

سامانه پیگیری بیماران



Chapter 757

Overview of Environmental Health and Children

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GLOBAL CLIMATE CHANGE

Pediatricians' primary goal is prevention. One dominant prevention challenge of the 21st century is the climate crisis. The Intergovernmental Panel on Climate Change concluded that the Earth is undergoing adverse global climate change and that anthropogenic (human-made) contributions are significant. These climate changes are creating conditions that have already affected public health, with disproportionate impacts on certain life stages, including children. Children are especially vulnerable to the impacts of climate change because their bodies are growing and developing, they have unique behaviors and interactions with their environment, and they must rely on parents or caregivers to provide for their basic needs. Climate change affects children's health as a result of their exposure to elevated temperatures; more frequent, severe, or longer-lasting extreme weather events; transmission rates of food-borne, water-borne, and vector-borne diseases; increases in air pollution from molds, pollens, and the burning of fossil fuels; and mental health stressors (Fig. 757.1). Natural disasters such as floods and hurricanes, damp housing, and mycotoxin-related illnesses are worsening as temperatures and sea levels rise. The impacts are being felt most among young children and those who are living in poverty. The need to reduce carbon dioxide in the environment has compelled many countries to sign the Paris Agreement. This agreement promises to keep the global temperature rise well below 2°C above preindustrial levels, and to try to limit the temperature increase to 1.5°C. Even though the Paris Agreement began in 2016, its promises have not been kept and the temperature is already 1.2°C higher than in the preindustrial era. Individual actions are another necessary step in carbon dioxide reduction. Parents and caregivers can work to reduce their family's burning of fossil fuels. They also can protect children's health by checking the air quality index and pollen counts and considering a limit to children's outdoor play time if levels are high. Parents can watch for signs of dehydration or overheating in their children and can prevent tick and mosquito bites by using insect repellent and protective clothing. Pediatricians and those who care for children can be highly effective advocates for an urgent governmental response to the climate crisis by speaking out at the community, national, and international level.

LOCALIZED ENVIRONMENTAL HAZARDS

Localized exposures to a wide variety of chemical, biologic, and physical agents can also harm children. Numerous epidemics of disease from chemical, biologic, and physical agents (both natural and human-made) over the past 80 years have documented a variety of adverse outcomes among children (Table 757.1). Some epidemics, such as those caused by the nighttime release of methyl isocyanate

from a factory in Bhopal, India, the nuclear meltdown in Chernobyl, and the melamine contamination of infant formula in China, received widespread attention and heightened the awareness of parents and pediatricians about hazards in the environment. For many people, the word *epidemic* conjures up images of hospital isolation wards, poor sanitation, and rapidly spreading infectious diseases. Epidemics of environmental origin often have served to elucidate new hazards for children. Many of the routinely used chemicals understood to be toxic to children were initially identified when a cluster of children was exposed and developed symptoms during a relatively short period of time. Unfortunately, the children served as the “canaries in the coal mine” to indicate that specific chemicals (including thallium, mercury, arsenic, and lead) contained in products for children such as diaper rinses, teething powders, and depilatory agents, posed a threat to their health. The comparison of children to canaries is apt: following underground mine explosions, canaries were used by miners throughout recent history to help detect elevated levels of carbon monoxide gas. Canaries were useful “carbon monoxide detectors” because of their rapid breathing rate and high metabolism, making them more sensitive to the effects of gases, including carbon monoxide. Likewise, young children have a rapid breathing rate and a high metabolic rate and may be more sensitive than adults to chemicals in the environment.

Table 757.1 summarizes major incidents of environmental poisoning that affected children. The characteristics of environmental exposure and the age and developmental stage of the child affect the likelihood of developing health problems. After the release of methyl isocyanate (used in the production of some pesticides) at Bhopal in 1984, an estimated 200,000 children living near the Bhopal chemical plant were affected by the gas release (see Table 757.1). Methyl isocyanate gas is 1.4 times heavier than air; thus higher concentrations of the gas were found near the ground or floor. Because of their short stature, children's breathing zones are closer to the ground or floor than adults' breathing zones; therefore children likely inhaled higher concentrations of the toxic gas. Children exposed to the same levels of methyl isocyanate as adults may have received larger doses because they have relatively greater lung surface area to body weight ratios and higher minute volume to weight ratios. Based on each of the poisoning events listed in Table 757.1, additional precautions were taken to avoid children's unnecessary exposure to the specific product or chemical implicated.

Although major poisonings such as those listed in Table 757.1 have caused substantial morbidity and mortality among children, environmental health hazards may also result in more subtle effects that may not manifest until later in life. In addition to the exposures received during large outbreaks, children receive smaller doses of chemicals on an almost daily basis through the water they drink, the food they eat, and the air they breathe. Because of their unique vulnerability, they may exhibit symptoms from these exposures earlier than do adults.

TOXINS VERSUS TOXICANTS

A toxin is a poisonous substance produced naturally by a living organism (e.g., aflatoxin). A toxicant is a poisonous substance made by humans or introduced into the environment by human activity (e.g., dioxins). Synthetic chemicals are referred to as toxicants.

MYCOTOXINS

Children's exposures to mycotoxins, the toxins produced by certain fungi on grains, nuts, and other crops, will likely increase as the

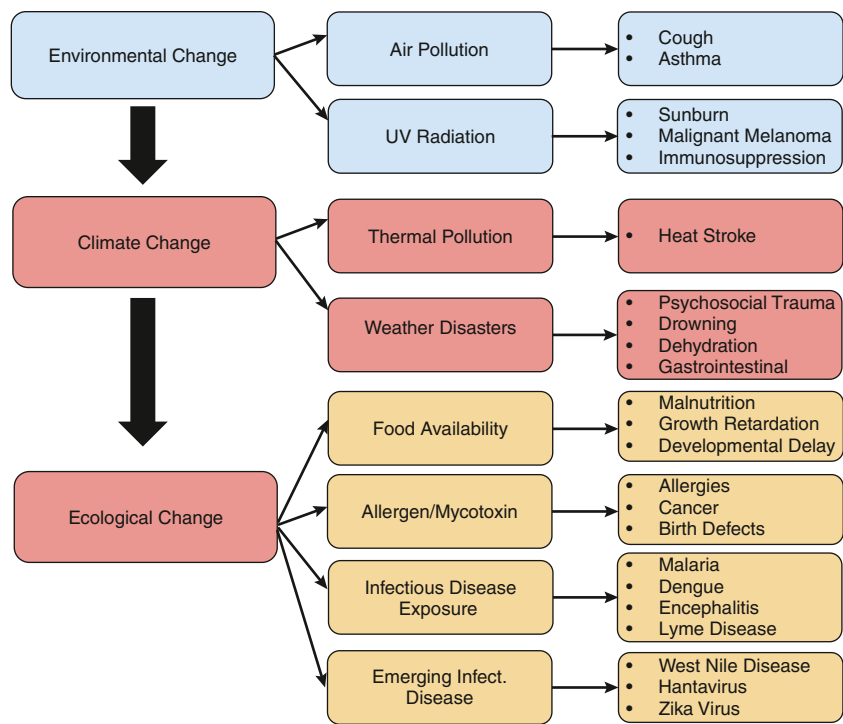


Fig. 757.1 The relationship between environmental change, climate change, ecologic change, and child health. (Adapted from Bunyavanich S, Landrigan CP, McMichael AJ, et al. The impact of climate change on child health. *Ambul Pediatr.* 2003;3:44–52. Fig. 2.)

Table 757.1 Epidemics of Environmental Disease Affecting Children						
CONTAMINANT	VEHICLE	DATE	COUNTRY	APPROX. # SICKENED	ILLNESS	APPROX. # WHO DIED
Thallium	Depilatory agents	1930	Grenada	16	Thallotoxicosis	13
Methylmercury	Fish and shellfish	1956	Japan	2,265	Cerebral palsy	1,784
Arsenic	Contaminated milk powder	1955	Japan	11,778	Fever, diarrhea darkened skin, swollen abdomen	113
Hexachlorobenzene	In human milk after pregnant women ate HCB-treated seed grain	1957	Turkey	~200	Pembe yara (pink sore) rash, weakness convulsions	<2yr ~200
Methyl isocyanate	Leak from chemical plant	1984	India	<15yr: 200,000	Coughing, eye irritation choking death	All ages 2,500-5,000
Dioxin	Chemical plant explosion	1976	Italy	193 (88%)	Chloracne	0
Radiation	Chernobyl	1986	Ukraine	<18yr: 4,000	Thyroid cancer	~8
Radiation	Scrapped medical machine stolen from hospital	1987	Goiânia, Brazil	249	Acute radiation syndrome	4 (1 child)
Fungi	Water-damaged homes	1990s	Ohio, US	30	Pulmonary hemorrhage	5
Aflatoxin	Grain	2004	Kenya	317	Aflatoxicosis	125
Melamine	Infant formula	2008	China	290,000	Kidney stones	6
Lead	Small-scale gold mining	2010	Nigeria	>2,000	Seizures, death	200

climate changes because their production is influenced by temperature, humidity, and rainfall. Exposure to mycotoxins results in different health outcomes dependent on the route of exposure. Exposure from eating or drinking may lead to gastrointestinal illness, tremors, and cancer in adulthood; exposure via breathing may result in acute respiratory illness during infancy. There also is emerging evidence linking

mycotoxin exposures among children, especially those in developing countries, to stunted growth.

Pediatric Conditions Linked to Mycotoxin Exposures
Exposures to mycotoxins have been linked to at least two conditions that affect children: neural tube defects and acute pulmonary hemorrhage.

Neural Tube Defects

Studies of an epidemic of birth defects in 1990 in south Texas suggested an association between maternal ingestion during pregnancy of high levels of fumonisin, universally present in corn and in corn-based products, and birth defects such as anencephaly and spina bifida. Fumonisin is known to interfere with cellular folate uptake.

Infant Pulmonary Hemorrhage

Several studies of a 1994 epidemic of acute pulmonary hemorrhage in Cleveland, Ohio, documented a novel association between life-threatening pulmonary hemorrhage and the presence of the toxigenic mold *Stachybotrys* in the water-damaged homes in which the infants were living. *Stachybotrys* produces mycotoxins that are lipid soluble and readily absorbed by the airways, as well as a hemolysin and several proteinases that can degrade vascular collagen. In subsequent

years, *Stachybotrys* and other toxigenic fungi including *Trichoderma* have been associated with acute pulmonary hemorrhage among infants in other areas of the United States, Canada, and New Zealand. The rapidly growing lungs of infants are especially vulnerable to the effects of the trichothecene mycotoxins produced by *Stachybotrys* and *Trichoderma*.

FOOD-BORNE DISEASES CAUSED BY ENVIRONMENTAL EXPOSURES

Contamination of food with viruses and bacteria is a major cause of childhood food-borne diseases (see Chapter 387), and children are also at risk from a variety of noninfectious food-borne hazards in the environment, which include natural hazards such as mycotoxins and synthetic persistent organic pollutants such as dioxins (see Chapter 759; Table 757.2).

Table 757.2 Food-Borne Illnesses (Noninfectious)

ETIOLOGY	INCUBATION PERIOD	SIGNS AND SYMPTOMS	DURATION OF ILLNESS	ASSOCIATED FOODS	LABORATORY TESTING	TREATMENT
Antimony	5 min to 8 hr usually <1 hr	Vomiting, metallic taste	Usually self-limited	Metallic container	Identification of metal in beverage or food	Supportive care
Arsenic	Few hours	Vomiting, colic, diarrhea	Several days	Contaminated food	Urine; may cause eosinophilia	Gastric lavage BAL (dimercaprol)
Cadmium	5 min to 8 hr usually <1 hr	Nausea, vomiting, myalgia, increase in salivation, stomach pain	Usually self-limited	Seafood, oysters, clams, lobster, grains, peanuts	Identification of metal in food	Supportive care
Ciguatera fish poisoning (ciguatera toxin)	2-6 hr	GI: abdominal pain, nausea, vomiting, diarrhea	Days to weeks to months	A variety of large reef fish, grouper, red snapper, amberjack, and barracuda (most common)	Radioassay for toxin in fish or a consistent history	Supportive care, IV mannitol; children more vulnerable
	3 hr	Neurologic: paresthesias, reversal of hot and cold, pain, weakness				
	2-5 days	Cardiovascular: bradycardia, hypotension, increase in T-wave abnormalities				
Copper	5 min to 8 hr usually <1 hr	Nausea, vomiting, blue or green vomitus	Usually self-limited	Metallic container	Identification of metal in beverage or food	Supportive care
Mercury	1 wk or longer	Numbness, weakness of legs, spastic paralysis, impaired vision, blindness, coma Pregnant women and developing fetuses are especially vulnerable	May be protracted	Fish exposed to organic mercury, grains treated with mercury fungicides	Analysis of blood, hair	Supportive care
Mushroom toxins, short-acting (museinol, muscarine, psilocybin, coprius artemetaris, ibotenic acid)	<2 hr	Vomiting, diarrhea, confusion, visual disturbance, salivation, diaphoresis, hallucinations, disulfiram-like reaction	Self-limited	Wild mushrooms (cooking may not destroy these toxins)	Typical syndrome and mushroom identified or demonstration of the toxin	Supportive care

Continued

Table 757.2 Food-Borne Illnesses (Noninfectious)—cont'd

ETIOLOGY	INCUBATION PERIOD	SIGNS AND SYMPTOMS	DURATION OF ILLNESS	ASSOCIATED FOODS	LABORATORY TESTING	TREATMENT
Mushroom toxin, long-acting (amanitin)	4-8 hr diarrhea; 24-48 hr liver failure	Diarrhea, abdominal cramps, leading to hepatic and renal failure	Often fatal	Mushrooms	Typical syndrome and mushroom identified and/or demonstration of the toxin	Supportive care, life-threatening, may need life support
Nitrite poisoning	1-2 hr	Nausea, vomiting, cyanosis, headache, dizziness, weakness, loss of consciousness, chocolate brown-colored blood	Usually self-limited	Cured meats, any contaminated foods, spinach exposed to excessive nitrification	Analysis of food, blood	Supportive care, methylene blue
Pesticides (organophosphates or carbamates)	Few minutes to few hours	Nausea, vomiting, abdominal cramps, diarrhea, headache, nervousness, blurred vision, twitching, convulsions, salivation, and meiosis	Usually self-limited	Any contaminated food	Analysis of food, blood	Atropine: 2-PAM (pralidoxime) is used when atropine is not able to control symptoms and is rarely necessary in carbamate poisoning
Puffer fish (tetrodotoxin)	<30 min	Paresthesias, vomiting, diarrhea, abdominal pain, ascending paralysis, respiratory failure	Death usually in 4-6 hr	Puffer fish	Detection of tetrodotoxin in fish	Life-threatening, may need respiratory support
Scombroid (histamine)	1 min to 3 hr	Flushing, rash, burning sensation of skin, mouth, and throat, dizziness, urticaria, paresthesias	3-6 hr	Fish: bluefin, tuna, skipjack, mackerel, marlin, escolar, and mahi mahi	Demonstration of histamine in food or clinical diagnosis	Supportive care, antihistamines
Shellfish toxins (diarrheic, neurotoxic, amnesic)	Diarrheic shellfish poisoning (DSP)—30 min to 2 hr	Nausea, vomiting, diarrhea, and abdominal pain accompanied by chills, headache, and fever	Hours to 2-3 days	A variety of shellfish, primarily mussels, oysters, scallops, and shellfish from the Florida coast and the Gulf of Mexico	Detection of the toxin in shellfish; high-pressure liquid chromatography	Supportive care, generally self-limiting
	Neurotoxic shellfish poisoning (NSP)—few minutes to hours	Tingling and numbness of lips, tongue, and throat, muscular aches, dizziness, reversal of the sensations of hot and cold, diarrhea, and vomiting				
	Amnesic shellfish poisoning (ASP)—24-48 hr	Vomiting, diarrhea, abdominal pain and neurologic problems such as confusion, memory loss, disorientation, seizure, coma				
Shellfish toxins (paralytic shellfish poisoning)	30 min to 3 hr	Diarrhea, nausea, vomiting leading to paresthesias of mouth, lips, weakness, dysphasia, dysphonia, respiratory paralysis	Days	Scallops, mussels, clams, cockles	Detection of toxin in food or water where fish are located; high-pressure liquid chromatography	Life-threatening, may need respiratory support

Table 757.2 Food-Borne Illnesses (Noninfectious)—cont'd

ETIOLOGY	INCUBATION PERIOD	SIGNS AND SYMPTOMS	DURATION OF ILLNESS	ASSOCIATED FOODS	LABORATORY TESTING	TREATMENT
Sodium fluoride	Few minutes to 2 hr	Salty or soapy taste, numbness of mouth, vomiting, diarrhea, dilated pupils, spasms, pallor, shock, collapse	Usually self-limited	Dry foods (e.g., dry milk, flour, baking powder, cake mixes) contaminated with sodium fluoride—containing insecticides and rodenticides	Testing of vomitus or gastric washings, analysis of food	Supportive care
Thallium	Few hours	Nausea, vomiting, diarrhea, painful paresthesias, motor polyneuropathy, hair loss	Several days	Contaminated foods	Urine, hair	Supportive care
Tin	5 min to 8 hr, usually <1 hr	Nausea, vomiting, diarrhea	Usually self-limited	Metallic container	Analysis of food	Supportive care
Vomitoxin	Few minutes to 3 hr	Nausea, headache, abdominal pain, vomiting	Usually self-limited	Grains such as wheat, corn, barley	Analysis of food	Supportive care
Zinc	Few hours	Stomach cramps, nausea, vomiting, diarrhea, myalgias	Usually self-limited	Metallic container	Analysis of food, blood, and feces, saliva, or urine	Supportive care

BAL, Bronchoalveolar lavage; GI, gastrointestinal; IV, intravenous.

Adapted from Centers for Disease Control and Prevention. Diagnosis and management of foodborne illnesses: a primer for physicians and other health care professionals. *MMWR*. 2004;53(No. RR-4):1–33.

Aflatoxins

Aflatoxins are poisonous substances that are formed as a result of mold growth on peanuts, corn, figs, oil-seeds, tobacco, and other products. The International Agency for Research on Cancer (IARC) has classified aflatoxin B1 as a group I carcinogen (known to be carcinogenic to humans). Ingestion of elevated levels of aflatoxin also can result in acute aflatoxicosis, characterized by vomiting, abdominal pain, hepatitis, and sometimes death.

Ochratoxin A

The mycotoxin ochratoxin A, produced by many different species of *Aspergillus* molds, is toxic to the kidneys. Ochratoxin A contaminates many foods, including barley, rye, and other cereals, cereal-derived foods, dry fruits, beans, cocoa, coffee, beer, wine, poultry, eggs, pork, and milk. Ochratoxin A is teratogenic, immunotoxic, genotoxic, and mutagenic. The IARC has indicated that ochratoxin is a possible human carcinogen (category 2B).

Fumonisin

Fumonisin are mycotoxins that may contaminate cornmeal and cereals. The fumonisins are known to interfere with sphingolipid metabolism. Consuming foods contaminated with fumonisins during pregnancy has been linked to an increased risk of having a child with a neural tube defect and an increased risk of esophageal cancer in adulthood.

Deoxynivalenol

This mycotoxin, often called *vomitoxin* because its predominant effect is vomiting, can be present in foods made from wheat and corn. Even after the grain is baked or cooked, vomitoxin retains its toxicity. Multiple epidemics of vomiting illness that occurred in China during 1961 to 1985 were associated with ingesting grain contaminated with vomitoxin. In India in 1987, almost 100 people

started vomiting after they ate wheat products that contained vomitoxin and other mycotoxins. For infants, the estimated tolerable daily intake is 1.5 µg/kg body weight. A suspected epidemic of vomitoxin-related illness that affected about 1,700 school children in the United States in 1997–98 was linked to burritos that had measurable levels of vomitoxin of 0.3 parts per million (ppm; the advisory level set by the U.S. Food and Drug Administration for adults is 1 ppm).

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Chapter 758

Biologic Effects of Ionizing Radiation on Children

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DIAGNOSTIC IMAGING, RADIATION THERAPY

Ionizing radiation is produced when energy is absorbed within an atom such that a bound electron is liberated, and the atom becomes ionized. Exposure to ionizing radiation is characterized by three

categories: (1) **absorbed dose**, (2) **equivalent dose**, and (3) **effective dose**. In terms of radiation interaction with humans, absorbed dose is defined as the energy imparted (i.e., absorbed) within a mass of tissue from a radiation source. Absorbed dose is calculated based on the attenuation properties of the irradiated tissue (e.g., attenuation is greater in bony tissue due to its higher electron density and mass than water equivalent, soft tissue organs). The units of absorbed dose, as defined by the International Commission of Radiation Units, are the **Gray** (Gy), the preferred unit, and the older radiation absorbed dose (**rad**). There are different types of radiation including x-ray, γ -ray, α particles (helium nucleus stripped of all electrons), β particles (unbound electrons), neutrons, and protons. Not all radiation has the same effect on biologic tissue for a given absorbed dose; for example, β particles are quite superficial, protons deposit most of their energy deeper within the body, and α particles and neutrons cause significantly more damage than x-rays or γ -rays. Diagnostic imaging uses x-rays and γ -rays. The therapeutic use of radiation for cancer treatment primarily uses x-rays, β particles, and protons depending on their application and location of disease within the body. **Equivalent dose** is a term used to define the relative effectiveness to cause biologic damage. The International Commission on Radiological Protection (ICRP) gives x-rays, γ -rays, and β particles a relative weighting of 1, protons a weighting of 2, neutrons a weighting of 2.5-20 (neutron weighting factor depends on the energy of the neutron), and α particles a weighting of 20. Thus, for the same level of radiation exposure to an organ, the equivalent dose, i.e., the relative level of biologic damage, would be higher for absorbed doses from protons compared with x-rays. **Effective dose** is a term that represents “the sum of the weighted [applying organ and tissue weighting factors] equivalent doses for the radiosensitive tissues and organs of the body” (National Council on Radiation Protection and Measurements). A list of relative organ and tissue weighting factors defined by the ICRP is provided in Table 758.1. Equivalent dose and effective dose are measured in units of **sievert** (Sv), with levels in diagnostic imaging typically in millisieverts (mSv), and the **rem** (older unit) (Table 758.2). Effective dose is not applied as a metric of dose to an individual but is a population average. Effective dose is not adjusted based on real or potential radiation susceptibilities for tissues for either gender or age.

Nuclear medicine and PET imaging examinations are described by the amount of radioactivity given, commonly injected intravenously. Administered radioactivity is referred to as the administered radiopharmaceutical dose, commonly defined in millicuries (mCi) or megabecquerels (MBq). Radiopharmaceutical dose may be converted to

effective dose by applying correction factors provided in ICRP reports 53, 80, 106, and 128.

For the average adult, ionizing radiation exposure occurs from both natural (60%) and medical (40%) sources, and for the average pediatric-age individual, ionizing radiation exposure occurs primarily from natural sources (91%) as compared to medical sources (9%) (National Council on Radiation Protection and Measurements). Radon gas accounts for the majority of natural radiation exposure. For the adult population, the percentage contribution from medical imaging to the total ionizing radiation exposure had been increasing in the late 20th and early 21st century, but is now declining since 2006. As of 2016, for the average adult, CT imaging comprised 63% of the total of ionizing radiation procedures (Fig. 758.1A), but medical imaging accounted for only 42% of the average adult population exposure to ionizing radiation; this has decreased slightly in the past decade due to technologic advances in imaging equipment and how we use the equipment in practice. For the pediatric patient population, CT remains the primary source of medical radiation exposure, accounting for 84% of the total medical exposure (annual per capita exposure) from ionizing radiation (see Fig. 758.1B). Despite efforts to educate the medical community and the public on radiation safety and the guiding principle of keeping radiation dosing “as low as reasonably achievable (ALARA),” understanding of sources, amounts, and potential risks of ionizing radiation can still be limited. Some imaging procedures do not produce ionizing radiation (Table 758.3), and not all ionizing radiation-producing modalities expose a child to the same amount of radiation (Table 758.4). To facilitate choosing the appropriate imaging modality for a patient’s clinical indications, American College of Radiology appropriateness criteria have been published (<https://www.acr.org/Clinical-Resources/ACR-Appropriateness-Criteria>) to assist referring physicians in making the most appropriate imaging or treatment decision for a specific clinical condition.

BIOLOGIC EFFECTS OF RADIATION

Biologic effects of radiation are divided into **tissue reactions** (previously known as **deterministic effects**) and **stochastic effects**. Tissue reactions do not occur below a threshold absorbed dose, and severity is directly related to the magnitude once the threshold is exceeded. No evidence of tissue reactions has been demonstrated from radiation dose levels typical of diagnostic imaging examinations (i.e., <100 mGy), but complicated interventional procedures have on rare occasions led to these effects. Typical tissue reactions can present as temporary hair loss (epilation) and skin reddening (erythema), which occur in regions of peak dose of >2 Gy (Table 758.5). Cataracts have been reported to occur with acute exposure of >0.5 Gy.

The second type of biologic effect is the **stochastic effects** that are of concern because they are assumed to potentially occur at any dose; that is, there is no threshold. Stochastic effects are most commonly discussed as cancer risk but also include heritable effects. The probability of a stochastic effect increases with rising level of absorbed dose, but not the severity. Cancer, if radiation induced, is not more severe with higher doses. It is generally accepted by the scientific and medical community that stochastic effects may be caused by any level of radiation striking vulnerable tissue (most importantly DNA, but cytoplasm also may be at risk) and causing irreversible damage. The most widely accepted model representing stochastic effects is the **linear no (dose) threshold (LNT) model**. This model maintains that any level of radiation dose has a potential risk, although this risk is currently uncertain at effective dose levels below 50-100 mSv. Greater than this range, there is a recognized, although very small, statistically significant risk of a stochastic effect. In the LNT model, no level of radiation exposure is assumed to be safe.

Table 758.1 Tissue Radiosensitive Weighting Factors; ICRP Report 103		
TISSUE	TISSUE WEIGHTING FACTOR (w_T)	$\sum w_T$
Red bone marrow, colon, lung, stomach, breast, remainder tissues*	0.12	0.72
Gonads	0.08	0.08
Bladder, esophagus, liver, thyroid	0.04	0.16
Bone surface, brain, salivary glands, skin	0.01	0.04
Total		1.00

*Remainder tissues: Adrenal glands, extrathoracic region, gallbladder, heart, kidneys, lymphatic nodes, muscle, oral mucosa, pancreas, prostate, small intestine, spleen, thymus, uterus/cervix

Table 758.2 Radiation Measurements

UNITS	RADIOACTIVITY	ABSORBED DOSE	EFFECTIVE DOSE	EXPOSURE
Common units	Curie (Ci)	rad	rem	Roentgen (R)
SI units*	Becquerel (Bq)	Gray (Gy)	Sievert (Sv)	Coulombs/kg
CONVERSION EQUIVALENTS				
1 millicurie (mCi) = 37 megabecquerels (MBq)				
100 rad = 1 Gy (1 rad = 1 cGy)				
100 rem = 1 Sv (1 rem = 10 mSv)				
Background radiation dose is approximately 10 μ Gy/day (1 millirad/day)				

*SI units: International System of Units.

Radiation can cause permanent cell injury leading to carcinogenesis, genetic variants, or cell death. The biologic effects of radiation result primarily from damage to DNA. **Direct effect** reactions occur mainly through interactions of high **linear energy transfer (LET)** particles, such as α particles or neutrons, directly with the DNA structure. A similar mechanism also can occur with x-ray or γ -ray photons by directly liberating an electron from atoms (called a recoil electron) near the DNA structure. The kinetic energy of the recoil electron or high LET particles may directly cleave chemical bonds in the DNA structure.

An **indirect effect** is caused by the formation of free radicals. This is the more common mechanism with x-rays and γ -rays used in medical imaging. Approximately 80% of the cell is water, so most of the energy deposited in a cell results in the production of aqueous free radicals. This occurs when the absorbed x-ray or γ -ray photon energy is converted to recoil electrons that create ion radicals (H_2O^+ and H_2O^-). The ion radicals promptly decay (10^{-18} to 10^{-3} seconds) into free radical species (OH^- , H^+ , H_3O^+). Approximately two thirds of DNA damage is believed to be caused by this indirect effect through creation of hydroxyl (OH^-) free radicals, which then primarily reacts with DNA by attaching to the hydrogen bound to the deoxyribose carbon resulting in a base release from the DNA structure and strand break of the DNA helix. The biochemical changes that follow either direct or indirect effects take hours or days to manifest, whereas the physiologic changes leading to the likely complex cascade of a variety of factors for cancer induction may take years to decades to manifest.

The results from DNA injury are variable. The cell containing the damaged DNA almost always repairs itself and continues as a viable cell for mitotic division. In some instances, the cell might die; one form of cell death is called **apoptosis**, which is a common pathway to eliminate heavily damaged and potentially mutable cells. Damage to a single base pair from radiation exposure is the most prevalent and least significant effect. Ninety percent of single-strand DNA breaks are repaired within an hour by naturally occurring DNA repair processes; therefore they usually have little biologic significance because each strand is repaired with use of the opposite strand as a template. Though less likely, a pathogenic variant can result from single-strand break repair if inaccurate repairs occur; however, large regions of the DNA genome on somatic cells are not active or do not have genes that are expressed. Inaccurate repair in these regions of the genome lead to minimal biologic effect and are sufficient to produce viable cells.

Breakage of both strands of DNA (i.e., double-strand break) is the least common event, but more problematic. The ultimate outcome for cell viability depends on the proximity of the break in each strand. If widely separated (greater than 10 base pairs), which is essentially two remote single-strand breaks, repairs occur rather seamlessly. If the breaks in the two strands are opposite or near each other (separated by less than 10 base pairs), repair is more difficult as there is no reciprocal base pair to serve as a “memory” template. Radiation-induced double-stranded breaks generally lead to cell death or **chromosomal misrepair**, potentially leading to pathogenic gene variants that may result in carcinogenesis.

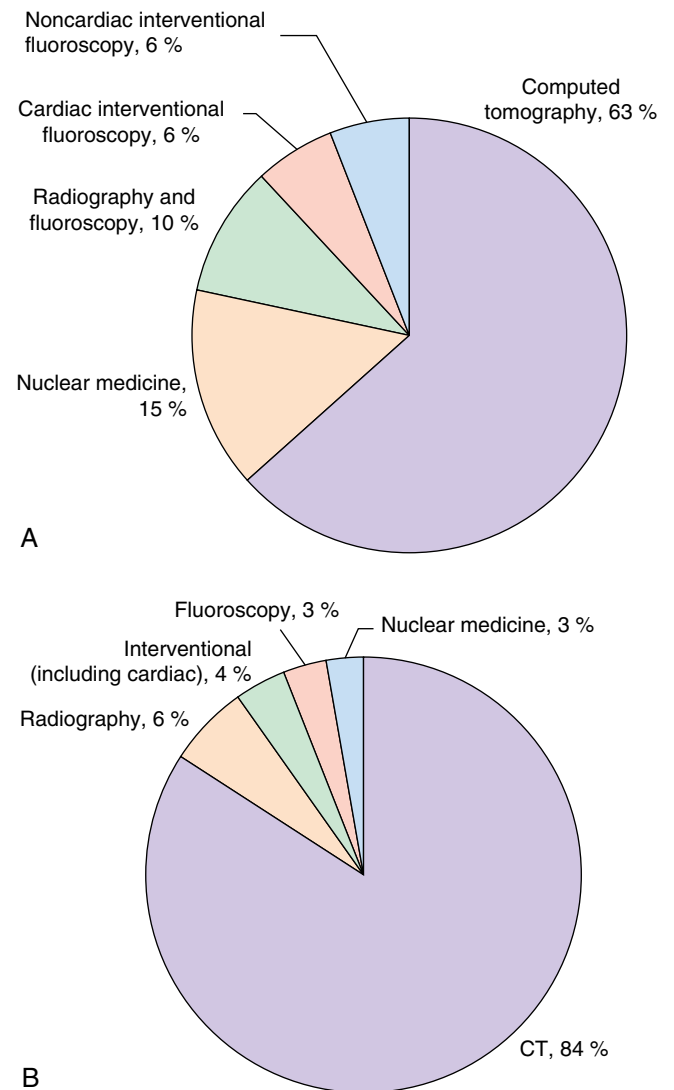


Fig. 758.1 Percentage radiation exposure by diagnostic imaging modality for (A) adult and (B) pediatric populations. (Adapted with permission of the National Council on Radiation Protection and Measurements, Report 184: Medical Radiation Exposure of Patients in the United States, 2019. Figs. 14.3 and 12.2.)

When misrepaired DNA damage occurs, aberrations may then be produced in chromosomes, resulting in an *unstable aberration* (usually lethal to dividing cells) or a *stable aberration*. Stable aberrations can result in failure of chromosomes to reunite (leading to deletions) or in abnormal rearrangement of chromosomes, such

as reciprocal translocation or aneuploidy. Although it is logical to think that these abnormalities in chromosomes lead to variants that can activate oncogenes or protooncogenes, or cause variants in

Table 758.3

Imaging Modalities

MODALITY	SOURCE
Radiography (digital plain film x-ray)	Radiation (x-ray)
Fluoroscopy and fluoroscopically guided procedures	Radiation (x-ray)
Ultrasonography	Sound beams
Computed tomography	Radiation (x-ray)
Magnetic resonance imaging	Magnetic field with radiofrequency
Nuclear medicine (including positron emission tomography)	Radiation (administered isotope)

Table 758.4

Average Radiation Dose by Imaging Test for Pediatric Population*

EXAMINATION (0-18 YEARS)	EFFECTIVE DOSE (mSv)
Interventional fluoroscopy: AP and lateral abdomen	0.2-1.1 mSv/min
Interventional fluoroscopy: head	0.02-0.08 mSv/min
Interventional fluoroscopy: cardiac	0.1-1 mSv/min
Digital radiography: 2-view chest	0.04-0.06
Digital radiography: 2-view abdomen	0.1-0.6
Computed tomography: brain	0.8-2
Computed tomography: chest	0.5-4
Computed tomography: abdomen/pelvis†	1-9
Nuclear medicine (^{99m} Tc methylene diphosphonate: bone)	2-5
Positron emission tomography (¹⁸ F-FDG; whole body)	2-11

*Background radiation reference = 0.01 mSv/day or 3 mSv/yr.
†Radiation dose upper limit includes young adult age population.

Table 758.5

Tissue Reaction Dose Levels

INJURY	APPROXIMATE THRESHOLD
SKIN	
Transient erythema	2 Gy (200 rad)
Dry desquamation	8 Gy (800 rad)
Moist desquamation	15 Gy (1,500 rad)
Temporary epilation	2 Gy (200 rad)
Permanent epilation	7 Gy (700 rad)
EYES	
Cataracts (acute)	2 Gy (200 rad)*

*Has been reported as occurring between 0.5 and 1 Gy.

tumor-suppressor genes (see Chapter 541), few radiation-induced cancers show specific translocations such as would be associated with activation of specific oncogenes or known tumor-suppressor genes. An exception is the radiation induction of papillary thyroid carcinoma in children, which probably results from activation of the RET oncogene (see Chapter 607).

A longitudinal study of the lifetime risks of excess cancer mortality to irradiation has been evaluated in atomic bomb survivors. More than 120,000 survivors since 1950 have been followed since exposure; additionally, 3,600 in utero survivors and their 77,000 progeny have been followed since 1945. Individual radiation doses were estimated by considering the person’s location in relation to distance from the epicenter and individual shielding situations (such as line of sight with respect to buildings and terrain). Radiation types were mixed, and most of the exposure was direct gamma irradiation; neutron exposure was out to approximately 2,000 m. Age at exposure, lifestyle, and other factors were considered in the analytic models when calculating cancer occurrence (Fig. 758.2).

The pediatric population is approximately two to three times more sensitive to radiation-induced carcinogenesis compared with middle-age adults; however, the risk even in this population is indirectly related to age where the neonate is more sensitive than the older child to an identical radiation exposure. Because of the higher risks associated with breast and thyroid cancer, females are also more sensitive than males. It must be understood that cancer rates in this study are mortality figures; the incidence of cancer is approximately twice that of the mortality incidence for all ages. The Centers for Disease Control and Prevention (CDC) reports no scientific evidence demonstrating noncancerous effects (e.g., malformations, growth, intellectual disability, etc.) from in utero exposure <50 mGy, an exposure level that is greater than essentially any single diagnostic examination using ionizing radiation. Additionally, noncancerous effects may only increase slightly with exposure levels between 50 and 500 mGy. In utero radiation exposure is associated with an excess risk of developing (all types) childhood cancer: 1% (<100 mGy), 1–6% (100-500 mGy), and >6% (>500 mGy) as compared to 0.7% naturally. Children are at increased risk of stochastic risks for identical levels of exposure seen in adults because (1) children are growing rapidly, with many

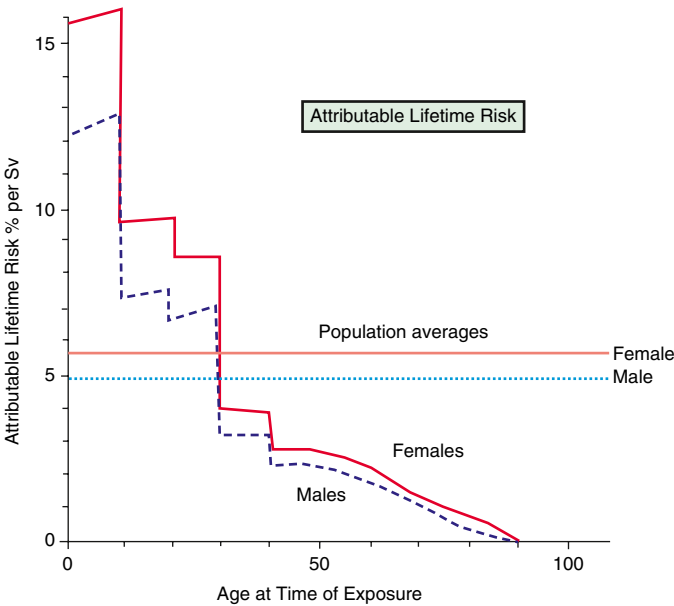


Fig. 758.2 Lifetime risk of excess cancer per sievert (Sv) as a function of age at the time of exposure. Data from the atomic bomb survivors. The average risk across all ages in a population is approximately 5% per Sv, but the risk varies considerably with age: children are much more sensitive than adults. At early ages, girls are more sensitive than boys. (From Hall EJ. Introduction to session I: Helical CT and cancer risk. *Pediatr Radiol.* 2002;32:225–227.)

Table 758.6 Inherited Human Syndromes Associated with Sensitivities to X-Rays

Ataxia-telangiectasia	Fanconi anemia
Basal cell nevoid syndrome	Gardner syndrome
Cockayne syndrome	Nijmegen breakage syndrome
Down syndrome	Usher syndrome

Modified from Davis JT, Frush DP. Biologic effects of diagnostic radiation on children. In: Coley BD, ed. *Caffey's Pediatric Diagnostic Imaging*, 13th ed. Philadelphia: Elsevier; 2019: p. 5; and Hall EJ. *Radiobiology for the Radiologist*, 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2006: p. 41.

cells undergoing mitotic activity dependent on undamaged DNA and chromosomes, and (2) radiation-induced tumors (except leukemia) take a relatively long time to develop and children have a longer life-time. Policies relating to the use of therapeutic abortion have been established by the ICRP and American College of Obstetricians and Gynecologists, which state that fetal doses <100 mGy should not be considered a reason for terminating pregnancy, and that every woman should be counseled that exposure from a single diagnostic procedure does not result in tissue effects to the fetus.

Most childhood tumors occur sporadically, but 10–15% of cases have a strong familial association. Familial tumors have specific chromosomal deletions in common. In some of these tumors (e.g., retinoblastoma), the two-hit hypothesis is apparent (see [Chapter 541](#)). Individuals with certain congenital diseases are at higher risk for the development of tumors after irradiation. [Table 758.6](#) lists diseases that are associated with sensitivity to radiation.

RADIATION EXPOSURE IN DIAGNOSTIC IMAGING OF CHILDREN

Imaging modalities utilizing ionizing radiation for diagnostic purposes (e.g., CT, nuclear medicine, PET, radiography, and fluoroscopy or fluoroscopically guided procedures) are commonly utilized; however, increased awareness of the long-term risk for cancer induction and mortality has led to declining pediatric CT use over the past decade. The European EPI-CT study found a significant dose-response relationship between CT-related radiation exposure and brain cancer as well as hematologic malignancies in a large international study cohort, supporting the concept that stochastic effects are a dose-dependent probability, with the probability of an effect increasing with radiation dose. Therefore it is important that we use the lowest dose necessary to get sufficient diagnostic images. Various federal agencies, healthcare accrediting bodies, and national professional organizations support this goal and provide recommendations or requirements for all imaging examinations to have some retrievable radiation dose estimate, and for institutions and clinics that provide ionizing radiation imaging services to track and review patient examination dose levels annually, comparing these dose levels with expected dose ranges and external benchmarks.

Dose reporting and aggregating software provides the ability to collect and analyze individual examination doses and gives healthcare providers a powerful tool to correct outlier examinations (i.e., over exposures), over utilization, and address other systemic errors present in imaging clinics (such as radiation dose creep with time).

DECREASING UNNECESSARY DIAGNOSTIC RADIATION IN CHILDREN WHILE STILL OBTAINING DIAGNOSTIC IMAGES

Ultimately, the lowest radiation dose examination is the imaging examination performed without ionizing radiation. For an increasing number of indications, utilization of nonionizing radiation modalities such as ultrasound or MRI may be the first consideration for diagnosis. Selecting the correct examination is the responsibility of the requesting healthcare provider and may involve consultation with the radiologist, preferably with pediatric expertise. Clinical decision support algorithms are also available to assist with examination appropriateness (e.g., American College of Radiology's Appropriateness Criteria). The risk of using ionizing radiation for imaging should be weighed against

other risks during imaging. CT (depending on the indication and region examined) may detect as many abnormalities as MRI, but CT involves ionizing radiation. However, sedation is often required to successfully obtain MRI imaging in young children; in these cases, consideration of the relative risks of cognitive impairment from moderate sedation and anesthetic versus potential radiation risks use should come into play.

Reducing Radiation from the CT Examination

The most common source of medical radiation for all ages is CT. CT offers the ability to acquire high-quality volumetric imaging datasets in seconds. For many years, adult parameters for CT settings were used for children, which led to dosages for children much higher than the dosage for adults. This occurs because lower energy x-rays that would have been absorbed in the near field in an adult pass into the entire child, with relatively greater organ irradiation for the same exposure. When comparing dosages given to newborns and adults during CT scanning of the head, with the same parameters in both groups, the dosage given to newborns can be four times that of the dosage given to adults; with abdominal imaging, the dosage is increased by 60%. It is the role of the radiologist and technologist, with the help of a medical physicist, to develop and monitor protocols that tailor the examination to the individual indication and for the variabilities in sizes found in the pediatric population.

Modern CT scanners have many tools to help administer the appropriate amount of radiation dose to a pediatric patient and acquire the necessary diagnostic image quality from the imaging examination. Radiologists should work in conjunction with medical physicists and vendor supplied application specialists to tailor specific examination protocols to the pediatric patient population by establishing appropriate scan parameters such as the kilovoltage (kV). Scan range should be limited to only the necessary area for diagnosis (e.g., a chest only scan should begin at the lung apices and extend to no more than a little below the lowest lung base). Multiphasic scanning should be only obtained when justified; for example, in pediatric abdominopelvic CT multiple phases should be necessary in no more than approximately 5% of examinations.

Technologic advances for modern CT scanners are using reconstruction algorithms, such as statistical iterative reconstruction (IR), model-based IR, and deep learning reconstruction (DLR), as well as photon counting technology. These algorithms have been shown to allow the reduction of radiation dose for IR algorithms by 15–30% and DLR algorithms by 44–83% in some patient populations while maintaining equivalent diagnostic confidence to the pre-dose reduced image datasets. Other practical steps to reduce pediatric population radiation dose include replacing older CT scanners with technologically advanced scanners; monitoring institution dose values, which can be compared with available benchmarks, such as **diagnostic reference levels (DRLs)**; and performing only examinations that are justified. Advances in technology and attention to proper performance of examinations have contributed to overall reductions in pediatric patient population doses by >50% during the past two decades.

RADIATION THERAPY: ACUTE AND LATE EFFECTS

Radiation therapy uses high doses to kill malignant cells. The sensitivity of normal cells is quite close to that of malignant cells, and to achieve significant cure rates, radiation oncologists must accept a given percentage of serious complications (5–10%). Radiation causes tissue loss plus injury to the underlying vasculature. The vascular change may be progressive, leading to arteriopathy and fibrosis and irreparable injury, in turn leading to further tissue loss.

The acute effects of therapy (occurring less than 3 months after therapy begins) are usually related to the area of the body being irradiated (except fatigue, which can begin during this time period). These acute effects include radiation-induced pneumonitis, dermatitis, mucositis and esophagitis, cerebral edema, and swelling of the organ irradiated. There may be changes in bowel movement patterns. Of these, one of the most severe acute reactions is pneumonitis. It can manifest within

Table 758.7 Late Effects of Radiation Therapy in Children Treated for Cancer

SYSTEM	LATE EFFECT	DOSE (GY)
Musculoskeletal	Muscular hypoplasia	>20
	Scoliosis, kyphosis, lordosis	>20
	Osteocartilaginous exostosis/ osteochondroma	>12
Neuroendocrine (cranial or cranial spinal)	Impaired growth hormone	>15
	Adrenocorticotrophic hormone deficiency	>30
	Thyrotropin-releasing deficiency	>40
	Precocious puberty (females mostly)	>18
Gonad failure	Gonadotropin deficiency	>30
	Ovarian failure	>10
	Testicular failure	>3
Central nervous system dysfunction	Structured changes	>18
	Cognitive changes/Processing speed	Variable
Other	Pulmonary fibrosis	>15
	Nephropathy	>20
	Liver disease	>30 (>60% liver volume)
	Cerebral arteriopathy	>50
	Eye impairment (cataracts, legally blind, double vision, dry eyes)	>5
	Hearing loss	>30
	Dental abnormalities	>20
	Cardiac impairment	>30

24 hours of irradiation when there is an exudation of proteinaceous material into the alveoli and interalveolar edema. Most often, however, radiation pneumonitis begins 2-6 months after the beginning of radiation with a clinical presentation of fever, cough, congestion, and pruritic pain. The late effects of therapy (beginning more than 3 months after therapy) are numerous (Table 758.7). The most common are abnormalities of musculoskeletal development, endocrine/reproductive function, pulmonary function, neurocognition, hearing loss, cardiac function, eye impairment, and dental abnormalities.

As of 2020, there are more than 500,000 childhood cancer survivors in the United States. The risk of developing a second cancer among cancer survivors is over fivefold higher than the general population. Second cancers account for 2.3% of all cancers in children; this reflects an overall standard incidence rate (SIR) of 5.5%. Primary malignancies with the highest cumulative incidence of a second neoplasm in the order of frequency are retinoblastoma (10.4%), CNS cancers (7.4%), cancers of bone (7.2%), soft tissue sarcomas (6.5%), hepatic cancer (5.9%), and neuroblastoma (5.9%) [data from the U.S. Surveillance, Epidemiology, and End Results program (SEER)]. Table 758.8 relates second cancers to primary cancer and latency period. Almost 70% of the second neoplasms are in the field of the original irradiation. Radiation therapy increases the risk of second cancers in a dose-dependent manner for nongenetic neoplasms.

The exact complications depend on the location of the treatment field. In children, because of the location of many childhood tumors, the normal brain is commonly in the treatment field. Standard irradiation of the brain in children results in cortical atrophy in more than half of patients who receive 20-60 Gy; 26% are left with white matter changes (leukoencephalopathy) and 8% with calcifications. The younger the child is at the time of irradiation, the greater the atrophy. Some patients also demonstrate mineralizing microangiopathy. Radiation-induced changes of the brain are potentiated by methotrexate administered before, during, or after radiation therapy.

Cerebral necrosis is a serious complication of radiation-induced vascular disease. It is usually diagnosed 1-5 years after irradiation but can occur up to a decade later. Brain necrosis may manifest as headache, increased intracranial pressure, seizures, sensory deficits, and psychotic changes.

Spinal cord irradiation may result in **radiation myelitis**, which may be either transient or permanent. Acute transient myelitis often appears 2-4 months after irradiation. Patients with myelitis usually present with **Lhermitte sign**, a sensation of little electrical shocks radiating down the spine into the arms and legs, occurring with neck flexion or other movements that stretch the spinal cord. Reversal of transient myelopathy usually occurs between 8 and 40 weeks and does not necessarily progress to delayed necrosis.

Delayed myelopathy occurs after a mean latent period of 20 months but can occur earlier if the total dose or the dose per fraction is high. It usually manifests as discontinuous deterioration and is irreversible. In the cervical and thoracic regions, sensory dissociation develops, followed by spastic and then flaccid paresis. In the lumbar cord, flaccid paresis is dominant. The mortality for high thoracic and cervical lesions reaches 70% with death commonly being due to pneumonia and urinary tract infections.

CNS irradiation may affect growth by compromising function of the pituitary-hypothalamic axis and leading to diminishing growth hormone production and release. Non-growth hormone tropins may also be affected by CNS irradiation, leading to gonadotropin deficiency or precocious puberty. Central hypothyroidism can also develop. CNS irradiation also compromises bone mineral deposition both locally (in the radiation field) and systemically.

Irradiation has other effects specific to children. Scoliosis and hypoplasia of bones may occur if fractionated treatment schemes exceed 4,000 rad. Fractionated doses higher than 25 Gy can result in slipped capital femoral epiphyses. An increase in the incidence of benign osteochondromas has been reported after childhood irradiation. Chest wall irradiation in females (besides causing breast cancer) may impair breast development and/or cause fibrosis and atrophy of breast tissue.

WHOLE BODY IRRADIATION

Uncontrolled Large- or Small-Scale Exposure to Radiation

Large-scale exposure to radiation can occur in an event of nuclear accidents, war, or terrorist attacks (Fig. 758.3). Radiation as well as explosive and thermal injury need to be considered.

Clinical Manifestations

A large single exposure of penetrating radiation can result in **acute radiation syndrome** (Table 758.9). The signs and symptoms of this syndrome result from damage to major organ systems that have different levels of radiation sensitivity, modulated by the rate at which the radiation exposure occurred. Delivery of 1 Gy in 1 minute would be symptomatic, but delivery of 1 cGy/day for 100 days would not be symptomatic.

The **hematopoietic syndrome** results from acute whole body doses >0.7-10 Gy; where healthy patients will almost always recover from doses <2 Gy. The dose that kills 50% of a population in 60 days is approximately 3.5-4.5 Gy, where effective blood transfusions and antibiotics may extend the dose range to 5-8 Gy. Doses >8 Gy almost always lead to hematopoietic-induced death. Symptoms of exposure consist of a *prodromal phase* during which the patient will experience nausea/vomiting, diarrhea, and fatigue within the first 12 hours, with symptoms usually lasting up to 48 hours. A *latent period* of 2-3 weeks, during which patients may feel quite well, follows. Although patients are asymptomatic, bone marrow impairment has occurred. The most obvious laboratory finding is lymphocyte depression (Table 758.10). Maximal bone marrow depression occurs approximately 30 days after exposure, when hemorrhage and infection can be major problems. If the bone marrow was not completely eradicated, a *recovery phase* then ensues. This radiation effect is similar to what occurs when whole body irradiation (given as 12 Gy in two treatments) is used

Table 758.8 Second Cancers and Their Relationship with Primary Cancers

SECOND CANCERS	PRIMARY CANCERS	LATENCY (MEDIAN IN YEARS)	RISK FACTORS
Brain tumors	ALL; brain tumors; HD	9-10	Radiation; younger age
Myelodysplastic syndromes/ acute myelogenous leukemia	ALL; HD; bone tumors	3-5	Topoisomerase II inhibitors; alkylating agents
Breast cancer	HD; bone tumors; soft tissue sarcomas; ALL; brain tumors; Wilms tumors; NHL	15-20	Radiation; female gender
Thyroid cancer	ALL; HD; neuroblastoma; soft tissue sarcomas; bone tumors; NHL	13-15	Radiation; younger age; female gender
Bone tumors	Retinoblastoma (heritable); other bone tumors; Ewing sarcoma; soft tissue sarcomas; ALL	9-10	Radiation; alkylating agents; removal of the spleen
Soft tissue sarcomas	Retinoblastoma (heritable); soft tissue sarcomas; HD; Wilms tumors; bone tumors; ALL	10-11	Radiation; younger age; anthracyclines

ALL, Acute lymphocytic leukemia; HD, Hodgkin disease; NHL, non-Hodgkin lymphoma.

From Bhatia S, Sklar S. Second cancers in survivors of childhood cancer. *Nat Rev Cancer*. 2002;2:124-132.

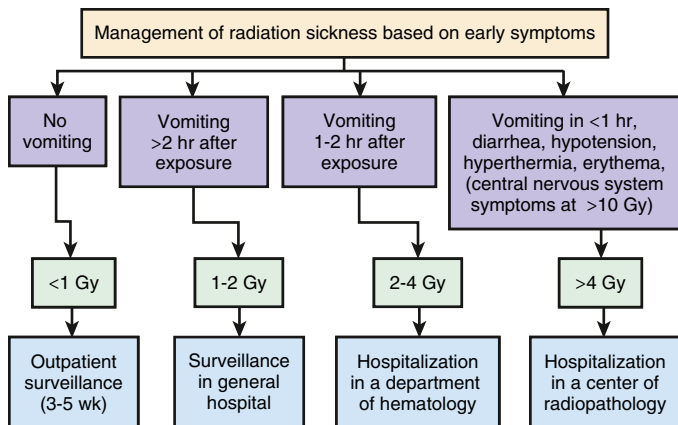


Fig. 758.3 Management algorithm for radiation sickness at different levels of medical care, depending on the appearance of early symptoms and the estimated radiation dose to the whole body. (From Turai I, Veress K, Günel B, et al. Medical response to radiation incidents and radionuclear threats. *BMJ*. 2004;328:568-572.)

to obliterate the bone marrow in children with leukemia before bone marrow transplantation.

The **gastrointestinal (GI) syndrome** occurs from acute whole body doses >6-10 Gy. Prompt onset of nausea, vomiting, and diarrhea follows. There is a latent period of approximately 1 week if intense medical treatment is administered. Following the latent period, recurrence of GI symptoms, sepsis, and electrolyte imbalance occurs, which results in death at about 2 weeks postexposure from GI tract and bone marrow destruction.

At dose levels exceeding 20-50 Gy, the **cardiovascular/CNS syndrome** predominates. Nausea, vomiting, prostration, hypotension, ataxia, and convulsions are almost immediate. The latent period occurs between 4 and 6 hours postexposure followed by severe manifestation of the initial illness stage leading to eventual coma and death within 2-3 days.

Treatment

For the hematopoietic and GI syndromes, treatment is supportive involving transfusions and Neupogen (filgrastim), Neulasta (pegfilgrastim) and other hematopoietic growth factors, fluids, and, if infected antibiotics and antiviral agents. Stem cell (bone marrow) transplantation may be needed in severe cases.

Localized Irradiation Clinical Manifestations

Because localized exposure involves a small amount of tissue, systemic manifestations may be less severe, and patients may survive even if locally absorbed doses are very high. The hand is the most common site for accidental localized irradiation injuries, usually as a result of picking up or playing with lost radiation sources. The second most common accidental site is the thigh and buttocks, predominantly from placing unsuspected highly radioactive sources in the pockets.

Table 758.11 lists the skin changes that occur after a single acute, localized irradiation. As opposed to other forms of thermal burns, signs of irradiation appear a period of days *after* the exposure. Vascular insufficiency may appear months to years later and cause ulcerations or necrosis in formerly healed areas. The penetrability of the radiation is an important factor in the outcome of local radiation injury. Beta particles from heavy radiation fallout can cause superficial skin burns because they have low penetrability.

Some tissues that may receive localized radiation exposure are relatively radiosensitive. **Cataract formation** (see Chapter 668) may occur with single γ -ray exposures in the range of <1 Gy. Such cataracts usually take from 2 months to several years to develop. **Oligospermia** may take up to 2 months to develop. Transient infertility in men may result from doses as low as 0.15 Gy, and permanent sterility may occur in males at dose levels between 3 and 6 Gy.

Treatment

Skin therapy is directed at prevention of infections. Treatment of localized injuries usually involves class II to III topical steroids and plastic surgery and grafting, if the radiation exposure was not deeply penetrating (see Chapter 89). The nature of the surgery depends on the dose at various depths in tissue and the location of the lesion. The full expression of radiation injury often is not apparent for 1-2 years due to slow arteriolar narrowing that can cause delayed necrosis. After relatively penetrating radiation, amputation may be necessary because of obliterative changes in small vessels.

INTERNAL CONTAMINATION

Epidemiology

Accidents involving internal contamination are rare and are usually the result of misadministration in hospital settings or voluntary ingestion of unsuspected contaminated radioactive materials. Other possible causes of internal contamination of children include ingestion of breast milk from mothers who have had diagnostic nuclear medicine scans and radiation exposure when a parent or sibling receives a therapeutic dose of iodine-131.

Table 758.9 Acute Radiation Syndrome

SYNDROME	DOSE*	PRODROMAL STAGE	LATENT STAGE	MANIFEST ILLNESS STAGE	RECOVERY
Hematopoietic (bone marrow)	>0.7 Gy (>70 rads) (<i>mild symptoms may occur as low as 0.3 Gy or 30 rads</i>)	<ul style="list-style-type: none"> Symptoms are anorexia, nausea and vomiting Onset occurs 1 hr to 2 days after exposure Stage lasts for minutes to days 	<ul style="list-style-type: none"> Stem cells in bone marrow are dying, although patient may appear and feel well Stage lasts 1-6 wk 	<ul style="list-style-type: none"> Symptoms are anorexia, fever, and malaise Drop in all blood cell counts occurs for several weeks Primary cause of death is infection and hemorrhage Survival decreases with increasing dose Most deaths occur within a few months after exposure 	<ul style="list-style-type: none"> In most cases, bone marrow cells will begin to repopulate the marrow There should be full recovery for a large percentage of individuals from a few weeks up to 2 yr after exposure Death may occur in some individuals at 1.2 Gy (120 rads) The LD_{50/60}[†] is about 2.5-5 Gy (250-500 rads)
Gastrointestinal (GI)	>10 Gy (>1,000 rads) (<i>some symptoms may occur as low as 6 Gy or 600 rads</i>)	<ul style="list-style-type: none"> Symptoms are anorexia, severe nausea, vomiting, cramps, and diarrhea Onset occurs within a few hours after exposure Stage lasts about 2 days 	<ul style="list-style-type: none"> Stem cells in bone marrow and cells lining GI tract are dying, although patient may appear and feel well Stage lasts <1 wk 	<ul style="list-style-type: none"> Symptoms are malaise, anorexia, severe diarrhea, fever, dehydration, and electrolyte imbalance Death is due to infection, dehydration, and electrolyte imbalance Death occurs within 2 wk of exposure 	<ul style="list-style-type: none"> The LD₁₀₀[‡] is about 10 Gy (1,000 rads)
Cardiovascular (CV)/central nervous system (CNS)	>50 Gy (5,000 rads) (<i>some symptoms may occur as low as 20 Gy or 2,000 rads</i>)	<ul style="list-style-type: none"> Symptoms are extreme nervousness and confusion; severe nausea, vomiting, and watery diarrhea; loss of consciousness; and burning sensations of the skin Onset occurs within minutes of exposure Stage lasts for minutes to hours 	<ul style="list-style-type: none"> Patient may return to partial functionality Stage may last for hours but often is less 	<ul style="list-style-type: none"> Symptoms are return of watery diarrhea, convulsions, and coma Onset occurs 5-6 hr after exposure Death occurs within 3 days of exposure 	<ul style="list-style-type: none"> No recovery is expected

*The absorbed doses quoted here are "gamma equivalent" values. Neutrons or protons generally produce the same effects as γ -, β -, or x-rays but at lower doses. If the patient has been exposed to neutrons or protons, consult radiation experts on how to interpret the dose.

[†]The LD_{50/60} is the dose necessary to kill 50% of the exposed population in 60 days.

[‡]The LD₁₀₀ is the dose necessary to kill 100% of the exposed population.

From Centers for Disease Control and Prevention. Acute radiation syndrome: a fact sheet for clinicians. Table 1. <https://www.cdc.gov/nceh/radiation/emergencies/arsphysicianfactsheet.htm>.

Table 758.10 Expected Outcome Based on Absolute Lymphocyte Count After Acute Penetrating Whole Body Irradiation

MINIMAL LYMPHOCYTE COUNT WITHIN FIRST 48 HR AFTER EXPOSURE	PROGNOSIS
1,000-3,000 (normal range)	No significant injury
1,000-1,500	Significant but probably nonlethal injury, good prognosis
500-1,000	Severe injury, fair prognosis
100-500	Very severe injury, poor prognosis
<100	Lethal without compatible bone marrow donor

Clinical Manifestations

The hazards from internal contamination depend on the nature of both the radionuclide (particularly in terms of its solubility in water, half-life, biologic half-life, and radioactive emission) and the chemical compound.

Treatment

The most effective treatment requires knowledge of both the radionuclide and the chemical form. Treatment must be instituted quickly to be effective (Table 758.12). **Removal treatment** involves cleaning a contaminated wound and performing gastric lavage or administration of cathartics in the case of ingestion. Administration of alginate-containing antacids (e.g., Gaviscon) also usually helps in removal by decreasing absorption in the GI tract. An example of **blocking therapy** is the administration of potassium iodine or other stable iodine-containing compounds to patients with known internal contamination with radioactive iodine. The stable iodine effectively blocks the thyroid, although its effectiveness decreases rapidly as time elapses after the contamination. The recommended dose of potassium iodine is 16 mg

for neonates (up to 1 month of age); 32 mg for children ages 1 month to 3 years; 65 mg for children ages 3-18 years (if less than 70 kg), and 130 mg for adults and adolescents >70 kg. Each dose protects for only 1 day. **Dilution therapy** is used in cases of tritium (radioactive hydrogen as water) contamination. Forcing fluids promotes excretion. Cases of internal contamination with transuranic elements (americium and

plutonium) may require **chelation therapy** with calcium diethylenetriamine pentaacetate.

Prussian blue is a drug approved by the FDA for patients with internal contamination with cesium or thallium. It can speed fecal elimination of radioactive cesium from the body. It acts by intercepting the cesium coming into the gut from the bile. Prussian blue prevents

Table 758.11 Skin Changes After a Single, Acute, Localized Radiation Exposure

APPROXIMATE THRESHOLD (GY)	CHANGE
2-4	Primary erythema within hours of exposure (appears more quickly after larger doses)
3	Second phase erythema (develops during the manifestation phase of local radiation injury); appears 14-21 days after exposure
3	Temporary epilation (14-18 days after exposure)
7	Definitive epilation (25-30 days after exposure)
10	Dry desquamation (20-28 days after exposure)
15	Moist desquamation, possible ulceration (15-25 days after exposure)
25	Desquamation with blistering, ulceration, and necrosis (>21 days after exposure)

Data from the International Atomic Energy Agency. *Safety Reports Series, No. 101: Medical management of radiation injuries*, 2020. https://www-pub.iaea.org/MTCD/Publications/PDF/PUB1891_web.pdf

Table 758.12 Decontamination of Common Elements in Industrial and Medical Accidents

ELEMENT	EMISSIONS	CRITICAL ORGAN	EFFECTIVE $T_{1/2}$ *	DECONTAMINATION
Cesium-137	Beta, gamma	Total body	70 days	Prussian blue (Radiogardase) 3 g po 3 times/day (adults and adolescents); 1 g po 3 times/day (2-12 yr old); consider lavage and purgatives
Cobalt-60	Beta, gamma	Total body	10 days	Lavage, purgatives, penicillamine
Iodine-125, iodine-131	Beta, gamma	Thyroid	Iodine-125, 42 days; iodine-131, 8 days	Potassium iodide: 0-1 mo, 16 mg/day > 1 mo to 3 yr, 32 mg/day > 3 mo to 3 yr, 32 mg/day > 3 to 12 yr and < 70 kg, 65 mg/day adults or ≥ 70 kg, 130 mg/day; consider lavage
Iridium-192	Beta, gamma	Lung	74 days	Lavage for large quantities
Technetium-99m	Gamma	Total body	5 hours	Potassium perchlorate to reduce thyroid dose
Tritium-3	Beta	Total body	12 days	Forced fluids
Uranium-235, uranium-238	Alpha	Kidney, [†] bone, liver, lung	Can be permanent if in bone	Bicarbonate to alkalinize the urine

*Effective $t_{1/2}$ combines radioactive and chemical properties and rates of elimination without decontamination efforts.

[†]The kidney is most vulnerable to large amounts of uranium because of the chemical properties of this heavy metal. Uranium can ultimately be deposited in bone.

po, Per os; qd, once per day.

Data from U.S. Food and Drug Administration. Prussian blue, Radiogardase, package insert. Available at: http://www.fda.gov/cder/drug/infopage/prussian_blue/default.htm; U.S.

Food and Drug Administration. Guidance: Potassium iodide as a thyroid blocking agent in radiation emergencies. Available at: <http://www.fda.gov/cder/guidance/4825fnl.htm>;

Management of Persons Accidentally Contaminated with Radionuclides. NCRP Report No. 65. Bethesda, MD: National Council on Radiation Protection and Measurements; 1980; and Jarrett D, ed. *Medical Management of Radiation Casualties: Handbook*. 2nd ed. AFRRRI Special Publication 03-1. Bethesda, MD: Armed Forces Radiobiology Research Institute; 2003. Available at: <http://www.afrrri.usuhs.mil>.

From Linder JA, Linder LS: Radiation accident—dispersed exposure. In Ciotto GR (ed). *Ciotto's Disaster Medicine*, 2nd ed. Philadelphia: Elsevier, 2016. Table 108-1.

Table 758.13 Nuclear Regulatory Commission Guidelines on Breastfeeding During the Period During a Nuclear Medicine Examination

RADIOPHARMACEUTICAL	BREASTFEEDING CESSATION
^{11}C , ^{13}N , ^{15}O , ^{82}Rb	None
^{18}F -labeled	12 hr
^{68}Ga -labeled	12 hr
$^{99\text{m}}\text{Tc}$ -labeled	24 hr
^{123}I Sodium iodide	7 days
^{111}In -leukocytes	7 days
$^{99\text{m}}\text{Tc}$ labeled	No interruption*
^{201}Tl chloride	14 days
^{67}Ga and ^{89}Zr	28 days
^{177}Lu , diagnostic	35 days
^{131}I -NaI	Stop breastfeeding
^{177}Lu , therapeutic	Stop breastfeeding
^{223}Ra and all alpha emitters	Stop breastfeeding

*The guideline for $^{99\text{m}}\text{Tc}$ compounds is a 24-hr interruption for >1110 MBq administered, 12 hr for 444–1110 MBq, and no interruption for <444 MBq administered. The normally administered activity is below activities that require any interruption.

From Dilsizian V, Metter D, Palestro C, Zanaonico P. The Advisory Committee on Medical Uses of Isotopes (ACMUI) Sub-Committee on Nursing Mother Guidelines for the Medical Administration of Radioactive Materials, 2018, p. 12. <https://www.nrc.gov/docs/ML1803/ML18033B034.pdf>

cesium from being absorbed again from the gut. Prussian blue can be given days after ingestion, unlike potassium iodine, which must be given initially in the first 12–24 hours after exposure.

In the case of breastfeeding after a nuclear medicine procedure, two primary concerns are considered: (1) the internal dose to the infant passed through the excreted milk and (2) the dose from the radiopharmaceutical absorption in the female breast that exposes the infant to external γ -rays while undergoing decay. Most imaging radiopharmaceuticals are below the activity calculated to expose the infant to a dose of 1 mSv via either internal or external mode of exposure. Table 758.13 provides a comprehensive list of radiopharmaceuticals and the recommended period for breastfeeding cessation by the U.S. Nuclear Regulatory Commission. In the case of delaying breastfeeding, pumped milk may be stored for the times indicated in Table 758.13, after which they will be safe to feed the infant.

EXTERNAL CONTAMINATION

The presence of external radioactive contamination on a patient's skin is not an immediate medical emergency. Management involves removing and controlling the spread of radioactive materials. If a patient has suspected surface contamination and no physical injuries, decontamination can be performed relatively easily. If substantial physical trauma or other life-threatening injuries are combined with external contamination, surface decontamination should proceed only after the patient has been stabilized physiologically. In many accident situations, essential medical care may be delayed inappropriately by hospital emergency staff because of fear of radiation or spread of contamination in the hospital. After a radiation accident, triaging of patients is critical and is based on exposure and symptoms (see Fig. 758.3).

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Chapter 759

Chemical Pollutants

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More than 85,000 new synthetic chemicals have been developed in the past 75 years. These chemicals are used in millions of products, ranging from food packaging to clothing, building materials, motor fuels, cleaning products, cosmetics, medical products, toys, and baby bottles.

Synthetic chemicals are widely disseminated in the environment. The Toxic Release Inventory of the U.S. Environmental Protection Agency (EPA) reports that in 2021, of 29.3 billion pounds of production-related chemical waste managed, nearly 3.3 billion pounds (11%) were discharged into air, water, and land in the United States. These chemicals are detected today in even the most remote corners of the planet, such as the polar icecaps and in the ocean depths.

All people are at daily risk of exposure to synthetic chemicals, and children are especially likely to be exposed to the nearly 3,000 chemicals that are produced in amounts of 1 million pounds or more per year, designated by the EPA as high-production-volume chemicals. Biomonitoring data on blood and urine levels of more than 400 high-production-volume chemicals are obtained annually by the Centers for Disease Control and Prevention in a sample of the U.S. population through the National Health and Nutrition Examination Survey (NHANES). These data document that most Americans, including children, are routinely exposed to scores of synthetic chemicals; exposure often falls disproportionately on poor children and children of color. Examples are wide ranging and include lead, air pollutants, endocrine disrupting chemicals like phthalates, and many others.

Toxic chemicals are exported in ever-increasing quantities to the world's poorer countries as these countries undergo industrial development. Environmental safeguards in those countries are typically not as stringent as in high-income countries, and the potential for serious exposure is therefore high. Examples of tragedies that have resulted from the movement of toxic chemicals to low- and middle-income countries include the Bhopal disaster in India, in which hundreds were killed and thousands injured by methylisocyanate gas released by an explosion in a pesticide production facility, and the ongoing export each year of more than 2 million tons of newly produced asbestos to the world's poorest countries, where this asbestos is responsible for nearly 200,000 deaths annually from asbestosis, lung cancer, and malignant mesothelioma.

SYNTHETIC CHEMICALS AND HUMAN HEALTH

A recurrent pattern is that chemicals are brought to market with great enthusiasm, presumed harmless, and undergo little or no premarket safety testing. Then years or decades later, after they had come into wide use, the chemicals were found to be harmful to children's health.

Often the first cases of disease caused by these chemicals are clinically severe, but as time passes, evidence of widespread subclinical toxicity comes to light.

Classic historical examples of epidemics caused by inadequately tested toxic chemicals include the following:

- **Tetraethyl lead:** This was added to gasoline in the United States from the early 1920s until 1980. It was responsible for widespread lead poisoning, initially evident as an epidemic of acute toxicity manifesting as encephalopathy, seizures, and even death, but later demonstrated to have caused subclinical neurotoxicity and reduction in IQ across two generations of U.S. children (see Chapter 761).
- **Dichlorodiphenyltrichloroethane (DDT):** This pesticide very nearly led to extinction of the osprey and the American bald eagle and more recently has been linked to increased risk for breast cancer among women exposed decades ago in utero.

- **Polychlorinated biphenyls (PCBs):** These are highly persistent pollutants banned from production in the United States in 1977, which continue today to contaminate major lakes and rivers and have been found also to be responsible for loss of IQ and disruption of behavior in children.
 - **Chlorofluorocarbons:** These destroy the ozone.
- Other examples of synthetic chemicals that came into wide use with little assessment of their safety and are now recognized as causing harm to children's health include the following:
- **Phthalates:** These chemicals are added to plastics, cosmetics, medical equipment like intravenous tubing, and common household products that are now linked to increased risk for reproductive abnormalities in male infants and heightened risk of behavioral abnormalities such as attention-deficit/hyperactivity disorder (see Chapter 50).
 - **Polybrominated diphenyl ethers:** These are used as flame retardants in carpets, furniture, and electronic equipment and are now linked to persistent loss of intelligence and disruption of behavior in children.
 - **Bisphenol A:** A plastics chemical linked to neurodevelopmental disorders.
- These chemicals are all produced in volumes of millions of tons per year, are widely disseminated in the environment, and are detectable in the bodies of nearly all Americans. Only decades after their introduction are these chemicals' risks to children beginning to be recognized.

CHILDREN'S UNIQUE SUSCEPTIBILITY TO SYNTHETIC CHEMICALS

The health effects of synthetic chemicals are especially serious when exposure occurs during windows of vulnerability in early life such as during pregnancy, infancy, and early childhood. Children are highly vulnerable to chemical pollutants for several reasons:

1. Children have proportionally greater exposure to environmental pollutants than adults. Because they drink more water, eat more food, and breathe more air per kilogram of body weight, children are more heavily exposed to pollutants in water, food, and air. Children's hand-to-mouth behavior and their play close to the ground further magnify their exposures.
2. Children's metabolic pathways, especially in the first few months after birth, are immature. Although in some instances children are better able than adults to cope with environmental toxicants because they cannot metabolize these chemicals to their active forms, more commonly children are not as able as adults to detoxify and excrete chemical pollutants.
3. Infants and children are growing and developing, and their complex, fast-moving, and highly choreographed developmental processes are exquisitely sensitive to disruption by chemical pollutants. Exposures to even minute doses of toxic chemicals during windows of vulnerability in early development have been shown to cause a wide array of diseases in childhood and to increase risk for chronic disease and disability lifelong (Table 759.1).
4. Because children have many future years of life, they have time for the development of multistage chronic diseases that may be triggered by early exposures.

SAFETY TESTING OF SYNTHETIC CHEMICALS

Legally mandated testing of chemicals for safety and toxicity coupled with strict controls on dangerous chemicals are the linchpins of chemical safety. Strong chemical safety policies are needed to protect children against disease and death caused by chemicals. A fundamental problem in environmental pediatrics today is that chemical safety policies in many countries are weak. Only approximately 65% of high-production-volume chemicals have been tested for their safety or potential hazard to human health, and fewer than 30% have been assessed for their pediatric or developmental toxicity.

Failure to test chemicals for safety and toxicity reflects the chemical industry's unwillingness to take responsibility for the products they produce coupled with long-standing failure of the previous U.S. federal law on chemical safety, the Toxic Substances Control Act (TSCA). Only five chemicals were banned or controlled under the original TSCA law:

Table 759.1 Effects of Selected Chemical Pollutants on Infants and Children

CHEMICAL POLLUTANT	EFFECT(S)
Air pollution	Asthma, other respiratory diseases, sudden infant death syndrome
Asbestos	Mesothelioma and lung cancer
Benzene, nitrosamine, vinyl chloride, ionizing radiation	Cancer
Environmental tobacco smoke	Increased risk of sudden infant death syndrome and asthma
Ethyl alcohol	Fetal alcohol syndrome after intrauterine exposure
Lead	Neurobehavioral toxicity from low-dose exposure
Methyl mercury	Developmental neurotoxicity
Organophosphate insecticides	Developmental neurotoxicity
Per- and poly-fluoroalkyl substances (PFAS)	Increased cholesterol levels, altered liver function tests, decreased antibody response to childhood vaccines
Polychlorinated biphenyls	Developmental neurotoxicity
Polybrominated diphenyl ethers	Developmental neurotoxicity
Phthalates	Developmental neurotoxicity and reproductive impairment
Trichloroethylene	Elevated risk of leukemia after intrauterine exposure

PCBs, the ozone-destroying chlorofluorocarbons, and three known human carcinogens—dioxin, asbestos, and hexavalent chromium.

To address the problem of exposure to untested chemicals, countries have enacted stronger chemical safety legislation. In 2007, the European Union enacted the Registration, Evaluation, Authorization, and Restriction of Chemical Substances (REACH) legislation. This law places responsibility on industry to generate data on potential risks of commercial chemicals and to register this information with the European Chemical Agency in Helsinki. The European Union is using this information to craft regulations to protect children's health. Since 2009 REACH has restricted more than 1,000 toxic substances.

In June 2016, the United States passed legislation to revamp TSCA. This law—the Frank R. Lautenberg Chemical Safety for the 21st Century Act—requires the EPA to assess the safety of any new chemical before it is allowed to enter the market, to prioritize safety testing of existing chemicals, and to use a risk-based standard to evaluate chemical safety that considers only hazards to health and is blind to the costs of protective action. This law holds much promise for improving the protection of children's health against toxic chemicals, but it also includes a federal preemption clause that could inhibit state-based protective regulations. Transparency, oversight, and advocacy is critical to ensuring that the law is implemented in a timely manner that is true to the intent to prioritize children's health.

The UN Environment Programme (UNEP) is the United Nations agency responsible for chemical safety. UNEP has called for "a global commitment to the sound management of chemicals. The agency supports and tracks the progress of international agreements and treaties limiting the manufacture, environmental release and global transport of persistent pollutants, pesticides, hazardous waste, and mercury." The Strategic Approach to International Chemicals Management, a program supported by UNEP, provides a platform for coordinating international control of toxic chemicals and hazardous waste across a broad

range of stakeholders. UNEP has worked closely with the World Health Organization (WHO) to coordinate the removal of lead from gasoline in countries around the world.

SYNTHETIC CHEMICALS AND DISEASE IN CHILDREN

A large and growing body of evidence documents that toxic chemicals can cause disease, disability, and death in children. High-dose exposures can cause acute, clinically evident disease. Lower-dose exposures can cause subclinical injury (injury that is very real but detectable only through special testing), such as decreases in intelligence, shortening of attention span, reductions in fertility, and slowing of lung growth. When exposure to a neurotoxic pollutant is widespread, the resulting widespread subclinical neurotoxicity can reduce the intelligence, creativity, and economic productivity of entire societies.

Exposures to toxic chemicals in early life are linked not only to increased risks of disease in childhood, but also to increased risks of disease in later life. This recognition, termed the *developmental origins of health and disease concept*, derives from studies conducted by Barker and colleagues who found that undernutrition in utero is associated decades later with increased risks for hypertension, obesity, diabetes, and cardiovascular disease. Epigenetic programming of gene expression during windows of vulnerability in early development appears to be the underlying mechanism. Increased risks for disease in adult life have now been associated also with early-life exposures to toxic chemicals and appear to be mediated through epigenetic changes in gene expression. Among the health problems linked to toxic chemical exposures in early life are decreased cognition in adults who were exposed as children to lead, neurobehavioral disorders in children exposed to a range of developmental neurotoxicants, and cancer.

CHEMICAL POLLUTANTS OF MAJOR CONCERN

Air Pollutants

Air pollution—ambient air pollution and household air pollution—is the world's largest environmental threat to health and, according to the WHO, is responsible for an estimated 6.7 million deaths each year. The air pollutants of greatest concern for children's health are particulate matter (especially fine particulates less than 2.5 microns in aerodynamic diameter), photochemical oxidants (especially ozone), oxides of nitrogen, sulfur oxides, and carbon monoxide; these are the "criteria air pollutants" regulated by the U.S. EPA in the Clean Air Act. In the United States, approximately 60% of children live in areas that do not meet national ambient air quality standards (NAAQS), most commonly particulate matter and ozone. Globally, ambient levels of air pollutants can be magnitudes higher than the United States.

Fuel combustion is the principal source of air pollution. In high- and middle-income countries, combustion of fossil fuels—coal, oil, and gas—accounts for most air pollution. In low-income and lower middle-income countries, the major source is burning of biomass, such as wood, dung, straw, and charcoal. Coal is the single most highly polluting fossil fuel and the most important source of the greenhouse gas emissions that drive global climate change, but fixed and mobile oil and gas combustion are also major contributors. As the climate changes, wildfires are becoming more common and are further contributing to air pollution and climate change.

Elevated levels of ambient air pollutants are associated with respiratory problems in children, including decreased expiratory volume, wheezing, exacerbations of asthma, and slowed lung growth. Slowed lung growth leads to decreased lung volume and increases risk for respiratory disease in childhood, adolescence, and adult life. Long-term improvements in ambient air quality, especially reductions in levels of particulates and oxides of nitrogen, are associated with statistically and clinically significant improvements in lung growth in children, effects that appear likely to persist into adulthood and to reduce lifetime risk of pulmonary and cardiovascular disease.

Aside from the criteria air pollutants, other pollutants emitted from mobile, stationary, and area sources are considered *hazardous air pollutants* (HAPs), which are known or suspected to cause cancer, reproductive effects, or birth defects. Some common examples are metals

such as mercury (neurotoxin), asbestos (mesothelioma, lung cancer), and volatile organic compounds such as polychloroethylene (reproductive effects, cancer). Diesel exhaust is a particularly concerning source of air pollution as it contains fine and ultrafine particulates (capable of reaching alveoli and getting absorbed into bloodstream) and multiple HAPs (e.g., formaldehyde), and has been classified by the International Agency for Research on Cancer as a known human carcinogen.

The effects of household air pollution on children's health are magnified by the fact that many children spend 80–90% of their time indoors, and pollutant levels can be 2–5 times higher indoors especially in poorly ventilated spaces. In 2020, the WHO estimated that 237,000 children <5 years old died from illnesses attributable to household air pollution. Secondhand tobacco smoke (SHS) is an especially hazardous constituent of indoor air pollution and a powerful trigger for asthma (see Chapter 759.1). Household products, particularly some disinfectants, cleaners, paints, and floor finishes, have also been connected to respiratory tract irritation and increased asthma morbidity. Allergens in indoor air can contribute to respiratory problems and include cockroach, mite, mold, and cat and dog allergens.

HEALTH HAZARDS OF UNCONVENTIONAL NATURAL GAS DEVELOPMENT (FRACKING)

Unconventional natural gas development (UNGD) using high-volume horizontal hydraulic fracturing (fracking) has made possible the cost-effective extraction of natural gas from previously inaccessible underground shale deposits and has catalyzed a 16-fold increase in fracking wells in the United States between 2000 and 2020. Natural gas has surpassed coal to become the major source of electricity generation in North America.

In fracking, large volumes of water containing a mix of chemicals (whose composition is a closely guarded secret) are injected at very high pressure through deep wells into shale deposits to break apart the rock and allow release of gas. The gas is brought up to the wellhead through return pipes, collected, and sent to market. In some areas, gas and oil occur together, and the gas may be burned off (flared) at the wellhead while the more valuable oil is piped to market.

The hazards of fracking to children's health include:

- **Toxic air pollution by volatile organic compounds released from fracking wells such as benzene, ethyl-benzene, hydrogen sulfide (H₂S), n-hexane, and methane:** Benzene and ethyl-benzene are known human carcinogens, H₂S and n-hexane are neurotoxicants, and methane is a climate pollutant that contributes to greenhouse gas emissions.
- **Traffic-related air pollution resulting from the large volumes of diesel truck traffic required to bring piping, chemicals, and water to drilling operations:** Diesel exhaust contains coarse and fine particulates, polycyclic aromatic hydrocarbons (PAHs), and formaldehyde, and has been classified by the International Agency for Research on Cancer as a known human carcinogen.
- **Water pollution by toxic chemicals:** Leaks of toxic materials into waterways occur commonly during fracking operations; in addition, much of the water injected into the wells returns to the surface containing proprietary injected chemicals, along with high concentrations of salt dissolved from underground deposits and naturally occurring radioactive materials. These chemicals have been shown to contaminate both ground and surface waters. Water pollution is a particularly severe problem in arid regions with limited water supplies.
- **Radon released from underground deposits:** Radon has been shown to contaminate air near wellheads, and high concentrations of radon have been identified in shipped gas. Additional, nonchemical hazards of fracking include incessant noise, high risk of vehicular injury to children from fast-moving heavy trucks on poorly maintained rural roads, societal disruption in rural communities, and extensive degradation of the environment.

Lead

See Chapter 761.

Mercury

See Chapter 760.

Asbestos

Between 1947 and 1973, asbestos was sprayed as insulation on classroom walls and ceilings in approximately 10,000 schools in the United States. It was also widely utilized in homes as pipe insulation and in floor tiles. Subsequent deterioration or unsafe removal of this asbestos can release asbestos fibers into the air. Asbestos is not a health hazard so long as it is intact, but once it becomes airborne, it can be inhaled by children to produce adverse health effects. Asbestos is a human carcinogen, and the two principal cancers caused by asbestos are lung cancer and mesothelioma. U.S. federal law requires that all schools be inspected periodically for asbestos and that the results be made public. Removal by an EPA-certified contractor is required only when asbestos is visibly deteriorating or is within the reach of children. In most cases, placement of barriers (drywall walls or drop ceilings) provides appropriate protection.

Pesticides

Pesticides are a diverse group of chemicals used to control insects, weeds, fungi, and rodents, and are used in large quantities in agriculture, homes, schools, parks, gardens, and recreational areas. Children are at risk of exposure when pesticides are used inside or outside in places where children live, learn, and play, and in rural areas they can be exposed to pesticide drift from fields that have been sprayed. Children employed in agriculture or living in migrant farm camps are at risk of direct exposure to pesticides. Diet is another major route of exposure because children are exposed to residual levels of multiple pesticides on fruit and vegetables, especially fruits and vegetables imported from countries where pesticide use is heavier than in the United States. Children can be acutely overexposed to pesticides and clinically evident poisoning results. High-dose exposure to neurotoxic insecticides such as the organophosphate and carbamate pesticides can cause acute neurotoxicity. Both classes of pesticides act through inhibition of acetylcholinesterase and are responsible for the largest number of acute poisoning cases. Symptoms include meiosis, excess salivation, abdominal cramping, vomiting, diarrhea, and muscle fasciculation. In severe cases, the child may experience loss of consciousness, cardiac arrhythmias, and death by respiratory arrest. The war gas sarin is an organophosphate. See [Chapter 94](#) for treatment of poisoning from drugs, chemicals, and plants.

Pesticides can also cause a range of chronic toxic effects that include polyneuropathy and central nervous system (CNS) dysfunction (organophosphates), hormonal disruption and reproductive impairment (DDT, kepone, dibromochloropropane), cancer (aldrin, dieldrin, chlorophenoxy herbicides [2,4,5-T]), and pulmonary fibrosis (paraquat).

Prenatal exposure to the organophosphate pesticide **chlorpyrifos** at levels that produce no evident toxicity in pregnant women has been associated with neurodevelopmental disability in children with reduced cognitive function (lowered IQ), disordered executive function, and functional and anatomic changes in the brain discernible by functional magnetic resonance imaging (fMRI).

Two classes of pesticides of concern are synthetic herbicides and the neonicotinoid insecticides. Herbicides account for about 48% of total pesticide use, and their application is increasing. A major use of herbicides is in production of *genetically modified (GM) food crops*, mainly corn and soybeans that are engineered to be tolerant to **glyphosate (Roundup)**, the most used herbicide worldwide. Herbicides can be sprayed on herbicide-resistant crops throughout the growing season, and glyphosate-resistant, “Roundup-Ready,” GM crops account for more than 90% of all corn and soybeans planted in the United States.

Studies of agricultural workers exposed occupationally to glyphosate and other herbicides have found evidence for increased incidence of non-Hodgkin lymphoma. On the basis of these studies and convergent results from toxicologic studies, the International Agency for Research on Cancer has determined that glyphosate is a “probable human carcinogen.” Measurable levels of glyphosate metabolites are commonly detected in the urine of Americans.

The **neonicotinoids** are a class of neurotoxic pesticides developed in the 1980s to replace the organophosphates and carbamates. Use

of neonicotinoids rose dramatically in the early 2000s, and the neonicotinoid insecticide, imidacloprid, is one of the most widely used insecticides in the world. A growing body of evidence indicates that neonicotinoids are toxic to bees and other pollinators at concentrations found currently in agricultural areas, and neonicotinoids are suspected of contributing to bee colony collapse disorder. In 2020, the EPA proposed a number of restrictions and precautions for neonicotinoid use. More than a dozen states have also introduced legislation limiting neonicotinoids, and several European countries have banned or severely restricted their use. Almost no information is available on the possible developmental or pediatric toxicity of the neonicotinoids. This is another example of a new pesticide in widespread use without prior testing for health impacts on children.

Children's exposures to pesticides can be reduced by minimizing applications to lawns, gardens, schools, and playgrounds; adapting techniques of integrated pest management; and reducing pesticide applications to food crops. Pediatricians and parents can look to resources including the National Pesticide Information Center (NPIC) and the EPA for guidance on integrated pest management and safer use of pesticides in and around the home. Consumption of organic produce has been shown to dramatically reduce pesticide exposure in school-age children. Families can choose organic produce when available and cost-competitive but should not avoid a diet rich in fruits and vegetables if organic options are not feasible.

Persistent Organic Pollutants: Per- and Poly-fluoroalkyl Substances and Chlorinated Hydrocarbons

Per- and Poly-fluoroalkyl Substances. Per- and poly-fluoroalkyl substances (PFAS) are a group of synthetic chemicals that have been used in industrial processes and consumer products because they are resistant to water and heat, and do not break down in the environment. In addition, they can move through soil into drinking water sources and can build up in fish and wildlife (bioaccumulate). They may make clothing stain resistant and also reduce friction. PFAS are also known as “forever chemicals” due to their persistence in the environment, as their strong carbon-fluorine chain is resistant to degradation. NHANES has documented universal exposure to some PFAS due to their ubiquity in consumer products (e.g., nonstick pans, take-out food containers, water-resistant textiles) and the food chain. PFAS have also been detected in drinking water sources (both municipal systems and private wells) across the United States. In March 2023, the EPA proposed a draft of enforceable maximum contaminant levels (MCLs) for six different PFAS chemicals in public drinking water systems; the final regulations are expected by the end of 2023. Several states have enacted their own MCLs for various PFAS compounds; these state MCLs will have to become at least as stringent as the federal MCLs (once finalized).

Ingestion of contaminated food, water, or household dust is the major route of exposure to these chemicals. PFAS can cross the placenta and enter breastmilk. The half-life in the body can be days to decades, depending on the specific PFAS compound. Epidemiologic studies suggest a link between PFAS exposure and increased cholesterol levels, altered liver function tests, decreased antibody response to childhood vaccines, increased risk of preeclampsia/high blood pressure during pregnancy, and cancer (kidney and testicular). Health outcome studies in highly exposed communities are ongoing.

Chlorinated Hydrocarbons. The chlorinated hydrocarbons are a large and diverse class of chemicals that include insecticides (DDT), plastics (polyvinyl chloride), electrical insulators (PCBs), and solvents (trichloroethylene). Highly toxic chlorinated dioxins and furans are formed during synthesis of chlorinated herbicides or as by-products of plastic combustion. These materials are widely dispersed and highly persistent in the environment. Dioxins and furans are known human carcinogens. Brominated flame retardants are used in carpets, furniture, and computers and are environmentally persistent.

The embryo, fetus, and young child are at particularly high risk of injury from halogenated hydrocarbons. All of these compounds are lipid soluble. They readily cross the placenta, and they accumulate in breast milk. Intrauterine exposure to PCBs and brominated flame retardants has been linked to persistent neurobehavioral dysfunction

in children manifested by cognitive impairment (reduced IQ), shortening of attention span, and behavioral disorders.

Consumption of fish from contaminated waters is a major source of children's exposure to PCBs. Children can be exposed in utero or through breast milk. To protect children and pregnant women against PCBs in fish, government agencies have issued advisories concerning fish consumption for certain lakes and rivers. Combustion of medical wastes containing polyvinyl chloride and the use of chlorine to bleach paper products are major preventable sources of environmental dioxin emissions and should be discouraged. Older fluorescent light ballasts that were installed decades ago in schools in the United States are another source of PCB exposure. PCB-containing ballasts should be removed from schools as soon as possible to prevent environmental contamination. Removal must be performed by trained workers.

Endocrine Disruptors

Endocrine disruptors are synthetic chemicals that mimic, block, or alter the actions of normal hormones such as estrogen, testosterone, growth hormone, insulin, and thyroid hormone. Synthetic endocrine disruptors are manufactured in volumes of millions of pounds per year. They include phthalates, bisphenol A, perchlorate, certain pesticides, brominated flame retardants, certain metals, and dioxins. These chemicals are widespread today in consumer products such as soaps, shampoos, perfumes, and plastics. They are widely disseminated in the environment and encountered in air, food, and drinking water.

Exposures to endocrine disruptors in early human development are especially hazardous. Even extremely low-dose exposures during critical early periods can lead to lasting impairments in organ function and to increased risk of disease. Reproductive effects are one consequence of early life exposures to endocrine disruptors. Endocrine disruption is implicated in the epidemiologic observations of a trend toward earlier thelarche and menarche in females, with rising rates of testicular cancer and hypospadias, and with diminishing sperm counts. Among the most clearly documented reproductive effects of early life exposures to endocrine disruptors are adenocarcinoma of the vagina in women and cryptorchidism in men whose mothers took diethylstilbestrol (DES). Another well-documented effect is shortening of the anogenital distance, a measure of in utero feminization, in infant males whose mothers had elevated exposures to phthalates during pregnancy.

Early life exposures to endocrine disruptors can have adverse effects on brain development. Prenatal exposure to low molecular weight phthalates is associated with shortening of attention span in children 4-9 years old, as well as with increased risk for autistic behaviors. Prenatal exposure to bisphenol A has also been linked to behavioral anomalies.

Endocrine disruptors have been reported to have adverse impacts on lipid metabolism and to increase the risk for obesity. Higher urinary levels of bisphenol A are associated with obesity-related outcomes, such as cardiovascular disease, in a cross-sectional analysis of NHANES 2003-2004 data in adults.

Early life exposures to endocrine disruptors, most notably DDT, are linked with increased risk for cancer. A long-term epidemiologic study of women in California found that those who were exposed in utero to high levels of DDT have increased risk for breast cancer in adult life 40-50 years later.

Environmental Carcinogens

Leukemia and brain cancer, the two most common forms of pediatric malignancy in the United States, both increased in incidence from 1972 to 2018, despite declining mortality. The cumulative increase in incidence for childhood leukemia was more than 20%, and for brain and CNS cancer more than 40%. In the same time period, testicular cancer in young men, ages 15-30 years, more than doubled in incidence and is occurring at younger ages. These increases are too rapid to be of genetic origin and are not likely due to better diagnostic capabilities. They are most probably the result of still undefined exposures in the environment. Cancer is now the second-leading cause of death in American children, surpassed only by injuries.

Children may be exposed to carcinogenic pollutants in utero or after birth. Children appear more sensitive than adults to certain chemical carcinogens and also to ionizing radiation (see Chapter 758). The potential for chemical carcinogenesis in utero was initially recognized with the discovery that clear cell adenocarcinoma of the vagina could develop in young women who were exposed in utero to DES.

Carcinogenesis may be associated with exposures in the home and community. Children of asbestos workers and children who have grown up near asbestos plants have been found to have an elevated incidence of mesothelioma. Children who attended elementary school in communities containing synthetic rubber plants have been shown to be at increased risk of leukemia as a result of their exposure to 1,3-butadiene, a known human carcinogen and a major component of synthetic rubber. Children who grow up on farms have elevated rates of leukemia; pesticides are suspected of playing an etiologic role. Intra-uterine exposure to trichloroethylene via contaminated drinking water has been associated with an increased incidence of leukemia among females living near an industrial facility and industrial waste site.

Routes of Exposure

Transplacental. Heavy metals such as lead and mercury, fat-soluble compounds such as PCBs and DDT, and endocrine disruptors such as phthalates, readily cross the placenta. They may have serious and irreversible toxic effects on the developing nervous, endocrine, and reproductive organs, even at very low levels. The American College of Obstetricians and Gynecologists have recognized the hazards of environmental exposures during pregnancy and provide detailed guidance for counseling to reduce these exposures in their 2021 statement Reducing Prenatal Exposure to Toxic Environmental Agents (Table 259.2).

Water. Approximately 200 chemicals have been detected at various levels in water supplies including contaminants like lead, solvents, pesticides, and emerging chemicals like PFAS. Lead is an especially common contaminant. Water supplies are generally lead-free at the source but can become contaminated by lead that dissolves from lead pipes and from lead-containing plumbing fixtures. Lead is especially likely to dissolve from pipes and plumbing when the water is acidic, as happened in Flint,

Table 759.2 Toxic Chemicals or Pollutants and Reported Association with Adverse Reproductive Health Outcomes*

CHEMICAL OR POLLUTANT WITH REPORTED ADVERSE ASSOCIATION	POTENTIAL HEALTH EFFECT
Antineoplastic drugs, bisphenol A (BPA), cigarette smoke, ethylene oxide, formaldehyde, polybrominated diphenyl ether (PBDE) flame retardants, solvents	Infertility and miscarriage
Air pollutants from fracking, ambient air pollutants, antineoplastic drugs, cigarette smoke, ethylene oxide, formaldehyde, perfluorochemicals (PFAS),* pesticides, phthalates, PBDEs, toluene	Preterm birth and low birthweight
Ambient air pollutants, BPA, lead, mercury, pesticides, phthalates, PBDE flame retardants, polychlorinated biphenyls (PCBs)	Neurodevelopmental impairment

*Associations noted are from reports of animal and limited human studies. Although there are reported associations between exposures and adverse obstetric outcomes, an association does not necessarily mean that the exposure is a cause of the outcome. More research is needed to understand if there is causality and, if so, at what level of exposure or use of a specific product. Modified from American College of Obstetricians and Gynecologists' Committee on Obstetric Practice. Reducing prenatal exposure to toxic environmental agents: ACOG Committee Opinion, Number 832. *Obstet Gynecol.* 2021;138(1):e40–e54. Table 1.

Michigan, in 2014. The highest levels of lead occur in water that has been standing in lead pipes overnight. It is wise therefore to run water for 2-3 minutes each morning before making up infant formula. Solvents and components of gasoline such as methyl tertiary-butyl ether and benzene are commonly encountered in groundwater. Chemical contaminants from gas drilling can contaminate water in areas where fracking is taking place. Herbicides, such as glyphosate and atrazine, are commonly found contaminants in drinking water in agricultural areas.

In the United States, the EPA regulates approximately 90 drinking water contaminants including organic chemicals, inorganic chemicals, radionuclides, and infectious agents in public water systems. The municipal water systems are responsible for ensuring that the regulated contaminants are below MCLs and will notify customers of any exceedance and steps to address the issue. Those families using private wells, however, are responsible for testing their water on a regular basis. Families with well water can be directed to the EPA private well website or their local health department for guidance on the recommended tests.

Air. Vehicular emissions are the major source of urban air pollution, notably ground-level ozone and particulate matter. Diesel exhaust is a human carcinogen. Coal-fired power plants are another major source of outdoor air pollution. In rural areas, wood smoke can contribute to air pollution. Pediatricians and parents can follow local air quality alerts that include recommendations to reduce risk especially for sensitive groups (airnow.gov). Children living in the vicinity of smelters and chemical production plants can be exposed to toxic industrial emissions such as lead, benzene, and 1,3-butadiene. Specific information about toxic air pollution release in a community can be obtained via the Toxics Release Inventory (www.epa.gov/toxics-release-inventory-tri-program).

Food. Many chemicals are intentionally added to food to improve appearance, taste, texture, or preservation, but many such chemicals have been poorly tested for potential toxicity. Residues of many pesticides are found in both raw and processed foods. Levels of pesticides are lower in organic produce than in conventionally grown fruits and vegetables. Children who consume organic produce have substantially lower urinary pesticide levels than children who eat conventional produce. Elevated levels of methylmercury can be found in large predator fish such as swordfish, shark, king mackerel, and tuna sushi; families should be encouraged to follow fish advisories. Baby foods can contain trace amounts of metals, and rice and rice-based products (especially those made of brown rice) can have inorganic arsenic.

Breast Milk. Breast milk provides many benefits to infants including protection from illness, reduction in allergic diseases like asthma, and reduced risk of obesity, among many others. Breast milk can also be a route of exposure to environmental chemicals including fat-soluble persistent organic pollutants, pesticides, and metals. In almost all situations, the benefits of breastfeeding outweigh the risks of these exposures, and numerous professional organizations support breast milk as the first choice for infant feeding. In addition, chemical regulation can further reduce unnecessary exposure through this route.

Work Clothes. Illnesses in children sometimes may be traced to contaminated dust from parents' work clothes; toxicity from lead, beryllium, dioxin, organophosphate pesticides, and asbestos has occurred. Such exposure (termed *fouling the nest*) can be prevented by providing facilities at work for changing and showering. If facilities are not available, caregivers can be advised to change clothes and shoes before returning home and wash work clothes separately from household laundry. Some work activities and hobbies that occur at home can also expose children to toxins including metals like lead and solvents.

School. Children may be exposed in schools, kindergartens, and nurseries to lead paint, molds, asbestos, tobacco smoke, pesticides, and hazardous arts and crafts materials. Substantial opportunities for prevention exist in the school environment, and pediatricians are often consulted for advice. The EPA has school related environmental health materials (www.epa.gov/schools) that can be shared with stakeholders.

Child Labor. Four to five million children and adolescents in the United States work for pay, and child labor is widespread around the world. Working children are at high risk of physical trauma and injury. They also may be exposed to a wide range of toxic chemicals, including

pesticides in agriculture and lawn work, asbestos in construction and building demolition, and benzene in pumping gasoline.

THE PHYSICIAN'S ROLE

Pediatricians have time and again played key roles in the initial recognition of diseases caused by toxic chemicals. Every pediatrician needs to be an "alert clinician" open to the possibility of discovering new diseases in children caused by hazardous exposures in the environment. In considering the origins of noninfectious disease, pediatricians should ask about the home environment, parental occupation, unusual exposures, and neighborhood factories. An environmental cause is particularly likely when several unusual cases of disease or constellations of findings occur together. Any adolescent with a traumatic injury may have been injured at work.

The history is the single most important instrument for obtaining information on environmental exposures ([Table 759.3](#)). Information about current and past exposures (including questions about work and travel to or residence in developing countries) should be sought routinely for every new patient. The age of the patient can help focus questions and provide anticipatory guidance on key exposures of concern, such as screening for common sources of lead exposure in young children. Patients with asthma should be evaluated for exposure to common allergens (mold, cockroaches, dust mites) and irritants (tobacco smoke, strong odors). Children with neurodevelopmental disorders should be assessed for pica and other behaviors that increase their risk of toxic exposures. Consider targeted environmental health history questions in patients with illness of unclear causation. Changes in patterns of exposure or new exposures may be especially important. If suspicious information is elicited, more detailed follow-up should be pursued. Referral to a state or local health department or to a Pediatric Environmental Health Specialty Unit may be indicated (<https://www.pehsu.net/>). Accurate diagnosis of an environmental cause of disease can lead to better care of sick children and prevention of disease in other children.

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759.1 Tobacco

Judith A. Groner

Cigarette smoking is the single most preventable cause of morbidity and mortality, contributing to over 480,000 annual deaths in the United States. The most common reason that people smoke is nicotine addiction, and people who start smoking at an earlier age are more likely to develop a severe addiction than those who start when they are older. In 2022, 4.5% of middle school students and 16.5% of high school students reported current tobacco use (see [Chapter 157.2](#)). While youth use a variety of tobacco products, e-cigarettes are the most common. E-cigarettes work by heating liquid to produce an aerosol that is then inhaled into the lungs; this process is called **vaping**. While the long-term health effects of vaping are still being evaluated, the 2019 E-cigarette or Vaping Use-Associated Lung Injury (EVALI) epidemic drew attention to the dangers associated with e-cigarette use (see [Chapter 450](#)).

COMPOSITION OF SECONDHAND SMOKE AND TOXICITIES

Along with active tobacco use, secondhand tobacco smoke (SHS) exposure is a very serious health hazard for both children and adults. SHS is a mixture of approximately 7,000 chemicals and is made up of the mainstream smoke exhaled by the smoker and side-stream smoke expelled from the end of a lit tobacco product. At least 70 carcinogens have been identified in SHS, along with 250 chemicals that are toxic to the CNS, immune system, heart, and liver.

SHS also contains particulate matter, which is an independent health hazard. Particulate matter is microscopic solid and liquid matter suspended in air, which can be inhaled and enter the circulation. The most studied of these include polycyclic aromatic hydrocarbons (PAHs) and the tobacco-specific nitrosamines, which are both carcinogenic. Most particulate matter in side-stream smoke is unfiltered by the smoker

Table 759.3 Clinical Tools for Incorporating Environmental Health into Patient Care

Tips for implementing a focused environmental health history:		Resources and tools for clinical practice:	
<ol style="list-style-type: none">1. Age: Patient age can help direct screening questions and anticipatory guidance on key exposures of concern, such as lead screening questions for young children. Refer to American Academy of Pediatrics (AAP) Bright Futures or the Pediatric Environmental Health Toolkit for age-specific information.2. Location: Local environmental conditions can help direct environmental guidance. For example, in rural communities with high prevalence of private wells for drinking water, families can be counseled on the importance of routine well water testing.3. Symptoms: Consider environmental exposures in the differential diagnosis. For example, carbon monoxide exposure should be on the differential for families presenting with headaches and flulike symptoms (afebrile, no cough).4. Asthma: assess for common environmental asthma triggers in the home such as mold, cockroaches, mice, environmental tobacco smoke, furry pets, cleaning chemicals, strong odors/fragrances5. Neurodevelopmental disorders: assess for pica behavior and other risk factors that may increase the likelihood of exposures (e.g., lead); assess for use of alternative medications		Environmental history forms: <ul style="list-style-type: none">• National Environmental Education Foundation (NEEF) has a general environmental history and an asthma-focused environmental history (English and Spanish): www.neefusa.org/resource/pediatric-environmental-history• World Health Organization (WHO) Paediatric Environmental Health History (Green Page) provides a series of concise questions to assess potential exposures: https://www.who.int/publications/m/item/children-s-environmental-record--green-page Evidence-based clinical resources: <ul style="list-style-type: none">• The Green Book: American Academy of Pediatrics. <i>Pediatric Environmental Health</i>. 4th ed. Etzel RA, Balk SJ, eds. Elk Grove Village, IL: American Academy of Pediatrics; 2019.• Pediatric Environmental Health Specialty Unit (PEHSU). One PEHSU is located in each of the 10 federal regions in the United States. The PEHSUs provide online classroom materials, resources, and access to network of experts in pediatric and reproductive environmental health: www.pehsu.net• The Pediatric Environmental Health Toolkit is an online clinical tool that providers can use to access information on common exposures, including identification of sources of exposure and provision of targeted anticipatory guidance: https://peht.ucsf.edu.• Bright Futures provides guidance for well child care for children and adolescents (includes key environmental anticipatory guidance): https://brightfutures.aap.org/.• American College of Obstetricians and Gynecologists (ACOG). Reducing Prenatal Exposure to Toxic Environmental Agents: https://pubmed.ncbi.nlm.nih.gov/34259492/ Resources for patients: <ul style="list-style-type: none">• Prescriptions for Prevention are tools that link patients to evidence-based simple steps to reduce or prevent common environmental exposures (English and Spanish): https://nyscheck.org/rx• National Institute of Environmental Health Sciences (NIEHS). Environmental health topics: https://www.niehs.nih.gov/health/toxics/index.cfm	
Components of environmental health history (can be adapted based on patient scenario):			
General home health and safety: <ul style="list-style-type: none">• Age and condition of home (lead paint in pre-1978 home)• Carbon monoxide and fire alarms• Heat and cooking sources (stove ventilation, safe space heater use)• Tobacco smoke• Radon (test basement and first/second floors)• Cleaning products-safe storage and use (e.g., bleach) Common indoor allergens: <ul style="list-style-type: none">• Water leaks/mold• Pests (cockroaches, mice) and pesticide use		Water and food: <ul style="list-style-type: none">• Drinking water source (well water requires routine testing)• Fish advisories (methylmercury) for pregnant persons and children• Fresh produce (rinse well before eating)• Rice-based products (vary grains to reduce arsenic exposure) Jobs and hobbies: <ul style="list-style-type: none">• Caregiver jobs (contaminant transfer from clothing, shoes)• Adolescent jobs (safety)• Hobbies in the home (paints, chemicals)• Sun protection outdoors• Noise from headphones, toys	

and is in the submicron (<1 µm diameter) range, meaning that it is classified as fine particulate matter. These are smaller than the particles in mainstream smoke and can penetrate deeper into the lungs, resulting in higher toxicity through oxidative stress and inflammation. Short- and long-term exposure to fine particulate matter contributes to the aggravation of asthma and other respiratory diseases, lung and other cancers, cardiovascular disease, and death.

SHS concentration in the indoor environment depends on the number of cigarettes smoked in a period, the volume of the room, the ventilation rate, and other processes that eliminate pollutants from the air. There are multiple mechanisms by which SHS causes injury to the respiratory tract, and injury to the cardiovascular system is due to endothelial cell dysfunction due to smoke exposure and its prothrombotic effects.

THIRDHAND SMOKE

Thirdhand smoke (THS) was defined in 2011 as consisting of the residual tobacco smoke pollutants that remain on surfaces and in dust after tobacco has been smoked. These toxins are reemitted into the gas phase or react with oxidants and other compounds in the environment to yield secondary pollutants. These residual pollutants can be detected in the indoor environment well after being generated. About half the particulate matter from SHS is still airborne after 5-6 hours. Many chemicals, such as nicotine and some PAHs, exist in both the gaseous and the particulate phase of SHS. Classified as “semi-volatile,” their ability to change form according to environmental conditions means that they remain detectable in the indoor environment for longer periods after active smoking has ceased. These components in dust and on surfaces can be ingested, inhaled, or

even absorbed through the skin. The health implications of THS are not well understood, but there is growing evidence both in vitro and in vivo of health harms of THS exposure, particularly respiratory symptoms. Young children are at higher risk of health issues due to THS absorption because of their hand to mouth behaviors, crawling near surfaces, time spent in the home, and increased respiratory rate.

TOBACCO USE AND EXPOSURE IS A HEALTH RISK DISPARITY

Tobacco use, and hence childhood exposure, is found disproportionately among socially disadvantaged low-income populations, who can least afford tobacco and SHS-related illness and evidenced-based treatment for nicotine addiction. There has been a profound decrease in smoking rates among the middle and upper classes within the United States since the 1960s (83% decrease), but the rate of decrease is much less (39%) among lower income groups. The smoking rate for the overall U.S. population is approximately 12.5%, but it is as high as 32% among adults with a high school equivalency degree. Because of these disparities in smoking rates among adults, children born into low-income homes are more likely to be exposed to SHS. More than 38% of U.S. children age 3-11 years were exposed to tobacco smoke from 2017 to 2018, based on a biologic marker of exposure, serum cotinine levels. Children from low-income homes have the highest rates of biologically measured SHS exposure; for every decrease in family income ratio, serum cotinine levels increase by 1.18 ng/L among children. Having a parent who smokes has also been shown to be an independent risk factor for food insecurity in children.

MATERNAL SMOKING DURING PREGNANCY AND TOBACCO SMOKE EXPOSURE DURING PREGNANCY

The effects of maternal smoking on the fetus are profound and can be divided into pregnancy-related and long-term effects. Fetal exposure is one of the most important modifiable risk behaviors for childhood and long-term health.

Pregnancy-Related Effects

Maternal smoking increases the risk of placenta-associated complications of pregnancy, with an increased rate of placental abruption and placenta previa among maternal smokers. Both active maternal smoking and secondhand maternal tobacco smoke exposure have been shown to reduce birthweight and to increase the risk of preterm birth. In utero tobacco exposure from either maternal active tobacco product use or maternal SHS exposure increases the rate of stillbirth. Smoking both during and after pregnancy is a risk factor for **sudden infant death syndrome (SIDS)**; one study found that any smoking during pregnancy was associated in a doubling of SIDS risk and that there was a linear correlation between the average number of cigarettes smoked daily and an increased risk for SIDS. These associations are modifiable by public policy. Several countries in Europe have shown decreased perinatal complications after comprehensive smoke-free laws; within the United States, pregnancy complications and SIDS are inversely related to tobacco taxation levels.

Long-Term Effects

Maternal smoking in early pregnancy is considered causal for orofacial clefts (Surgeon General Report 2014).

Both active smoking during pregnancy and SHS exposure of the mother increases the *child's* later risk of being overweight or obese. This finding may appear surprising due to the long-known relationship between smoking during pregnancy and low birthweight. This relationship has been shown in multiple epidemiologic studies and is robust to adjustment for potential confounders, such as parental body mass index (BMI), breastfeeding, family diet, and lifestyle.

Maternal smoking during pregnancy has been associated with both an increased risk of learning problems and neurobehavioral issues during childhood. The adverse effects of prenatal smoking on child neurodevelopment include poor language development and reduction in cognitive functioning. Prenatal exposure to smoking may also reduce the child's motor performance, mental development (measured by the Bayley Scales of Infant Development), IQ scores, and language development through age 3 years. This exposure may also increase the risks of several child behavioral problems, including externalization of aggressive and hyperactive behavior, prolonged periods of verbal or physical aggression and socially undesirable behavior (conduct disorder) throughout childhood, and delinquency in later childhood. In one study, a dose-response relationship with increasing severity of poor school performance was related to the number of cigarettes the mother smoked during pregnancy.

Maternal Smoking During Pregnancy and Lung Development

Smoking during pregnancy is associated with poor lung growth and function in the offspring and with a greater risk for wheezing between age 2–4 years. According to the Surgeon General Report (2014), there is sufficient evidence to consider this relationship to be causal.

POSTNATAL SECONDHAND SMOKE EXPOSURE—EFFECTS ON THE CHILD

Respiratory

Children exposed to SHS have a higher rate of asthma prevalence and greater asthma severity. The Surgeon General Report (2006) concluded that there is a causal relationship between parental smoking and cough, phlegm, wheezing, and breathlessness, along with asthma, among school-age children. Children with SHS exposure have a weakened response to inhaled corticosteroids. Children with asthma who are SHS-exposed are more likely to have an acute care visit, an overnight hospital stay, and a higher number of hospital admissions than children with asthma and no SHS exposure. The rate of hospital readmissions for asthma has been

associated with the level of the child's saliva cotinine, a biomarker of smoke exposure, and this is true even at very low levels of exposure.

Tobacco smoke exposure is a cause of lower respiratory tract infection in children. Findings of the Surgeon General in 2006 were updated by a systemic review of parental and household smoking and risk of lower respiratory tract infections in infancy in 2011. The strongest relationship was for bronchiolitis, where the risk of any household smoke exposure was increased in the first two years of life.

SHS exposure during childhood increases the rate of middle ear disease, including acute, recurrent otitis media and chronic middle ear effusion. The Surgeon General Report (2006) rated this evidence as sufficient to infer a causal relationship between parental smoking and middle ear disease in children.

Cardiovascular Effects

Tobacco smoke exposure during adulthood has been linked to an increased risk of cardiovascular disease. Evidence links childhood exposure to findings of preclinical atherosclerosis. These include increased carotid intima-media thickness and decreased flow-mediated dilation, both indirect tests for preclinical changes leading to atherosclerosis during adulthood. Other findings have included increased inflammation as measured by C-reactive protein, abnormal lipid profiles, higher blood pressure, and increased rates of metabolic syndrome among SHS-exposed children and youth.

Infection

Childhood exposure to SHS is related to increased rates of invasive meningococcal disease in children less than 5 years old. SHS in the home doubled the risk of invasive meningococcal disease with some evidence of a dose-response relationship. The strongest effect was seen in children under 5 years, with SHS exposure more than doubling the rate of meningococcal disease. This relationship was seen both with prenatal smoking and postnatal exposure.

SHS exposure has also been shown to increase the severity of influenza among children hospitalized for the disease. Children with SHS exposure were 4.7 times more likely to be admitted to intensive care and had a 70% longer length of stay than nonexposed children, after controlling for multiple potential confounding factors.

Healthcare Utilization

Children and teens age 3–19 years who are SHS-exposed had higher healthcare utilization compared with nonexposed peers based on an analysis of NHANES data from 2009–2012. Children with high SHS exposure based on serum cotinine were almost three times more likely to have an overnight hospital stay and two times as likely to have a higher number of total hospital admissions as children with no exposure.

Special Vulnerable Pediatric Populations

There is evidence that SHS exposure exacerbates disease processes among children with significant chronic health conditions. Children with sickle cell disease who are exposed to SHS have increased morbidity, specifically increased rates of emergency department visits, and hospitalizations for vasoocclusive crisis and acute chest syndrome (see [Chapter 511.1](#)). In addition, tobacco smoke exposure is also associated with pulmonary function abnormalities among children with sickle cell disease, independent of their baseline disease.

Children with cystic fibrosis (CF) are another vulnerable population in which SHS exposure presents an additive threat to overall health. Core health issues for this group of children include problems with growth, lung function, and pulmonary infections (see [Chapter 454](#)). SHS-exposed children with CF had decreased growth between 4 and 12 months compared with non-SHS exposed infants. Furthermore, tobacco smoke exposure was associated with increased bronchodilator responsiveness and air trapping, and with increased methicillin-resistant *Staphylococcus aureus* and anaerobic growth on respiratory culture. Tobacco smoke exposure can be considered a modifiable risk factor for children with sickle cell disease and CF.

TREATMENT FOR TOBACCO USE AND SECONDHAND TOBACCO SMOKE EXPOSURE

There is no risk-free level of youth tobacco use or SHS exposure. Thus the best method to treat tobacco use and SHS exposure is to eliminate this exposure by helping adolescents and their caregivers quit smoking. Methods to reduce exposure such as “smoking outside” or wearing a “smoking jacket” have not been shown to eliminate biochemically confirmed SHS exposure. A meta-analysis of six controlled trials aimed specifically at SHS exposure reduction for children (not parental smoking cessation) showed some reduction in tobacco smoke pollution post intervention. However, all homes had significant tobacco-related air pollution at the end of the study period.

The pediatric office has long been considered an excellent venue for pediatricians to screen for youth tobacco use as well as children's SHS exposure and to intervene with youth and their caregivers. The American Academy of Pediatrics (AAP) recommends that providers:

1. Inquire about tobacco use and tobacco smoke exposure as part of health supervision visits and visits for diseases that may be caused or exacerbated by tobacco smoke exposure.
2. Include tobacco use prevention as part of anticipatory guidance.
3. Address parent/caregiver tobacco dependence as part of pediatric healthcare.
4. Offer tobacco dependence treatment and/or referral to adolescents who want to stop smoking.

The United States Preventative Services Task Force also recommends that primary care clinicians provide school-age children and adolescents who have not started to use tobacco with interventions (including education or brief counseling) to prevent initiation of tobacco use. The “Ask-Counsel-Treat” (ACT) model developed by the AAP provides tips on addressing youth tobacco use in the office (available at <https://www.aap.org/en/patient-care/tobacco-control-and-prevention/youth-tobacco-cessation/tobacco-use-considerations-for-clinicians/>); it is recommended that screening begin at age 11. The Clinical Effort Against Secondhand Smoke Exposure (CEASE) is a program that trains pediatricians and their office staff to systematically provide cessation counseling and interventions to caregivers who smoke. The CEASE model is (1) **ask** if anyone in the home or who cares for the child smokes; (2) **assist** the patient or caregiver with quitting by providing brief counseling, pharmacotherapy, or appropriate referrals; and (3) **refer** the smoker to evidence based cessation treatments, including telephone-based Quitlines or Text to Quit services. The CEASE model (found at <https://www.massgeneral.org/children/cease-tobacco>) involves training pediatricians to provide smoking cessation pharmacotherapy to caregivers who wish to quit smoking; it includes tools to both identify caregivers who smoke and facilitate pediatric healthcare providers' delivery of counseling, medications, and referral for tobacco treatment.

Despite the AAP recommendations for pediatricians to incorporate these methods into practice, a meta-analysis in 2016 of controlled trials in routine healthcare settings of child SHS exposure reduction did not show an intervention effect. However, three controlled trials of maternal postpartum smoking relapse prevention did demonstrate beneficial outcomes of the intervention.

Decreasing smoking initiation among youth will prevent the children of the future from SHS exposure. Ninety percent of smokers initiate use before 19 years of age, and 80% of youth who are smokers persist in smoking in adulthood. Of those, half will die earlier than their nonsmoking peers. After many years of individual states working to enact stricter tobacco laws, new federal legislation known as Tobacco 21 was signed in 2019 that raised the minimum age for sale of tobacco products from 18 to 21 years nationwide. By increasing the age of tobacco purchase to 21 years, there is hope that a whole generation of smoking can be prevented.

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759.2 Marijuana Smoke Exposure

Karen M. Wilson

Unlike tobacco smoke exposure, which has long been recognized as a cause of morbidity and mortality among nonsmokers, marijuana

smoke exposure is far less well studied. In 2021, 13.2 million persons age 12 years or older used marijuana on a daily or almost daily basis in the past 12 months, an increase from the 5.7 million daily or almost daily users in 2013 (see [Chapter 157.3](#)). The use of marijuana has been increasing in both acceptability and legality in the past 20 years. Current use of marijuana is more common among males and younger adults (18–34 years vs 35 years or older), and those with less than a high school degree. As of 2023, 38 states allow the legal use of marijuana for medical reasons, and 24 states plus Washington DC and Guam have legalized its recreational use. Analysis of poison control center calls for exposure to marijuana for children under 6 years of age showed an increase of 148% from 2006 to 2013; from 4.2/1 million children to 10.4/1 million. Tobacco-smoking parents with young children residing in the home are four times more likely to use marijuana as compared with nontobacco smoking parents. About 38% of young children in the United States are exposed to tobacco smoke, compared to an estimate of 15% of children exposed to marijuana smoke. Studies examining the presence of biomarkers of marijuana smoke exposure have found an exposure prevalence of 16% in young children hospitalized for bronchiolitis in Colorado, and 21% in children 0–3 years being seen at a clinic in New York City.

COMPONENTS OF MARIJUANA SMOKE

While marijuana can also be aerosolized or ingested as hash oil or leaf, combusted marijuana is still the most common form. A recent analysis of data from the U.S. National Health and Nutrition Examination Survey (NHANES) finds that daily marijuana users have higher levels of combustion biomarkers (e.g., volatile organic compounds and polycyclic aromatic hydrocarbons (PAHs) than nonusers. In addition to the particulates and other chemicals of combustion, marijuana comprises two primary active chemicals: Δ 9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Exposure to combustion products likely extends to adjacent nonusers, as has been shown for tobacco smoke. Most states with legal marijuana use do not have any restrictions on combustible marijuana use in the presence of children.

IMPACT OF MARIJUANA SMOKE EXPOSURE

While there is clear research on the dangers of secondhand tobacco smoke (SHS), there have been very few studies examining the impact of marijuana smoke exposure. Secondhand marijuana smoke contains particulate matter that is known to be harmful when inhaled, in addition to other toxic and carcinogenic chemicals such as volatile organic compounds, PAHs, and aromatic amines. Studies in adults have demonstrated that it is possible to get a “contact high” from intense exposure. Even brief exposures have been found to impair vascular endothelial function in animal models. Children can be exposed to secondhand and thirdhand marijuana smoke when parents or other household contacts smoke indoors, similar to children living with tobacco smokers. Also similar to tobacco, children could be exposed to marijuana smoke through incursions from neighboring apartments; in a New York City sample, 31% of parents reported marijuana incursions, whereas 34% reported tobacco incursions. Neonates can be exposed to marijuana prenatally or through breast milk. Prenatal exposure has been linked to growth restriction and neonatal intensive care admissions, as well as behavioral issues such as impulsivity. Prenatal exposure has also been linked to impaired executive functioning in young adulthood. One study examined the role of indoor cannabis smoke and health; although they found increased particulates in homes with cannabis use, there was no statistically significant difference in health outcomes.

TREATMENT

In the absence of convincing data showing that marijuana is not harmful, parents should be counseled to avoid exposing their children to marijuana smoke, to lock marijuana in a safe place out of reach of any children, to avoid edibles in appealing or non-child proof packaging, and to be cautious about their own level of impairment if they do choose to use legal marijuana.

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Chapter 760

Heavy Metal Intoxication

Prashant V. Mahajan

Lead, mercury, arsenic, and cadmium, four of the World Health Organization's (WHO) "Ten chemicals of greatest public health concern," are the heavy metals posing the greatest threats to humans. The most prevalent of these exposures is lead (see Chapter 761).

Heavy metal intoxication results in multiorgan toxicity through widespread disruption of vital cellular functions. A meticulous history of environmental exposure may be necessary to correctly identify heavy metals as the source of the protean manifestations associated with such exposure. Arsenic exposure can occur from contaminated food or water; globally, more than 140 million people are estimated to be chronically exposed to drinking water containing high arsenic levels. Mercury exposure occurs primarily through food; fish is a major source of methyl mercury exposure.

ARSENIC

Arsenic is a metalloid that exists in four forms: elemental arsenic, arsine gas, inorganic arsenic salts (pentavalent arsenate form or trivalent arsenite form), and organic arsenic compounds. Toxic manifestations are higher in the more soluble and higher-valence compounds. **Arsine gas** is the most toxic form of arsenic. Mass poisonings from exposure to arsenic have occurred throughout history, including one in 1998 in Wakayama, Japan, in which 70 people were poisoned. Children may be poisoned after exposure to inorganic arsenic found in pesticides, herbicides, dyes, homeopathic medicines, and certain contaminated folk remedies from China, India, and Southeast Asia (see Chapter 94). Soil deposits contaminate artesian well water. Groundwater contamination with arsenic is a common problem in developing countries and has been reported to be a common well contaminant in many areas of the United States as well (Fig. 760.1). The Southwest has the highest arsenic concentrations in the country with more than 16% of sampled wells exceeding the maximum contaminant level. Food products (e.g., rice,

organic brown rice syrup, fruit juices) cooked in contaminated water may absorb arsenic, thus concentrating it in the food (Fig. 760.2). The WHO and United States Environmental Protection Agency (EPA) have set 10 µg/L as the upper limit of safety. In many parts of Asia and South America, this limit is frequently exceeded. Arsenic concentrations in a quarter of the wells in Bangladesh exceed 50 µg/L, and 35-77 million of the 125 million inhabitants of Bangladesh regularly consume arsenic-contaminated water. Occupational exposure may occur in industries involved in the manufacturing, mining, smelting, or refining of glass, pottery, electronic and semiconductor components, and lasers. Although arsenic is no longer produced in the United States, it is produced in many countries and is imported into the United States for industrial use. Organic arsenic compounds may be found in seafood, pesticides, and some veterinary pharmaceuticals. In contrast to mercury, the organic forms of arsenic found in seafood are nontoxic.

Pharmacokinetics

Elemental arsenic is insoluble in water and bodily fluids, and thus is insignificantly absorbed and nontoxic. Inhaled arsine gas is rapidly absorbed through the lungs. The inorganic arsenic salts are well absorbed through the gastrointestinal tract, lungs, and skin. The organic arsenic compounds are well absorbed through the gastrointestinal tract. After acute exposure, arsenic initially is bound to the protein portion of hemoglobin in the red blood cells (RBCs) and rapidly distributed to all tissues. Inorganic arsenic is methylated and is eliminated predominantly by the kidneys, with approximately 95% excreted in the urine and 5% excreted in the bile. Most of the arsenic is eliminated in the first few days, with the remainder slowly excreted over a period of several weeks. Arsenic concentrates in hair, nails, and skin. Arsenic can also accumulate in the fetus, as it can cross the placenta. Measurement of the distance of **Mees lines** (transverse white striae on the nail) from the nailbed can provide an estimate of time of exposure (nails grow at the rate of 0.4 mm/day) (Fig. 760.3).

Pathophysiology

After exposure to arsine gas, absorbed arsine enters RBCs and is oxidized to arsenic dihydride and elemental arsenic. Complexing of these derivatives with red cell sulfhydryl groups results in cell membrane instability and massive hemolysis. The inorganic arsenic salts poison enzymatic processes vital to cellular metabolism. Trivalent arsenic binds to sulfhydryl groups, resulting in decreased production of

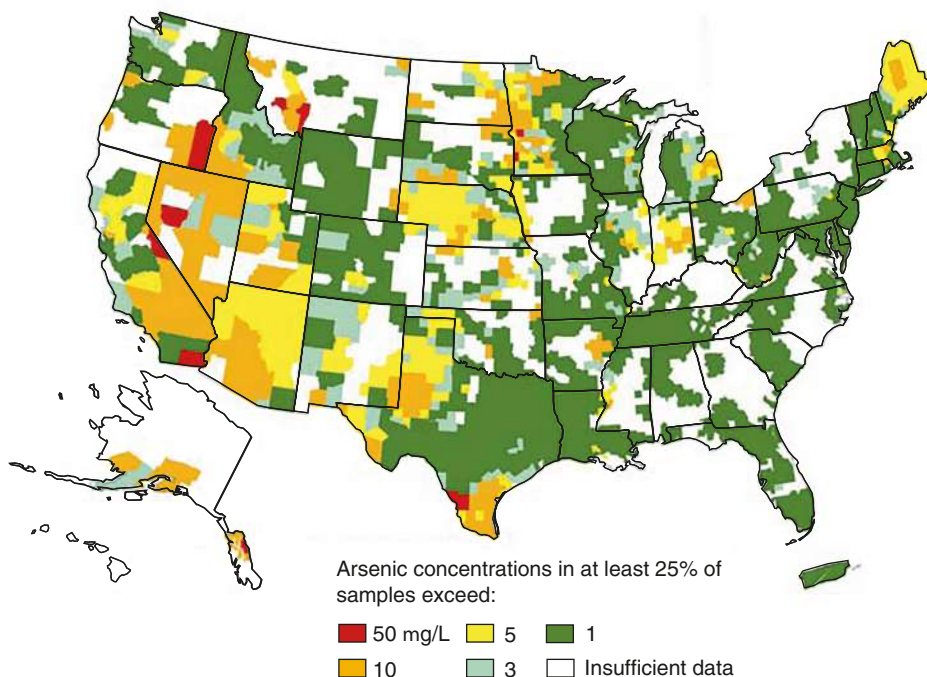


Fig. 760.1 U.S. Geological Survey map of arsenic in groundwater. Groundwater may also contain elevated concentrations of arsenic from agricultural runoff, contamination from runoff from wood preservatives containing arsenic, improperly disposed arsenical chemicals, or mining. For the latest on the US Geological survey: <https://www.usgs.gov/mission-areas/water-resources/science/arsenic-and-drinking-water#overview>. (Modified from Agency for Toxic Substances and Disease Registry: Arsenic toxicity. What Are the Routes of Exposure for Arsenic? Fig 1. https://www.atsdr.cdc.gov/csem/arsenic/what_routes.html.)

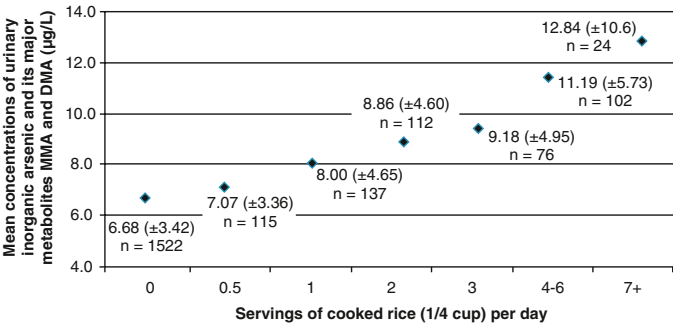


Fig. 760.2 Mean concentrations of urinary inorganic arsenic and its major metabolites monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA) by categories of rice intake in children ages 6-17, National Health and Nutrition Examination Survey (NHANES) 2003-2008, excluding subjects with recent seafood consumption. (From Lai PY, Cottingham KL, Steinmaus C, et al. *Arsenic and rice: Translating research to address health care providers' needs.* *J Pediatr.* 2015;167[4]:797-803. Fig. 1.)

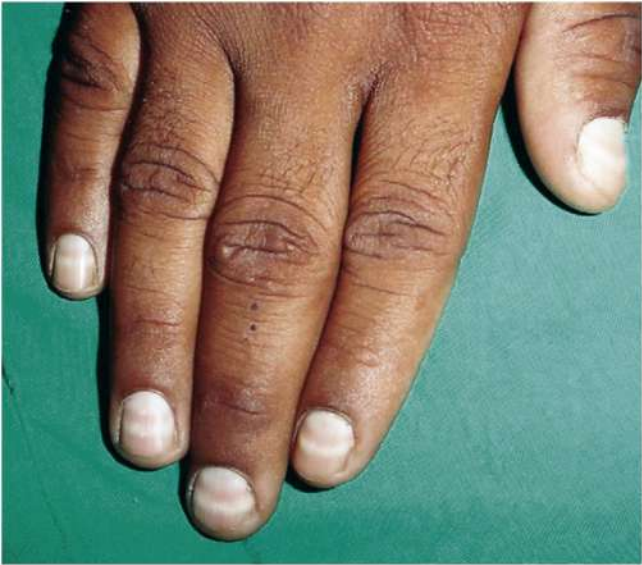


Fig. 760.3 Mees lines. Transverse white bands are clearly visible on the nails. (From Chauhan S, D'Cruz S, Singh R, et al. *Mees' lines.* *Lancet.* 2008;372[9647]:1410.)

adenosine triphosphate through the inhibition of enzyme systems such as the pyruvate dehydrogenase and α -ketoglutarate complexes. Pentavalent arsenic may be biotransformed to trivalent arsenic or substituted for phosphate in the glycolytic pathway, resulting in uncoupling of oxidative phosphorylation.

Clinical Manifestations

Arsine gas is colorless, odorless, nonirritating, and highly toxic. Inhalation causes no immediate symptoms. After a latent period of 2-24 hours, exposed individuals experience massive hemolysis, malaise, headache, weakness, dyspnea, nausea, vomiting, abdominal pain, hepatomegaly, pallor, jaundice, hemoglobinuria, and renal failure (Table 760.1). Acute ingestion of arsenic produces gastrointestinal toxicity within minutes to hours and is manifested as nausea, vomiting, abdominal pain, and diarrhea. Hemorrhagic gastroenteritis with extensive fluid loss and third spacing may result in hypovolemic shock. Cardiovascular toxicity includes QT interval prolongation, polymorphous ventricular tachycardia, congestive cardiomyopathy, pulmonary edema, and cardiogenic shock. Acute neurologic toxicity includes delirium, seizures, cerebral edema, encephalopathy, and coma. Lethal doses of arsenates are 5-50 mg/kg; lethal doses of arsenites are <5 mg/kg.

Table 760.1 Effects of Arsenic on Organ Systems	
ORGAN SYSTEM	EFFECTS OF ARSENIC
Gastrointestinal system	Submucosal vesicles, watery or bloody diarrhea, severe hematemesis, pancreatitis, jaundice, toxic hepatitis
Cardiovascular system	Reduced myocardial contractility, prolonged QT intervals, tachyarrhythmias, torsades de pointes, pericarditis Vasodilation, hypotension, shock
Kidneys	Hematuria, proteinuria, oliguria, renal failure
Nervous system	Toxic encephalopathy with seizures, headache, cerebral edema, and coma Chronic exposure: peripheral painful sensorimotor neuropathy, paresthesias
Hematologic and lymphatic system	Anemia, leukopenia, and thrombocytopenia; acute hemolysis with arsine gas, basophilic stippling
Liver	Fatty degeneration with central necrosis
Skin	Desquamation, alopecia, hyperkeratosis, nail changes (Mees lines), brown pigmentation Chronic exposure: hyperkeratosis, hyperpigmentation
Teratogenic	Neural tube defects in the fetus
Oncologic	Urologic cancer, other malignancies

Late sequelae include hematuria, proteinuria, and acute kidney injury. A delayed sensorimotor peripheral neuropathy may appear days to weeks after acute exposure, secondary to axonal degeneration. Neuropathy manifests as painful dysesthesias followed by diminished vibratory, pain, touch, and temperature sensation; decreased deep tendon reflexes; and in the most severe cases, an ascending paralysis with respiratory failure mimicking Guillain-Barré syndrome (see Chapter 656). Adult survivors of infant arsenic poisoning experience higher mortality from disorders of the nervous system compared with adults without such exposure.

Subacute toxicity is characterized by prolonged fatigue, malaise, weight loss, headache, chronic encephalopathy, peripheral sensorimotor neuropathy, leukopenia, anemia, thrombocytopenia, chronic cough, and gastroenteritis. Mees lines in the nails become apparent 1-2 months after exposure in approximately 5% of patients. Dermatologic findings include alopecia, oral ulceration, peripheral edema, a pruritic macular rash, and desquamation.

Chronic arsenic toxicity causes significant morbidity in children resulting in skin lesions, lung disease, and deficits in intellectual function. **Chronic exposure** to low levels of arsenic is usually from environmental or occupational sources. Over the course of years, dermatologic lesions develop, including hyperpigmentation, hypopigmentation, hyperkeratoses (especially on the palms and soles), squamous and basal cell carcinomas, and **Bowen disease** (cutaneous squamous cell carcinoma in situ). Encephalopathy and peripheral neuropathy may be present. Hepatomegaly, hypersplenism, noncirrhotic portal fibrosis, and portal hypertension occur. **Blackfoot disease** is an obliterative arterial disease of the lower extremities associated with chronic arsenic exposure that has been described in Taiwan. Carcinogenicity of chronic arsenic exposure is reflected in increased rates of cancers of the skin, lung, liver, bladder, and kidney as well as of angiosarcomas. Arsenic is carcinogenic, possibly through epigenetic dysregulation. The effects of prenatal exposure to arsenic are uncertain but may include low birthweight.

Laboratory Findings

The diagnosis of arsenic intoxication is based on characteristic clinical findings, a history of exposure, and elevated urinary arsenic values, the last of which confirm the exposure. A spot urine arsenic level should be determined for symptomatic patients before chelation, although initially the result may be negative. Because urinary excretion of arsenic is intermittent, definitive diagnosis depends on a 24-hour urine collection. Concentrations greater than 50 µg/L in a 24-hour urine specimen are consistent with arsenic intoxication (Table 760.2). Urine specimens must be collected in metal-free containers. Ingestion of seafood containing nontoxic arsenobetaine and arsenocholine can cause elevations of urinary arsenic. Blood arsenic levels rarely are helpful because of their high variability and the rapid clearance of arsenic from the blood in acute poisonings. Elevated arsenic values in the hair or nails must be interpreted cautiously because of the possibility of external contamination. Abdominal radiographs may demonstrate ingested radiopaque arsenic.

Later in the course of illness, a complete blood cell count may show anemia, thrombocytopenia, and leukocytosis, followed by leukopenia, karyorrhexis, and basophilic stippling of RBCs. The serum concentrations of creatinine, bilirubin, and transaminases may be elevated; urinalysis may show proteinuria, pyuria, and hematuria; and examination of the cerebrospinal fluid may show protein elevations.

MERCURY

Mercury exists in three forms: elemental mercury, inorganic mercury salts, and organic mercury (Table 760.3). **Elemental mercury** is present in thermometers, sphygmomanometers, barometers, batteries, gold or silver smelting processes, and some latex paints produced before 1991. Workers in industries producing these products may expose their children to the toxin when mercury is brought home on contaminated clothing. Vacuuming of carpets contaminated with mercury and breaking of mercury fluorescent light bulbs may result in elemental mercury vapor exposure. Severe inhalation poisonings have resulted from attempts to separate gold from gold ore by heating mercury and forming a gold-mercury amalgam. Elemental mercury has been used in folk remedies by Asian and Mexican populations for chronic stomach pain, by Latin Americans and Caribbean natives in occult practices, and as a skin-lightening agent. Dental amalgams containing elemental mercury release trace amounts of mercury. An expert panel for the National Institutes of Health concluded that existing scientific evidence does not indicate that dental amalgams pose a health risk and should not be replaced merely to decrease mercury exposure. A 2009 WHO expert panel concluded that a global near-term ban on amalgam would be problematic for public and dental health. However, this committee recommended that alternatives to amalgam should be sought as part of a phase-out of the use of mercury-containing amalgams.

Inorganic mercury salts are found in pesticides, disinfectants, antiseptics, pigments, dry batteries, and explosives and as preservatives in some medicinal preparations. **Organic mercury** in the diet, especially fish containing methyl mercury, is a major source of mercury exposure among the general population. Industries that may produce mercury-containing effluents include chlorine and caustic soda production, mining and metallurgy, electroplating, chemical and textile manufacturing, paper and pharmaceutical manufacturing, and leather tanning. Mercury compounds in the environment are methylated to

methyl mercury by soil and water microorganisms. Methyl mercury in the water rapidly accumulates in fish (swordfish, king mackerel, fresh tuna, tile fish, shark) and other aquatic organisms, which are in turn consumed by humans. To address concerns that maternal consumption of large quantities of fish during pregnancy may expose the fetus to concentrations of mercury with adverse consequences, the longitudinal Seychelles Child Development Study has been ongoing since the late 1980s. The first cohort of the study involved nearly 800 mother-child pairs, with subsequent cohorts enrolled. Despite a high maternal fish intake (mean of 12 fish meals per week), follow-up of children at least through 9 years of age has revealed no consistent adverse developmental effects. Well-known large outbreaks of methyl mercury intoxication include the incidents in Japan in the 1950s (**Minamata disease**, from consumption of contaminated seafood) and in Iraq in 1971 (from consumption of grain treated with a methyl mercury fungicide).

Thimerosal is a mercury-containing preservative used in some vaccines. Thimerosal contains 49.6% mercury by weight and is metabolized to ethyl mercury and thiosalicylate. During an ongoing review of biologic products in response to the U.S. Food and Drug Administration (FDA) Modernization Act of 1997, the FDA determined that infants who received thimerosal-containing vaccines at multiple visits might have been exposed to more mercury than recommended by federal guidelines. As a precautionary measure, the American Academy of Pediatrics, American Academy of Family Physicians, Advisory Committee on Immunization Practices, and U.S. Public Health Service issued a joint recommendation in 1999 that thimerosal be removed from vaccines as quickly as possible. *In the United States, thimerosal has been removed from all vaccines in the recommended childhood immunization schedule.* Infants and children who have received thimerosal-containing vaccines do not need to undergo blood, urine, or hair testing for mercury because the concentrations of mercury would be quite low and would not require treatment. The larger risks of not vaccinating children far outweigh any known risk of exposure to thimerosal-containing vaccines. Studies do *not* demonstrate a link between thimerosal-containing vaccines and autism spectrum disorders (see Chapter 58), and no evidence supports a change in the standard of practice regarding administration of thimerosal-containing vaccines in areas of the world where they are used. A rise in blood mercury levels following a single dose of hepatitis vaccine was seen in preterm infants, but the clinical significance is unknown.

Pharmacokinetics

Inhaled elemental mercury vapor is 80% absorbed by the lungs and is distributed rapidly to the central nervous system because of its high lipid solubility. The elemental mercury is oxidized by catalase to the mercuric ion, which is the reactive form that causes cellular toxicity. Elemental mercury liquid is poorly absorbed from the gastrointestinal tract, with less than 0.1% being absorbed. The half-life of elemental mercury in the tissues is approximately 60 days, with most of the excretion occurring in the urine.

Inorganic mercury salts are approximately 10% absorbed from the gastrointestinal tract and cross the blood-brain barrier to a lesser extent than elemental mercury. Mercuric salts are more soluble than mercurous salts and therefore produce greater toxicity. Elimination occurs primarily in the urine, with a half-life of approximately 40 days.

Table 760.2 Acceptable and Toxic Levels of Arsenic and Mercury

	ARSENIC	MERCURY
Molecular weight	74.9 Da	200.59 Da
Acceptable blood level	<5µg/L (<0.665nmol/L)	<10µg/L (<50nmol/L)
Acceptable urine level	<50µg/L (<6.65nmol/L) 24-hr urine sample	<20µg/L (<100nmol/L)
Intervene at blood level		>35µg/L (>175nmol/L)
Intervene at urine level	>100µg/L (>13.3nmol/L) 24-hr urine sample	>150µg/L (>750nmol/L)

Table 760.3	Differential Characteristics of Mercury Exposure		
	ELEMENTAL	INORGANIC (SALT)	ORGANIC (ALKYL)
Primary route of exposure	Inhalation	Oral	Oral
Primary tissue distribution	CNS, kidney	Blood (transient, acute), kidney, CNS (delayed)	CNS, kidney, liver, blood, hair
Clearance	Kidney, GI	Kidney, GI	Methyl: GI Aryl: kidney, GI
CLINICAL EFFECTS			
CNS	Tremor	Tremor, erethism (irritability)	Paresthesias, ataxia, tremor, tunnel vision, dysarthria
Pulmonary	+++	—	—
Gastrointestinal	+	+++ (caustic)	+
Renal	+	+++ (acute tubular necrosis)	+
Acrodynia	+	++	—
Therapy	BAL, succimer	BAL, succimer	Succimer (early)

+, mild; ++, moderate; +++, severe; BAL, British antilewisite (also known as dimercaprol); CNS, central nervous system; GI, gastrointestinal.
From Sue YJ. Mercury (heavy metals). In: Nelson LS, Howland MA, Lewin NA, et al., eds. *Goldfrank's Toxicologic Emergencies*, 11th ed. New York: McGraw-Hill; 2019: Table 95.3.

Methyl mercury is the most avidly absorbed of the organic mercury compounds, with approximately 90% absorbed from the gastrointestinal tract. The lipophilic, short-chain alkyl structure of methyl mercury allows it to distribute rapidly across the blood-brain barrier and placenta. Methyl mercury is approximately 90% excreted in the bile, with the remainder being excreted in the urine. The half-life is 70 days.

Pathophysiology

After absorption, mercury is distributed to all tissues, particularly the central nervous system and kidneys. Mercury reacts with sulfhydryl, phosphoryl, carboxyl, and amide groups, resulting in disruption of enzymes, transport mechanisms, membranes, and structural proteins. Widespread cellular dysfunction or necrosis results in the multiorgan toxicity characteristic of mercury poisoning.

Clinical Manifestations

Five syndromes describe the clinical presentation of mercury poisoning. **Acute inhalation of elemental mercury vapor** results in rapid onset of cough, dyspnea, chest pain, fever, chills, headaches, and visual disturbances. Gastrointestinal findings include metallic taste, salivation, nausea, vomiting, and diarrhea. Depending on the severity of the exposure, the illness may be self-limited or may progress to necrotizing bronchiolitis, interstitial pneumonitis, pulmonary edema, and death from respiratory failure. Younger children are more susceptible to pulmonary toxicity. Survivors may demonstrate restrictive lung disease. Renal dysfunction and neurologic disturbances (ataxia, persistent weakness, emotional lability) may develop subacutely. Chronic exposure to volatilized elemental mercury in dental amalgams has not been found to be of any clinical significance.

Acute ingestion of inorganic mercury salts (typically secondary to ingestion of a button battery) can manifest in a few hours as corrosive gastroenteritis, signified by metallic taste, oropharyngeal burns, nausea, hematemesis, severe abdominal pain, hematochezia, acute tubular necrosis, cardiovascular collapse, and death.

Chronic inorganic mercury intoxication produces the classic triad consisting of tremor, neuropsychiatric disturbances, and gingivostomatitis. The syndrome may result from long-term exposure to elemental mercury, inorganic mercury salts, or certain organic mercury compounds, all of which may be metabolized to mercuric ions. The tremor starts as a fine intention tremor of the fingers that is abolished during sleep but that may later involve the face and progress to choreoathetosis and spasmodic ballismus. Mixed sensorimotor neuropathy and visual disturbances may also be present. The neuropsychiatric disturbances include emotional lability, delirium, headaches, memory

loss, insomnia, anorexia, and fatigue. Renal dysfunction ranges from asymptomatic proteinuria to nephrotic syndrome.

Acrodynia, or **pink disease**, is a rare idiosyncratic hypersensitivity reaction to mercury that occurs predominantly in children exposed to mercurous powders. The symptom complex includes generalized pain, paresthesias, and an acral (hands, feet) rash that may spread to involve the face. The rash typically is red-pink, papular, pruritic, and painful; it may progress to desquamation and ulceration. Morbilliform, vesicular, and hemorrhagic variants have been described. Other important features include anorexia, apathy, photophobia, and hypotonia, especially of the pectoral and pelvic girdles. Irritability, tremors, diaphoresis, insomnia, hypertension, and tachycardia may be present. Some cases initially were diagnosed as pheochromocytoma. The outcome is good after removal of the source of mercury exposure.

Methyl mercury intoxication (also known as **Minamata disease** after the widespread mercury poisoning that occurred at Minamata Bay in Japan in people who had ingested contaminated fish) manifests as delayed neurotoxicity that appears after a latent period of weeks to months. It is characterized by ataxia; dysarthria; paresthesias; tremors; movement disorders; impairment of vision, hearing, smell, and taste; memory loss; progressive dementia; and death. Infants exposed in utero are the most severely affected, with low birthweight, microcephaly, profound developmental delay, cerebral palsy, deafness, blindness, and seizures. Although there is significant residual morbidity from methyl mercury neurotoxicity, observations on long-term follow-up of children exposed in Iraq reveal complete or partial resolution in most cases.

Laboratory Findings

The diagnosis of mercury intoxication is based on characteristic clinical findings, a history of exposure, and elevation of whole blood or urine mercury values, the last of which confirms the exposure. Thin-layer and gas chromatographic techniques can be used to distinguish organic from inorganic mercury. Blood should be collected in special tubes for trace elements from laboratories that capably perform those tests. Levels <10 µg/L in whole blood and <20 µg/L in a 24-hour urine specimen are considered normal (see Table 760.2). Although blood mercury levels may reflect acute exposure, they decrease as mercury redistributes into the tissues. Urine mercury levels are most useful for identifying long-term exposures, except in the case of methyl mercury, which undergoes minimal urinary excretion. Urinary mercury levels are used in monitoring efficacy of chelation therapy, whereas blood levels are used primarily in monitoring organic mercury poisonings. Hair analysis for mercury is not reliable because hair reflects

both endogenous and exogenous mercury exposure (hair avidly binds mercury from the environment). Abdominal radiographs may demonstrate ingested radiopaque mercury.

Urinary markers of early nephrotoxicity include microalbuminuria, retinol-binding protein, β_2 -microglobulin, and *N*-acetyl- β -D-glucosaminidase. Early neurotoxicity may be detected with neuropsychiatric testing and nerve conduction studies, whereas severe central nervous system toxicity is apparent on CT or MRI.

TREATMENT OF ARSENIC AND MERCURY INTOXICATION

The principles of management for arsenic and mercury intoxication include prompt removal from the source of poisoning, aggressive stabilization and supportive care, decontamination, and chelation therapy when appropriate. Once the diagnosis is suspected, the local poison control facility should be contacted, and care coordinated with physicians who are familiar with the management of heavy metal poisoning.

Supportive care for patients exposed to arsine gas requires close monitoring for signs of hemolysis, including evaluation of the peripheral blood smear and urinalysis. Transfusion of packed RBCs may be necessary, as may administration of intravenous fluids, sodium bicarbonate, and mannitol to prevent renal failure secondary to the deposition of hemoglobin in the kidneys. After inhalation of elemental mercury vapor, patients require careful monitoring of respiratory status, which may include pulse oximetry, arterial blood gas analysis, and chest radiography. Supportive care involves administration of supplemental oxygen and, in severe cases, intubation and mechanical ventilation.

Acute ingestion of inorganic arsenic and mercury salts results in hemorrhagic gastroenteritis, cardiovascular collapse, and multiorgan dysfunction. Fluid resuscitation, pressor agents, and transfusion of blood products may be required for management of cardiovascular instability. Severe respiratory distress, coma with loss of airway reflexes, intractable seizures, and respiratory paralysis are indications for intubation and mechanical ventilation. Renal function must be monitored carefully for signs of renal failure and the need for hemodialysis.

Gastrointestinal decontamination after ingestion of inorganic arsenic and mercury salts has not been well studied. Because of the corrosive effects of these compounds, induced emesis is not recommended, and endoscopy may be considered before gastric lavage. Arsenic and mercury are not well adsorbed to activated charcoal, but its use may be helpful if coingestants are suspected. Whole bowel irrigation is used to remove any radiopaque material remaining in the gastrointestinal tract.

Chelation for acute arsenic and mercury poisoning is most effective when administered as soon as possible after exposure. Chelation should be continued until 24-hour urinary arsenic or mercury levels return to normal ($<50 \mu\text{g/L}$ for arsenic and $<20 \mu\text{g/L}$ for mercury), the patient is symptom-free, or the remaining toxic effects are believed to be irreversible. The efficacy of chelation in long-term exposures is reduced because heavy metal in the tissue compartment is relatively nonexchangeable and some degree of irreversible toxicity has already occurred.

Dimercaprol, also known as *2,3-dimercaptopropanol* or *British anti-lewisite (BAL)*, is the chelator of choice for a patient who cannot tolerate oral therapy, as often is true for critically ill patients and after ingestion of the corrosive inorganic arsenic and mercury salts. Dimercaprol is available in 3-mL ampules at a concentration of 100 mg/mL for deep intramuscular (IM) injection. It is formulated in a peanut oil and benzyl benzoate suspension; as such, it is not suitable for patients with peanut allergy. For **arsenic poisoning**, the recommended regimen of dimercaprol is 2.5 mg/kg IM q4 hours for six doses, then every 6 hours for four doses, then every 8 hours for three doses, then every 12 hours for two doses, followed by once daily for 10 days. For severe arsenic poisoning, the dose of dimercaprol is increased to 3.5–5 mg/kg; the same dosing interval is followed. The dose of dimercaprol for **inorganic mercury poisoning** is 5 mg/kg every 4 hours IM for 24–48 hours, and then 2.5 mg/kg IM q12 hours for 10 days. The dimercaprol-heavy metal complex is excreted in the urine and bile. A period of

Table 760.4 Potential Strategies for Reducing Exposure of Arsenic in Rice

1. Diversify the diet
 - Eat a well-balanced diet and a variety of grains^{†,‡,§}
 - Identify children at risk for high consumption of rice and rice products (e.g., gluten-free diets, highly allergic)
2. Consider alternatives to rice for first food
 - Start infants on barley, oats, or other grains^{†,‡}
 - If rice cereal must be used for infants, limit to one serving per day[§]
3. Adopt strategies that help minimize exposure
 - Rinse rice in a colander before cooking[§]
 - Cook rice like pasta, with plenty of extra water[§]
 - Choose lower-arsenic varieties of rice (e.g., basmati)[§]
 - Avoid or limit use of rice milk or other rice beverages for infants[‡] and children under 5 yr old^{§,¶}
 - Read labels of processed foods: choose alternatives to foods sweetened with brown rice syrup or thickened with rice products
4. Regulatory action
 - Federal agencies should establish regulatory limits for arsenic content in rice and rice products[§]

[†]U.S. Food and Drug Administration.

[‡]American Academy of Pediatrics.

[§]Consumer Reports.

[¶]United Kingdom Food Standard Agency.

From Lai PY, Cottingham KL, Steinmaus C, et al. Arsenic and rice: translating research to address health care providers' needs. *J Pediatr*. 2015;167(4):797–803.

5 days between courses of chelation is recommended. Adverse effects of dimercaprol include pain at the injection site, hypertension, tachycardia, diaphoresis, nausea, vomiting, abdominal pain, a burning sensation in the oropharynx, and a feeling of constriction in the chest. Dimercaprol may cause hemolysis in glucose-6-phosphate dehydrogenase-deficient individuals. It is important to note that dimercaprol is contraindicated for chelation of methyl mercury because dimercaprol redistributes methyl mercury to the brain from other tissue sites, resulting in increased neurotoxicity.

Oral chelating agents are used to replace the painful dimercaprol injections when the patient is stable enough to tolerate oral therapy and prolonged chelation is necessary. **Succimer**, also known as *2,3-dimercaptosuccinic acid* (DMSA), is an orally administered water-soluble derivative of dimercaprol. DMSA is available in 100 mg capsules. The recommended regimen of DMSA for both arsenic and mercury poisoning is 10 mg/kg orally every 8 hours for 5 days followed by 10 mg/kg orally every 12 hours for 14 days. The DMSA-heavy metal complex is excreted in the urine and bile. A period of 2 weeks between courses of chelation is recommended. Mild adverse effects include nausea, vomiting, diarrhea, loss of appetite, and transient elevations in liver enzyme levels. DMSA also may cause hemolysis in glucose-6-phosphate dehydrogenase-deficient patients.

D-Penicillamine is an orally administered chelator that has been used in the past for less-severe mercury poisoning or as an adjunct to dimercaprol therapy in arsenic poisoning. Its use is largely restricted because of the potential for significant leukopenia, thrombocytopenia, and proteinuria along with the improved tolerability of succimer.

Patients with ingestion of elemental mercury require no follow-up unless there is an underlying disease that decreases the gastrointestinal transit time. Serial abdominal radiographs to document the progression of the metal are recommended. Acute inhalation of mercury fumes and ingestion of inorganic mercury require hospitalization to monitor the respiratory and gastrointestinal status, respectively. Therapeutic abortion may be considered in pregnant patients because of the teratogenic effect of mercury.

Strategies to reduce arsenic exposure in rice are noted in Table 760.4.

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Chapter 761

Lead Poisoning

Morri Markowitz

Lead is a metal that exists in four isotopic forms. Clinically it is purely a toxicant; no organism has an essential function that is lead dependent. Chemically its low melting point and ability to form stable compounds have made it useful in the manufacture of hundreds of products; this commercial attractiveness has resulted in the processing of millions of tons of lead ore, leading to widespread dissemination of lead in the human environment.

The **blood lead level (BLL)** is the gold standard for determining risk of health effects. The threshold level at which lead begins to cause biochemical, subclinical, or clinical disturbance remains to be determined. In 2021, the Centers for Disease Control and Prevention (CDC) designated 3.5 $\mu\text{g}/\text{dL}$ as the “reference value based on the 97.5th percentile of the population of US children aged 1-5 years.” It is the BLL that identifies the 2.5% of children with the highest BLLs. As a measure of the distribution of BLLs in young American children rather than a toxicity threshold, this number will change in a manner dependent on the epidemiology of BLLs. Surveillance by the CDC has shown that the prevalence of elevated BLLs has declined markedly. Approximately 500,000 U.S. children ages 1-5 years currently have BLLs $\geq 3.5 \mu\text{g}/\text{dL}$. Fortunately, children with levels high enough to be life-threatening ($>100 \mu\text{g}/\text{dL}$) are rarely seen in the United States, though deaths continue to occur in other areas of the world. Although BLL $\geq 3.5 \mu\text{g}/\text{dL}$ is stated as a reference value, it is likely that clinicians and departments of health will consider this a threshold for action.

PUBLIC HEALTH HISTORY

In the late 1970s, nearly all preschool-age children in the United States had BLLs above the current reference value of 3.5 $\mu\text{g}/\text{dL}$. Over the next 25 years, government regulations resulted in the significant reduction of three main contributors to lead exposure by means of (1) the elimination of the use of tetraethyl lead as a gasoline additive, (2) the banning of lead-containing solder to seal food- and beverage-containing cans, and (3) the application of a federal rule that limited the amount of lead allowed in paint intended for household use to less than 0.06% by weight (further reduced by the Consumer Product Safety Commission to 0.009% in 2008). Factors identified by the CDC in the late 1970s that indicate increased risk of lead poisoning, in addition to preschool age, include low socioeconomic status; living in older housing, built primarily before 1960; urban location; and Black race. Another high-risk group that has been identified consists of recent immigrants from less wealthy countries, including adoptees. These risk factors largely persist currently, as indicated by an analysis of over 1 million BLLs obtained from U.S. children between October 2018 and February 2020 and analyzed in a commercial lab. In addition, these data indicated that over half of the children still have measurable BLLs, i.e., $\geq 1 \mu\text{g}/\text{dL}$.

Progress is also being made globally. In Mexico, the introduction of unleaded gasoline in 1990 was associated with a decline in BLLs among first-grade students, from 17 $\mu\text{g}/\text{dL}$ in 1990 to 6.2 $\mu\text{g}/\text{dL}$ in 1997. Algeria, the last country to use leaded gasoline for cars and trucks, phased out its use in 2021. In Malta, after the import of red lead paint was banned and the use of lead-treated wood for fuel in bakeries was prohibited, mean BLLs of pregnant women and newborns decreased by 45%. After it was documented that children living in the neighborhood of a battery factory in Nicaragua had a mean BLL of 17.2 $\mu\text{g}/\text{dL}$, but children in the control community had a mean BLL of 7.4 $\mu\text{g}/\text{dL}$, the factory was closed. Despite these advances, in 2021 the World Health Organization (WHO), citing research for UNICEF by the Institute for Health Metrics and Evaluation, estimated that 815 million children globally may have elevated BLLs above 5 $\mu\text{g}/\text{dL}$. The majority live in developing countries, where in some regions BLLs may be 10- to 20-fold higher than in developed countries.

Unfortunately, local lead-related harms continue to occur. When the water source for Flint, Michigan, was changed (2014) to the Flint River and utilized a water treatment plant with poor corrosion control, the lead level of Flint tap water increased, as did the BLLs of children <5 years of age. Flint is not unique; many other cities have lead pipes that can result in water contamination. In 2021 the US government allocated \$15 billion for lead pipe removal.

In 2010, the CDC and WHO identified numerous lead-contaminated villages in northern Nigeria. The grinding of ore to extract gold caused widespread lead dust dissemination. It is likely that hundreds of children died because of this activity, and all remaining children in some of the villages assessed were lead poisoned, with 97% having a BLL $\geq 45 \mu\text{g}/\text{dL}$, the threshold for chelation therapy in the United States. Unfortunately, such disasters continue to occur in Nigeria and neighboring countries from similar metal extraction activities.

SOURCES OF EXPOSURE

Lead poisoning may occur in utero because lead readily crosses the placenta from maternal blood. The spectrum of toxicity is similar to that experienced by children after birth. The source of maternal blood lead content is either redistribution from endogenous stores (i.e., the mother's skeleton) or lead newly acquired from ongoing environmental exposure.

Several hundred products contain lead, including paint, batteries, cable sheathing, cosmetics, mineral supplements, plastics, toys (Table 761.1), and traditional medicines (Table 761.2). Major sources of exposure vary among and within countries; the major source of exposure in the United States remains old lead-based paint. Approximately 34.6 million homes, mainly built before 1950, have lead-based paint (2021 estimate), of which the CDC has estimated that 22.3 million are in a hazardous state. As paint deteriorates, it chinks, flakes, and turns to dust. Improper rehabilitation work of painted surfaces (e.g., sanding) can result in dissemination of lead-containing dust throughout a home. The dust can coat all surfaces, including children's hands. All of these forms of lead can be ingested. If heat is used to strip paint, then lead vapor concentrations in the room can reach levels sufficient to cause lead poisoning via inhalation. There is an increased awareness that tap water in both homes and schools may have substantial amounts of lead. The latter arose from the discovery of contaminated water in most New York City public schools. Moreover, this occurrence raised questions about the safety of the US Environmental Protection Agency (EPA) lead-in-water-standard of 15 parts per billion (ppb; μg of Pb/L of water) that water distribution companies must meet in at least 90% of homes in their service areas. This standard was not based on achieving health safety but rather on what the water companies felt was financially feasible. After review, in 2021 the EPA recommended lowering the “trigger” level to 10 ppb. Breaching this value requires water companies to prepare an intervention plan should the level subsequently go over 15 ppb. It does not require action to reduce the amount of lead in that water supply. Even 10 ppb is still much greater than the 1 ppb recommended by the American Academy of Pediatrics as the limit for allowable lead in drinking water. It should be noted that the EPA lead in water standard does not apply to schools, although many states have set their own standards.

In other parts of the world, especially in poorer countries, additional sources can be found. These include contaminated neighborhoods as the result of car/truck battery lead recycling, aluminum cookware made with recycled metals, spices, and traditional medicines.

METABOLISM

The nonnutritive hand-to-mouth activity of young children is the most common pathway for lead to enter the body. In most cases, lead is ingested either as a component of dust licked off of surfaces or in swallowed paint chips, through water contaminated by its flow through lead pipes or brass fixtures, or from otherwise contaminated foods or liquids. Cutaneous contamination with inorganic lead compounds, such as those found in pigments, does not result in a substantial amount of absorption. Organic lead compounds, such as tetraethyl lead, may penetrate through skin; however, these are rarely encountered.

The percentage of lead absorbed from the gut depends on several factors: particle size, pH, other material in the gut, and nutritional status of

Table 761.1 Sources of Lead

Paint chips
Dust
Soil
Parent's or household contact's occupational exposure (auto repair, smelting, construction, remodeling, plumbing, gun/bullet (firing range) exposure, painting, e-scrap)
Glazed ceramics
Herbal remedies (e.g., Ayurvedic medications)
Home remedies, including antiperspirants, deodorants (lithargirio)
Jewelry (toys or parents')
Stored battery casings or recycling (or living near a battery smelter)
Lead-based gasoline (in aviation fuel for propeller planes)
Moonshine alcohol
Mexican candies; Ecuadorian chocolates
Ceremonial spices
Indoor firing ranges
Retained bullet fragments
Imported spices (suanuri marili, zafron, kuzhambu)
Lead-based cosmetics (kohl, surma, kajal)
Lead plumbing (water)
Imported foods in lead-containing cans
Domestic foods (applesauce pouches, others)
Imported toys
Home renovations
Antique toys or furniture
Kratom

Table 761.2 Cases of Lead Encephalopathy Associated with Traditional Medicines by Type of Medication

TRADITIONAL MEDICAL SYSTEM	NO. (%) CASES OF LEAD ENCEPHALOPATHY	NO. (%) PEDIATRIC CASES WITHIN CAM SYSTEM OR MEDICATION
Ayurveda	5 (7)	1 (20)
Ghasard	1 (1)	1 (100)
Traditional Middle Eastern practices	66 (87)	66 (100)
Azarcon and Greta	2 (3)	2 (100)
Traditional Chinese medicine	2 (3)	2 (100)
Total	76 (100)	72 (95)

CAM, Complementary and alternative medicines.

From Karri SK, Saper RB, Kales SN. Lead encephalopathy due to traditional medicines. *Curr Drug Saf.* 2008;3:54–59.

essential elements. Large paint chips are difficult to digest and are mainly excreted; this chemical characteristic of lead compounds is fortunate, as a single chip may contain a potentially lethal dose of lead. Fine dust can be dissolved more readily, especially in an acid medium. Lead eaten on an empty stomach is better absorbed than that taken with a meal. The presence of **calcium** and **iron** may decrease lead absorption by direct competition for binding sites; iron (and probably calcium) deficiency results in enhanced lead absorption, retention, and toxicity.

After absorption, lead is disseminated throughout the body via blood. It circulates bound to erythrocytes; approximately 97–99% of lead in blood is bound on or in the red blood cells. The plasma fraction is too small to be measured by conventional techniques employing atomic absorption spectroscopy or anodic stripping voltammetry; it is presumably the plasma portion that may leave the blood compartment to enter cells and induce toxicity. Thus clinical laboratories report the BLL, not the serum or plasma lead level. The increasing availability and decreasing cost of inductively coupled plasma mass spectrometry, which is capable of measuring lead in ng/dL quantities, may eventually

result in clinical availability of tools to measure plasma lead, a more proximal measure to where toxicity is actually occurring.

Most retained lead accumulates in bone, where it resides for years. But in all cells, lead has multiple effects. It binds to enzymes, particularly those with available sulfhydryl groups, changing the contour and diminishing function. For example, three of eight enzymes in the ubiquitously distributed heme pathway are susceptible to lead inhibitory effects. The accumulation of excess amounts of heme precursors is also toxic. The last enzyme in this pathway, ferrochelatase, enables protoporphyrin to chelate iron, thus forming heme. **Erythrocyte protoporphyrin (EP)** levels higher than 35 µg/dL (laboratory dependent) are abnormal and are consistent with lead poisoning, iron deficiency, or recent inflammatory disease. Measurement of the EP level is thus a useful tool for monitoring biochemical lead toxicity. EP levels begin to rise several weeks after BLLs have reached 20 µg/dL in a susceptible portion of the population and are elevated in nearly all children with BLLs higher than 50 µg/dL. A drop in EP levels also lags behind a decline in BLLs by several weeks because it depends on both cell turnover and cessation of further overproduction by marrow red blood cell precursors. The test can be ordered either as the free EP or the zinc protoporphyrin. Results are reported in µg/dL. When reported in µmol/mmol this likely indicates that the analysis has been standardized to a hematocrit of 45, an unwarranted assumption in young children.

A second mechanism of lead toxicity works via its competition with calcium. Many calcium-binding proteins have a higher affinity for lead than for calcium. Lead bound to these proteins may alter function, resulting in abnormal intracellular and intercellular signaling. Neurotransmitter release is, in part, a calcium-dependent process that is adversely affected by lead.

Although these two mechanisms of toxicity may be reversible, a third mechanism prevents the development of the normal tertiary brain structure. In immature mammals the normal neuronal pruning process that results in elimination of multiple intercellular brain connections is affected by lead. Failure to construct the appropriate tertiary brain structure during infancy and childhood may result in a permanent abnormality. In a longitudinal study of childhood lead poisoning, MRI examinations of the participants when in their 20s found smaller areas of brain in the prefrontal cortex and hippocampus regions, areas involved in decision-making and memory formation.

CLINICAL EFFECTS

The BLL is the best-studied measure of the lead burden in children. Although subclinical and clinical findings correlate with BLLs in populations, there is considerable interindividual variability in this relationship. **Lead encephalopathy** is more likely to be observed in children with BLLs higher than 100 µg/dL; however, one child with a BLL of 300 µg/dL may have no symptoms, whereas another with the same level may be comatose. Susceptibility may be associated with polymorphisms in genes coding for lead-binding proteins, such as Δ -aminolevulinic acid dehydratase, an enzyme in the heme pathway.

Several **subclinical effects** of lead have been demonstrated in cross-sectional epidemiologic studies. Hearing and height are inversely related to BLLs in children; in neither case, however, does the lead effect reach a level that would bring an individual child to medical attention. As BLLs increase in the study populations, more sound (at all frequencies) is needed to reach the hearing threshold. Children with higher BLLs are shorter than those with lower levels; for every 10 µg increase in the BLL, the children are 1 cm shorter. Chronic lead exposure also may delay puberty.

Several longitudinal studies have followed cohorts of children for decades after birth and examined the relationship between BLLs and cognitive test scores over time. In general, there is agreement that BLLs, expressed either as levels obtained concurrently with cognitive testing or as a measure that integrates multiple BLLs drawn from subjects over time, are inversely related to cognitive test scores. From these studies, no BLL above 0 µg/dL appears safe. On average, for each 1 µg/dL elevation in BLL, the cognitive score is approximately 0.25–0.50 points lower, though the relationship is not linear across the BLL spectrum.

Because the BLLs from early childhood are predictors of the cognitive test results performed years later, this finding implies that the effects of lead can be permanent.

The effect of in utero lead exposure is less clear. Scores on the Bayley Scale of Mental Development were obtained repeatedly every 6 months for the first 2 years of life in a cohort of infants born to middle-class families. Results correlated inversely with cord BLLs, a measure of in utero exposure. However, after 2 years of age, all other cognitive tests performed on the cohort over the next 10 years correlated with the BLLs at age 2 years but not with cord BLLs, indicating that the effects of prenatal lead exposure on brain function were superseded by early childhood events and later BLLs. Later studies, performed in cohorts of Mexican children monitored from the prenatal period, confirm the association between in utero lead exposure and later cognitive outcomes. In these studies, maternal plasma lead levels, obtained especially during the first trimester, were more strongly associated with cognitive scores in the offspring than with the traditionally measured maternal whole BLLs.

Behavior also is adversely affected by lead exposure. Hyperactivity is noted in young school-age children with histories of lead poisoning or with concurrent elevations in BLL. Older children with higher bone lead content are more likely to be aggressive and to have behaviors that are predictive of later juvenile delinquency. One report supports the concept of long-term effects of early lead exposure. In this longitudinal study, the mothers of a cohort were enrolled during their pregnancies. BLLs were obtained early in pregnancy, at birth, and then multiple times in the offspring during the first 6 years. The investigators report that the later relative rate of arrests, especially for violent crimes, increased significantly in relationship to the presence of these BLLs early in life. For every 5 µg/dL increase in BLL, the adjusted arrest rate was 1.40 for prenatal BLLs and 1.27 for 6-year BLLs. Epidemiologic data support the findings in this observational study. In an analysis that combined two national datasets, total annual leaded gasoline use (U.S. Geological Survey) and total reported violent criminal acts (U.S. Department of Justice), the amount of leaded gasoline used yearly was found to be strongly associated with violent criminal behavior with a lag time of 23 years; that is, early childhood exposure was followed two decades later by violent behavior rising and falling in close tandem. A similar association was found, this time between urban air lead levels and later violent crime, with a similar best-fit model employing a lag of approximately 22 years.

An intervention study, in which children with moderate lead poisoning and initial BLLs of 20–55 µg/dL were aggressively managed over 6 months, addressed the issue of the effects of treatment on cognitive development. Components of treatment included education regarding sources of lead and its abatement, nutritional guidance, multiple home and clinic visits, and for a subset, chelation therapy. Average BLLs declined, and cognitive scores were inversely related to the change in BLLs. For every 1 µg/dL fall in BLLs, cognitive scores were 0.25 point higher. A randomized placebo-controlled treatment study of 2-year-old children with initial BLLs of 20–44 µg/dL that employed the chelating agent succimer administered over 6 months found no difference in mean cognitive scores at age 4 years. However, as in the earlier treatment study, regression analysis did find an inverse relation between *change* scores; that is, a change in BLLs was associated with an inverse change in cognitive scores.

Whether the behavioral effects of lead are reversible is unclear. In one small, short-term study, 7-year-old hyperactive children with BLLs in the 20s were randomly allocated to receive a chelating agent (penicillamine), methylphenidate, or placebo. Teacher and parent ratings of behavior improved for the first two groups but not the placebo group. BLLs declined only in the chelated group. Two-year-old lead-poisoned children enrolled in a placebo-controlled trial of the chelating agent succimer showed no mean difference in behavior at 4 or 7 years of age. However, mean BLLs were also not different in the two groups at those ages.

These studies support the concept that early exposure to lead can result in long-term deficits in cognition and behavior; they also hold

out the possibility that reductions in lead burden may be associated with improvement in cognitive test scores.

CLINICAL SYMPTOMS

Gastrointestinal symptoms of lead poisoning include anorexia, abdominal pain, vomiting, and constipation, often occurring and recurring over a period of weeks. Children with BLLs higher than 20 µg/dL are twice as likely to have gastrointestinal complaints as those with lower BLLs. **Central nervous system** symptoms are related to worsening cerebral edema and increased intracranial pressure. Headaches, change in mentation, lethargy, papilledema, seizures, and coma leading to death are rarely seen at levels lower than 100 µg/dL but have been reported in children with a BLL as low as 70 µg/dL. The last-reported death directly attributable to lead toxicity in the United States was in 2006 in a child with a BLL of 180 µg/dL. There is no clear cutoff BLL value for the appearance of hyperactivity, but it is more likely to be observed in children who have levels higher than 20 µg/dL.

Other organs also may be affected by lead toxicity, but symptoms usually are not apparent in children. At high levels (>100 µg/dL), renal tubular dysfunction is observed. Lead may induce reversible Fanconi syndrome. In addition, at high BLLs, red blood cell survival is shortened, possibly contributing to a hemolytic anemia, although most cases of anemia in lead-poisoned children are a result of other factors, such as iron deficiency and hemoglobinopathies. Older patients may develop peripheral neuropathy leading to wrist drop and foot drop, as well as hypertension.

DIAGNOSIS

Screening

It is estimated that 99% of lead-poisoned children are identified by screening procedures rather than through clinical recognition of lead-related symptoms. Until 1997, universal screening by blood lead testing of all children at ages 12 and 24 months was the standard in the United States. Given the national decline in the prevalence of lead poisoning, the recommendations have been revised to target blood lead testing of high-risk populations. High risk is based on an evaluation of the likelihood of lead exposure. Departments of health are responsible for determining the local prevalence of lead poisoning, as well as the percentage of housing built before 1950, the period of peak lead paint use. When this information is available, informed screening guidelines for practitioners can be issued. For instance, in New York State, where a large percentage of housing was built before 1950, the Department of Health mandates that all children be tested for lead poisoning via blood analyses. *In the absence of such data, the practitioner should continue to test all children at both 12 and 24 months.* In areas where the prevalence of lead poisoning and old housing is low, targeted screening may be performed on the basis of a risk assessment. Three questions form the basis of most published questionnaires (Table 761.3), and items that are pertinent to the locale or individual may be added. If there is a lead-based industry in the child's neighborhood, the child is a recent immigrant from a country that until recently still permitted the use of leaded gasoline, or the child has **pica** (pattern of eating non-food materials) or developmental delay, blood lead testing would be appropriate. All Medicaid-eligible children should be screened by blood lead testing. Venous sampling is preferred to capillary sampling because the chances of false-positive and false-negative results are less with the former. However, capillary screening can be performed rapidly in the office with a point of care (POC) instrument; use of such instruments in primary care offices substantially increases screening rates. Other screening guidelines vary by federal, state, and even local governmental agencies. Contacting your local Department of Health is one way to determine local primary care obligations.

The threshold for lead effects and the reference level for risk management purposes are not the same. Laboratory issues make the interpretation of values more difficult at low levels. Most labs achieve quality control of ± 2 µg/dL for reports of BLL, but federal regulations allow laboratories that perform BLL testing to operate with an allowable error of ± 4 µg/dL. A capillary screening value ≥ 3.5 µg/dL requires a venous sample for confirmation (Table 761.4). If the diagnostic (venous) test

Table 761.3 Minimum Personal Risk Questionnaire

1. Does the child live in or regularly visit a house that was built before 1950? (Include settings such as daycare, babysitter's, or relative's home.)
2. Does the child live in or regularly visit a house built before 1978 with recent (past 6 months) or ongoing renovations or remodeling?
3. Does the child have a sibling or playmate who has or did have lead poisoning?

From Screening young children for lead poisoning. Guidance for state and local public health officials. Atlanta: Centers for Disease Control and Prevention, 1997.

Table 761.4 Recommended Schedule for Obtaining a Confirmatory Venous Sample

BLOOD LEAD LEVEL ($\mu\text{g}/\text{dL}$)	TIME TO CONFIRMATION TESTING*
≥ 3.5 -9	Within 3 mo
10-19	Within 1 mo
20-44	Within 2 wk
≥ 45	Within 48 hr

*The higher the blood lead level is on the initial screening capillary test, the more urgent it is to get a venous sample for confirmatory testing.

Courtesy Centers for Disease Control and Prevention, 2022. https://www.cdc.gov/nceh/lead/advisory/acclpp/actions-blls.htm#anchor_86654

confirms that the BLL is elevated, then further testing is required by the recommended schedule (Table 761.5). A confirmed venous BLL of 45 $\mu\text{g}/\text{dL}$ or higher requires prompt chelation therapy.

Other Tools for Assessment

BLL determinations remain the gold standard for evaluating children because of ready availability and its correlation with health outcomes in populations. Techniques are available to measure lead in other tissues and body fluids. Experimentally, the method of x-ray fluorescence (XRF) allows direct and noninvasive assessment of bone lead stores. XRF methodology was used to evaluate a population that had long-term exposure to lead from a polluting battery-recycling factory. The study found that the school-age children had elevated lead levels in bone but not in venous blood, a finding that is consistent with our understanding of the slow turnover of lead in bone, which is measurable in years, in contrast to that in blood, which is measurable in weeks. It also indicates that children may have substantial lead in their bodies that is not detected by routine blood lead testing. This stored lead may be released to toxic levels if bone resorption rates suddenly increase, as occurs with prolonged immobilization of longer than a week and during pregnancy. Thus children with histories of elevated BLLs are potentially at risk for recrudescence of lead toxicity long after ingestion has stopped and may pass this lead to the next generation. XRF methodology is not available for clinical use in children.

Lead also can be measured in urine. Spontaneous excretion, even in children with high BLLs, is usually low. Lead excretion may be stimulated by treatment with chelating agents, and this property of these drugs forms the basis of their use as a component of lead treatment. It also has been used to develop a test that differentiates children with lead burdens responsive to chelation therapy, the **lead mobilization test**. In this test, a timed urine collection follows one or two doses of chelating agent, and the lead content is determined. However, this test is no longer recommended.

Lead in hair, nails, and saliva also is measurable but has problems of contamination and interpretability; thus these have no clinical utility. Radiographs of long bones may show dense bands at the metaphyses ("lead lines"), which may be difficult to distinguish from growth arrest

Table 761.5 Schedule for Follow-Up Blood Lead Testing

VENOUS BLOOD LEAD CONCENTRATIONS ($\mu\text{g}/\text{dL}$)	EARLY FOLLOW-UP TESTING (2-4 TESTS AFTER INITIAL TEST ABOVE SPECIFIC VENOUS BLLs)	LATER FOLLOW-UP TESTING AFTER BLL DECLINING
≥ 3.5 -9	3 mo*	6-9 mo
10-19	1-3 mo*	3-6 mo
20-44	2 wk to 1 mo	1-3 mo
≥ 45	As soon as possible	As soon as possible

BLL, Blood lead level.

Courtesy Centers for Disease Control and Prevention, 2022. <https://www.cdc.gov/nceh/lead/advisory/acclpp/actions-blls.htm>



Fig. 761.1 Anteroposterior radiograph of the abdomen demonstrates retention of radiopaque lead-based paint chips within bowel, predominantly clustered in the ascending colon. Other etiologies resembling "paint chips" include certain medications, eggshells, other heavy metals including iron- and calcium-containing supplements. Dense "lead lines" are noted in the proximal femoral metaphyses. (From Swenson DW, Walters MM. *Musculoskeletal imaging*. In: Walters MM, Robertson RL, eds. *Pediatric Radiology: The Requisites*, 4th ed. Philadelphia: Elsevier; 2017: Fig. 7.50, p. 214.)

lines but, if caused by lead, are indicative of months to years of exposure (Fig. 761.1). For children with acute symptoms, when a BLL result is not immediately available, a **kidneys-ureters-bladder (KUB) radiograph** may reveal **radiopaque flecks** in the intestinal tract, a finding that is consistent with recent ingestion of lead-containing plaster or paint chips (see Fig. 761.1). However, the absence of radiographic findings does not rule out lead poisoning.

Because BLLs reflect recent ingestion or redistribution from other tissues but do not necessarily correlate with the body burden of lead or lead toxicity in an individual child, tests of lead effects also may be useful. After several weeks of lead accumulation and a BLL higher than 20 $\mu\text{g}/\text{dL}$, increases in EP values to more than 35 $\mu\text{g}/\text{dL}$ may occur. An elevated EP value that cannot be attributed to iron deficiency or recent inflammatory illness is both an indicator of lead effect and a useful means of assessing the success of the treatment; the EP level will begin to fall a few weeks after successful interventions that reduce lead ingestion and increase lead excretion. Because EP is light sensitive, whole blood samples should be covered in aluminum foil (or equivalent) until analyzed.

TREATMENT

All BLLs ≥ 3 $\mu\text{g}/\text{dL}$ should be reported to state or local health departments. Once lead is in bone, it is released slowly and is difficult to remove even with chelating agents. Because the cognitive/behavioral effects of lead may be irreversible, the main effort in treating lead poisoning is to prevent it from occurring and to prevent further ingestion by already-poisoned children. The main components in the effort to eliminate lead poisoning are universally applicable to all children (and adults) and are as follows: (1) identification and elimination of environmental sources of lead exposure, (2) behavioral modification to reduce nonnutritive hand-to-mouth activity, and (3) dietary counseling to ensure sufficient intake of the essential elements calcium and iron and their supporting vitamins, D and C. For the small minority of children with more severe lead poisoning, drug treatment is available that enhances lead excretion. How effective these interventions may be at reducing BLLs or improving cognitive function remains unclear at the lower BLLs commonly observed currently in young children in the United States.

During health maintenance visits a limited risk assessment is warranted, which includes questions pertaining to the most common sources of lead exposure: the condition of old paint, secondary occupational exposure via an adult living in the home, and/or proximity to an industrial source of pollution. If such a source is identified, its elimination usually requires the assistance of public health and housing agencies as well as education for the parents. It would be safest for the family to move out of a lead-contaminated apartment until repairs are completed. During repairs, repeated washes of surfaces and the use of high-efficiency particle accumulator (HEPA) vacuum cleaners help reduce exposure to lead-containing dust. Careful selection of a contractor who is certified to perform lead abatement work is necessary. Sloppy work can cause dissemination of lead-containing dust and chips throughout a home or building and result in further elevation of a child's BLL. After the work is completed, dust wipe samples should be collected from floors and windowsills or wells to verify that the risk from lead has abated. The standards for what are considered acceptable lead dust levels have recently been modified by the EPA to lower limits that are more protective.

A single case of lead poisoning is often discovered in a household with multiple family members, including other young children, and even in a household with a common source of exposure such as peeling lead-based paint. The mere presence of lead in an environment does not produce lead poisoning. Parental efforts at reducing the hand-to-mouth activity of the affected child are necessary to reduce the risk of lead ingestion. Handwashing with soap and water effectively removes lead, but in a home with lead-containing dust, lead rapidly begins to reaccumulate on the child's hands after washing. Therefore handwashing is best limited to the period immediately before nutritive hand-to-mouth activity occurs.

Because there is competition between lead and essential metals, it is reasonable to promote a healthy diet that is sufficient in calcium and iron. The recommended daily intakes of these metals vary somewhat with age. In general, for children 1 year of age and up, a calcium intake of about 1 g/day is sufficient and convenient to remember (roughly the calcium content of a quart of milk [$\sim 1,200$ mg/qt] or calcium-fortified orange juice). Calcium absorption is vitamin D dependent; milk is fortified with vitamin D, but other nutritional sources of calcium often are not. A multivitamin containing vitamin D may be prescribed for children who do not drink sufficient milk or who have inadequate sunlight exposure. Iron requirements also vary with age, ranging from 6 mg/day for infants to 12 mg/day for adolescents. For children identified biochemically as being iron deficient, therapeutic iron at a daily dose of up to 5–6 mg/kg/day for 3 months is appropriate. Iron absorption from vegetables is enhanced when iron is ingested with vitamin C (ascorbic acid), which is found in citrus juices. Giving additional calcium or iron above the recommended daily intake to mineral-sufficient children has not been shown to be of therapeutic benefit in the treatment of lead poisoning.

For children with BLLs of ≥ 20 $\mu\text{g}/\text{dL}$, an abdominal x-ray should be considered to check for lead-based paint chips or leaded foreign bodies, if not already obtained. If radiopaque fragments are visualized on imaging, bowel decontamination (typically with whole bowel irrigation) should be initiated (see Chapter 94).

Drug treatment to remove lead is lifesaving for children with lead encephalopathy. In nonencephalopathic children, it prevents symptom progression and further toxicity. Guidelines for **chelation** are based on the BLL. *A child with a venous BLL of 45 $\mu\text{g}/\text{dL}$ or higher should be treated.* Four drugs have been used in the United States: 2,3-dimercaptosuccinic acid (DMSA [succimer]), CaNa_2EDTA (versenate), British anti-lewisite (BAL [dimercaprol]), and penicillamine. DMSA and penicillamine can be given orally, whereas CaNa_2EDTA and BAL can be administered only parenterally. The choice of agent is guided by the severity of the lead poisoning, the effectiveness of the drug, and the ease of administration (Table 761.6). Children with BLLs of 44–70 $\mu\text{g}/\text{dL}$ may be treated with a single drug, preferably DMSA. Those with BLLs of 70 $\mu\text{g}/\text{dL}$ or greater require two-drug treatment: CaNa_2EDTA in combination with either DMSA or BAL for those without evidence of encephalopathy, or CaNa_2EDTA and BAL for those with encephalopathy. Published data on the combined treatment with CaNa_2EDTA and DMSA for children with BLLs higher than 100 $\mu\text{g}/\text{dL}$ are very limited. However, anecdotal information derived from the treatment of hundreds of severely lead-poisoned children in northern Nigeria indicates that single-drug treatment with DMSA is lifesaving, although the degree of long-term residual damage in survivors has not been reported.

Drug-related toxicities are minor and reversible. These include gastrointestinal distress, transient elevations in transaminases, active urinary sediment, and neutropenia. These types of events are least common for CaNa_2EDTA and DMSA, and more common for BAL and penicillamine. All of the drugs are effective in reducing BLLs when given in sufficient doses and for the prescribed time. These drugs also may increase lead absorption from the gut and should be administered to children in lead-free environments. Some authorities also recommend the administration of a cathartic immediately before or concomitant with the initiation of chelation to eliminate any lead already in the gut.

None of these agents removes all lead from the body. Within days to weeks after completion of a course of therapy, the BLL rises, even in the absence of new lead ingestion. The source of this rebound in the BLL is believed to be release from bone. Serial examinations of bone lead content have shown that chelation with CaNa_2EDTA is associated with a decline in bone lead levels, but that residual bone lead remains detectable even after multiple courses of treatment.

Repeat chelation is indicated if the BLL rebounds to 45 $\mu\text{g}/\text{dL}$ or higher. Children with initial BLLs higher than 70 $\mu\text{g}/\text{dL}$ are likely to require more than one course. A minimum of 3 days between courses is recommended to prevent treatment-related toxicities, especially in the kidney.

The indication for chelation therapy for children with BLLs < 45 $\mu\text{g}/\text{dL}$ is less clear. Although use of these drugs in children with BLLs from 20–45 $\mu\text{g}/\text{dL}$ will result in transiently lowered BLLs, and in some cases reversal of lead-induced enzyme inhibition, few such children increase their excretion of lead significantly during chelation, raising the question of whether any long-term benefit is achieved. A study of 2-year-old children with BLLs of 20–44 $\mu\text{g}/\text{dL}$ who were randomized to receive either DMSA or placebo found that the drop in BLLs was greater in the first 6 months after enrollment in the DMSA-treated group, but the levels converged by 1 year of follow-up. Mean cognitive test scores obtained at 4 and 7 years of age were not statistically different between the groups. Chelation with DMSA (and CaNa_2EDTA) is not recommended for all children with BLLs < 45 $\mu\text{g}/\text{dL}$. Further work needs to be done to determine whether there are subgroups of children with BLLs < 45 $\mu\text{g}/\text{dL}$ who might benefit from chelation. It also remains to be demonstrated whether other chelating agents available in the United States or elsewhere are effective at either substantially reducing body stores (bone) of lead or reversing the cognitive deficits attributable to lead at these BLLs.

Table 761.6 Chelators Used for Lead Poisoning

CHELATOR	DOSAGE	INDICATIONS	CONTRAINDICATIONS	ADVERSE EFFECTS
Succimer (DMSA)	1050 mg/m ² /day divided into 3 doses for 5 days, then 700 mg/m ² /day divided into 2 doses for 14 days (maximum 500 mg per dose for children)	BLL >45 µg/dL	None	Nausea, vomiting Diarrhea Metallic taste Transient increase in AST/ALT
CaNa ₂ EDTA	1,500 mg/mm ² /day continuous intravenous (IV) infusion for encephalopathy Otherwise: 1,000 mg/m ² /day divided in 2 to 4 doses for up to 5 days, IV or IM	BLL >70 µg/dL (starting after first dose of BAL or succimer) May substitute for succimer if that drug is not tolerated	Severe renal disease Hepatitis	Nephrotoxicity Transient increase in AST/ALT Arrhythmia (bradycardia)
Dimercaprol (BAL)	4 mg/kg deep IM injection every 4 hours for 5 days in children and adults	BLL >70 µg/dL and encephalopathy Consider succimer as alternative	Peanut allergy Organic mercury poisoning Hepatic insufficiency	Pain at injection site Hypertension and tachycardia Nausea, vomiting Headache Fever (especially in children) Nephrotoxicity in the setting of an acidic urine
D-Penicillamine	1-1.5 g/day (children: 20-30 mg/kg/day), in 3 or 4 divided doses for 1-6 months To minimize adverse reactions, start at 250 mg/day (children: 10 mg/kg/day) and increase to 50% during week 2 and to a full dose by week 3 Maximum adult daily dose is 2 g	BLL of 45 to 69 µg/dL AND succimer not tolerated	Penicillin allergy	Leukopenia Thrombocytopenia Enuresis Abdominal pain Rashes

Note: Indications for chelation and dosing regimens may change. Consult with a medical toxicologist or regional poison center for the most up-to-date recommendations. BAL, British antilewisite; BLL, blood lead level; CaNa₂EDTA, calcium disodium ethylenediaminetetraacetic acid; DMSA, 2,3-dimercaptosuccinic acid; IM, intramuscular; AST, alanine transaminase; ALT, aspartate transaminase.

Modified from Theobald JL, Mycyk MB. Iron and heavy metals. In: Walls RM, ed. *Rosen's Emergency Medicine*, 10th ed. Philadelphia: Elsevier; 2023: Table 146.5.

With successful intervention, BLLs decline, with the greatest fall in BLL occurring in the first 2 months after therapy is initiated. Subsequently, the rate of change in BLL declines slowly, so that by 6-12 months after identification, the BLL of the average child with moderate lead poisoning (BLL >20 µg/dL) will be 50% lower. Children with more markedly elevated BLLs may take years to reach the current CDC reference level, 3.5 µg/dL, even if all sources of lead exposure have been eliminated, behavior has been modified, and nutrition has been maximized. Early screening remains the best way of avoiding and therefore obviating the need for the treatment of lead poisoning.

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Chapter 762

Nonbacterial Food Poisoning

762.1 Mushroom Poisoning

Diane P. Calello and Katherine Baranowski

Mushrooms are an ideal food. They are low in calories, fat free, and high in protein, making them a great source of nutrition. Unfortunately, some are highly toxic if ingested. Picking (foraging) and consumption of wild mushrooms are increasingly popular in the United

States. This rise in popularity has led to increased reports of severe and fatal mushroom poisonings.

The clinical syndromes produced by mushroom poisoning are divided according to the rapidity of onset of symptoms and the predominant system involved (Table 762.1). The symptoms are caused by the principal toxin present in the ingested mushrooms. The eight major toxins produced by mushrooms are categorized as cyclopeptide (*amatoxin* and *phallotoxin*), gyromitrin, muscarine, coprine, ibotenic acid and muscimol, psilocybin, orellanine, and gastrointestinal tract-specific irritants. The edible wild mushroom *Tricholoma equestre* is associated with delayed rhabdomyolysis, and *Clitocybe amoenolens* and *Clitocybe acromelalga* have been reported to cause erythromelalgia, although toxins responsible for these effects are unknown.

Symptoms after eating mushrooms may not be the direct effect of a toxin but may be an allergic reaction or a toxic effect of pesticides or other contaminants. In addition, all who ate the same mushroom may not become sick, or if they do, they may become sick at different intervals. Table 762.2 lists general principles of management. Wherever possible, identification of the implicated mushroom is encouraged via mycologist or regional Poison Control Center.

GASTROINTESTINAL

Rapid Onset

Many mushrooms from various genera (such as *Chlorophyllum* species) produce local gastrointestinal manifestations. The causative toxins are diverse and largely unknown. Within 1 hour of ingestion, patients experience acute abdominal pain, nausea, vomiting, and diarrhea. Symptoms may last hours to days, depending on the species of mushroom.

Treatment is mainly supportive. Children with large fluid losses may require parenteral fluid therapy. It is imperative to differentiate ingestion of mushrooms of this class from ingestion of *Amanita* and

Table 762.1 Summary of Common Mushroom-Associated Syndromes			
TOXIN	SYNDROME	CLINICAL COURSE	TYPICAL CAUSATIVE MUSHROOM(S)
Cyclopeptides, principally amatoxins	Delayed gastroenteritis followed by hepatic failure	Stage 1: 6-24 hr after ingestion: onset of nausea, vomiting, profuse cholera-like diarrhea, abdominal pain, hematuria Stage 2: 12-48 hr after ingestion: apparent recovery; levels of hepatic enzymes are rising during this stage Stage 3: 24-72 hr after ingestion: progressive hepatic and renal failure, coagulopathy, cardiomyopathy, encephalopathy, convulsions, coma, death	"Deadly <i>Amanitas</i> ," (<i>A. phalloides</i> , <i>A. bisporigera</i>) <i>Galerina</i> species
General gastrointestinal irritants	Early gastroenteritis, may be severe	30 min to 2 hr after ingestion: nausea, vomiting, abdominal cramping, diarrhea; may recover without treatment	<i>Chlorophyllum molybdites</i> , backyard mushrooms ("little brown mushrooms"), many others
Gyromitrin	Delayed gastroenteritis with central nervous system toxicity, seizures	6-24 hr after ingestion: nausea, vomiting, diarrhea, abdominal pain, muscle cramps, delirium, convulsions, coma; hemolysis, and methemoglobinemia may occur	<i>Gyromitra esculenta</i> ("false morel")
Orellanine	Delayed onset gastroenteritis and renal failure	Abdominal pain, anorexia, vomiting starting over 30 hr after ingestion, followed by progressive renal failure 3-14 days later	<i>Cortinarius</i> species
Muscarine	Cholinergic syndrome	30 min to 2 hr after ingestion: bradycardia, bronchorrhea, bronchospasm, salivation, perspiration, lacrimation, convulsions, coma	<i>Clitocybe</i> species, <i>Inocybe</i> species, <i>Boletus</i> species, some <i>Amanita</i> species
Coprine	Disulfiram-like reaction with ethanol	30 min after drinking ethanol (may occur up to 1 week after eating coprine-containing mushrooms): flushing of skin of face and trunk, hypotension, tachycardia, chest pain, dyspnea, nausea, vomiting, extreme apprehension	<i>Coprinus atramentarius</i>
Ibotenic acid and muscimol	Hyperactivity, delirium, coma	30 min to 2 hours after ingestion: delirium, hallucinations, and coma	<i>Amanita muscaria</i> , <i>Amanita pantherina</i>
Psilocybin	Hallucinations	30 min to 3 hr after ingestion: hallucinations, euphoria, drowsiness, compulsive behavior, agitation	<i>Psilocybe</i> species

Modified from Brent J, Palmer RB: Mushrooms. In: Shannon MW, Borron SW, Burns MJ, eds. *Haddad and Winchester's Clinical Management of Poisoning and Drug Overdose*, 4th ed. Philadelphia: WB Saunders; 2007: Table 23-1.

Table 762.2	General Management of Mushroom Ingestion
<ol style="list-style-type: none">1. Determine history of ingestion: how many types of mushrooms ingested, what time, if anyone else ate them, and what symptoms are present.2. Attempt to determine which of the possible syndromes (see Table 762.1) the patient may have. For example, gastrointestinal symptoms occurring more than 6 hr after ingestion strongly suggest cyclopeptide, gyromitrin, or <i>Cortinarius</i> poisoning.3. Administer activated charcoal. If the patient has diarrhea, do not give a cathartic. If a cathartic is used, give it only with the first dose of activated charcoal. Use repeated doses of activated charcoal for suspected amatoxin poisonings.4. If feasible and when indicated, send gastric aspirate or emesis, along with any remaining mushrooms, to a mycologist for identification.5. Try to perform a preliminary identification of mushroom and spores. Start to develop a spore print as soon as possible.6. Maintain supportive measures, including airway support, intravenous fluids, and vasopressors (if needed). Monitor volume status.7. Avoid antispasmodics for gastrointestinal symptoms.8. Anticipate the clinical course.	

From Brent J, Palmer RB: Mushrooms. In: Shannon MW, Borron SW, Burns MJ, eds. *Haddad and Winchester's Clinical Management of Poisoning and Drug Overdose*, 4th ed. Philadelphia: WB Saunders; 2007: Box 23.1.

Galerina species containing cyclopeptide toxins, which present with symptoms after 6 hours of ingestion.

Delayed Onset
Cyclopeptide (Amatoxin) Poisoning

Poisonings by species of *Amanita* (death cap mushroom) and *Galerina* account for 95% of the fatalities from mushroom intoxication; the mortality rate for this group is 5–10%. Most species produce two classes of **cyclopeptide toxins**: (1) **phallotoxins**, which are heptapeptides believed to be responsible for the early symptoms of *Amanita* poisoning, and (2) **amatoxins**, octapeptides that inhibit nuclear RNA polymerase II and subsequent production of messenger RNA leading to impaired protein synthesis and cell death. Cells with high turnover rates, such as those in the gastrointestinal mucosa, kidneys, and liver, are the most severely affected. Other suggested toxin effects are induction of apoptosis, glutathione depletion in the liver, and oxygen free radical formation. Acute yellow atrophy of the liver and necrosis of the proximal renal tubules are found in lethal cases.

The clinical course of poisoning with *Amanita* or *Galerina* species is biphasic. Nausea, vomiting, and severe abdominal pain ensue 6-24 hours after ingestion. Profuse watery diarrhea follows shortly thereafter and may last for 12-24 hours or longer. During this time, patients become severely dehydrated. From 24 to 48 hours

after poisoning, jaundice, hypertransaminasemia (peaking at 72–96 hours), renal failure, and coma occur. Death occurs 4–7 days after the ingestion. A prothrombin time less than 10% of control is a poor prognostic factor. Of note, there are species of *Amanita* mushrooms that may present with earlier onset of symptoms and confound diagnosis, such as *Amanita smithiana*, which grows in the Pacific Northwest.

Treatment

Treatment for *Amanita* poisoning is both supportive and specific. Fluid loss from severe diarrhea during the early course of the illness is profound, requiring aggressive correction of fluid loss, electrolytes, and acid-base disturbances. In the late phase of the disease, management of renal and hepatic failure is also necessary.

Specific therapy for *Amanita* poisoning is designed to remove the toxin rapidly and to block binding at its target site. Oral activated charcoal is recommended as part of the initial treatment for children with *Amanita* poisoning. For significant ingestions, intravenous silibinin or intravenous penicillin G may be considered after discussion with a toxicologist or Poison Control Center. Silibinin and penicillin G inhibit binding of both toxins, interrupt enterohepatic recirculation of amatoxin, and protect the liver from further injury, although their effectiveness is controversial. *N*-acetylcysteine should be given for hepatoprotective effect. Hemodialysis or hemoperfusion may be beneficial in removing toxin. Orthotopic liver transplantation may be required for children with severe hepatic failure.

Gyromitrin Poisoning

Species of *Gyromitra* contain **gyromitrin**, which decomposes in the stomach to form **monomethylhydrazine** (CH_3NHNH_2) and inhibits central nervous system (CNS) enzymatic production of γ -aminobutyric acid (GABA). Monomethylhydrazine also oxidizes iron in hemoglobin, resulting in methemoglobinemia. Children with *Gyromitra* poisoning often experience vomiting, diarrhea, and abdominal pain within 6–24 hours of ingestion of the toxin. CNS symptoms such as vertigo, diplopia, headache, ataxia, and seizures develop later in the clinical course. Hemolysis and methemoglobinemia (see Chapter 511.6) are rare but potential life-threatening complications of gyromitrin poisoning.

Treatment

Hypovolemia from gastrointestinal fluid losses and seizures require supportive intervention. **Pyridoxal phosphate**, the coenzyme that catalyzes the production of GABA, can reverse the effects of monomethylhydrazine when administered in high doses. Pyridoxine hydrochloride (25 mg/kg infused over 30 minutes) is given at a frequency that is dependent on clinical improvement. Diazepam is given for persistent seizures. Parenteral administration of methylene blue is indicated if the methemoglobin concentration exceeds 30%. Blood transfusions may be required for significant hemolysis.

RENAL

Orellanine Poisoning

Species of *Cortinarius* mushrooms contain the heat-stable toxin bipyridyl **orellanine**, which causes severe nonglomerular renal injury characterized by interstitial fibrosis and acute tubular necrosis. Although the exact mechanism of injury is not fully understood, a metabolite of orellanine is thought to inhibit renal protein synthesis. *Cortinarius* poisoning is characterized by delayed onset of nausea, vomiting, and diarrhea that manifest 36–48 hours after ingestion. Although the initial symptoms may be trivial, more serious renal toxicity occurs in several days. Acute renal failure occurs in 30–50% of those affected, beginning with polyuria and progressing to renal failure (see Chapter 572).

Treatment

Treatment for orellanine poisoning is supportive. Early presentation, within 4–6 hours after ingestion, can be treated with activated charcoal and gastric lavage. Hemodialysis may be needed in patients suffering from renal failure. Most patients recover within 1 month, but chronic

renal insufficiency develops in one third to one half of patients who subsequently require renal transplantation.

AUTONOMIC NERVOUS SYSTEM

Muscarine Poisoning

Mushrooms of the genera *Inocybe* and, to a lesser degree, *Clitocybe* contain **muscarine** or muscarine-related compounds. These quaternary ammonium derivatives bind to postsynaptic receptors, producing an exaggerated cholinergic response.

The onset of symptoms is rapid (30 minutes to 2 hours after consumption), and intoxication is characterized by symptoms of cholinergic excess: diaphoresis, excessive lacrimation, salivation, miosis, bradycardia, hypotension, urinary and fecal incontinence, and vomiting. Respiratory distress caused by bronchospasm and increased bronchopulmonary secretions is the most serious complication. The symptoms subside spontaneously within 6–24 hours.

Treatment

Atropine sulfate, the specific antidote, is administered intravenously (0.01 mg/kg; maximum: 2 mg). This is repeated until the pulmonary symptoms resolve or the patient becomes overtly tachycardic.

Coprine Poisoning

Coprinus atramentarius and *Clitocybe clavipes* contain **coprine**. Like disulfiram (Antabuse; Odyssey Pharmaceuticals, Inc.), coprine inhibits the metabolism of acetaldehyde after ethanol ingestion. The clinical manifestations result from accumulation of acetaldehyde.

Coprine intoxication becomes apparent after ethanol ingestion and may be delayed up to 5 days after consumption of the mushroom. Hyperemia of the face and trunk, tingling of the hands, metallic taste, tachycardia, and vomiting occur acutely. Hypotension may result from intense peripheral vasodilation.

The syndrome typically is self-limited and lasts only several hours. No specific antidote is available. If hypotension is severe, vascular reexpansion with isotonic parenteral solutions may be required.

CENTRAL NERVOUS SYSTEM

Ibotenic acid and Muscimol Poisoning

Although *Amanita muscaria* and *Amanita pantherina* may contain muscarine, the toxins responsible for the CNS symptoms after ingestion of these mushrooms are primarily **muscimol** and **ibotenic acid**, the heat-stable derivatives of the isoxazoles. Muscimol, a hallucinogen, and ibotenic acid, an insecticide, act as GABA agonists. From 30 minutes to 3 hours after ingestion, CNS symptoms appear: obtundation, alternating lethargy and agitation, and occasionally seizures. Nausea and vomiting are uncommon. If large amounts of muscarine are contained in the mushroom, symptoms of cholinergic crisis also may occur.

Specific therapy must be carefully selected, and in most cases supportive care will suffice. If an exaggerated cholinergic response is observed, atropine should be administered. Conversely, because ingestions of *A. muscaria* or *A. pantherina* may cause anticholinergic findings, the acetylcholinesterase inhibitor physostigmine can be used to reverse the delirium and coma. Benzodiazepines also are used for the agitation and delirium. Seizures can be controlled with diazepam. In the majority of patients, however, early supportive care and close observation are all that is required.

Psilocybin Intoxication

Mushrooms belonging to the genus *Psilocybe* (“magic mushrooms”) contain **psilocybin** and **psilocin**, two psychotropic compounds. Within 30 minutes after ingestion, patients experience euphoria and hallucinations, often accompanied by tachycardia and mydriasis. Fever and seizures have also been observed in children with psilocybin poisoning. These symptoms are short-lived, usually lasting for 6 hours after consumption of the mushroom. Treatment consists of rest and observation in a quiet environment. Severely agitated patients may respond to diazepam.

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762.2 Solanine Poisoning

Katherine Baranowski and Diane P. Calello

Solanine is an alkaloid found in plants of the nightshade family (Solanaceae), specifically tomatoes, eggplant, paprika and pepper-based spices, and most significantly, white potatoes. The majority of solanine poisoning reported has arisen from the ingestion of greened potatoes. When exposed to light and allowed to turn green and/or sprout, potatoes produce several alkaloid glycosides containing the cholesterol derivative *solanidine*. Two of these glycosides, α -solanine and α -chaconine, are found in highest concentration in the peels and sprouts. Some solanine can be removed by boiling but not by baking. The major effect of α -solanine and α -chaconine is the reversible inhibition of cholinesterase. Cardiotoxic and teratogenic effects have also been reported.

Clinical manifestations of solanine and chaconine poisoning occur within 7–19 hours after ingestion. The most common symptoms are vomiting, abdominal pain, and diarrhea; in more severe instances of poisoning, neurologic symptoms, including drowsiness, apathy, confusion, weakness, and vision disturbances, are rarely followed by coma or death.

Treatment of solanine poisoning is largely supportive. In the most severe cases, symptoms resolve within 1–2 weeks.

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762.3 Seafood Poisoning

Diane P. Calello and Katherine Baranowski

CIGUATERA FISH POISONING

The most frequently reported seafood toxin illness in the world is ciguatera fish poisoning. Grouper is the most commonly identified source of the toxin, followed by snapper, kingfish, amberjack, dolphin, eel, and barracuda. Poisoning has also been associated with farm-raised salmon.

The dinoflagellate *Gambierdiscus toxicus*, a microscopic unicellular organism found along coral reefs, produces high concentrations of **ciguatoxin** and **maitotoxin**. The toxins are passed along the food chain from small herbivorous fish that consume the dinoflagellate to larger predatory fish and then to humans. These toxins are harmless in fish but produce distinct clinical symptoms in humans.

Ciguatoxins are odorless, colorless, and tasteless and are not destroyed by cooking or freezing. Ciguatoxins increase the sodium ion permeability of excitable membranes and depolarize nerve cells, actions that are inhibited by calcium and tetrodotoxin.

Between 2 and 30 hours after ingestion, ciguatera fish poisoning typically produces a biphasic illness. The initial symptoms are non-specific and are of gastrointestinal origin (diarrhea, vomiting, nausea, and abdominal pain). The second phase occurs within a few days of ingestion and consists of intense itching, anxiety, myalgias, painful intercourse, feeling of loose teeth, and rash on palms and soles; the neurologic symptoms of **circumoral dysesthesias** and **cold allodynia** (reversal of hot and cold sensation) are characteristic of this disease and may last for months. Tachycardia, bradycardia, hypotension, and death occur very infrequently. Eating fish organs, roe, or viscera is associated with greater symptom severity. The diagnosis of ciguatera fish poisoning is based on clinical presentation and a compatible epidemiologic history; the diagnosis is confirmed by testing the ingested fish for toxin. There is no human biomarker to confirm ciguatera fish poisoning.

Treatment

Treatment of ciguatera fish poisoning is supportive. Intravenous fluids may be required for severe diarrhea, and careful observation for hypovolemic shock is advised. Once adequate hydration is established, mannitol (0.5–1.0 g/kg intravenously over 30–45 minutes), given within 48–72 hours of the toxic fish ingestion, is recommended for reduction

of acute symptoms (especially neurologic symptoms) and possible prevention of chronic neurologic symptoms. Various other medications and herbal remedies have been tried, with variable results. Most cases are self-limited with a favorable prognosis.

SCOMBROID (PSEUDOALLERGIC) FISH POISONING

Ingestion of members of the **Scombridae** families, including albacore, mackerel, tuna, bonito, and kingfish, have been linked to major outbreaks of pseudoallergic fish poisoning. Non-scombroid fish such as mahi-mahi (dolphin fish), swordfish, and bluefish also are associated with poisoning.

The bacterial transformation of histidine to histamine is responsible for the clinical syndrome. Histidine is found in high concentrations in the flesh of scombroid fish; if refrigeration is inadequate, the action of bacterial decarboxylases during putrefaction converts histidine to histamine. Fish containing more than 20 mg of histamine per 100 g of flesh are toxic. In patients receiving isoniazid, a potent histaminase blocker, ingestion of fish flesh containing a lower concentration of histamine may be toxic.

The onset of clinical manifestations is acute and occurs within 10 minutes to 2 hours of ingestion. The most common symptoms and signs are diarrhea, erythema, sweating, flushing, diaphoresis, urticaria, nausea, and headache (Fig. 762.1). Abdominal pain, tachycardia, oral burning or numbness, dizziness, respiratory distress, hives, and facial swelling also occur. The illness is usually self-limited, terminating within 8–24 hours.

Treatment

Treatment is mainly supportive. With severe diarrhea, fluid replacement may be necessary. Antihistamines and antiemetics have been variably successful.

PARALYTIC SHELLFISH POISONING

Mussels, clams, oysters, scallops, and other filter-feeding mollusks may become contaminated during dinoflagellate blooms or “**red tides**.” During periods of contamination, water in coastal areas can be colored red by the algae; this sign is the origin of the term *red tide*. (Such discoloration does not necessarily indicate the presence of toxin, and toxin may be present in high quantities without discoloration. Nonetheless, discolored water should be regarded with suspicion.) The dinoflagellates *Alexandrium* spp. and *Gymnodinium catenatum* often are responsible for these red tides and contain several potent neurotoxins. Paralytic shellfish poisoning is a distinctive neurologic illness caused by 20 closely related heat-stable paralytic shellfish toxins, generally referred to as **saxitoxins**. These compounds prevent nerve conduction by inhibiting the sodium-potassium pump. Consumption of bivalves, such as mussels, scallops, and clams, is the usual pathway of intoxication, although crustaceans and fish have been implicated as well.

The onset of clinical manifestations of paralytic shellfish poisoning occurs rapidly, 30 minutes to 2 hours after ingestion. Abdominal pain and nausea are common. Paresthesias are common and occur circum-orally or in a stocking-glove distribution, or both. Perioral numbness or tingling, diplopia, ataxia, dysarthria, and the sensation of floating are seen less commonly. In severe cases, respiratory failure from diaphragmatic paralysis may result. Swimming in the water during a red tide episode does not appear to have neurologic sequelae, although skin or mucosal irritation may result.

Treatment

No antidote for paralytic shellfish poisoning is known. Supportive care, including mechanical ventilation, may be needed. Although the symptoms are usually self-limited and short-lived, weakness and malaise may persist for weeks after ingestion.

NEUROTOXIC SHELLFISH POISONING

Neurotoxic shellfish poisoning is a rare disease that occurs after consumption of molluscan shellfish contaminated with brevetoxins. Shellfish harvested along the Gulf of Mexico during or right after a red tide are at risk of contamination with brevetoxins produced by the

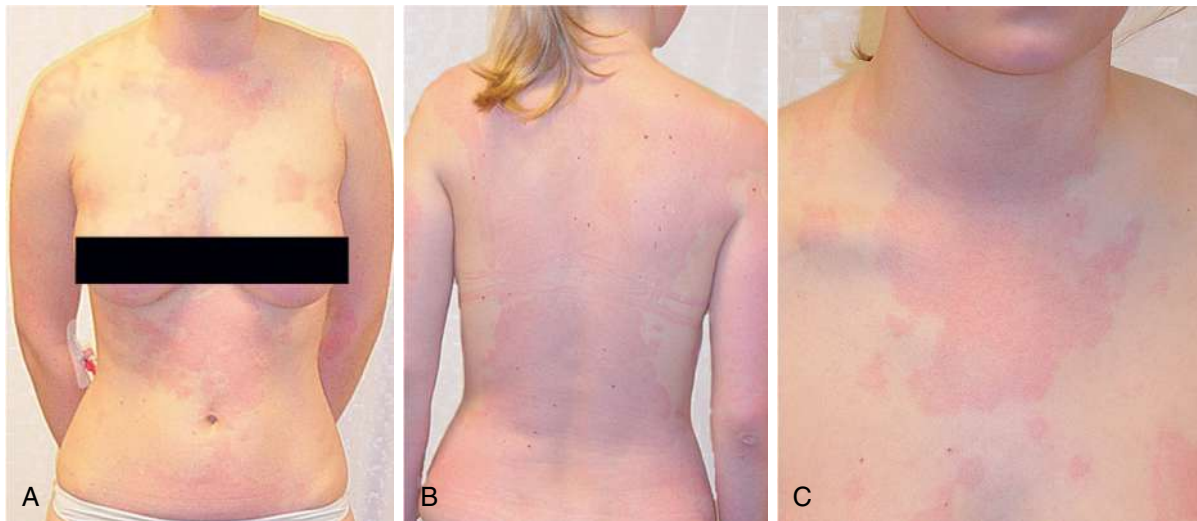


Fig. 762.1 Scombroid fish poisoning. A and B, Widespread erythematous rash predominantly on the face (not shown) and trunk of patient 1. C, Close-up view of the upper chest area. Note the absence of wheals. (Modified from Jantschitsch C, Kinaciyan T, Manafi M, et al. Severe scombroid fish poisoning: an underrecognized dermatologic emergency. *J Am Acad Dermatol*. 2011;65[1]:246–247. Fig. 1.)

dinoflagellate *Karenia brevis*; some raphidophytes (*Chattonella* spp.) also produce brevetoxins. **Brevetoxins** are a group of more than 10 lipid-soluble neurotoxins that activate sodium ion channels, causing nerve membrane depolarization. Shellfish are not affected by brevetoxins. Rinsing, cleaning, cooking, and freezing do not destroy the toxins, which also cannot be detected by taste or smell.

The onset of clinical manifestations of neurotoxic shellfish poisoning occurs from within a few minutes up to 18 hours after consumption. Most symptoms are gastrointestinal (nausea, vomiting, and diarrhea) or neurologic (numbness and tingling of the lips, mouth, face, and extremities, ataxia, partial limb paralysis, reversal of hot and cold sensation, slurred speech, headache, and fatigue). Neurotoxic shellfish poisoning is similar to a mild case of paralytic shellfish poisoning.

Treatment

There are no specific antidotes for brevetoxins. Treatment involves mostly supportive care. Brevenal, a natural antagonist of brevetoxin produced by *K. brevis*, may be used as a form of treatment in the future.

DIARRHETIC SHELLFISH POISONING

Several outbreaks of diarrhetic shellfish poisoning have been reported in Europe after consumption of mussels, cockles, and other shellfish. The dinoflagellates *Dinophysis* and *Prorocentrum* produce **okadaic acid** and its derivatives, the **dinophysistoxins**. These compounds inhibit protein phosphatases. The intracellular accumulation of phosphorylated proteins causes increased fluid secretion by gut cells via calcium influx, which is mediated by cyclic adenosine monophosphate and prostaglandins.

Patients have severe diarrhea. Care is supportive and directed at rehydration. The illness is self-limited, and recovery occurs in 3–4 days; few patients require hospitalization.

AMNESIC SHELLFISH POISONING

Amnesic shellfish poisoning has been identified after consumption of shellfish from the United States, Spain, and the United Kingdom. The responsible toxin, **domoic acid**, comes from a diatom, *Pseudonitzschia multiseries*, and is a potent glutamate agonist, disrupting neurochemical transmission in the brain. It also binds to glutamate receptors, which increase calcium influx, producing neuronal swelling in the hippocampal area of the brain and death.

The initial clinical manifestations are gastrointestinal with nausea, vomiting, diarrhea, and abdominal cramps within 24 hours of ingestion. Neurologic symptoms may follow including headache, confusion, and short-term memory loss. Memory loss is closely related to advanced age with those >50 years more likely to suffer from memory loss lasting months to years.

PUFFERFISH POISONING

The consumption of pufferfish (blowfish) in certain geographic areas such as Japan and the Indo-Pacific Ocean is associated with a lethal neurotoxic illness due to **tetrodotoxin**. Fugu, a Japanese delicacy, is sought after in part because of the subtle neurotoxic effects experienced upon eating, including perioral paresthesias and a dissociative feeling. While a trained fugu chef will remove the most toxic parts of the fish, the toxin is still found in varying degrees.

Tetrodotoxin, which is also found in the blue-ringed octopus, causes a paralytic illness due to the blockade of voltage-dependent sodium channels. Early symptoms include paresthesias, nausea, and dizziness, which progresses to weakness, numbness, and incoordination. Autonomic compromise may also occur with bradycardia and hypotension. In the most severe of cases, respiratory compromise requires assisted ventilation.

There is no specific antidote for tetrodotoxin pufferfish poisoning.

AZASPIRACID POISONING

The azaspiracids are a class of algal toxins associated with **harmful algal blooms (HABs)**. Azaspiracid poisoning results from ingestion of contaminated bivalve shellfish, especially mussels. Azaspiracid toxins are distributed throughout the muscle tissue in the shellfish. Azaspiracid is cytotoxic to cells and an inhibitor of Ca^{2+} channels in plasma membranes. Symptoms start 6–18 hours after ingestion and include nausea, vomiting, severe stomach cramps, and diarrhea, which often persist up to 5 days.

Cyanobacteria (blue-green algae) also produce HABs; exposure is usually during recreational water sports and may be cutaneous or gastrointestinal. Symptoms include rash, cough, abdominal pain, diarrhea, nausea, emesis, muscle aches, watery eyes, weakness, or sore throat.

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762.4 Melamine Poisoning

Katherine Baranowski and Diane P. Calello

Melamine (1,3,5-triazine-2,4,6-triamine, or $C_3H_6N_6$) is found in many plastics, adhesives, laminated products, cement, cleansers, fire retardant paint, and more. Melamine poisoning from food products was unheard of until 2007, when melamine-tainted pet food caused the death of many dogs and cats in the United States. In 2008, feeding of melamine-tainted infant formula to more than 300,000 children resulted in urolithiasis and resultant kidney injuries, 50,000 hospitalizations, and 6 deaths in China. This was the first reported epidemic of melamine-tainted milk products.

Melamine contains 66% nitrogen by mass. The illegal addition of melamine to infant formula can give the formula a milky appearance and falsely raise the protein content as measured by nitrogen testing. Melamine, combined with cyanuric acid, forms cyanurate crystals in the kidneys. Along with protein, uric acid, and phosphate, melamine forms renal calculi. The melamine stones and gravel can be treated with hydration, alkalinization, or lithotripsy. Acute renal failure requires supportive care and dialysis if needed.

Clinical manifestations are initially subtle and nonspecific. The severity is dose related. The first symptoms in affected infants are unexplained crying (especially when urinating), vomiting, and discolored urine caused by the formation of stones and gravel in the urinary tract. Urinary obstruction and acute renal failure follow. In the absence of a specific diagnosis, death from renal failure may occur. Whether children with melamine-induced renal failure will have chronic renal sequelae is currently unknown.

In addition to the more well-known renal toxicity, cognitive defects can be seen after acute, chronic, or prenatal exposure. Dissolved and insoluble melamine and its insoluble metabolites all have the potential to cause neurotoxicity.

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Chapter 763

Biological and Chemical Terrorism

Theodore J. Cieslak, Jonathan Newmark,
and Mark G. Kortepeter

In April of 2017, an attack on the town of Khan Shaykhun in Syria employed a poisonous “nerve agent” (likely sarin) that resulted in the deaths of at least 92 civilians, many of them young children. The attack intentionally targeted civilian neighborhoods at the time children were getting ready for school, which is strong evidence that its purpose was terror, not warfare. Terrorist actions targeting children are not novel. Brought to the forefront of American consciousness by Timothy

McVeigh's references to child fatalities as “collateral damage” during the Oklahoma City bombing in April 1995, the intentional targeting of children became a global reality with the attack upon a school in Beslan, Russia, in September 2004. The attack, which left 334 dead (including 186 children), presaged additional attacks specifically directed against children. School shootings have become an all too frequent occurrence in the United States with over 175 children dying from mass shootings on school grounds since 1999.

Paralleling the targeting of children is an apparent trend toward the use of “unconventional” weapons of terror. In 1984, members of the Rajneeshee cult employed *Salmonella typhi* in a wave of intentional poisonings that affected 751 persons, including 142 teenage patrons of a popular pizza parlor. In 1995, the Aum Shinrikyo cult killed 12 and sickened thousands by intentionally releasing sarin nerve agent in the Tokyo subway system. A disgruntled scientist allegedly deployed anthrax spores via the U.S. mail in October 2001, killing 5 and injuring 17 in an attack upon a nation already reeling in the wake of the 9/11 attacks. Conflicts in Afghanistan, Syria, and Iraq from 2012 to 2016 led to another spike in chemical attacks.

These developments remind us that terrorists can strike at any time, utilizing any number of unconventional weapons, including biologic and chemical agents. Children will not be spared in these attacks on civilians, and indeed schools and daycare sites may be the targets of these actions.

ETIOLOGY

Although terrorists may choose to use **weapons of opportunity**, agents that are readily available to some member of the terrorist group, the motives of terrorists often are obscure and difficult to predict. Prevention and response strategies should thus concentrate not on those agents most likely to be used but, rather, on those agents that, if used, would constitute the gravest potential threats to public health and security.

Biologic threat agents, including pathogens and toxins, have been divided by the Centers for Disease Control and Prevention (CDC) into three categories, with **category A** including diseases caused by those six agents posing the greatest threat: anthrax, plague (see Chapter 249.3), tularemia (see Chapter 252), smallpox, botulism (see Chapter 256), and the viral hemorrhagic fevers, including Ebola (see Chapter 317).

Terrorists could also procure and release a vast array of potentially harmful chemicals. The Chemical Threat Risk Assessment prepared by the U.S. Department of Homeland Security lists over 170 chemical compounds as potential threats in accidental or deliberate scenarios. Tank cars full of flammable industrial gases and liquids, corrosive industrial acids and bases, poisonous compounds such as cyanides and nitrites, pesticides, dioxins, and explosives traverse our railways and roads daily. Four classes of “military-grade” chemicals with a history of use in warfare or manufactured specifically for use as weapons include the organophosphate-based nerve agents, vesicants, cyanides (misleadingly referred to as “blood agents”), and certain pulmonary irritants or “choking agents.”

EPIDEMIOLOGY AND PEDIATRIC-SPECIFIC CONCERNS

Large-scale attacks on civilian targets will likely involve pediatric victims. Children may be more susceptible than adults to the effects of certain biologic and chemical agents (see [Chapter 759](#)). A thinner and less-keratinized epidermis makes dermally active agents, such as mustard or trichothecene mycotoxins, a greater risk to children than to adults. A larger surface area per unit volume further increases the problem. A small relative blood volume makes children more susceptible to the volume losses associated with enteric infections such as cholera and to gastrointestinal intoxications such as might be seen with exposure to the staphylococcal enterotoxins. The high minute ventilation of children, compared with that of adults, increases the threat of agents delivered via the inhalational route. The fact that children live “closer to the ground” compounds this effect when heavier-than-air chemicals are involved.

*The views expressed herein are those of the authors and do not necessarily reflect the position of the University of Nebraska, the U.S. Department of Defense, Health and Human Services, and Veterans' Affairs, or their component entities.

An immature blood-brain barrier may heighten the risk of central nervous system toxicity from nerve agents. Developmental considerations make it less likely that a child would readily flee an area of danger, thereby increasing exposure to these various adverse effects. Moreover, children are more likely to be terrified at the sight of responders in personal protective ensembles.

Children appear to have a unique susceptibility to certain agents that might be used by terrorists. Although adults generally suffer only a brief, self-limited incapacitating illness after infection with Venezuelan equine encephalitis virus, young children are more likely to experience seizures, permanent neurologic sequelae, and death. In the case of smallpox, waning herd immunity may disproportionately affect children. Vaccine-induced immunity to smallpox diminishes significantly after 3–10 years. Although most adults are considered susceptible to smallpox given that routine civilian immunization ceased in the early 1970s, older adults may have some residual protection from death, if not from the development of disease. Today's children are among the first to grow up in a world without any individual or herd immunity to smallpox.

Children also may experience unique disease manifestations not seen in adults. Suppurative parotitis is a common characteristic finding among children with melioidosis but is not generally seen in adults with *Burkholderia pseudomallei* infection (see Chapter 251.2). Seizures, often the presenting symptom of cyanide or nerve agent poisoning, may be much more difficult to recognize clinically in children than in adults, more likely presenting as unresponsiveness or change in mental status than tonic-clonic episodes.

Pediatricians are likely to experience unique problems in managing childhood victims of a biologic or chemical attack. Many of the drugs useful in treating such casualties are unfamiliar to pediatricians or have relative contraindications in childhood. The fluoroquinolones and tetracyclines are commonly cited as agents of choice in the treatment and prophylaxis of anthrax, plague, tularemia, brucellosis, and Q fever. Both drug classes are often avoided in children, although the risk of morbidity and mortality from diseases induced by agents of bioterrorism far outweighs the minor risk associated with short-term use of these agents. Ciprofloxacin received, as its first licensed pediatric indication, approval from the FDA for use in the prophylaxis of anthrax after inhalational exposure during a terrorist attack; doxycycline and levofloxacin are licensed specifically in children for the same indication. Levofloxacin is also licensed for postexposure prophylaxis of children against plague, and moxifloxacin is considered an acceptable alternative to first-line therapies for the treatment of plague in those less than 18 years of age. Immunizations potentially useful in preventing biologic agent–induced diseases are often not approved for use in pediatric patients. The available anthrax vaccine is licensed only for those between 18 and 65 years. The plague vaccine, currently out of production and probably ineffective against inhalational exposures, was approved only for individuals ages 18–61 years. The live replicating smallpox vaccine (ACAM2000), a live vaccine employing vaccinia virus, can cause fetal demise when given to pregnant women. A nonreplicating smallpox (and mpox) vaccine (Jynneos) was introduced in 2019.

Many otherwise useful pharmaceutical agents are not available in pediatric dosing regimens. The military distributes nerve agent antidote kits consisting of prefilled autoinjectors designed for the rapid administration of atropine and pralidoxime. Many emergency departments and some ambulances stock these kits. The doses of agents contained in the nerve agent antidote kit are calculated for soldiers and thus are inappropriate for young children, and pediatric pralidoxime autoinjectors are not yet available. Atropine autoinjectors specifically formulated for children are approved by the FDA, although their availability is limited. Unfortunately, there is no pediatric combination autoinjector containing atropine and pralidoxime, the backbone of acute nerve agent treatment in adults. Moreover, children smaller than 7 kg (15 pounds) are too small for safe use of atropine autoinjectors, while obtaining venous access may be time-consuming and extremely difficult in a contaminated environment.

Although physical protective measures and devices (e.g., “gas masks”) are likely to be of little utility in a civilian terrorism setting, such commercially available devices are not often available in pediatric sizes. The Israeli experience during the first Gulf War suggests that frightened parents may improperly use such masks on their children, resulting in inadvertent suffocation.

In the event of a large-scale terrorist attack, there may be an insufficient number of pediatric hospital beds. In any large disaster, excess bed capacity might potentially be provided at civilian and veterans hospitals under the auspices of the National Disaster Medical System. Although that system now specifically tracks pediatric beds, none of these would be found in the Veterans Administration system and few are likely to exist elsewhere. The situation is even more dire regarding burn unit beds, which may be needed in an attack with vesicants such as sulfur mustard.

CLINICAL MANIFESTATIONS

Should a terrorist attack occur, clinicians may be called on to make prompt diagnoses and render rapid lifesaving treatments before the results of confirmatory diagnostic tests are available. Although each potential agent of terrorism produces its own unique clinical manifestations, it is useful for the frontline clinician to consider their effects in terms of a limited number of distinct clinical syndromes. This approach helps clinicians make prompt, rational decisions regarding empirical therapy. Casualties resulting from a terrorist attack would either experience symptoms immediately upon exposure to an agent (or within the first several hours after exposure) or would see their symptoms develop slowly over a period of days to weeks. In the former case, the sinister nature of the event is often obvious and the etiology more likely to be conventional or chemical in nature.

Biologic agents differ from conventional, chemical (see Chapter 759), and nuclear (see Chapter 758) weapons in that they have inherent incubation periods. Consequently, patients are likely to present distant in time and place from the point of an unannounced and unnoticed exposure to a biologic agent. Whereas traditional first responders, such as firefighters and paramedics, may be at the forefront of a conventional or chemical terrorism response, the primary care physician or emergency room is likely to constitute the first line of defense against the effects of a biologic agent.

Casualties can thus be categorized as either immediate or delayed in presentation. Within each of these categories, patients can be further classified as having primarily respiratory, neuromuscular, or dermatologic manifestations (Table 763.1). A limited number of agents may cause each particular syndrome, permitting institution of empiric therapy targeted at a short list of potential etiologies. The viral hemorrhagic fevers might manifest as fever and a bleeding diathesis; these agents are considered separately in Chapter 317. In most cases, supportive care is the mainstay of hemorrhagic fever treatment, although two drugs (Inmazeb, Ebanga) have recently been licensed for the treatment of adults and children with Ebola.

Sudden-Onset Neuromuscular Syndrome: Nerve Agents

The very rapid onset of neuromuscular symptoms after an exposure should lead the clinician to consider nerve agent intoxication. The nerve agents (*tabun*, *sarin*, *soman*, and *VX*) are **organophosphate** analogs of common pesticides that act as potent inhibitors of the enzyme acetylcholinesterase. The so-called “Novichok” agents, used in deliberate attacks upon Russian targets in Salisbury, UK (2018) and Tomsk, Russia (2020), also belong to this agent class. The nerve agents are hazardous via ingestion, inhalation, or cutaneous absorption (see Chapter 94).

The inhibition of cholinesterase by these compounds results in the accumulation of acetylcholine at neural and neuromuscular junctions, causing excess stimulation. The resultant **cholinergic**

Table 763.1 Diseases Caused by Agents of Chemical and Biologic Terrorism, Classified by Syndrome

	NEUROMUSCULAR SYMPTOMS PROMINENT	RESPIRATORY SYMPTOMS PROMINENT	DERMATOLOGIC FINDINGS PROMINENT
Sudden-onset or intermediate-onset	Nerve agents	Chlorine Phosgene Cyanide	Mustard Lewisite
Delayed-onset	Botulism	Anthrax Plague Tularemia Ricin	Smallpox

syndrome involves central, nicotinic, and muscarinic effects. Central effects are both muscarinically and nicotinically mediated and include altered mental status progressing rapidly to lethargy and coma, as well as ataxia, convulsions, and central respiratory depression. Studies on pesticide exposure suggest that children may be more prone to central neurologic dysfunction with organophosphate toxicity than adults. The most lethal effects are respiratory, which result not only from central effects but also from direct paralysis of the diaphragm and other respiratory muscles (nicotinic effects), as well as bronchospasm and bronchorrhea (muscarinic effects). Nicotinic effects include muscle fasciculations and twitching, followed by weakness, which can progress to flaccid paralysis as muscles fatigue. Importantly, flaccid paralysis is not present initially, as in a patient with botulinum toxin poisoning. In botulinum toxin poisoning, neurotransmitter cannot be released from the presynaptic terminal, whereas in nerve agent poisoning, excess neurotransmitter accumulates because acetylcholinesterase, the enzyme that turns off the transmitter, is inhibited. Muscarinic effects include miosis (the clinical hallmark of a patient who has suffered a non-life-threatening nerve agent challenge), visual blurring, profuse lacrimation, and watery rhinorrhea. Bronchospasm and increased bronchial secretions lead to cough, wheezing, dyspnea, and cyanosis. Cardiovascular manifestations include bradycardia, hypotension, and atrioventricular block. Flushing, sweating, salivation, nausea, vomiting, diarrhea, abdominal cramps, and urinary incontinence are also seen. In the absence of prompt intervention, death can quickly result from a combination of central effects and respiratory muscle paralysis.

The classic neuromuscular syndrome of extremely acute symptoms most commonly results from an aerosol or vapor exposure, the most likely route in a terrorist attack. But nerve agents are liquids at standard temperature and pressure and do not cause immediate irritation to skin. Liquid nerve agent may thus pass through the skin and enter the systemic circulation, causing cholinergic crisis. This can be delayed by minutes to hours, depending upon dose and body site. In children, because the stratum corneum of the skin forms only gradually, skin transit time will be reduced. Miosis may be a late development. *If the clinician suspects that the child may have been exposed to nerve agent via the cutaneous route, they should immediately treat, even if miosis has not yet developed.*

Cyanide poisoning is a major differential diagnosis of nerve agent poisoning in an attack scenario. Cyanide poisons cytochrome a3 in the mitochondrial electron transport chain and can cause an almost immediate and rather similar syndrome of loss of consciousness, immediate rapid breathing, status epilepticus, and rapid progression to cardiac arrest. Important clinical differential points include miosis, which is usually absent in cyanide poisoning, and the usual lack of cyanosis (ironically) due to the tissues' inability to use oxygen from the blood, causing venous blood to retain oxygen and remain red. In an emergency, it may be necessary to treat for both nerve agent and cyanide poisoning until the cause is definitively identified.

Delayed-Onset Neuromuscular Syndrome: Botulism

The delayed onset (hours to days after exposure) of neuromuscular symptoms is characteristic of botulism. Botulism, an intoxication rather than an infection, occurs after exposure to one of eight related neurotoxins produced by certain strains of *Clostridium botulinum*, a strictly anaerobic, spore-forming, gram-positive bacillus commonly found in soil. Naturally occurring botulism (see Chapter 256) usually follows ingestion of preformed toxin (food poisoning) or results from intestinal toxin production (infantile botulism). An aerosol exposure to the toxin would likely result in a case of clinical botulism indistinguishable from that caused by natural exposures.

Following exposure to botulinum toxin, clinical manifestations typically begin with bulbar palsies, causing patients to complain of ptosis, photophobia, and blurred vision resulting from difficulty in accommodation. Symptoms can progress to include dysarthria, dysphonia, dysphagia, and finally, a descending symmetric paralysis. Sensation and sensorium are typically not affected. In the absence of intervention, death often results from respiratory muscle failure. The mechanism of action of botulinum toxin is, in many ways, the opposite of that of nerve agent intoxication. Seizures, loss of consciousness, and peripheral twitching and fasciculations, typical of nerve agent poisoning, are not seen in botulism.

Sudden-Onset Respiratory Syndrome: Chlorine, Phosgene, and Cyanide

The acute onset of respiratory symptoms shortly after exposure should prompt the clinician to consider a range of potential chemical agents. Of note, nerve agents, discussed previously, may affect respiration via massive bronchial hypersecretion, bronchospasm, and respiratory muscle paresis. However, the nerve agent casualty will likely have generalized muscle involvement and central nervous system manifestations. In contrast, the toxic inhalants chlorine and phosgene produce respiratory distress without neuromuscular involvement or other features of cholinergic crisis. Several other pulmonary toxicants may produce similar clinical toxidromes.

Chlorine is a dense, acrid, yellow-green gas that is heavier than air. After mild to moderate exposure, ocular and nasal irritation occurs, followed by cough, a choking sensation, bronchospasm, and substernal chest tightness. Pulmonary edema, mediated by hydrochloric acid and free oxygen radical generation, follows moderate to severe exposures within 30 minutes to several hours. Hypoxemia and hypovolemia secondary to noncardiogenic pulmonary edema are the factors responsible for death.

Phosgene, like chlorine, is a common industrial compound that was used as a weapon on the battlefields of World War I. Its odor has been described as similar to "new-mown hay." Like chlorine, phosgene exposure also is thought to result in the generation of hydrochloric acid, contributing particularly to upper airway, nasal, and conjunctival irritation. Acylation reactions caused by the effects of phosgene on the pulmonary alveolar-capillary membrane lead to pulmonary edema. Phosgene lung injury also may be mediated, in part, by an inflammatory reaction associated with leukotriene production. Patients with mild to moderate exposures to phosgene

may be asymptomatic, a fact that may cause victims to remain in a contaminated area. Noncardiogenic pulmonary edema or “dry land drowning” occurs 4–24 hours after exposure and is dose dependent, with heavier exposures causing earlier symptoms. Dyspnea may precede radiologic findings. In severe exposures, pulmonary edema may be so marked as to result in hypovolemia and hypotension. As in the case of chlorine, death results from hypoxemia and asphyxia.

Cyanide, by contrast, is a cellular poison capable of causing profound clinical manifestations, not a pulmonary toxicant. Initially, cyanide toxicity is most likely to manifest as tachypnea and hyperpnea, progressing rapidly to apnea in cases with significant exposure (see Chapter 94). The efficacy of cyanide as a chemical terrorism agent is limited by its volatility in open air and relatively low lethality compared with nerve agents. Released in a closed room, however, cyanide could have devastating effects, as evidenced by its use in the Nazi gas chambers during World War II. Cyanide inhibits cytochrome a3, interfering with normal mitochondrial oxidative metabolism and leading to cellular anoxia and lactic acidosis. In addition to respiratory distress, early findings among cyanide victims include tachycardia, flushing, dizziness, headache, diaphoresis, nausea, and vomiting. With greater exposure, seizures, coma, apnea, and cardiac arrest may follow within minutes. An elevated anion gap metabolic acidosis is typically present and decreased peripheral oxygen utilization leads to an elevated mixed venous oxygen saturation value.

Delayed-Onset Respiratory Syndrome: Anthrax, Plague, Tularemia, and Ricin

A delayed onset of respiratory symptoms (days after exposure) is characteristic of several infectious diseases and at least one toxin that might be adapted for sinister purposes by terrorists. Among the most threatening and problematic of these are anthrax, plague, tularemia, and ricin.

Anthrax is caused by infection with the gram-positive spore-forming rod *Bacillus anthracis*. Its ability to form a spore enables the anthrax bacillus to survive for long periods in the environment and enhances its potential as a weapon.

The vast majority of naturally occurring anthrax cases are cutaneous, acquired by close contact with the hides, wool, bone, and other by-products of infected ruminants (principally cattle, sheep, and goats). Cutaneous anthrax is amenable to therapy with a variety of antibiotics and is readily recognizable to experienced clinicians in endemic areas; consequently, it is rarely fatal. Although it is common in parts of Asia and sub-Saharan Africa, only two cases of cutaneous anthrax had occurred in the United States in the 9 years that preceded the attacks of 2001 (when 11 cutaneous cases were seen). Gastrointestinal anthrax has been described only once in the United States, in a drum circle participant whose drum heads were made from imported animal hides. In general, however, it occurs after the ingestion of contaminated meat. In the past, inhalational anthrax, or **woolsorters' disease**, was an occupational hazard of abattoir and textile workers. Now eliminated as a naturally occurring disease in the United States, it is this inhalational form of anthrax that poses the greatest terror threat. Following an inadvertent release in 1979 from a bioweapons facility at Sverdlovsk in the former Soviet Union, 66 of 77 (86%) known adult victims of inhalational anthrax died. In the 2001 attacks involving contaminated mail in the United States, 5 of 11 (46%) patients with inhalational anthrax died. Whether better intensive care modalities, changes in antibiotic therapy, or earlier recognition accounted for this improved mortality rate remains unknown.

Symptomatic *inhalational* anthrax typically begins 1–6 days after exposure, although incubation periods of up to several weeks have been reported. The disease begins as a flulike illness, characterized by fever, myalgia, headache, and cough. A brief intervening period of improvement sometimes follows, but rapid deterioration then ensues; high fever, dyspnea, cyanosis, and shock mark this second

phase. Hemorrhagic meningitis occurs in up to 50% of cases. Chest radiographs obtained late in the course of illness may reveal a widened mediastinum or prominent mediastinal lymphadenopathy; pleural effusions also may be seen. Bacteremia is often so profound that Gram stains of peripheral blood may demonstrate the organism at this stage. Prompt treatment is imperative. Death occurs in as many as 95% of inhalational anthrax cases if such treatment is begun more than 48 hours after the onset of symptoms.

Whereas inhalational anthrax is a disease primarily of mediastinal lymphatic tissue, exposure to aerosolized plague bacilli typically leads to a primary pneumonia. Endemic **plague** is usually transmitted via the bites of fleas and is discussed in Chapter 249.3. The causative organism of all forms of human plague, *Yersinia pestis*, is a bipolar-staining, gram-negative facultative intracellular bacillus. An ability to survive within the macrophage aids its dissemination to distant sites following inoculation or inhalation. “Buboes,” markedly swollen, exquisitely tender regional lymph nodes in the distribution of a bite, are the hallmark feature of bubonic plague. Fever and malaise are typically present, and septicemia often develops as bacteria gain access to the circulation. Petechiae, purpura, and overwhelming disseminated intravascular coagulopathy commonly occur, and 80% of bubonic plague victims ultimately have positive blood cultures. Plague is extremely lethal, as illustrated by the fact that the “Black Death” eliminated one-third of the population of Europe during the Middle Ages.

Intentional aerosol dissemination of *Y. pestis* would likely result in a preponderance of pneumonic plague cases. Pneumonic plague may also arise secondarily after seeding of the lungs of septicemic patients. Symptoms include fever, chills, malaise, headache, and cough. Chest radiographs may reveal a patchy consolidation, and the classic clinical finding is blood-streaked sputum. Disseminated intravascular coagulation and overwhelming sepsis typically develop as the disease progresses. Untreated pneumonic plague has a fatality rate approaching 100%.

Tularemia is a highly infectious disease caused by the gram-negative coccobacillus *Francisella tularensis*. Naturally occurring tularemia is discussed in Chapter 252. The high degree of infectivity of *F. tularensis* (<10 organisms are thought to be necessary to produce infection via inhalation), as well as its survivability in the environment, contributes to its inclusion on the CDC's list of Category A agents. Several clinical forms of endemic tularemia are known, but inhalational exposure resulting from a terrorist attack would likely lead to a plaguelike primary pneumonia or to typhoidal tularemia, manifesting as a variety of nonspecific symptoms, including fever, malaise, and abdominal pain.

Ricin is a protein toxin derived from the castor bean plant (*Ricinus communis*) that inhibits ribosomal protein synthesis. It is highly toxic in animal studies when inhaled and may result in the delayed onset of respiratory distress, pulmonary edema, and acute respiratory failure. If injected, it may cause a sepsis-like syndrome that may progress to multiorgan system failure; ingestion can lead to severe gastroenteritis. Ricin-containing letters were mailed to a U.S. Senate office building in 2004, to President Obama and New York City Mayor Bloomberg in 2013, and to President Trump in 2020, although no persons were sickened in any of the attacks.

Intermediate-Onset Dermatologic Syndrome: Mustard and Lewisite

The development of skin lesions within hours to days of exposure is characteristic of the chemical vesicants. These compounds, often referred to as **blistering agents**, are cellular poisons and include the alkylating agent mustard and the organic arsenical agent lewisite. Injury to rapidly reproducing cells begins within minutes of contact with these agents. Clinical effects typically become evident several hours after exposure to mustard, whereas patients exposed to lewisite feel immediate pain. Both mustard and lewisite affect the eyes and respiratory tract, and their inadvertent ingestion may produce significant gastrointestinal symptoms. Mustard exposure may lead, several days later, to bone marrow suppression. With

a large inhalational challenge, mustard may also cause an acute respiratory syndrome, particularly affecting the upper airway and presenting with laryngospasm and stridor.

Delayed-Onset Dermatologic Syndrome: Smallpox

The appearance of an exanthem days to weeks after exposure is likely to be a presenting feature of smallpox. Caused by infection with variola virus, a member of the *Orthopoxvirus* family, smallpox has an incubation period of 7-17 days. This would likely permit the wide dispersal of asymptomatic exposed persons, thus contributing to the spread of an outbreak. During the incubation period, the virus replicates in the upper respiratory tract. A primary viremia ensues, during which time seeding of the liver and spleen occurs. A secondary viremia then develops, the skin is seeded, and the classic exanthem of smallpox appears.

Symptoms of smallpox begin abruptly during the phase of secondary viremia and include fever, rigors, vomiting, headache, backache, and extreme malaise. Within 2-4 days, macules appear on the face and extremities and then progress in synchronous fashion to papules, pustules, and finally scabs. As the scabs separate, survivors often are left with disfiguring, depigmented scars. The synchronous nature of the rash and its centrifugal distribution distinguish smallpox from chickenpox, which has a centripetal distribution. Historically, smallpox had a 30% mortality rate, with death typically resulting from visceral organ involvement.

DIAGNOSIS

In some cases, the terrorist nature of a chemical or biologic attack may be obvious; for example, a chemical attack in which victims succumb in close temporal and geographic proximity to a dispersal device or when terrorists announce their attack. In other instances, the clinician may need to rely on epidemiologic clues to suspect an intentional release of chemical or biologic agents. The presence of large numbers of victims clustered in time and space should raise the index of suspicion, as should cases of unexpected death or unexpectedly severe disease. Diseases unusual in a given locale, in a given age group, or during a certain season likewise may warrant further investigation. Simultaneous outbreaks of a disease in non-contiguous areas should cause one to consider an intentional release (as in the 2001 mail-borne anthrax attacks), as should outbreaks of multiple diseases in the same area. Even a single case of a rare disorder such as anthrax or certain viral hemorrhagic fevers would be suspicious, and a single case of smallpox would almost certainly be the result of an intentional dissemination. Large numbers of dying animals might provide evidence of an unnatural aerosol release, as would evidence of disparate attack rates between those known to be indoors and outdoors at a given time.

In a mass casualty setting, diagnoses may be made largely on clinical grounds. The diagnosis of nerve agent intoxication is based primarily on clinical recognition and patient response to antidotal therapy. Several simple rapid detection devices developed for military use can detect the presence of nerve agents in the environment. Some of these are now commercially available and are stocked in certain emergency departments and public safety vehicles. Measurements of acetylcholinesterase in plasma or erythrocytes of nerve agent victims may be helpful in long-term prognostication, but the correlation between cholinesterase levels and clinical effects is often poor, and the test is rarely available on an emergency basis.

Botulism should be suspected clinically among patients presenting with a symmetric, descending, flaccid paralysis. Although the differential diagnosis of botulism includes other uncommon neurologic disorders, such as myasthenia gravis and the Guillain-Barré syndrome, the presence of multiple casualties with similar symptoms should aid in the determination of a botulism outbreak. Electromyography is useful in supporting the diagnosis.

Initially the diagnosis of cyanide poisoning also will likely be made on clinical grounds in the presence of the appropriate

toxidrome. An unusually high anion gap metabolic acidosis with elevated serum lactate and an oxygen concentration greater than expected in mixed venous blood lend support to the clinical diagnosis. Elevated blood cyanide concentrations can confirm the clinical suspicion.

Of all the chemical and biological agents, the only ones for which immediate therapy without waiting for definitive diagnosis is potentially lifesaving and mandatory are nerve agents and cyanide poisoning. If these are suspected, they should be treated before waiting for further diagnostic certainty.

Anthrax should be suspected upon finding gram-positive bacilli in skin biopsy material (in the case of cutaneous disease), blood smears, pleural fluid, or spinal fluid. Chest radiographs demonstrating a widened mediastinum in the context of fever and constitutional signs and, in the absence of another obvious explanation (e.g., blunt trauma or postsurgical infection), should also lead one to consider the diagnosis. Confirmation can be obtained by blood culture.

A diagnosis of plague can be suspected on finding bipolar “safety-pin”-staining bacilli in Gram or Wayson stains of sputum or aspirated lymph node material; confirmation is obtained by culturing *Y. pestis* from blood, sputum, or lymph node aspirate. The organism grows on standard blood or MacConkey TRA agars, but it is often misidentified by automated systems. *F. tularensis*, the causative agent of tularemia, grows poorly on standard media; its growth is enhanced on media containing cysteine. Because of its extreme infectivity, however, many laboratories prefer to make a diagnosis via polymerase chain reaction or serologically using an enzyme-linked immunosorbent assay or serum agglutination assay.

Smallpox should be suspected on clinical grounds and can be confirmed by culture or electron microscopy of scabs or vesicular fluid, although the manipulation of clinical material from suspected smallpox victims should be attempted only at public health laboratories able to employ maximum biocontainment (Biosafety Level 4) precautions. Similar caution should be exercised with specimens from patients with various viral hemorrhagic fevers.

PREVENTION

Preventive measures can be considered in both a preexposure and a postexposure context. **Preexposure protection** against a chemical or biologic attack may consist of physical, chemical, or immunologic measures. **Physical protection** against primary attack often involves gas masks and protective suits; such equipment is used by the military and by certain hazardous materials response teams, but it is unlikely to be available to civilians at the precise moment that a release occurs. Medical personnel need to understand the principles of physical protection as they apply to infection control and the spread of contamination.

Pneumonic plague is spread through respiratory droplets. Droplet precautions, including the use of simple surgical masks, are thus warranted for providers caring for patients with plague. Smallpox is transmitted by droplet nuclei. Airborne precautions, including (ideally) a high-efficiency particulate air filter mask, are thus warranted with smallpox victims. Patients with certain viral hemorrhagic fevers, such as those caused by filoviruses (Ebola, Marburg) and arenaviruses, should be managed using a combination of droplet and contact precautions, ideally in a specialized biocontainment unit. Most other biologic agent victims can be safely cared for with the use of standard precautions. In the case of chemical agents, residual mustard or nerve agent on the skin or clothing of victims might potentially pose a hazard to medical personnel. For such victims, whenever possible, clothing should be removed, and the patients decontaminated using copious amounts of water before extensive medical care is rendered. Most other chemical agents are volatile enough that spread of an agent among patients or from patient to caregiver is unlikely.

Preexposure chemical prophylaxis might be used on the basis of credible intelligence reports. Should officials deem that the threatened release of a specific biologic agent appears imminent, antibiotics might be distributed to a population before exposure. Opportunities to employ such a strategy are likely to be limited, although federal and state officials are examining various mechanisms for such employment. In military settings, pyridostigmine is FDA-approved as pretreatment against expected nerve agent attack. It is not approved for use in children, and it is not likely to be recommended in civilian settings.

Although licensed vaccines (**preexposure immunologic measures**) against anthrax and smallpox have been developed, widespread use of either vaccine is likely to be problematic, especially in children. The anthrax vaccine is licensed only for those persons age 18 years and older, is given as a five-dose series over 18 months, and requires annual booster doses. These considerations make civilian employment of the current anthrax vaccine on a large scale unlikely, although recombinant anthrax vaccines requiring fewer doses are in development.

Significant obstacles to the widespread employment of smallpox vaccine also exist, although public health officials have contemplated the resumption of a smallpox vaccination campaign. Whereas in the past, the live replicating smallpox vaccine (prepared from vaccinia virus, an *Orthopoxvirus* related to variola) was used safely and successfully in young infants, it has a relatively high rate of serious complications in certain patients. *Fetal vaccinia* and demise can occur when pregnant women are vaccinated. *Vaccinia gangrenosa*, an often fatal complication, can occur when immunocompromised persons are vaccinated. *Eczema vaccinatum* occurs in those with preexisting dermatoses (atopic dermatitis). Severe vaccine-related encephalitis was well known during the era of widespread vaccination; because it occurs only in primary vaccines, it would disproportionately affect pediatric patients. Autoinoculation can occur when the virus present at the site of vaccination is manually transferred to other areas of skin or to the eye. Young children would presumably be at greater risk for such inadvertent transmission. Myocarditis has been reported following vaccinations of military recruits. A new nonreplicating vaccine may alleviate some of these concerns.

To manage complications associated with use of the replicating vaccine, vaccinia immune globulin should be available when one is undertaking a vaccination campaign. Vaccinia immune globulin (6000 U/kg intravenously) may be given to vaccine recipients who experience severe complications or to significantly immunocompromised individuals exposed to smallpox and in whom vaccination would be unsafe. In 2018, tecovirimat was approved by the FDA for the treatment of persons (including children) experiencing severe complications from vaccine. Vaccine, as well as vaccinia immune globulin and tecovirimat, can be obtained as needed upon consultation with officials at the CDC. In addition to a potential role in preexposure prophylaxis, vaccination may be effective in postexposure prophylaxis if given within the first 4 days after exposure.

Anthrax vaccine might similarly be employed in a postexposure setting. Some authorities recommend three doses of this vaccine as an adjunct to postexposure chemoprophylaxis after documented exposure to aerosolized anthrax spores. Nonetheless, postexposure administration of oral antibiotics constitutes the mainstay of management for asymptomatic victims believed to have been exposed to anthrax as well as to other bacterial agents such as plague and tularemia. [Table 763.2](#) lists appropriate prophylactic regimens for various biologic exposures.

TREATMENT

Although [Tables 763.2, 763.3, and 763.4](#) provide recommended therapies for overt diseases caused by various chemical and biologic agents, it is likely that the clinician attending to victims will need to make therapeutic decisions before the results of confirmatory diagnostic tests are available and in situations in which the diagnosis is

not known with certainty. In particular, decontamination by hospital personnel in appropriate personal protective equipment is required for patients exposed to chemical agents who have not been adequately decontaminated in the prehospital setting (see [Table 763.4](#)). In such cases, it is useful to note that many diseases and symptoms caused by chemical and biologic agents will resolve with supportive care. Most cases of chlorine or phosgene exposure can be successfully managed by providing meticulous attention to oxygenation and fluid balance. Mustard victims may require intensive multisystem support, but no specific antidote or therapy is available. Many viral diseases, including most viral hemorrhagic fevers, as well as equine encephalitides, are also managed supportively.

In addition to ensuring adequate oxygenation, ventilation, and hydration, the clinician may need to provide specific empiric therapies on an urgent basis. Patients suffering from the sudden onset of severe neuromuscular symptoms may have nerve agent intoxication and should be given atropine (0.05–0.1 mg/kg) promptly for its antimuscarinic effects. Although atropine relieves bronchospasm and bradycardia, reduces bronchial secretions, and ameliorates the gastrointestinal effects of nausea, vomiting, and diarrhea, it does not improve skeletal muscle paralysis. 2-Pralidoxime chloride (2-PAM) cleaves the organophosphate moiety from cholinesterase and regenerates intact enzyme if “aging” has not occurred. The effect is most prominent at the neuromuscular junction and leads to improved muscle strength. Its prompt use (at a dose of 25–50 mg/kg) as an adjunct to atropine is recommended in all serious cases.

Ideally, both atropine and pralidoxime should be administered intravenously (IV) in severe cases, although the intraosseous route is acceptable. In the field, as time is of the essence in treating nerve agent poisoning, first responders are trained to administer atropine IM via autoinjector. Some experts also recommend that atropine be given IM in the presence of hypoxia to avoid arrhythmias associated with IV administration. Many emergency management services stock military-style autoinjector kits consisting of atropine and 2-PAM for IM injection. Pediatric atropine autoinjectors containing 0.5 or 1 mg of atropine are licensed and held in the Strategic National Stockpile, although kits intended for adults (with 2 mg of atropine and 600 mg of pralidoxime) may be used in children >2–3 years of age ([Table 763.5](#)). Autoinjectors cannot easily be used in the smallest infants.

Animal studies support the routine prophylactic administration of anticonvulsant doses of benzodiazepines, even in the absence of observable convulsive activity. Although diazepam has long been employed for this purpose, midazolam was recently granted FDA approval, and animal studies have shown it to have superior efficacy in treating acute nerve agent poisoning. Military and civilian stocks of diazepam autoinjectors are being replaced by midazolam autoinjectors.

Delayed neuromuscular symptoms in the setting of terrorism might be due to botulism. Supportive care, with meticulous attention to ventilatory support, is the mainstay of botulism treatment. Such support may be necessary for several months, making the management of a large-scale botulism outbreak especially problematic in terms of medical resources. A licensed heptavalent antitoxin (types A–G) is available through the CDC (1-800-232-4636). Administration of this antitoxin is unlikely to reverse disease in symptomatic patients but may prevent further progression. In addition, a pentavalent product (containing antibody against toxin types A–E but licensed only for treatment of type A or B intoxication), Botulism Immune Globulin Intravenous (Human; BabyBIG), is available through the California Department of Health Services (1-510-231-7600) specifically for the treatment of infant botulism.

The *rapid onset of respiratory symptoms* may signal an exposure to chlorine, phosgene, cyanide, or a number of other toxic industrial chemicals. Although the mainstay of therapy in virtually all of these exposures consists of removal to fresh air and intensive supportive care, cyanide intoxication often requires the administration of specific antidotes.

Table 763.2 CDC Category A Agents of Bioterrorism

DISEASE	CLINICAL FINDINGS	INCUBATION PERIOD (DAYS)	ISOLATION PRECAUTIONS	INITIAL TREATMENT	PROPHYLAXIS
Anthrax (inhalational) Patients who are clinically stable after 14 days can be switched to a single oral agent (as described in the prophylaxis section of this table) to complete a 60-day course	Febrile prodrome with rapid progression to mediastinal lymphadenitis and mediastinitis, sepsis, shock, and meningitis	1-5	Standard	See Table 763.3.	Ciprofloxacin 30 mg/kg/day PO divided q12h* (max 500 mg/dose) or doxycycline 4.4 mg/kg/day PO divided q12h (max 100 mg/dose) or clindamycin 30 mg/kg/day PO divided q8h (max 900 mg/dose) or levofloxacin 16 mg/kg/day PO divided q12h (max 250 mg/dose) or amoxicillin 75 mg/kg/day PO divided q8h† (max 1 g/dose) or penicillin VK 50-75 mg/kg/day divided q6-8h
Plague (pneumonic)	Febrile prodrome with rapid progression to fulminant pneumonia, hemoptysis, sepsis, disseminated intravascular coagulation	2-3	Droplet (for first 3 days of therapy)	Gentamicin** 1.25- 2.5 mg/kg IV q8h or doxycycline 2.2 mg/kg IV q12h or ciprofloxacin 15 mg/kg IV q12h or levofloxacin 8 mg/kg IV/PO q12h	Doxycycline 2.2 mg/kg PO q12h or ciprofloxacin 20 mg/kg PO q12h or levofloxacin 8 mg/kg PO q12h
Tularemia	Pneumonic: abrupt onset of fever with fulminant pneumonia Typhoidal: fever, malaise, abdominal pain	2-10	Standard	Options same as for plague‡, gentamicin preferred	Same as for plague‡
Smallpox	Febrile prodrome with synchronous, centrifugal, vesiculopustular exanthema	7-17	Airborne (+ contact)	Tecovirimat Oral dosage by body weight: 13 kg to <25 kg: 200 mg q12h 25 kg to <40 kg: 400 mg q12h 40 kg to <120 kg: 600 mg q12h ≥120 kg: 600 mg q8h Intravenous infusion dosage by body weight: 3 kg to <35 kg: 6 mg/kg q12h by IV infusion over 6 hr 35 kg to <120 kg: 200 mg q12h by IV infusion over 6 hr ≥120 kg: 300 mg q12h by IV infusion over 6 hr	Vaccination may be effective if given within the first several days after exposure
Botulism	Afebrile descending symmetric flaccid paralysis with cranial nerve palsies	1-5	Standard	Supportive care; antitoxin (see text) may halt the progression of symptoms but is unlikely to reverse them	No licensed preexposure prophylaxis is available; postexposure administration of antitoxin may prevent the development of symptoms
Viral hemorrhagic fevers	Febrile prodrome with rapid progression to shock, purpura, and bleeding diatheses	4-21	Contact (consider airborne in cases of massive hemorrhage)	Supportive care; ribavirin may be beneficial in treating Lassa fever, and perhaps other arenaviral hemorrhagic fevers	Ribavirin has been shown to be efficacious in the postexposure prophylaxis of Lassa fever

*Preferred drugs are shown in **bold**.

**Some experts say 4.5-7.5 mg/kg/day.

†Penicillin and amoxicillin should only be used when the strain of *Bacillus anthracis* is known to be susceptible.

‡Levofloxacin (as well as moxifloxacin) is licensed by the U.S. Food and Drug Administration for the prophylaxis and treatment of plague in the setting of a bioterror attack, but not tularemia. PO, By mouth; IV, intravenously.

Table 763.3 Treatment of Inhalational Anthrax in Children

WHEN MENINGITIS PRESENT OR HAS NOT RULED OUT*	WHEN MENINGITIS CAN BE RULED OUT*
<p>1. A bactericidal fluoroquinolone: Ciprofloxacin 30 mg/kg/day IV divided q8h[†] (max 400 mg/dose) or Levofloxacin 24 mg/kg/day IV divided q12h (max 250 mg/dose) or Moxifloxacin 12 mg/kg/day IV divided q12h (max 200 mg/dose; for children 3 mo to 2 yr); 10 mg/kg/day IV divided q12h (for children 2-5 yr); 8 mg/kg/day IV divided q12h (for children 6-11 yr); 400 mg IV qd (for children >12 yr and >45 kg)</p> <p>2. A second bactericidal antimicrobial: Meropenem 120 mg/kg/day IV divided q8h (max 2 g/dose) or Imipenem 100 mg/kg/day IV divided q6h (max 1 g/dose) or Doripenem 120 mg/kg/day IV divided q8h (max 1 g/dose) or Vancomycin 60 mg/kg/day IV divided q8h or Penicillin G** 400,000 U/kg/day IV divided q4h[†] (max 4 MU/dose) [if PCN sensitive] or Ampicillin 400 mg/kg/day IV divided q6h (max 3 g/dose)</p> <p>3. A protein synthesis inhibitor: Linezolid 30 mg/kg/day IV divided q8h (for children <12 yr); 30 mg/ kg/day IV divided q12h (for children >12 yr; max 600 mg/dose) or Clindamycin 40 mg/kg/day IV divided q8h (max 900 mg/dose) or Rifampin 20 mg/kg/day IV divided q12h (max 300 mg/dose) or Chloramphenicol 100 mg/kg/day IV divided q6h</p>	<p>1. A bactericidal antimicrobial: Ciprofloxacin 30 mg/kg/day IV divided q8h (max 400 mg/dose) or Levofloxacin 20 mg/kg/day IV divided q12h (max 250 mg/dose) or Imipenem 100 mg/kg/day IV divided q6h (max 1 g/dose) or Vancomycin 60 mg/kg/day IV divided q8h or Penicillin G 400,000 U/kg/day IV divided q4h (max 4 MU/dose) [if PCN sensitive] or Ampicillin 200 mg/kg/day IV divided q6h (max 3 g/dose)</p> <p>2. A protein synthesis inhibitor: Clindamycin 40 mg/kg/day IV divided q8h (max 900 mg/dose) or Linezolid 30 mg/kg/day IV divided q8h (for children <12 yr); 30 mg/kg/ day IV divided q12h (for children >12 yr; max 600 mg/dose) or Rifampin 20 mg/kg/day IV divided q12h (max 300 mg/dose) or Doxycycline 4.4 mg/kg/day IV loading dose (for children <45 kg; max 200 mg), followed by 4.4 mg/kg/day IV divided q12h; 200 mg IV loading dose, followed by 100 mg IV q12h (for children >45 kg)</p>

*Meningitis occurs in approximately 50% of patients with inhalational anthrax.

**Some experts provide a range of 400,000–600,000 U/kg/d.

[†]Preferred drugs are shown in **bold**.

[†]Penicillin and amoxicillin should only be used when the strain of *Bacillus anthracis* is known to be susceptible.

IV, Intravenous; qd, every day; PCN, penicillin.

Data from Bradley JS, Peacock G, Krug SE, et al. Pediatric anthrax clinical management. *Pediatrics*. 2014;133:e1411–e1436. Appendices 3 & 4.

The classic **cyanide antidote** utilizes a nitrite along with sodium thiosulfate and is given in two stages. The methemoglobin-forming agent (e.g., sodium nitrite) is administered first, because methemoglobin has a high affinity for cyanide and causes it to dissociate from cytochrome oxidase. Nitrite dosing in children should be based on body weight to avoid excessive methemoglobin formation and nitrite-induced hypotension. For the same reasons, nitrites should be infused slowly over 5–10 minutes. A sulfur donor, such as sodium thiosulfate, is given next. This compound is used as a substrate by the hepatic enzyme rhodanese, which converts cyanide to thiocyanate, a less toxic compound excreted in the urine. Thiosulfate treatment itself is efficacious and relatively benign and may be used alone for mild to moderate cases. Sodium nitrite and sodium thiosulfate are packaged together in standard antidote kits, along with amyl nitrite, a sodium nitrite substitute that can be inhaled in prehospital settings in which IV access is not available.

Many first responder agencies in the United States have replaced the traditional two-part cyanide antidote kit with hydroxocobalamin, which exchanges its hydroxy group for cyanide, forming harmless cyanocobalamin (vitamin B₁₂) that is subsequently excreted by the kidneys. Hydroxocobalamin use is not complicated by the potential for nitrite-induced hypotension or methemoglobinemia, and it has low toxicity. The recommended dose is 5 g in adults or 70 mg/kg in children, administered IV over 15 minutes. A second dose (5 g in adults; 70 mg/kg in children) may be repeated in severely affected patients. Side effects include modest hypertension and reddening of skin, mucous membranes, and urine that may last several days. Although no human controlled trials are currently available to compare hydroxocobalamin with nitrite/thiosulfate-based therapies, many authorities believe that hydroxocobalamin's efficacy and safety profile favor it as the cyanide antidote of choice, especially for children in the mass casualty context. To use hydroxocobalamin, however, the solution must be mixed immediately before use, in the field if need be, so first responders need to be properly trained to employ it.

Animal research suggests a modest benefit of steroid therapy in mitigating lung injury after chlorine inhalation; thus steroids may be considered for patients with chlorine exposure, especially as an adjunct to bronchodilators in those with bronchospasm and/or a history of asthma. Symptomatic relief has also been reported following chlorine exposure with nebulized 3.75% sodium bicarbonate therapy, though the impact of this regimen on pulmonary damage is unknown. Animal models have also suggested a benefit from antiinflammatory agents, including ibuprofen and *N*-acetylcysteine, which appear to ameliorate phosgene-induced pulmonary edema, as well as the utilization of low tidal volume ventilation (protective ventilation), although the results of such interventions have not yet been reported in clinical trials.

In cases in which the delayed onset of respiratory symptoms may be the result of a terrorist attack, consideration should be given to the empirical administration of an antibiotic effective against anthrax, plague, and tularemia. Ciprofloxacin (10–15 mg/kg IV q12 hours), levofloxacin (8 mg/kg IV q12 hours), or doxycycline (2.2 mg/kg IV q12 hours) is a reasonable choice. Although naturally occurring strains of *B. anthracis* usually are quite sensitive to penicillin G, these agents are chosen because penicillin-resistant strains of *B. anthracis* exist. Moreover, ciprofloxacin and doxycycline are effective against almost all known strains of *Y. pestis* and *F. tularensis*. Concerns about inducible β -lactamases in *B. anthracis* have led experts to recommend one to two additional antibiotics in patients with inhalational anthrax. Rifampin, vancomycin, penicillin or ampicillin, clindamycin, and imipenem are reasonable choices based on in vitro sensitivity data. Because *B. anthracis* relies on the production of two protein toxins, edema toxin and lethal toxin, for its virulence, drugs that act at the ribosome to disrupt protein synthesis (e.g., clindamycin, the macrolides) provide a theoretical advantage. Frequent meningeal involvement among inhalational anthrax victims makes agents with superior central nervous system penetration desirable. The treatment of anthrax is detailed in [Table 763.3](#).

Table 763.4 Critical Chemical Agents of Terrorism

AGENT	TOXICITY	CLINICAL FINDINGS	ONSET	DECONTAMINATION*	MANAGEMENT								
NERVE AGENTS													
Tabun, sarin, soman, VX	Anticholinesterase: muscarinic, nicotinic, central nervous system effects	Vapor: miosis, rhinorrhea, dyspnea Liquid: diaphoresis, vomiting Both: coma, paralysis, seizures, apnea	Seconds: vapor Minutes to hours: liquid	Vapor: fresh air, remove clothes, wash hair Liquid: remove clothes, wash skin, hair with copious soap and water, ocular irrigation	ABCs. Atropine: 0.05-0.1 mg/kg IV [†] , IM [‡] (min: 0.1 mg, max: 5 mg), repeat q2-5 min prn for marked secretions, bronchospasm AND Pralidoxime: 25-50 mg/kg IV, IM [§] (max: 1 g IV; 2 g IM), may repeat within 30-60 min prn, then again q1h for one or two doses prn for persistent weakness, high atropine requirement AND Diazepam: 0.3 mg/kg (max: 10 mg) IV or Lorazepam: 0.1 mg/kg IV, IM (max: 4 mg) or Midazolam: 0.2 mg/kg (max: 10 mg) IM prn for seizures or severe exposure								
VESICANTS													
Mustard	Alkylation	Skin: erythema, vesicles Eye: inflammation Respiratory tract: inflammation	Hours	Skin: soap and water Eyes: water (effective only if done within minutes of exposure)	Symptomatic care								
Lewisite	Arsenical		Immediate pain	Skin: soap and water Eyes: water (effective only if done within minutes of exposure)	Possibly British antilewisite (BAL) 3mg/kg IM q4-6h for systemic effects of lewisite in severe cases								
PULMONARY AGENTS													
Chlorine, phosgene	Liberate hydrochloric acid, alkylation	Eye, nose, and throat irritation (especially chlorine) Respiratory: bronchospasm, pulmonary edema (especially phosgene)	Minutes: eye, nose, and throat irritation, bronchospasm Hours: pulmonary edema	Fresh air Skin: water	Symptomatic care (see text)								
CYANIDE													
	Cytochrome oxidase Inhibition: cellular anoxia, lactic acidosis	Tachypnea, coma, seizures, apnea	Seconds	Fresh air Skin: soap and water	ABCs, 100% oxygen Na bicarbonate prn metabolic acidosis; hydroxocobalamin 70 mg/kg IV (max: 5g) or nitrite/thiosulfate, given as follows (see text): <table><tr><th>Na nitrite (3%): dose (mL/kg) (max: 10 mL)</th><th>Estimated hemoglobin concentration (g/dL)</th></tr><tr><td>0.27</td><td>10</td></tr><tr><td>0.33</td><td>12 (estimated for average child)</td></tr><tr><td>0.39</td><td>14</td></tr></table> Followed by Na thiosulfate (25%): 1.65 mL/kg (max: 50 mL)	Na nitrite (3%): dose (mL/kg) (max: 10 mL)	Estimated hemoglobin concentration (g/dL)	0.27	10	0.33	12 (estimated for average child)	0.39	14
Na nitrite (3%): dose (mL/kg) (max: 10 mL)	Estimated hemoglobin concentration (g/dL)												
0.27	10												
0.33	12 (estimated for average child)												
0.39	14												

*Decontamination, especially for patients with significant nerve agent or vesicant exposure, should be performed by healthcare providers garbed in adequate personal protective equipment. For emergency department staff, this equipment consists of a nonencapsulated, chemically resistant body suit, boots, and gloves with a full-face air-purifier mask/hood.

[†]Intraosseous route is likely equivalent to intravenous.

[‡]Atropine might have some benefit via endotracheal tube or inhalation, as might aerosolized ipratropium. See also Table 741.5.

[§]Pralidoxime is reconstituted to 50 mg/mL (1 g in 20 mL water) for IV administration, and the total dose infused over 30 min, or may be given by continuous infusion (loading dose 25 mg/kg over 30 min, and then 10 mg/kg/hr). For IM use, it might be diluted to a concentration of 300 mg/mL (1 g added to 3 mL water—by analogy to the U.S. Army's Mark 1 autoinjector concentration) to effect a reasonable volume for injection. See also Table 741.5.

ABCs, Airway, breathing, and circulatory support; IM, intramuscularly; IV, intravenously; max, maximum; min, minimum; prn, as needed.

Adapted from Henretig FH, Cieslak TJ, Eitzen EM. Biological and chemical terrorism. *J Pediatr*. 2002;141:311–326.

Table 763.5 Pediatric Autoinjector Recommendations for Mass Casualties or Prehospital Care*

ATROPINE AUTOINJECTOR THERAPY			
APPROXIMATE AGE	APPROXIMATE WEIGHT (KG)	AUTOINJECTOR SIZE (MG)	
<6mo	<7.5	0.25	
6mo to 4years	7.5-18	0.5	
5-10 years	18-30	1.0	
>10years	>30	2.0	

PRALIDOXIME AUTOINJECTOR THERAPY			
APPROXIMATE AGE (YEARS)	APPROXIMATE WEIGHT (KG)	NUMBER OF AUTOINJECTORS	PRALIDOXIME DOSE (MG/KG)
3-7	13-25	1	24-46
8-14	26-50	2	24-46
>14	>50	3	<35

*Consider adult pralidoxime autoinjector use for severely affected mass casualties when intravenous (IV) access or more precise mg/kg intramuscular (IM) dosing is logistically impractical. The initial dose using atropine autoinjectors is one autoinjector of each recommended size. The initial dose using pralidoxime autoinjectors is the recommended number of (adult-intended, 600mg) autoinjectors. These latter may also be injected into an empty sterile vial; the contents redrawn through a filter needle into a small syringe may then provide a ready source of concentrated (300mg/mL) pralidoxime solution for IM injection to infants. Autoinjectors may become available that provide adult doses of both atropine and pralidoxime in one injector; these could be used in children ≥ 3 years in lieu of two individual injectors and dosed as noted above for pralidoxime alone.

Raxibacumab, a monoclonal antibody that inhibits anthrax antigen binding to cell receptors, thus preventing toxins from entering cells, is approved for the treatment of inhalation anthrax in combination with antibiotics, as is obiltoxaximab, which neutralizes anthrax toxins. The adult dose of raxibacumab is 40 mg/kg given IV over 2 hours and 15 minutes. The dose for children is weight based: ≤ 15 kg, 80 mg/kg; >15 -50 kg, 60 mg/kg; >50 kg, 40 mg/kg. Premedication with diphenhydramine IV or by mouth (PO) is recommended 1 hour before the infusion.

In patients with an established diagnosis of tularemia, gentamicin (5 mg/kg IV/IM divided 2 or 3 times/day) is the preferred choice for therapy due to the limited availability of streptomycin (15 mg/kg IM q12 hours). Bioterrorism-related plague should be treated with two distinct antibiotic classes until sensitivity patterns are known; gentamicin, streptomycin, ciprofloxacin, and levofloxacin are all approved agents for treatment of pneumonic plague in children (see Table 763.2). To be effective, therapy for pneumonic plague must be initiated within 24 hours of the onset of symptoms. There is little clinical experience with ricin-induced pulmonary injury. The mainstay of therapy is expected to be supportive care.

The management of **vesicant-induced injury** is similar to that for burn victims and is largely symptomatic (see Chapter 89). The major difference between thermal burns and vesicant burns is that vesicant casualties do not need the large volumes of fluid required by thermal burn victims, as their epidermis remains intact. These patients are at risk of overhydration if treated using thermal burn protocols. Mustard victims will benefit from the application of soothing skin lotions such as calamine and the administration of analgesics. Early intubation of severely exposed patients is warranted to guard against edematous airway compromise. Oxygen and mechanical ventilation may be needed, and meticulous attention to hydration is of paramount importance. Ongoing research suggests a role for oral *N*-acetylcysteine in mitigating chronic pulmonary effects due to mustard injury. Lewisite victims can be managed in much the same manner as mustard victims. Dimercaprol (British

antilewisite) in peanut oil, given IM, may help ameliorate the systemic effects of lewisite, although few hospitals or pharmacies are likely to have this drug on hand.

The management of symptomatic smallpox victims also is largely supportive, with attention to pain control, hydration status, and respiratory sufficiency of primary importance. The parenteral antiviral compound cidofovir, licensed for the treatment of cytomegalovirus retinitis in HIV-infected patients, has in vitro efficacy against variola and other orthopoxviruses. Its utility in treating smallpox victims is untested. Moreover, in the face of a large outbreak of disease, wide parenteral use of this drug would be problematic. Tecovirimat demonstrates excellent in vitro activity against orthopoxviruses, but its utility in treating patients with smallpox is likewise untested.

In all chemical casualties, but especially if a liquid agent such as VX or mustard is suspected, decontamination is crucial and should be considered a primary medical intervention. Although this has been part of casualty doctrine in the civilian and military environments for decades, a 2016 study showed that disrobing eliminated 90% of contamination in normal volunteers; following this with showering using water or soap and water eliminated 99% of contamination. This has huge implications for the hospital management of possibly contaminated casualties, including children, and hospitals must plan to execute the decontamination mission at all levels.

For those faced with an acute chemical emergency, especially a mass casualty situation, a useful resource is the Chemical Hazard Emergency Medical Management website (<https://chemm.hhs.gov>), maintained by the Assistant Secretary for Preparedness and Response within the U.S. Department of Health and Human Services. Among its features is a decision support tool, CHEMM-IST, which aids in identification of the chemical a patient was exposed to.

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Chapter 764

Mass Psychogenic Illness

Jonathan W. Mink

Mass psychogenic illness refers to the rapid spread of illness signs and symptoms affecting members of a cohesive group, originating from a nervous system disturbance involving excitation, loss, or alteration of function, whereby physical complaints that are exhibited unconsciously have no corresponding organic etiology. Mass psychogenic illness shares features in common with **conversion disorder (functional neurologic system disorder)** (see Chapter 35) in that the symptoms are not consciously produced and are typically sensorimotor in nature. The physical symptoms are associated with significant distress and impairment; they commonly interfere with function at school or home and affect peer relationships. Some experts have argued that “functional” is a better used term than “psychogenic” because it does not imply etiology and does not reinforce dualist thinking about the mind being separate from the brain.

Much less is known about the biologic underpinnings and clinical features of mass psychogenic illness than is known about conversion disorder and other somatic symptom disorders. However, there are some important features in common with conversion disorder. These include sudden abrupt onset, inconsistency with known anatomy and physiology, atypical features, and inconsistency of symptoms over time. Specific features of mass psychogenic illness are the occurrence of these symptoms in a cohesive group; the presence of increased anxiety; spread of symptoms via sight, sound, or oral communication (including social media); and a high female:male ratio.

CLINICAL FEATURES AND DIAGNOSIS

There are many examples of mass psychogenic illness throughout history. The best known is perhaps that of the Salem “witches.” Most widely reported examples of mass psychogenic illness are in adults, but there are several reports in children as well. In 2004, 10 teenage females from a school in rural North Carolina developed paroxysmal episodes resembling epilepsy or syncope. These females were from a cohesive social group (school-age students in a small school) and had similar symptoms. The symptoms were shown not to be consistent with either syncope or epilepsy, and they eventually resolved after a two-week holiday break from school. Another episode in Le Roy, New York, was an outbreak of a “tic-like” illness among high school students. The symptoms were atypical for tics because they were not preceded by a premonitory urge and could not be suppressed with effort. In addition, the symptoms were remarkably similar across the affected patients. Symptoms resolved over time. In the Le Roy example, there was likely an exacerbating role of both social media and mass media, which amplified the cohesiveness of the group. There has been a surge of cases of “tic-like” symptoms in adolescents during the COVID-19 pandemic. It has been suggested that social media, especially videos presented on the TikTok platform, has played an important role in the spread of these symptoms.

In a study of 280 environmental chemical incidents in the United Kingdom between 2007 and 2008, 7% were classified as mass psychogenic illness according to five diagnostic criteria: (1) presence of somatic (bodily) symptoms, (2) preexisting social connection between

two or more of the affected people, (3) epidemic spread of symptoms, (4) attribution of symptoms by affected individuals (or by their parents or caregivers) to a threatening external agent of a physical (usually chemical, biologic, or radiologic) or spiritual nature, and (5) symptoms and signs that are not compatible with the environmental exposure specified by the affected individuals nor with any other environmental exposure that could reasonably be expected to have been present at the time of (or shortly before) the onset of symptoms.

One study has examined experimentally induced mass psychogenic illness. In a randomized controlled experiment, participants were assigned to one of three groups to study the effects of a simulated biologic threat and elements of social contagion. The three groups were (1) no-intervention control group, (2) psychogenic illness induction group, and (3) psychogenic illness induction plus media group. Groups 2 and 3 were told that the purpose of the study was to test the side effects of a carrier compound for an antiinfluenza medication. They were told that the compound did not produce serious side effects but was being evaluated with regard to mild side effects. In groups 2 and 3, professional actors were placed among the participants to feign illness during the study with symptoms of nausea, dizziness, and headache. Group 3 was also shown a documentary about the 1918 flu pandemic. The video contained interviews with survivors and vivid images of death and illness. The two psychogenic induction groups had 11 times more symptoms than did the control group. If a subject had a lifetime history of a traumatic event or depression, he or she was more likely to have symptoms. The documentary viewing was not associated with a higher rate of symptoms. This study confirmed the role of “**social contagion**” in mass psychogenic illness and provided a model for future studies of factors leading to such contagion.

TREATMENT STRATEGIES

Mass psychogenic illness is usually self-limited, but treatment requires careful reassurance and communication between physician and patient. Explanation models should be communicated in a sensitive manner so as not to appear dismissive of symptoms. When doctors and patients do not agree on the “reality” of the illness, the prognosis is worse. Thus media attention, medical and scientific disagreement, and legal proceedings must be managed in a way that does not exacerbate the symptoms or the illness.

In the Le Roy illness, treatment varied across individuals. The treatment strategies included cognitive-behavioral therapy, supportive psychotherapy, education, pharmacotherapy for coexisting anxiety, and alteration of social setting. Many of the patients sought multiple medical opinions. There were frequent discussions among public health and other medical officials and the local media outlets. Reduced media attention seemed to lead to more rapid improvement of symptoms in some patients.

It is helpful for healthcare providers to avoid the dichotomy of approaching illness using a medical model in which diseases are considered as being either physically or psychologically based. In contrast, a biobehavioral continuum of disease better characterizes illness as occurring across a spectrum ranging from a predominantly biologic etiology on one end to a predominantly psychosocial etiology on the other. It is beneficial to the patient for the treating physician to try to shift the emphasis from understanding the etiology to a path toward recovery.

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Chapter 765

Animal and Human Bites

David A. Hunstad

Many animals, besides domestic and stray dogs and cats, inflict bites on humans. The profile of such bites varies by country and region, based on community and living conditions, indigenous species, and opportunity for encounter.

EPIDEMIOLOGY

Worldwide there are tens of millions of dog bites each year, resulting in nearly 60,000 deaths annually from rabies (see Chapter 320). **Dog bites** represent approximately 80–90% of all bites in the United States, while 5–15% are from cats, 2–5% from rodents, and the remainder from rabbits, ferrets, farm animals, monkeys, and reptiles. An estimated 4.5 million persons in the United States are bitten by dogs annually; over 800,000 of those seek medical care. Bites from dogs are also most common in Bangladesh, India, Pakistan, and Myanmar, whereas in Nepal cattle and buffalo account for more than half of bites, followed by dogs, pigs, and horses. Approximately 1% of dog bite wounds and 6% of cat bite wounds in the United States require hospitalization. During the past three decades, there have been several dozen deaths per year in the United States from dog-inflicted injuries; the majority of these occurred in children under 11 years of age. Various studies have examined the incidence of dog bite injuries by dog breed. Compared with other breeds, bites by pit bull terriers and mixed-breed dogs account for higher rates of hospital admission, lower Glasgow Coma Scores at admission, and an increased risk of death. Unaltered male dogs account for approximately 75% of attacks, while nursing female dogs may inflict injury when humans attempt to handle their puppies.

The majority of dog attacks on children in the United States occur between the ages of 6 and 11 years, with a slight predominance in males. Approximately 65% of attacks occur around the home, 75% of biting animals are known by the children, and 50% of attacks are said to be unprovoked. Similar statistics apply in Canada, where 70% of all bites reported in one study were sustained by children age 2–14 years; 65% of dogs involved in biting were part of the family or extended family.

Of the approximately 450,000 reported **cat bites** per year occurring in the United States, nearly all are inflicted by known household animals. Because rodent bites (rat, mouse, gerbil) do not represent reportable conditions, little is known about the epidemiology of these injuries or the incidence of infection after rodent-inflicted bites or scratches.

Few data exist on the incidence and demographics of **human bite** injuries in pediatric patients; however, preschool and early school-age children appear to be at greatest risk of sustaining an injury from a human bite, often in daycare or preschool settings. In some series, the proportion of human bites is highest among adolescents, an age group in which fist-to-teeth injuries (so-called “fight bites”) become more common.

CLINICAL MANIFESTATIONS

Dog bite-related injuries can be divided into three categories of almost equal incidence: abrasions, puncture wounds, and lacerations with or without an associated avulsion of tissue. Bites from larger dogs may also involve crush injury to tissues. In contrast, the most common type of injury from cat bites is a puncture wound, often penetrating deep into tissue or joint spaces. Human bite injuries are of two types: an occlusion injury that is incurred when the

upper and lower teeth come together on a body part, or a clenched-fist injury that occurs when the injured fist, usually on the dominant hand, strikes the teeth of another individual.

DIAGNOSIS

Management of the bite victim should begin with a thorough history and physical examination. Careful attention should be paid to the circumstances surrounding the bite event (e.g., species and number of animals, type of animal [domestic or wild], whether the attack was provoked or unprovoked, location of the attack), a history of drug allergies, and the immunization status of the child (tetanus) and animal (rabies). During physical examination, meticulous attention should be paid to the type, size, and depth of the injury; the presence of any foreign material in the wound; the status of underlying structures; and, when the bite is on an extremity, the exact location of the injury, an assessment of possibly involved structures, and the range of motion of the affected area. Photographs of the injury should be recorded in the patient's medical record. Radiographs of the affected part should be considered if it is likely that a bone or joint was penetrated or fractured or if foreign material is present in the wound. The possibility of a fracture or penetrating injury of the skull should particularly be considered in infants who have sustained dog bite injuries to the face or head.

COMPLICATIONS

Infection is the most common complication of bite injuries regardless of the species of biting animal. In most cases, culture specimens from a fresh dog bite wound are not likely to be clinically useful. Although potentially pathogenic bacteria have been isolated from up to 80% of dog bite wounds that are brought to medical attention within 8 hours of the bite, the infection rate for wounds receiving medical attention in <8 hours is relatively low (2.5–20%). Cultures should be obtained from the wound if there is clinical evidence of infection or if the patient is immunocompromised. *Capnocytophaga canimorsus* is isolated from approximately 5% of infected wounds in immunocompromised patients (especially asplenia) and can cause serious systemic infection in these individuals. In contrast to dogs, the infection rate in cat bite wounds, even those that receive prompt medical attention, is >50%; therefore cat bites should be closely monitored for signs of infection.

The rate of infection after rodent bite injuries is not known. Most of the oral flora of rats is similar to that of other mammals; however, up to 50% of rats, depending on worldwide geography, may harbor strains of *Streptobacillus moniliformis* and *Spirillum minus*, both of which cause rat bite fever (see Chapter 766).

All human bite wounds, regardless of the mechanism of injury, should be considered high risk for infection. Current recommendations do not support obtaining cultures at the time of the bite as it does not change empiric antibiotic therapy; however, any infected wounds should be cultured.

Table 765.1 lists common causes of soft tissue bacterial infections after dog, cat, or other animal bites. Bites of humans or cats, those in which treatment is delayed, those in immunocompromised patients, and those associated with deep puncture wounds or significant crush injury carry a higher risk for infection. An elevated risk for infection is also present if the bite is to certain anatomic regions (e.g., hand, foot, or genitals) or there is penetration of bone or tendons.

TREATMENT

Table 765.2 outlines the management of human or animal bite wounds to reduce risk for infection. The wound should be anesthetized, cleaned, and irrigated with sterile saline using moderate pressure. Irrigation with antibiotic-containing solutions provides no advantage over saline alone and may cause local irritation of the tissues. Puncture wounds should be thoroughly cleansed and

Table 765.1 Microorganisms Associated with Animal Bites**DOG BITES**

Staphylococcus species
Streptococcus species
Eikenella species
Pasteurella species
Proteus species
Klebsiella species
Haemophilus species
Enterobacter species
Capnocytophaga canimorsus
Bacteroides species
Moraxella species
Corynebacterium species
Neisseria species
Fusobacterium species
Prevotella species
Porphyromonas species

CAT BITES

Pasteurella species
Actinomyces species
Propionibacterium species
Bacteroides species
Fusobacterium species
Clostridium species
Wolinella species
Peptostreptococcus species
Staphylococcus species
Streptococcus species

HERBIVORE BITES

Actinobacillus lignieresii
Actinobacillus suis
Pasteurella multocida
Pasteurella caballi

SWINE BITES

Pasteurella aerogenes
Pasteurella multocida
Bacteroides species
Proteus species
Actinobacillus suis
Streptococcus species
Flavobacterium species
Mycoplasma species

RODENT BITES

Streptobacillus moniliformis
Spirillum minus (in Asia)

PRIMATE BITES

Bacteroides species
Fusobacterium species
Eikenella corrodens
Streptococcus species
Enterococcus species
Staphylococcus species
Enterobacteriales
Herpes B virus

LARGE REPTILE (CROCODILE, ALLIGATOR) BITES

Aeromonas hydrophila
Pseudomonas pseudomallei (in Asia)
Pseudomonas aeruginosa
Proteus species
Enterococcus species
Clostridium species

Adapted from Perkins Garth A, Harris NS, Spanierman CS. Animal bites in emergency medicine. Available at: <http://emedicine.medscape.com/article/768875-overview>, updated October 7, 2021; accessed November 27, 2021. Reprinted with permission from eMedicine.com.

Table 765.2 Initial Management of Bite Wounds**HISTORY**

Animal bite: Ascertain the type of animal, whether the bite was provoked or unprovoked, and the situation/environment in which the bite occurred. Follow rabies guidelines (see Chapter 320) for details on management of bites that carry a risk of rabies.

Patient: Obtain information on antimicrobial allergies, current medications, splenectomy, liver disease, or immunosuppressive conditions.

PHYSICAL EXAMINATION

If possible, photograph the wound and record its location, type, and approximate depth; range of motion; possibility of joint penetration; presence of edema or crush injury; nerve and tendon function; and signs of infection.

CULTURE

Aerobic and anaerobic cultures should be taken from infected wounds (not from fresh wounds).

IRRIGATION AND DEBRIDEMENT

Irrigate with water or sterile saline and debride devitalized or necrotic tissue.

RADIOGRAPHS

Plain radiographs should be obtained if bony penetration is possible or suspected; radiographs can also provide a baseline for future evaluation of osteomyelitis.

WOUND CLOSURE

Primary wound closure is usually not advocated unless wounds are extensive and closure is necessary for cosmetic or functional reasons, especially large facial or neck wounds or those overlying the joints. When possible, delayed primary closure or allowing the wound to close by secondary intention is recommended.

ANTIMICROBIAL THERAPY

Early presenting (uninfected) wounds: provide prophylactic antimicrobials for (1) moderate-to-severe injuries, especially if preexisting edema or significant crush injury is present; (2) bone or joint space penetration; (3) deep hand wounds; (4) immunocompromised patients; (5) wounds adjacent to prosthetic material; and (6) wounds in close proximity to the genital area. In most cases, coverage should include *Pasteurella* (*Eikenella* in human bites), *Staphylococcus*, *Streptococcus*, and anaerobes including *Fusobacterium*, *Porphyromonas*, *Prevotella*, and *Bacteroides* spp. See Table 765.3 for recommended antibiotics.

Infected wounds: See Table 765.3 for oral antibiotic recommendations. In cases where intravenous antibiotics are deemed necessary, antimicrobial choices include ampicillin/sulbactam, piperacillin-tazobactam, cefoxitin, or ertapenem.

HOSPITALIZATION

Indications include signs and symptoms of systemic toxicity and worsening infection.

IMMUNIZATIONS

Provide tetanus and rabies immunization, if indicated.

ELEVATION

Elevation may be required if edema is present. Lack of elevation is a common cause of therapeutic failure.

IMMOBILIZATION

For significant injuries, immobilize the extremity, especially the hands, with a splint.

FOLLOW-UP

Patients should be reminded to follow up within 48 hours or sooner for worsening or unresolved infections and continued pain.

REPORTING

Reporting the incident to a local health department may be required.

Adapted from Goldstein EJC, Abrahamian FM. Bites. 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 315-3.

Table 765.3 Recommended Empirical Oral Antibiotics for Bite Wound Prophylaxis and Treatment

ANTIBIOTIC	RECOMMENDED ADULT DOSE	RECOMMENDED CHILD DOSE*
AGENT OF CHOICE		
(A) Amoxicillin-clavulanate	875/125 mg twice daily	45 mg/kg per dose (amoxicillin component) twice daily
ALTERNATE COMBINATION THERAPY: B OR C (WITH ANAEROBIC ACTIVITY) PLUS E, F, G, H, OR I		
(B) Metronidazole	500 mg three times daily	10 mg/kg per dose three times daily
Or:		
(C) Clindamycin	450 mg three times daily	10 mg/kg per dose three times daily
PLUS, ONE OF THE FOLLOWING:		
(D) Doxycycline	100 mg twice daily	Not for use in children <8 yr old
(E) Trimethoprim-sulfamethoxazole	160/800 mg (1 DS tab) twice daily	4 to 5 mg/kg (trimethoprim component) per dose* twice daily
(F) Penicillin V potassium	500 mg four times daily	12.5 mg/kg per dose four times daily
(G) Cefuroxime	500 mg twice daily	10 mg/kg per dose twice daily
(H) Moxifloxacin	400 mg once daily	Use with caution in children

*Child dose should not exceed recommended adult dose.

From Phillips LL, Semple J: Bites and injuries inflicted by wild and domestic animals. In Auerbach PS, Cushing TA, Harris NS (editors): *Auerbach's Wilderness Medicine*, 7th ed, vol 1. Philadelphia: Elsevier, 2017; Table 30.3, p. 623.

gently irrigated with a catheter or blunt-tipped needle; blind, high-pressure irrigation should not be employed. Avulsed or devitalized tissue should be debrided and any fluctuant areas incised and drained.

Surgical approaches to management of bite wounds may include primary closure, delayed primary closure (i.e., in 3-5 days), or healing by secondary intention. Factors to be considered are the type, size, and depth of the wound; the anatomic location; the presence of infection; the time since the injury; and the potential for cosmetic disfigurement. Appropriate surgical consultation (e.g., general pediatric surgery; plastic, hand, or orthopedic surgery) should be obtained promptly for all patients with deep or extensive wounds; wounds involving the hands, face, or bones and joints; and infected wounds that require open drainage. Although there is general agreement that visibly infected wounds and those that are more than 24 hours old should not be sutured, there is a spectrum of practice regarding the closing of wounds <8 hours old with no evidence of infection. Because all bite wounds to the hand are at high risk for infection, particularly if there has been disruption of the tendons or penetration of the bones, surgical consultation is almost always indicated, and delayed primary closure is recommended for many bite wounds of the hands. Facial lacerations are at lower risk for secondary infection because of the excellent blood supply to this region. Given this fact and cosmetic considerations, many plastic surgeons advocate primary closure of facial bite wounds that have been brought to medical attention within 8 hours.

Similarly, there are few comparative trials addressing the efficacy and selection of antimicrobial agents for **prophylaxis** of bite injuries. The bacteriology of bite wound infections is more often a reflection of the oral flora of the biting animal than the skin flora of the victim (see Table 765.1). Because many aerobic and anaerobic bacterial species colonizing the oral cavity of the biting animal have the potential to invade local tissue, multiply, and cause tissue destruction, most bite wound infections are polymicrobial.

Despite substantial homology in the oral bacterial flora of humans, dogs, and cats, important differences exist among the biting species, reflected in the types of wound infections that occur. The predominant bacterial species isolated from infected dog bite wounds are *Staphylococcus aureus* (20–30%), *Pasteurella multocida*

(20–30%), *Staphylococcus intermedius* (25%), and *C. canimorsus*; approximately one-half of dog bite wound infections also contain mixed anaerobes. Similar species are isolated from infected cat bite wounds; however, *P. multocida* is the predominant species in at least 50% of cat bite wound infections. At least 50% of rats harbor *S. moniliformis* in the oropharynx, and approximately 25% in Asia harbor *S. minus*, a small, uncultivable gram-negative organism. In infected human bite wounds, nontypable strains of *Haemophilus influenzae*, *Eikenella corrodens*, *S. aureus*, α -hemolytic streptococci, and β -lactamase-producing aerobes (~50%) are the predominant species. Clenched-fist injuries are particularly prone to infection by *Eikenella* spp. (25%) and other anaerobes (50%).

The choice between oral and parenteral antimicrobial therapy should be based on the severity of the wound, the presence and degree of overt infection, signs of systemic toxicity, and the patient's immune status. **Amoxicillin-clavulanate is an excellent choice for empiric oral therapy** for human and animal bite wounds because of its activity against most bacteria that are isolated from infected bites (Table 765.3). Similarly, **ampicillin-sulbactam or piperacillin-tazobactam is preferred for patients who will receive empiric parenteral therapy**. Penicillin G is the drug of choice for prophylaxis and treatment of rat bite injuries, as this agent has excellent activity against *S. moniliformis* and *S. minus*. Because first-generation cephalosporins have limited activity against *P. multocida* and *E. corrodens*, they should not be used for prophylaxis or empiric therapy of bite wound infections. Therapeutic alternatives for bite wound infections in penicillin-allergic patients are limited; clindamycin plus trimethoprim-sulfamethoxazole is the most commonly suggested regimen for these patients. Tetracycline is the drug of choice for penicillin-allergic patients who have sustained rat bite injuries.

Although **tetanus** occurs only rarely after human or animal bite injuries, it is important to obtain a detailed immunization history and to provide tetanus toxoid to all patients who are incompletely immunized or who received their most recent tetanus immunization more than five years prior. The need for postexposure **rabies** vaccination in victims of dog and cat bites depends on whether the biting animal is known to have been vaccinated and, most importantly, on local experience with rabid animals in the community. Bites from bats, foxes, skunks, and raccoons should be considered

high risk for rabies, and postexposure prophylaxis is uniformly indicated. For dogs, cats, and other animals that are known or captured, observation for 7–10 days by the local animal control department is indicated, and rabies prophylaxis can be delayed as long as the animal remains asymptomatic. If a biting dog or cat has escaped, a decision about rabies prophylaxis can be based on the circumstances surrounding the bite and advice from local infectious disease specialists and/or health department officials. Worldwide, animal bites and contacts result annually in more than 10 million courses of rabies postexposure prophylaxis.

In human bites where the biter's blood may have contaminated the wound, risk for hepatitis B, hepatitis C, and HIV infections should be considered (see Chapters 322 and 406).

PREVENTION

It is possible to reduce the risk of animal bite injury with anticipatory guidance. Parents should be routinely counseled during prenatal visits and routine health maintenance examinations about the risks of having potentially biting pets in the household. All patients should be cautioned against harboring exotic animals as pets. All young children should be closely supervised, particularly when in the presence of animals, and from a very early age should be taught to respect animals and to be aware of their potential to inflict injury. Reduction of the rate of human bite injuries, particularly in daycare centers and schools, can be achieved by good surveillance of the children and adequate teacher-to-child ratios.

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Chapter 766

Rat Bite Fever

David A. Hunstad

ETIOLOGY

Rat bite fever is a generic term that has been applied to at least two distinct clinical syndromes, each caused by a different microbial agent. Rat bite fever caused by *Streptobacillus moniliformis* is most commonly reported in the United States as well as in Brazil, Canada, Mexico, Paraguay, Great Britain, and France; it has been identified elsewhere in Europe and in Australia. *S. moniliformis* is a gram-negative bacillus that is present in the nasopharyngeal flora of many laboratory and wild rats. Infection with *S. moniliformis* most commonly occurs following the bite of a rat; however, infection has also been reported in individuals who have been scratched by rats, in those who have handled dead rats, and in those who have ingested milk contaminated with the bacterium (termed **Haverhill fever**). Rat bite fever may also be transmitted by bites from wild mice. Rat bite fever caused by *Spirillum minus*, called **sodoku** (after the Japanese for “rat” and “poison”), is most commonly reported in Asia. *S. minus* is a small, spiral, aerobic gram-negative organism. Reports of rat bite fever from Africa are rare, suggesting under recognition rather than absence of the disease.

CLINICAL COURSE

The incubation period for the streptobacillary form of rat bite fever is variable, ranging from 3–10 days. The illness is characterized by an abrupt onset of fever up to 41°C (105.8°F) in over 90% of reported cases, as well as severe throbbing headache, intense myalgias, chills, and vomiting. In virtually all instances, the lesion at the cutaneous inoculation



Fig. 766.1 Morbilliform rash on the hands/palms (A) and feet (B) of a patient with rat bite fever. (From Vetter NM, Feder HM Jr, Ratzan RM. Rat bite fever caused by a kiss. *Am J Emer Med*. 2015;34:1190.e3–1190.e4. Figs. 1 and 3.)



Fig. 766.2 Hemorrhagic vesicles on the first and third toes of a patient with advanced rat bite fever. (From Elliott SP. Rat bite fever and *Streptobacillus moniliformis*. *Clin Microbiol Rev*. 2007;20:13–22. Fig. 3.)

site has healed by the time that systemic systems first appear. Shortly after the onset of the fever, a polymorphous rash occurs in up to 75% of patients. In most patients, the rash consists of blotchy red maculopapular lesions that often have a petechial component; the distribution of the rash is variable, but it is typically most dense on the extremities (Fig. 766.1). Hemorrhagic vesicles may develop on the hands and feet and are very tender to palpation (Fig. 766.2).

Approximately 50% of patients have arthritis, which first manifests toward the end of the first week of disease; early on, the arthritis may be migratory. If untreated, fever, rash, and arthritis last from 14–21 days, often with a biphasic pattern to the fever and arthritis. A wide range of complications are reported in patients with rat bite fever, the most common being pneumonia, persistent arthritis, brain and soft tissue abscesses, and, less commonly, myocarditis or endocarditis. The mortality rate in untreated rat bite fever is estimated to be 10–15%.

The incubation period of sodoku is longer (14–21 days) than that of the streptobacillary form of disease. The hallmark of *Spirillum*-induced disease is fever associated with an indurated, often suppurative, non-healing lesion at the bite site. Lymphadenitis and lymphadenopathy are invariably present in the regional nodes that drain the inoculation site, and many patients have a generalized macular rash most prominent

when fever is present. In untreated patients, sodoku has a relapsing and remitting course; symptoms abate after 5-7 days of chills and fever but recur 7-10 days later. There may be multiple cycles if the disease is not recognized and treated.

DIAGNOSIS

Diagnosis of the streptobacillary form of rat bite fever is difficult because the disease is uncommon and can be confused with Rocky Mountain spotted fever or (less commonly) meningococcemia. Furthermore, *S. moniliformis* is difficult both to isolate and to identify with classic bacteriologic techniques. The organism is fastidious and is inhibited by sodium polyanethol sulfonate, an additive present in many commercial blood culture bottles. Therefore the clinical microbiology laboratory should be notified when this infection is suspected so that additional media can be inoculated. A definitive diagnosis is made when *S. moniliformis* is recovered from blood or joint fluid or is identified in human samples by polymerase chain reaction (PCR), which has been used successfully in humans.

Diagnosis of sodoku is made on clinical grounds because there are no diagnostic serologic tests and culture of *S. minus* has not been achieved in laboratory media. Rarely, the organism may be visualized in Gram-stained smears of pus from the inoculation site. Approximately 50% of patients exhibit a false-positive Venereal Disease Research Laboratory (VDRL) test.

TREATMENT

Penicillin is the drug of choice for both forms of rat bite fever. Intravenous penicillin G or intramuscular penicillin G procaine is recommended for 7-10 days; a regimen of IV penicillin G for 5-7 days followed by oral penicillin V for an additional 7 days has also been used. Doxycycline, gentamicin, or streptomycin represent effective alternatives for penicillin-allergic patients. Patients with endocarditis caused by *S. moniliformis* require high-dose penicillin G for 4 weeks; the addition of streptomycin or gentamicin might be helpful.

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Chapter 767

Mpox (Monkeypox)

David A. Hunstad

Since the eradication of **smallpox** (variola), mpox (formerly known as monkeypox) virus has, for humans, become the most important member of the genus *Orthopoxvirus*. Monkeys are the predominant host for the virus; however, it may be endemic in African rainforest squirrels and is present in African rats, mice, domestic pigs, hedgehogs, and opossums. It has also been identified in and transmitted by imported prairie dogs in the United States and has affected elephants in zoos. Severity of infection varies by viral strain and by host; for example, disease is relatively mild in cynomolgus monkeys but severe in orangutans.

Mpox was first observed in humans from West and Central Africa in the 1970s at the time that smallpox had been eradicated from the area. In the 1970s, the secondary attack rate was around 3% (a stark comparison to the 80% seen in unvaccinated smallpox contacts). Few cases were observed over the next 2 decades; however, during a subsequent outbreak in the 1990s, when immunity to smallpox was no longer prevalent in the population, the secondary attack rate exceeded 75%. Mpox was introduced into the United States in 2003, presumably through rodents from Ghana that infected prairie dogs that were subsequently distributed as pets. Before 2022, primary transmission of the disease was from infected animal to human by

bite or by human contact with an infected animal's blood, wound discharge, or other body fluids. Human-to-human transmission was previously thought to be uncommon, but a global outbreak in 2022 was linked to a shift to human-to-human transmission.

As of early 2023, nearly 87,000 cases were documented globally. Although children have comprised up to 40% of cases in previous outbreaks, the epidemiology of the current outbreak is different; less than 700 cases (<2%) have been reported in children and adolescents ≤20 years old. Mpox is currently spread predominantly through close human-to-human contact. The most recent outbreak has affected mostly gay, bisexual, and other men who have sex with men. Patients living with advanced HIV (with low CD4 counts) are at increased risk for severe disease. Although children typically acquire mpox from household contact, sexual contact is the primary route of transmission for adolescents. Mpox virus can persist on surfaces in households with an affected person.

CLINICAL COURSE

The classic clinical signs, symptoms, and course of mpox are similar to those of smallpox, although typically milder. After an incubation period of 10-14 days, during which the mpox virus replicates in lymphoid tissues, humans experience an abrupt onset of malaise, fever, myalgia, headache, and severe backache. Nonproductive cough, nausea, vomiting, and abdominal pain may be present. Generalized lymphadenopathy, a finding unusual in smallpox, is invariably present during the acute stages of mpox illness. After a prodrome of 2-4 days, an exanthem appears on the face and progresses inferiorly, including the palms and soles. As the rash spreads, fevers begin to abate. The rash is initially macular but transforms within hours to firm papules that rapidly vesiculate and become pustular over 2-3 days (Table 767.1). Unlike smallpox lesions but similar to chickenpox lesions, the lesions of mpox tend to occur in crops (Fig. 767.1). Late into the second week of illness, the lesions begin to desiccate, crust, scab, and fall off. During the 2022 global outbreak, lesions often occurred in the genital and anorectal areas and in the mouth (Fig. 767.2); cutaneous lesions are

Table 767.1 Mpox: Lesion Progression Through the Scab Stage

STAGE	STAGE DURATION (DAYS)*	CHARACTERISTICS
Enanthem		Sometimes, lesions first form on the tongue and in the mouth.
Macules	1-2	Macular lesions appear.
Papules	1-2	Lesions typically progress from macular (flat) to papular (raised).
Vesicles	1-2	Lesions then typically become vesicular (raised and filled with clear fluid).
Pustules	5-7	Lesions then typically become pustular (filled with opaque fluid) – sharply raised, usually round, and firm to the touch (deep seated). Finally, lesions typically develop a depression in the center (umbilication). The pustules will remain for approximately 5-7 days before beginning to crust.
Scabs	7-14	By the end of the second week, pustules have crusted and scabbed over. Scabs will remain for about a week before beginning to fall off.

*This is a typical timeline, but timelines can vary.

From Centers for Disease Control and Prevention. Key Characteristics for identifying Mpox. <https://www.cdc.gov/poxvirus/mpox/clinicians/clinical-recognition.html>



Fig. 767.1 A, Legs and feet of an mpox (endemic) patient. B, Legs and feet of a smallpox patient at an analogous stage of rash (pustular). (A, Courtesy Joseph M. Harvey, MD. B, Courtesy J. Nobel, Jr., MD, Centers for Disease Control and Prevention.)



Fig. 767.2 Clinical presentation of mpox. A, Pustules in the genital and pubic region, in which the initial umbilication has progressed to necrotic crust with central depression. B, Three semiconfluent pustular lesions with a depressed center located on the left side of the tongue dorsum. C, Pearly acral vesicles embedded in the thick stratum corneum of the palmar skin, shotty on palpation. D, Scattered papules, pustules, and umbilicated pustules surrounded by an erythematous halo on the lateral aspect of the chest and left arm. E, Pustules circumferentially distributed on the anal margin and perianal skin. F, A pustular lesion with a crusted center on the semimucosa of the lower lip, close to the right oral commissure. G, Primary inoculation site with a large, crusted lesion on the right cheek. H, The right palatine tonsil is reddened and enlarged and has a fibrin-covered ulcer. I, The penile glans and foreskin have lesions of varying sizes and stages of evolution, with edema surrounding the larger ulcer. (From Tarín-Vicente EJ, Alemany A, Agud-Dios M, et al. Clinical presentation and virological assessment of confirmed human monkeypox virus cases in Spain: a prospective observational cohort study. *Lancet*. 2022;400[10353]:661–669. Fig. 1; Photos A–C, E–G, I taken by Eloy José Tarín-Vicente, MD; Photos D, H by Maria Ubals, MD.)

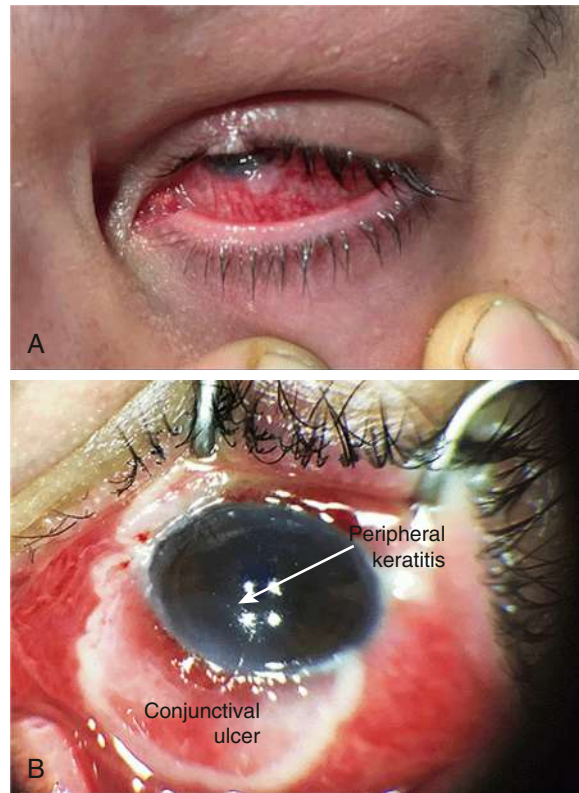


Fig. 767.3 Left eye in a patient with HIV-associated immunocompromise and ocular mpox, with conjunctivitis and conjunctival lesion earlier in the course of mpox illness (A), and with conjunctival ulcer and peripheral keratitis later in the course of mpox illness (B) — United States, August–September 2022. (A courtesy Nathanael Adjei-Kyeremeh. B courtesy Dharmendra R. Patel; From Cash-Goldwasser S, Labuda SM, McCormick DW, et al. Ocular monkeypox – United States, July–September 2020. *MMWR*. 2022;71:1343–1347. Fig. 2.)

less often disseminated with occasionally only a single lesion noted. Additionally, fever and other systemic symptoms may occur before the rash, *after* the rash, or *not at all*. Disseminated systemic or focal disease may include encephalitis, pharyngitis, myocarditis, arthritis, proctitis, lymphadenopathy, pneumonia, and ocular involvement (Fig. 767.3).

Mpox should be suspected in any child or adolescent who has the characteristic prodrome associated with a poxlike eruption and a history of close contact with someone who has been diagnosed with mpox, residence in Africa, or contact with prairie dogs or exotic mammals such as Gambian rats and rope squirrels. Diagnosis is by isolation of mpox viral DNA by polymerase chain reaction (PCR) from a skin lesion, including exudate or lesion crust. Oropharyngeal swabs may be considered in high-risk contacts of known or probable cases who have not yet developed a rash that can be swabbed (Table 767.2).

Cowpox, another *Orthopoxvirus*, often acquired from a pet rat, may produce similar cutaneous lesions. Regional lymphadenopathy and mild system features may also be present. Diagnosis is confirmed by a specific cowpox virus PCR.

PREVENTION AND TREATMENT

In 2019, the U.S. Food and Drug Administration (FDA) approved a new live-attenuated, replication-deficient vaccinia virus vaccine (branded Jynneos in the United States and Imvamune in the

European Union [EU]; Bavarian Nordic) for use in patients ≥ 18 years old who are at risk for mpox acquisition. Despite evidence that preexposure administration of classical smallpox vaccine is 85% effective in preventing or attenuating mpox disease, the rarity of mpox infection does not warrant universal vaccination. However, following the recent 2022 outbreak, the U.S. Centers for Disease Control and Prevention recommends vaccinating high-risk patients (Table 767.3). This vaccine has a very low side effect profile and can be safely used in immunocompromised individuals, a significant advantage over classical (replication-competent) live smallpox vaccines.

For most immunocompetent patients with mild to moderate disease, supportive care is recommended. However, treatment should be considered for those with severe disease (hemorrhagic disease, large number of confluent lesions, necrotic lesions, severe lymphadenopathy that is necrotic or obstructing, involvement of multiple organ systems and comorbidities, or those who require hospitalization) or those with involvement of anatomic areas where scarring or stricture might cause serious sequelae (Fig. 767.4). In addition, treatment may be considered in patients at high risk for severe disease, including children less than 1 year old, immunocompromised or pregnant patients, or those with reduced skin integrity (e.g., eczema). Treatment options include tecovirimat, brincidofovir, cidofovir, or trifluridine ophthalmic solution; these medications were originally developed for treatment of other viral infections and

Table 767.2 Mpox Case Definitions

CLINICAL AND LABORATORY CLASSIFICATION	CRITERIA
Suspected	New characteristic rash* OR Meets one of the epidemiologic criteria and has high clinical suspicion [†] for mpox
Probable	No suspicion of other recent <i>Orthopoxvirus</i> exposure (e.g., vaccinia virus in ACAM2000 vaccination) AND demonstration of the presence of <ul style="list-style-type: none"> • <i>Orthopoxvirus</i> DNA by polymerase chain reaction testing of a clinical specimen OR • <i>Orthopoxvirus</i> using immunohistochemical or electron microscopy testing methods OR • Demonstration of detectable levels of anti-<i>Orthopoxvirus</i> IgM antibody during the period of 4-56 days after rash onset
Confirmed	Demonstration of the presence of mpox virus DNA by polymerase chain reaction testing or next-generation sequencing of a clinical specimen OR Isolation of mpox virus in culture from a clinical specimen
EPIDEMIOLOGIC CLASSIFICATION	
Within 21 days of illness onset:	Reports having contact with a person or persons with a similar appearing rash or with a person who has received a diagnosis of confirmed or probable mpox OR Had close or intimate in-person contact with persons in a social network experiencing mpox infections. This includes MSM who meet partners through an online website, digital application ("app"), or social event (e.g., a bar or party) OR Traveled, within 21 days of illness onset outside the United States to a country with confirmed cases of mpox or where mpox virus is endemic OR Had contact with a dead or live wild animal or exotic pet that is an African endemic species, or used a product derived from such animals (e.g., game meat, creams, lotions, powders, etc.)
EXCLUSIONS	
A case might be excluded as a suspected, probable or confirmed case if:	An alternative diagnosis* can fully explain the illness OR A person with symptoms consistent with mpox does not develop a rash within 5 days of illness onset OR A case where high-quality specimens do not demonstrate the presence of <i>Orthopoxvirus</i> or mpox virus or antibodies to <i>Orthopoxvirus</i>

*The characteristic rash associated with mpox lesions involves the following: deep-seated and well-circumscribed lesions, often with central umbilication; and lesion progression through specific sequential stages: macules, papules, vesicles, pustules, and scabs. The rash can sometimes be confused with other diseases that are more commonly encountered in clinical practice (e.g., syphilis, herpes, and varicella-zoster). Historically, sporadic accounts of patients co-infected with mpox virus and other infectious agents (e.g., varicella-zoster, syphilis) have been reported; so patients with a characteristic rash should be considered for *Mpox virus* testing, even if tests for other infectious agents are positive.

[†]Clinical suspicion may exist if lesions consistent with those from more common infections (e.g., syphilis, herpes, and varicella-zoster) coexist with lesions that may be characteristic of mpox.

From Centers for Disease Control and Prevention. Updated case-finding guidance: Mpox outbreak – United States, 2022. <https://emergency.cdc.gov/han/2022/han00468.asp#:~:text=>

Table 767.3 Mpox Vaccination Basics

Centers for Disease Control and Prevention recommends vaccination against mpox if:

- You had known or suspected exposure to someone with mpox
- You had a sex partner in the past 2 weeks who was diagnosed with mpox
- You are a gay, bisexual, or other man who has sex with men or a transgender, nonbinary, or gender-diverse person who in the past 6 months has had any of the following:
 - A new diagnosis of one or more sexually transmitted diseases (e.g., chlamydia, gonorrhea, or syphilis)
 - More than one sex partner
- You have had any of the following in the past 6 months:
 - Sex at a commercial sex venue (like a sex club or bathhouse)
 - Sex related to a large commercial event or in a geographic area (city or county for example) where mpox virus transmission is occurring
 - Sex in exchange for money or other items
- You have a sex partner with any of the above risks
- You anticipate experiencing any of the above scenarios
- You have HIV or other causes of immune suppression and have had recent or anticipate future risk of mpox exposure from any of the above scenarios
- You work in settings where you may be exposed to mpox:
 - You work with orthopoxviruses in a laboratory
 - You are part of an *Orthopoxvirus* and healthcare worker response team

are thought to complement the immune response by reducing replication, maturation, and spread of mpox. Vaccinia immune globulin intravenous (VIGIV) may be considered in immunocompromised patients who cannot mount an appropriate immune response to clear the virus. In addition to antiviral medications, careful attention should be paid to skin hygiene, maintenance of adequate nutrition and hydration, and prompt implementation of local or systemic therapy for secondary bacterial infection that may occur. Pain management is a common reason for hospitalization because both cutaneous and mucosal lesions can be very painful. For prevention of human-to-human spread of disease, a combination of contact, droplet, and airborne infection control procedures should be implemented.

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From Centers for Disease Control and Prevention. Mpox Vaccination Basics. <https://www.cdc.gov/poxvirus/mpox/vaccines/index.html>

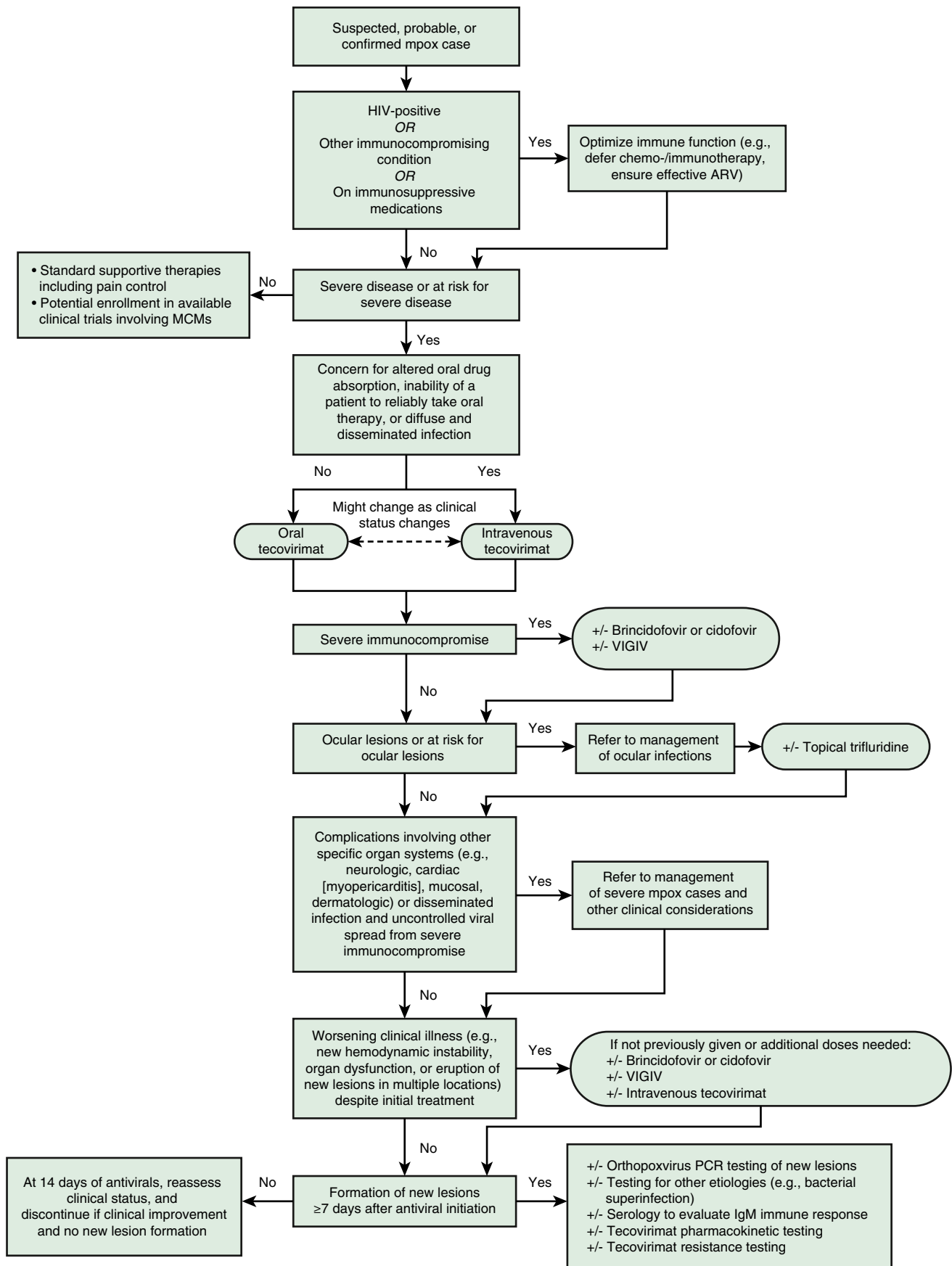


Fig. 767.4 Algorithmic approach to treatment*†‡ of patients with severe§ or at risk¶ for severe manifestations of mpox** : United States, February 2023.††

* Treatment includes MCMs (i.e., tecovirimat, brincidofovir, cidofovir, VIGIV, and trifluridine) and supportive therapies, including pain management. <https://www.cdc.gov/poxvirus/monkeypox/clinicians/pain-management.html>

† Most immunocompetent patients should display signs of clinical improvement within 4 days of antiviral initiation (i.e., tecovirimat, brincidofovir, cidofovir, and trifluridine). Tecovirimat is expected to reach steady-state concentrations by day 6 of dosing in healthy volunteers; therefore worsening clinical illness after 7 days of treatment in patients with severe illness could prompt additional evaluations.

‡ Concern for altered drug absorption includes the inability to tolerate or take oral therapy (e.g., nothing by mouth), or possibility that the oral drug absorption might be altered because of inability to consume a high-fat meal, severity of symptoms (e.g., systemic illness), comorbidities (e.g., history of gastric bypass or underlying GI disease), or other factors that might alter oral drug absorption.

§ Hemorrhagic disease, a large number of confluent or necrotic lesions, severe lymphadenopathy that is necrotizing or obstructing (e.g., of the upper airway causing airway compromise or of the GI tract necessitating parenteral feeding), edema that is obstructing (e.g., of the lower GI tract), extradermatologic manifestations (e.g., pulmonary nodules, encephalitis, myopericarditis, or ocular infections), and sepsis. Detailed characteristics of severe disease are available at https://www.cdc.gov/poxvirus/monkeypox/clinicians/treatment.html#anchor_1655488137245.

¶ Persons with underlying medical conditions (e.g., severe or moderate immunocompromise [<https://www.cdc.gov/poxvirus/monkeypox/clinicians/people-with-HIV.html>]); bacterial superinfections; or complications, including strictures, edema, and infections of the penile foreskin, vulva, urethral meatus, or anorectum, which could require procedural intervention (e.g., urethral catheterization, colostomy, or surgical debridement). This also includes those with or at risk for ocular lesions (i.e., presence of eyelid lesions, facial lesions near the eyes, or finger or hand lesions in patients unable to avoid touching their eyes [for whom autoinoculation is a concern]). Detailed characteristics of persons at risk for severe disease are available at https://www.cdc.gov/poxvirus/monkeypox/clinicians/treatment.html#anchor_1655488137245.

** <https://www.cdc.gov/poxvirus/monkeypox/clinicians/case-definition.html>

†† This figure is a comprehensive synthesis of heterogeneous evidence and is intended to foster strategic decision-making rather than serve as a prescriptive treatment guideline.

ARV, Antiretroviral medications; GI, gastrointestinal; IgM, immunoglobulin M; MCM, medical countermeasure; PCR, polymerase chain reaction; VIGIV, vaccinia immune globulin intravenous. (From Rao AK, Schrodt CA, Minhaj FS, et al. Interim clinical treatment considerations of severe manifestations of Mpox – United States, February 2023. *MMWR*. 2023;72:232–243.)

Chapter 768

Envenomations

Sing-Yi Feng

Envenomations due to snakes, spiders, scorpions, and other venomous animals can cause significant morbidity and mortality, although the majority cause only localized pain and swelling. In the 2020 report of the American Association of Poison Control Centers, approximately 42,800 out of 2.1 million phone consultations were related to bites and stings of various creatures, with approximately 14,000 involving children <20 years of age.

Not every bite from a venomous creature is harmful. In many cases, no venom is injected; these are called **dry bites**. A dry bite may occur for many reasons, including failure of the venom delivery mechanism and depletion of venom. Up to 20% of pit viper, 80% of coral snake, and approximately 50% of all venomous snake bites are dry.

GENERAL APPROACH TO THE ENVENOMATED CHILD

Children may be bitten or stung as they play and explore their environment. The evaluation may be hampered by an unclear history of the circumstances and the possible offending organism, particularly with preverbal children. The overall effects of some venomous bites and stings may be relatively more severe in children than in adults because children generally receive a similar venom load from the offending animal yet have less circulating blood volume to dilute its effects.

General Management

The majority of envenomations require local wound care, pain control, and reassurance. However, the severely envenomated child may require advanced life support interventions including endotracheal intubation and mechanical ventilation. Intravenous access should be obtained in an unaffected extremity if possible (see Chapters 91 and 92) to provide fluids and vasopressors as needed. Early hypotension is usually due to vasodilation and should be treated with volume expansion using

appropriate infusion of intravenous crystalloid solution (normal saline boluses of 20 mL/kg; repeated as needed up to three times). Shock unresponsive to volume repletion may require addition of a vasopressor agent such as epinephrine or norepinephrine (in addition to antivenom administration if appropriate). If the presentation is suspicious for an anaphylactic reaction to venom, treatment (including epinephrine) should be initiated as soon as possible (see Chapter 190) along with the appropriate **antivenom**.

The affected body part should be immobilized in a position of function and any areas of edema should be marked, measured, and monitored. If antivenom is available for the envenomation, efforts should be initiated to locate and secure an adequate amount to treat the patient. In the United States, regional poison control centers are available via the national phone number 1-800-222-1222 to facilitate this effort, especially if the species is exotic. Guidance in dosing the antivenom should be obtained from experienced toxicologists via the regional poison center.

General Wound Care

Bites and stings require basic wound care, including copious tap water or normal saline irrigation under pressure when possible. For small puncture wounds, this is impractical, but the skin should still be thoroughly cleansed with soap and water. Tetanus immunization should be updated as needed. Intact bullae should be left to act as a natural sterile dressing to prevent infection, whereas ruptured bullae should be debrided. Exposed tissue should be covered with wet to dry dressings. Necrotic wounds, as seen in some snake and spider bites, should be judiciously debrided, with removal of only clearly necrotic tissue. Reconstructive surgery with skin grafts or muscle/tendon grafts may be necessary later. Prophylactic antibiotics are usually not necessary because venom is bacteriostatic. Antibiotics should generally be reserved for signs of established secondary infection.

SNAKE BITES

Most snake bites are inflicted by nonvenomous species and are of no more consequence than a potentially contaminated puncture wound. Anatomic features including head shape, pupil shape, and anal plate arrangement can be used to differentiate venomous and nonvenomous snakes (Fig. 768.1). Medically important venomous snakes in the United States belong to two families: **Crotalinae** and **Elapidae** (Table 768.1). Most snakebites occur

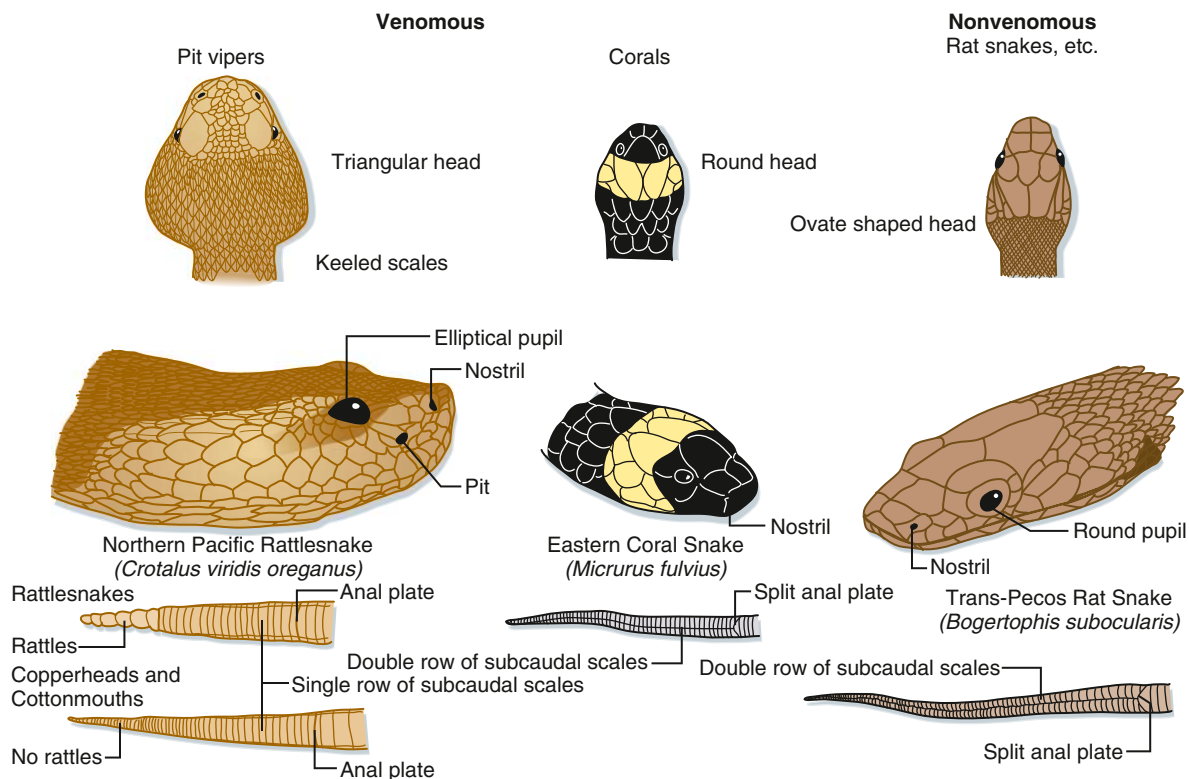


Fig. 768.1 Anatomic comparison of pit vipers, coral snakes, and nonvenomous snakes of the United States. (Modified from Adams JG, ed. Emergency Medicine. Philadelphia: WB Saunders; 2008. Drawing by Marlin Sawyer.)

Table 768.1 Important Venomous Snake Families in the United States			
FAMILY	EXAMPLES	TOXIN EFFECTS/OTHER COMMENTS	ANTIVENOM
Crotalinae (pit vipers)	Rattlesnakes (<i>Crotalus</i> and <i>Sistrurus</i> spp.), cottonmouths and copperheads (<i>Agkistrodon</i> spp.)	Heat-sensing “pit” between each eye and nostril Toxins cause tissue damage, coagulopathy, cardiovascular collapse Exception: Mojave rattlesnake (<i>Crotalus scutulatus</i>) – neurotoxic venom	<i>Crotalinae</i> polyvalent immune Fab
Elapidae	Coral snakes (<i>Micrurus</i> spp.)	Venom is neurotoxic	Antivenin (<i>Micrurus fulvius</i>)

from April through September, when snakes are at their most active. Males sustain 75% of bites and children <5 years of age account for 10–15%. Bites are usually located on extremities, although other parts of the body have been reported. In the United States, approximately 98% of venomous snake bites are inflicted by pit vipers (Crotalinae). A small fraction of bites are caused by coral snakes (Elapidae) in the southern and southwestern states and by exotic pet snakes that have been imported.

Venoms and Effects

Snake venoms are complex mixtures of proteins including enzymes that cause local tissue destruction and other enzymes that have potentially lethal systemic effects including coagulopathy and neurotoxicity. The symptoms and severity of an envenomation vary according to the type of snake, the amount of venom injected, and the location of the bite. About 25% of snakebites are “dry bites,” where the patient has fang marks and puncture wounds but no pain, swelling, or systemic effects as no venom was injected. Most pit viper bites cause significant local pain, swelling, and ecchymosis and may result in necrosis of the affected extremity (Fig. 768.2). Pain and swelling typically begin quickly after the bite and may progress over hours to days. Serious envenomation may result in

a consumptive coagulopathy, hypotension, and respiratory distress. In contrast, venom from the Elapidae is neurotoxic with little or no local tissue damage. These bites cause variable local pain, and the onset of systemic effects can be delayed for hours. Manifestations of neurotoxicity generally are caused by curare-like blockade at the neuromuscular junction. Symptoms usually begin with cranial nerve palsies such as ptosis, dysarthria, and dysphagia and may progress to respiratory failure and complete paralysis. Some pit vipers, including the Southern Pacific rattlesnake (*Crotalus oreganus helleri*), western diamondback rattlesnake (*Crotalus atrox*), timber rattlesnake (*Crotalus horridus*), and Mojave rattlesnake (*Crotalus scutulatus*), can also cause significant neurotoxicity, like the Elapidae. Regional poison control centers and toxicologists should be consulted early in the course of treatment.

Management

Prehospital care should focus on rapid transport to the emergency department while providing supportive care. Constrictive clothing, jewelry, and watches should be removed, and the injured body part should be immobilized in a position of function at the level of the heart. Many popularized field treatments for snake bites, such as



Fig. 768.2 Southern Pacific rattlesnake bite (*Crotalus oreganus helleri*) in a 2-yr-old child. Note the fang marks, swelling, and bruising of the tissues (photograph taken 2 hours following the bite). (Courtesy Sean Bush, MD.)

tourniquets, ice, electric shock, incision, and suction, have proven ineffective or deleterious.

At the hospital, supportive care should be continued as an effort is made to identify the offending snake and secure the appropriate antivenom (if applicable). In severe envenomations, advanced respiratory support may be required, including endotracheal intubation and mechanical ventilation. Intravenous access should be established in an unaffected extremity, intravenous fluids administered as needed, and standard laboratory specimens obtained, including complete blood count, coagulation studies, fibrinogen concentration, and serum chemistry analysis including total creatine kinase. Laboratory studies should initially be repeated every 4–6 hours to monitor the patient's progress and response to therapy. If tourniquets are placed in the field, they should be cautiously removed after venous access is obtained due to possible adverse effects that may follow from a sudden release of venom into the systemic circulation. The bitten extremity should be marked with the leading edge of the erythema and edema as well as the time to monitor progression of the swelling.

Assessment of the severity of the envenomation in the field and at the hospital is essential in determining the appropriateness of antivenom therapy for the snakebite victim (Table 768.2). Antivenoms are relatively specific for the genus of snake whose venom they are designed to neutralize. If it is determined that the patient requires antivenom, appropriating the correct antivenom should begin as soon as possible by discussing the matter with the hospital pharmacy, regional poison control center, and perhaps local zoos and museums that keep captive snakes because they often stock exotic snake antivenom.

Table 768.3 lists the indications for administering antivenom. CroFab, a Crotalinae polyvalent immune Fab antivenom (FabAV), is approved by the U.S. Food and Drug Administration (FDA) for use in crotalid envenomations. FabAV is derived from sheep (ovine) antibodies to crotalid snake venom, and side effects include both immediate and delayed hypersensitivity reactions. FabAV is derived from four snakes, three from the genus *Crotalus* (the eastern diamondback rattlesnake, the western diamondback rattlesnake, and the Mojave rattlesnake) and one from the genus *Agkistrodon* (the cottonmouth or water moccasin). It is effective against the venoms of all Crotalinae snakes in the United States. There is cross reactivity with FabAV against venom from copperhead snakes (*Agkistrodon contortrix*). However, copperhead bites often do not require treatment with antivenom because they cause fewer systemic effects and less severe local tissue damage. Most copperhead envenomations cause only local tissue swelling, ecchymosis, and pain and generally do well with good supportive care and pain control. Any child with evidence of systemic toxicity should receive FabAV.

Initial dosing of FabAV is aimed at control of symptoms (progressive tissue swelling, thrombocytopenia, coagulopathy, neurotoxicity, or systemic toxicity). The dose is repeated until initial control of toxicity is achieved (see Table 768.3). Subsequent maintenance dosing may be needed to prevent or treat recurrence of venom effects because, due to its small molecular size, the half-life of FabAV is considerably shorter than that of crotalid venom constituents. Patients with significant envenomation should be followed for late hematologic abnormalities (coagulopathy) that can occur up to 2 weeks after the bite. Although these tend to be mild laboratory coagulopathies without clinical bleeding, rare cases of severe delayed bleeding have been reported. Further antivenom therapy should be considered for such delayed or recurrent coagulopathy as outlined in Table 768.4.

In April 2021, the U.S. FDA approved a crotaline immune Fab2 antivenin (Fab2AV) to treat adult and pediatric patients with North American Crotaline envenomations marketed as AnaVIP. This antivenom is an equine-derived antivenin and, due to it being a Fab2 fragment, has a longer half-life than the FabAV. It has a similar side effect profile as the FabAV including anaphylactoid and hypersensitivity reactions. Initial dosing is 10 vials given intravenously over 60 minutes. If the symptoms continue to progress, then 10 vials can be given every hour until there is no further progression of symptoms. Patients should be observed for a minimum of 18 hours after the Fab2AV infusion. If a patient has reemerging symptoms including coagulopathies, then an additional four vials of the Fab2AV can be infused (Table 768.5).

Envenomation of the extremities can mimic compartment syndrome, with severe pain and swelling. It is important to treat these patients aggressively with FabAV or Fab2AV and pain control to control the severe pain and swelling. Although fasciotomy was once advocated for the treatment of crotalid snakebites of the extremities, it is now a treatment of last resort only if aggressive FabAV or Fab2AV treatment is unable to stop the progression of pain and swelling and true compartment syndrome is documented with measurement of intracompartmental pressure.

The antivenom for coral snakes (*Micrurus fulvius*) has been the recommended treatment for envenomation by the eastern coral snake (*M. fulvius*) and the Texas coral snake (*Micrurus tener*). Indications for this antivenom are the development of any neurologic signs and symptoms of coral snake envenomation including paresthesias, slurred speech, respiratory difficulties, muscle weakness, and fasciculations. Due to it being equine in origin, its side effect profile includes anaphylaxis and allergic reactions. Most hospitals do not carry this antivenom and local poison centers should be notified to help locate supplies. Respiratory supportive care including endotracheal intubation and mechanical ventilation for respiratory failure remains the mainstay of treatment.

Disposition

If, after observation for 6–8 hours, a patient exhibits only fang-induced puncture marks with no local or systemic symptoms, the wounds can be considered dry bites and the patient can be safely discharged home. Patients with significant toxicity and those requiring treatment with antivenom should be admitted to the hospital. Patients with a history of eastern or Texas coral snakebite should be admitted to a monitored setting for 24 hours to observe for neurologic toxicity so that respiratory support can be provided as needed. Children should be admitted to an intensive care setting if they develop severe and progressive local tissue toxicity or evidence of systemic toxicity including coagulopathy, neurotoxicity, hemodynamic instability, or respiratory difficulties.

SPIDER BITES

In the United States, 18 genera of spiders have been identified that cause clinically significant envenomation. The spiders of importance in the United States include the *Latrodectus* species (the widow spiders) and the *Loxosceles* species (the recluse spiders).

Table 768.2 Pit Viper Envenomation Classification

GRADE	CLINICAL FEATURES	ANTIVENOM	DISPOSITION
0 (None)	No evidence of envenomation. A fang wound may be present. Pain is minimal, with less than 1 inch of surrounding edema and erythema. No systemic manifestations are present during the first 12 hr after the bite. No laboratory changes occur.	No	Observe for 8-12 hr. May be discharged if repeat labs are normal and no signs of envenomation develop.
I (Minimal)	Pain is moderate or throbbing and localized to the fang wound, surrounded by 1-5 inches of edema and erythema. No evidence of systemic involvement is present after 12 hr of observation. No laboratory changes occur.	No	Admission for 12-24 hr. Repeat labs every 6 hr. May be discharged if repeat labs are normal and no signs of envenomation develop.
II (Moderate)	There is more severe and widely distributed pain, edema spreading toward the trunk, and petechiae and ecchymoses limited to the area of edema. Nausea, vomiting, and a mild elevation in temperature are usually present.	Yes	Admission to intensive care unit.
III (Severe)	This may initially resemble a grade I or II; however, within 12 hr, edema spreads up the extremity and may involve part of the trunk. Petechiae and ecchymoses may be generalized. Systemic manifestations may include tachycardia and hypotension. Laboratory abnormalities may include an elevated white blood cell count, creatine phosphokinase, prothrombin time, and partial thromboplastin time, as well as elevated fibrin degradation products and D-dimer. Decreased platelets and fibrinogen are common. Hematuria, myoglobinuria, increased bleeding time, and renal or hepatic abnormalities may also occur.	Yes	Admission to intensive care unit.
IV (Very severe)	Sudden pain, rapidly progressive swelling that may reach and involve the trunk within a few hours, ecchymoses, bleb formation, and necrosis. Systemic manifestations, often commencing within 15 min of the bite, usually include weakness, nausea, vomiting, vertigo, and numbness or tingling of the lips or face. Muscle fasciculations, painful muscular cramping, pallor, sweating, cold and clammy skin, rapid and weak pulse, incontinence, convulsions, and coma may also be observed. An intravenous bite may result in cardiopulmonary arrest soon after the bite.	Yes	Admission to intensive care unit.

From Curtis AM, Erickson TB. Venomous animal injuries. Walls RM, ed. *Rosen's Emergency Medicine*, 10th ed. Philadelphia: Elsevier; 2023: Table 53.2, p. 696.

Table 768.3 Crotaline Fab Antivenom Dosing Guidelines

DOSE	RECOMMENDATIONS
Initial dose: four to six vials IV	<ul style="list-style-type: none"> Reconstitute each vial of FabAV in 18 mL normal saline for injection and mix with continuous manual inversion at the rate of one to two inversions per second until no solid material is visible in the vial. Further dilute four to six vials of reconstituted FabAV in 250 mL normal saline. Infuse FabAV over 1 hr IV. Start with slow infusion rate of 25-50 mL/hr for 10 min. If no acute allergic reaction occurs, increase rate to 250 mL/hr to complete infusion. The volume of the infusion may be decreased for the very small child or volume-sensitive patient. Observe 1 hr after initial dose to assess for control of envenomation. Repeat four to six vials of FabAV as needed to gain initial control.
Maintenance dose: two vials IV every 6 hr × 3 doses	<ul style="list-style-type: none"> Monitor for delayed or recurrent toxicity requiring additional FabAV. Antivenom dose requirements vary depending on the individual patient's response and clinical course. Patients with mild envenomation may not require maintenance dosing beyond the initial dose.

Adapted from Goto CS, Feng SY. Crotalidae polyvalent immune Fab for the treatment of pediatric crotaline envenomations. *Ped Emerg Care*. 2009;25(4):273-279; and from Crofab Package Insert (revised 2018).

Table 768.4 Indications for Administration of Additional Antivenom in Patients with Recurrent Coagulopathy or Thrombocytopenia After Initial Control

- Evidence of clinically significant bleeding
- Platelet count below 25,000/mm³
- International normalized ratio (INR) >3
- Activated partial thromboplastin time (aPTT) >50 seconds
- Fibrinogen <50 mg/dL
- Presence of multicomponent coagulopathy
- Worsening trend in a patient with prior severe coagulopathy
- High-risk behavior for trauma
- Certain comorbid conditions (e.g., systemic vasculitis, seizure disorders, prior stroke)

From Norris RL, Bush SP, Cardwell MD. Bites by venomous reptiles in Canada, the U.S. and Mexico. In: Auerbach PS, ed. *Wilderness Medicine*, 7th ed. Philadelphia: Elsevier; 2017.

Latrodectus Spiders

The *Latrodectus* species are found throughout the United States and include *L. mactans* (Fig. 768.3; **black widow spider**), *L. hesperus* (western black widow), *L. bishop* (red widow spider), *L. variolus*, and *L. geometricus* (brown widow spider). They are indigenous to every state except Alaska. The classic hourglass-shape marking is found only in *L. mactans*. They like to live close to the ground in secluded and dimly lit areas such as barns, sheds, and garages.

Venoms and Effects

Latrodectus spiders possess venoms that act at neuromuscular and autonomic nervous system synapses, resulting in excessive release of

Table 768.5 Crotaline Fab2 Antivenom Dosing Guidelines	
Initial Dose: 10 vials (*no known maximum dose of Crotaline Fab2 antivenom)	<ul style="list-style-type: none">• Reconstitute 10 vials for less than 1 min each using 10 mL sterile normal saline per vial• Combine all vials and dilute to a total volume of 250 mL sterile normal saline• Infuse at 25-50 mL/hr for 10 min; if tolerated at 250 mL/hr to completion
Evaluate for control	60 minutes after infusion, check for: <ul style="list-style-type: none">• Local injury not progressing• Coagulation parameters improving• Systemic effects resolved
Observe	<ul style="list-style-type: none">• Observe for at least 18 hr after initial control• If symptoms reemerge, can administer four vials in 250 mL

Adapted from AnaVIP package insert.



Fig. 768.3 Female black widow spider (*Latrodectus mactans*). Note the red hourglass-shaped marking on the underside of her abdomen. (From The Centers for Disease Control and Prevention Public Health Image Library, Image #5449.)

neurotransmitters. All of the widow spiders possess similar venoms, with the most important neurotoxin being α -latrotoxin.

Bites by the neurotoxic spiders tend to be very painful, and the offending spider is often seen. Systemic effects may include hypertension, tachycardia, bradycardia, hypersalivation, diaphoresis, and diffuse muscle spasm. Nausea, vomiting, abdominal pain, and abdominal rigidity may mimic appendicitis or another acute abdominal emergency.

Management

The management of a neurotoxic spider envenomation centers on sound supportive care. Generous doses of opioid analgesics and benzodiazepines should be utilized to ease severe pain and muscle spasm. *Latrodectus* antivenom (Wyeth) is equine-derived and may be considered to reverse severe systemic effects of widow spider envenomation. Although effective, it is associated with anaphylaxis, serum sickness, and anaphylactoid reactions and should be reserved for high-risk patients such as pregnant women at risk of spontaneous abortion due to the severe pain. One vial is administered via intravenous infusion. Efficacy is usually noted within 1 hour of administration, with reversal of systemic toxicity and relief of pain. Occasionally a second vial is necessary. Due to the possibility of severe or life-threatening reactions, the risks and benefits should be carefully considered and the antivenom



Fig. 768.4 Male recluse spider (*Loxosceles* spp.). Note the distinct violin-shaped marking on the dorsum of the cephalothorax. (Courtesy Michael Cardwell/Extreme Wildlife Photography)

infused slowly with continuous monitoring and preparation to treat anaphylaxis should it occur.

**Loxosceles Spiders
Venoms and Effects**

The spiders most notorious for their dermonecrotic potential are the recluse spiders of the genus *Loxosceles*. The best-known member of this genus is the **brown recluse** (*Loxosceles reclusa*; Fig. 768.4), found in the midwestern and southern regions of the United States. The venom of *Loxosceles* spiders contains a phospholipase enzyme, sphingomyelinase D, as well as hyaluronidase. Hyaluronidase is the spreading factor that enables the venom to penetrate tissues, but it does not induce tissue damage. Sphingomyelinase D causes necrosis, red blood cell hemolysis, and platelet serotonin release. The bite of this spider is generally painless and initially goes unnoticed. A few hours after the bite, the area begins to blister and bleed and become painful. Within a day or two, the site will ulcerate and develop violaceous necrosis with surrounding ecchymosis and a rim of pale ischemia (“red, white, and blue” reaction). The lesion may gradually expand over a period of days to weeks until necrotic tissue sloughs and healing begins (Fig. 768.5).

Rare cases of systemic loxoscelism appear to be more common in young children. Patients present with systemic toxicity, including fever, chills, nausea, malaise, diffuse macular rash, and petechiae; they may experience hemolysis, coagulopathy, and renal failure.

In cases of necrotic dermal lesions with no identified spider as the culprit, a broad differential diagnosis must be considered to ensure appropriate management. The differential diagnosis includes skin infections (particularly methicillin-resistant *Staphylococcus aureus*; see Chapter 227), pyoderma gangrenosum, or ecthyma gangrenosum.

Management

The management of necrotizing spider bites includes good wound care, updating of tetanus status, and administration of antibiotics if there is secondary bacterial infection. Daily wound cleansing and splinting of the affected area should be provided until the wound has healed.

No therapy has been definitively proven effective in limiting the extent of necrosis after a recluse spider bite, including steroids, dapsone, colchicine, cyproheptadine, nitroglycerin, hyperbaric oxygen, and early excision of tissue. Meticulous wound care is the mainstay of treatment, and large lesions may require delayed secondary closure with skin grafting after clear tissue demarcation has occurred.

Patients with signs and symptoms of systemic loxoscelism should be admitted to the hospital for supportive treatment of hypovolemia, coagulopathy, hemolysis, and acute kidney injury. There is no commercially available antivenom in the United States for the management of necrotizing spider bites such as those from *Loxosceles* species.

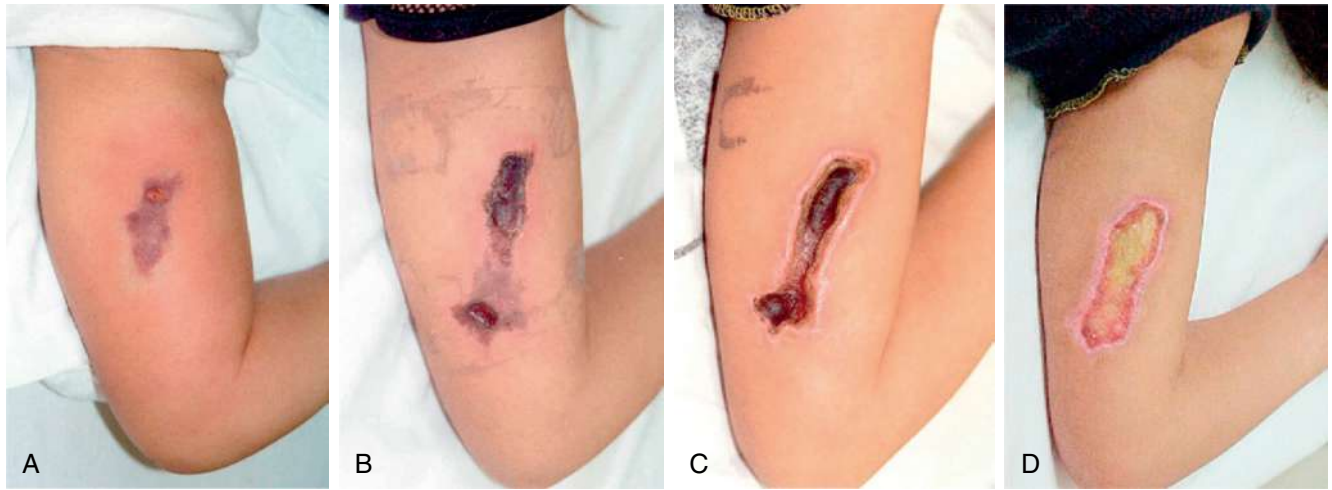


Fig. 768.5 Progression of cutaneous loxoscelism in a Brazilian patient who was bitten inside a house while putting on a shirt. Ulceration and necrosis at day 1 (A), day 9 (B), day 16 (C), and day 25 (D). (From Isbister G, Fan HW. Spider bite. *Lancet*. 2011;378:2039–2046. Fig. 3. Photographs by Ceila MS Malaque.)

Disposition

Victims with necrotic skin lesions should be monitored with frequent outpatient wound checks to determine progression of the lesion. Children with rapidly progressive dermonecrosis or systemic toxicity should be admitted to the hospital for supportive therapy, which may include intensive care admission for hemolysis, coagulopathy, renal failure, or hypotension.

SCORPION STINGS

There are more than 650 species of scorpions worldwide, some of which are capable of causing severe or lethal envenomation. In the United States, there are two clinically significant scorpions: *Centruroides exilicauda* (the bark scorpion) and *Centruroides vittatus*. Most scorpion envenomations occur in the southwestern United States, and fatalities are rare. In other regions of the world, especially Latin America, Africa, the Middle East, and Asia, a number of scorpions regularly cause fatalities.

Venoms and Effects

Centruroides scorpion venom contains phospholipase, acetylcholinesterase, hyaluronidase, serotonin, and neurotoxins, resulting in severe pain and paresthesia as well as systemic symptoms of excessive nerve depolarization and release of acetylcholine and catecholamines. The manifestations of scorpion stings in children vary from mild to severe and can include autonomic and somatic toxicity. Autonomic toxicity includes hypertension, tachycardia, hypersalivation, emesis, diaphoresis, and bronchoconstriction, although respiratory failure is rare. Somatic motor toxicity includes ataxia, fasciculations, myoclonus, and opsoconus. Patients are often restless or agitated, and cranial nerve dysfunction may occur.

Management

Most scorpion stings do not produce severe effects and require only wound care and orally administered pain medications. However, patients with more severe symptoms may require intravenous opioids for analgesia and benzodiazepines for severe muscle spasm or agitation.

A bark scorpion-specific antivenom, Anascorp (Bioclon, Mexico), is approved by the FDA. This antivenom is recommended for critically ill patients with neurotoxicity or other severe symptoms, including intractable pain that is not responsive to adequate doses of opioid analgesics. Small children are more likely than adults to develop such severe symptoms. It is best to discuss antivenom therapy with the regional poison control center for guidance.

Disposition

Patients who have had mild scorpion stings with only local effects can be safely discharged home with wound care instructions, analgesics, and close outpatient follow-up. Patients with evolving symptoms, intractable pain, neurotoxicity, or other systemic toxicity should be admitted to the hospital, especially if scorpion antivenom is being considered. Those with severe toxicity should be admitted to an intensive care unit.

HYMENOPTERA STINGS

The insect order Hymenoptera includes the stinging ants, bees, and wasps, which are characterized by the presence of a modified ovipositor (the “sting” or “stinger”) at the end of the abdomen through which venom is injected. Various members of the order can be found throughout the world.

Venoms and Effects

Hymenoptera venom is a complex mixture of proteins, enzymes, and vasoactive substances that result in local tissue injury and inflammation. Most stings cause only local pain, redness, and swelling followed by itching and resolution. Some patients experience a large local reaction in which swelling progresses beyond the sting site, possibly involving the entire extremity. Approximately 0.4–0.8% of children and 3% of adults are at risk for acute, life-threatening allergic reactions as a result of Hymenoptera venom sensitivity; anaphylaxis due to Hymenoptera envenomation causes an average of 62 deaths annually in the United States (see Chapter 187). Rare cases of delayed serum sickness can follow Hymenoptera stings (see Chapter 191). Africanized honeybees (*Apis mellifera scutellata*), an aggressive hybrid of western honeybee species with African bee species, can cause massive stinging episodes resulting in systemic venom toxicity with hypotension, respiratory failure, shock, hemolysis, and renal failure.

Management

Patients with typical local reactions can be treated with supportive care including analgesics and antihistamines as needed. Patients with large local reactions should also receive a course of oral corticosteroids and a prescription for an epinephrine autoinjection kit including instructions in its use before discharge. Patients presenting with urticaria, angioedema, wheezing, or hypotension should be treated with aggressive supportive care including standard therapy for anaphylaxis such as intramuscular epinephrine, corticosteroids, antihistamines, intravenous fluids, oxygen, and airway management as needed (see Chapter 190). Patients suffering massive stinging episodes may also require critical care resuscitation.

Disposition

Patients with local reactions can be discharged with continued outpatient care that may include analgesia and antihistamines. More difficult disposition decisions are involved for children with systemic manifestations. Children with only diffuse urticaria who are stable after a period of observation can be discharged home to continue a short course of antihistamines and steroids and to carry an epinephrine self-administration kit. These children are at low risk for progressing to systemic anaphylaxis with future stings. Children suffering more than simple urticaria (e.g., wheezing, evidence of laryngeal edema or cardiovascular instability) should be treated aggressively and admitted for at least 24 hours of observation. They should receive a referral to allergy/immunology to test for Hymenoptera venom sensitivity and possible immunotherapy. Immunotherapy reduces the risk of systemic anaphylaxis from future stings in high-risk patients from 30–60% to <5%.

MARINE ENVENOMATION

The classes of venomous marine animals that cause the most morbidity and mortality in humans are the **Cnidaria** (including jellyfish, the Portuguese man-of-war, Pacific blue bottle, fire coral, sea nettles, anemones, and others), **Mollusca** (blue-ringed octopus and cone snails), **Chondrichthyes** (stingrays), and members of the family **Scorpaenidae** (lionfish, scorpionfish, and stonefish).

Venoms and Effects

All members of the Cnidaria have unique stinging cells called nematocysts. These cells contain a highly folded tubule that discharges on contact, penetrates the skin, and injects venom. The venom is antigenic and can be dermonecrotic, hemolytic, cardiotoxic, or neuropathic, depending on the species. The **Pacific box jellyfish** (*Chironex fleckeri*) of Australia, with its cardiotoxic venom, is known to cause stings that are rapidly fatal due to cardiac arrest and pulmonary edema. Although fatal anaphylaxis to jellyfish stings has been reported in coastal waters of the United States, these events are rare. For clinicians in the Americas, the primary concern with Cnidaria envenomation is localized pain that may be associated with paresthesias or pruritus. Occasionally, victims may have systemic symptoms such as nausea, vomiting, headache, and chills.

The phylum **Mollusca** includes octopi and cone snails (*Conus* sp.). The **octopus** of toxicologic significance is the *Hapalochlaena maculosa* (blue-ringed octopus), which is primarily found in Australian waters. The blue-ringed octopus secretes **tetrodotoxin** (the same toxin found in pufferfish) in its salivary gland. The beak of the octopus punctures the skin and delivers the tetrodotoxin. Tetrodotoxin blocks sodium channels in neurons, leading to paralysis. The venom also contains other toxins, including vasoactive agents and enzymes that cause local tissue injury. Cone snails have a hollow proboscis with a tooth that can be extended to inject venom into the victim. Venom of the *Conus* species contains conotoxins that target multiple receptors, including voltage, ligand, and G-mediated receptors. Conotoxins cause a variety of symptoms including severe pain, weakness, tissue ischemia, cyanosis, and numbness. Systemic symptoms are usually neurologic and include aphonia, aphasia, weakness, paralysis, respiratory failure, cardiovascular collapse, and ultimately death.

The **stingray** has a sharp, retroserrated spine and associated venom gland at the base of its tail. Envenomation often occurs when the victim steps on the animal hidden in the surf and the tail is whipped around to puncture the lower extremity. Injuries involve jagged lacerations from

the spine, often with retained debris (spine fragments, glandular tissue, and sand). The venom has vasoconstrictive properties that can result in tissue necrosis and poor wound healing. Stingray envenomations are noteworthy for immediate and intense pain at the site of injury that lasts 24–48 hours. Some patients experience nausea, vomiting, and muscle cramps. Rarely, hypotension or seizures occur.

The Scorpaenidae have venomous dorsal, pelvic, and anal spines that become erect when the animal is threatened. The venom glands associated with these spines contain multiple toxins, enzymes, and vasoactive substances. Envenomation causes immediate severe pain that may persist for hours or days. Victims may experience local tissue destruction, and superinfections are common. Systemic symptoms include diaphoresis, nausea, vomiting, diarrhea, abdominal pain, muscle cramping, and headache. In severe cases, paralysis, respiratory failure, hypotension, dysrhythmias, and cardiovascular collapse have been reported.

Management

Treatment of Cnidaria stings should begin immediately after envenomation. Dousing the sting site with vinegar has been shown to inhibit nematocyst discharge. If vinegar is not immediately available, the area should be washed with seawater; freshwater should be avoided as it is thought to stimulate firing of remaining nematocysts. Visible tentacle fragments should be removed with a gloved hand or forceps, and microscopic fragments may be removed by gently shaving the affected area. Folk remedies such as rubbing the sting with sand and applying urine are not helpful and cause more irritation. Meat tenderizer is usually not effective. Antihistamines and corticosteroids are indicated for swelling and urticaria. An acute anaphylactic reaction should be treated with intramuscular epinephrine. Antibiotics are usually not necessary.

Patients who have been envenomated by Mollusca are treated supportively. There are no antivenoms available for either the blue-ringed octopus or the cone snails. Adequate pain control should be provided as needed. Cardiovascular support may be required, and severe neurologic toxicity such as respiratory failure should be managed via airway management and mechanical ventilation.

Treatment of stingray and Scorpaenidae stings is similar. These toxins are heat-labile, and immersion in hot water (approximately 42°C [107.6°F]) for 30–60 minutes denatures the protein constituents and decreases pain significantly. The wounds should be thoroughly cleansed and explored with use of local or regional anesthesia to rule out retention of spine or integument fragments. Stingray spines are radiopaque and may be seen on radiographs or identified by ultrasonography. Lacerations should be treated with delayed primary closure or allowed to heal by secondary intention. Systemic analgesia should be provided as needed. Because of the risk of secondary bacterial infection, there should be a low threshold for administering prophylactic antibiotics to cover *Staphylococcus*, *Streptococcus*, and *Vibrio* species, and wounds should be rechecked at 3 and 7 days postinjury. An equine Fab stonefish antivenom is available for severe stonefish envenomation with systemic toxicity or intractable pain.

Disposition

After wound care and effective analgesia, most victims can be discharged home. If there are significant systemic effects, the patient should be admitted for monitoring and further care as needed.

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