resulting in partial immune suppression. The human host response to *Plasmodium* infection includes natural immune mechanisms that prevent infection by other *Plasmodium* spp., such as those of birds or rodents, as well as several alterations in erythrocyte physiology that prevent or modify malarial infection. Erythrocytes containing **hemoglobin S** (sickle erythrocytes) resist malaria parasite growth, erythrocytes lacking Duffy blood group antigen are relatively resistant to *P. vivax*, and erythrocytes containing **hemoglobin F** (fetal hemoglobin) and ovalocytes are resistant to *P. falciparum*. In hyperendemic areas, newborns rarely become ill with malaria, in part because of passive maternal antibody and high levels of fetal hemoglobin. Children 3 months to 2-5 years of age have little specific immunity to malaria species and therefore suffer yearly attacks of debilitating and potentially fatal disease. Immunity is subsequently acquired, and severe cases of malaria become less common. Severe disease may occur during pregnancy, particularly first pregnancies or after extended residence outside the endemic region. Both T-cell and antibody responses are important in development of biologic and clinical immunity to *Plasmodium* spp.

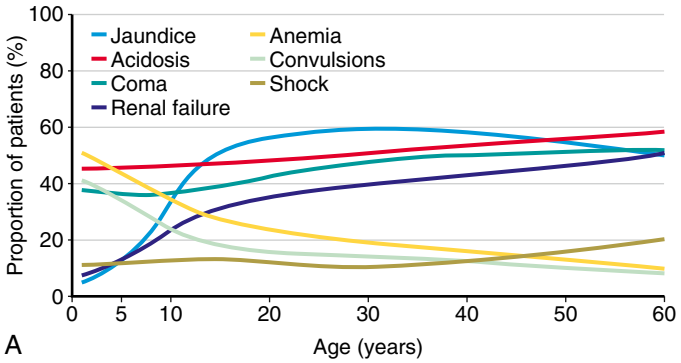
CLINICAL MANIFESTATIONS

Children and adults are asymptomatic during the initial phase of infection, the incubation period of malaria infection. The usual incubation periods are 9-14 days for *P. falciparum,* 12-17 days for *P. vivax,* 16-18 days for *P. ovale,* and 18-40 days for *P. malariae*. The incubation period can be as long as 6-12 months for *P. vivax* and can also be prolonged for patients with partial immunity or incomplete chemoprophylaxis. A prodrome lasting 2-3 days is noted in some patients before parasites are detected in the blood. Prodromal symptoms include headache, fatigue, anorexia, myalgia, slight fever, and pain in the chest, abdomen, and joints.

Children with malaria often lack the typical paroxysms seen in adults (high fever, followed by shaking chills and then diaphoresis) and may have nonspecific symptoms, including fever (may be low grade but is often >40°C [104°F]), headache, drowsiness, anorexia, nausea, vomiting, and diarrhea. Although the rupture of schizonts that occurs every 48 hours with *P. vivax* and *P. ovale* and every 72 hours with *P. malariae* can result in a classic pattern of fevers every other day (*P. vivax* and *P. ovale*) or every third day *(P. malariae),* periodicity is less apparent with *P. falciparum* and mixed infections and may not be apparent early on in infection, when parasite broods have not yet synchronized. Patients with primary infection, such as travelers from non-endemic regions, also may have irregular symptomatic episodes for 2-3 days before regular paroxysms begin, so most travelers presenting with malaria lack a classic malaria fever pattern. Distinctive physical signs may include fever, pallor as a consequence of anemia, and splenomegaly or hepatomegaly. Typical laboratory findings include anemia, thrombocytopenia, and a normal or raised leukocyte count.

P. falciparum is the most severe form of malaria and is associated with higher-density parasitemia and a number of complications (Fig. 334.4). The most common serious complication is severe **anemia**, which also is associated with other malaria species. Serious complications that appear unique to *P. falciparum* include cerebral malaria, respiratory distress from metabolic acidosis, acute renal failure, hypotension, and bleeding diatheses (Table 334.1) (see "Severe Malaria").

The diagnosis of *P. falciparum* malaria in a nonimmune individual constitutes a medical emergency. Severe complications and death can occur if appropriate therapy is not instituted promptly. In contrast to malaria caused by *P. ovale, P. vivax,* and *P. malariae,* which usually result in parasitemias of <2%, malaria caused by *P. falciparum* can be associated with parasitemia levels as high as 60%. The differences in parasitemia reflect that *P. falciparum* infects both immature and mature erythrocytes, whereas *P. ovale* and *P. vivax* primarily infect immature erythrocytes and *P. malariae* infects only mature erythrocytes. Like *P.*



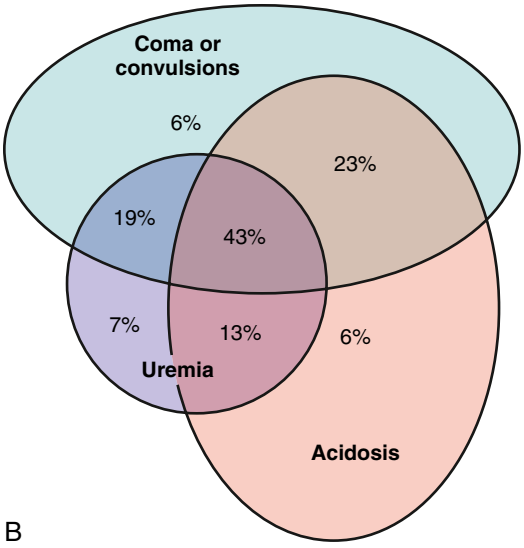


Fig. 334.4 Manifestations of severe falciparum malaria by age (A) and mortality in children associated with central nervous system involvement, acidosis, and uremia (B). Data from 3,228 prospectively studied African children with severe falciparum malaria. *Uremia* here is defined as a blood urea nitrogen >7.14 mmol/L. Surface areas denote the relative prevalence of the different severity signs, which frequently coexist. The percentages denote the observed mortality associated with the presenting signs. *(From White NJ, Pukrittayakamee S, Hien TT, et al. Malaria. Lancet. 2014;383:723–735.)*

Table 334.1 World Health Organization Criteria for Severe Malaria, 2021

SEVERE MALARIA CRITERION	DEFINITION
Impaired consciousness	Glasgow Coma Scale score <11 in adults or Blantyre coma score <3 in children
Prostration	Generalized weakness so that a person is unable to sit, stand, or walk without assistance
Multiple convulsions	More than two episodes of convulsions within 24 hr
Acidosis	A base deficit of >8 mEq/L, a plasma bicarbonate level of <15 mmol/L, or venous plasma lactate ≥5 mmol/L. Severe acidosis manifests clinically as respiratory distress (rapid, deep, labored breathing)
Hypoglycemia	Blood or plasma glucose <40 mg/dL (<2.2 mmol/L)
Severe malarial anemia	Hemoglobin concentration ≤5 g/dL or hematocrit ≤15% in children <12 years of age (<7 g/dL and <20%, respectively, in those ≥12 years) with parasite count >10,000/μL
Renal impairment (acute kidney injury)	Plasma or serum creatinine >3 mg/dL (265 μmol/L) or blood urea >20 mmol/L
Jaundice	Plasma or serum bilirubin >50 μmol/L (3 mg/dL) with a parasite count >100,000/μL (approximately 2%).
Pulmonary edema	Radiographically confirmed or oxygen saturation <92% on room air with respiratory rate >30/min, often with chest indrawing and crepitation on auscultation
Significant bleeding	Includes recurrent or prolonged bleeding from the nose, gums, or venipuncture sites; hematemesis, or melena
Shock	Compensated shock is defined as capillary refill ≥3 sec or temperature gradient on leg (mid to proximal limb) but no hypotension. Decompensated shock is defined as systolic blood pressure <70 mm Hg in children or <80 mm Hg in adults, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill)
Hyperparasitemia	*P. falciparum* parasitemia >10% (>500,000/μL)

falciparum, *P. knowlesi* has a 24-hour replication cycle and can also lead to very high density parasitemia.

P. vivax malaria has long been considered less severe than *P. falciparum* malaria, but recent reports suggest that in some areas it is as frequent a cause of severe disease and death as *P. falciparum*. Severe disease and death from *P. vivax* are usually caused by severe anemia and sometimes splenic rupture. *P. ovale* malaria is the least common type of malaria. It is similar to *P. vivax* malaria and usually is found in conjunction with *P. falciparum* malaria. Case reports of worsening *P. ovale* disease with respiratory symptoms and pulmonary infiltrates and/or effusions after antimalarial treatment have been reported, but all resolved with completion of treatment. *P. malariae* is the mildest and most chronic of all malaria infections. **Nephrotic syndrome** is a rare complication of *P. malariae* infection that is not observed with any other human malaria species. Nephrotic syndrome associated with *P. malariae* infection is poorly responsive to corticosteroids. Low-level, undetected *P. malariae* infection may be present for years and is sometimes unmasked by immunosuppression or physiologic stress such as splenectomy or corticosteroid treatment. *P. knowlesi* malaria is most often uncomplicated but can lead to severe malaria and death if high-density parasitemia is present.

The definition of severe *P. vivax* or *P. ovale* malaria is the same as that of severe falciparum malaria except that there are no parasite density thresholds. The definition of severe malaria due to *P. knowlesi* differs from that of severe falciparum malaria; the threshold parasite density is >100,000/μL (alone) or >20,000/μL in patients with jaundice.

Recrudescence after a primary attack may occur from the survival of erythrocyte forms in the bloodstream. Long-term relapse is caused by release of merozoites from a pre-erythrocytic source in the liver, which occurs with *P. vivax* and *P. ovale*, or from persistence within the erythrocyte, which occurs with *P. malariae* and rarely with *P. falciparum*. A history of typical symptoms in a person >4 weeks after return from an endemic area is therefore more likely to be *P. vivax*, *P. ovale*, or *P. malariae* infection than *P. falciparum* infection. In the most recent survey of malaria in the United States (2013) by the CDC, among individuals in whom a malaria species was identified, 61% of cases were caused by *P. falciparum*,14% by *P. vivax*, 2% by *P. malariae*, 4% by *P. ovale*, and 2% by mixed-species infection; 94% of *P. falciparum* infections were diagnosed within 30 days of arrival in the United States,

and 99% within 90 days of arrival. In contrast, 54% of *P. vivax* cases occurred >30 days after arrival in the United States.

Congenital malaria is acquired from the mother prenatally or perinatally but is rarely reported in the United States. Congenital malaria usually occurs in the offspring of a nonimmune mother with *P. vivax* or *P. malariae* infection, although it can be observed with any of the human malaria species. The first sign or symptom typically occurs between 10 and 30 days of age (range: 14 hours to several months of age). Signs and symptoms include fever, restlessness, drowsiness, pallor, jaundice, poor feeding, vomiting, diarrhea, cyanosis, and hepatosplenomegaly. **Malaria in pregnancy** is a major health problem in malaria-endemic countries, can be severe, and is associated with adverse outcomes in the fetus or neonate, including intrauterine growth restriction and low birthweight, even in the absence of transmission from mother to child.

Severe Malaria

WHO has identified 12 complications of *P. falciparum* malaria that define severe malaria (see Table 334.1 and Fig. 334.4). The most common complications in children are severe anemia, impaired consciousness (including cerebral malaria), respiratory distress (a result of metabolic acidosis), acute kidney injury, multiple seizures, prostration, and jaundice. A more complete discussion of severe malaria is provided in the treatment section (see "Treatment of Severe Malaria"), where treatment for these complications is also described.

DIAGNOSIS

Any child who presents with fever or unexplained systemic illness and has traveled or resided in a malaria-endemic area within the previous year should be evaluated for malaria. Malaria should be considered regardless of the use of chemoprophylaxis. Important criteria that suggest *P. falciparum* malaria include symptoms occurring <1 month after return from an endemic area, >2% parasitemia, ring forms with double-chromatin dots, and erythrocytes infected with greater than one parasite.

The diagnosis of malaria is established by identification of organisms on Giemsa-stained smears of peripheral blood (see Fig. 334.3) or by rapid immunochromatographic assay (rapid diagnostic test). Giemsa stain is superior to Wright stain or Leishman stain. Both thick and thin blood smears should be examined. The concentration of erythrocytes on a **thick smear** is 20-40 times that on a thin smear and is used to quickly scan large numbers of erythrocytes. The **thin smear** allows for positive identification of the malaria species and determination of the percentage of infected erythrocytes and is useful in following the response to therapy. Identification of the species is best made by an experienced microscopist and checked against color plates of the various *Plasmodium* spp. (see Fig. 334.3). Morphologically, it is impossible to distinguish *P. knowlesi* from *P. malariae,* so polymerase chain reaction (PCR) detection by a reference laboratory or the CDC is required. Although *P. falciparum* is most likely to be identified from blood just after a febrile paroxysm, most children with malaria will have a positive blood smear regardless of the time the smear is obtained. Most guidelines recommend at least three negative blood smears to rule out malaria in children in whom malaria is strongly suspected, because low-level parasitemia could potentially go undetected early in the illness. However, few data are available on the utility of repeated blood smears for malaria detection, and most case reports and series document a positive initial smear.

The BinaxNOW Malaria test is approved by the U.S. Food and Drug Administration (FDA) for rapid diagnosis of malaria. This immunochromatographic test for *P. falciparum* histidine-rich protein (HRP2) and aldolase is approved for testing for *P. falciparum* and *P. vivax*. **Aldolase** is present in all five of the malaria species that infect humans; thus a positive result for *P. vivax* could be because of *P. ovale* or *P. malariae* infection. Sensitivity and specificity for *P. falciparum* (94–99% and 94–99%, respectively) and *P. vivax* (87–93% and 99%, respectively) are good, but sensitivity for *P. ovale* and *P. malariae* is lower. Sensitivity for *P. falciparum* decreases at lower levels of parasitemia, so microscopy is still advised in areas where expert microscopy is available. The test is simple to perform and can be done in the field or laboratory in 10 minutes. PCR is more sensitive than microscopy but is technically more complex. It is available in some reference laboratories and can be useful for confirmation and for diagnosis of multiple species of malaria. The time delay in availability of results typically precludes its use for acute diagnosis of malaria, but it is useful to send where available, as it can confirm the diagnosis, allow for detection of multiple infections, and detect malaria not detected by standard microscopy because of low levels of parasitemia (particularly nonfalciparum malaria). PCR detection may detect asymptomatic parasitemia in children with very low level parasitemia (e.g., internationally adopted children from malaria-endemic areas), with greater sensitivity than microscopy, and may be the preferred method of detection in these children, who, because they are asymptomatic, do not require immediate treatment.

Differential Diagnosis

The differential diagnosis of malaria is broad. In a child traveler returning to or arriving in the United States from an endemic area, diseases that may mimic malaria include viral infections such as influenza and hepatitis, sepsis, pneumonia, meningitis, encephalitis, endocarditis, gastroenteritis, pyelonephritis, babesiosis, brucellosis, leptospirosis, tuberculosis, relapsing fever, typhoid fever, yellow fever, viral hemorrhagic fevers, amebic liver abscess, neoplasm, and collagen vascular disease. There is also considerable clinical overlap between features of malaria (uncomplicated or severe) and other common bacterial and viral infections. Malaria in child travelers returning to or arriving in the United States is typically the sole reason for the clinical symptoms the child presents with, but the relatively nonspecific presentation may require a larger workup and empiric treatment for other conditions while awaiting testing results.

TREATMENT

Physicians caring for patients with malaria or traveling to endemic areas need to be aware of current information regarding malaria because resistance to antimalarial drugs has complicated therapy and prophylaxis. The CDC website provides excellent guidance on diagnosis and treatment of malaria in individuals in the United States (https://www.cdc.gov/malaria/diagnosis_treatment/diagnosis.html). Specific pages provide general guidelines (https://www.cdc.gov/malaria/diagnosis_treatment/clinicians1.html), a treatment algorithm (https://www.cdc.gov/malaria/resources/pdf/Malaria_Management_Algorithm.pdf, Fig. 334.5), a treatment table for all forms of uncomplicated and severe malaria (https://www.cdc.gov/malaria/resources/pdf/Malaria_Treatment_Table.pdf, Tables 334.2-334.6), and specific guidance on obtaining artesunate, which is now available commercially in the United States as an FDA-approved drug (https://www.cdc.gov/malaria/diagnosis_treatment/artesunate.html) and must be ordered emergently by hospitals that do not have in it stock. Severe malaria care requires infectious diseases consultation. In cases where treatment is unclear or complex, calling the CDC Malaria Hotline is strongly recommended. CDC expert malaria guidance is available to physicians 24 hours a day (844-856-4713, from 9 AM to 5 PM Eastern Time Monday-Friday, and 770-488-7100 at all other times and on holidays; request to speak to the CDC Malaria Branch Expert).

General Principles

Treatment for malaria should be based on laboratory confirmation of the diagnosis. "Presumptive treatment," i.e., without laboratory confirmation, may be required in children with severe disease in a setting where prompt laboratory diagnosis is not available. Once the diagnosis of malaria has been made, appropriate antimalarial treatment should be initiated immediately. Treatment is influenced by multiple factors, including infecting *Plasmodium* species; clinical status of the patient; expected drug susceptibility of the infecting parasite as determined by the geographic area where the infection was acquired; and previous use of antimalarials, including those taken for malaria chemoprophylaxis.

Fever without an obvious cause in any patient who has left a *P. falciparum*–endemic area within 30 days and is nonimmune should be

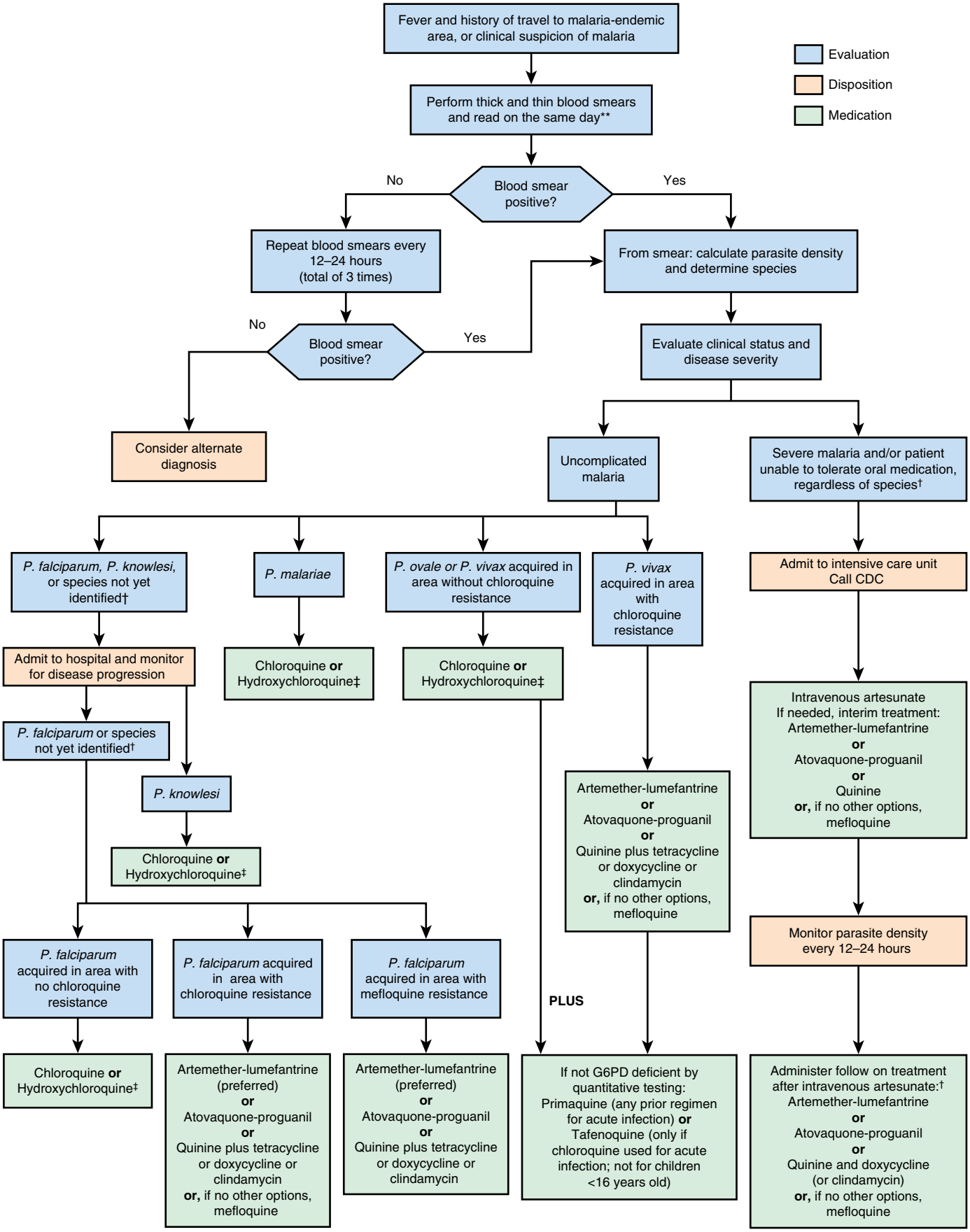


Fig. 334.5 Algorithm for approach to patient with malaria in the United States. Treatment for special populations (children and pregnant women) can be found in the Centers for Disease Control and Prevention (CDC) Treatment Guidelines and Treatment Table at https://www.cdc.gov/malaria/resources/pdf/Malaria_Treatment_Table.pdf. **If rapid diagnostic test performed, smear should also be performed with results available as soon as possible. †If species later identified as *P. vivax* or *P. ovale*, add primaquine if not glucose-6-phosphate (G6PD) deficient by quantitative testing. Tafenoquine can only be used if chloroquine or hydroxychloroquine used for acute infection. ‡Drug options for chloroquine-resistant *P. falciparum* may be used. *(From Centers for Disease Control and Prevention.* http://www.cdc.gov/malaria/resources/pdf/algorithm.pdf*)*

considered a medical emergency. Thick and thin blood smears should be obtained immediately, and all children with symptoms of severe disease should be hospitalized. If negative, blood films should be repeated every 12 hours until three smears are documented as negative. If the patient is severely ill, antimalarial therapy should be initiated immediately. Outpatient therapy generally is not given to nonimmune children but may be considered in immune or semi-immune children who have low-level parasitemia (<1%), no evidence of complications defined by WHO, no vomiting, and a lack of toxic appearance; who are able to contact the physician or emergency department at any time; and in whom follow-up within 24 hours is ensured.

TREATMENT OF UNCOMPLICATED MALARIA

P. falciparum or Species Not Identified: Acquired in Areas with Chloroquine Resistance

Treatment regimens for children with uncomplicated malaria in the United States are summarized in Tables 334.2-334.5. For *P. falciparum* infections acquired in areas with chloroquine resistance, four treatment options are available. These include artemether-lumefantrine (Coartem), which is the preferred option if readily available, and atovaquone-proguanil (Malarone). These are fixed-dose combination therapies that can be used for pediatric patients >5 kg. Quinine sulfate plus doxycycline, tetracycline, or clindamycin is the next treatment option. For the quinine sulfate combination options, quinine sulfate plus either doxycycline or tetracycline is generally preferred to quinine sulfate plus clindamycin because there are more data on the efficacy of quinine plus doxycycline or tetracycline. Quinine should be given for 3 days, except for infections acquired in Southeast Asia where 7 days of treatment is required. The fourth option, mefloquine, is associated with rare but potentially severe neuropsychiatric reactions when used at treatment dose, and it is recommended only if the other options cannot be used.

For infections attributed to "species not identified" in areas with chloroquine resistance that are subsequently diagnosed as being due to *P. vivax* or *P. ovale,* additional treatment with primaquine or tafenoquine should be administered, as described in the section on *P. vivax* and *P. ovale* treatment.

P. falciparum or Species Not Identified: Acquired in Areas Without Chloroquine Resistance

For *P. falciparum* infections acquired in areas without chloroquine-resistant strains, which include Central America west of the Panama Canal, Haiti, and the Dominican Republic, patients can be treated with oral chloroquine. Alternatively, hydroxychloroquine may be used at recommended doses. In addition, any of the regimens listed for the treatment of chloroquine-resistant malaria may be used for the treatment of chloroquine-sensitive *P. falciparum* malaria. Prompt initiation of an effective regimen is vitally important as delay of initiation of treatment may increase the risk of progression to severe disease in patients with *P. falciparum* infection. If infections initially attributed to "species not identified" are subsequently diagnosed as being due to *P. vivax* or *P. ovale,* additional treatment with primaquine or tafenoquine should be administered, as outlined in the sections on *P. vivax* and *P. ovale*.

P. vivax and *P. ovale*

Chloroquine (or hydroxychloroquine) remains an effective choice for *P. vivax* and *P. ovale* infections except for *P. vivax* infections acquired in Papua New Guinea or Indonesia, as there is high prevalence of chloroquine-resistant *P. vivax* in these countries. Rare cases of chloroquine-resistant *P. vivax* have also been documented in Burma (Myanmar), India, and Central and South America. Persons acquiring *P. vivax* infections from regions other than Papua New Guinea or Indonesia should initially be treated with chloroquine. If chloroquine is not available, or if the infection was acquired in an area with a high frequency of chloroquine resistance (Indonesia or Papua New Guinea), artemether-lumefantrine, atovaquone-proguanil, quinine sulfate plus doxycycline or tetracycline or clindamycin, or mefloquine should be used (mefloquine should be used only if the other drugs are not available or contraindicated). If chloroquine is given and the patient has an inadequate response including persistence or worsening of clinical symptoms or no decrease in parasite density, treatment should be changed to one of the regimens recommended for chloroquine-resistant *P. vivax* infections.

In addition to requiring the acute phase treatment of blood-stage parasites, *P. vivax* and *P. ovale* infections can relapse due to hypnozoites, which are dormant forms that remain in the liver. To eradicate the hypnozoites, patients should be treated with either tafenoquine (Krintafel) or primaquine phosphate. If primaquine phosphate is used, the CDC recommends a dose of 30 mg (base) by mouth daily for 14 days for adults, and a dose of 0.5 mg/kg (base) by mouth, to a maximum of 30 mg (base) daily for children.

P. malariae and *P. knowlesi*

There has been no widespread evidence of chloroquine resistance in *P. malariae* and *P. knowlesi* species; therefore chloroquine (or hydroxychloroquine) may still be used for both of these species. In addition, any of the regimens listed previously for the treatment of chloroquine-resistant *P. falciparum* may be used for the treatment of *P. malariae* and *P. knowlesi* infections. Due to the risk of complications among patients with *P. knowlesi,* clinicians should consider hospitalization to monitor clinical response and check parasite density every 12-24 hours until clinical presentation improves and a decrease in parasite density becomes apparent.

TREATMENT OF SEVERE MALARIA

General Principles

Death due to severe malaria can occur within hours of presentation, so prompt assessment and initiation of effective antimalarial therapy is essential. Equally important is the concurrent administration of supportive therapy to manage life-threatening complications of the disease. Supportive measures such as oxygen therapy, blood transfusion, rehydration, control of convulsions, correction of metabolic derangements like hypoglycemia, and institution of antibiotics in children with features of sepsis should be instituted as indicated by clinical findings. Children with severe malaria should be managed in an intensive care unit (ICU).

The risk of death due to severe malaria is greatest in the first 24 hours after clinical presentation. Independent predictors for fatality among African children with severe malaria include acidosis, impaired consciousness, elevated blood urea nitrogen, and acute kidney injury. Early diagnosis and prompt initiation of antimalarial medication and appropriate supportive care can reduce mortality.

Drug treatment guidelines in this chapter are based on treatment for children in the United States (Table 334.6). Children in other areas have other drugs and treatments available, and local or WHO guidelines for malaria treatment are available at https://www.who.int/publications/i/item/guidelines-for-malaria.

Intravenous Antimalarial Therapy for Severe Malaria

Treatment of severe malaria involves initial treatment with intravenous (IV) artesunate, followed by a full dose of effective artemisinin combination therapy (ACT). In the United States, the only FDA-approved treatment for severe malaria is IV artesunate. Quinidine, which was previously approved for treatment of severe malaria, ceased to be manufactured in 2019. Artesunate dosing need not be adjusted for hepatic or renal failure, nor for concomitant or previous therapy with other medications. Artesunate is well tolerated with few side effects. Adverse effects include nausea, vomiting, anorexia, and dizziness, although these may be due to malaria rather than drug toxicity. In nonimmune patients, delayed onset of anemia has been noted in some cases, so patients treated with IV artesunate should be monitored for delayed hemolytic anemia, and repeat hemoglobin testing at 7, 14, and 30 days should be considered.

In the United States, IV artesunate was approved by the FDA through the CDC as part of an expanded-use investigational new drug (IND) protocol in May 2020. As of June 2021, the drug can be obtained through major drug distributors. Healthcare providers treating patients meeting the following criteria and who are unable to obtain

Table 334.2 Treatment of Uncomplicated Malaria: *Plasmodium falciparum* or Unknown Species[1–3] (If Later Diagnosed as *P. vivax* or *P. ovale*, See Table 334.3 for Antirelapse Treatment)

DRUG SUSCEPTIBILITY (BASED ON WHERE ACQUIRED)	RECOMMENDED ADULT REGIMENS	RECOMMENDED PEDIATRIC REGIMENS[4]
Chloroquine resistant or unknown resistance (All malaria-endemic regions except those in Central America west of Panama Canal, Haiti, and Dominican Republic)	A. **Artemether-lumefantrine (Coartem)**[5] (1 tab: 20 mg artemether and 120 mg lumefantrine) Adults: 4 tabs PO per dose Three-day course: Day 1: Initial dose and second dose 8 hr later Days 2 and 3: 1 dose bid B. **Atovaquone-proguanil (Malarone)**[6] (Adult tab: 250 mg atovaquone and 100 mg proguanil) 4 adult tabs PO qd × 3 days C. **Quinine sulfate**[7] **plus doxycycline,**[8] **tetracycline,**[8] **or clindamycin**[9] Quinine sulfate: 542 mg base (650 mg salt) PO tid × 3 or 7 days[7] Doxycycline: 100 mg PO bid × 7 days Tetracycline: 250 mg PO qid × 7 days Clindamycin: 20 mg/kg/day PO divided tid × 7 days D. **Mefloquine**[10] Dose 1: 684 mg base (750 mg salt) PO Dose 2 at 6-12 hr: 456 mg base (500 mg salt) PO	A. **Artemether-lumefantrine (Coartem)**[5] (1 tab: 20 mg artemether and 120 mg lumefantrine) 5 to <15 kg: 1 tab PO per dose 15 to <25 kg: 2 tabs PO per dose 25 to <35 kg: 3 tabs PO per dose ≥35 kg: 4 tabs PO per dose Three-day course: Day 1: Initial dose and second dose 8 hr later Days 2 and 3: 1 dose bid B. **Atovaquone-proguanil (Malarone)**[6] (Adult tab: 250 mg atovaquone and 100 mg proguanil; Peds tab: 62.5 mg atovaquone and 25 mg proguanil) 5 to <8 kg: 2 peds tabs PO qd × 3 days 8 to <10 kg: 3 peds tabs PO qd × 3 days 10 to <20 kg: 1 adult tab PO qd × 3 days 20 to <30 kg: 2 adult tabs PO qd × 3 days 30 to <40 kg: 3 adult tabs PO qd × 3 days ≥40 kg: 4 adult tabs PO qd × 3 days C. **Quinine sulfate**[7] **plus doxycycline,**[8] **tetracycline,**[8] **or clindamycin**[9] Quinine sulfate: 8.3 mg base/kg (10 mg salt/kg) PO tid × 3 or 7 days[7] Doxycycline: 2.2 mg/kg PO bid × 7 days Tetracycline: 25 mg/kg/day PO divided qid × 7 days Clindamycin: 20 mg /kg/day PO divided tid × 7 days D. **Mefloquine**[10] Dose 1: 13.7 mg base/kg (15 mg salt/kg) PO Dose 2 at 6-12 hr: 9.1 mg base/kg (10 mg salt/kg) PO
Chloroquine sensitive[11] (Central America west of Panama Canal, Haiti, and Dominican Republic)	**Chloroquine phosphate (Aralen and generics)** Dose 1: 600 mg base (1,000 mg salt) PO Doses 2-4 (3 additional doses) at 6, 24, and 48 hr: 300 mg base (500 mg salt) PO per dose *OR* **Hydroxychloroquine (Plaquenil and generics)** Dose 1: 620 mg base (800 mg salt) PO Doses 2-4 (3 additional doses) at 6, 24, and 48 hr: 310 mg base (400 mg salt) PO per dose	**Chloroquine phosphate (Aralen and generics)** Dose 1: 10 mg base/kg (16.7 mg salt/kg) PO Doses 2-4 (3 additional doses) at 6, 24, and 48 hr: 5 mg base/kg (8.3 mg salt/kg) PO per dose *OR* **Hydroxychloroquine (Plaquenil and generics)** Dose 1: 10 mg base/kg (12.9 mg salt/kg) PO Doses 2-4 (3 additional doses) at 6, 24, and 48 hr: 5 mg base/kg (6.5 mg salt/kg) PO per dose

[1]qd, once a day; bid, twice a day; tid, three times a day; qid, four times a day; PO, by mouth; tab(s), tablet(s).
[2]If an antimalarial is taken for chemoprophylaxis, a different drug should be used for treatment.
[3]Option A preferred, Options B and C adequate alternatives and should be used if more readily available than Option A. Option D should be used only if other options not available.
[4]Not to exceed adult dose.
[5]Artemether-lumefantrine can be used in second and third trimesters of pregnancy and, if no other options available, in first trimester as well. Not for infants <5 kg or women breastfeeding infants <5 kg.
[6]Atovaquone-proguanil not recommended during pregnancy, in infants <5 kg, or in women breastfeeding infants <5 kg. May be considered if other treatment options not available or not tolerated, and benefits outweigh risks.
[7]Quinine to be given for 3 days, except for infections acquired in Southeast Asia, where 7 days of treatment are required. Quinine available in the United States has 324 mg (salt) per capsule, therefore two capsules for adult dosing. Pediatric dosing may need compounding pharmacy.
[8]Doxycycline or tetracycline combined with quinine preferred due to more efficacy data, but not recommended during pregnancy or in children <8 yr old unless no other options and benefits outweigh risks.
[9]Clindamycin with quinine preferred option for pregnant women and children <8 yr old.
[10]Mefloquine not recommended for infections acquired in Southeast Asia due to drug resistance. Not recommended if other options available or in patients with neuropsychiatric history.
[11]Regimens used to treat chloroquine-resistant *P. falciparum* infections may be used if chloroquine and hydroxychloroquine not available.
From Centers for Disease Control and Prevention. Malaria Treatment Tables. https://www.cdc.gov/malaria/resources/pdf/Malaria_Treatment_Table.pdf

commercially available artesunate within 24 hours should call the CDC Malaria Hotline to obtain IV artesunate.

If artesunate is not immediately available, oral antimalarials can be given while waiting to obtain IV artesunate. Choices include artemether-lumefantrine (preferred), atovaquone-proguanil, quinine sulfate, and mefloquine (Table 334.2).

FOLLOW-UP ORAL ANTIMALARIAL THERAPY FOR SEVERE MALARIA

Parenteral artesunate should be given for three doses over 24 hours at 0, 12, and 24 hours. If parasite density is <1% at 20 hours and the patient can take oral medication, treatment should be completed with an effective oral medication, such as artemether-lumefantrine (preferred),

Table 334.3 Treatment of Uncomplicated Malaria: *P. vivax* or *P. ovale*[1,2]

DRUG SUSCEPTIBILITY (BASED ON WHERE ACQUIRED)	RECOMMENDED ADULT REGIMENS (BOTH ACUTE AND ANTIRELAPSE TREATMENTS RECOMMENDED)	RECOMMENDED PEDIATRIC REGIMENS[3] (BOTH ACUTE AND ANTIRELAPSE TREATMENTS RECOMMENDED)
Chloroquine sensitive (All malaria-endemic regions except Papua New Guinea and Indonesia)	Acute treatment[4]: **Chloroquine phosphate (Aralen and generics)** Dose 1: 600 mg base (1,000 mg salt) PO Doses 2-4 (3 additional doses) at 6, 24, and 48 hr: 300 mg base (500 mg salt) PO per dose *OR* **Hydroxychloroquine (Plaquenil and generics)** Dose 1: 620 mg base (800 mg salt) PO Doses 2-4 (3 additional doses) at 6, 24, and 48 hr: 310 mg base (400 mg salt) PO per dose **AND** **Antirelapse treatment[5]:** Primaquine phosphate[6–8] 30 mg base PO qd × 14 days *OR* **Tafenoquine (Krintafel)**[6,7,9] 300 mg PO × 1 dose	Acute treatment[4]: **Chloroquine phosphate (Aralen and generics)** Dose 1: 10 mg base/kg (16.7 mg salt/kg) PO Doses 2-4 (3 additional doses) at 6, 24, and 48 hr: 5 mg base/kg (8.3 mg salt/kg) PO per dose *OR* **Hydroxychloroquine (Plaquenil and generics)** Dose 1: 10 mg base/kg (12.9 mg salt/kg) PO Doses 2-4 (3 additional doses) at 6, 24, and 48 hr: 5 mg base/kg (6.5 mg salt/kg) PO per dose **AND** **Antirelapse treatment[5]:** Primaquine phosphate[6–8] 0.5 mg base/kg PO qd × 14 days *OR* **Tafenoquine (Krintafel)**[6,7,9] 300 mg PO × 1 dose, only for patients ≥16 yr old
Chloroquine resistant (Papua New Guinea and Indonesia)	Acute treatment: A. **Artemether-lumefantrine (Coartem)**[10] (1 tab: 20 mg artemether and 120 mg lumefantrine) Adults: 4 tabs PO per dose Three-day course: Day 1: Initial dose and second dose 8 hr later Days 2 and 3: 1 dose bid B. **Atovaquone-proguanil (Malarone)**[11] (Adult tab: 250 mg atovaquone and 100 mg proguanil) 4 adult tabs PO qd × 3 days C. **Quinine sulfate**[12] **plus doxycycline,**[13] **tetracycline,**[13] **or clindamycin**[14] Quinine sulfate: 542 mg base (650 mg salt) PO tid × 3 days Doxycycline: 100 mg PO bid × 7 days Tetracycline: 250 mg PO qid × 7 days Clindamycin: 20 mg/kg/day PO divided tid × 7 days D. **Mefloquine**[15] Dose 1: 684 mg base (750 mg salt) PO Dose 2 at 6-12 hr: 456 mg base (500 mg salt) PO **AND** **Antirelapse treatment**[16]**:** **Primaquine phosphate**[17,18,19] 30 mg base PO qd × 14 days	Acute treatment: A. **Artemether-lumefantrine (Coartem)**[10] (1 tab: 20 mg artemether and 120 mg lumefantrine) 5 to <15 kg: 1 tab PO per dose 15 to <25 kg: 2 tabs PO per dose 25 to <35 kg: 3 tabs PO per dose ≥35 kg: 4 tabs PO per dose Three-day course: Day 1: Initial dose and second dose 8 hr later Days 2 and 3: 1 dose bid B. **Atovaquone-proguanil (Malarone)**[11] (Adult tab: 250 mg atovaquone and 100 mg proguanil; peds tab: 62.5 mg atovaquone and 25 mg proguanil) 5 to <8 kg: 2 peds tabs PO qd × 3 days 8 to <10 kg: 3 peds tabs PO qd × 3 days 10 to <20 kg: 1 adult tab PO qd × 3 days 20 to <30 kg: 2 adult tabs PO qd × 3 days 30 to <40 kg: 3 adult tabs PO qd × 3 days ≥40 kg: 4 adult tabs PO qd × 3 days C. **Quinine sulfate**[12] **plus doxycycline,**[13] **tetracycline,**[13] **or clindamycin**[14] Quinine sulfate: 8.3 mg base/kg (10 mg salt/kg) PO tid × 3 days Doxycycline: 2.2 mg/kg PO q12h × 7 days Tetracycline: 25 mg/kg/day PO divided qid × 7 days Clindamycin: 20 mg/kg/day PO divided tid × 7 days D. **Mefloquine**[10] Dose 1: 13.7 mg base/kg (15 mg salt/kg) PO Dose 2 at 6-12 hr: 9.1 mg base/kg (10 mg salt/kg) PO **AND** **Antirelapse treatment**[16]**:** **Primaquine phosphate**[17–19] 0.5 mg base/kg PO qd × 14 days

[1]qd, once a day; bid, twice a day; tid, three times a day; qid, four times a day; PO, by mouth; tab(s), tablet(s).
[2]If an antimalarial is taken for chemoprophylaxis, a different drug should be used for treatment.
[3]Not to exceed adult dose.
[4]Regimens used to treat chloroquine-resistant *P. vivax* infections may be used if chloroquine and hydroxychloroquine not available.
[5]Either option for antirelapse treatment recommended if chloroquine or hydroxychloroquine used for acute treatment. If regimens other than either chloroquine or hydroxychloroquine are used for acute treatment, primaquine is the only option for antirelapse treatment.
[6]Primaquine and tafenoquine associated with hemolytic anemia in those with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Before use, quantitative G6PD testing needed to confirm normal activity. For those with intermediate G6PD deficiency, weekly primaquine may be used (45 mg/wk) for 8 wk with close monitoring for hemolysis. Those with G6PD deficiency may be given chloroquine 300 mg (base) PO weekly for 1 yr from acute infection to prevent relapses.
[7]Primaquine and tafenoquine must not be used during pregnancy; pregnant patients with *P. vivax* and *P. ovale* infections should receive chloroquine 300 mg (base) PO weekly after acute treatment for the remainder of pregnancy. After delivery, patients with normal G6PD activity can be given primaquine or tafenoquine depending on breastfeeding, or continue with chloroquine prophylaxis for a total of 1 yr from acute infection. Primaquine can be used during breastfeeding if infant found to also have normal G6PD activity; tafenoquine not recommended during breastfeeding.
[8]Dose of primaquine in patients ≥70 kg should be adjusted to a total dose of 6 mg/kg, divided into doses of 30 mg per day.
[9]Tafenoquine can only be used if chloroquine or hydroxychloroquine administered for acute treatment due to limited data on efficacy when used in combination with other regimens.
[10]Artemether-lumefantrine can be used in second and third trimesters of pregnancy and, if no other options available, in first trimester as well. Not for infants <5 kg or women breastfeeding infants <5 kg.
[11]Atovaquone-proguanil not recommended during pregnancy, in infants <5 kg, or in women breastfeeding infants <5 kg. May be considered if other treatment options not available or not tolerated, and benefits outweigh risks.
[12]Quinine available in the United States has 324 mg (salt) per capsule, therefore, two capsules for adult dosing. Pediatric dosing may need compounding pharmacy.

Table 334.3 Treatment of Uncomplicated Malaria: *P. vivax* or *P. ovale*[1,2]—cont'd

[13]Doxycycline or tetracycline combined with quinine preferred due to more efficacy data, but not recommended during pregnancy or in children <8 yr old unless no other options and benefits outweigh risks.
[14]Clindamycin with quinine preferred option for pregnant women and children <8 yr old.
[15]Use only if no other options available. Not for use in patients with neuropsychiatric history.
[16]Primaquine is the only option if regimens other than either chloroquine or hydroxychloroquine are used for treatment of acute infection.
[17]Primaquine associated with hemolytic anemia in those with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Before use, quantitative G6PD testing needed to confirm normal activity. For those with intermediate G6PD deficiency, weekly primaquine may be considered (45 mg/wk) for 8 wk with close monitoring for hemolysis. Those with G6PD deficiency may be given chloroquine 300 mg (base) PO weekly for 1 yr from acute infection to prevent relapses.
[18]Primaquine must not be used during pregnancy; pregnant patients with *P. vivax* and *P. ovale* infections should receive chloroquine 300 mg (base) PO weekly after acute treatment for the remainder of pregnancy. After delivery, patients with normal G6PD activity can be given primaquine depending on breastfeeding or continue with chloroquine prophylaxis for a total of 1 yr from acute infection. Primaquine can be used during breastfeeding if infant found to also have normal G6PD activity.
[19]Dose of primaquine in patients ≥70 kg should be adjusted to a total dose of 6 mg/kg, divided into doses of 30 mg/day.
From Centers for Disease Control and Prevention. Malaria Treatment Tables. https://www.cdc.gov/malaria/resources/pdf/Malaria_Treatment_Table.pdf

Table 334.4 Treatment of Uncomplicated Malaria: *P. malariae* or *P. knowlesi*[1,2]

DRUG SUSCEPTIBILITY (BASED ON WHERE ACQUIRED)	RECOMMENDED ADULT REGIMENS	RECOMMENDED PEDIATRIC REGIMENS[3]
Chloroquine sensitive (All malaria-endemic regions, no known resistance)	A. **Chloroquine phosphate (Aralen and generics)** Dose 1: 600 mg base (1,000 mg salt) PO Doses 2-4 (3 additional doses) at 6, 24, and 48 hr: 300 mg base (500 mg salt) PO per dose *OR* **Hydroxychloroquine (Plaquenil and generics)** Dose 1: 620 mg base (800 mg salt) PO Doses 2-4 (3 additional doses) at 6, 24, and 48 hr: 310 mg base (400 mg salt) PO per dose B. **Artemether-lumefantrine (Coartem)**[4] (1 tab: 20 mg artemether and 120 mg lumefantrine) Adults: 4 tabs PO per dose Three-day course: Day 1: Initial dose and second dose 8 hr later Days 2 and 3: 1 dose bid C. **Atovaquone-proguanil (Malarone)**[5] (Adult tab: 250 mg atovaquone and 100 mg proguanil) 4 adult tabs PO qd × 3 days D. **Quinine sulfate**[6] **plus doxycycline,**[7] **tetracycline,**[7] **or clindamycin**[8] Quinine sulfate: 542 mg base (648 mg salt) PO tid × 3 days Doxycycline: 100 mg PO bid × 7 days Tetracycline: 250 mg PO qid × 7 days Clindamycin: 20 mg/kg/day PO divided tid × 7 days E. **Mefloquine**[9] Dose 1: 684 mg base (750 mg salt) PO Dose 2 at 6-12 hr: 456 mg base (500 mg salt) PO	A. **Chloroquine phosphate (Aralen and generics)** Dose 1: 10 mg base/kg (16.7 mg salt/kg) PO Doses 2-4 (3 additional doses) at 6, 24, and 48 hr: 5 mg base/kg (8.3 mg salt/kg) PO per dose *OR* **Hydroxychloroquine (Plaquenil and generics)** Dose 1: 10 mg base/kg (12.9 mg salt/kg) PO Doses 2-4 (3 additional doses) at 6, 24, and 48 hr: 5 mg base/kg (6.5 mg salt/kg) PO per dose B. **Artemether-lumefantrine (Coartem)**[4] (1 tab: 20 mg artemether and 120 mg lumefantrine) 5 to <15 kg: 1 tab PO per dose 15 to <25 kg: 2 tabs PO per dose 25 to <35 kg: 3 tabs PO per dose ≥35 kg: 4 tabs PO per dose Three-day course: Day 1: Initial dose and second dose 8 hr later Days 2 and 3: 1 dose bid C. **Atovaquone-proguanil (Malarone)**[5] (Adult tab: 250 mg atovaquone and 100 mg proguanil; peds tab: 62.5 mg atovaquone and 25 mg proguanil) 5 to <8 kg: 2 peds tabs PO qd × 3 days 8 to <10 kg: 3 peds tabs PO qd × 3 days 10 to <20 kg: 1 adult tab PO qd × 3 days 20 to <30 kg: 2 adult tabs PO qd × 3 days 30 to <40 kg: 3 adult tabs PO qd × 3 days ≥40 kg: 4 adult tabs PO qd × 3 days D. **Quinine sulfate**[6] **plus doxycycline,**[7] **tetracycline,**[7] **or clindamycin**[8] Quinine sulfate: 8.3 mg base/kg (10 mg salt/kg) PO tid × 3 days Doxycycline: 2.2 mg/kg PO bid × 7 days Tetracycline: 25 mg/kg/day PO divided qid × 7 days Clindamycin: 20 mg /kg/day PO divided tid × 7 days E. **Mefloquine**[9] Dose 1: 13.7 mg base/kg (15 mg salt/kg) PO Dose 2 at 6-12 hr: 9.1 mg base/kg (10 mg salt/kg) PO

[1]qd, once a day; bid, twice a day; tid, three times a day; qid, four times a day; PO, by mouth; tab(s), tablet(s).
[2]If an antimalarial is taken for chemoprophylaxis, a different drug should be used for treatment.
[3]Not to exceed adult dose.
[4]Artemether-lumefantrine can be used in second and third trimesters of pregnancy and, if no other options available, in first trimester as well. Not for infants <5 kg or women breastfeeding infants <5 kg.
[5]Atovaquone-proguanil not recommended during pregnancy, in infants <5 kg, or in women breastfeeding infants <5 kg. May be considered if other treatment options not available or not tolerated, and benefits outweigh risks.
[6]Quinine available in the United States has 324 mg (salt) per capsule, therefore, two capsules for adult dosing. Pediatric dosing may need compounding pharmacy.
[7]Doxycycline or tetracycline combined with quinine preferred due to more efficacy data, but not recommended during pregnancy or in children <8 yr old unless no other options and benefits outweigh risks.
[8]Clindamycin with quinine preferred option for pregnant women and children <8 yr old.
[9]Use only if no other options available. Not for use in patients with neuropsychiatric history.
From Centers for Disease Control and Prevention. Malaria Treatment Tables. https://www.cdc.gov/malaria/resources/pdf/Malaria_Treatment_Table.pdf

Table 334.5 Treatment of Uncomplicated Malaria in Pregnant Women[1,2]

SPECIES AND DRUG SUSCEPTIBILITY (BASED ON WHERE ACQUIRED)	RECOMMENDED ADULT REGIMENS
Chloroquine resistant[3] *P. falciparum* (All malaria-endemic regions except Central America west of Panama Canal, Haiti, and Dominican Republic) *P. vivax* or *P. ovale* (Papua New Guinea and Indonesia)	Preferred for second and third trimesters: **Artemether-lumefantrine (Coartem)[4]** (1 tab: 20 mg artemether and 120 mg lumefantrine) Adults: 4 tabs PO per dose Three-day course: Day 1: Initial dose and second dose 8 hr later Days 2 and 3: 1 dose bid **All trimesters: Quinine sulfate plus clindamycin** Quinine sulfate: 542 mg base (650 mg salt) PO tid × 3 or 7 days[5] Clindamycin: 20 mg/kg/day PO divided tid × 7 days **If no other options, all trimesters: Mefloquine** Dose 1: 684 mg base (750 mg salt) PO Dose 2 at 6-12 hr: 456 mg base (500 mg salt) PO **AND if *P. vivax* or *P. ovale*:** **Chloroquine** 500 mg salt (300 mg base) weekly until delivery, then consider antirelapse treatment (Table 334.3 for options and dosing) Antirelapse treatment with either primaquine or tafenoquine contraindicated during pregnancy
Chloroquine sensitive *P. falciparum* (Central America west of Panama Canal, Haiti, and Dominican Republic) *P. vivax* or *P. ovale* (All malaria-endemic regions except Papua New Guinea and Indonesia) *P. malariae* or *P. knowlesi*	**Chloroquine phosphate (Aralen and generics)** Dose 1: 600 mg base (1,000 mg salt) PO Doses 2-4 (3 additional doses) at 6, 24, and 48 hr: 300 mg base (500 mg salt) PO per dose OR **Hydroxychloroquine (Plaquenil and generics)** Dose 1: 620 mg base (800 mg salt) PO Doses 2-4 (3 additional doses) at 6, 24, and 48 hr: 310 mg base (400 mg salt) PO per dose **Options above for chloroquine-resistant malaria parasites** **AND if *P. vivax* or *P. ovale*:** **Chloroquine** 500 mg salt (300 mg base) weekly until delivery, then consider antirelapse treatment (Table 334.3 for options and dosing) Antirelapse treatment with either primaquine or tafenoquine contraindicated during pregnancy

[1]bid, twice a day; tid, three times a day; PO, by mouth; tab(s), tablet(s).
[2]If an antimalarial is taken for chemoprophylaxis, a different drug should be used for treatment.
[3]Atovaquone-proguanil not listed due to insufficient data on its safety during pregnancy but may be considered if other treatment options not available or not tolerated, and benefits outweigh risks.
[4]Artemether-lumefantrine may be considered during first trimester if other treatment options not available or not tolerated, and benefits outweigh risks.
[5]Quinine to be given for 3 days for *P. falciparum* and *P. vivax* infections, except for *P. falciparum* infections acquired in Southeast Asia where 7 days of treatment is required.
From Centers for Disease Control and Prevention. Malaria Treatment Tables. https://www.cdc.gov/malaria/resources/pdf/Malaria_Treatment_Table.pdf

atovaquone-proguanil, quinine sulfate, or mefloquine (mefloquine only if the other options are not available) (Table 334.6). If parasite density is >1%, continue IV artesunate daily up to 6 more days until the parasite density is <1%. After this, the oral regimen can be completed (Table 334.6).

Supportive Care for Severe Malaria

It is the malaria-associated complications that might kill the patient, so intensive nursing care, preferably in an ICU where possible, is required. Clinical observations should be made as frequently as possible and should include monitoring of vital signs, coma score, and urine output. Blood glucose should be monitored every 4 hours, if possible, particularly in unconscious patients.

Severe malarial anemia (SMA) is defined as the presence of *P. falciparum* parasitemia in an individual with a hemoglobin of <5 g/dL. In endemic areas, WHO includes a parasitemia cutoff of >10,000 parasites per microliter for this definition. SMA is the most common severe complication of malaria in children and is the leading cause of anemia leading to hospital admission in African children. The etiology of SMA is complex, involving increased destruction and removal of infected and uninfected RBCs and reduced RBC production due to bone marrow dyserythropoiesis. Timely blood transfusion is critical, and mortality in this condition is low with timely transfusion. However, SMA is not benign; it contributes to significant long-term morbidity, including impaired neurocognitive function, repeated hospitalizations, and postdischarge mortality.

Cerebral malaria is defined as the presence of coma in a child with *P. falciparum* parasitemia and an absence of other reasons for coma. Children with altered mental status who are not in a coma fall into the larger category of *impaired consciousness*. Cerebral malaria is most common in children in areas of midlevel transmission and in adolescents or adults in areas of very low transmission. It is less frequently seen in areas of very high transmission. Cerebral malaria often develops after the patient has been ill for several days but may develop precipitously. Cerebral malaria has a fatality rate of 15–40% and is associated with long-term cognitive impairment in children. Repeated seizures are frequent in children with cerebral malaria. Hypoglycemia is common, but children with true cerebral malaria fail to arouse from coma even after receiving a dextrose infusion that normalizes their glucose level. Physical findings may include high fever, seizures, muscular twitching, rhythmic movement of the head or extremities, contracted or unequal pupils, retinal hemorrhages, hemiplegia, absent or exaggerated deep tendon reflexes, and a positive Babinski sign. Lumbar puncture reveals increased pressure and mildly increased cerebrospinal fluid protein, typically with no cerebrospinal fluid (CSF) pleocytosis. and a normal CSF glucose. Studies suggest that funduscopic findings of **malaria retinopathy** (retinal hemorrhages, peripheral whitening, macular whitening, vessel changes) are relatively specific for cerebral malaria, so children with cerebral malaria who do not have malaria retinopathy should be carefully assessed for other causes of coma. However, they should still be treated for cerebral malaria because a growing body of evidence suggests that even in these children, *P. falciparum* is a contributor to their comatose state. Beyond antimalarial medications, treatment of cerebral malaria is largely supportive and includes evaluation and treatment of seizures and hypoglycemia. A study using MRI to assess children with cerebral malaria documented that cerebral edema with increased intracranial pressure is the leading cause of death in children with cerebral malaria, and treatment with mannitol and corticosteroids has not improved outcomes in these children.

Respiratory distress syndrome (RDS) is best characterized by signs of acute respiratory distress and deep acidotic breathing. The acidosis is partly due to impaired tissue perfusion secondary to RBC sequestration and reduced oxygen-carrying capacity. RDS is a poor prognostic indicator in severe malaria and in children it appears to be caused by **metabolic acidosis** rather than intrinsic pulmonary disease. The kidney is important in acid metabolism and excretion and is believed to contribute to the acidosis seen in severe malaria. To date, no successful interventions for treatment of metabolic acidosis in children with severe malaria have been described, and primary therapy of malaria appears to be the most effective way to address acidosis.

Table 334.6 Treatment of Severe Malaria[1–5]

SPECIES AND DRUG SUSCEPTIBILITY (BASED ON WHERE ACQUIRED)	RECOMMENDED ADULT REGIMEN	RECOMMENDED PEDIATRIC REGIMEN
All species, drug susceptibility not relevant for acute treatment of severe malaria If *P. vivax* or *P. ovale* infections, in addition to acute treatment listed here, antirelapse treatment needed (Table 334.3)	**IV artesunate:** Commercially available. If not in stock or available within 24 hr, contact CDC Malaria Hotline: (770) 488-7100 or (855) 856-4713 (toll free) Mon–Fri, 9 am–5 pm EST; (770) 488-7100 after hours, weekends, and holidays. 1 dose = 2.4 mg/kg IV doses (3 in total) at 0, 12, and 24 hr **PLUS reassessment and follow-on the following treatment**	
	If IV artesunate not readily available, give oral antimalarials while obtaining IV artesunate. When IV artesunate arrives, discontinue oral antimalarial and initiate IV treatment. Interim treatment options (Table 334.2 for dosing): • Artemether-lumefantrine (Coartem) (preferred), or • Atovaquone-proguanil (Malarone), or • Quinine sulfate, or • Mefloquine (only if no other options available) If oral therapy not tolerated, consider administration via nasogastric (NG) tube or after an antiemetic	
	Reassessment and follow-on treatment: **Reassess parasite density at least 4 hr after the third dose** **Parasite density ≤1% and patient able to tolerate oral medications:** Give a complete follow-on oral regimen. Options include (Table 334.2 for dosing): • Artemether-lumefantrine (Coartem) (preferred), or • Atovaquone-proguanil (Malarone), or • Quinine plus doxycycline or, in children <8 yr old and pregnant women, clindamycin, or • Mefloquine (only if no other options available) **Parasite density >1%:** Continue IV artesunate, same dose, qd up to 6 more dys until parasite density ≤1%. When parasite density ≤1%, give complete follow-on oral regimen as listed previously (Table 334.2 for dosing) **Parasite density ≤1% but patient unable to take oral medication:** Continue IV artesunate, same dose, qd up to 6 more days until patient able to take oral therapy	

[1]qd, once a day; IV, intravenous.
[2]If an antimalarial is taken for chemoprophylaxis, a different drug should be used for treatment.
[3]Laboratory-confirmed or suspected malaria cases with ≥1 clinical criteria for severe disease (impaired consciousness/convulsions/coma, severe anemia [hemoglobin <7 mg/dL], acute kidney injury, acute respiratory distress syndrome, circulatory shock, disseminated intravascular coagulation, acidosis, jaundice [plus at least one other sign]); and/or parasite density ≥5%. Information on how to estimate parasite density available at www.cdc.gov/dpdx.
[4]Parasite density should be repeated every 12-24 hr until negative.
[5]Exchange transfusion no longer recommended based on a systematic review of the literature and analysis of US malaria surveillance data showing no added benefit.
From Centers for Disease Control and Prevention. Malaria Treatment Tables. https://www.cdc.gov/malaria/resources/pdf/Malaria_Treatment_Table.pdf

Seizures are a common complication of severe malaria, occurring in up to 70% of children with severe malaria; subclinical seizures occur in 15–20% of cases. Most of the seizures are associated with cerebral malaria, but it is important to evaluate for other common causes of seizure such as hypoglycemia and fever and to treat accordingly. Benzodiazepines are first-line therapy for seizures. Diazepam (0.4 mg/kg) can be administered IV or per rectum; lorazepam (0.1 mg/kg) can be administered IV or intraosseously. These doses can be repeated once if seizures do not cease within 5 minutes of the initial dose. Benzodiazepines should not be combined due to risk of respiratory depression. For persistent seizures, phenobarbital or phenytoin are the standard medications used. Phenobarbitone is given at dose of 15-20 mg/kg, slow IV push) while phenytoin is given at a dose of 18 mg/kg diluted in 100 mL normal saline, infused over 20 minutes. Phenytoin may be preferred for seizure treatment, particularly in hospitals or clinics where ventilatory support is not available. However, no comparative trials of the two drugs have been performed. Routine seizure prophylaxis should not be given in children with rapid resolution of seizures during their hospital course. There are currently no drugs recommended for seizure prophylaxis in children with severe malaria. Phenobarbital prophylaxis decreased seizure activity but increased mortality in one major study of children with severe malaria, probably because the respiratory depression associated with phenobarbital may have been exacerbated by benzodiazepine therapy.

Hypoglycemia is a complication of malaria that is more common in children, pregnant women, and patients receiving quinine therapy. Patients may have a decreased level of consciousness that can be confused with cerebral malaria. Any child with impaired consciousness and malaria should have a glucose level checked, and if glucometers are not immediately available, an empirical bolus of dextrose should be given. Hypoglycemia is associated with increased mortality and neurologic sequelae.

Shock is a rare complication that manifests as hypotension, hypothermia, rapid weak pulse, shallow breathing, pallor, and vascular collapse. It is most likely caused by bacterial superinfection, because up to 15% of children in endemic areas with severe malaria may have concurrent bacteremia. Death may occur within hours. Any child with severe malaria and hypotension or hypoperfusion should have a blood culture obtained and should be treated empirically for bacterial sepsis.

Acute kidney injury (AKI) is increasingly being recognized as an important complication of severe malaria and an independent predictor of mortality, occurring in >40% of children with severe malaria in one study of Ugandan children. The WHO 2023 definition of renal impairment in children with severe malaria (creatinine of ≥3.0 mg/dL) uses almost certainly too high a creatinine cutoff value, as severe AKI associated with increased mortality has been seen in children with much lower creatinine levels. Ongoing work seeks to use Kidney Disease: Improving Global Outcomes (KDIGO) criteria to establish better creatinine values to define AKI and renal impairment in children with severe malaria. Although data suggest AKI is related to reduced kidney perfusion, additional studies are needed to evaluate the spectrum of AKI over hospitalization to define the etiology and pathophysiology of AKI in pediatric severe malaria. In adults, use of acetaminophen has been associated with decreased AKI, and studies are investigating this possibility in children. Other urinary tract complications in children include **blackwater fever (or dark urine syndrome)**, which has reemerged as a clinical problem in some areas of Africa. The syndrome is thought to be associated in part with increased use of artemisinin derivatives and is associated with increased risk of readmission or death.

Prostration is defined as the inability to sit, stand, or eat without support, in the absence of impaired consciousness. Prostration has also been associated with increased mortality in some studies, but the pathophysiology of this process is not well understood.

In children, **abnormal bleeding** and **pulmonary edema** are uncommon, though the latter may sometimes be seen after treatment in *P. vivax* or *P. ovale* malaria.

Long-Term Complications of Malaria

Neurocognitive impairment and behavioral and mental health problems occur in children after episodes of cerebral malaria and severe malarial anemia. **Epilepsy** also occurs in a subset of children after severe malaria. The mechanisms leading to brain injury and subsequent neurocognitive complications due to severe malaria are still being investigated. Clinical predictors of neurocognitive impairment in children with cerebral malaria include duration of coma, number of seizures, acute kidney injury, and severe malarial anemia. CSF cytokines and metabolites like tumor necrosis factor (TNF)-α and kynurenic acid, as well as plasma and CSF levels of tau, a marker of neuronal injury, are elevated acutely in children with cerebral malaria who subsequently develop cognitive impairment. Additional studies are needed to delineate the mechanisms leading to neurocognitive complications in severe malaria, particularly in children without overt clinical signs suggestive of brain injury. Interventions to rehabilitate children with cognitive impairment have provided only short-term improvement in specific areas of function, and further studies in this area are needed.

Hyperreactive malarial splenomegaly (HMS) is a chronic complication of *P. falciparum* malaria in which massive splenomegaly persists after treatment of acute infection. Major criteria include splenomegaly (>10 cm), IgM >2 SD above local mean, high levels of antibodies to a blood-stage *P. falciparum* antigen, and a clinical response to an antimalarial drug. HMS occurs exclusively in children in endemic areas with repeated exposure to malaria and is thought to be caused by an impaired immune response to *P. falciparum* antigens. Prolonged antimalarial prophylaxis (for at least 1 year, typically with chloroquine, quinine, or mefloquine) is required to treat this syndrome if the child remains in a malaria-endemic area. Spleen size gradually regresses on antimalarial prophylaxis but often increases again if prophylaxis is stopped.

PREVENTION

Malaria prevention consists of reducing exposure to infected mosquitoes and chemoprophylaxis. The most accurate and current information on areas in the world where malaria risk and drug resistance exist can be obtained by contacting local and state health departments or the CDC or consulting *Health Information for International Travel,* which is published by the U.S. Public Health Service.

Travelers to endemic areas should remain in well-screened areas from dusk to dawn, when the risk for transmission is highest. They should sleep under permethrin-treated mosquito netting and spray insecticides indoors at sundown. During the day, travelers should wear clothing that covers the arms and legs, with trousers tucked into shoes or boots. Mosquito repellent should be applied to thin clothing and exposed areas of the skin, with applications repeated as noted on the repellent instructions, and at least every 4 hours. A child should not be taken outside from dusk to dawn, but if at risk for exposure, a solution with 25–35% *N,N*-diethyltoluamide (DEET) (not >40%) should be applied to exposed areas, except for the eyes, mouth, or hands. Hands are excluded because they are often placed in the mouth. DEET should then be washed off as soon as the child comes back inside. The American Academy of Pediatrics recommends that DEET solutions be avoided in children <2 months old. Adverse reactions to DEET include rashes, toxic encephalopathy, and seizures, but these reactions occur almost exclusively with inappropriate application of high concentrations of DEET. **Picaridin** is an alternative and sometimes better tolerated repellent. Even with these precautions, a child should be taken to a physician immediately if the child develops illness when traveling to a malarious area.

Chemoprophylaxis is necessary for all visitors to and residents of the tropics who have not lived there since infancy, including children of all ages (Tables 334.7 and 334.8). Healthcare providers should consult the latest information on resistance patterns before prescribing prophylaxis for their patients. Chloroquine is given in the few remaining areas of the world free of chloroquine-resistant malaria strains. In areas where chloroquine-resistant *P. falciparum* exists, atovaquone-proguanil, mefloquine, or doxycycline may be given as chemoprophylaxis. **Atovaquone-proguanil** is generally recommended for shorter trips (up to 2 weeks) because it must be taken daily. Pediatric tablets are available and are generally well tolerated, although the taste is

Table 334.7 Drugs Used in the Prophylaxis of Malaria

DRUG	USAGE	ADULT DOSE	PEDIATRIC DOSE	COMMENTS
Atovaquone-proguanil	Prophylaxis in all areas	Adult tablets contain 250 mg atovaquone and 100 mg proguanil hydrochloride. 1 adult tablet orally, daily	Pediatric tablets contain 62.5 mg atovaquone and 25 mg proguanil hydrochloride. 5-8 kg: ½ pediatric tablet daily >8-10 kg: ¾ pediatric tablet daily >10-20 kg: 1 pediatric tablet daily >20-30 kg: 2 pediatric tablets daily >30-40 kg: 3 pediatric tablets daily >40 kg: 1 adult tablet daily	Begin 1-2 days before travel to malarious areas. Take daily at the same time each day while in the malarious area and for 7 days after leaving such areas. Contraindicated in people with severe renal impairment (creatinine clearance <30 mL/min). Atovaquone-proguanil should be taken with food or a milky drink. Not recommended for prophylaxis for children weighing <5 kg, pregnant women, and women breastfeeding infants weighing <5 kg. Partial tablet doses may need to be prepared by a pharmacist and dispensed in individual capsules
Chloroquine	Prophylaxis only in areas with chloroquine-sensitive malaria	300 mg base (500 mg salt) orally, once/wk	5 mg/kg base (8.3 mg/kg salt) orally, once/wk, up to maximum adult dose of 300 mg base	Begin 1-2 wk before travel to malarious areas. Take weekly on the same day of the week while in the malarious area and for 4 wk after leaving such areas. May exacerbate psoriasis
Doxycycline	Prophylaxis in all areas	100 mg orally, daily	≥8 yr of age: 2.2 mg/kg up to adult dose of 100 mg/day	Begin 1-2 days before travel to malarious areas. Take daily at the same time each day while in the malarious area and for 4 wk after leaving such areas. Contraindicated in children <8 yr of age and pregnant women

Continued

Table 334.7 Drugs Used in the Prophylaxis of Malaria—cont'd

DRUG	USAGE	ADULT DOSE	PEDIATRIC DOSE	COMMENTS
Hydroxychloroquine	An alternative to chloroquine for prophylaxis only in areas with chloroquine-sensitive malaria	310 mg base (400 mg salt) orally, once/wk	5 mg/kg base (6.5 mg/kg salt) orally, once/wk, up to a maximum adult dose of 310 mg base	Begin 1-2 wk before travel to malarious areas. Take weekly on the same day of the week while in the malarious area and for 4 wk after leaving such areas
Mefloquine	Prophylaxis in areas with mefloquine-sensitive malaria	228 mg base (250 mg salt) orally, once/wk	≤9 kg: 4.6 mg/kg base (5 mg/kg salt) orally, once/wk >9-19 kg: ¼ tablet once/wk >19-30 kg: ½ tablet once/wk >30-45 kg: ¾ tablet once/wk >45 kg: 1 tablet once/wk	Begin ≥2 wk before travel to malarious areas. Take weekly on the same day of the week while in the malarious area and for 4 wk after leaving such areas. Contraindicated in people allergic to mefloquine or related compounds (quinine, quinidine) and in people with active depression, a recent history of depression, generalized anxiety disorder, psychosis, schizophrenia, other major psychiatric disorders, or seizures. Use with caution in people with psychiatric disturbances or a previous history of depression. Not recommended for people with cardiac conduction abnormalities
Primaquine[1]	Prophylaxis for short-duration travel to areas with principally *P. vivax*	30 mg base (52.6 mg salt) orally, daily	0.5 mg/kg base (0.8 mg/kg salt) up to adult dose orally, daily	Begin 1-2 days before travel to malarious areas. Take daily at the same time each day while in the malarious area and for 7 days after leaving such areas
	Presumptive antirelapse therapy (PART or terminal prophylaxis) to decrease the risk for relapses of *P. vivax* and *P. ovale*	30 mg base (52.6 mg salt) orally, daily	0.5 mg/kg base (0.8 mg/kg salt) up to adult dose orally, daily	PART indicated for people with prolonged exposure to *P. vivax, P. ovale,* or both: daily for 14 days after departure from the malarious area Contraindicated in people with G6PD deficiency. Also contraindicated during pregnancy and lactation, unless the infant being breastfed has a documented normal G6PD level
Tafenoquine[1]	Prophylaxis in all areas	200 mg orally	Not indicated in children <16 yr old	Begin taking daily for 3 days before travel to malarious areas. Then, take weekly while at the malarious area, and for 1 wk after leaving the malarious area
	Presumptive antirelapse therapy (PART or terminal prophylaxis) to decrease the risk for relapses of *P. vivax* and *P. ovale*	300 mg orally once	300 mg orally once for children ≥16 yr old	PART indicated for people who had prolonged exposure to *P. vivax, P. ovale,* or both: Administered as a single dose Contraindicated in people with G6PD deficiency. Also contraindicated during pregnancy and lactation unless the infant being breastfed has a documented normal G6PD level

[1]All people who take primaquine or tafenoquine should have a documented normal G6PD level before starting the medication.
PART, presumptive antirelapse therapy; G6PD, glucose-6-phosphate dehydrogenase.
From Tan KR, Arguin PM: Malaria. In Centers for Disease Control and Prevention. CDC Yellow Book 2020: Health Information for International Travel. New York: Oxford University Press; 2017. Table 4.10. https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-related-infectious-diseases/malaria#5217

Table 334.8 Considerations When Choosing a Drug for Malaria Prophylaxis

DRUG	REASONS TO CONSIDER USE OF THIS DRUG	REASONS TO CONSIDER AVOIDING USE OF THIS DRUG
Atovaquone-proguanil	• Good for last-minute travelers because the drug is started 1-2 days before travel • Some people prefer to take a daily medicine • Good choice for shorter trips because the traveler takes the medicine for only 7 days after traveling rather than 4 wk. • Well tolerated; side effects uncommon • Pediatric tablets are available and may be more convenient	• Cannot be used by women who are pregnant or breastfeeding a child that weighs <5 kg • Cannot be taken by people with severe renal impairment • Tends to be more expensive than some of the other options (especially for long trips) • Some people (including children) would rather not take a medicine every day
Chloroquine	• Some people would rather take medicine weekly • Good choice for long trips because it is taken only weekly • Some people are already taking hydroxychloroquine chronically for rheumatologic conditions; in those instances, they may not have to take an additional medicine • Can be used in all trimesters of pregnancy	• Cannot be used in areas with chloroquine or mefloquine resistance • May exacerbate psoriasis • Some people would rather not take a weekly medication • For short trips, some people would rather not take medication for 4 wk after travel • Not a good choice for last-minute travelers, because drug needs to be started 1-2 wk before travel
Doxycycline	• Some people prefer to take a daily medicine • Good for last-minute travelers because the drug is started 1-2 days before travel • Tends to be the least expensive antimalarial • People who are already taking doxycycline chronically to prevent acne do not have to take an additional medicine • Doxycycline also can prevent some additional infections (such as rickettsial infections and leptospirosis), so it may be preferred by people planning to hike, camp, and swim in fresh water	• Cannot be used by pregnant women and children age <8 yr • Some people would rather not take a medicine every day • For short trips, some people would rather not take medication for 4 wk after travel • Women prone to getting vaginal yeast infections when taking antibiotics may prefer taking a different medicine • People may want to avoid the increased risk of sun sensitivity • Some people are concerned about the potential of getting an upset stomach from doxycycline
Mefloquine	• Some people would rather take medicine weekly • Good choice for long trips because it is taken only weekly • Can be used in all trimesters of pregnancy	• Cannot be used in areas with mefloquine resistance • Cannot be used in patients with certain psychiatric conditions • Cannot be used in patients with a seizure disorder • Not recommended for people with cardiac conduction abnormalities • Not a good choice for last-minute travelers because drug needs to be started ≥2 wk before travel • Some people would rather not take a weekly medication • For short trips, some people would rather not take medication for 4 wk after travel
Primaquine	• It is the most effective medicine for preventing *P. vivax,* so it is a good choice for travel to places with >90% *P. vivax* • Good choice for shorter trips because you only have to take the medicine for 7 days after traveling rather than 4 wk • Good for last-minute travelers because the drug is started 1-2 days before travel • Some people prefer to take a daily medicine	• Cannot be used in patients with G6PD deficiency • Cannot be used in patients who have not been tested for G6PD deficiency • There are costs and delays associated with getting a G6PD test; however, it only has to be done once. Once a normal G6PD level is verified and documented, the test does not have to be repeated the next time primaquine is considered • Cannot be used by pregnant women • Cannot be used by women who are breastfeeding, unless the infant has also been tested for G6PD deficiency • Some people (including children) would rather not take a medicine every day • Some people are concerned about the potential of getting an upset stomach from primaquine
Tafenoquine	• One of the most effective drugs for prevention of *P. vivax* malaria but also prevents *P. falciparum* • Good choice for shorter trips because the traveler takes the medicine once, 1 wk after traveling rather than 4 wk • Good for last-minute travelers because the drug is started 3 days before travel	• Cannot be used in people with G6PD deficiency • Cannot be used in patients who have not been tested for G6PD deficiency • There are costs and delays associated with getting a G6PD test; however, it only has to be done once. Once a normal G6PD level is verified and documented, the test does not have to be repeated the next time tafenoquine or primaquine is considered • Cannot be used by children • Cannot be used by pregnant women • Cannot be used by women who are breastfeeding • Not recommended in those with psychotic disorders

From Tan KR, Arguin PM: Malaria. In Centers for Disease Control and Prevention. CDC Yellow Book 2020: Health Information for International Travel. New York: Oxford University Press; 2017. Table 4.9. https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-related-infectious-diseases/malaria#5217

sometimes unpleasant to very young children. For longer trips, **mefloquine** is preferred, because it is given only once a week. Mefloquine does not have a pediatric formulation and has an unpleasant taste that usually requires that the cut tablet be disguised in another food, such as chocolate syrup. Mefloquine should not be given to children if they have a known hypersensitivity to mefloquine, are receiving cardiotropic drugs, have a history of convulsive or certain psychiatric disorders, or travel to an area where mefloquine resistance exists (the borders of Thailand with Myanmar and Cambodia, western provinces of Cambodia, and eastern states of Myanmar). Atovaquone-proguanil is started 1-2 days before travel, and mefloquine is started 2 weeks before travel. It is important that these doses are given, both to allow therapeutic levels of the drugs to be achieved and to be sure that the drugs are tolerated. **Doxycycline** is an alternative for children >8 years old. It must be given daily and should be given with food. Side effects of doxycycline include photosensitivity and vaginal yeast infections. **Primaquine** is a daily prophylaxis option for children who cannot tolerate any of the other options, but it should be provided in consultation with a travel medicine specialist if needed, and all children should be checked for glucose-6-phosphate dehydrogenase (G6PD) deficiency before prescribing this medication, because it is contraindicated in children with G6PD deficiency. Provision of medication can be considered in individuals who refuse to take prophylaxis or will be in very remote areas without accessible medical care. Provision of medication for self-treatment of malaria should be done in consultation with a travel medicine specialist, and the medication provided should be different than that used for prophylaxis.

A number of other efforts are currently underway to prevent malaria in malaria-endemic countries. Some have been highly successful, leading to a significant decrease in malaria incidence in many countries in Africa, Asia, and South America in the past decade. These interventions include the use of **insecticide-treated bed nets** (which have decreased all-cause mortality in children <5 years old in several highly malaria-endemic areas by approximately 20%), indoor residual spraying with long-lasting insecticides, and the use of **artemisinin-combination therapy** for first-line malaria treatment.

Intermittent prevention treatment is successfully used in many African countries for seasonal chemoprevention treatment in areas with seasonal malaria transmission. **Sulfadoxine-pyrimethamine** given to infants at the second and third doses of the diphtheria, tetanus toxoid, and pertussis vaccine is safe and relatively effective. Intermittent prevention treatment has also been given to pregnant women; three doses of sulfadoxine-pyrimethamine have resulted in a reduction of low birthweight infants. Treatment of African children in malaria-endemic areas who have severe anemia with **dihydroartemisinin-piperaquine** reduces their risk of readmission and death, and this intervention is under consideration for standard treatment of severe anemia in children in several African countries.

The first malaria vaccine to have any degree of efficacy is the **RTS,S vaccine,** which is based on the circumsporozoite protein of *P. falciparum*. The RTS,S vaccine was approved by WHO in 2021 for use in children <2 years of age in malaria-endemic regions, in combination with other malaria prevention strategies. WHO approval was based on the results of phase IV studies showing a 30% reduction in severe malaria in children who received the four-dose vaccine series. WHO also approved the R21/Matrix-M vaccine in 2023 for use in children <2 years of age in malaria-endemic regions. Numerous other vaccines are also in current clinical trials. There is currently no vaccine with sufficient efficacy to be considered for prevention of malaria in travelers. A trial of monoclonal antibodies showed short-term efficacy in prevention of malaria, and this intervention could potentially be useful in malaria prevention in travelers and the military if efficacy is reproduced in larger studies. Trials of monoclonal antibodies for prevention of seasonal malaria in African children are also ongoing. If monoclonal antibodies can be produced at low cost, they may have a role in prevention in areas of seasonal malaria transmission.

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Chapter 335

Babesiosis *(Babesia)*

Peter J. Krause

Babesiosis is a malaria-like disease caused by intraerythrocytic protozoa that are transmitted by hard body **(ixodid)** ticks. The clinical manifestations of babesiosis range from subclinical illness to fulminant disease resulting in death.

ETIOLOGY

More than 100 species of *Babesia* infect a wide variety of wild and domestic animals throughout the world. Only a few of these species have been reported to infect humans, including *Babesia crassa*-like agent, *Babesia divergens, Babesia duncani, Babesia microti, Babesia motosi,* and *Babesia venatorum*.

EPIDEMIOLOGY

Babesia organisms are transmitted to humans from vertebrate reservoir hosts by the *Ixodes ricinus* family of ticks. *B. microti* is the most common cause of babesiosis in humans. The primary reservoir for *B. microti* in the United States is the white-footed mouse, *Peromyscus leucopus*, and the primary vector is *Ixodes scapularis*, the black-legged tick. *I. scapularis* ticks also transmit the causative agents of **Lyme disease**, human granulocytic anaplasmosis, *Borrelia mayonii, Borrelia miyamotoi* infection, *Ehrlichia muris eauclairensis*, and Powassan virus encephalitis and may simultaneously transmit two or more microorganisms. White-tailed deer *(Odocoileus virginianus)* serve as the host on which adult ticks most abundantly feed but are incompetent reservoirs of *B. microti*. Babesiosis may be transmitted through blood transfusion, and *B. microti* has been one of the most frequently reported transfusion-transmitted microbial agents in the United States. Rarely, babesiosis is acquired by transplacental transmission or organ transplantation.

In the United States, human *B. microti* infection is endemic in the Northeast and Upper Midwest with more than 2,000 reported cases a year, although the actual number of cases is probably much greater (Fig. 335.1). Most cases occur in June, July, and August. *B. duncani* infects humans along the Pacific coast and is reported sporadically, with less than 50 cases having been described to date. *B. divergens*–like infections have been described in Arkansas, Kentucky, Missouri, and Washington State. In Europe, human babesiosis caused by *B. divergens, B. microti,* and *B. venatorum* occurs sporadically. In Asia, *B. venatorum* and *Babesia crassa*–like agent are endemic in northeastern China. Cases of *B. microti* infection are endemic in southwestern China and also have been described in Taiwan and Japan. Infection due to *Babesia motosi* has been reported in Korea. Human babesiosis also has been documented in Africa, Australia, Canada, Cuba, Egypt, India, Mexico, South America, and Turkey.

In certain sites and in certain years of high transmission, babesiosis constitutes a significant public health burden. On Nantucket Island, case rates as high as 280 per 100,000 population have been recorded, placing the community burden of disease in a category with gonorrhea as "moderately common." Comparable incidence rates have been described elsewhere on the southern New England coast.

PATHOGENESIS

The pathogenesis of human babesiosis is not well understood. Lysis of infected erythrocytes with resultant anemia and the excessive production of proinflammatory cytokines such as tumor necrosis factor and interleukin-1 may account for most of the clinical manifestations and complications of the disease. Cytoadherence of *Babesia*-infected red blood cells to vascular epithelium with subsequent vascular obstruction and tissue anoxia might also cause complications. The spleen has an important role in clearing parasitemia, as do T and B cells, macrophages, polymorphonuclear leukocytes, cytokines, antibody, and complement.

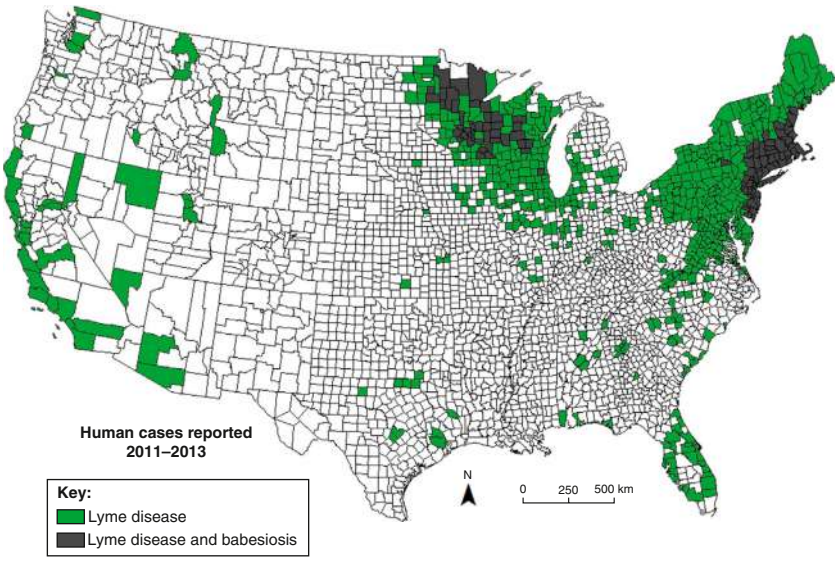

Fig. 335.1 Human babesiosis emerging in areas endemic for Lyme disease. This U.S. map is based on data obtained from the Centers for Disease Control and Prevention that recorded the names of counties that reported cases of Lyme disease and/or babesiosis from 2011 to 2013. Counties with ≥3 cases of Lyme disease but <3 cases of babesiosis are depicted in *green*. Counties with ≥3 cases of Lyme disease and ≥3 cases of babesiosis are depicted in *gray*. No county reported ≥3 cases of babesiosis but <3 cases of Lyme disease. *(Adapted from Diuk-Wasser M, Vannier E, Krause PJ. Coinfection by Ixodes tick-borne pathogens: ecological, epidemiological, and clinical consequences. Trends Parasitol. 2016;32:30–42.)*

CLINICAL MANIFESTATIONS

The clinical severity of babesiosis ranges from subclinical infection to fulminant disease and death. In clinically apparent cases, symptoms of babesiosis begin after an incubation period of 1-9 weeks from the beginning of tick feeding or 1 week to 6 months after transfusion. Typical symptoms in moderate to severe infection include intermittent fever to as high as 40°C (104°F) accompanied by any combination of chills, sweats, headache, and myalgias. Less common are arthralgias, sore throat, abdominal pain, nausea, vomiting, emotional lability, hyperesthesia, conjunctival injection, photophobia, weight loss, and nonproductive cough. The findings on physical examination generally are minimal, often consisting only of fever. Splenomegaly, hepatomegaly, or both are noted occasionally, but rash is seldom reported. Abnormal laboratory findings include moderately severe hemolytic anemia, elevated reticulocyte count, thrombocytopenia, proteinuria, and elevated bilirubin, BUN, and creatinine levels. The leukocyte count is normal to slightly decreased, often with neutropenia. Complications include respiratory failure, disseminated intravascular coagulation, congestive heart failure, renal failure, liver failure, coma, and death. Babesiosis symptoms usually last for 1-2 weeks, although prolonged recovery of over 1 year may occur in highly immunocompromised hosts who experience relapsing infection despite multiple courses of antibabesial therapy. Such patients include those with cancer and asplenia, those receiving immunosuppressive therapy, and those with HIV/AIDS. In one study, more than 20% of these patients died, while the remainder were cured after an average of 3 months (range: 1-24 months) of antibabesial therapy.

Risk factors for severe disease include aging, neonatal prematurity, anatomic or functional asplenia, malignancy, HIV/AIDS, immunosuppressive drugs, acquisition of infection through blood transfusion, or organ transplantation. Concurrent babesiosis and Lyme disease has been reported in 3–11% of patients experiencing Lyme disease, depending on location in the United States. Such co-infection results in more severe Lyme disease illness. Moderate to severe babesiosis may occur in children, but infection generally is less severe than in adults. About half of infected children are asymptomatic or experience minimal symptoms. Neonates may develop severe illness and usually are infected from blood transfusion.

DIAGNOSIS

Diagnosis of *B. microti* infection in human hosts is confirmed by microscopic demonstration of the organism using Giemsa-stained thin blood films. Parasitemia may be exceedingly low, especially early in the course of illness. Thick blood smears may be examined, but the organisms may be mistaken for stain precipitate or iron inclusion bodies. Polymerase chain reaction (PCR) is a sensitive and specific test for detection of *Babesia* DNA and can be used in addition to or instead of blood smear to confirm the diagnosis. Serologic testing can be useful in supporting the diagnosis of *Babesia* infection. The indirect immunofluorescence serologic assay for both IgG and IgM antibodies is sensitive and specific, although it may reflect past infection rather than acute disease. The diagnosis of babesiosis is most reliably made in patients who have lived or traveled in an area where babesiosis is endemic, who experience viral infection–like symptoms, and who have identifiable parasites on blood smear or amplifiable *Babesia* DNA in blood. The diagnosis of active babesial infection based on seropositivity alone is suspect.

TREATMENT

The combination of **clindamycin** (7-10 mg/kg given intravenously [IV] or orally [PO] every 6-8 hr, up to maximum of 600 mg/dose) and **quinine sulfate** (8 mg/kg PO every 8 hr, up to maximum of 650 mg/dose) for 7-10 days was the first effective therapeutic combination for the treatment of babesiosis; however, adverse reactions associated with this regimen are common, especially tinnitus and abdominal distress. The combination of **atovaquone** (20 mg/kg PO every 12 hr, up to maximum of 750 mg/dose) and **azithromycin** (10 mg/kg/day PO once on day 1, up to maximum of 500 mg/dose, and 5 mg/kg once daily thereafter, up to maximum of 250 mg/dose) for 7-10 days is as effective as clindamycin and quinine but has far fewer adverse effects. Atovaquone with azithromycin has been used successfully to treat babesiosis in infants and should be used initially in all children experiencing babesiosis. Clindamycin with quinine is an alternative choice. Treatment failure with atovaquone-azithromycin and clindamycin-quinine may occur in highly immunocompromised hosts. Consultation with an infectious diseases expert is recommended in these cases. Exchange blood transfusion can decrease parasitemia rapidly and remove toxic by-products of infection. Partial or complete exchange transfusion is recommended for children with high-grade parasitemia (>10%), severe anemia (hemoglobin <10 g/dL), or severe pulmonary, renal, or hepatic compromise.

PROGNOSIS

Moderate to severe disease is frequently observed in some highly endemic areas but mostly in adults. The babesiosis case fatality rate was estimated at 5% in a retrospective study of 136 New York cases but may be as high as 21% in immunocompromised hosts and those who acquire babesiosis through blood transfusion. Clearance of infection is sometimes delayed, with low-level asymptomatic parasitemia persisting for as long as 26 months after symptoms have resolved, or with relapsing symptomatic disease in immunocompromised hosts.

PREVENTION

Prevention of babesiosis can be accomplished by avoiding areas where ticks, deer, and mice are known to thrive. Use of clothing that covers the

lower part of the body and that is sprayed or impregnated with diethyltoluamide (DEET), dimethyl phthalate, or permethrin (Permanone) is recommended for those who travel in the foliage of endemic areas. DEET can be applied directly to the skin. A search for ticks should be carried out and the ticks removed using tweezers. Prospective blood donors with a history of babesiosis are excluded from giving blood to prevent transfusion-related cases.

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Chapter 336

Toxoplasmosis *(Toxoplasma gondii)*

Rima McLeod and Kenneth M. Boyer

Toxoplasma gondii, an obligate, intracellular, apicomplexan protozoan, is acquired perorally, transplacentally, or rarely parenterally in laboratory accidents, transfusions, or from a transplanted organ. In immunologically normal children, acute acquired infection most often is asymptomatic or unrecognized but may cause lymphadenopathy or affect almost any organ. *Once acquired, latent encysted organisms persist in the host throughout life.* In immunocompromised persons, initial acquisition or recrudescence of latent organisms can cause signs or symptoms related to the central nervous system (CNS) or result in systemic disease, as in bone marrow transplant recipients. If untreated, congenital infection causes disease that manifests either perinatally or later in life, most frequently chorioretinitis and CNS lesions. Other manifestations include intrauterine growth restriction, prematurity, cognitive and motor deficits, fever, lymphadenopathy, rash, hearing loss, pneumonitis, hepatitis, thrombocytopenia, and cerebrospinal fluid (CSF) inflammatory changes. Unrecognized congenital toxoplasmosis in infants with HIV infection may be fulminant.

ETIOLOGY

T. gondii is a coccidian protozoan that multiplies only in living cells. It is descended from an ancient, free-living, single-celled extracellular parasite called *Colpodella,* which shares some ultrastructural features with *T. gondii* (Fig. 336.1A). Tachyzoites are the pathogenic form of the parasite in active infections and are oval or crescent-like, measuring 2-4 × 4-7 μm (see Fig. 336.1B). Tissue cysts are 10-100 μm in diameter, may contain thousands of latent parasites called **bradyzoites** (see Fig. 336.1C), and will remain in tissues, especially the CNS and skeletal and heart muscle, for the life of the host. *Toxoplasma* can multiply in all tissues of mammals and birds. There is also a dormant "stressed persister" form of the parasite that arrests and does not progress through the G1 phase of the cell cycle, unable to pass a checkpoint into the tachyzoite replicative phase of the cell cycle. In recent years critical transcription factors that can distinguish *Toxoplasma* bradyzoites from **tachyzoites** and **merozoites** have been identified.

Oocysts are another form of the parasite and are formed in the cat intestine (see Fig. 336.1D). Newly infected, nonimmune cats and other Felidae species are the definitive hosts of *T. gondii* and represent the location where genetic exchange occurs during a sexual cycle. *Toxoplasma* organisms are transmitted to cats when the cat ingests infected meat containing encysted bradyzoites or ingests oocysts containing **sporozoites** excreted by other recently infected cats. The parasites then multiply through schizogonic merozoite and other gametogonic cycles in the distal ileal epithelium of the cat intestine. Intestinal delta-6-desaturase activity and linoleic acid determine the host range of oocyst formation in cats. Genes in the parasite that promote fusion of the female and male gamete to form a zygote and are critical for conception have been identified. Oocysts containing two sporocysts are excreted, and under the proper temperature and moisture conditions each sporocyst matures into four sporozoites. For approximately 2 weeks the cat excretes 10^5-10^7 oocysts daily, which may retain their viability for >1 year in a suitable environment. Oocysts sporulate 1-5 days after excretion and are then infectious. They are killed by drying or boiling but are resistant to bleach. Oocysts have been isolated from soil and sand frequented by cats, and outbreaks associated with contaminated food and water have been reported. Oocysts and tissue cysts are sources of animal and human infections (see Fig. 336.1D).

There are genetically distinct types of *T. gondii* that differ in virulence for mice, form different numbers of cysts in the brain of outbred mice, and cause different clinical manifestations for humans. In the United States, there are four predominant clonal lineages called **types I**, **II**, **III**, and **IV** (haplogroup XII) in addition to atypical, recombinant types. There is one predominant clonal type (type II) in France, Austria, and Poland, and nonarchetypal parasites are prevalent in Brazil, Guyana, French Guiana, and Central America. Hypervirulent parasites containing a single stranded RNA virus appear to cause epidemics of disease in Guiana and Victoria Canada.

EPIDEMIOLOGY

Toxoplasma infection is ubiquitous in animals and is one of the most common latent infections of humans throughout the world, infecting and persisting in approximately 2 billion people. Prevalence varies considerably among people and animals in different geographic areas. In different areas of the world, approximately 3–35% of pork, 7–60% of lamb, and 0–9% of beef contain *T. gondii* organisms. Significant antibody titers are detected in 50–80% of residents of some localities, such as France, Brazil, and Central America, and in <5% of populations in other areas. The current overall prevalence estimate in the United States is 10%, but prevalence varies among different demographic groups and in different geographic locations. For example, in a study of pregnant women in an Amish community in Lancaster County, Pennsylvania, prevalence was 50%. There appears to be a higher prevalence of infection in some warmer, more humid climates. Non–type II parasites are more common in mothers of congenitally infected infants in warm, moist southern climates, in rural areas, in those with lower socioeconomic status and with Hispanic ethnicity in the United States. Non–type II parasites are more often associated with prematurity and severe congenital infection in the United States.

Human infection in older children and adults is usually acquired orally by eating undercooked or raw meat that contains cysts or food or other material contaminated with oocysts from acutely infected cats. Fruits and vegetables that have not been properly washed may carry oocysts, consistent with the high overall prevalence of *Toxoplasma* oocysts in the soil and water in many regions of the globe. Freezing meat to −20°C (−4°F) or heating meat to 66°C (150.8°F) renders the tissue cysts noninfectious. Outbreaks of acute acquired infection have occurred in families, at social gatherings, and in restaurants where people have consumed the same infected food or water. It was previously thought that *T. gondii* could not be transmitted from person to person except for transplacental infection from mother to fetus and, rarely, by organ transplantation or transfusion. However, there is now increasing evidence of the ability of both humans and animals to pass *T. gondii* from male to female via sperm.

Seronegative transplant recipients who receive an organ, bone marrow, or stem cells from seropositive donors have experienced life-threatening illness requiring immediate therapy. Seropositive recipients who receive an infected donor organ may have increased serologic titers without recognized, associated disease. Laboratory accidents have resulted in infections, including fatalities.

Transmission to the fetus usually follows acquisition of primary infection by an immunologically normal pregnant woman during gestation. Congenital transmission from mothers infected before pregnancy is extremely rare except for immunocompromised women who are chronically infected. The estimated incidence of congenital infection in the United States ranges from 1 in 1,000 to 1 in 8,000 live births. An estimated 15 million people are living with congenital toxoplasmosis worldwide. The incidence of infection among pregnant women depends on the general risk for infection in the specific locale and the proportion of the population that has not been infected previously.

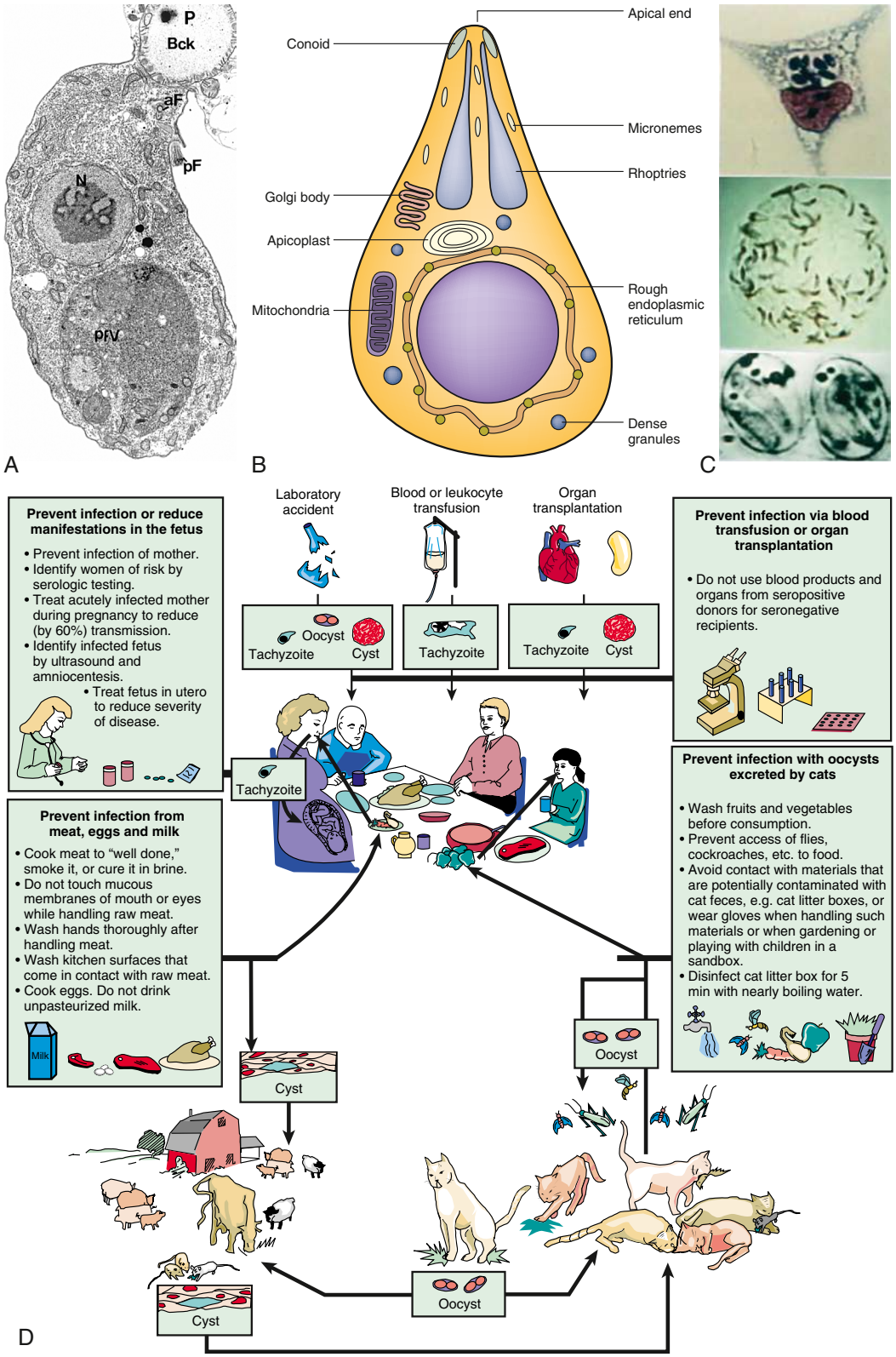

Fig. 336.1 The parasite: *Toxoplasma* ancient ancestor, ultrastructure, and life cycle stages affecting humans. **A,** *Colpodella vorax,* an ancient progenitor to the apicomplexans. **B,** Ultrastructure of *T. gondii* tachyzoite. **C,** Light micrographs of, *top to bottom,* tachyzoite, bradyzoite, and sporozoite stages of *T. gondii*. **D,** Life cycle of *Toxoplasma gondii* and prevention of toxoplasmosis by interruption of transmission to humans. N, nucleus; PBck, prey being ingested; aF, anterior flagellum; pF, posterior flagellum; pFV, posterior food vacuole. (*A from Brugerolle G. Colpodella vorax: Ultrastructure, predation, life-cycle, mitosis, and phylogenetic relationships. Eur J Protistol. 2002;38[2]:113–125; B from Wheeler K. Characterization of Toxoplasma gondii dense granule protein 1: Genetic, functional, and mechanistic analyses (Undergraduate Honors thesis), Kelsey Wheeler; C, bottom panel, from Dubey JP, Miller N, Frenkel JK. The Toxoplasma gondii oocyst from cat feces. J Exp Med. 1970;132[4]:636–662.)*

PATHOGENESIS

T. gondii is acquired by children and adults from ingesting food that contains cysts or that is contaminated with oocysts from acutely infected cats. Oocysts also may be transported to food by flies and cockroaches and may be carried to people on the fur of dogs. When the organism is ingested, bradyzoites are released from cysts or sporozoites are produced from oocysts. The organisms enter gastrointestinal (GI) cells, where they multiply, rupture cells, infect contiguous cells, enter the lymphatics and blood, and disseminate lymphohematogenously throughout the body. **Tachyzoites** proliferate, producing necrotic foci surrounded by a cellular reaction. With development of a normal immune response that is both humoral and cell mediated, tachyzoites disappear from tissues. In immunocompromised individuals and also in some apparently immunocompetent people, acute infection progresses and may cause pneumonitis, myocarditis, or encephalitis, sometimes resulting in lethal disease.

Alterations of T-lymphocyte populations during acute *T. gondii* infection are common and include lymphocytosis, increased $CD8^+$ T-cell count, and decreased $CD4^+/CD8^+$ ratio. Characteristic histopathologic changes in lymph nodes during acute infection include (1) reactive follicular hyperplasia with irregular clusters of epithelioid histiocytes that encroach on and blur margins of germinal centers, and (2) focal distention of sinuses with monocytoid cells. Depletion of $CD4^+$ T cells in patients with AIDS predisposes to severe manifestations of toxoplasmosis.

Cysts form as early as 7 days after infection and remain in the host for life. During latent infection they produce little or no inflammatory response but can cause recrudescent disease in immunocompromised persons. **Recrudescent chorioretinitis** can occur in children and adults with postnatally acquired infection and in older children and adults with congenitally acquired infection. Host and parasite genetics influence outcomes.

When a mother acquires infection during gestation, organisms may disseminate hematogenously to the placenta. Infection may be transmitted to the fetus transplacentally or to the infant during vaginal delivery. Of untreated maternal infections acquired in the first trimester, approximately 17% of fetuses are infected, usually with severe disease. Of untreated maternal infection acquired in the third trimester, approximately 65% of fetuses are infected, usually with disease that is milder and sometimes inapparent at birth (Fig. 336.2). These different rates of transmission and outcomes are most likely related to placental blood flow, virulence, inoculum of *T. gondii,* and immunologic capacity of the mother and fetus to limit parasitemia.

Examination of the placenta of infected newborns may reveal chronic inflammation and cysts. Tachyzoites can be seen with Wright or Giemsa stains but are best demonstrated with the immunoperoxidase technique. Tissue cysts stain well with periodic acid–Schiff and silver stains as well as with the immunoperoxidase technique. Gross or microscopic areas of necrosis may be present in many tissues, especially the CNS, choroid and retina, heart, lungs, skeletal muscle, liver, and spleen. Areas of calcification occur in the brain.

Almost all congenitally infected individuals who are not treated develop signs or symptoms of infection by adolescence. Some severely affected infants with congenital infection appear to have *Toxoplasma* antigen–specific cell-mediated hyporesponsiveness, which may be important in the pathogenesis of disease.

CLINICAL MANIFESTATIONS

Manifestations of primary infection with *T. gondii* are highly variable and are influenced primarily by host immunocompetence. Clinical features range from no signs or symptoms to severe disease. Reactivation of previously asymptomatic congenital toxoplasmosis usually manifests as ocular toxoplasmosis.

Acquired Toxoplasmosis

Immunocompetent children who acquire infection postnatally generally do not have clinically recognizable symptoms. When clinical

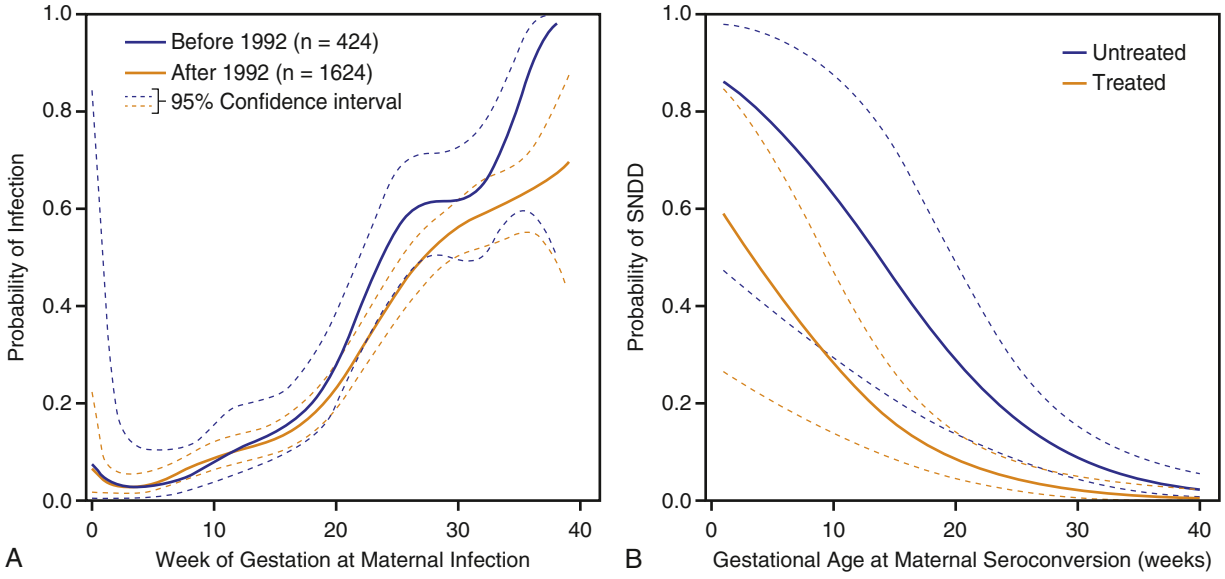

Fig. 336.2 Probability and severity of congenital toxoplasmosis and relationship to gestational age. **A,** Probability of fetal infection according to gestational age at the time of maternal infection before (n = 451) and after (n = 1624) mid-1992, Lyon cohort (1987–2008). **B,** Risk of severe neurologic disease or death (SNDD) in children with congenital toxoplasmosis (CT) according to antepartum treatment. Probability of SNDD according to imputed gestational age at seroconversion and 95% Bayesian credible limits. *Gold* lines denote treated pregnancies; *purple lines* denote untreated pregnancies. (SNDD is a composite outcome comprising a pediatric report at any age of microcephaly; insertion of an intraventricular shunt; an abnormal or suspicious neurodevelopmental examination that resulted in referral to a specialist; seizures during infancy or at an older age that required anticonvulsant therapy; severe bilateral visual impairment [visual acuity of Snellen ≤6/60 in both eyes assessed after 3 yr]; cerebral palsy; or death from any cause before age 2 years, including termination of pregnancy [consistency of SSND findings was checked through multiple assessments].) Severe neurologic sequelae were assessed at a median of 4 years' follow-up, death was assessed by age 2 yr, and severe bilateral visual impairment was included in the composite outcome of severe neurologic sequelae. *(A from Wallon M, Peyron F, Cornu C, et al. Congenital toxoplasmosis infection: monthly prenatal screening decreases transmission rate and improves clinical outcome at age 3 years. Clin Infect Dis. 2013;56:1229; B from Cortina-Borja M, Tan HK, Wallon M, et al. Prenatal treatment of serious neurologic sequelae of congenital toxoplasmosis: an observational prospective cohort study. PLoS Med. 2010;7:e1000351.)*

manifestations are apparent, they may include almost any combination of fever, stiff neck, myalgia, arthralgia, maculopapular rash that spares the palms and soles, localized or generalized lymphadenopathy, hepatomegaly, hepatitis, reactive lymphocytosis, meningitis, brain abscess, encephalitis, confusion, malaise, pneumonia, polymyositis, pericarditis, pericardial effusion, and myocarditis. **Chorioretinitis** occurs in approximately 1% of U.S. cases and in 20% of cases in epidemics in Brazil at 2 years after infection. Approximately 10% of mothers of congenitally infected infants have eye lesions on dilated indirect ophthalmoscopic examinations. Postnatally acquired chorioretinal lesions cannot be distinguished from congenitally acquired lesions based on appearance. In some areas of Brazil, 80% of the population is infected, with 50% of infected individuals >50 years old and 20% of infected individuals having retinal involvement. Symptoms and signs of active ocular infection may be present for a few weeks only or may persist for many months.

The most common manifestation of acute acquired toxoplasmosis is enlargement of one or a few cervical lymph nodes. Cases of *Toxoplasma* **lymphadenopathy** can resemble infectious mononucleosis, lymphoma, or other lymphadenopathies (see Chapter 539). Pectoral, mediastinal, mesenteric, and retroperitoneal lymph nodes may be involved. Involvement of intraabdominal lymph nodes may be associated with fever, mimicking appendicitis. Nodes may be tender but do not suppurate. Lymphadenopathy may wax and wane for as long as 1-2 years. However, almost all patients with lymphadenopathy recover spontaneously without antimicrobial therapy. Significant organ involvement in immunologically normal persons is uncommon, although some individuals have significant morbidity, including rare cases of encephalitis, brain abscesses, hepatitis, myocarditis, pericarditis, and polymyositis. In persons acquiring *T. gondii* in Guyana near the Maroni River and along Amazon tributaries, a severe form of life-threatening, multi-visceral involvement with fever has occurred. The causative parasites in these cases are genetically different from the parasites in others.

Ocular Toxoplasmosis

In the United States and Western Europe, *T. gondii* is estimated to cause 35% of cases of **chorioretinitis** (Fig. 336.3). In Brazil, *T. gondii* retinal lesions are common. Clinical manifestations include blurred vision, visual floaters, photophobia, epiphora, and, with macular involvement, loss of central vision. Ocular findings of **congenital toxoplasmosis** also include strabismus, microphthalmia, microcornea, cataracts, anisometropia, nystagmus, glaucoma, optic neuritis, and optic atrophy. Episodic recurrences are common, but precipitating factors have not been defined. Recurrent, active disease usually occurs at school-entry age and during adolescence. Anecdotally, stress or trauma seems to precipitate symptoms. Recurrences are most common closest to the time of acquisition of infection, and treatment leads to resolution of activity. PD-L1 may contribute to susceptibility to recurrent active retinal disease.

Immunocompromised Persons

Host factors play a prominent role in susceptibility to disease due to *T. gondii* and in the outcome of toxoplasmosis. Disseminated *T. gondii* infection among older children who are **immunocompromised** by AIDS, malignancy, cytotoxic therapy, corticosteroids, or immunosuppressive drugs given for organ transplantation involves the CNS in 50% of cases and may also involve the heart, lungs, and GI tract. Stem cell transplant recipients present a special problem, because active infection is difficult to diagnose serologically. After transplantation, *T. gondii*–specific antibody levels may remain the same, increase, or decrease, and can even become undetectable. Toxoplasmosis in transplantation patients results from reactivation of latent organisms or transplantation from a seropositive donor to a seronegative recipient; thus knowledge of the serologic status of the donor and recipient is essential. Prompt diagnosis is of utmost importance, as active infection is often fulminant and rapidly fatal without treatment.

Congenital *T. gondii* infection in infants with HIV infection is rare in the United States but can be a severe and fulminant disease with substantial CNS involvement. Alternatively, it may be more indolent in presentation, with focal neurologic deficits or systemic manifestations such as pneumonitis occurring with progressive CD4 depletion in infants who are not receiving highly active antiretroviral therapy (HAART).

Up to 50% of persons with *T. gondii* antibodies and HIV infection who are not on antiretroviral treatment eventually experience **toxoplasmic encephalitis**, which is fatal if not treated. HAART and trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis to prevent *Pneumocystis jirovecii* have reduced the incidence of toxoplasmosis in patients with HIV infection, but toxoplasmic encephalitis remains a presenting manifestation in some adult patients with AIDS. Typical findings include fever, headache, altered mental status, psychosis, cognitive impairment, seizures, and focal neurologic defects such as hemiparesis, aphasia, ataxia, visual field loss, cranial nerve palsies, dysmetria, and movement disorders. In adult patients with AIDS, toxoplasmic retinal lesions are often large with diffuse necrosis and contain many organisms but little inflammatory cellular infiltrate. Diagnosis of presumptive toxoplasmic encephalitis based on neuroradiologic studies in patients with AIDS necessitates a prompt therapeutic trial of medications effective against *T. gondii*. Clear clinical improvement within 7-14 days and improvement of neuroradiologic findings within 3 weeks make the presumptive diagnosis almost certain.

Congenital Toxoplasmosis

Congenital toxoplasmosis usually occurs when a woman acquires primary infection while pregnant. Most often, maternal infection is asymptomatic or without specific symptoms or signs. As with other adults with acute toxoplasmosis, lymphadenopathy is the most commonly identified physical finding.

In monozygotic twins the clinical pattern of involvement is most often similar, whereas in dizygotic twins the manifestations often differ, including cases of congenital infection in only one twin. The major histocompatibility complex class II gene DQ3 appears to be more common than DQ1 among HIV-infected persons seropositive for *T. gondii* who develop toxoplasmic encephalitis, as well as in children with congenital toxoplasmosis who develop hydrocephalus. These findings suggest that the presence of HLA-DQ3 is a risk factor for severity of toxoplasmosis. Other allelic variants of genes, including *COL2A, ABC4R, P2X7R, NALP1, ALOX12, TLR9, TIRAP MAL,* and *ERAAP,* are also associated with increased susceptibility.

Congenital infection may present as a mild or severe neonatal disease (Table 336.1). It may also present with sequelae or relapse of a previously undiagnosed and untreated infection later in infancy or even later in life (see Table 336.1). There is a wide variety of manifestations of congenital infection, ranging from hydrops fetalis and perinatal death to small size for gestational age, prematurity, peripheral or central retinal scars, persistent jaundice, mild thrombocytopenia, CSF pleocytosis, and the characteristic triad of chorioretinitis, hydrocephalus, and cerebral calcifications (Figs. 336.4 and 336.5). More than 50% of congenitally infected infants are considered normal in the perinatal period, but almost all such children will develop ocular involvement later in life if they are not treated during infancy. Neurologic signs such as convulsions, setting-sun sign with downward gaze, and increased head circumference due to ventricular dilatation or hydrocephalus caused by relatively mild involvement with inflammation or marked destruction of tissue obstructing the aqueduct of Sylvius or foramen of Monroe or inflammation resulting in stiff ventricles may be associated with substantial cerebral damage. If affected infants are treated promptly with antimicrobial therapy and placement of a ventriculoperitoneal shunt, signs and symptoms may resolve and development may be normal, making evidence of hydrocephalus a medical emergency. Early signs of potential congenital toxoplasmosis, such as ventricular dilatation or hydrocephalus, should be treated as a pediatric emergency. Outcomes are better with prompt placement of a ventriculoperitoneal shunt when indicated than when shunt placement is delayed. Head circumference crossing percentiles and obviously dilated ventricles with increased intracranial pressure require shunt placement, and ventricular dilatation without obvious increased pressure can also benefit from shunt placement.

The spectrum and frequency of neonatal manifestations of 210 newborns with congenital *Toxoplasma* infection identified by a serologic screening program of pregnant women in France were described in 1984. In this study, 10% had severe congenital toxoplasmosis with CNS involvement, eye lesions, and general systemic manifestations; 34% had mild

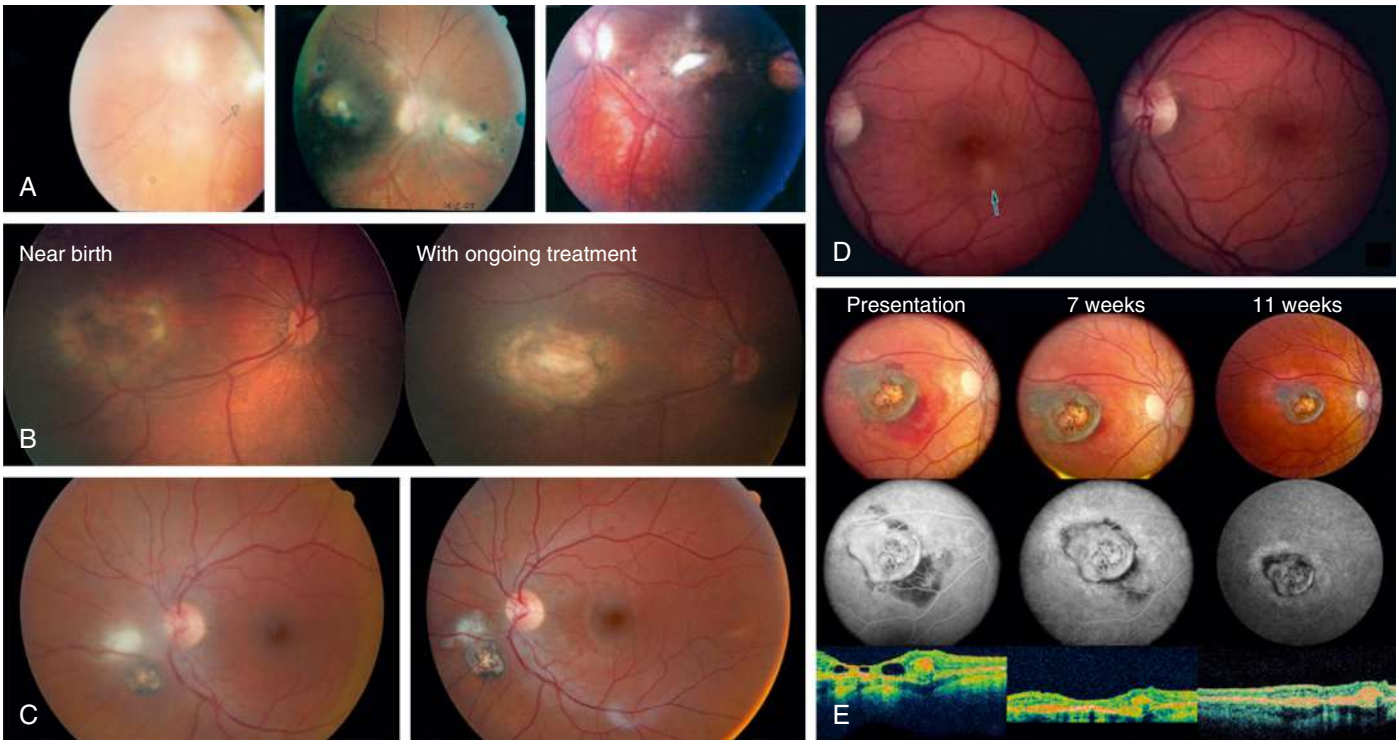

Fig. 336.3 Toxoplasmic chorioretinitis. **A,** Retinal photographs of a child with severe vitreitis that is less intense than the classic "headlight in fog" appearance *(left).* Resolving vitreitis caused by underlying active lesion *(middle).* Resolved healed lesion without vitreitis *(right).* **B,** Retina photographs for a newborn infant with active vitreitis (*left,* "near birth") with clearing of vitreitis and marked, but not complete, resolution of activity of the lesion 3 wk later (*right,* "with ongoing treatment"). **C,** Retinal photographs of a child showing an active lesion at presentation *(left),* and scarred lesion *(right).* **D,** Retinal photographs showing an active retinal lesion before treatment *(left)* and a completely resolved normal appearing retina within 1 mo of initiating treatment *(right).* **E,** Active choroidal neovascular membranes in a child. Fundus photographs *(top row),* fluorescein angiogram *(middle row),* and ocular coherence tomography *(bottom row)* of a child at presentation *(first column),* 7 wk after first ranibizumab (Lucentis, antibody to vascular endothelial growth factor [VEGF]) injection *(second column),* and 11 wk after first ranibizumab injection *(third column).* (**A-D,** *Adapted from Delair E, Latkany P, Noble AG, et al. Clinical manifestations of ocular toxoplasmosis. Ocul Immunol Inflamm. 2011;19:91–102;* **E,** *Adapted from Benevento JD, Jager RD, Noble AG, et al. Toxoplasmosis-associated neovascular lesions treated successfully with ranibizumab and antiparasitic therapy. Arch Ophthalmol. 2008;126:1152–1156.)*

involvement with normal clinical examination results other than retinal scars on dilated indirect exams or isolated intracranial calcifications in brain CT scans; and 55% had no detectable manifestations. These numbers represent an *underestimation* of the incidence of severe congenital infection for several reasons: the most severe cases, including most who died, were not referred; therapeutic abortion sometimes was performed when acute acquired infection of the mother was diagnosed early during pregnancy; in utero **spiramycin** therapy prevented or diminished the severity of infection; and only 13 of 210 congenitally infected newborns had brain CT, and only 77% of these 210 infants had a CSF examination. Routine newborn examinations often yield normal findings for congenitally infected infants, but more careful evaluations may reveal significant abnormalities. A 2012 analysis of the **National Collaborative Chicago-Based Congenital Toxoplasmosis Study** (NCCCTS, 1981–2009) data found that 72% of children at or near birth had chorioretinal scars, 70% had CNS calcifications, 12% had microcephaly, 37% had hydrocephalus, 41% had thrombocytopenia, 39% had hepatomegaly, 32% had splenomegaly, and 41% were born prematurely. In a study of 28 infants in New England identified by a universal state-mandated serologic screening program for *T. gondii*–specific immunoglobulin (Ig) M, 26 (93%) had normal findings on routine newborn examination, but 14 (50%) had significant abnormalities detected with more careful evaluation. The abnormalities included retinal scars (seven infants), active chorioretinitis (three infants), and CNS abnormalities (eight infants). In Fiocruz, Belo Horizonte, Brazil, infection is common, affecting 1 in 600 live births. Half of these infected infants have active chorioretinitis at birth.

There is also a wide spectrum of symptoms of untreated congenital toxoplasmosis that presents later in the first year of life. These children may have IQ scores of <70, convulsions, and severely impaired vision. When the infection is acquired in utero and the fetus is treated by drug therapy of the pregnant woman with pyrimethamine, sulfadiazine, and leucovorin, ocular and neurologic sequelae in the infant may be prevented.

SYSTEMIC SIGNS

From 25–50% of infants with clinically apparent disease at birth are born prematurely. Parasite clonal types other than type II are more often associated with prematurity and more severe disease. Intrauterine growth restriction, low Apgar scores, and temperature instability are common. Other manifestations may include lymphadenopathy, hepatosplenomegaly, myocarditis, pneumonitis, nephrotic syndrome, vomiting, diarrhea, and feeding problems. Bands of metaphyseal lucency and irregularity of the line of provisional calcification at the epiphyseal plate may occur without periosteal reaction in the ribs, femurs, and vertebrae. Congenital toxoplasmosis may be confused with erythroblastosis fetalis resulting from isosensitization, although the Coombs test result is usually negative with congenital *T. gondii* infection.

Prematurity, growth restriction, signs suggesting sepsis, thrombocytopenia, and abnormal CSF cells, protein, and glucose in the perinatal period should suggest congenital toxoplasmosis.

Skin

Cutaneous manifestations among newborn infants with congenital toxoplasmosis include rashes and jaundice and/or petechiae secondary to thrombocytopenia, but ecchymoses and large hemorrhages secondary to thrombocytopenia also occur. Rashes may be fine punctate, diffuse maculopapular, lenticular, deep blue-red, sharply defined macular, or diffuse blue and papular. Macular rashes involving the entire body including the palms and soles, exfoliative dermatitis, and cutaneous calcifications have been described. **Jaundice** with hepatic involvement and/or hemolysis, cyanosis due to interstitial pneumonitis from congenital infection, and edema

Table 336.1 Signs and Symptoms Occurring Before Diagnosis or During the Course of Untreated Acute Congenital Toxoplasmosis in 152 Infants (A) and in 101 of These Same Children After They Had Been Followed ≥4 Years (B)

	FREQUENCY OF OCCURRENCE IN PATIENTS WITH	
SIGNS AND SYMPTOMS	**"NEUROLOGIC" DISEASE***	**"GENERALIZED" DISEASE†**
A. Infants	**108 Patients (%)**	**44 Patients (%)**
Chorioretinitis	102 (94)	29 (66)
Abnormal cerebrospinal fluid	59 (55)	37 (84)
Anemia	55 (51)	34 (77)
Convulsions	54 (50)	8 (18)
Intracranial calcification	54 (50)	2 (4)
Jaundice	31 (29)	35 (80)
Hydrocephalus	30 (28)	0 (0)
Fever	27 (25)	34 (77)
Splenomegaly	23 (21)	40 (90)
Lymphadenopathy	18 (17)	30 (68)
Hepatomegaly	18 (17)	34 (77)
Vomiting	17 (16)	21 (48)
Microcephaly	14 (13)	0 (0)
Diarrhea	7 (6)	11 (25)
Cataracts	5 (5)	0 (0)
Eosinophilia	6 (4)	8 (18)
Abnormal bleeding	3 (3)	8 (18)
Hypothermia	2 (2)	9 (20)
Glaucoma	2 (2)	0 (0)
Optic atrophy	2 (2)	0 (0)
Microphthalmia	2 (2)	0 (0)
Rash	1 (1)	11 (25)
Pneumonitis	0 (0)	18 (41)
B. Children ≥4 Yr Old	**70 Patients (%)**	**31 Patients (%)**
Intellectual impairment	62 (89)	25 (81)
Convulsions	58 (83)	24 (77)
Spasticity and palsies	53 (76)	18 (58)
Severely impaired vision	48 (69)	13 (42)
Hydrocephalus or microcephaly	31 (44)	2 (6)
Deafness	12 (17)	3 (10)
Normal	6 (9)	5 (16)

*Patients with otherwise undiagnosed central nervous system disease in the first year of life.
†Patients with otherwise undiagnosed nonneurologic diseases during the first 2 mo of life.
Adapted from Eichenwald H. A study of congenital toxoplasmosis. In: Slim JC, ed. *Human Toxoplasmosis*. Copenhagen: Munksgaard; 1960: pp 41–49. Study performed in 1947. The most severely involved institutionalized patients were not included in the later study of 101 children.

secondary to myocarditis or nephrotic syndrome may be present. Jaundice and conjugated hyperbilirubinemia may persist for months.

Endocrine Abnormalities

Endocrine abnormalities may occur secondary to hypothalamic or pituitary involvement or end-organ involvement but are not common. Occasionally reported endocrine manifestations include myxedema, persistent hypernatremia with vasopressin-sensitive diabetes insipidus, sexual precocity, and partial anterior hypopituitarism.

Central Nervous System

Neurologic manifestations of congenital toxoplasmosis vary from massive acute encephalopathy to subtle neurologic syndromes. Toxoplasmosis should be considered as a potential cause of any undiagnosed neurologic disease in children <1 year old, especially if retinal lesions are present.

Hydrocephalus may be the sole neurologic manifestation of congenital toxoplasmosis and almost always requires shunt placement (see Fig. 336.5). Hydrocephalus may present prenatally and progress during the perinatal period or, much less often, may present later in life. Patterns of seizures

are protean and have included focal motor seizures, petit and grand mal seizures, muscular twitching, opisthotonos, and hypsarrhythmia. Spinal or bulbar involvement may be manifested by paralysis of the extremities, difficulty swallowing, and respiratory distress. **Microcephaly** usually reflects severe brain damage, but some children with microcephaly caused by congenital toxoplasmosis who have been treated promptly have normal or even superior cognitive function. Seizures, focal motor defects, and intellectual impairment may become apparent after the newborn period, even when infection is subclinical at birth.

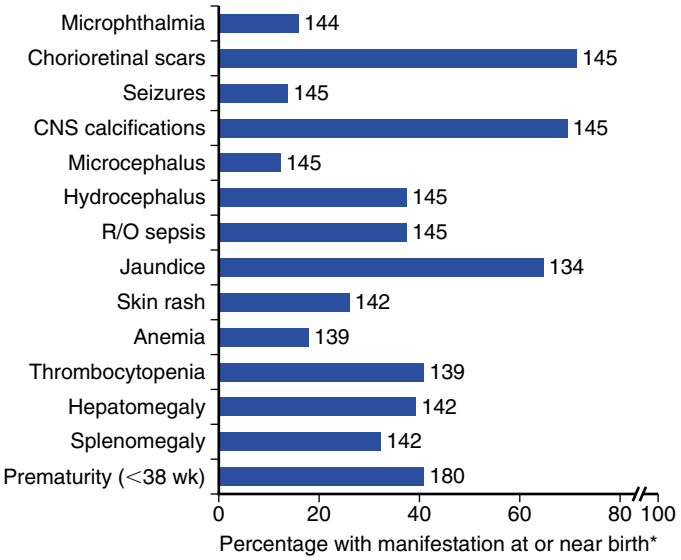

Fig. 336.4 Congenital toxoplasmosis: manifestations at presentation. National Collaborative Chicago-Based Congenital Toxoplasmosis Study (NCCCTS, 1981–2009). *Infants diagnosed with congenital toxoplasmosis in the newborn period and referred to the NCCCTS during the first year of life. Numbers adjacent to histogram bars represent number of infants with this manifestation and are based on information in birth records. Sample size dependent on available birth records/diagnoses at birth. R/O, Rule out; CNS, central nervous system. *(Adapted from McLeod R, Boyer KM, Lee D, et al. Prematurity and severity are associated with Toxoplasma gondii alleles [NCCCTS, 1981–2009]. Clin Infect Dis. 2012;54:1595–1605.)*

Other Neurologic Disease

T. gondii infection is a cause of epilepsy and other neurologic disorders that improve with medical treatment. Ketogenic diet has led to resolution of seizures refractory to other treatments due to *T. gondii*. Symptomatic spinal cord lesions may be evident as T2-weighted abnormalities and can also resolve with medical treatment.

Symptomatic spinal cord lesions may be evident as T2 weighted abnormalities on MRI and can resolve with medical treatment.

CSF abnormalities occur in at least 50% of infants with congenital toxoplasmosis. A CSF protein level >1 g/dL is characteristic of severe CNS toxoplasmosis and is usually accompanied by hydrocephalus. Local production of *T. gondii*–specific IgG and IgM antibodies may be demonstrated. CT of the brain is useful to detect calcifications, determine ventricular size, and demonstrate porencephalic cystic structures (see Fig. 336.5). MRI is used to assess ventricular size and configuration and can detect T2-weighted abnormalities associated with active disease. **Calcifications** occur throughout the brain, but there is a propensity for development of calcifications in the caudate nucleus and basal ganglia, choroid plexus, and subependyma. MRI and contrast-enhanced CT brain scans are useful for detecting active inflammatory lesions. Rapid MRI or ultrasonography may be useful for following ventricular size. Medical treatment in utero and in the first year of life results in improved neurologic outcomes and oftentimes diminution or disappearance of calcifications.

Eyes

Almost all untreated congenitally infected infants develop **chorioretinal lesions** by adulthood and may have severe visual impairment. *T. gondii* causes a **focal necrotizing retinitis** in congenitally infected individuals (see Fig. 336.3). Retinal detachment may occur. Any part of the retina may be involved, either unilaterally or bilaterally, including the maculae. The optic nerve may be involved, and toxoplasmic lesions that involve projections of the visual pathways in the brain or the visual cortex also may lead to visual impairment. In association with severe retinal lesions and vitritis, secondary anterior uveitis may develop and occasionally lead to erythema of the external eye.

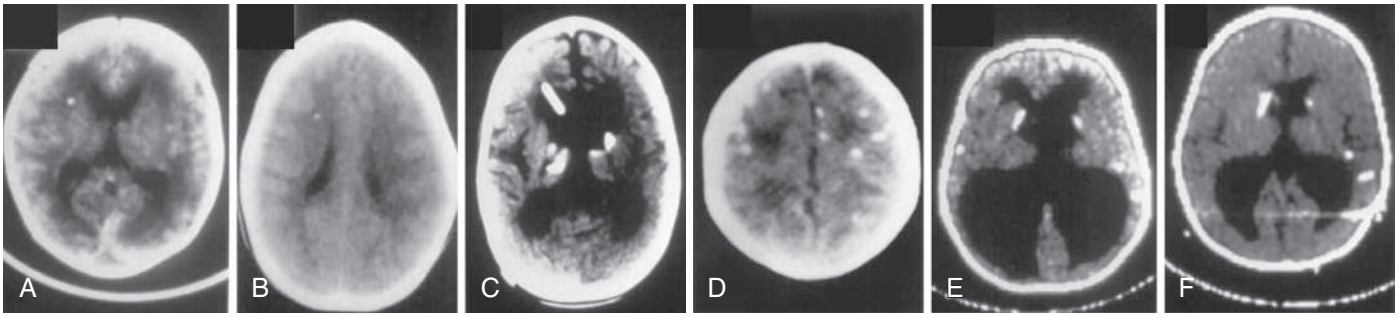

Fig. 336.5 Head CT scans of infants with congenital toxoplasmosis. **A,** CT scan at birth that shows areas of hypolucency, mildly dilated ventricles, and small calcifications. **B,** CT scan of the same child at 1 yr of age (after antimicrobial therapy for 1 yr). This scan is normal, with the exception of two small calcifications. This child's Mental Development Index (MDI) at 1 yr old was 140 by the Bayley Scale of Infant Development. **C,** CT scan from a 1-yr-old infant who was normal at birth. His meningoencephalitis became symptomatic in the first few weeks of life but was not diagnosed correctly and remained untreated during his first 3 mo of life. At 3 mo old, development of hydrocephalus and bilateral macular chorioretinitis led to the diagnosis of congenital toxoplasmosis, and antimicrobial therapy was initiated. This scan shows significant residual atrophy and calcifications. This child had substantial motor dysfunction, development delays, and visual impairment. **D,** CT scan obtained during the first month of life of a microcephalic child. Note the numerous calcifications. This child's IQ scores using the Stanford-Binet Intelligence Scale for children when she was 3 yr old and Wechsler Preschool and Primary Scale Intelligence when she was 5 yr old were 100 and 102, respectively. She received antimicrobial therapy during her first year of life. **E,** CT scan with hydrocephalus caused by aqueductal obstruction, before placement of a ventricular shunt. **F,** Scan from the same patient as the scan in **E,** after shunt placement. This child's IQ scores using the Stanford-Binet Intelligence Scale for children were approximately 100 when she was 3 yr old and 6 yr old. *(**A-F** adapted from McAuley J, Boyer K, Patel D, et al. Early and longitudinal evaluations of treated infants and children and untreated historical patients with congenital toxoplasmosis: the Chicago Collaborative Treatment Trial. Clin Infect Dis. 1994;18:38–72.)*

Other ocular findings include cells and protein in the anterior chamber, large keratic precipitates, posterior synechiae, nodules on the iris, and neovascular formation on the surface of the iris, sometimes with increased intraocular pressure and glaucoma. Rarely, the extraocular musculature may also be involved directly. Other manifestations include strabismus, nystagmus, visual impairment, and microphthalmia. Enucleation has been required for a blind, phthisic, painful eye. The **differential diagnosis** of ocular toxoplasmosis includes congenital coloboma and inflammatory lesions caused by cytomegalovirus (CMV), lymphocytic choriomeningitis virus, *Bartonella henselae, Toxocara canis*, *Treponema pallidum, Mycobacterium tuberculosis,* varicella-zoster virus, Zika virus, or vasculitis. Ocular toxoplasmosis may be a recurrent and progressive disease that requires multiple courses of therapy. Limited data suggest that occurrence of lesions in the early years of life may be prevented by instituting **antimicrobial treatment** with pyrimethamine and sulfadiazine during the first year of life. Initiation of treatment of the infected fetus in utero followed by treatment in the first year of life further reduces the incidence and the severity of retinal disease.

Ears

Both mild and severe sensorineural hearing loss may occur. It is not known whether this hearing loss is a static or progressive disorder. Treatment in the first year of life is associated with decreased frequency of hearing loss.

DIAGNOSIS

Diagnosis of acute *T. gondii* infection can be established by a number of methods (Table 336.2): isolation of *T. gondii* from blood or body fluids; identification of tachyzoites in sections or preparations of tissues and body fluids, amniotic fluid, or placenta; identification of cysts in the placenta or tissues of a fetus or newborn; and characteristic lymph node histologic features. Serologic tests are very useful for diagnosis. Polymerase chain reaction (PCR) is useful to identify *T. gondii* DNA in CSF and amniotic fluid and has been reported to be useful with infant peripheral blood and urine to establish the diagnosis definitively and in immunocompromised patients for diagnosis and monitoring treatment.

Isolation or Identification of *T. gondii*

Organisms can be isolated by inoculation of body fluids, leukocytes, or tissue specimens into mice or tissue culture cells. Body fluids should be processed and inoculated immediately, but *T. gondii* has been isolated from tissues and blood that have been stored overnight or even for 4-5 days at 4°C (39.2°F). Freezing or treatment of specimens with formalin kills *T. gondii*. From 6-10 days after inoculation into mice, or earlier if mice die, peritoneal fluids should be examined for tachyzoites. If inoculated mice survive for 6 weeks and seroconvert, definitive diagnosis is made by visualization of *Toxoplasma* cysts in mouse brain. If cysts are not seen, **subinoculation** of mouse tissue into other mice is performed. Treatment of subinoculated mice with corticosteroids appears to enhance ability to isolate the parasite.

Microscopic examination of tissue culture cells inoculated with *T. gondii* shows necrotic, heavily infected cells with numerous extracellular tachyzoites. Isolation of *T. gondii* from blood or body fluids reflects acute infection. Except in the fetus or neonate, it is usually not possible to distinguish acute from past infection by isolation of *T. gondii* from tissues (e.g., skeletal muscle, lung, brain, eye) obtained by biopsy or at autopsy.

Diagnosis of acute infection can be established by visualization of tachyzoites in biopsy tissue sections, bone marrow aspirates, or body fluids (e.g., CSF, amniotic fluid). Immunofluorescent antibody and immunoperoxidase staining techniques may be necessary, because it is often difficult to distinguish the tachyzoite using ordinary stains. Tissue cysts are diagnostic of infection but do not differentiate between acute and chronic infection, although the presence of many cysts suggests recent acute infection. Cysts in the placenta or tissues of the newborn infant establish the diagnosis of congenital infection. Characteristic histologic features strongly suggest the diagnosis of toxoplasmic lymphadenitis.

Serologic Testing

Serologic tests are useful in establishing the diagnosis of congenital or acutely acquired *T. gondii* infection. Each laboratory that reports serologic test results must have established values for their tests that diagnose infection in specific clinical settings, provide interpretation of their results, and ensure appropriate quality control before therapy is based on serologic test results. Serologic test results used as the basis for therapy should ideally be confirmed in a reference laboratory.

The **Sabin-Feldman dye test** is sensitive and specific. This test measures primarily IgG antibodies. Results should be expressed in international units (IU/mL), based on international standard reference sera available from the World Health Organization (WHO).

The **IgG indirect fluorescent antibody (IgG-IFA) test** measures the same antibodies as the Sabin-Feldman dye test, and the titers tend to be parallel. These antibodies usually appear 1-2 weeks after infection, reach high titers (≥1:1,000) after 6-8 weeks, and then decline over months to years. Low titers (1:4 to 1:64) usually persist for life. Antibody titer does not correlate with severity of illness.

An **agglutination test** (bioMérieux, Lyon, France) available commercially in Europe uses formalin-preserved whole parasites to detect IgG antibodies. This test is accurate, simple to perform, and inexpensive.

The **IgM-IFA test** is useful for the diagnosis of acute acquired infection with *T. gondii* in the older child because IgM antibodies appear earlier, often by 3-5 days after infection, and diminish more quickly than IgG antibodies. In most instances, IgM antibodies rise rapidly (1:50 to ≥1:1,000) and then fall to low levels (1:10 or 1:20) or disappear after weeks or months. However, some patients continue to have positive IgM levels with low titers for several years. The IgM-IFA test detects *Toxoplasma*-specific IgM in only approximately 25% of congenitally infected infants at birth. IgM antibodies may not be present in sera of immunocompromised patients with acute toxoplasmosis or in patients with reactivation of ocular toxoplasmosis. The IgM-IFA test may yield false-positive results as a result of rheumatoid factor (RF).

The **double-sandwich IgM enzyme-linked immunosorbent assay (IgM-ELISA)** is also useful for detection of *Toxoplasma* IgM antibodies. In the older child, serum IgM-ELISA *Toxoplasma* antibodies of >2 (a value of one reference laboratory; each laboratory must establish its own value for positive results) indicates that *Toxoplasma* infection most likely has been acquired recently. The IgM-ELISA identifies approximately 50–75% of infants with congenital infection. IgM-ELISA avoids both the false-positive results from RF and the false-negative results from high levels of passively transferred maternal IgG antibody in fetal serum, as may occur with the IgM-IFA test. Results obtained with commercial kits must be interpreted with caution, because false-positive reactions can occur. Care must also be taken to determine whether kits have been standardized for diagnosis of infection in specific clinical settings, such as in the newborn infant. The **IgA-ELISA** also is a sensitive test for detection of maternal and congenital infection, and results may be positive when those of the IgM-ELISA are not.

The **immunosorbent agglutination assay (ISAGA)** combines trapping of a patient's IgM to a solid surface and use of formalin-fixed organisms or antigen-coated latex particles. It is read as an agglutination test. There are no false-positive results from RF or antinuclear antibodies (ANAs). **IgM-ISAGA** is more sensitive and may detect specific IgM antibodies before and for longer periods than IgM-ELISA.

At present, IgM-ISAGA and IgA-ELISA are the most useful tests for diagnosis of congenital infection in the newborn but are not positive in all infected infants. The IgE-ELISA and IgE-ISAGA are also sometimes useful in establishing the diagnosis of congenital toxoplasmosis or acute acquired *T. gondii* infection. The presence of IgM antibodies in the older child or adult can never be used alone to diagnose acute acquired infection. The lateral immunochromatographic test (ICT) can identify IgG and/or IgM in serum or whole blood from fingerstick precisely and rapidly. Western blot II is highly accurate for identifying *T. gondii*-specific IgG and for IgM.

Table 336.2 Generalizations Concerning Clinical Presentations, *Toxoplasma*-Specific Diagnostic Tests, and Treatment

CLINICAL SETTING AND MANIFESTATION	SAMPLE SOURCE	*TOXOPLASMA*-SPECIFIC DIAGNOSTIC TESTS								TREATMENT				
		G	M	A	E	AV	AC/HS	PCR KARIUS	SUBINOCULATION	SP	PSL*	CO	LU	NONE
PRENATAL														
Acute infection in pregnant woman ≤15 wk amenorrhea in gestation *and* no clinical evidence of fetal infection	Mother	+	+	+	+	L	Acute	AF (17-18 wk)	NS	+	+ †No P first trimester			
Acute infection in pregnant woman ≤15 wk amenorrhea in gestation *and* signs of fetal infection	Mother	+	+	+	+	L	Acute	AF (may not be necessary)	NS		+ †No P first trimester			
Acute infection in pregnant woman at >18 wk gestation	Mother	+	+	+	+	L	Acute	AF	NS		+			
Congenital infection in infant	Infant	+	+	+	+	L	Acute	Placenta/buffy coat	Placenta/buffy coat		+	‡		
POSTNATAL														
Acute, symptomatic Acute, self-limited symptoms	Child	+	+	+	+	L	Acute	NS	NS		+			+
Chronic, asymptomatic	Child	+	–	–	–	H	Chronic	NS	NS					
Acute, severely symptomatic	Child	+	+	+	+	L	Acute	§	Body fluids/buffy coat		+			
Immune compromised¶	Child	+/–	+/–	+/–	+/–	+/–	+/–	§	Body fluids/buffy coat					
Laboratory accident#	Child	+/–	+/–	+/–	+/–	+/–	+/–	NS	NS		+			
Eye Disease														
Quiescent scar**	Child	+	+/–	+/–	+/–	+/–	+/–	NS	NS					+
Active chorioretinitis**	Child	+	+/–	+/–	+/–	+/–	+/–	NS	NS		+			
Active CNVM**	Child	+	+/–	+/–	+/–	+/–	+/–	NS	NS		+		††	

*Pyrimethamine and leucovorin should be adjusted for granulocytopenia; complete blood counts, including platelets, should be monitored each Monday and Thursday. If there is sulfonamide allergy, alternative medicines include azithromycin (first choice), clarithromycin, or clindamycin in place of sulfadiazine.

†*Do not* use pyrimethamine in the first 14 weeks of gestation.

‡Occasionally, corticosteroids (prednisone) have been used when CSF protein is ≥1 g/dL or when active chorioretinitis threatens vision and should be continued until signs of inflammation or active chorioretinitis that threatens vision have subsided; then dosage can be tapered and the steroids discontinued.

§Utility of PCR depends on clinical setting. For example, the following may be useful to establish the diagnosis: PCR of body fluids such as amniotic fluid or CSF; cells from bronchoalveolar lavage from a patient with pneumonia; or tissue such as placenta where the presence of parasites or parasite DNA would support a diagnosis of infection.

¶In some cases, in immunocompromised persons, there is no detectable serologic response to *T. gondii*. However, if clinical presentation is indicative of infection in the absence of positive serologic results, CSF, buffy coat of peripheral blood, histopathology of tissue samples, or body fluids tested with PCR or subinoculation may be useful. If PCR demonstrates the presence of *T. gondii* DNA in the sample, it is useful for diagnosis. However, the sensitivity of PCR has been variable in this setting. In some circumstances, presumptive treatment may be warranted.

#Whether a person should be treated for a laboratory accident depends on the nature of the accident, the serology of the person before the accident, and other factors. When there is risk of infection, prompt treatment is given, considering the possible genetic manipulation of the laboratory strain.

**Serologic results depend on whether infection is acute (recently acquired) or chronic. When testing serum from persons with ocular toxoplasmosis, *T. gondii*–specific IgG may be demonstrable only in an undiluted serum sample.

††Corticosteroids (prednisone) are used if inflammation or edema caused by infection threatens vision and should be continued until signs of inflammation or active chorioretinitis that threatens vision have subsided; then dosage can be tapered and the steroids discontinued.

+, Positive; –, negative; +/–, equivocal; A, *T. gondii*–specific IgA; AC/HS, differential agglutination test where A represents acetone fixed parasites and H represents formalin fixed antigen; AF, amniotic fluid; Av, *T. gondii*–specific IgG avidity; CNVM, choroidal neovascular membrane; Co, corticosteroids (prednisone); CSF, cerebrospinal fluid; E, *T. gondii*–specific IgE; G, *T. gondii*–specific IgG; L, leucovorin; Lu, Lucentis (antibody to vascular endothelial growth factor); M, *T. gondii*–specific IgM; NS, not standard to obtain; P, pyrimethamine; PCR, polymerase chain reaction; PSL, pyrimethamine (P), sulfadiazine (S), leucovorin (L) (folinic acid); Sp, spiramycin.

Adapted from Remington JS, McLeod R, et al. Toxoplasmosis. In: Remington JS, Klein JO, eds. *Infectious Diseases of the Fetus and Newborn Infant*. 6th ed. Philadelphia: Saunders; 2006.

The **differential agglutination test (HS/AC)** compares antibody titers obtained with formalin-fixed tachyzoites (**HS antigen**) with titers obtained using acetone-fixed tachyzoites (**AC antigen**) to differentiate recent and remote infections in adults and older children. This method may be particularly useful in differentiating remote infection in pregnant women, because levels of IgM and IgA antibodies detectable by ELISA or ISAGA may remain elevated for months to years in adults and older children.

The **avidity test** can be helpful to establish time of acquisition of infection. A high-avidity test result indicates that infection began >12-16 weeks earlier, which is especially useful in determining time of acquisition of infection in the first or final 16 weeks of gestation. A low-avidity test result may be present for many months or even years and does not definitively identify recent acquisition of infection.

A relatively higher level of *Toxoplasma* antibody in the aqueous humor or in CSF demonstrates local production of antibody during active ocular or CNS toxoplasmosis. This comparison yields a coefficient [C], which is calculated as follows:

$$C = \frac{\text{Antibody titer in body fluid}}{\text{Antibody titer in serum}} \times \frac{\text{Concentration of IgG in serum}}{\text{Concentration of IgG in body fluid}}$$

Significant coefficients [C] are >8 for ocular infection, >4 for congenital CNS infection, and >1 for CNS infection in patients with AIDS. If the serum dye test titer is >300 IU/mL, it is not possible to demonstrate significant local antibody production using this formula with either the dye test or the IgM-IFA test titer. IgM antibody may be detectable in CSF.

Comparative **Western immunoblot** tests of sera from a mother and infant may detect congenital infection. Infection is suspected when the mother's serum and her infant's serum contain antibodies that react with different *Toxoplasma* antigens.

The **enzyme-linked immunofiltration assay** using micropore membranes permits simultaneous study of antibody specificity by immunoprecipitation and characterization of antibody isotypes by immunofiltration with enzyme-labeled antibodies. This method is able to detect 85% of cases of congenital infection in the first few days of life.

Serologic tests in development include multiplex antibody tests for IgG-, IgM-, and IgA-specific antibodies and point-of-care tests designed to provide accurate and rapid identification of recent infection or seroconversion in pregnant women. The ICT point-of-care IgG-IgM test (LDBIO Diagnostic, Lyon, France) has shown very high diagnostic sensitivity and specificity and has been CE marked for use in Europe.

Nucleic Acid Detection

PCR on amniotic fluid is used to detect a repetitive *T. gondii* gene such as the 529 bp multi-copy gene or the 20 copy B1 gene and is the method of choice for establishing the diagnosis of congenital *Toxoplasma* infection in the fetus. Sensitivity and specificity of PCR on amniotic fluid obtained between 17 and 21 weeks of gestation are approximately 95% for diagnosing congenital infection. PCR of peripheral white blood cells, CSF, and urine has been used to detect congenital infection at birth or postnatally. PCR of vitreous or aqueous fluids has been used to diagnose ocular toxoplasmosis. Karius test also detects nucleic acid. Abnormalities in MRI studies of brain and spinal cord may demonstrate activity of infection and are indicative (see Fig. 336.4). Both patient and parasite genetics contribute to severity and manifestations of illness (see Figs. 336.3 to 336.5).

Other Tests

Lymphocyte blastogenesis to *T. gondii* antigens has been used to diagnose congenital toxoplasmosis when the diagnosis is uncertain and other test results are negative. However, a negative result does not exclude the diagnosis, as immune tolerance sometimes interferes with response of neonatal peripheral blood lymphocytes to *T. gondii* antigens. Novel biomarkers such as microRNAs and certain proteins may indicate active infection.

Acquired Toxoplasmosis

Recent infection is diagnosed by seroconversion from a negative to a positive IgG antibody titer (in the absence of transfusion), a two-tube increase in *Toxoplasma*-specific IgG titer when serial sera are obtained 3 weeks apart and tested in parallel, or the detection of *Toxoplasma*-specific IgM antibody in conjunction with other tests, but never alone.

Ocular Toxoplasmosis

IgG antibody titers of 1:4 to 1:64 are typical in older children with active *Toxoplasma* chorioretinitis. The presence of antibodies measurable only when serum is tested undiluted is also helpful in establishing the diagnosis. The diagnosis of ocular infection is likely with characteristic retinal lesions and positive serologic tests. PCR of aqueous or vitreous fluid has been used to diagnose ocular toxoplasmosis but is performed infrequently because of the risks associated with obtaining intraocular fluid and because the diagnosis can be made based on clinical appearance and history.

Immunocompromised Persons

Toxoplasma IgG antibody titers may be low and *Toxoplasma* IgM is often absent in immunocompromised stem cell transplant recipients but not in kidney or heart transplant recipients with toxoplasmosis. Demonstration of *Toxoplasma* DNA by PCR in serum, blood, and CSF may identify disseminated *Toxoplasma* infection in immunocompromised persons. Resolution of CNS lesions during a therapeutic trial of pyrimethamine and sulfadiazine has been useful to diagnose toxoplasmic encephalitis in patients with AIDS. Brain biopsy has been used to establish the diagnosis if there is no response to a therapeutic trial and to exclude other possible diagnoses such as CNS lymphoma.

Congenital Toxoplasmosis

Fetal ultrasound examination performed every 2 weeks during gestation beginning at diagnosis of acute acquired infection in a pregnant woman and PCR analysis of amniotic fluid are used for prenatal diagnosis. Examination of the placenta at delivery by histology and by PCR may facilitate diagnosis of congenital infection but is not sufficiently sensitive or specific for routine diagnosis.

Newborns suspected of having congenital toxoplasmosis should be evaluated by general, ophthalmologic, and neurologic examinations; head CT scan; and ideally all of the following tests: an attempt to detect *T. gondii* in the placenta and the infant's leukocytes from peripheral blood buffy coat; measurement of serum *Toxoplasma*-specific IgG, IgM, IgA, and IgE antibodies and the levels of total serum IgM and IgG; lumbar puncture, including analysis of CSF for cells, glucose, protein, *Toxoplasma*-specific IgG and IgM antibodies, and level of total IgG; and testing of CSF for *T. gondii* by PCR and inoculation into mice. Presence of *Toxoplasma*-specific IgM in CSF that is not contaminated with blood or confirmation of local antibody production of *Toxoplasma*-specific IgG antibody in CSF establishes the diagnosis of congenital *Toxoplasma* infection.

Serologic tests are also useful in establishing a diagnosis of congenital toxoplasmosis. Either persistent or rising titers in the Sabin-Feldman dye test or the IgG-IFA test or a positive IgM-ELISA or IgM-ISAGA result is diagnostic of congenital toxoplasmosis. The half-life of IgM is approximately 2 days, so presence of detectable IgM antibodies in the infant's serum decreases relatively quickly, usually within 1 week. Passively transferred maternal IgG antibodies may require many months to a year to disappear from the infant's serum, depending on the magnitude of the original titer. The half-life of passively transferred maternal IgG is approximately 30 days, so the titer diminishes by half each 30 days. Synthesis of *Toxoplasma* antibody is usually demonstrable by the third month of life if the infant is untreated, although the rate of IgG synthesis varies considerably in infants <1 year old. If the infant is treated, synthesis may be delayed for as long as the ninth month of life and occasionally does not occur at all. When an infant begins to synthesize IgG antibody, infection may be documented serologically even without demonstration of IgM antibodies by an increase in the ratio of specific serum IgG antibody titer to the total IgG. In contrast, the ratio of specific serum IgG to the total IgG will decrease if the specific IgG antibody has been passively transferred from the mother.

Many manifestations of congenital toxoplasmosis are similar to findings that occur in other perinatal infections, especially congenital CMV infection. Because neither cerebral calcification nor chorioretinitis is pathognomonic, a negative urine culture or PCR for CMV soon after birth is a useful adjunctive test. The clinical picture in the newborn infant may also be compatible with sepsis, aseptic meningitis, syphilis,

or hemolytic disease. Some children <5 years old with chorioretinitis have postnatally acquired *T. gondii* infection.

TREATMENT

Currently available treatments are effective against the active tachyzoite form of the parasite. No commercially available medicines to date eliminate the latent encysted form of the parasite, although promising preclinical data suggest that such treatments will be possible in the future. Table 336.1 summarizes treatments in each clinical category.

A number of therapeutic agents, including pyrimethamine, sulfonamides, and macrolides, have been used to treat toxoplasmosis in its various clinical manifestations. In general, they have activity that is limited to the pathogenic tachyzoite stage of the parasite's life cycle. No clinically available antimicrobial agent has yet been found capable of eliminating the encysted bradyzoite stage. Thus, active disease may be effectively treated, but not ultimately cured, by current therapies. In a person with normal cell-mediated immunity, a single course of therapy may be sufficient. In immune-compromised patients and congenital infection, recurrences may be a long-term management problem. Curative therapies remain an area of continuing active research, with several promising candidates. Table 336.2 summarizes treatment according to clinical category of disease.

Pyrimethamine and **sulfadiazine** act synergistically against *Toxoplasma,* and combination therapy is **considered the treatment of choice** and is indicated for all clinical presentations of toxoplasmosis that require treatment, except for acute *Toxoplasma* infection acquired during the first trimester of pregnancy (see Table 336.2). Pyrimethamine is contraindicated during the first trimester of pregnancy because of teratogenic effects. Pyrimethamine and sulfadiazine are used in Austria and Germany and now sometimes in France and the United States for treatment of newly seropositive mothers after 15 weeks of gestation.

In contrast to mammals, *Toxoplasma* cannot take up folinic acid, a precursor for folate synthesis. Thus folinic acid protects the human bone marrow from toxicity due to pyrimethamine, which inhibits the enzyme dihydrofolate reductase (DHFR), blocking synthesis of folic acid. By correcting an enzymatic pathway accessible in human cells but not in *Toxoplasma,* leucovorin (folinic acid) renders pyrimethamine/sulfadiazine a safer and more selective antiparasitic combination. Leucovorin is always given in conjunction with pyrimethamine and in the week after discontinuing pyrimethamine because of pyrimethamine's long half-life.

Pyrimethamine levels can be measured to make certain that they are in a therapeutic, nontoxic range of less than approximately 2.3 mg/dL and more than approximately 0.5 mg/dL for pyrimethamine when older children are treated for retinal disease or in other circumstances when medicines may be continued for longer times and reach high levels. Therapeutic endpoint is until resolution of the active retinal lesion and then at least 1 month beyond that, with no immune compromise, immune deficiency, or immune immaturity (for infants).

For treatment of those with primary, acute acquired toxoplasma in gestation to prevent or treat infection in the fetus, pyrimethamine is contraindicated during the first trimester of pregnancy. Pyrimethamine sulfadiazine is used in Austria and Germany, and now sometimes in France and the United States for treatment of those newly seropositive mothers after 15 weeks amenorrhea during gestation.

Spiramycin is used to attempt to prevent vertical transmission of infection to the fetus of acutely infected pregnant women in the first trimester. A recent meta-analysis adds to the evidence of significant reduction in mother-to-child transmission rates following spiramycin treatment of diagnosed gestational *T. gondii* infection. In 2018, Mandelbrot et al. reported results of a randomized controlled trial that compared treatment with pyrimethamine sulfadiazine promptly following seroconversion after 15 weeks rather than using spiramycin until 17 weeks' gestation with pyrimethamine sulfadiazine initiated only for PCR-positive amniotic fluid. Hypersensitivity for the mother is a greater risk in the group that receives pyrimethamine sulfadiazine earlier and may make diagnosis more difficult by obscuring evidence of infection in the fetus and infant. There was a very small increase in the number of infants with severe findings in the group that received pyrimethamine sulfadiazine initiated at the later time.

The merits of this gestational treatment approach have been examined in cost-benefit analyses examining both the United States and Austria, and the first direct cost-benefit comparison of prenatal and neonatal in the context of France (not yet published) all indicate better outcomes for affected infants and the healthcare system if treatment is started in utero, rapidly following seroconversion. Toxoplasma cannot take up folinic acid, a precursor for folate synthesis, whereas mammalian cells can take up folinic acid. Thus, folinic acid protects the human bone marrow from toxicity due to pyrimethamine. Use of pyrimethamine is contraindicated in the first trimester of pregnancy; it inhibits the enzyme dihydrofolate reductases and thus synthesis of folic acid.

Spiramycin is a macrolide antibiotic that is active against *Toxoplasma* in the placenta but does not reach sufficient levels in other tissues to treat a fetus or to be used postnatally. Hence, it has been used successfully to prevent congenital toxoplasmosis in pregnant women who have documented seroconversion in the first trimester when pyrimethamine is contraindicated.

Azithromycin is a macrolide that is used in severe or recurrent disease when sulfonamide allergy precludes the use of sulfadiazine. Azithromycin has been used to suppress infection and prevent recurrences of retinochoroiditis.

TMP-SMX is less active than pyrimethamine/sulfadiazine, with a suboptimal ratio of the DHFR and para-amino benzoic acid synthase inhibitors and with a shorter half-life of trimethoprim relative to pyrimethamine. Treatment failures have occurred with TMP-SMX, underscoring the importance of treating with pyrimethamine and sulfadiazine if at all possible. Clindamycin and atovaquone have also been used as second line agents but not as single antimicrobial agents.

Reversible neutropenia is the most common adverse effect in pyrimethamine-treated infants and typically responds to temporary holding of doses. All patients treated with pyrimethamine should have leukocyte counts twice weekly. Medicines may be held temporarily. GCSF treatment is rarely needed. Improper preparation of medicine, not making it fresh each week, is a cause of increased difficulties with neutropenia. Seizures may occur with overdose of pyrimethamine. Potential toxic effects of sulfonamides include crystalluria, hematuria, and rash. Profound neutropenia is a risk with sulfonamide overdosage, which has occurred when pharmacies make large quantities of the suspension and there is settling of the medication with the starch binder. The protocol for preparation for infants should be followed carefully, with fresh medicine prepared weekly and the bottle shaken well. Hypersensitivity reactions occur, especially in patients with AIDS. For older children and adults, eight glasses of a nonacidic beverage should be consumed each day while taking the medicine. Hypersensitivity reactions occur, especially frequently in patients with AIDS. As mentioned above, folinic acid, as calcium leucovorin, should always be administered concomitantly and for 1 week after treatment with pyrimethamine is discontinued to prevent bone marrow suppression.

Acquired Toxoplasmosis

Patients with acquired toxoplasmosis and lymphadenopathy usually do not need specific treatment unless they have severe and persistent symptoms or evidence of damage to vital organs (see Table 336.2). If such signs and symptoms occur, treatment with pyrimethamine, sulfadiazine, and leucovorin should be initiated. Patients who appear to be immunocompetent but have severe and persistent symptoms or damage to vital organs (e.g., chorioretinitis, myocarditis) need specific therapy until these specific symptoms resolve, followed by therapy for an additional 2 weeks. Therapy often is administered for at least 4-6 weeks, though the optimal duration of therapy has not been defined. A loading dose of pyrimethamine for older children is 2 mg/kg/day divided twice daily (maximum 50 mg bid), given for the first 1-2 days of treatment. The maintenance dose begins on the third day and is 1 mg/kg/day (maximum 50 mg/day). Sulfadiazine is administered at 100 mg/kg/day bid (maximum 4 g/day). Leucovorin is administered orally at 5-20 mg 3 times weekly (or 10 mg daily depending on the leukocyte count).

Ocular Toxoplasmosis

Patients with active ocular toxoplasmosis are treated with pyrimethamine, sulfadiazine, and leucovorin (see Table 336.2). They are treated while disease is active and then for at least several weeks after the lesion has developed a quiescent appearance (i.e., sharp borders, pigmentation at margins of the lesion, and resolution of associated inflammatory cells in the vitreous), which usually occurs in 2-4 weeks when treatment is initiated promptly. Within 7-10 days, the borders of the retinal lesions sharpen, and visual acuity usually returns to the level before development of the acute lesion. Systemic corticosteroids have been administered concomitantly with antimicrobial treatment when lesions involve the macula, optic nerve head, or papillomacular bundle. Corticosteroids must never be given alone but may be initiated after loading doses of pyrimethamine and sulfadiazine have been administered (2 days). With recurrences, new lesions often appear contiguous to old ones. Very rarely, vitrectomy and removal of the lens are needed to restore visual acuity. Active choroidal neovascular membranes as a result of toxoplasmic chorioretinitis have been treated successfully in children with intravitreal injection of antibody to vascular endothelial growth factor in addition to oral anti-*Toxoplasma* medicines. Suppressive treatment has prevented frequent recurrences of vision-threatening lesions.

Immunocompromised Persons

Serologic evidence of acute infection in an immunocompromised patient, regardless of whether signs and symptoms of infection are present or tachyzoites are demonstrated in tissue, is indication for therapy similar to that described for immunocompetent persons with symptoms of organ injury (see Table 336.2). It is important to establish the diagnosis as rapidly as possible and institute treatment early. In immunocompromised patients other than those with AIDS, therapy should be continued for at least 4-6 weeks beyond complete resolution of all signs and symptoms of active disease and resolution of immune compromise. Careful follow-up of these patients is imperative because relapse may occur, requiring prompt reinstitution of therapy. Relapse was once common in AIDS patients without antiretroviral treatment, and suppressive therapy with pyrimethamine and sulfadiazine, or TMP-SMX, was continued for life. Now it is possible to discontinue maintenance therapy when the CD4 count remains at >200 cells/μL for 4 months and all lesions have resolved. Therapy usually induces a beneficial response clinically but does not eradicate cysts. Treatment of *T. gondii*–seropositive patients with AIDS should be continued as long as CD4 counts remain at <200/μL. Prophylactic TMP-SMX therapy for *P. jirovecii* pneumonia significantly reduces the incidence of toxoplasmosis in AIDS patients.

Congenital Toxoplasmosis

All fetuses and newborns infected with *T. gondii* should be treated regardless of whether they have clinical manifestations of infection, because treatment may be effective in interrupting acute disease that damages vital organs (see Table 336.2). The fetus is treated by treating the pregnant woman with pyrimethamine, sulfadiazine, and leucovorin after the first trimester. Infants should be treated for 1 year with pyrimethamine (2 mg/kg/day orally [PO] bid for 2 days, then 1 mg/kg/day for 2-6 months, and then 1 mg/kg given on Monday, Wednesday, and Friday), sulfadiazine (100 mg/kg/day PO bid), and leucovorin (5-10 mg PO given on Monday, Wednesday, and Friday, or more often depending on neutrophil count). The relative efficacy in reducing sequelae of infection and the safety of treatment with 2 months vs 6 months of the higher dosage of pyrimethamine are being compared in the U.S. National Collaborative Study. (Updated information about this study and these regimens is available from Dr. Rima McLeod, 773-834-4131.) Pyrimethamine and sulfadiazine are available only in tablet form but can be prepared as suspensions. **Prednisone** (1 mg/kg/day PO bid) has been used in addition when active chorioretinitis involves the macula or otherwise threatens vision or when the CSF protein is >1,000 mg/dL at birth, but the efficacy of this adjunctive therapy is not established. Prednisone is continued only for as long as the active inflammatory process in the posterior pole of the eye is vision-threatening or the CSF protein is >1,000 mg/dL and is then tapered rapidly if the duration of treatment has been brief.

Pregnant Women with *Toxoplasma gondii* Infection

The immunologically normal pregnant woman who acquires *T. gondii* >6 months before conception does not need treatment to prevent congenital infection of her fetus. Although data are not available to allow for a definitive time interval, if infection occurs during or shortly before the pregnancy, it is reasonable to evaluate the fetus by PCR on amniotic fluid and ultrasonography and to treat to prevent congenital infection in the fetus (see Table 336.2).

Treatment of a pregnant woman who acquires infection at any time during pregnancy reduces the chance of congenital infection in her infant. If the mother develops acute toxoplasmosis during the first trimester of pregnancy, **spiramycin** (1 g PO every 8 hours without food) or sulfadiazine is recommended for prevention of fetal infection. Spiramycin is available in the United States on an "emergency use" request by a physician through the FDA Division of Anti-Infective Drugs (301-796-1400) after the diagnosis of acute infection is confirmed in a reference laboratory (Palo Alto Medical Facility Toxoplasma Serology Lab, 650-853-4828). With this approval, the physician can then contact the spiramycin manufacturer, Sanofi Pasteur (1-800-822-2463), to obtain spiramycin for the patient. Adverse reactions to spiramycin are infrequent and include paresthesia, rash, nausea, vomiting, and diarrhea.

For treatment of the pregnant woman whose fetus has a confirmed or probable infection in the second or third trimester, the combination of pyrimethamine, sulfadiazine, and leucovorin is recommended. Following a loading dose of pyrimethamine (50 mg bid) for 2 days, then pyrimethamine is administered at 50 mg once daily beginning on the third day. Sulfadiazine (1.5-2.0 g PO bid) and leucovorin (10 mg PO once daily) are initiated on the first day of treatment with pyrimethamine and continued for the full course of treatment. Delay in maternal treatment during gestation results in greater brain and eye disease in the infant. Diagnostic amniocentesis should be performed at >17-18 weeks of gestation in pregnancies when there is high suspicion of fetal infection. After 24 weeks of gestation, incidence of transmission is relatively high, and all pregnant women who are infected acutely after that time are treated with pyrimethamine, sulfadiazine, and leucovorin to treat the fetus.

The approach in France to congenital toxoplasmosis includes systematic serologic screening of all pregnant women beginning at ≤11 weeks of gestational age. For women who are seronegative, testing is performed again each month during gestation, at birth, and 1 month after birth. Mothers with acute infection early in gestation and without evidence of involvement of the fetus are treated with spiramycin to prevent transmission and sulfadiazine and pyrimethamine to treat possible fetal infection. Ultrasonography and amniocentesis for PCR at approximately week 17-18 of gestation are used for fetal diagnosis and have 97% sensitivity and 100% specificity. Confidence intervals for sensitivity are larger early and late in gestation. Fetal infection is treated with pyrimethamine, sulfadiazine, and leucovorin after 14 weeks of gestation, and termination of pregnancy is very rare at present. Prompt initiation of treatment with pyrimethamine, sulfadiazine, and leucovorin during pregnancy usually results in an excellent outcome, with normal development of children in most cases. Only 19% of infants have findings of congenital infection, including intracranial calcifications (13%) and chorioretinal scars (6%), although the prevalence of chorioretinal scars is 39% at follow-up later in childhood. Several studies have demonstrated improved outcomes with shorter times between diagnosis and initiation of treatment. In Germany, for seroconverting women who are between 15 and 17 weeks' gestation and before amniocentesis, administration of pyrimethamine, sulfadiazine, and leucovorin results in good outcomes for infants but is sometimes associated with sulfadiazine hypersensitivity in mothers.

Chronically infected pregnant women who are immunocompromised have transmitted *T. gondii* to their fetuses. Such women should be treated with spiramycin throughout gestation. The optimal

management for prevention of congenital toxoplasmosis in the fetus of a pregnant woman with HIV infection, a CD4 count <200 cells/μL, and inactive *T. gondii* infection is unknown. Fortunately, this situation now is rarely encountered in the United States. If the pregnancy is not terminated, some experts suggest that the mother should be treated with spiramycin or sulfadiazine alone during the first 14 weeks of gestation and thereafter with pyrimethamine, sulfadiazine, and leucovorin until term. There are no universally accepted guidelines at present.

In a study of adult patients with AIDS and toxoplasmic encephalitis, pyrimethamine (75 mg PO once daily) combined with high dosages of intravenous clindamycin (1,200 mg every 6 hr) appeared equal in efficacy to pyrimethamine and sulfadiazine in the treatment of toxoplasmic encephalitis. Other experimental agents include the macrolides clarithromycin and azithromycin.

Future Treatments

Many potential future treatments are currently being studied, including tetrahydroquinolones and another cytochrome b/c inhibitor as a prodrug, calcium kinase inhibitors, DHFR inhibitors, and nanoparticle technology. Research is ongoing regarding the molecular targets of a toxoplasmosis vaccine that could be administered to mothers, children, or the general population. One group has developed an effective, porous, nanoparticle-based, intranasally administered vaccine against latent and congenital toxoplasmosis that protects nonhuman primates.

PROGNOSIS

Early institution of specific treatment for congenitally infected infants usually rapidly controls the active manifestations of toxoplasmosis, including active chorioretinitis, meningitis, encephalitis, hepatitis, splenomegaly, and thrombocytopenia. Rarely, hydrocephalus resulting from aqueductal obstruction may develop or become worse during therapy. Treatment appears to reduce the incidence of diminished cognitive and abnormal motor function. Chorioretinitis often recurs in untreated patients and sometimes recurs in treated patients. Treated children with extensive involvement at birth may function normally later in life or have mild to severe impairment of vision, hearing, cognitive function, and other neurologic functions. Delays in diagnosis and therapy, perinatal hypoglycemia, hypoxia, hypotension, repeated shunt infections, and severe visual impairment are associated with a poorer prognosis. The prognosis is not necessarily poor for infected babies. Currently available treatments do not eradicate encysted parasites.

Studies in France have demonstrated that outcome of treated fetal toxoplasmosis, even when infection is acquired early in gestation, is usually favorable if no hydrocephalus is detected on ultrasound and treatment with pyrimethamine, sulfadiazine, or leucovorin is initiated promptly. The **Systematic Review on Congenital Toxoplasmosis** (SYROCOT) study in Europe indicated that neurologic outcome is improved with shorter times between diagnosis and initiation of treatment of fetal toxoplasmosis. Work in Lyon, France, has indicated a low incidence of recurrent eye disease in children with congenital toxoplasmosis who had been treated in utero and in their first year of life. The NCCCTS (1981–2004) in the United States found that neurologic, developmental, audiologic, and ophthalmologic outcomes are considerably better for most children who were treated in the first year of life with pyrimethamine, sulfadiazine, and leucovorin compared with children who had not been treated or were treated for only 1 month in earlier decades described in the literature.

PREVENTION

Counseling pregnant women about the methods of preventing transmission of *T. gondii* (see Fig. 336.1) during pregnancy can reduce acquisition of infection during gestation. Women who do not have specific antibody to *T. gondii* before pregnancy should only eat well-cooked meat during pregnancy and should avoid contact with materials contaminated with oocysts excreted by cats, when possible. Cats that are kept indoors, maintained on prepared food, and not fed fresh, uncooked meat should not contact encysted *T. gondii* or shed oocysts. Serologic screening, ultrasound monitoring, and treatment of pregnant women during gestation can also reduce the incidence and manifestations of congenital toxoplasmosis.

Point-of-care testing to facilitate gestational screening, recent developments in medicines for treatment of active and chronic infections, and progress toward vaccines to prevent infections in humans and oocyst shedding by cats are all recent advances with promise to prevent or improve outcomes for *Toxoplasma gondii* infections. There is a point-of-care test that has been CE marked for use in Europe and is currently moving toward completion of feasibility studies in the United States with consideration of FDA clearance, potentially marking the beginning of more widespread testing for optimal obstetrical care to prevent congenital toxoplasmosis and for public health initiatives to identify prevalence of toxoplasmosis in specific high-risk areas of the globe.

ACKNOWLEDGMENT

We gratefully acknowledge the participant families, physicians, and other personnel of the National Collaborative Congenital Toxoplasmosis Study (NCCTS), and colleagues, for helping to create the understanding and knowledge in this chapter; and the Cornwell Mann, Rodriguez, and Morel families. Taking out Toxo (TOT), TRI, and NIH, NIAID/DMID ROI AI27530 and RO1 AI071319-01 for support. We also thank Andrew Grose for his assistance in preparing this chapter.

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Section 16
Helminthic Diseases

Chapter 337
Ascariasis (*Ascaris lumbricoides*)

Katherine R. Dobbs and Arlene E. Dent

ETIOLOGY

Ascariasis is caused by the nematode, or **roundworm**, *Ascaris lumbricoides.* Adult worms of *A. lumbricoides* inhabit the lumen of the small intestine. The reproductive potential of *Ascaris* is prodigious; a gravid female worm produces 200,000 eggs per day. The fertile ova are oval in shape with a thick, mamillated covering measuring 45-70 μm in length and 35-50 μm in breadth (Fig. 337.1). After passage in the feces, the eggs embryonate and become infective in 5-10 days under favorable environmental conditions. Adult worms can live for 12-18 months (Fig. 337.2).

EPIDEMIOLOGY

Ascariasis occurs globally and is the most prevalent human **helminthiasis** in the world. It is most common in tropical areas (South America, Africa, Asia) where environmental conditions are optimal for maturation of ova in the soil. Approximately 1 billion persons are estimated to be infected. Although the number of cases in the United States is not known precisely, the highest prevalence is thought to be in high-poverty areas of the South and Appalachia. Pig farming is also associated with *Ascaris* species. Key factors linked with a higher prevalence of infection include poor socioeconomic conditions, use of human feces as fertilizer, and geophagia. Even though infection can occur at any age, the highest rate is in preschool or early school-age children. Transmission is primarily hand to mouth but may also involve ingestion of

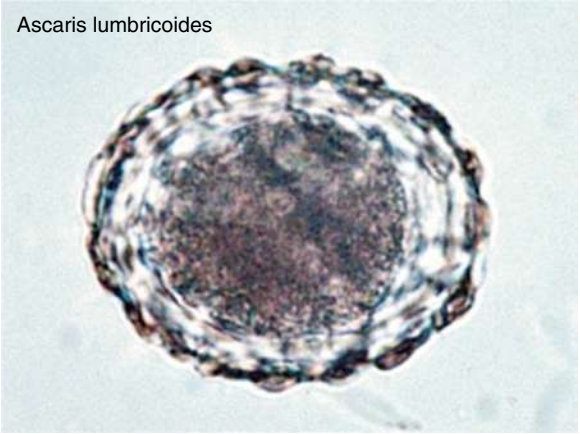

Fig. 337.1 Soil-transmitted helminth eggs (*Ascaris lumbricoides*). *(From Bethony J, Brooker S, Albonico M, et al. Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm. Lancet. 2006;367:1521–1532.)*

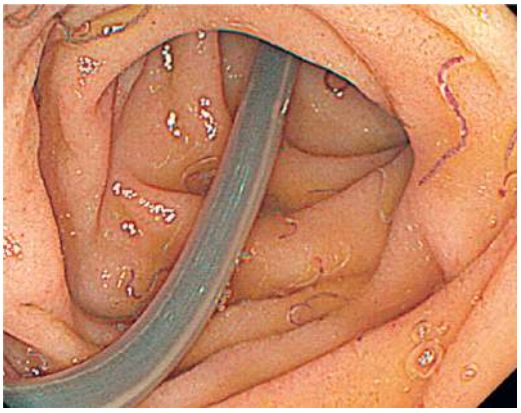

Fig. 337.2 Endoscopic image of intestinal *Ascaris lumbricoides* and hookworm co-infection. The ascaris worm is large in relation to the lumen and multiple blood-filled hookworms. *(Courtesy Dr. Kunimitsu Inoue, Nakamura Hospital, Oita, Japan.)*

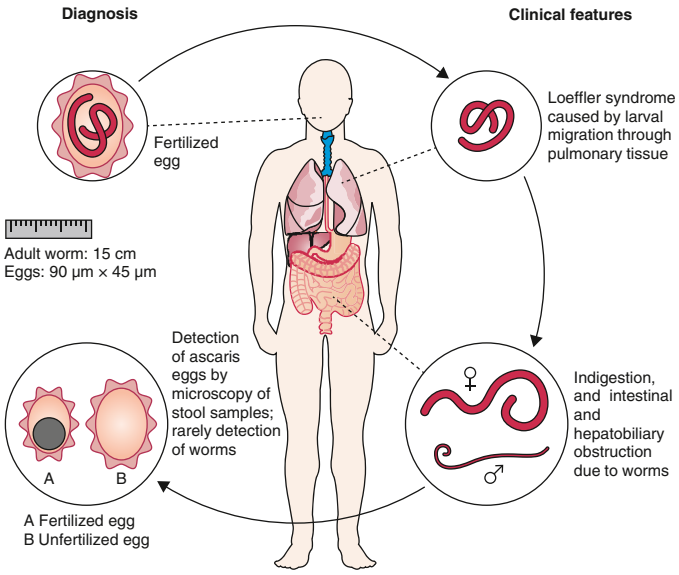

Fig. 337.3 Transmission of *Ascaris lumbricoides*: diagnosis and clinical features. *(From Jourdan PM, Lamberton PHL, Fenwick A, Addiss DG. Soil-transmitted helminth infections. Lancet. 2018;391:252–262. Fig 2A.)*

contaminated raw fruits and vegetables. Transmission is enhanced by the high output of eggs by fecund female worms and resistance of ova to the outside environment. *Ascaris* eggs can remain viable at 5–10°C (41–50°F) for as long as 2 years.

PATHOGENESIS

Ascaris ova hatch in the small intestine after ingestion by the human host. Larvae are released, penetrate the intestinal wall, and migrate to the lungs by way of the venous circulation. The parasites then cause **pulmonary ascariasis** as they enter into the alveoli and migrate through the bronchi and trachea (Fig. 337.3). They are subsequently swallowed and return to the intestines, where they mature into adult worms. Female *Ascaris* begin depositing eggs in 8-10 weeks.

CLINICAL MANIFESTATIONS

The clinical presentation depends on the intensity of infection and the organs involved. Most individuals have low to moderate worm burdens and have no symptoms or signs. The most common clinical problems are from **pulmonary disease** and **obstruction of the intestinal or biliary tract**. Larvae migrating through these tissues may cause allergic symptoms, fever, urticaria, and granulomatous disease. The pulmonary manifestations resemble Loeffler syndrome and include transient respiratory symptoms such as cough and dyspnea, pulmonary infiltrates, and blood eosinophilia. Larvae may be observed in the sputum. Vague abdominal complaints have been attributed to the presence of adult worms in the small intestine, although the precise contribution of the parasite to these symptoms is difficult to ascertain. A more serious complication occurs when a large mass of worms leads to acute bowel obstruction. Children with heavy infections may present with vomiting, abdominal distention, and cramps. In some cases, worms may be passed in the vomitus or stools. *Ascaris* worms occasionally migrate into the biliary and pancreatic ducts, where they cause cholecystitis or pancreatitis. Worm migration through the intestinal wall can lead to peritonitis. Dead worms can serve as a nidus for stone formation. Studies show that chronic infection with *A. lumbricoides* (often coincident with other helminth infections) impairs growth, physical fitness, and cognitive development.

DIAGNOSIS

Microscopic examination of fecal smears can be used for diagnosis because of the high number of eggs excreted by adult female worms (see Fig. 337.1). A high index of suspicion in the appropriate clinical context is needed to diagnose pulmonary ascariasis or obstruction of the gastrointestinal tract. Ultrasound examination of the abdomen is capable of visualizing intraluminal adult worms.

TREATMENT

Although several chemotherapeutic agents are effective against ascariasis, none has documented utility during the pulmonary phase of infection. Treatment options for gastrointestinal ascariasis include **albendazole** (400 mg orally once, for all ages), **mebendazole** (100 mg orally twice daily for 3 days or 500 mg once, for all ages), **pyrantel pamoate** (11 mg/kg orally once; maximum dose: 1g), or **ivermectin** (200 μg/kg orally once). **Nitazoxanide** (100 mg orally twice per day for 3 days for children 1-3 years old; 200 mg twice per day for 3 days for children 4-11 years; 500 mg twice per day for 3 days for adolescents and adults) produces cure rates comparable to single-dose albendazole. **Piperazine citrate** (75 mg/kg/day for 2 days; maximum dose: 3.5 g/day), which causes neuromuscular paralysis of the parasite and rapid expulsion of the worms, is a good treatment for intestinal or biliary obstruction but has been withdrawn from the market in many regions due to toxicity and good alternatives. Surgery may be required for cases with severe obstruction. Drug resistance has not been reported, but repeated treatment for ascariasis may be necessary because reinfection is common.

PREVENTION

Although ascariasis is the most prevalent worm infection in the world, little attention has been given to its control (Table 337.1). **Anthelmintic**

Table 337.1 Clinical and Public Health Control of Soil-Transmitted Helminthiasis

	CLINICAL DIAGNOSIS AND MANAGEMENT	PUBLIC HEALTH CONTROL
Diagnosis	Individual	Community level (e.g., in select schools)
Diagnostic criteria	Parasitologic	Residence in an area with soil-transmitted helminthiasis prevalence >20%
Treatment approach	Single dose or multiple dose	Single-dose periodic mass treatment
Threshold for treatment	Travel history, symptoms and signs, positive laboratory test	Estimated prevalence of infection in target population
Treatment objective	Parasitologic cure	Decreased worm burden; reduction in transmission
Ancillary treatment	Based on clinical signs and symptoms	Typically, only if included in mass treatment (e.g., vitamin A supplementation)
Follow-up	Parasitologic test of cure; improvement in associated health conditions	Not usually done
Health education (sanitation/hygiene)	Recommended	Recommended

From Jourdan PM, Lamberton PHL, Fenwick A, Addiss DG. Soil-transmitted helminth infections. *Lancet*. 2018;391:252–262. Table 1.

chemotherapy programs can be implemented in one of three ways: (1) offering universal treatment to all individuals in an area of high endemicity; (2) offering treatment targeted to groups with high frequency of infection, such as children attending primary school; or (3) offering individual treatment based on intensity of current or past infection. Improving education about and practices of sanitary conditions and sewage facilities, discontinuing the practice of using human feces as fertilizer, and education are the most effective long-term preventive measures.

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Chapter 338

Hookworms (*Necator americanus* and *Ancylostoma* spp.)

Peter J. Hotez

ETIOLOGY

Two major genera of hookworms, which are nematodes, or roundworms, infect humans. *Necator americanus,* the only representative of its genus, is a major **anthropophilic** hookworm and is the most common cause of human hookworm infection. Hookworms of the genus *Ancylostoma* include the anthropophilic hookworm *Ancylostoma duodenale,* which also causes classic hookworm infection, and the less common **zoonotic** species *Ancylostoma ceylanicum* (restricted mostly to Southeast Asia). Human zoonotic infection with the dog hookworm *Ancylostoma caninum* is associated with an eosinophilic enteritis syndrome. The larval stage of *Ancylostoma braziliense,* whose definitive hosts include dogs and cats, is the principal cause of cutaneous larva migrans.

The infective larval stages of the anthropophilic hookworms live in a developmentally arrested state in warm, moist soil. Larvae infect humans either by penetrating through the skin (*N. americanus* and *A. duodenale*) or when they are ingested *(A. duodenale).* Larvae entering the human host by skin penetration undergo **extraintestinal migration** through the venous circulation and lungs before they are swallowed, whereas orally ingested larvae may undergo extraintestinal migration or remain in the gastrointestinal (GI) tract (Figs. 338.1 and 338.2). Larvae returning to the small intestine undergo two molts to become adult, sexually mature, male and female worms ranging in length from 5-13 mm. The buccal capsule of the adult hookworm is armed with cutting plates *(N. americanus)* or teeth *(A. duodenale)* to facilitate attachment to the mucosa and submucosa of the small intestine. Hookworms can remain in the intestine for 1-5 years, where they mate and produce eggs. Although up to 2 months is required for the larval stages of hookworms to undergo extraintestinal migration and develop into mature adults, *A. duodenale* larvae may remain developmentally arrested for many months before resuming development in the intestine. Mature *A. duodenale* female worms produce about 30,000 eggs per day; daily egg production by *N. americanus* is <10,000/day (Fig. 338.3). The eggs are thin shelled and ovoid, measuring approximately 40-60 μm. Eggs that are deposited on soil with adequate moisture and shade develop into first-stage larvae and hatch. Over the ensuing several days and under appropriate conditions, the larvae molt twice to the **infective** stage. Infective larvae are developmentally arrested and nonfeeding. They migrate vertically in the soil until they either infect a new host or exhaust their lipid metabolic reserves and die.

EPIDEMIOLOGY

Hookworm infection is one of the most prevalent infectious diseases of humans. The Global Burden of Disease Study 2015 reported that approximately 428 million people are infected with hookworms, with further estimates indicating that hookworm infection globally results in 4.1 million disability-adjusted life-years, possibly leading all **neglected tropical diseases** in years lost through disability. In the case of hookworm infection, all the years lost through disability are attributed to anemia from intestinal blood loss. There is also a massive socioeconomic impact from hookworm infection, with estimates that hookworm can cause up to $139 billion in losses from diminished productivity.

Because of the requirement for adequate soil moisture, shade, and warmth, hookworm infection is usually confined to rural areas, especially where human feces are used for fertilizer or where sanitation is inadequate. Hookworm is an infection associated with *economic underdevelopment and poverty* throughout the tropics and subtropics. Sub-Saharan Africa, East Asia, and tropical regions of the Americas have the highest prevalence of hookworm infection. High rates of infection are often associated with cultivation of certain agricultural products, such as tea in India; sweet potato, corn, cotton, and mulberry trees in China; coffee in Central and South America; and rubber in Africa. It is not uncommon to find dual *N. americanus* and *A. duodenale* infections. *N. americanus* predominates in Central and South America as well as in southern China and Southeast Asia, whereas *A. duodenale* predominates in North Africa, in northern India, in China north of the Yangtze River,

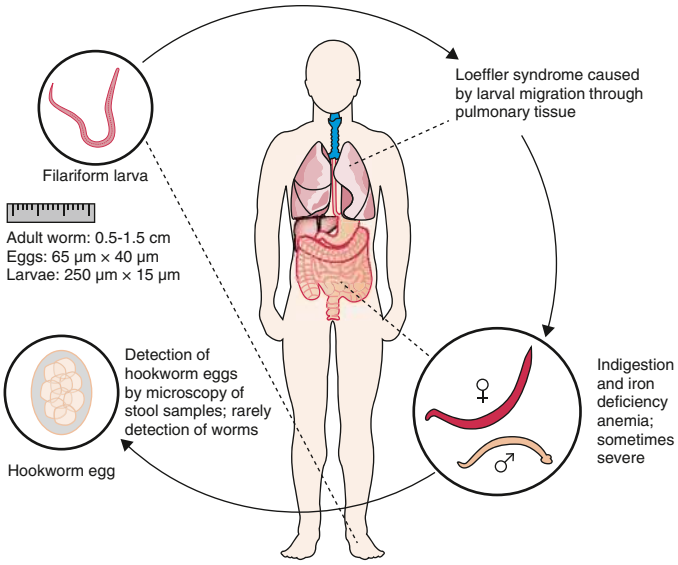

Fig. 338.1 Transmission of hookworm (*Ancylostoma duodenale* and *Necator americanus*): diagnosis and clinical features. *(From Jourdan PM, Lamberton PHL, Fenwick A, Addiss DG. Soil-transmitted helminth infections. Lancet. 2018;391:252–262. Fig 2C.)*

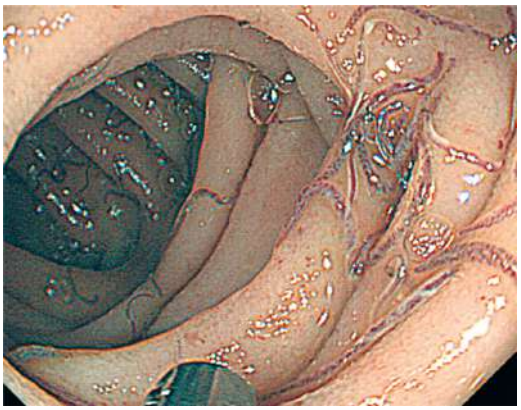

Fig. 338.2 Endoscopic images of intestinal hookworm infection. *(Courtesy Dr. Kunimitsu Inoue, Nakamura Hospital, Oita, Japan.)*

Fig. 338.3 Soil-transmitted hookworm helminth eggs. *(From Bethony J, Brooker S, Albonico M, et al. Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm. Lancet. 2006;367:1521–1532.)*

and among aboriginal people in Australia. The ability of *A. duodenale* to withstand somewhat harsher environmental and climatic conditions may reflect its ability to undergo arrested development in human tissues. *A. ceylanicum* infection occurs in India and Southeast Asia.

Eosinophilic enteritis caused by *A. caninum* was first described in Queensland, Australia, with two reported cases in the United States. Because of its global distribution in dogs, it was initially anticipated that human *A. caninum* infections would be identified in many locales, but this has not been found.

PATHOGENESIS

The major morbidity of human hookworm infection is a direct result of **intestinal blood loss**. Adult hookworms adhere tenaciously to the mucosa and submucosa of the proximal small intestine by using their cutting plates or teeth and a muscular esophagus that creates negative pressure in their buccal capsules. At the attachment site, host inflammation is downregulated by the release of antiinflammatory polypeptides by the hookworm. Rupture of capillaries in the lamina propria is followed by blood extravasation, with some of the blood ingested directly by the hookworm. After ingestion, the blood is anticoagulated, the red blood cells are lysed, and the hemoglobin is released and digested. Each adult *A. duodenale* hookworm causes loss of an estimated 0.2 mL of blood/day; blood loss is less for *N. americanus*. Individuals with light infections have minimal blood loss and thus may have hookworm infection but not hookworm disease. There is a direct correlation between the number of adult hookworms in the gut and the volume of fecal blood loss. Hookworm disease results only when individuals with moderate and heavy infections experience sufficient blood loss to develop iron deficiency and anemia. Hypoalbuminemia and consequent edema and anasarca from the loss of intravascular oncotic pressure can also occur. These features depend heavily on the dietary reserves of the host.

CLINICAL MANIFESTATIONS

Chronically infected children with moderate and heavy hookworm infections suffer from intestinal blood loss that results in **iron deficiency** and can lead to anemia as well as protein malnutrition. Prolonged iron deficiency associated with hookworms in childhood can lead to physical growth retardation and cognitive and intellectual deficits.

Anthropophilic hookworm larvae elicit dermatitis sometimes referred to as **ground itch** when they penetrate human skin. The vesiculation and edema of ground itch are exacerbated by repeated infection. Infection with a zoonotic hookworm, especially *A. braziliense,* can result in lateral migration of the larvae to cause the characteristic cutaneous tracts of **cutaneous larva migrans** (see Chapter 338.1). Cough subsequently occurs in *A. duodenale* and *N. americanus* hookworm infection when larvae migrate through the lungs to cause laryngotracheobronchitis, usually about 1 week after exposure. Pharyngitis also can occur. The onset of eosinophilia coincides with the entry of hookworm larvae into the GI tract. Upper abdominal pain can occur during this period, but it eventually subsides.

Chronic intestinal hookworm infection is not typically associated with specific GI complaints, although pain, anorexia, and diarrhea have been attributed to the presence of hookworms. The major clinical manifestations are related to intestinal blood loss. Heavily infected children exhibit all the signs and symptoms of **iron-deficiency anemia** and **protein malnutrition**. In some cases, children with chronic hookworm disease acquire a yellow-green pallor known as **chlorosis.**

An infantile form of **ancylostomiasis** resulting from heavy *A. duodenale* infection has been described. Affected infants experience diarrhea, melena, failure to thrive, and profound anemia. Infantile ancylostomiasis has significant mortality.

Eosinophilic enteritis caused by *A. caninum* is associated with colicky abdominal pain that begins in the epigastrium and radiates outward and is usually exacerbated by food. Extreme cases may mimic acute appendicitis.

DIAGNOSIS

Children with hookworm release eggs that can be detected by direct fecal examination (see Fig. 338.3). Quantitative methods are available

to determine whether a child has a heavy **worm burden** that can cause hookworm disease. The eggs of *N. americanus* and *A. duodenale* are morphologically indistinguishable. Species identification typically requires egg hatching and differentiation of third-stage infective larvae; methods using polymerase chain reaction (PCR) have been developed but are not generally used in clinical practice.

In contrast, eggs are generally not present in the feces of patients with eosinophilic enteritis caused by *A. caninum*. Eosinophilic enteritis is often diagnosed by demonstrating ileal and colonic ulcerations by colonoscopy in the presence of significant blood eosinophilia. An adult canine hookworm may occasionally be recovered during colonoscopic biopsy. Patients with this syndrome develop IgG and IgE serologic responses.

TREATMENT

The goal of **deworming** is removal of the adult hookworms with an **anthelmintic** drug. The **benzimidazole** anthelmintics, mebendazole and albendazole, are effective at eliminating hookworms from the intestine, although multiple doses are sometimes required. **Albendazole** (400 mg orally [PO] once, for all ages) often results in cure, although *N. americanus* adult hookworms are sometimes more refractory and require additional doses. **Mebendazole** (100 mg PO twice daily [bid] for 3 days, for all ages) is also effective. In many developing countries, mebendazole is administered as a single dose of 500 mg; however, the cure rates with this regimen can be as low as 10% or less. According to the World Health Organization (WHO), children should be encouraged to chew tablets of albendazole or mebendazole, because forcing very young children to swallow large tablets may cause choking or asphyxiation. Mebendazole is recommended for *A. caninum*–associated eosinophilic enteritis, although recurrences are common. Because the benzimidazoles have been reported to be embryotoxic and teratogenic in laboratory animals, their safety during pregnancy and in young children is a potential concern, and the risks vs benefits must be carefully considered. WHO currently supports the use of benzimidazoles in infected children ≥1 year old but at a reduced dose (200 mg for albendazole) in the youngest age-group (1-2 years old). The most up to date guidelines for treating these populations are available from the US Centers for Disease Control and Prevention https://www.cdc.gov/parasites/hookworm/health_professionals/index.html#tx. In some countries, **pyrantel pamoate** (11 mg/kg PO once daily for 3 days; maximum dose: 1 g) is available in liquid form and is an effective alternative to the benzimidazoles. A newer drug known as **tribendimidine** is still under clinical development and may be available in the future. Replacement therapy with oral iron is not usually required to correct hookworm-associated iron deficiency in children.

PREVENTION

In 2001, the World Health Assembly urged its member states to implement programs of periodic deworming so as to control the morbidity of hookworm and other soil-transmitted helminth infections (see Table 337.1 in Chapter 337). Although anthelmintic drugs are effective at eliminating hookworms from the intestine, the high rates of drug failure from single-dose mebendazole or albendazole and post-treatment reinfection among children suggest that mass drug administration alone is not effective for controlling hookworm in highly endemic areas. Moreover, data suggest that the efficacy of mebendazole decreases with frequent, periodic use, leading to concerns about the possible emergence of **anthelminthic drug resistance**. To reduce the reliance exclusively on anthelminthic drugs, a recombinant human hookworm vaccine has been developed and is undergoing clinical testing. Economic development and associated improvements in sanitation, health education, and avoidance of human feces as fertilizer remain critical for reducing hookworm transmission and endemicity.

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338.1 Cutaneous Larva Migrans

Peter J. Hotez

ETIOLOGY

Cutaneous larva migrans **(creeping eruption)** is caused by the larvae of several nematodes, primarily hookworms, which are not usually parasitic for humans. *A. braziliense,* a hookworm of dogs and cats, is the most common cause, but other animal hookworms may also produce the disease.

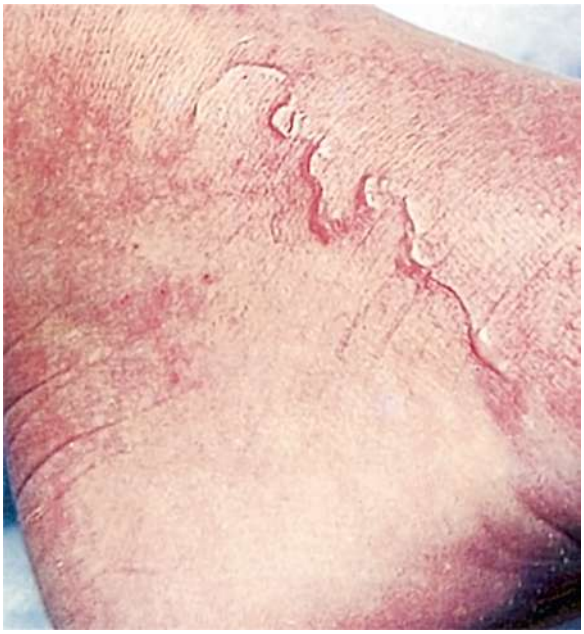

Fig. 338.4 Creeping eruption of cutaneous larva migrans. *(From Korting GW. Hautkrankheitenbeikindern und jugendlichen. Stuttgart, Germany: FK Schattauer Verlag, 1969.)*

EPIDEMIOLOGY

Cutaneous larva migrans is usually caused by *A. braziliense,* which is endemic to the southeastern United States and Puerto Rico. Travelers account for a significant percentage of the cases. Recently, autochthonous cases have been reported from Europe.

CLINICAL MANIFESTATIONS

After penetrating the skin, larvae localize at the epidermal-dermal junction and migrate in this plane, moving at a rate of 1-2 cm/day. The response to the parasite is characterized by raised, erythematous, serpiginous tracks, which occasionally form bullae (Fig. 338.4). These lesions may be single or numerous and are usually localized to an extremity, although any area of the body may be affected. As the organism migrates, new areas of involvement may appear every few days. Intense localized pruritus, without any systemic symptoms, may be associated with the lesions. Bacterial superinfection can occur.

DIAGNOSIS

Cutaneous larva migrans is diagnosed by clinical examination of the skin. Patients are often able to recall the exact time and location of exposure because the larvae produce intense itching at the site of penetration. Eosinophilia may occur but is uncommon.

TREATMENT

If left untreated, the larvae die, and the syndrome resolves within a few weeks to several months. Treatment with **ivermectin** (200 μg/kg PO in a single dose for children over 15 kg; considered drug of choice by some investigators), **albendazole** (400 mg PO daily for 3 days, for children over the age of 2 years), or topical **thiabendazole** hastens resolution, if symptoms warrant treatment. The U.S. Food and Drug Administration has not approved these drugs for cutaneous larva migrans. The safety of ivermectin in young children (weighing <15 kg) and pregnant women remains to be established. Albendazole should be taken with a fatty meal. The latest guidelines from the US Centers for Disease Control and Prevention can be found at https://www.cdc.gov/parasites/zoonotichookworm/health_professionals/index.html#tx.

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Chapter 339

Trichuriasis (*Trichuris trichiura*)

Katherine R. Dobbs and Arlene E. Dent

ETIOLOGY

Trichuriasis is caused by the **whipworm**, *Trichuris trichiura,* a nematode, or roundworm, that inhabits the cecum and ascending colon. The principal hosts of *T. trichiura* are humans, who acquire infection by ingesting embryonated, barrel-shaped eggs (Fig. 339.1). The larvae escape from the shell in the upper small intestine and penetrate the intestinal villi. The worms slowly move toward the cecum, where the anterior three-quarters whiplike portion remains within the superficial mucosa and the short posterior end is free in the lumen (Fig. 339.2). In 1-3 months, the adult female worm begins producing 5,000-20,000 eggs per day. After excretion in the feces, embryonic development occurs in 2-4 weeks with optimal temperature and soil conditions. The adult worm life span is approximately 2 years.

EPIDEMIOLOGY

Trichuriasis occurs throughout the world and is especially common in poor rural communities with inadequate sanitary facilities and soil contaminated with human or animal feces. Trichuriasis is one of the most prevalent human helminthiases, with an estimated 1 billion infected individuals worldwide. In many parts of the world, where protein-energy malnutrition and anemia are common, the prevalence of *T. trichiura* infection can be as high as 95%. Although trichuriasis occurs in the rural southeastern United States, its prevalence has not been reported. The highest rate of infection occurs among children 5-15 years old. Infection develops after ingesting embryonated ova by direct contamination of hands, food (raw fruits and vegetables fertilized with human feces), or drink (Fig. 339.3). Transmission can also occur indirectly through flies or other insects.

CLINICAL MANIFESTATIONS

Most persons harbor low worm burdens and do not have symptoms. Some individuals may have a history of right lower quadrant or vague periumbilical pain. Adult *Trichuris* ingest approximately 0.005 mL of blood per worm per day. Children, who are most likely to be heavily infected, frequently suffer from disease. Clinical manifestations include chronic dysentery, rectal prolapse, anemia, poor growth, as well as developmental and cognitive deficits. There is no significant eosinophilia, even though a portion of the worm is embedded in the mucosa of the large bowel.

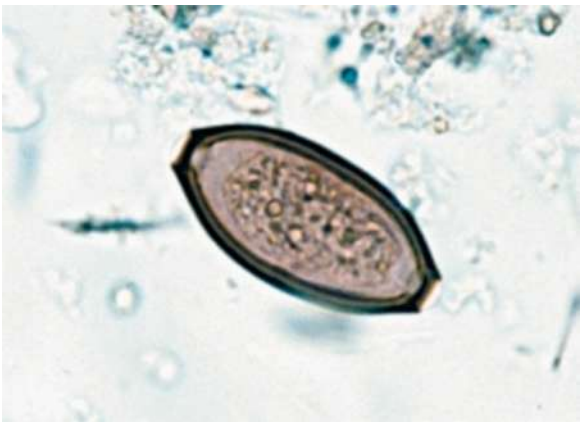

Fig. 339.1 *Trichuris trichiura.* Soil-transmitted helminth eggs. *(From Bethony J, Brooker S, Albonico M, et al. Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm. Lancet. 2006;367:1521–1532.)*

Fig. 339.2 *Trichuris trichiura* infection. *(Courtesy Dr. Kunimitsu Inoue, Nakamura Hospital, Oita, Japan.)*

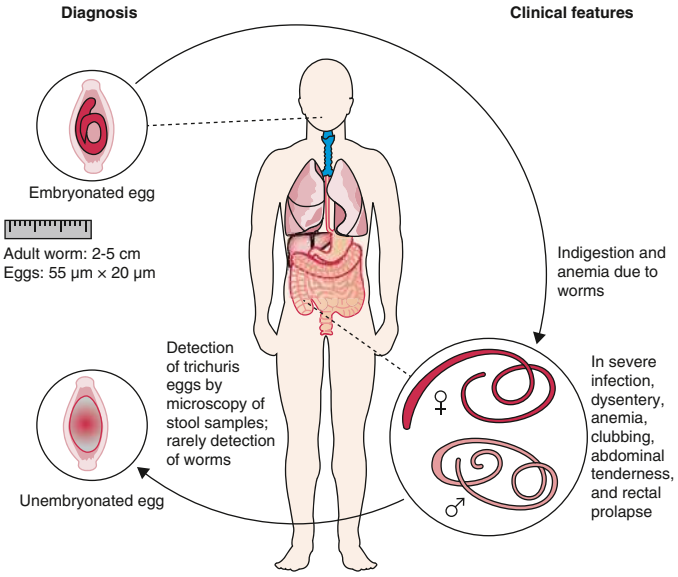

Fig. 339.3 Transmission of *Trichuris trichiura*: diagnosis and clinical features. *(From Jourdan PM, Lamberton PHL, Fenwick A, Addiss DG. Soil-transmitted helminth infections. Lancet. 2018;391:252–262. Fig 2B.)*

DIAGNOSIS

Because egg output is so high, fecal smears frequently reveal the characteristic barrel-shaped ova of *T. trichiura.*

TREATMENT

Albendazole (400 mg orally for 3 days, for all ages) is the drug of choice and is safe and effective, in part because it is poorly absorbed from the gastrointestinal tract. It reduces egg output by 90–99% and has cure rates of 70–90%, although reinfection and resumption of egg production by live worms that presumably survive after treatment may occur. Alternatives include **mebendazole** (100 mg orally twice daily for 3 days) and **ivermectin** (600 µg/kg orally for 3 days). Single-day treatment with albendazole, nitazoxanide, or albendazole plus nitazoxanide leads to cure rates that are low and short-lived. Combination treatment with **oxantel pamoate** (20 mg/kg) plus 400 mg albendazole on consecutive days may have the highest cure rate.

PREVENTION

Disease can be prevented by personal hygiene, improved sanitary conditions, and eliminating the use of human feces as fertilizer (see Table 337.1 in Chapter 337).

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Chapter 340

Enterobiasis *(Enterobius vermicularis)*

Katherine R. Dobbs and Arlene E. Dent

ETIOLOGY

The cause of enterobiasis, or **pinworm** infection, is *Enterobius vermicularis,* which is a small (1 cm in length), white, threadlike nematode, or roundworm that typically inhabits the cecum, appendix, and adjacent areas of the ileum and ascending colon. Gravid females migrate at night to the perianal and perineal regions, where they deposit up to 15,000 eggs. Ova are convex on one side and flattened on the other and have diameters of approximately 30 × 60 µm. Eggs embryonate within 6 hours and remain viable for 20 days. Human infection occurs by the fecal-oral route typically by ingestion of embryonated eggs that are carried on fingernails, clothing, bedding, or house dust. After ingestion, the larvae mature to form adult worms in 36-53 days.

EPIDEMIOLOGY

Enterobiasis infection occurs in individuals of all ages and socioeconomic levels. It is prevalent in regions with temperate climates and is the most common helminth infection in the United States. It infects 30% of children worldwide, and humans are the only known host. Infection occurs primarily in institutional or family settings that include children. The prevalence of pinworm infection is highest in children 5-14 years of age. It is common in areas where children live, play, and sleep close together, thus facilitating egg transmission. Because the life span of the adult worm is short, chronic parasitism is likely caused by repeated cycles of reinfection. **Autoinoculation** can occur in individuals who habitually put their fingers in their mouth.

PATHOGENESIS

Enterobius infection may cause symptoms by mechanical stimulation and irritation, allergic reactions, and migration of the worms to anatomic sites where they become pathogenic. *Enterobius* infection has been associated with concomitant *Dientamoeba fragilis* infection, which causes diarrhea.

CLINICAL MANIFESTATIONS

Pinworm infection is innocuous and rarely causes serious medical problems. The most common complaints include itching and restless sleep secondary to nocturnal perianal or **perineal pruritus**. The precise cause and incidence of pruritus are unknown but may be related to the intensity of infection, psychologic profile of the infected individual and the family, or allergic reactions to the parasite. Eosinophilia is not observed in most cases, because tissue invasion does not occur. Aberrant migration to ectopic sites occasionally may lead to appendicitis, chronic salpingitis, pelvic inflammatory disease, peritonitis, hepatitis, and ulcerative lesions in the large or small bowel.

DIAGNOSIS

A history of nocturnal **perianal pruritus** in children strongly suggests enterobiasis. Definitive diagnosis is established by identification of parasite eggs or worms. Microscopic examination of adhesive cellophane tape pressed against the perianal region early in the morning frequently demonstrates eggs (Fig. 340.1). Repeated examinations increase the chance of detecting ova; one examination detects 50% of infections, three examinations 90%, and five examinations 99%. Worms seen in the perianal region should be removed and preserved in 75% ethyl alcohol until microscopic examination can be performed. Digital rectal examination may also be used to obtain samples for a wet mount. Routine stool samples rarely demonstrate *Enterobius* ova.

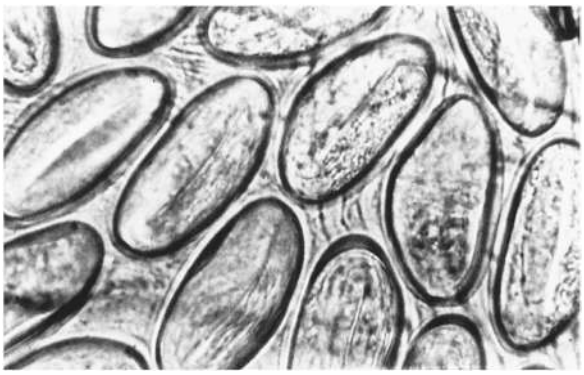

Fig. 340.1 Eggs of *Enterobius vermicularis. (From Guerrant RL, Walker DH, Weller PF, et al. Tropical Infectious Diseases. Philadelphia: Churchill Livingstone, 2006. p. 1248.)*

TREATMENT

Anthelmintic drugs should be administered to infected individuals and their family members. **Albendazole** (400 mg orally with a repeat dose 2 week later for all age-groups) is the treatment of choice and results in cure rates exceeding 90%. Alternatives include **mebendazole** (100 mg orally with a repeat dose 2 weeks later) and **pyrantel pamoate** (11 mg/kg base orally 3 times a day up to a maximum of 1 g; repeat at 2 weeks). Morning bathing removes a large portion of eggs. Frequent changing of underclothes, bedclothes, and bedsheets decreases environmental egg contamination and may decrease the risk for autoinfection.

PREVENTION

Household contacts can be treated at the same time as the infected individual. Repeated treatments every 3-4 months may be required in circumstances with repeated exposure, such as with institutionalized children. Good hand hygiene is the most effective method of prevention.

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Chapter 341

Strongyloidiasis *(Strongyloides stercoralis)*

Katherine R. Dobbs and Arlene E. Dent

ETIOLOGY

Strongyloidiasis is caused by the nematode, or roundworm, *Strongyloides stercoralis.* Only adult female worms inhabit the small intestine. The nematode reproduces in the human host by parthenogenesis and releases eggs containing mature larvae into the intestinal lumen. **Rhabditiform** larvae immediately emerge from the ova and are passed in feces, where they can be visualized by stool examination. Rhabditiform larvae either differentiate into free-living adult male and female worms or metamorphose into the infectious **filariform** larvae. Sexual reproduction occurs only in the free-living stage. Humans are usually infected through skin contact with soil contaminated with infectious larvae (Fig. 341.1). Larvae penetrate the skin, enter the venous circulation, and then pass to the lungs, break into alveolar spaces, and migrate up the bronchial tree. They are then swallowed and pass through the stomach, and adult female worms develop in the small intestine. Egg deposition begins approximately 28 days after initial infection.

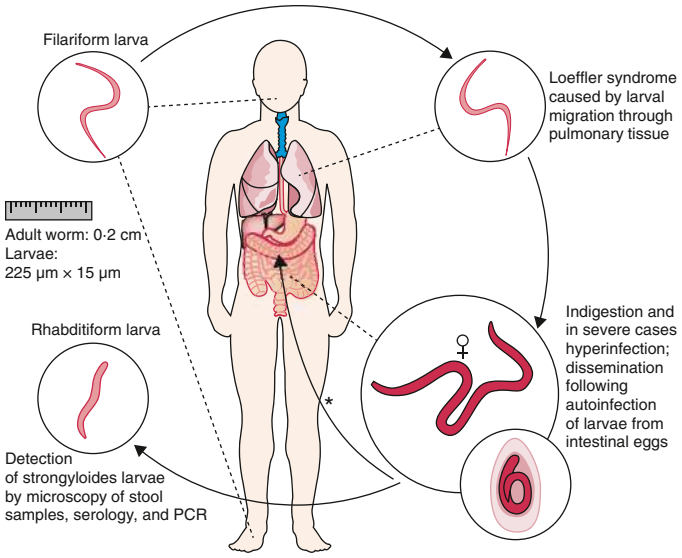

Fig. 341.1 Transmission of *Strongyloides stercoralis*: diagnosis and clinical features. *(From Jourdan PM, Lamberton PHL, Fenwick A, et al. Soil-transmitted helminth infections. Lancet. 2018;391:252–262. Fig 2D.)*

The **hyperinfection syndrome** occurs when large numbers of larvae transform into infective organisms during their passage in feces and then reinfect **(autoinfect)** the host by way of the lower gastrointestinal (GI) tract or perianal region. This cycle may be accelerated in immunocompromised persons, particularly those with depressed T-cell function.

EPIDEMIOLOGY

S. stercoralis infection is prevalent in tropical and subtropical regions of the world and is endemic in several areas of Europe, the southern United States, and Puerto Rico. Transmission requires appropriate environmental conditions, particularly warm, moist soil. Poor sanitation and crowded living conditions are conducive to high levels of transmission. Dogs and cats can act as reservoirs. The highest prevalence of infection in the United States occurs in impoverished areas and among socially marginalized groups, such as immigrants, refugees, and indigenous or ethnic minority groups. Infection may be especially common among residents of mental institutions, veterans who were prisoners of war in areas of high endemicity, and refugees and immigrants. Because of internal autoinfection, individuals may remain infected for decades. Infection may be transmitted by organ transplantation. Individuals with hematologic malignancies, autoimmune diseases, malnutrition, and drug-induced immunosuppression (especially corticosteroids) are at high risk for the hyperinfection syndrome. Patients with AIDS may experience a rapid course of disseminated strongyloidiasis with a fatal outcome.

PATHOGENESIS

The initial host immune response to infection is production of immunoglobulin E and eosinophilia in blood and tissues, which presumably prevents dissemination and hyperinfection in the immunocompetent host. Adult female worms in otherwise healthy and asymptomatic individuals may persist in the GI tract for years. If infected persons become immunocompromised, the reduction in cellular and humoral immunity may lead to an abrupt and dramatic increase in parasite load with systemic dissemination.

CLINICAL MANIFESTATIONS

Approximately 30% of infected individuals are asymptomatic. The remaining patients have symptoms that correlate with the three stages of infection: invasion of the skin, migration of larvae through the lungs, and parasitism of the small intestine by adult worms. **Larva currens** is the manifestation of an allergic reaction to filariform larvae that migrate through the skin, where they leave pruritic, tortuous, urticarial tracks. The lesions may recur and are typically found over the lower abdominal wall, buttocks, or thighs, resulting from larval migration from defecated stool. Pulmonary disease secondary to larval migration through the lung rarely occurs and may resemble **Loeffler syndrome** (cough, wheezing, shortness of breath, transient pulmonary infiltrates accompanied by eosinophilia). GI strongyloidiasis is characterized by indigestion, crampy abdominal pain, vomiting, diarrhea, steatorrhea, protein-losing enteropathy, protein-caloric malnutrition, and weight loss. Edema of the duodenum with irregular mucosal folds, ulcerations, and strictures can be seen radiographically. Infection may be chronic in nature and is associated with **eosinophilia**.

Strongyloidiasis is potentially lethal because of the ability of the parasite to replicate within the host and cause overwhelming hyperinfection in immunocompromised persons. The **hyperinfection syndrome** is characterized by an exaggeration of the clinical features that develop in symptomatic immunocompetent individuals. The onset is usually sudden, with generalized abdominal pain, distention, and fever. Multiple organs can be affected as massive numbers of larvae disseminate throughout the body and introduce bowel flora. The latter may result in bacteremia and septicemia. Cutaneous manifestations may include petechiae and purpura. Cough, wheezing, and hemoptysis are indicative of pulmonary involvement. Whereas eosinophilia is a prominent feature of strongyloidiasis in immunocompetent persons, this sign may be absent in immunocompromised persons. Because of the low incidence of strongyloidiasis in industrialized countries, it is often misdiagnosed, resulting in a significant delay in treatment.

DIAGNOSIS

Intestinal strongyloidiasis is diagnosed by examining feces or duodenal fluid for the characteristic larvae (Fig. 341.2). Several stool samples should be examined by direct smear, the Koga agar plate method, or the Baermann test. Alternatively, duodenal fluid can be sampled by the **enteric string test** (Entero-Test) or aspiration via endoscopy. In children with the hyperinfection syndrome, larvae may be found in sputum, gastric aspirates, and rarely in small intestinal biopsy specimens. An enzyme-linked immunosorbent assay for IgG antibody to *Strongyloides* may be more sensitive than parasitologic methods for diagnosing intestinal infection in the immunocompetent host. The utility of the assay in diagnosing infection in immunocompromised patients with the hyperinfection syndrome has not been determined. Eosinophilia is common.

TREATMENT

Treatment is directed at eradication of infection. **Ivermectin** (200 µg/kg/day once daily orally for 2 days) is the drug of choice for uncomplicated strongyloidiasis. Alternatively, **albendazole** (400 mg orally twice daily for 7 days) may be used. Patients with the hyperinfection syndrome should be treated with ivermectin for 7-14 days and may require repeated courses. Reducing the dose of immunosuppressive therapy and treatment of concomitant bacterial infections are essential in the management of the **hyperinfection syndrome**. Close follow-up with repeated stool examination is necessary to ensure complete elimination of the parasite. *Strongyloides* antibodies decrease within 6 months after successful treatment.

PREVENTION

Sanitary practices designed to prevent soil and person-to-person transmission are the most effective control measures (see Table 337.1). Wearing **shoes** is a main preventive strategy. Reducing transmission in institutional settings can be achieved by decreasing fecal contamination of the environment, such as by the use of clean bedding. Because infection is uncommon in most settings, case detection and treatment are advisable. Individuals who will be given prolonged high-dose corticosteroids, immunosuppressive drugs before organ transplantation, or cancer chemotherapy should have a screening examination for *S. stercoralis*. If infected, they should be treated before immunosuppression is initiated.

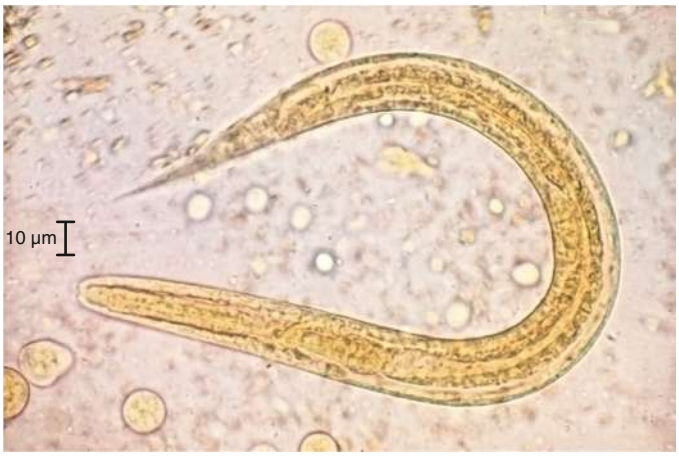

Fig. 341.2 Larvae of intestinal strongyloidiasis.

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Chapter 342

Lymphatic Filariasis (*Brugia malayi*, *Brugia timori*, and *Wuchereria bancrofti*)

Katherine R. Dobbs and Arlene E. Dent

ETIOLOGY

The filarial worms *Brugia malayi* **(Malayan filariasis)**, *Brugia timori,* and *Wuchereria bancrofti* **(bancroftian filariasis)** are threadlike nematodes that cause similar infections. Infective larvae are introduced into humans during blood feeding by the **mosquito** vector. Over 4-6 months, the larval forms develop into sexually mature adult worms. Once an adequate number of male and female worms accumulate in the afferent lymphatic vessels, adult female worms release large numbers of microfilariae that circulate in the bloodstream. The life cycle of the parasite is completed when mosquitoes ingest microfilariae in a blood meal, which molt to form infective larvae over 10-14 days. Adult worms have a 5–7-year life span.

EPIDEMIOLOGY

More than 120 million people living in tropical Africa, Asia, and Latin America are infected; approximately 10–20% of these individuals have clinically significant morbidity attributable to filariasis. *W. bancrofti* is transmitted in Africa, Asia, and Latin America and accounts for 90% of lymphatic filariasis. *B. malayi* is restricted to the South Pacific and Southeast Asia, and *B. timori* is restricted to several islands of Indonesia. Travelers from nonendemic areas of the world who spend brief periods in endemic areas are rarely infected. Global programs have targeted elimination in >80% of endemic countries by 2030.

CLINICAL MANIFESTATIONS

The clinical manifestations of *B. malayi, B. timori,* and *W. bancrofti* infection are similar; manifestations of acute infection include transient, recurrent lymphadenitis and lymphangitis. The early signs and symptoms include episodic fever, lymphangitis of an extremity, lymphadenitis (especially the inguinal and axillary areas), headaches, and myalgias that last a few days to several weeks. These symptoms are caused by an acute inflammatory response triggered by death of adult worms. Initial damage to lymphatic vessels may remain subclinical for years. The syndrome is most frequently observed in persons 10-20 years old. Manifestations of chronic lymphatic filariasis occur mostly in adults ≥30 years old and result from anatomic and functional obstruction to lymph flow. This obstruction results in lymphedema of the legs, arms, breasts, and/or genitalia. Male genital involvement, such as hydrocele, is very common in *W. bancrofti* infection, but uncommon in *Brugia* spp. infection. Chronic lymphedema predisposes affected extremities to bacterial superinfections, sclerosis, and verrucous skin changes, resulting in **elephantiasis**, which may involve one or more limbs, the breasts, or genitalia. It is uncommon for children to have overt signs of chronic filariasis.

Tropical Pulmonary Eosinophilia

The presence of microfilariae in the body has no apparent pathologic consequences except in persons with tropical pulmonary eosinophilia, a syndrome of filarial etiology in which microfilariae are found in the lungs and lymph nodes but not the bloodstream. It occurs only in individuals who have lived for years in endemic areas. Men 20-30 years old are most likely to be affected, although the syndrome occasionally occurs in children. The presentation includes paroxysmal nocturnal cough with dyspnea, fever, weight loss, and fatigue. Rales and rhonchi are found on auscultation of the chest. The x-ray findings may occasionally be normal, but increased bronchovascular markings, discrete opacities in the middle and basal regions of the lung, or diffuse miliary lesions are usually present (Fig. 342.1). Recurrent episodes may result in interstitial fibrosis and chronic respiratory insufficiency in untreated individuals. Hepatosplenomegaly and generalized lymphadenopathy are often seen in children. The **diagnosis** is suggested by residence in a filarial endemic area, eosinophilia (>2,000/µL), compatible clinical symptoms, increased serum IgE (>1,000 IU/mL), and high titers of antimicrofilarial antibodies in the absence of microfilaremia. Although microfilariae may be found in sections of lung or lymph node, biopsy of these tissues is unwarranted in most situations. The clinical response to **diethylcarbamazine** (2 mg/kg/dose orally 3 times daily for 12-21 days) is the final criterion for diagnosis; the majority of patients improve with this therapy. If symptoms recur, a second anthelmintic course should be administered. Patients with chronic symptoms are less likely to show improvement than those who have been ill for a short time.

DIAGNOSIS

Demonstration of microfilariae in the blood is the primary means for confirming the diagnosis of lymphatic filariasis. Because microfilaremia is **nocturnal** in most cases, blood samples should be obtained between 10 PM and 2 AM. Anticoagulated blood is passed through a Nuclepore filter that is stained and examined microscopically for microfilariae. Adult worms or microfilariae can be identified in tissue specimens obtained at biopsy. Infection with *W. bancrofti* in the absence of bloodborne microfilariae may be diagnosed by detection of parasite antigen in the serum. Adult worms in lymphatic vessels can be visualized by ultrasonography.

TREATMENT

The use of antifilarial drugs in the management of acute lymphadenitis and lymphangitis is controversial. No controlled studies demonstrate that administration of drugs such as diethylcarbamazine modifies the course of acute lymphangitis. Diethylcarbamazine may be given to asymptomatic microfilaremic persons to lower the intensity of parasitemia. The drug also kills a proportion of the adult worms. Because treatment-associated complications such as pruritus, fever, generalized body pain, hypotension, and even death may occur, especially with high microfilarial levels, the dose of **diethylcarbamazine** should be increased gradually (*children*: 1 mg/kg orally as a single dose on day 1,

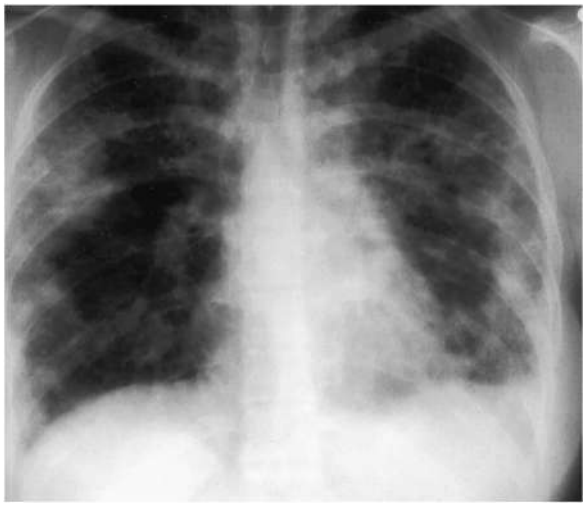

Fig. 342.1 Chest radiograph of tropical pulmonary eosinophilia. Reticulonodular opacities are scattered throughout both lungs. *(From Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases, 6th ed. Philadelphia: Elsevier, 2006. p. 3274.)*

1 mg/kg 3 times daily on day 2, 1-2 mg/kg 3 times daily on day 3, and 2 mg/kg 3 times daily on days 4-14; *adults*: 50 mg orally on day 1, 50 mg 3 times daily on day 2, 100 mg 3 times daily on day 3, and 2 mg/kg 3 times daily on days 4-14). For patients with no microfilaria in the blood, the full dose (2 mg/kg/day orally divided 3 times daily) can be given beginning on day 1. Repeat doses may be necessary to further reduce the microfilaremia and kill lymph-dwelling adult parasites. *W. bancrofti* is more sensitive than *B. malayi* to diethylcarbamazine.

Global programs to control and ultimately eradicate lymphatic filariasis from endemic populations outside of sub-Saharan Africa currently recommend triple drug treatment with one or two annual doses of **diethylcarbamazine** (6 mg/kg orally once), **albendazole** (400 mg orally once), and **ivermectin** (150 µg/kg orally once) (mass drug administration). In co-endemic areas of filariasis and **onchocerciasis**, mass drug applications with single-dose ivermectin and albendazole are used because of severe adverse reactions with diethylcarbamazine in onchocerciasis-infected individuals.

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Chapter 343

Other Tissue Nematodes

Katherine R. Dobbs and Arlene E. Dent

ONCHOCERCIASIS (*ONCHOCERCA VOLVULUS*)

Infection with *Onchocerca volvulus* leads to onchocerciasis or **river blindness**. Onchocerciasis occurs primarily in West Africa but also in Central and East Africa and is the world's second leading infectious cause of blindness. There have been scattered foci in South America and Yemen. *O. volvulus* larvae are transmitted to humans by the bite of *Simulium* black flies that breed in fast-flowing streams. The larvae penetrate the skin and migrate through the connective tissue and eventually develop into adult worms that can be found tangled in fibrous tissue. Adult worms can live in the human body for up to 14 years. Female worms produce large numbers of microfilariae that migrate through the skin, connective tissue, and eye. Most infected individuals are asymptomatic. In heavily infected individuals, clinical manifestations are a result of localized host inflammatory reactions to dead or dying microfilariae and subcutaneous adult worms surrounded by a palpable fibrous capsule. Cutaneous and ocular reactions to microfilariae produce pruritic dermatitis, punctate keratitis, corneal pannus formation, and chorioretinitis. Adult worms in subcutaneous nodules are not painful and tend to occur over bony prominences of the hip. The **diagnosis** can be established by obtaining snips of skin covering the scapulae, iliac crests, buttocks, or calves. The snips are immersed in saline for several hours and examined microscopically for microfilariae that have emerged into the fluid. The diagnosis can also be established by demonstrating microfilariae in the cornea or anterior chamber on slit-lamp examination or finding adult worms on a nodule biopsy specimen. Ophthalmology consultation should be obtained before treatment of eye lesions.

A single dose of **ivermectin** (150 µg/kg orally) is the drug of choice and clears *O. volvulus* microfilariae from the skin for several months but has no effect on the adult worm. Treatment with ivermectin should be repeated every 6-12 months until the patient is asymptomatic or has no evidence of eye infection. Adverse effects of ivermectin therapy include fever, urticaria, and pruritus, which are more frequent in individuals not born in endemic areas who acquired the infection after periods of intense exposure, such as Peace Corps volunteers. Patients with concurrent high-density microfilaremia from loiasis may develop potentially fatal encephalopathy with ivermectin therapy. Treatment with ivermectin should be withheld until *Loa loa* microfilaremia can be reduced. **Moxidectin** is a promising new agent. Personal protection includes avoiding areas where biting flies are numerous, wearing protective clothing, and using insect repellent. Programs of mass treatment with ivermectin have been implemented in Africa and South America in an effort to reduce the prevalence of onchocerciasis.

The World Health Organization (WHO) set goals for onchocerciasis elimination by 2025 using mass drug administration with ivermectin. Elimination can be declared only after 3 years of posttreatment surveillance without microfilaria detection in skin biopsies.

Nodding syndrome, a form of epilepsy in African children living in focal areas of Uganda and South Sudan, was epidemiologically associated with onchocerciasis, but an etiologic link was not established. Recently, researchers identified neurotoxic autoantibodies that cross-react with *O. volvulus* proteins, which were found more frequently in people with nodding syndrome than in those in the same village without the syndrome. Nodding syndrome may be an autoimmune epileptic disorder triggered by *O. volvulus* infection.

LOIASIS (*LOA LOA*)

Loiasis is caused by infection with the tissue nematode *Loa loa*. The parasite is transmitted to humans by diurnally biting flies *(Chrysops)* that live in the rain forests of West and Central Africa. Migration of adult worms through skin, subcutaneous tissue, and subconjunctival area can lead to transient episodes of pruritus, erythema, and localized edema known as **Calabar swellings**, which are nonerythematous areas of subcutaneous edema 10-20 cm in diameter typically found around joints such as the wrist or the knee (Fig. 343.1). They resolve over several days to weeks and may recur at the same or different sites. Lifelong residents of *L. loa*–endemic regions may have microfilaremia and eosinophilia but are often asymptomatic. In contrast, travelers to endemic regions may have a hyperreactive response to *L. loa* infection characterized by frequent recurrences of swelling, high level eosinophilia, debilitation, and serious complications such as glomerulonephritis and encephalitis. **Diagnosis** is usually established on clinical grounds, often assisted by the infected individual reporting a worm being seen crossing the conjunctivae. Microfilariae may be detected in blood smears collected between 10 AM and 2 PM. Adult worms should be surgically excised when possible.

Diethylcarbamazine is the treatment of choice for loiasis, as there is evidence that it kills both microfilariae and adult worms and results in a sustained decrease in microfilarial intensity after treatment. Because treatment-associated complications such as pruritus, fever, generalized body pain, hypertension, and even death may occur, especially

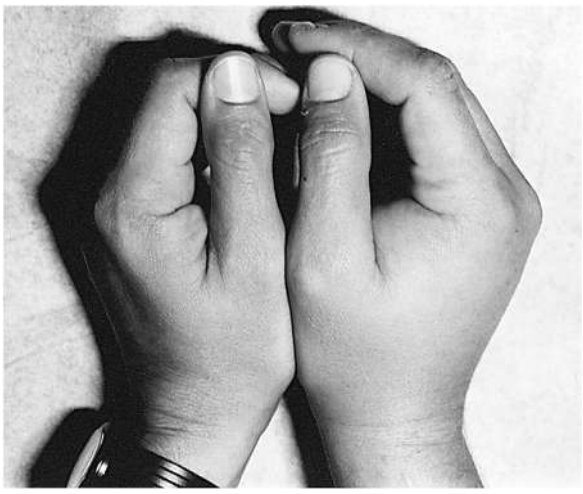

Fig. 343.1 Calabar swelling of the right hand. *(From Guerrant RL, Walker DH, Weller PF, et al. Tropical Infectious Diseases. Philadelphia: Churchill Livingstone, 2006: p. 1165.)*

with high microfilaria levels, the dose of diethylcarbamazine should be increased gradually in such cases (*children*: 1 mg/kg orally on day 1, 1 mg/kg three times daily on day 2, 1-2 mg/kg three times daily on day 3, 3 mg/kg three times daily on days 4-21; *adults*: 50 mg orally on day 1, 50 mg three times daily on day 2, 100 mg three times daily on day 3, 3 mg/kg three times daily on days 4-21). Full doses can be instituted on day 1 in persons without microfilaremia (3 mg/kg orally times daily for 21 days). A 3-week course of **albendazole** can also be used to slowly reduce *L. loa* microfilarial levels as a result of embryotoxic effects on the adult worms. Antihistamines or corticosteroids may be used to limit allergic reactions secondary to killing of microfilariae. Personal protective measures include avoiding areas where biting flies are present, wearing protective clothing, and using insect repellents. Diethylcarbamazine (300 mg orally once weekly) prevents infection in travelers who spend prolonged periods in endemic areas. *L. loa* do not harbor *Wolbachia* endosymbionts, and therefore doxycycline has no effect on infection.

INFECTION WITH ANIMAL FILARIAE

The most commonly recognized zoonotic filarial infections are caused by members of the genus *Dirofilaria*. The worms are introduced into humans by the bites of mosquitoes containing third-stage larvae. The most common filarial zoonosis in the United States is *Dirofilaria tenuis,* a parasite of raccoons. In Europe, Africa, and Southeast Asia, infections are usually caused by the dog parasite *Dirofilaria repens.* The **dog heartworm**, *Dirofilaria immitis,* is the second most frequently encountered filarial zoonosis worldwide. Other genera, including *Dipetalonema*-like worms, *Onchocerca,* and *Brugia,* are rare causes of zoonotic filarial infections.

Animal filariae do not undergo normal development in the human host. The clinical manifestations and pathologic findings correspond to the anatomic site of infection and can be categorized into four major groups: subcutaneous, lung, eye, and lymphatic. Pathologic examination of affected tissue reveals a localized foreign body reaction around a dead or dying parasite. The lesion consists of granulomas with eosinophils, neutrophils, and tissue necrosis. *D. tenuis* does not leave the subcutaneous tissues, whereas *Brugia beaveri* eventually localizes to superficial lymph nodes. Infections may be present for up to several months. *D. immitis* larvae migrate for several months in subcutaneous tissues and most frequently result in a well-circumscribed, coinlike lesion in a single lobe of the lung. The chest radiograph typically reveals a solitary pulmonary nodule 1-3 cm in diameter. Definitive **diagnosis** and cure depend on surgical excision and identification of the nematode within the surrounding granulomatous response. *D. tenuis* and *B. beaveri* infections present as painful, rubbery, 1-5 cm nodules in the skin of the trunk, of the extremities, and around the orbit. Patients often report having been engaged in activities predisposing to exposure to infected mosquitoes, such as working or hunting in swampy areas. Management is by **surgical excision**.

ANGIOSTRONGYLUS CANTONENSIS

Angiostrongylus cantonensis, the **rat lungworm,** is the most common cause of **eosinophilic meningitis** worldwide. Rats are the definitive host. Human infection follows ingestion of third-stage larvae in raw or undercooked intermediate hosts such as snails and slugs, or transport hosts such as freshwater prawns, frogs, and fish. Most cases are sporadic, but clusters have been reported, including clusters related to consumption of lettuce contaminated with intermediate or transport hosts. Even though most infections have been described in Southeast Asia, the South Pacific, and Taiwan, shipboard travel of infected rats has spread the parasite to Madagascar, Africa, the Caribbean, and most recently Australia and North America. Larvae penetrate the vasculature of the intestinal tract and migrate to the meninges, where they usually die but induce eosinophilic aseptic meningitis. Patients present 2-35 days after ingestion of larvae with severe headache, neck pain or nuchal rigidity, hyperesthesias and paresthesias (often migrating), fatigue, fever, rash, pruritus, nausea, and vomiting. Neurologic involvement varies from asymptomatic to paresthesias, severe pain, weakness, and focal neurologic findings such as cranial nerve palsies. Symptoms can last for several weeks to months, especially headache. Coma and death from hydrocephalus occur rarely in heavy infections. Peripheral blood eosinophilia is not always present on initial examination but peaks about 5 weeks after exposure, often when symptoms are improving. Cerebrospinal fluid (CSF) analysis reveals pleocytosis with >10% eosinophils in more than half of patients, with mildly elevated protein, a normal glucose level, and an elevated opening pressure. Head CT or MRI is usually unremarkable. The **diagnosis** is established clinically with supporting travel and diet history. A sensitive and specific enzyme-linked immunosorbent assay (ELISA) is available on a limited basis from the Centers for Disease Control and Prevention (CDC) for testing CSF or serum.

Treatment is primarily supportive because the majority of infections are mild, and most patients recover within 2 months without neurologic sequelae. Analgesics should be given for headache. Careful, repeated lumbar punctures should be performed to relieve hydrocephalus. Anthelmintic drugs have not been shown to influence the outcome and may exacerbate neurologic symptoms. The use of corticosteroids may shorten the duration of persistent and severe headaches. There is a higher incidence of permanent neurologic sequelae and mortality among children than among adults. Infection can be avoided by not eating raw or undercooked crabs, prawns, or snails.

ANGIOSTRONGYLUS COSTARICENSIS

Angiostrongylus costaricensis is a nematode that infects several species of rodents and causes abdominal **angiostrongyliasis**, which has been described predominantly in Latin America and the Caribbean. The mode of transmission to humans, who are accidental hosts, is unknown. It is speculated that infectious larvae from a molluscan intermediate host, such as the slug *Vaginulus plebeius,* contaminate water or vegetation that is inadvertently consumed (chopped up in salads or on vegetation contaminated with the slug's mucous secretions). Although this slug is not indigenous to the continental United States, it has been found on imported flowers and produce. The incubation period for abdominal angiostrongyliasis is unknown, but limited data suggest that it ranges from 2 weeks to several months after ingestion of larvae. Third-stage larvae migrate from the gastrointestinal tract to the mesenteric arteries, where they mature into adults. These eggs degenerate and elicit an eosinophilic granulomatous reaction. The clinical findings of abdominal angiostrongyliasis mimic **appendicitis,** although the former is typically more indolent. Children can have fever, right lower quadrant pain, a tumor-like mass, abdominal rigidity, and a painful rectal examination. Most patients have leukocytosis with eosinophilia. Radiologic examination may show bowel wall edema, spasticity, or filling defects in the ileocecal region and the ascending colon. Examination of stool for ova and parasites is not useful for *A. costaricensis* but is useful for evaluating the presence of other intestinal parasites. An

ELISA is available for **diagnosis** on a limited basis from the CDC, but the test has a low specificity and is known to cross react with *Toxocara, Strongyloides,* and *Paragonimus.*

Many patients undergo laparotomy for suspected appendicitis and are found to have a mass in the terminal ileum to the ascending colon. *No specific treatment is known for abdominal angiostrongyliasis.* Even though the use of anthelmintic therapy has not been studied systematically, thiabendazole or diethylcarbamazine has been suggested. The prognosis is generally good. Most cases are self-limited, although surgery may be required in some patients. Cornerstones of **prevention** include avoidance of slugs and not ingesting raw food and water that may be contaminated with imperceptible slugs or slime from slugs. Rat control is also important in preventing the spread of infection.

DRACUNCULIASIS *(DRACUNCULUS MEDINENSIS)*

Dracunculiasis is caused by the guinea worm, *Dracunculus medinensis.* WHO has targeted dracunculiasis for eradication in 2030. Eradication efforts have been hampered by conflicts as well as increasing rates of infections in animals such as dogs. As of 2021, transmission of the infection was occurring in Chad, Ethiopia, Mali, South Sudan, Angola, and Cameroon. Humans become infected by drinking contaminated stagnant water that contains immature forms of the parasite in the gut of tiny crustaceans (copepods or water fleas). Larvae are released in the stomach, penetrate the mucosa, mature, and mate. Approximately 1 year later, the adult female worm (1-2 mm in diameter and up to 1 m long) migrates and partially emerges through the human host skin, usually of the legs. Thousands of immature larvae are released when the affected body part is immersed in the water. The cycle is completed when larval forms are ingested by the crustaceans. Infected humans have no symptoms until the worm reaches the subcutaneous tissue, causing a **stinging papule** that may be accompanied by urticaria, nausea, vomiting, diarrhea, and dyspnea. The lesion vesiculates, ruptures, and forms a painful ulcer in which a portion of the worm is visible. **Diagnosis** is established clinically. Larvae can be identified by microscopic examination of the discharge fluid.

Metronidazole (25 mg/kg/day orally divided into three doses for 10 days; maximum dose: 750 mg) decreases local inflammation. Although the drug does not kill the worm, it facilitates its removal. The worm must be physically removed by rolling the slowly emerging 1 m–long parasite onto a thin stick over a week. Topical corticosteroids shorten the time to complete healing, while topical antibiotics decrease the risk of secondary bacterial infection. Dracunculiasis can be prevented by boiling or chlorinating drinking water or passing the water through a cloth sieve before consumption. Eradication is dependent on behavior modification and education.

GNATHOSTOMA SPINIGERUM

Gnathostoma spinigerum is a dog and cat nematode endemic to Southeast Asia, Japan, China, Bangladesh, and India, but it has been sporadically reported in numerous countries worldwide. Infection is acquired by ingesting intermediate hosts containing larvae of the parasite, such as raw or undercooked freshwater fish, chickens, pigs, snails, or frogs. Penetration of the skin by larval forms and prenatal transmission has also been described. Nonspecific signs and symptoms such as generalized malaise, fever, urticaria, anorexia, nausea, vomiting, diarrhea, and epigastric pain develop 24-48 hours after ingestion of *G. spinigerum.* Ingested larvae penetrate the gastric wall and migrate through soft tissue for up to 10 years. Moderate to severe eosinophilia can develop. Cutaneous **gnathostomiasis** manifests as intermittent episodes of localized, migratory nonpitting edema associated with pain, pruritus, or erythema. Central nervous system involvement in gnathostomiasis is suggested by focal neurologic findings, initially neuralgia followed within a few days by paralysis or changes in mental status. Multiple cranial nerves may be involved, and CSF may be xanthochromic but typically shows an eosinophilic pleocytosis. **Diagnosis** of gnathostomiasis is based on clinical presentation and epidemiologic background. Brain and spinal cord lesions may be seen on CT or MRI. Serologic testing varies in sensitivity and specificity and is available through the CDC.

There is no well-documented effective chemotherapy, although **albendazole** (400 mg orally twice daily for 21 days) as first-line therapy or **ivermectin** (200 μg/kg for 2 days) as an alternative is recommended without or with surgical removal. Multiple courses may be needed. Corticosteroids have been used to relieve focal neurologic deficits. **Surgical resection** of the *Gnathostoma* is the major mode of therapy and the treatment of choice. Blind surgical resection of subcutaneous areas of diffuse swelling is not recommended because the worm can rarely be located. **Prevention** through the avoidance of ingestion of poorly cooked or raw fish, poultry, or pork should be emphasized for individuals living in or visiting endemic areas.

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Chapter 344

Toxocariasis (Visceral and Ocular Larva Migrans)

Katherine R. Dobbs and Arlene E. Dent

Most cases of human toxocariasis are caused by the **dog roundworm**, *Toxocara canis.* Adult female *T. canis* worms live in the intestinal tracts of young puppies and their lactating mothers. Large numbers of eggs are passed in the feces of dogs and embryonate under optimal soil conditions. *Toxocara* eggs can survive relatively harsh environmental conditions and are resistant to freezing and extremes of moisture and pH. Humans ingest embryonated eggs contaminating soil, hands, or fomites. The larvae hatch and penetrate the intestinal wall and travel via the circulation to the liver, lung, and other tissues. Humans do not excrete *T. canis* eggs because the larvae are unable to complete their maturation to adult worms in the intestine. The **cat roundworm**, *Toxocara cati,* is responsible for far fewer cases of **visceral larva migrans (VLM)** than *T. canis.* Ingestion of infective larvae of the raccoon ascarid *Baylisascaris procyonis* rarely leads to VLM but can cause **neural larva migrans**, resulting in fatal eosinophilic meningitis. Ingestion of larvae from the opossum ascarid *Lagochilascaris minor* leads to VLM rarely.

EPIDEMIOLOGY

Human *T. canis* infections have been reported in almost all parts of the world, primarily in temperate and tropical areas where dogs are popular household pets. Young children are at highest risk because of their unsanitary play habits and tendency to place fingers in the mouth. Other behavioral risk factors include **pica**, contact with puppy litters, and institutionalization. In North America, the highest prevalence of infection is in the southeastern United States and Puerto Rico, particularly among socially disadvantaged Black and Hispanic children. In the United States, serosurveys show that 3–3.9% of children are infected. Assuming an unrestrained and untreated dog population, toxocariasis is prevalent in settings where other **geohelminth infections**, such as ascariasis, trichuriasis, and hookworm infections, are common.

PATHOGENESIS

T. canis larvae secrete large amounts of immunogenic glycosylated proteins. These antigens induce immune responses that lead to eosinophilia and polyclonal and antigen-specific immunoglobulin E production. The characteristic histopathologic lesions are granulomas containing eosinophils, multinucleated giant cells (histiocytes), and collagen. Granulomas are typically found in the liver but may also

Table 344.1 Clinical Syndromes of Human Toxocariasis

SYNDROME	CLINICAL FINDINGS	AVERAGE AGE	INFECTIOUS DOSE	INCUBATION PERIOD	LABORATORY FINDINGS	ELISA
Visceral larva migrans	Fevers, hepatomegaly, asthma	5 yr	Moderate to high	Weeks to months	Eosinophilia, leukocytosis, elevated IgE	High (≥1:16)
Ocular larva migrans	Visual disturbances, retinal granulomas, endophthalmitis, peripheral granulomas	12 yr	Low	Months to years	Usually none	Low
Covert toxocariasis	Abdominal pain, gastrointestinal symptoms, weakness, hepatomegaly, pruritus, rash	School-age to adult	Low to moderate	Weeks to years	± Eosinophilia ± Elevated IgE	Low to moderate

ELISA, Enzyme-linked immunosorbent assay; IgE, immunoglobulin E; ±, with or without.
Adapted from Glickman LT, Schantz PM. Epidemiology and pathogenesis of zoonotic toxocariasis. *Epidemiol Rev.* 1981;3:230–250.

occur in the lungs, central nervous system (CNS), and ocular tissues. Clinical manifestations reflect the intensity and chronicity of infection, anatomic localization of larvae, and host granulomatous responses.

CLINICAL MANIFESTATIONS

Three major clinical syndromes are associated with human toxocariasis: VLM, **ocular larva migrans (OLM)**, and **covert toxocariasis** (Table 344.1). The classic presentation of VLM includes eosinophilia, fever, and hepatomegaly and occurs most often in toddlers with a history of pica and exposure to puppies. The findings include fever, cough, wheezing, bronchopneumonia, anemia, hepatomegaly, leukocytosis, eosinophilia, and positive *Toxocara* serology. Cutaneous manifestations such as pruritus, eczema, and urticaria can be present. OLM tends to occur in older children without signs or symptoms of VLM. Presenting symptoms include unilateral visual loss, eye pain, white pupil, or strabismus that develops over weeks. Granulomas occur on the posterior pole of the retina and may be mistaken for retinoblastoma. Serologic testing for *Toxocara* has allowed the identification of individuals with less obvious or covert symptoms of infection. These children may have nonspecific complaints that do not constitute a recognizable syndrome. Common findings include hepatomegaly, abdominal pain, cough, sleep disturbance, failure to thrive, and headache with elevated *Toxocara* antibody titers. Eosinophilia may be present in 50–75% of cases. The prevalence of positive *Toxocara* serology in the general population supports that most children with *T. canis* infection are asymptomatic and will not develop overt clinical sequelae over time. A correlation between positive *Toxocara* serology and allergic asthma has also been described.

DIAGNOSIS

A presumptive diagnosis of toxocariasis can be established in a young child with **eosinophilia** (>20%), leukocytosis, hepatomegaly, fevers, wheezing, and a history of geophagia and exposure to puppies or unrestrained dogs. Supportive laboratory findings include hypergammaglobulinemia and elevated isohemagglutinin titers to A and B blood group antigens. Most patients with VLM have an absolute eosinophil count >500/μL. Eosinophilia is less common in patients with OLM. Biopsy confirms the diagnosis. When biopsies cannot be obtained, an enzyme-linked immunosorbent assay using excretory-secretory proteins harvested from *T. canis* larvae maintained in vitro is the standard serologic test used to confirm toxocariasis. A titer of 1:32 is associated with a sensitivity of approximately 78% and a specificity of approximately 92%. The sensitivity for OLM is significantly less. The diagnosis of OLM can be established in patients with typical clinical findings of a retinal or peripheral pole granuloma or endophthalmitis with elevated antibody titers. Vitreous and aqueous humor fluid anti-*Toxocara* titers are usually greater than serum titers. The diagnosis of covert toxocariasis should be considered in individuals with chronic weakness, abdominal pain, or allergic signs with eosinophilia and increased IgE. In temperate regions of the world, nonparasitic causes of eosinophilia that should be considered in the differential diagnosis include allergies, drug hypersensitivity, lymphoma, vasculitis, and idiopathic hypereosinophilic syndrome (see Chapter 169).

TREATMENT

Most patients do not require treatment because signs and symptoms are mild and subside over weeks to months. Several anthelmintic drugs have been used for symptomatic cases, often with adjunctive corticosteroids to limit inflammatory responses that presumably result from release of *Toxocara* antigens by dying parasites. **Albendazole** (400 mg orally twice daily for 5 days for all ages) has demonstrated efficacy in both children and adults. **Mebendazole** (100-200 mg PO twice daily for 5 days for all ages) is also useful. Anthelmintic treatment of CNS and ocular disease should be extended (3-4 weeks). Even with no clinical trials on OLM therapy, a course of oral corticosteroids such as **prednisone** (1 mg/kg/day PO for 2-4 weeks) has been recommended to suppress local inflammation while treatment with anthelmintic agents is initiated.

PREVENTION

Transmission can be minimized by public health measures that prevent dog feces from contaminating the environment. These include keeping dogs on leashes and excluding pets from playgrounds and sandboxes that toddlers use. Children should be discouraged from putting dirty fingers in their mouth and eating dirt. Vinyl covering of sandboxes reduces the viability of *T. canis* eggs. Widespread veterinary use of broad-spectrum anthelmintics effective against *Toxocara* may lead to a decline in parasite transmission to humans.

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Chapter 345

Trichinellosis (*Trichinella spiralis*)

Katherine R. Dobbs and Arlene E. Dent

ETIOLOGY

Human trichinellosis (also called **trichinosis**) is caused by consumption of meat containing encysted larvae of *Trichinella spiralis,* a tissue-dwelling nematode with a worldwide distribution. After ingestion of raw or inadequately cooked meat from pigs (or other commercial meat sources such as horses) containing viable *Trichinella* larvae, the organisms are released from the cyst by acid-pepsin digestion of the cyst walls in the stomach and then pass into the small intestine. The larvae invade the small intestine columnar epithelium at the villi base and develop into adult worms. The adult female worm produces about 500 larvae over 2 weeks and is then expelled in the feces. The larvae enter the bloodstream and seed striated muscle by burrowing into individual muscle fibers. Over a period of 3 weeks, they coil as they increase about 10 times in length and become capable of infecting a new host if ingested. The larvae eventually become encysted and can remain viable for years. **Sylvatic** *Trichinella* spp. (*T. britovi, T. nativa, T. pseudospiralis,* and *T. murrelli*) are present in traditional native foods, such as walrus meat, and **game meat** may also cause disease similar to that caused by *T. spiralis*.

EPIDEMIOLOGY

Despite public health efforts to control trichinellosis by eliminating the practice of feeding garbage to domestic swine, epidemics and isolated cases of *Trichinella* spp. infection continue to be a health problem in many areas of the world. It is most common in Asia, Latin America, and Central Europe. Swine fed with garbage may become infected when given uncooked trichinous scraps, usually pig meat, or when the carcasses of infected wild animals such as rats are eaten. Prevalence rates of *T. spiralis* in domestic swine range from 0.001% in the United States to ≥25% in China. The resurgence of this disease can be attributed to translocations of animal populations, human travel, and export of food as well as ingestion of sylvatic *Trichinella* through game meat. In the United States from 2008 to 2012, wild game meat (especially bear or wild boar meat) was the most common source of infection. Most outbreaks occur from the consumption of *T. spiralis*–infected pork (or horse meat in areas of the world where horse is eaten) obtained from a single source.

PATHOGENESIS

During the first 2-3 weeks after infection, pathologic reactions to infection are limited to the gastrointestinal (GI) tract and include a mild, partial villous atrophy with an inflammatory infiltrate of neutrophils, eosinophils, lymphocytes, and macrophages in the mucosa and submucosa. Larvae are released by female worms and disseminate over the next several weeks. Skeletal muscle fibers show the most striking changes with edema and basophilic degeneration. The muscle fiber may contain the typical coiled worm, the cyst wall derived from the host cell, and the surrounding lymphocytic and eosinophilic infiltrate.

CLINICAL MANIFESTATIONS

The development of symptoms depends on the number of viable larvae ingested. Most infections are asymptomatic or mild, and children often show milder symptoms than adults who consumed the same amount of infected meat. Watery diarrhea is the most common symptom corresponding to maturation of the adult worms in the GI tract, which occurs during the first 1-2 weeks after ingestion. Patients may also complain of abdominal discomfort and vomiting. Fulminant **enteritis** may develop in individuals with extremely high worm burdens. The classic symptoms of facial and periorbital edema, fever, weakness, malaise, and myalgia peak approximately 2-3 weeks after the infected meat is ingested, as the larvae migrate and then encyst in the muscle. Headache, cough, dyspnea, dysphagia, subconjunctival and splinter hemorrhages, and a macular or petechial rash may occur. Patients with high-intensity infection may die from myocarditis, encephalitis, or pneumonia. In symptomatic patients, **eosinophilia** is common and may be dramatic.

DIAGNOSIS

The Centers for Disease Control and Prevention (CDC) diagnostic criteria for trichinellosis require positive serology or muscle biopsy for *Trichinella* with one or more compatible clinical symptoms (eosinophilia, fever, myalgia, facial or periorbital edema). To declare a discrete outbreak, at least one person must have positive serology or muscle biopsy. Antibodies to *Trichinella* are detectable approximately 3 weeks after infection. Severe muscle involvement results in elevated serum creatine phosphokinase and lactic dehydrogenase levels. Muscle biopsy is not usually necessary, but if needed, a sample should be obtained from a tender swollen muscle. A history of eating undercooked meat supports the diagnosis. The cysts may calcify and may be visible on radiograph.

TREATMENT

Recommended treatment of trichinellosis diagnosed at the GI phase is **albendazole** (400 mg orally twice daily for 8-14 days for all ages) to eradicate the adult worms if a patient has ingested contaminated meat within the previous 1 week. An alternative regimen is mebendazole (200-400 mg PO 3 times daily for 3 days followed by 400-500 mg 3 times daily for 10 days). There is no consensus for treatment of muscle-stage trichinellosis. Corticosteroids may be used, although evidence for efficacy is anecdotal.

PREVENTION

Trichinella larvae can be killed by cooking meat (≥55°C [131°F]) until there is no trace of pink fluid or flesh, or by storage in a freezer (−15°C [5°F]) for ≥3 wk. Freezing to kill larvae should only be applied to pork meat, because larvae in horse, wild boar, or game meat can remain viable even after 4 weeks of freezing. Smoking, salting, and drying meat are unreliable methods of killing *Trichinella.* Strict adherence to public health measures, including garbage feeding regulations, stringent rodent control, prevention of exposure of pigs and other livestock to animal carcasses, constructing barriers between livestock, wild animals, and domestic pets, and proper handling of wild animal carcasses by hunters, can reduce infection with *Trichinella.* Current meat inspection for trichinellosis is by direct digestion and visualization of encysted larvae in meat samples. Serologic testing does not have a role in meat inspection.

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Chapter 346

Schistosomiasis *(Schistosoma)*

Amaya L. Bustinduy, Sophie Pach, and Katja Doerholt

The term **schistosomiasis** (also known as **bilharzia**) encompasses the acute and chronic inflammatory disorders caused by human infection with *Schistosoma* spp. parasites. Disease is related to both the systemic and the focal effects of schistosome infection and its consequent host immune responses triggered by parasite eggs deposited in the tissues. For the affected individuals, this frequently manifests as disabling chronic morbidity.

ETIOLOGY

Schistosoma organisms are trematodes, or **flukes**, that parasitize the bloodstream. Five schistosome species are known to infect humans: *Schistosoma haematobium, S. mansoni, S. japonicum, S. intercalatum,* and *S. mekongi*. Humans are infected through contact with water contaminated with *cercariae*, the free-living infective stage of the parasite. These motile, forked-tail organisms emerge from infected snails and are capable of penetrating intact human skin. As they reach maturity, adult worms migrate to specific anatomic sites characteristic of each schistosome species: *S. haematobium* adults are found in the perivesical and periureteral venous plexus, *S. mansoni* in the inferior mesenteric veins, and *S. japonicum* in the superior mesenteric veins. The less common *S. intercalatum* and *S. mekongi* are usually found in the mesenteric vessels. Adult schistosome worms (1-2 cm long) are clearly adapted for an intravascular existence. The female accompanies the male in a groove formed by the lateral edges of its body. On fertilization, female worms begin oviposition in the small venous tributaries. The eggs of the three main schistosome species have characteristic morphologic features: *S. haematobium* has a terminal spine, *S. mansoni* has a lateral spine, and *S. japonicum* has a smaller size with a short, curved spine (Fig. 346.1). Parasite eggs provoke a significant granulomatous inflammatory response that allows them to ulcerate through host tissues to reach the lumen of the urinary tract or the intestines. They are carried to the outside environment in urine or feces (depending on the species), where they will hatch if deposited in freshwater. Motile miracidia emerge, infect specific freshwater snail intermediate hosts, and divide asexually. After 4-12 weeks, the infective cercariae are released by the snails into the contaminated water.

EPIDEMIOLOGY

Schistosomiasis affects more than 300 million people worldwide with more than 700 million people at risk, primarily children and young adults. There are 1.8 million disability-adjusted life-years (DALYs) attributed to schistosomiasis, making it the second most disabling parasitic disease after malaria. Prevalence is increasing in many areas as population density increases and new irrigation projects provide broader habitats for the intermediate **snail** hosts. Humans are the main definitive hosts for the five clinically important species of schistosomes, although *S. japonicum* is also a zoonosis, infecting animals such as dogs, rats, pigs, and cattle. *S. haematobium* is prevalent in Africa and the Middle East with cases reported in the Mediterranean (Corsica in France); *S. mansoni* is prevalent in Africa, the Middle East, the Caribbean, and South America; and *S. japonicum* is prevalent in China, the Philippines, and Indonesia, with some sporadic foci in parts of Southeast Asia. The other two species are less prevalent. *S. intercalatum* is found in West and Central Africa, and *S. mekongi* is found only along the upper Mekong River in Asia.

Transmission depends on water contamination by human excreta (urine and stool), the presence of specific intermediate snail hosts, and the patterns of water contact and social habits of the population (Fig. 346.2). The distribution of infection in endemic areas shows that prevalence increases with age, to a peak at 10-20 years old. Exposure to infected water starts early in life for children living in endemic areas. Passive water contact by infants (accompanying mothers in their daily household activities) evolves to more active water contact as preschool and school-age children pursue recreational activities such as swimming and wading.

Measuring intensity of infection (by quantitative egg count in urine or feces) demonstrates that the heaviest worm loads are found in school-age and adolescent children. Even though schistosomiasis is most prevalent and most severe in older children and young adults, who are at maximal risk for suffering from its acute and chronic sequelae, preschool children can also exhibit significant disease manifestations.

PATHOGENESIS

Both early and late manifestations of schistosomiasis are immunologically mediated. *Acute* schistosomiasis, known as **snail fever** or **Katayama syndrome**, is a febrile illness that represents an immune complex disease associated with early infection and oviposition 4-8 weeks after cercarial skin penetration. The major pathology of infection occurs later, with *chronic* schistosomiasis, in which retention of eggs in the host tissues is associated with chronic granulomatous injury. Eggs may be trapped at sites of deposition (urinary bladder, ureters, cervix, intestine) or may be carried by the bloodstream to ectopic sites, most frequently the liver and less often the lungs and central nervous system (CNS). The host response to these eggs involves local as well as systemic manifestations. The cell-mediated immune response leads to granulomas composed of lymphocytes, macrophages, and eosinophils that surround the entrapped eggs and add significantly to the degree of tissue destruction. Granuloma formation in the bladder wall and at the ureterovesical junction results in the major disease manifestations of *S. haematobium* infection: hematuria, dysuria, and obstructive uropathy. Granulomata in the genital tissues also contributes to reproductive organ obstruction and local inflammation. Intestinal as well as hepatic granulomas underlie the pathologic sequelae of the other schistosome infections: ulcerations and fibrosis of intestinal wall, hepatosplenomegaly, and portal hypertension caused by presinusoidal obstruction of blood flow. In terms of systemic disease, antischistosome inflammation increases circulating levels of proinflammatory cytokines such as tumor necrosis factor-α and interleukin-6, associated with elevated levels of C-reactive protein. These responses are associated with hepcidin-mediated inhibition of iron uptake and use, leading to anemia of chronic inflammation. Schistosomiasis-related undernutrition and decreased cognition may be the result of similar pathways of chronic inflammation. Acquired partial protective immunity against schistosomiasis has been demonstrated in some animal species and may occur in humans.

CLINICAL MANIFESTATIONS

Two main chronic clinical syndromes arise from *Schistosoma* spp. infection: **urogenital schistosomiasis** caused by *S. haematobium* and **intestinal schistosomiasis** caused by *S. mansoni* or *S. japonicum*. Most chronically infected individuals experience mild symptoms and may not seek medical attention; the more severe symptoms of schistosomiasis occur mainly in those who are heavily infected or who have been infected over longer periods. In addition to organ-specific morbidities, infected patients frequently demonstrate anemia (often complicated by malaria in endemic regions), chronic pain, diarrhea, exercise intolerance, and chronic undernutrition manifesting as growth stunting. Cercarial penetration of human skin may result in a pruritic papular rash known as **schistosomal dermatitis** or **swimmer's itch**. Skin manifestations are more pronounced in previously exposed individuals and are characterized by edema and intense cellular infiltrates in the dermis and epidermis.

Acute schistosomiasis (Katayama syndrome) may occur 4-8 weeks after exposure and is most commonly seen in *S. japonicum* endemic

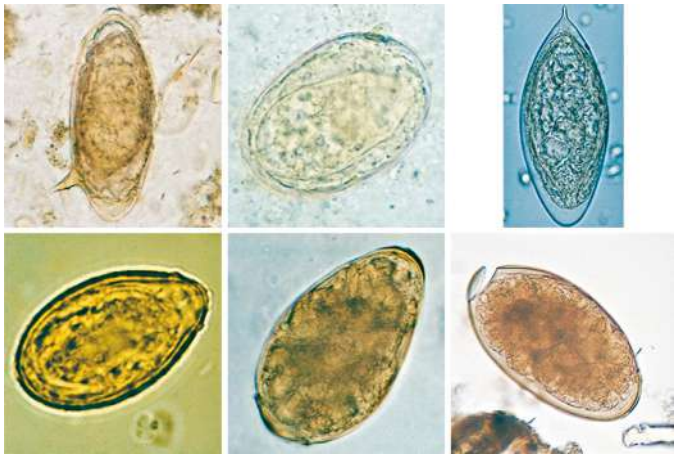

Fig. 346.1 Eggs of common human trematodes. Clockwise from upper left: *Schistosoma mansoni, S. japonicum, S. haematobium, Clonorchis sinensis, Paragonimus westermani,* and *Fasciola hepatica* (note the partially open operculum). *(From Centers for Disease Control and Prevention. DPDx: laboratory identification of parasites of public health concern.* http://www.cdc.gov/dpdx/az.html*)*

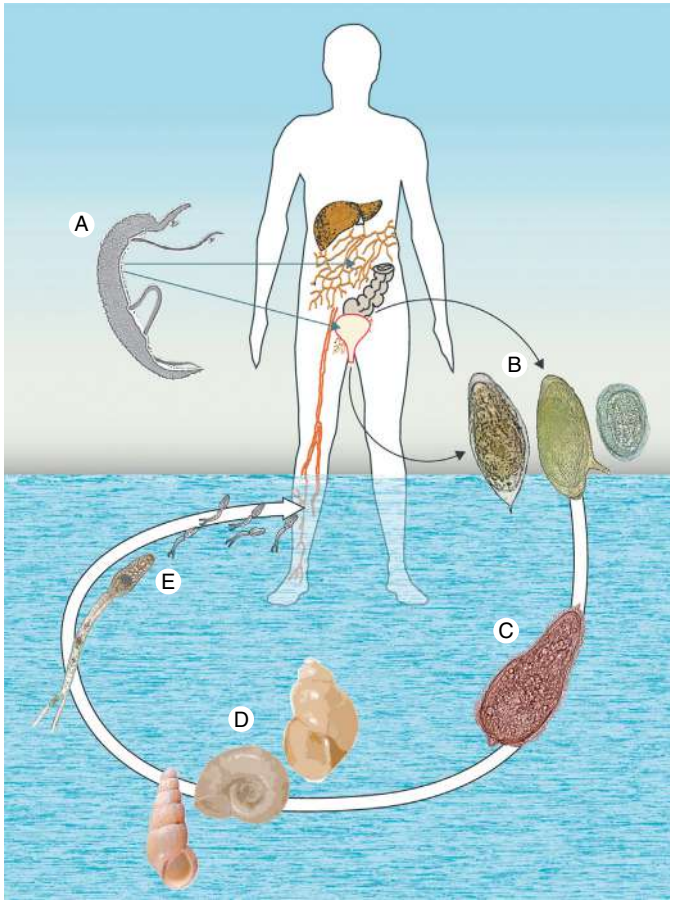

Fig. 346.2 Life cycle of *Schistosoma mansoni, S. haematobium,* and *S. japonicum*. *A,* Paired adult worms (larger male enfolding slender female). *B,* Eggs (left to right, *S. haematobium, S. mansoni, S. japonicum). C,* Ciliated miracidium. *D,* Intermediate host snails (left to right, *Oncomelania, Biomphalaria, Bulinus). E,* Cercariae. *(From Colley DG, Bustinduy AL, Secor WE, King CH. Human schistosomiasis. Lancet. 2014;383:2253–2264. Fig 1.)*

areas, though it can occur with all species. This is a serum sickness–like syndrome manifested by the acute onset of fever, cough, chills, sweating, abdominal pain, lymphadenopathy, hepatosplenomegaly, and eosinophilia. Acute schistosomiasis typically presents in first-time visitors to endemic areas who experience primary infection at an older age.

Chronic schistosomiasis occurs after granuloma formation in the organs where eggs have entrapped. In urogenital schistosomiasis, caused by *S. haematobium*, symptomatic children usually complain of frequency, dysuria, and macro- and micro-hematuria. Urine examination shows erythrocytes, parasite eggs, and occasional eosinophiluria. In endemic areas, moderate to severe pathologic lesions have been demonstrated in the urinary tract of >20% of infected children. The extent of disease correlates with the intensity of infection, but significant morbidity can occur even in lightly infected children, including children under 5 years of age. The advanced stages of urogenital schistosomiasis are associated with chronic renal failure, secondary infections, and squamous cell carcinoma of the bladder.

An important complication of *S. haematobium* infection to consider, particularly in adolescent females, is **female genital schistosomiasis (FGS)**. Eggs migrate from the vesical plexus to lodge in the female genital tract, where they induce a granulomatous inflammatory response that can manifest as contact bleeding, pain after sex, ectopic pregnancies, and infertility. Symptoms start before sexual debut and get later confused with those of sexually transmitted infections. There is a threefold to fourfold greater risk of HIV transmission. Pathognomonic lesions can be visualized in the cervix by colposcopy. **Male genital schistosomiasis (MGS)** can present in adolescent males with hematospermia, pain, erectile dysfunction, and infertility and is likely to contribute to increased male-to-female HIV transmission.

Children with **chronic intestinal schistosomiasis** due to *S. mansoni, S. japonicum,* and, less commonly, *S. intercalatum* or *S. mekongi* can present with intestinal symptoms; colicky abdominal pain and bloody diarrhea are the most common. However, the intestinal phase may remain subclinical, and the late syndrome of hepatosplenomegaly, portal hypertension, ascites, and hematemesis may then be the first clinical presentation in later years. Liver disease is caused by granuloma formation and subsequent **periportal fibrosis**; no appreciable liver cell injury occurs, and hepatic function may be preserved for a long time. Schistosome eggs can escape into the lungs, causing **pulmonary hypertension** and cor pulmonale. *S. japonicum* worms may migrate to the brain vasculature and produce localized lesions that cause seizures. **Transverse myelitis**, spinal compression, and other CNS involvement (meningoencephalitis) are rare but well-known complications in children or young adults with either acute or chronic *S. haematobium* or *S. mansoni* infection.

Although end-organ scarring is pathognomonic, affected children may also have persistent long-term systemic effects of infection, including poor growth, anemia, decreased aerobic capacity, and cognitive impairment and poor school performance.

DIAGNOSIS

Parasitologic diagnosis entails finding schistosome eggs in the excreta of infected individuals; quantitative methods should be used to provide an indication of the burden of infection. For the diagnosis of *S. haematobium* infection, a volume of 10 mL of urine should be collected around midday, the time of maximal egg excretion, and filtered for microscopic examination. Stool examination by the Kato-Katz thick smear procedure and detection of parasite antigen in patient serum or urine are the methods of choice for diagnosis and quantification of other schistosome infections (*S. mansoni* and *S. japonicum*). More sensitive **antigenic diagnosis** includes the unique schistosome antigens in urine or plasma: *circulating anodic antigen* (CAA), which is not yet commercially available, and *circulating cathodic antigen* (CCA) from stool for the detection only of *S. mansoni* and *S. japonicum*.

Morbidity diagnosis can be ascertained by abdominal ultrasonography; in urogenital schistosomiasis, by the detection of **bladder polyps** and derived renal complications, and in intestinal schistosomiasis, by the detection of **periportal fibrosis** in the liver. **Colposcopy** and **semen** analysis are useful in adolescent children suspected of having FGS and MGS.

TREATMENT

Treatment of children with schistosomiasis should be based on an appreciation of the intensity of infection and the extent of disease. The World Health Organization (WHO)–recommended treatment for schistosomiasis is **praziquantel.** For infection due to *S. mansoni, S. haematobium*, or *S. intercalatum*, the dose of praziquantel is 40 mg/kg/day PO divided into two doses for 1 day. For infection due to *S. japonicum* or *S. mekongi*, the dose of praziquantel is 60 mg/kg/day PO divided into three doses for 1 day. A second treatment 4-6 weeks after the first course is advised by some experts, allowing for maturation of immature forms not cleared initially. Praziquantel is well tolerated but can give side effects that correlate with intensity of infection, including abdominal pain and cramps, sweating, and somnolence. Pregnant and lactating women with schistosomiasis can safely be treated with praziquantel at usual doses starting at the second trimester of pregnancy.

PREVENTION

Transmission in endemic areas may be decreased by reducing the parasite load in the human population. WHO recommends praziquantel to be given as a single dose to school-age children through mass drug administration programs once or twice a year depending on parasite endemicity levels. Recently, preschool children 2 years and older have also been included in control strategies. When added to national drug-based control programs, other measures such as improved sanitation, antiparasitic treatment given at well child visits, focal application of molluscicidals, and animal vaccination may prove useful in breaking the cycle of transmission. Ultimately, control of schistosomiasis is closely linked to economic and social development.

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Chapter 347

Flukes (Liver, Lung, and Intestinal)

Amaya L. Bustinduy, Sophie Pach, and Katja Doerholt

Several different **trematodes**, or flukes, can parasitize humans and cause disease. Flukes are endemic worldwide but are more prevalent in the less developed parts of the world. They include *Schistosoma,* or the blood flukes (see Chapter 346), as well as fluke species that cause infection in the human biliary tree, lung tissue, and intestinal tract. These latter trematodes are characterized by complex life cycles (Fig. 347.1). Sexual reproduction of adult worms in the definitive host produces eggs that are passed in the stool. Larvae, called **miracidia**, develop in freshwater. These, in turn, infect certain species of mollusks (aquatic snails or clams), in which asexual multiplication by parasite larvae produces cercariae. Cercariae then seek a second intermediate host, such as an insect, crustacean, or fish, or attach to vegetation to produce infectious **metacercariae**. Humans acquire liver, lung, and intestinal fluke infections by eating uncooked, lightly cooked, pickled, or smoked foods containing these infectious parasite cysts. The "alternation of generations" requires that flukes parasitize more than one host (often three) to complete their life cycle. Because parasitic flukes are dependent on these nonhuman species for transmission, the distribution of human fluke infection closely matches the ecologic range of the flukes' intermediate hosts. As a group, these parasites are commonly referred to as **food-borne trematodes**.

LIVER FLUKES

Fascioliasis (*Fasciola hepatica*)

Fasciola hepatica, the sheep liver fluke, infects cattle, other ungulates, and occasionally humans. This infection affects approximately 17 million people worldwide and has been reported in many different parts of the world, particularly South America, Europe, Africa, China, Australia, and Cuba. Although *F. hepatica* is enzootic in North America, reported cases are extremely rare. Humans are infected by ingestion of metacercariae attached to vegetation, especially wild watercress, lettuce, and alfalfa. In the duodenum, the parasites excyst and penetrate the intestinal wall, liver capsule, and parenchyma. They wander for a few weeks before entering the bile ducts, where they mature. Adult *F. hepatica* (1-2.5 cm) commence oviposition approximately 12 weeks after infection; the eggs are large (75-140 μm) and operculated. They pass to the intestines with bile and exit the body in the feces (see Fig. 347.1). On reaching freshwater, the eggs mature and hatch into miracidia, which infect specific snail intermediate hosts to multiply into many cercariae. These then emerge from infected snails and encyst on aquatic grasses and plants.

Clinical manifestations usually occur either during the liver migratory phase of the parasites or after their arrival at their final habitat in upper bile ducts. Fever, right upper quadrant pain, and hepatosplenomegaly characterize the first phase of illness. Peripheral blood eosinophilia is usually marked. As the worms enter bile ducts, most of the acute symptoms subside. On rare occasions, patients may have obstructive jaundice or biliary cirrhosis, with signs of cholestasis, ascending cholangitis, cholelithiasis and jaundice and increased liver enzymes, direct bilirubin, and γ-glutamyl transpeptidase. *F. hepatica* infection is diagnosed by identifying the characteristic eggs in fecal smears or duodenal aspirates. **Diagnosis** can be suggested by positive serology and imaging that reveals acute, hypodense liver lesions that change over time. Presentation can be dramatic in children, with features including generalized edema, hepatic cirrhosis with esophageal varices, and in severe cases, death from generalized organ failure.

The recommended **treatment** of fascioliasis is triclabendazole (10 mg/kg orally [PO] once or twice) or bithionol (30-50 mg/kg PO once daily on alternate days for a total of 10-15 doses). In the United States, bithionol is not generally available, but it may be available from compounding pharmacies.

Clonorchiasis (*Clonorchis sinensis*)

Infection of bile passages with *Clonorchis sinensis,* the Chinese or oriental liver fluke, is endemic in China, South Korea, northern Vietnam,

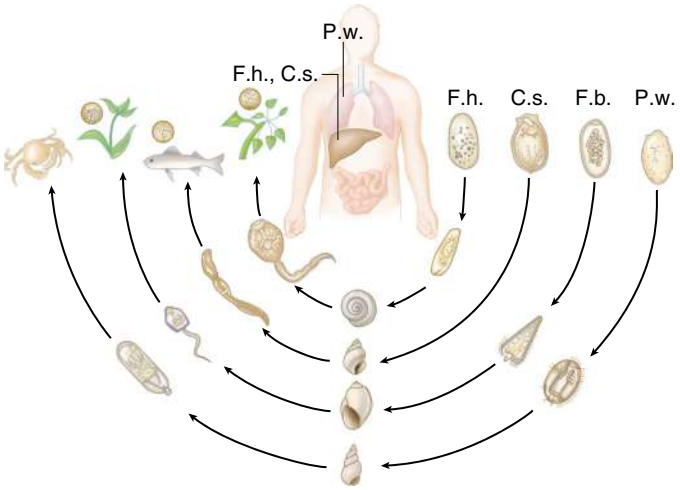

Fig. 347.1 Life cycle of parasitic liver, lung, and intestinal flukes. C.s., *Clonorchis sinensis*; F.b., *Fasciolopsis buski*; F.h., *Fasciola hepatica*; P.w., *Paragonimus westermani. (Adapted from Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases, 7th ed. Philadelphia: Elsevier, 2010: Fig 289-2.)*

and parts of Russia and Japan, affecting more than 15 million people. Humans acquire infection by ingestion of raw or inadequately cooked **freshwater fish** carrying the encysted metacercariae of the parasite under their scales or skin. Metacercariae excyst in the duodenum and pass through the ampulla of Vater to the common bile duct and bile capillaries, where they mature into hermaphroditic adult worms (3-15 mm). *C. sinensis* worms deposit small operculated eggs (14-30 μm), which are discharged through the bile duct to the intestine and feces (see Fig. 347.1). The eggs mature and hatch outside the body, releasing motile miracidia into local freshwater streams, rivers, or ponds. If these are taken up by the appropriate snails, they develop into cercariae, which are, in turn, released from the snail to encyst under the skin or scales of freshwater fish.

Clinical manifestations are minimal in most individuals with *C. sinensis* infection, particularly those with few organisms. Among heavily infected individuals, who tend to be older (>30 years), localized obstruction of a bile duct results from repeated local trauma and inflammation. In these patients, **cholangitis and cholangiohepatitis** may lead to liver enlargement and jaundice. In Hong Kong, Korea, and other parts of Asia, **cholangiocarcinoma** is associated with chronic *C. sinensis* infection.

Diagnosis of clonorchiasis is made by examination of feces or duodenal aspirates for the parasite eggs and serology. Radiologic imaging (CT scan) can detect fibrosis in the biliary tract and cholangiocarcinoma. The recommended **treatment** of clonorchiasis is praziquantel (75 mg/kg/day PO divided 3 times daily [tid] for 2 days). An alternative, used in adults, is albendazole (10 mg/kg once daily PO for 7 days). Tribendimidine (400 mg PO for 3 days) has been used in China with good cure rates.

Opisthorchiasis (*Opisthorchis* spp.)

Infections with species of *Opisthorchis* are clinically similar to those caused by *C. sinensis. Opisthorchis felineus* and *Opisthorchis viverrini* are liver flukes of cats and dogs that infect humans through ingestion of metacercariae in freshwater fish. Infection with *O. felineus* is endemic in Eastern Europe and Southeast Asia, and *O. viverrini* is found mainly in Thailand, affecting an estimated 10 million people. Most individuals are minimally symptomatic; liver enlargement, relapsing cholangitis, and jaundice may occur in heavily infected individuals. *O. viverrini* is a known carcinogen, much like *Clonorchis* spp. responsible for **cholangiocarcinoma.** Diagnosis is based on recovering eggs from stools or duodenal aspirates and serology. The recommended **treatment** of opisthorchiasis is praziquantel (75 mg/kg/day PO tid for 2 days).

LUNG FLUKES

Paragonimiasis (*Paragonimus* spp.)

Human infection by the lung fluke *Paragonimus westermani,* and less frequently other species of *Paragonimus,* occurs throughout the Far East, in localized areas of West Africa, and in several parts of Central and South America, affecting approximately 20 million people. The highest incidence of paragonimiasis occurs in older children and adolescents 11-15 years of age. Although *P. westermani* is found in many carnivores, human cases are relatively rare and seem to be associated with specific dietary habits, such as eating raw **freshwater crayfish or crabs**. These crustaceans contain the infective metacercariae in their tissues. After ingestion, the metacercariae excyst in the duodenum, penetrate the intestinal wall, and migrate to their final habitat in the lungs. Adult worms (5-10 mm) encapsulate within the lung parenchyma and deposit brown operculated eggs (60-100 μm) that pass into the bronchioles and are expectorated by coughing (see Fig. 347.1). Ova can be detected in the sputum of infected individuals or in their feces. If eggs reach freshwater, they hatch and undergo asexual multiplication in specific snails. The cercariae encyst in the muscles and viscera of crayfish and freshwater crabs.

Clinical Manifestations

Most individuals infected with *P. westermani* harbor low or moderate worm loads and are minimally symptomatic. The clinical manifestations include cough, production of rust-colored sputum, and **hemoptysis** *(mimicking tuberculosis),* which is the principal manifestation and occurs in 98% of symptomatic children. In addition, children with paragonimiasis have pleural effusions, hepatomegaly, and subcutaneous nodules. For the **diagnosis**, there are no characteristic physical findings, but laboratory examination usually demonstrates marked **eosinophilia.** Chest radiographs often reveal small, **patchy infiltrates** or radiolucencies in the middle lung fields; however, radiographs may appear normal in one fifth of infected individuals. In rare circumstances, lung abscess, pleural or pericardial effusion, or bronchiectasis may develop. Extrapulmonary localization of *P. westermani* in the brain, peritoneum, intestines, or pericardium may rarely occur. **Cerebral paragonimiasis** occurs primarily in heavily infected individuals living in highly endemic areas of the Far East. The clinical presentation resembles jacksonian epilepsy or the symptoms of cerebral tumors. Definitive diagnosis of paragonimiasis is established by identification of eggs in fecal or sputum smears and serology. The recommended **treatment** of paragonimiasis is praziquantel (75 mg/kg/day PO tid for 2 days). Triclabendazole can also be used (10 mg/kg PO daily for 1-2 days).

INTESTINAL FLUKES

Several wild and domestic animal intestinal flukes, including *Fasciolopsis buski, Nanophyetus salmincola,* and *Heterophyes heterophyes,* may accidently infect humans who eat uncooked or undercooked fish or water plants. For example, *F. buski* is endemic in the Far East, where humans who ingest metacercariae encysted on aquatic plants become infected. These develop into large flukes (1-5 cm) that inhabit the duodenum and jejunum. Mature worms produce operculated eggs that pass with feces; the organism completes its life cycle through specific snail intermediate hosts. Individuals with *F. buski* infection are usually asymptomatic; heavily infected patients complain of **abdominal pain and diarrhea** and show signs of malabsorption. **Diagnosis** of fasciolopsiasis and other intestinal fluke infections is established by fecal examination and identification of the eggs (see Fig. 347.1). As for other fluke infections, praziquantel (75 mg/kg/day PO tid for 2 days) is the drug of choice.

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Chapter 348

Adult Tapeworm Infections

Philip R. Fischer and A. Clinton White Jr.

Tapeworms are adult forms of **cestodes**, multicellular helminth parasites, that live in human intestines and cause non–life-threatening illness. Invasive larval forms of cestodes are associated with cysts that lead to severe human disease such as neurocysticercosis (*Taenia solium*; see Chapter 349) and echinococcosis (mostly *Echinococcus granulosa* and *E. multilocularis*; Chapter 350). The adult worms themselves are flat and multisegmented, varying in length from 8 mm to 10 meters (m). Table 348.1 summarizes the key features of tapeworms that affect children.

ETIOLOGY

The **beef tapeworm** *(Taenia saginata)*, the **pork tapeworm** *(T. solium),* and the Asian tapeworm *(Taenia asiatica)* are long worms (4-10 m) named for their intermediate hosts *(T. saginata, T. solium)* or geographic distribution (*T. asiatica*; larval host is the pig). The adult worms are found only in the human intestine. As with the adult stage of all

Table 348.1 Key Features of Common Tapeworms in Children

PARASITE SPECIES	GEOGRAPHY	SOURCE	SYMPTOMS	TREATMENT
Taenia saginata	Asia, Africa, Latin America	Cysts in beef	Abdominal discomfort, motile proglottid migration, passing segments	Praziquantel or niclosamide, possibly nitazoxanide
Taenia solium	Asia, Africa, Latin America	Cysticerci in pork	Minimal, proglottids in stool	Praziquantel or niclosamide
Taenia asiatica	Asia	Pigs	Minimal	Praziquantel or niclosamide
Dibothriocephalus latus	Europe, North America	Plerocercoid cysts in freshwater fish	Usually minimal; with prolonged or heavy infection with D. latus, vitamin B_{12} deficiency	Praziquantel or niclosamide
Dibothriocephalus nihonkaiense	Northeast Asia, North Pacific coast of North America	Plerocercoid cysts in saltwater fish	Usually minimal; passing proglottids	Praziquantel or niclosamide
Adenocephalus pacificus	Pacific Coast of South America	Infected fish	Usually none or mild	Praziquantel or niclosamide
Hymenolepis	Worldwide, often northern areas	Infected humans, rodents	Mild abdominal discomfort	Praziquantel, niclosamide, or nitazoxanide
Dipylidium caninum	Worldwide	Domestic dogs and cats	Proglottids in stool, anal pruritus confused with pinworm	Praziquantel or niclosamide

tapeworms, their body is a series of hundreds or thousands of flattened segments **(proglottids)** with an anterior attachment organ **(scolex)** that anchors the parasite to the bowel wall. New segments arise from the distal aspect of the scolex with progressively more mature segments attached distally. The gravid terminal segments contain 50,000-100,000 eggs, and the eggs or even detached intact proglottids pass out of the child through the anus (with or separate from defecation). These tapeworms differ most significantly in that the intermediate stage of the pork tapeworm **(cysticercus)** can also infect humans and cause significant morbidity (see Chapter 349), whereas the larval stage of *T. saginata* does not cause human disease. *T. asiatica* is similar to and often confused with the beef tapeworm.

EPIDEMIOLOGY

The pork and beef tapeworms are distributed worldwide, with the highest risk for infection in Latin America, Africa, India, Southeast Asia, and China, where the relevant intermediate host is raised domestically. The prevalence in adults may not reflect the prevalence in young children, because cultural practices may dictate how well meat is cooked and how much is served to children.

PATHOGENESIS

When children ingest raw or undercooked meat containing larval cysts, gastric acid and bile facilitate release of immature scolices that attach to the lumen of the small intestine. The parasite grows, adding new segments at the base of the scolex. The terminal segments mature and after 2-3 months produce eggs that are released in stool. The surface of proglottids serves as an absorptive organ to "steal" nutritional elements from the child's small bowel for use by the parasite. There is sometimes a transient eosinophilia before the parasite matures enough to release eggs.

CLINICAL MANIFESTATIONS

Nonspecific abdominal symptoms have been reported with beef and pork tapeworm infections, but the most bothersome symptom is the psychologic distress caused by seeing proglottids in the stool or undergarments. The released segments of the worms are motile (especially those of *T. saginata*) and sometimes lead to anal pruritus. The adult beef and pork tapeworms are only rarely associated with other symptoms.

DIAGNOSIS

Identification of the infecting tapeworm species facilitates understanding of risk for invasive disease. Carriers of adult pork tapeworms are at increased risk for transmitting eggs with the pathogenic intermediate stage (cysticercus) to themselves or others, whereas children infected with the beef tapeworm or *T. asiatica* are a risk only to livestock. Because proglottids are generally passed intact, visual examination for gravid proglottids in the stool is a sensitive test; these segments may be used to identify species. Eggs, by contrast, are often absent from stool and cannot distinguish between *T. saginata* and *T. solium* (Fig. 348.1). If the parasite is completely expelled, the scolex of each species is diagnostic. The scolex of *T. saginata* has only a set of four anteriorly oriented suckers, whereas *T. solium* is armed with a double row of hooks in addition to suckers. The proglottids of *T. saginata* have >20 branches from a central uterine structure, and the proglottids of *T. solium* have ≤10 branches. Expelled proglottid segments are usually approximately 0.5 × 1-2 × 0.1 cm in size. Molecular methods can distinguish *T. saginata* from *T. asiatica*. Antigen detection tests are increasingly available.

DIFFERENTIAL DIAGNOSIS

Anal pruritus may mimic symptoms of pinworm *(Enterobius vermicularis)* infection. Broad tapeworms such as *Dibothriocephalus latus* (formerly *Diphyllobothrium latum*) and *Ascaris lumbricoides* (a long round worm) may be mistaken for *T. saginata* or *T. solium* in stools.

TREATMENT

Infections with all adult tapeworms respond to praziquantel (25 mg/kg orally [PO] once). When available, an alternative treatment for **taeniasis** is niclosamide (50 mg/kg PO once for children; 2 g PO once for adults). Nitazoxanide is sometimes effective as well. The parasite is usually expelled on the day of administration. Treatment with electrolyte–polyethylene glycol bowel preparations can increase the yield of passage of scolices.

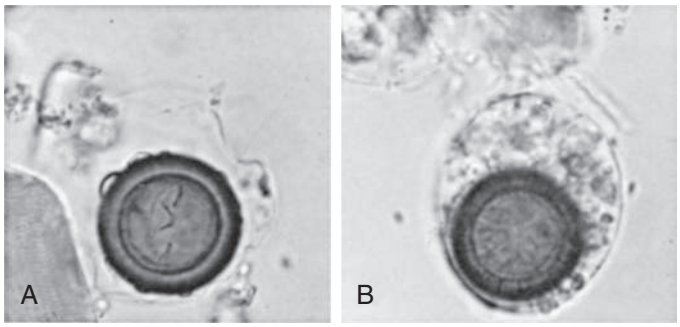

Fig. 348.1 Eggs of *Taenia saginata* recovered from feces (original magnification ×400). **A** and **B,** The eggs are generally bile-stained, dark, and prismatic. There is occasionally some surrounding cellular material from the proglottid in which the egg develops, which is more evident in **B** than in **A.** The larva within the egg shows three pairs of hooklets (**A**), which may occasionally be observed in motion.

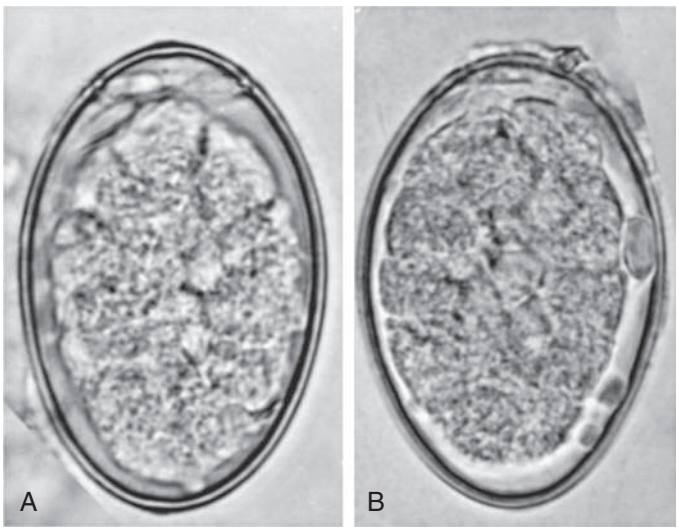

Fig. 348.2 Eggs of *Dibothriocephalus latus* as seen in feces (original magnification ×400). **A** and **B,** The caplike operculum is at the upper end of the eggs here.

PREVENTION

Prolonged freezing or thorough cooking of beef and pork kills the larval cystic forms of the parasite. Appropriate human sanitation can interrupt transmission by preventing infection in livestock. Mass treatment does not lead to lasting reductions in prevalence.

DIPHYLLOBOTHRIASIS (*DIBOTHRIOCEPHALUS* SPP.)

Etiology

The **broad tapeworms** of the order Diphyllobothriidea are the longest human tapeworms, reaching >10 m in length, and have an anatomic organization similar to that of other adult cestodes. An elongated scolex, equipped with slits **(bothria)** along each side but no suckers or hooks, is followed by thousands of segments looped in the small bowel. Gravid terminal proglottids detach periodically but tend to disintegrate before expulsion, thus releasing eggs rather than intact worm segments in the feces. In contrast to taeniids, the life cycle of Diphyllobothriid spp. requires two intermediate hosts. Small, freshwater crustaceans (copepods) take up the larvae that hatch from parasite eggs. The parasite passes up the food chain as small fish eat the copepods and are, in turn, eaten by larger fish. In this way, the juvenile parasite becomes concentrated in pike, walleye, perch, burbot, and salmon. Consumption of raw or undercooked fish leads to human infection with adult fish tapeworms. Recent molecular studies have led to marked revision in the taxonomy with regional differences in the predominant species (*Dibothriocephalus latus* in Europe, North America; *Dibothriocephalus nihonkaiense* in Japan, Northeast Asia, and the northern Pacific coast of North America, and *Adenocephalus pacificus* in coastal South America).

Epidemiology

The fish tapeworms are most prevalent in the temperate climates of Europe, North America, and northeastern Asia and along the Pacific coast of South America and in Africa. In North America the prevalence is highest in Alaska, Canada, and northern areas of the continental United States. The tapeworm is found in fish from those areas that are then taken to market. Persons who prepare raw fish for home or commercial use or who sample fish before cooking are particularly at risk for infection.

Pathogenesis

The adult worm of *Dibothriocephalus latus* (found in northern Europe) has high-affinity receptors and efficiently scavenges vitamin B_{12} for its own use in the constant production of large numbers of segments and as many as 1 million eggs per day. As a result, diphyllobothriasis causes **megaloblastic anemia** in 2–9% of infections. Interestingly, other Diphyllobothriid spp. do not out-compete the host for vitamin B_{12}. Children with other causes of vitamin B_{12} or folate deficiency, such as chronic infectious diarrhea, celiac disease, or congenital malabsorption, are more likely to develop symptomatic infection.

Clinical Manifestations

Infection is largely asymptomatic. Segments may be noted in stool. Those who develop vitamin B_{12} or folate deficiency present with megaloblastic anemia with leukopenia, thrombocytopenia, glossitis, and/or signs of spinal cord posterior column dysfunction (loss of vibratory sense, proprioception, and coordination).

Diagnosis

Parasitologic examination of the stool is useful because eggs are abundant in the feces and have morphology distinct from that of all other tapeworms. The eggs are ovoid and have an **operculum**, which is a cap structure at one end that opens to release the embryo (Fig. 348.2). The worm itself has a distinct scolex and proglottid morphology; however, these are not likely to be passed spontaneously.

Differential Diagnosis

A segment or a whole section of the worm might be confused with *Taenia* or *Ascaris* after it is passed. Pernicious anemia, bone marrow toxicity, and dietary restriction may contribute to or mimic the nutritional deficiencies associated with diphyllobothriasis.

Treatment

As with all adult tapeworms, *D. latus* infections respond to praziquantel (5-10 mg/kg PO once). Niclosamide (50 mg/kg PO in a single dose) is also effective.

Prevention

The intermediate stage is easily killed by brief cooking or prolonged freezing of fish before ingestion. Because humans are the major reservoir for adult worms, health education is one of the most important tools for preventing transmission, together with improved human sanitation.

HYMENOLEPIASIS (*HYMENOLEPIS*)

Infection with *Hymenolepis nana,* the **dwarf tapeworm,** is very common in developing countries. Most cases are asymptomatic. However, heavy infection has been associated with diarrhea, weight loss, fever, anemia, and eosinophilia. The intermediate stage of *Hymenolepis diminuta* develops in various hosts (e.g., rodents, ticks, fleas), but the entire life cycle of *H. nana* is completed in humans. Therefore hyperinfection with thousands of small adult worms in a single child may occur. A similar infection may occur less often with *H. diminuta.* Eggs

but not segments may be found in the stool. *H. nana* infection responds to praziquantel (25 mg/kg PO once). Nitazoxanide is effective in about three fourths of children (100 mg PO twice daily [bid] for 3 days for children 1-3 years old, 200 mg bid for 3 days for children 4-11 years old, and 500 mg bid for 3 days for older children).

DIPYLIDIASIS (*DIPYLIDIUM CANINUM*)

Dipylidium caninum is a common tapeworm of domestic dogs and cats. Human infection is relatively rare. Direct transmission between pets and humans does not occur; human infection requires ingestion of the parasite's intermediate host, the dog or cat flea. Infants and small children are particularly susceptible because of their level of hygiene, generally more intimate contact with pets, and activities in areas where fleas can be encountered. Thus children are most at risk of inadvertent ingestion of fleas infected with the larvae. The most common symptom is passage of proglottids in stool. The proglottids are similar in size and shape to white rice grains. Anal pruritus, vague abdominal pain, and diarrhea have at times been associated with dipylidiasis, which is thus sometimes confused with pinworm *(E. vermicularis)*. Dipylidiasis responds to treatment with praziquantel (5-10 mg/kg PO once) and niclosamide (50 mg/kg PO as a single dose). **Deworming** of pets and **flea control** are the best preventive measures.

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Chapter 349

Cysticercosis

A. Clinton White Jr., Miguel M. Cabada, and Philip R. Fischer

Taenia solium, also known as the **pork tapeworm**, causes two different infections in children. In its normal life cycle, children can acquire the tapeworm form by ingestion of undercooked pork containing the larval cysts (see Chapter 348). In the intestines, the cyst converts into the tapeworm form. Children are also susceptible to infection by the eggs shed by tapeworm carriers. After the eggs are ingested, the larvae are released from the eggs, invade through the intestines, and migrate through the bloodstream to the muscles (and other organs), where they form tissue cysts (0.2-2.0 cm fluid-filled bladders containing a single invaginated **scolex**). Infection with the cystic form is termed **cysticercosis**, and involvement of the central nervous system (CNS) is termed **neurocysticercosis.** The tapeworm form only develops after ingestion of undercooked pork. Ingestion of pork is not necessary to develop cysticercosis, but individuals harboring an adult worm may infect themselves with the eggs by the fecal-oral route.

EPIDEMIOLOGY

The pork tapeworm is widely distributed wherever pigs are raised and have contact with human fecal material. Intense transmission occurs in Central and South America, southern and Southeast Asia, and much of sub-Saharan Africa. In these areas, approximately 30% of cases of seizures may be a result of cysticercosis. Most cases of cysticercosis in the United States are imported; however, local transmission has been documented.

PATHOGENESIS

Living, intact cystic stages usually suppress the host immune and inflammatory responses. Intact cysts can be associated with disease when they obstruct the flow of cerebrospinal fluid. Most cysts remain asymptomatic for a few years. Symptoms typically develop as the cysticerci begin to degenerate, associated with a host inflammatory response. The natural history of cysts is eventually to resolve by complete resorption or calcification, but this process may take years. Cysticerci can also present as subcutaneous nodules, ocular infection, or spinal lesions with myelopathy or radiculopathy.

CLINICAL MANIFESTATIONS

Seizures and headache are the presenting findings in the vast majority of children with neurocysticercosis. Less common manifestations include hydrocephalus, diffuse cerebral edema, or focal neurologic findings. It is important to classify neurocysticercosis as parenchymal, intraventricular, subarachnoid, spinal, or ocular on the basis of anatomic location, clinical presentation, and radiologic appearance because the prognosis and management vary with location.

Parenchymal neurocysticercosis typically presents with seizures. The seizures are usually focal, but often generalize. Children may present with a single seizure or recurrent epilepsy. Mild neurocognitive defects have been documented from cysticerci alone but are more commonly associated with poorly controlled seizures. A fulminant encephalitis-like presentation may rarely occur after a massive initial infection associated with cerebral edema. **Intraventricular** neurocysticercosis (up to 20% of cases) is associated with obstructive hydrocephalus and acute, subacute, or intermittent signs of increased intracranial pressure, usually without localizing signs. **Subarachnoid** neurocysticercosis is rare in children. It can be associated with basilar arachnoiditis that can present with signs of meningeal irritation, communicating hydrocephalus, cerebral infarction, or **spinal** disease with radiculitis or transverse myelitis. Cysticerci in the tissues may present with focal findings from mass effect. **Ocular** neurocysticercosis causes decreased visual acuity because of cysticerci in the retina or vitreous, retinal detachment, or iridocyclitis.

DIAGNOSIS

Neurocysticercosis should be suspected in a child with onset of seizures or hydrocephalus and who also has a history of residence in an endemic area and/or a care provider from an endemic area. The most useful diagnostic study for parenchymal disease is MRI of the head. MRI provides the most information about cyst location, cyst viability, and associated inflammation. The scolex can appear as a 1-2 mm nodule attached to the cyst wall, and, when identified, is diagnostic for cysticercosis (Fig. 349.1A). The MRI also better detects basilar arachnoiditis (Fig. 349.1B), intraventricular cysts (Fig. 349.1C), and cysts in the spinal cord. CT is best for identifying calcifications. A solitary parenchymal cyst, with or without contrast enhancement, or CNS calcifications are the most common findings in children (Fig. 349.2). Plain films may reveal calcifications in muscle or brain consistent with cysticercosis. In children from endemic regions, the presentation with a single enhancing lesion that is round and <2 cm in diameter, absence of symptoms or signs of other diseases (e.g., no fever or lymph nodes), no focal findings, and no evidence of increased intracranial pressure is highly specific for neurocysticercosis.

Serologic diagnosis using the enzyme-linked immunotransfer blot is available commercially in the United States and through the Centers for Disease Control and Prevention (CDC). Serum antibody testing is highly specific but is frequently negative in children with single lesions or just calcifications. Antigen-detection assays and polymerase chain reaction assays show promise for diagnosis of ventricular and subarachnoid disease and are available from the Laboratory for Parasitic Diseases, National Institutes of Health (NIH). They are not commercially available in the United States.

Differential Diagnosis

Neurocysticercosis is often confused clinically with other seizure disorders. Clinical suspicion is based on travel history, a history of contact with an individual who might carry an adult tapeworm, or suggestive

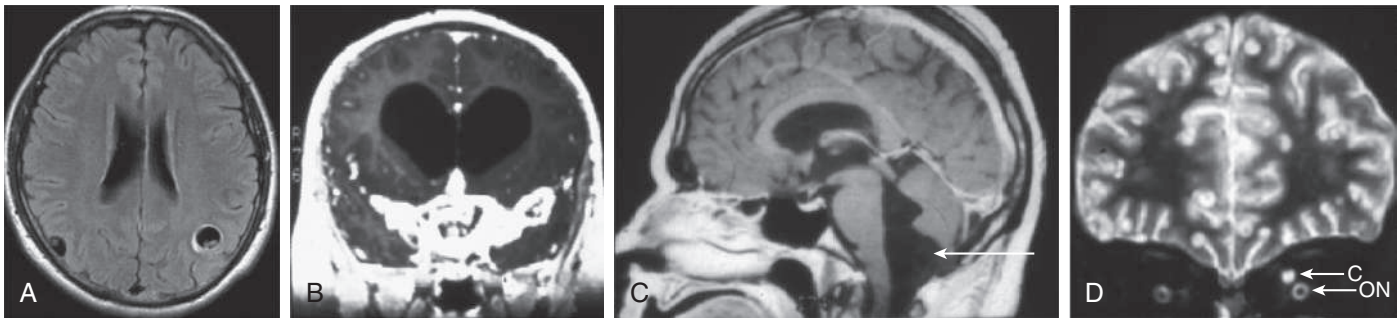

Fig. 349.1 Neurocysticercosis. **A,** T1-weighted MRI demonstrating two parenchymal cysts with scolices. **B,** T1-weighted MRI of cysticercal basilar arachnoiditis. **C,** T1-weighted MRI showing a cyst below the fourth ventricle *(arrow)*. **D,** T2-weighted MRI showing a cysticercus *(C)* above the optic nerve *(ON)*.

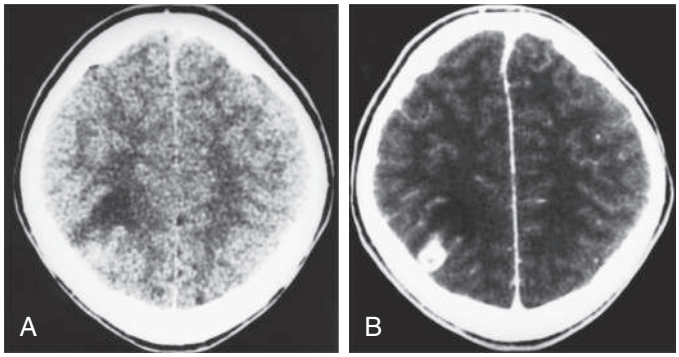

Fig. 349.2 Neurocysticercosis. CT image of a solitary lesion with **(A)** and without **(B)** contrast, showing contrast enhancement. *(Courtesy Dr. Wendy G. Mitchell and Dr. Marvin D. Nelson, Children's Hospital, Los Angeles.)*

imaging studies. The imaging appearance can be confused with brain abscess, granulomas (including tuberculomas, fungal infections, Langerhans histiocytosis, and toxoplasmosis), and tumors.

TREATMENT

The initial management of cysticercosis should focus on symptomatic therapy for seizures and/or hydrocephalus. Seizures can usually be controlled using standard antiepileptic drugs. If the lesions resolve, antiepileptic drugs can often be tapered and stopped. Frequent seizures or the development of calcified lesions are risk factors for recurrent seizures and indications for prolonged or lifelong antiepileptic therapy.

The natural history of **parenchymal** lesions is to resolve spontaneously, with or without antiparasitic drugs, but this process is often prolonged (months to years). Solitary parenchymal cysts resolve slightly more rapidly with antiparasitic therapy. Antiparasitic drugs also decrease the frequency of recurrent seizures. Other forms of the disease are less common in children. In adults with cystic lesions, randomized controlled trials suggested an overall 50% decrease in recurrence of generalized seizures with albendazole treatment. The benefit to children was significantly less, perhaps because most of these infections were with only one to two cysts. Corticosteroids likely also decrease seizure frequency.

The most commonly used antiparasitic is **albendazole** (15 mg/kg/day orally [PO] divided twice daily [bid]). It should be taken with a fatty meal to improve absorption. The most common duration of therapy is 7 days for single parenchymal lesions. However, longer duration (months), higher doses (up to 30 mg/kg/day), or combination therapy with praziquantel is often required for multiple lesions or subarachnoid disease. For example, in adults with more than two cysticerci, trials note improved resolution with combination therapy with corticosteroids, albendazole, and praziquantel (50 mg/kg/day PO divided three times daily for 14 days). **Praziquantel** (50-100 mg/kg/day for 28 days) may be used as an alternative to albendazole. First-pass metabolism is common with corticosteroids or antiepileptic drugs. **Cimetidine** can be used in conjunction with praziquantel to blunt the first-pass metabolism. A worsening of symptoms can follow the use of either drug based on the host's inflammatory response to the dying parasite. Patients should be medicated with prednisone (1-2 mg/kg/day) or oral dexamethasone (0.15 mg/kg/day) beginning before the first dose of antiparasitic drugs and continuing for at least 2 weeks.

Most patients with hydrocephalus require neurosurgical interventions. Some cases require emergent placement of a ventriculostomy, but most can be managed by cystectomy alone. For obstructive hydrocephalus caused by ventricular cysticercosis, many patients can be cured by minimally invasive surgery. **Neuroendoscopy** is the preferred approach to cysticerci in the lateral or third ventricle. Cysticerci in the fourth ventricle can be removed by a suboccipital craniotomy. There are also reports of endoscopic removal of fourth ventricular cysticerci using flexible neuroendoscopy. Adherent cysticerci that cannot be removed can be treated by placement of a ventriculoperitoneal shunt (VPS). However, there is a high rate of shunt failure, which can be minimized somewhat by treatment with antiparasitic drugs plus corticosteroids.

Subarachnoid disease has a poor prognosis. The prognosis is much improved by aggressive therapy, including antiparasitic drugs, antiinflammatory treatment, and neurosurgical procedures for hydrocephalus (e.g., VPS placement). However, the duration of antiparasitic and antiinflammatory therapy often needs to be prolonged. **Methotrexate** and/or tumor necrosis factor inhibitors can be used as a steroid-sparing agent in patients requiring prolonged anti-inflammatory therapy. **Ocular** cysticercosis is usually treated surgically, although there are reports of cure using medical therapy alone.

PREVENTION

In areas with evolved public health systems, cysticercosis can largely be eliminated by meat inspection, condemnation of infected meat, thorough cooking of pork, and improved sanitation. This approach has not worked in countries where most meat is butchered informally. Mass chemotherapy for tapeworm carriers, mass treatment of pigs, and improved personal hygiene have decreased or eliminated transmission in some areas. Screening family members and those preparing food for index cases for cysticercosis has a very low yield, in part because of the poor sensitivity of current tests. Those who have noted passing material consistent with taeniasis should be treated with praziquantel regardless of the results of stool studies. Veterinary vaccines for several cestode infections have a high degree of efficacy and have a potential role in decreasing parasite transmission.

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Chapter 350

Echinococcosis (*Echinococcus granulosus sensu lato* and *Echinococcus multilocularis*)

Miguel M. Cabada, Philip R. Fischer, and A. Clinton White Jr.

ETIOLOGY

Echinococcosis (**hydatid disease** or **hydatidosis**) is a widespread, serious human cestode infection (Fig. 350.1). Two major *Echinococcus* groups of species are responsible for distinct clinical presentations. *Echinococcus granulosus sensu lato* causes **cystic echinococcosis, and** *Echinococcus multilocularis* causes **alveolar echinococcosis**. The adult parasites are small (2-7 mm) tapeworms with only two to six segments that inhabit the intestines of canines such as dogs, wolves, dingoes, jackals, coyotes, and foxes. Canines are infected by ingesting contaminated viscera from ungulates *(E. granulosus sensu lato)* or mice *(E. multilocularis)*. These carnivores pass the eggs in their stool, which contaminate the soil, pasture, and water, as well as their own fur. Domestic animals, such as sheep, goats, cattle, and camels, ingest *E. granulosus* complex eggs while grazing. Some species of *E. granulosus sensu lato* have a **sylvatic** cycle involving wild cervids such as moose, elk, and deer. For *E. multilocularis*, the main intermediate hosts are small rodents. Humans are infected by consuming eggs by direct contact with infected canines or from ova in the environment. In Europe, contamination of gardens by fox excrement is a major risk factor for transmission. The larvae hatch, penetrate the gut, and are carried by the vascular or lymphatic systems to the liver, lungs, and less frequently, bones, kidney, brain, or heart in *E. granulosus* infection. *E. multilocularis* larvae infect the liver almost exclusively.

Echinococcus granulosus sensu lato comprises several recognized species, including *E. granulosus sensu stricto*, *E. equinus*, *E. ortleppi*, and *E. canadensis*. The species within *E. granulosus sensu lato* show significant variation not only in genetics but also in ecology. While *E. granulosus sensu stricto* is mainly found in domesticated ovines and dogs around the world, *E. canadensis* is found in a sylvatic wolf/moose cycle in North America and Siberia and has been identified in bovines and swine in South America.

EPIDEMIOLOGY

There is potential for transmission of *E. granulosus* to humans wherever dogs are allowed to ingest the entrails of herd animals. Disease is highly endemic in the Middle East and Central Asia. Cysts have been detected in up to 10% of the human population in northern Kenya and western China. In South America, the disease is prevalent in sheep-herding areas of the Andes, the beef-herding areas of the Brazilian/Argentine Pampas, and Uruguay. Among developed countries, the disease is recognized in Italy, Greece, Portugal, Spain, and Australia and is reemergent in dogs in Great Britain. In North America, transmission occurs rarely through a sylvatic cycle in the Artic regions and in sheep-raising areas of the western United States.

Transmission of *E. multilocularis* occurs primarily in Western China, Central Europe, Siberia, and Turkey. Transmission is now rare in western Canada and the Arctic regions of North America. Ingestion of infected rodents by dogs or foxes facilitates transmission to children. Separate species, *E. vogeli* and *E. oligarthrus*, have mainly a sylvatic cycle involving canines and felines causing polycystic disease in northern South America.

PATHOGENESIS

E. granulosus sensu lato parasites are often acquired in childhood, and cysts require many years to become large enough to be detected or cause symptoms. In children the lung is a common site of infection, whereas in adults up to 70% of cysts develop in the liver. Cysts can also develop in bone, the genitourinary system, spleen, subcutaneous tissues, and brain. The host surrounds the primary cyst with a tough, fibrous capsule. Inside this capsule, the parasite produces a thick lamellar layer with the consistency of a soft-boiled egg white. Inside the lamellar layer is the thin germinal layer of cells responsible for production of 1000s of protoscoleces that remain attached to the wall or float free in the cyst fluid (Video 350.1). Smaller internal daughter cysts may develop within the primary cyst capsule. The fluid in a healthy cyst is clear, colorless, and watery. Rupture of the cyst, which can occur

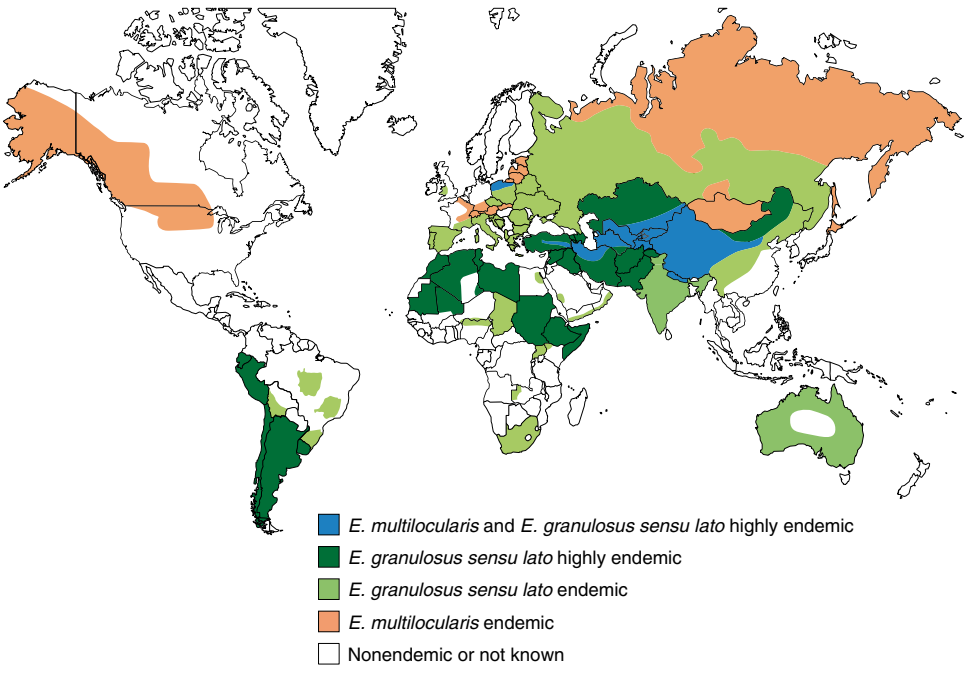

Fig. 350.1 Global distribution of cystic echinococcosis and alveolar echinococcosis. *(From Wen H, Vuitton L, Tuxun T, et al. Echinococcosis: advances in the 21st century. Clin Microbiol Rev. 2019;32[2]:e00075–18. Fig 3.)*

spontaneously, with trauma, or during surgery, can be associated with immediate hypersensitivity reactions, including anaphylaxis. Protoscoleces released into the tissues can also develop into new cysts.

E. multilocularis almost always involves the liver. The lesions grow very slowly and rarely present in children. The secondary reproductive units bud externally and are not confined within a single, well-defined structure. Thus the lesions are invasive and often confused with a malignancy. Furthermore, the cyst tissues are poorly demarcated from those of the host, making surgical removal difficult. The secondary cysts are also capable of distant metastatic spread. The growing cyst mass eventually replaces a significant portion of the liver and compromises adjacent tissues and structures.

CLINICAL MANIFESTATIONS

In the liver, cysts may remain asymptomatic, may regress spontaneously, or may produce nonspecific symptoms. Symptomatic cysts can cause increased abdominal girth, hepatomegaly, a palpable mass, vomiting, or abdominal pain. In the lung, cysts produce chest pain, chronic cough, or hemoptysis. Expectorated fluid from ruptured lung cysts is often described as "salty." Mass effects can be noted in the brain and bone. Serious complications result from compression of adjacent structures or spillage of cyst contents. Type I hypersensitivity reactions, including **anaphylaxis,** can occur with spontaneous spillage or with cyst rupture from trauma or during surgery. Fluid from ruptured lung cysts can cause hypersensitivity pneumonitis. Spillage of fluid from a viable cyst can cause catastrophic long-term complications. Each protoscolex can form a new cyst and fill up the abdominal cavity or other spaces, including the pleura, biliary tree, and pelvis. Jaundice from cystic hydatid disease is rare.

Alveolar hydatid disease is sometimes diagnosed incidentally, but often the proliferating mass compromises the biliary system and/or hepatic tissue, causing progressive obstructive jaundice and hepatic failure. Symptoms also occur from expansion of extrahepatic foci.

DIAGNOSIS

Ultrasonography is the most valuable tool for both the diagnosis and treatment of cystic echinococcosis of the liver. The World Health Organization (WHO) standardized ultrasound criteria for classification of liver cystic echinococcosis have been shown to be reliable with excellent inter/intraobserver reliability. Ultrasonography staging has a direct use in defining optimal therapy with cystic echinococcosis types 1 and type 2 (CE1 and CE2) cysts considered fully active, CE3a and CE3b transitional, and CE4 and CE5 inactive (Fig. 350.2). Chest radiographs frequently reveal characteristic rounded masses in lung cystic echinococcosis (Fig. 350.3). Alveolar disease resembles a diffuse solid tumor. CT findings are similar to those of ultrasonography and may at times be useful in distinguishing alveolar from cystic echinococcosis in geographic regions where both occur (Fig. 350.4). CT or MRI is also important in planning a surgical intervention.

Serologic studies are used to confirm the diagnosis of cystic echinococcosis, although some children with active cystic echinococcosis do not have detectable levels of specific antibody. Cross-reaction with other helminths is possible when using crude hydatid fluid antigens for the serology. The sensitivity and specificity of serologic assays to diagnose cystic echinococcosis vary significantly by location of the cyst, stage, and treatment status. The enzyme-linked immunosorbent assay performs better than Western blot and indirect hemagglutination with the highest sensitivity for CE2, CE3, and CE1 cysts (64–99%) compared to CE4 and CE5 (51–91%). The sensitivity is higher for hepatic or bone disease, but the false-negative rate may be >50% with pulmonary or central nervous system (CNS) infection.

Differential Diagnosis

Benign hepatic cysts are common but can be distinguished from cystic echinococcosis by the absence of a distinct three-layer wall, internal membranes, and hydatid sand. The density of bacterial hepatic abscesses is distinct from the watery cystic fluid characteristic of *E. granulosus* infection, but *Echinococcus* cysts may also be complicated

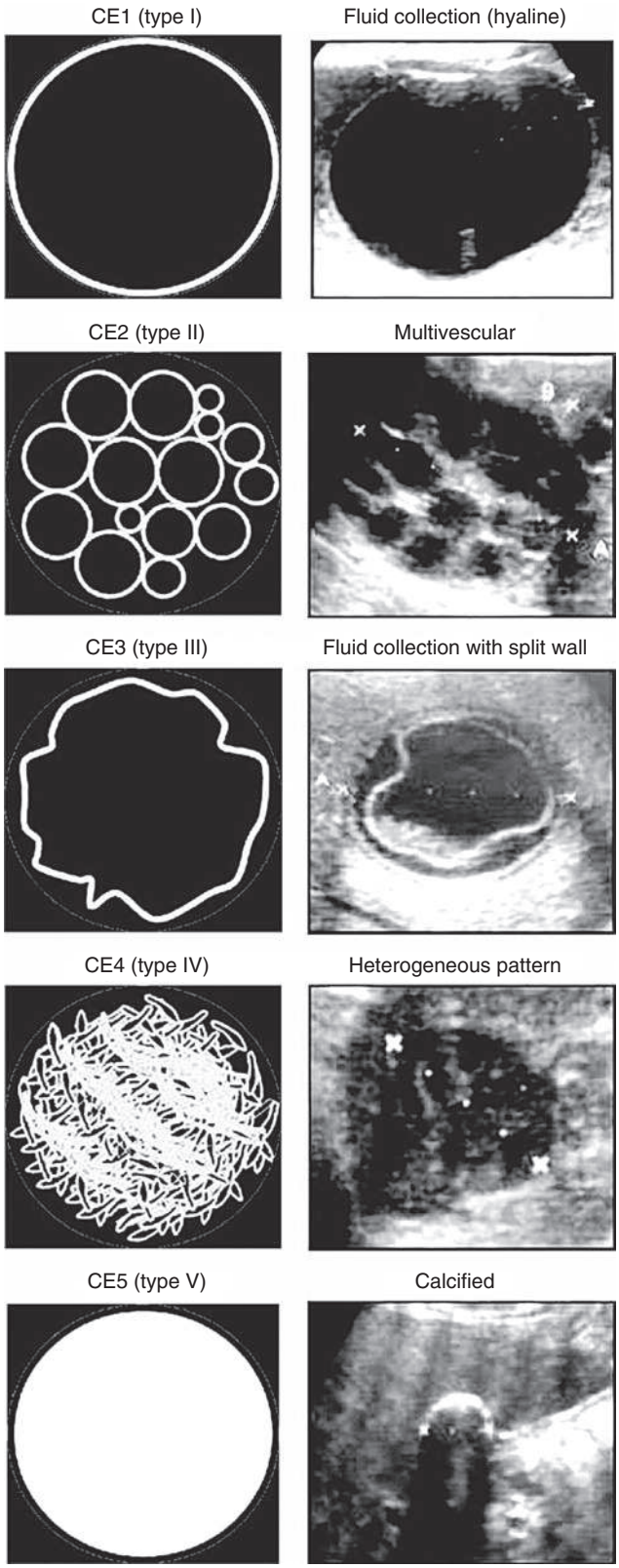

Fig. 350.2 Ultrasound classification of cystic echinococcosis (CE) cysts. The WHO informal working group on echinococcosis classification differs from that of Gharbi and colleagues by the addition of a "cystic lesion" (CL) stage (undifferentiated) *(not shown)* and by reversing the order of CE types 2 and 3. CE3 transitional cysts may be differentiated into CE3a (with detached endocyst) and CE3b (predominantly solid with daughter vesicles). CE1 and CE3a are early-stage cysts and CE4 and CE5 late-stage cysts. *(From McManus DP, Gray DJ, Zhang W, Yang Y. Diagnosis, treatment, and management of echinococcosis. BMJ. 2012;344:e3866. Fig 4.)*

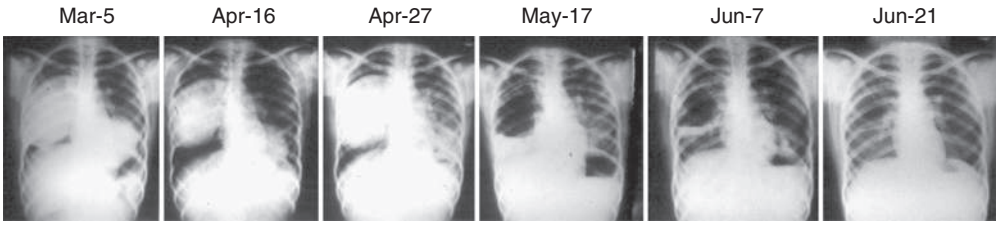

Fig. 350.3 Serial chest radiographs of bilateral hydatid cysts. After 2 months of albendazole therapy, sudden rupture of the right cyst was associated with massive aspiration and acute respiratory distress.

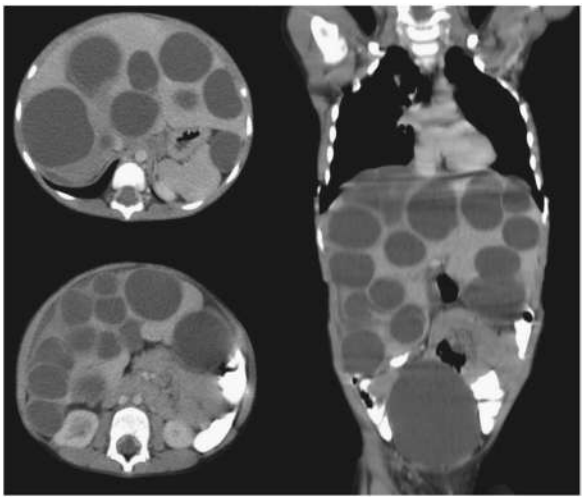

Fig. 350.4 Liver cystic echinococcosis (hydatid disease). Abdominal CT revealed hepatomegaly and multiple (>20) liver cysts. *(From Ben-Shimol S, Zelcer I. Liver hydatid cysts. J Pediatr. 2013;163:1792.)*

by secondary bacterial infection. Alveolar echinococcosis is often confused with hepatoma or metastatic tumor.

TREATMENT

Management of cystic echinococcosis should be individualized and guided by disease stage and location. Approaches range from surgical resection for disease that tends to respond poorly to drugs and complicated cysts to watchful waiting for cysts that have already degenerated. For CE1 or CE3a cysts (see Fig. 350.2) that are <5 cm in diameter, **albendazole** chemotherapy alone (15 mg/kg/day orally divided twice daily for 1-6 months; maximum 800 mg/day) may result in a high rate of cure. Adverse effects include occasional alopecia, mild gastrointestinal disturbance, and elevated transaminases on prolonged use. Because of leukopenia, the U.S. Food and Drug Administration (FDA) recommends that blood counts be monitored at the beginning and every 2 weeks during the first 3 months of therapy and monthly afterward. Medical treatment with albendazole may also be used for cysts that are not suitable for interventions such as **PAIR** (percutaneous, aspiration, instillation, and reaspiration) or surgery, but response rates are low.

For larger CE1 and CE3a lesions, ultrasound- or CT-guided PAIR is the preferred therapy. Compared with surgical treatment alone, PAIR plus albendazole results in similar cyst disappearance with fewer adverse events and fewer days in the hospital. Spillage with PAIR is uncommon, but prophylactic albendazole therapy is routinely administered at least 1 week before PAIR and 1 month afterward. PAIR is contraindicated in pregnancy and for bile-stained cysts, which may indicate the presence of a biliary fistula. The scolicidal agents instilled during PAIR may increase risk for biliary complications in these patients. Surgery with albendazole treatment is the recommended approach for CE2 and CE3b cysts of the liver. In experienced centers, cysts with thick internal septation (CE2) can be managed using a trocar to break up the membranes and external drainage. CE4 and CE5 cysts do not require immediate interventions and are followed ultrasonographically for signs of reactivation.

Surgery is the treatment of choice for complicated **cysts**, including ruptured cysts, cysts communicating with the biliary tract, large pulmonary cysts, or cysts of the CNS or bones. Small thoracic cysts may resolve with albendazole, but most cysts require operative removal.

For conventional surgery, the inner cyst wall (only laminate and germinal layers are of parasite origin) can be easily peeled from the fibrous layer, although some studies suggest that removal of the whole capsule has a better outcome in terms of recurrent disease. Considerable care must be taken to avoid spillage of cyst contents, and surgical drapes should be soaked in hypertonic saline because cyst fluid contains viable protoscoleces, each capable of producing secondary cysts. An additional risk is anaphylaxis because of spilled cyst fluid, making it useful to employ a surgeon experienced in this surgery. For hepatic cysts, patients should begin therapy with albendazole (ideally in combination with praziquantel) for several days to weeks preoperatively. Antiparasitic drugs should be continued for 4-12 weeks postoperatively.

Alveolar hydatidosis frequently requires radical surgery, including partial hepatectomy, lobectomy, or liver transplantation. Medical therapy with albendazole should be continued for at least 2 years after presumably curative surgery. In patients who are not operative candidates or whose lesions are not amenable to surgical cure, albendazole long-term suppressive therapy should be used to slow the progression, but the infection generally recurs if albendazole is stopped.

PROGNOSIS

Factors predictive of success with chemotherapy are age of the cyst (<2 years), low internal complexity of the cyst, and small size. The site of the cyst is not important, although cysts in bone respond poorly. For alveolar echinococcosis, if surgical removal is unsuccessful, the average mortality is 92% by 10 years after diagnosis.

PREVENTION

Important measures to interrupt transmission include thorough **handwashing**, avoiding contact with dogs in endemic areas, and boiling or filtering water when camping. Strict procedures for proper disposal of refuse from slaughterhouses must be instituted and followed so that dogs and wild carnivores do not have access to entrails. Other useful measures are control or treatment of the feral dog population and regular praziquantel treatment of pets and working dogs in endemic areas. Vaccines have been developed to prevent infection in grazing animals but are not widely used.

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