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Rheumatic Diseases of Childhood (Connective Tissue Disease, Collagen Vascular Diseases)

PART XIV

Chapter 194

Evaluation of Suspected Rheumatic Disease

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Rheumatic diseases are defined by the constellation of results of the physical examination, autoimmune markers and other serologic tests, tissue pathology, and imaging. Defined diagnostic criteria exist for most rheumatic diseases. Recognition of *clinical patterns* remains essential for diagnosis because there is no single diagnostic test, and tests may be positive in the absence of disease. Further complicating diagnosis, children sometimes present with partial criteria that evolve over time or with features of more than one rheumatic disease (overlap syndromes). The primary mimics of rheumatic diseases are infection and malignancy but also include metabolic, orthopedic, immune deficiencies, autoinflammatory diseases, and chronic pain conditions. Exclusion of possible mimicking disorders is essential before initiation of treatment for a presumptive diagnosis, especially corticosteroids. After careful evaluation has excluded nonrheumatic causes, referral to a pediatric rheumatologist for confirmation of the diagnosis and treatment should be considered.

SYMPTOMS SUGGESTIVE OF RHEUMATIC DISEASE

There are no classic symptoms of rheumatic diseases, but common symptoms include joint pain, fever, fatigue, and rash. Presenting signs and symptoms help direct the evaluation and limit unnecessary testing. Once a differential diagnosis is developed based on history and physical findings, a directed assessment assists in determining the diagnosis.

Arthralgias are common in childhood and are a frequent reason for referral to pediatric rheumatologists. Arthralgias without physical findings for arthritis suggest infection, malignancy, orthopedic conditions, benign syndromes, or pain syndromes such as fibromyalgia (Table 194.1). Although rheumatic diseases may manifest as arthralgias, **arthritis** is a stronger predictor of the presence of rheumatic disease and a reason for referral to a pediatric rheumatologist. The timing of joint pain along with associated symptoms, including poor sleep and interference with normal activities, provides important clues. Poor sleep, debilitating generalized joint pain that worsens with activity, school absences, and normal physical and laboratory findings in an adolescent suggest an amplified **pain syndrome** (see Chapter 212). If arthralgia is accompanied by a history of dry skin, hair loss, fatigue, growth disturbance, or cold intolerance, testing for **thyroid disease** is merited. Nighttime awakenings because of severe pain along with decreased platelet or white blood cell (WBC) count or, alternatively, a very high WBC count, may lead to the diagnosis of malignancy, especially marrow-occupying lesions such as **acute lymphocytic leukemia** and **neuroblastoma**. Pain with physical activity suggests a mechanical problem such as an overuse syndrome or orthopedic condition. An adolescent presenting with knee pain aggravated by walking up stairs and on patellar distraction likely has **patellofemoral syndrome**. Children age 3-10 years with a history of episodic pain occurring at night, especially after increased daytime physical activity, that is relieved by rubbing but who have no limp or complaints in the morning likely have **growing pains**. There is often a positive family history for growing pains, which may aid in this diagnosis. Intermittent pain in a child, especially a girl 3-10 years old, that is increased with activity and is associated with hyperextensible joints on examination likely has **benign hypermobility syndrome**. Many febrile illnesses cause arthralgias that improve when the temperature normalizes, and arthralgias are part of the diagnostic criteria for **acute rheumatic fever** (**ARF**; see Chapter 229.1).

Arthralgia may also be a presenting symptom of pediatric **systemic lupus erythematosus** (**SLE**) and chronic childhood arthritis such as **juvenile idiopathic arthritis (JIA)**. Interestingly, many children with JIA do not complain of joint symptoms at presentation. Other symptoms more suggestive of arthritis include morning stiffness, joint swelling, limited range of motion, pain with joint motion, gait disturbance, fever, and fatigue or stiffness after physical inactivity *(gelling phenomenon)*. A diagnosis of JIA cannot be made without the finding of arthritis on physical examination (see Chapters 196 and 197). No laboratory test is diagnostic of JIA.

Fatigue is a nonspecific symptom that may point to the presence of a rheumatic disease but is also common in nonrheumatic causes, such as viral infections, pain syndromes, depression, and malignancy. Fatigue, rather than the specific complaints of muscle weakness, is a common presenting complaint in **juvenile dermatomyositis (JDM)**. It is also frequently present in SLE, vasculitis, and chronic childhood arthritis. Overwhelming fatigue with inability to attend school is more suggestive of chronic fatigue syndrome, pediatric fibromyalgia, or other amplified pain syndrome.

SIGNS SUGGESTIVE OF RHEUMATIC DISEASE

A complete physical examination is essential in any child with suspected rheumatic disease, because subtle physical findings may further refine the differential diagnosis. In addition, many rheumatic diseases have multisystem effects, and a stepped assessment should focus on delineating the extent of organ system involvement (e.g., skin, joints, muscle, hepatic, renal, cardiopulmonary).

Presence of a **photosensitive malar rash** that spares the nasolabial folds is suggestive of SLE (Table 194.2; see Fig. 199.1A). Diffuse facial rash is more indicative of JDM. A hyperkeratotic rash on the face or around the ears may represent discoid lupus (see Fig. 199.1D). A palpable purpuric rash on the extensor surfaces of the lower extremities points to **IgA vasculitis (Henoch-Schönlein purpura)** (see Fig. 210.2A). Less localized purpuric rashes and petechiae are present in systemic vasculitis or blood dyscrasias, including coagulopathies. Nonblanching erythematous papules on the palms are seen in vasculitis, SLE, and endocarditis. Gottron papules (see Fig. 200.3) and heliotrope rashes (see Fig. 200.2) along with erythematous rashes on the elbows and knees are pathognomonic

Table 194.1 Symptoms Suggestive of Rheumatic Disease

SYMPTOM	RHEUMATIC DISEASE(S)	POSSIBLE NONRHEUMATIC DISEASES CAUSING SIMILAR SYMPTOMS
Fevers	Systemic JIA, SLE, vasculitis, acute rheumatic fever, sarcoidosis, MCTD	Malignancies, infections and postinfectious syndromes, inflammatory bowel disease, periodic fever (autoinflammatory) syndromes, Kawasaki disease, HSP*
Arthralgias	JIA, SLE, rheumatic fever, JDM, vasculitis, scleroderma, sarcoidosis	Hypothyroidism, trauma, endocarditis, other infections, pain syndromes, growing pains, malignancies, overuse syndromes
Weakness	JDM, myositis secondary to SLE, MCTD, and deep localized scleroderma	Muscular dystrophies, metabolic and other myopathies, hypothyroidism
Chest pain	Juvenile idiopathic arthritis, SLE (with associated pericarditis or costochondritis)	Costochondritis (isolated), rib fracture, viral pericarditis, panic attack, hyperventilation
Back pain	Enthesitis-related arthritis, juvenile ankylosing spondylitis	Vertebral compression fracture, diskitis, intraspinal tumor, spondylolysis, spondylolisthesis, bone marrow–occupying malignancy, pain syndromes, osteomyelitis, muscle spasm, injury
Fatigue	SLE, JDM, MCTD, vasculitis, JIA	Pain syndromes, chronic infections, chronic fatigue syndrome, depression

HSP, Henoch-Schönlein purpura; JDM, juvenile dermatomyositis; JIA, juvenile idiopathic arthritis; MCTD, mixed connective tissue disease; SLE, systemic lupus erythematosus.
*Also know as IgA vasculitis.

Table 194.2 Signs Suggestive of Rheumatic Disease

SIGN	RHEUMATIC DISEASES	COMMENTS	NONRHEUMATIC CAUSES
Malar rash	SLE, JDM	SLE classically spares nasolabial folds	Sunburn, parvovirus B19 (fifth disease), Kawasaki disease
Oral ulcers	SLE, Behçet disease	Behçet disease also associated with genital ulcers	HSV infection, PFAPA syndrome
Purpuric rash	Vasculitis (e.g., ANCA-associated vasculitis), HSP*	HSP* typically starts as small lesions on lower extremities and buttocks that coalesce	Meningococcemia, thrombocytopenia, clotting disorders
Gottron papules	JDM	Look for associated heliotrope rash, periungual telangiectasias	Psoriasis, eczema
Arthritis	Juvenile idiopathic arthritis, SLE, vasculitis, HSP*, MCTD, scleroderma, acute rheumatic fever, reactive arthritis	Chronic joint swelling (>6 wk) required for diagnosis of JIA; MCTD associated with diffuse puffiness of hands	Postviral arthritis, reactive arthritis, trauma, infection, Lyme disease, Kawasaki disease, malignancy, overuse syndromes

ANCA, Antineutrophil cytoplasmic antibody; HSP, Henoch-Schönlein purpura; HSV, herpes simplex virus; JIA, juvenile idiopathic arthritis; JDM, juvenile dermatomyositis; MCTD, mixed connective tissue disease; PFAPA, periodic fever, aphthous stomatitis, pharyngitis, and adenitis; SLE, systemic lupus erythematosus.
*Also know as IgA vasculitis.

of JDM. Dilated capillary loops in the nail beds (periungual telangiectasias; see Fig. 200.4) are common in JDM, scleroderma, and secondary Raynaud phenomenon. An evanescent macular rash associated with fever is part of the diagnostic criteria for systemic-onset arthritis (see Fig. 196.12). Sun sensitivity or photosensitive rashes are indicative of SLE or JDM but can also be caused by antibiotics.

Mouth ulcers are part of the diagnostic criteria for SLE and Behçet disease (see Fig. 199.1C); painless nasal ulcers and erythematous macules on the hard palate are also common in SLE. Cartilage loss in the nose, causing a saddle nose deformity, is classically present in granulomatosis with polyangiitis (formerly Wegener granulomatosis; see Fig. 210.8) but is also seen in relapsing polychondritis and syphilis. Alopecia can be associated with SLE but is also found in localized scleroderma (see Fig. 201.4) and JDM. **Raynaud phenomenon** may be a primary benign idiopathic disorder or can be a presenting complaint in the child with scleroderma, lupus, mixed connective tissue disease (MCTD), or an overlap syndrome. Diffuse lymphadenopathy is present in many rheumatic diseases, including SLE, polyarticular JIA, and systemic JIA. Irregular pupils may represent the insidious and unrecognized onset of **uveitis** associated with JIA. Erythematous conjunctivae may be a result of uveitis or episcleritis associated with JIA, SLE, sarcoidosis, spondyloarthropathies, or vasculitis.

A pericardial rub and orthopnea are suggestive of **pericarditis**, often seen in systemic JIA, SLE, and sarcoid. Coronary artery dilation is strongly suggestive of Kawasaki disease and multisystem inflammatory syndrome in children (MIS-C) but may also be a finding in systemic arthritis and other forms of systemic vasculitis. Interstitial lung disease, suggested by dyspnea on exertion or the finding of basilar rales with decreased carbon monoxide diffusion capacity, occurs in SLE, MCTD, and systemic sclerosis. Signs consistent with pulmonary hemorrhage point to granulomatosis with polyangiitis, microscopic angiitis, or SLE. Pulmonary vascular aneurysms are indicative of Behçet disease.

Arthritis is defined by the presence of intraarticular swelling or two or more of the following findings on joint examination: pain on motion, loss of motion, erythema, and heat. Arthritis is present in all the chronic childhood arthritis syndromes, along with SLE, JDM, vasculitis, Behçet disease, sarcoidosis, Kawasaki disease, and Henoch-Schönlein purpura. Nonrheumatic causes of arthritis include malignancy, septic arthritis, Lyme disease, osteomyelitis, viral infections (e.g., rubella, hepatitis B, parvovirus B19, chikungunya), and postinfectious etiologies such as Epstein-Barr virus (EBV), ARF, and reactive arthritis. ARF typically involves a migratory (lasting hours to days), painful arthritis. Pain on palpation of long bones is suggestive of malignancy. Specific muscle testing for weakness should be performed in a child presenting with fatigue or difficulty with daily tasks, because both these symptoms may be manifestations of muscle inflammation.

LABORATORY TESTING

There are no specific screening tests for rheumatologic disease. Once a differential diagnosis is determined, appropriate testing can be performed (Tables 194.3 and 194.4). Initial studies are generally performed in standard local laboratories. Screening for specific autoantibodies can be performed in commercial laboratories, but confirmation of results in a tertiary care center immunology laboratory is often necessary.

Table 194.3 Autoantibody Specificity and Disease Associations

ANTIBODY	DISEASE	PREVALENCE (%)	SPECIFICITY
Antinuclear antibody (ANA)	SLE, juvenile rheumatoid arthritis, dermatomyositis, scleroderma, psoriatic arthritis, MCTD	—	Associated with increased risk of uveitis in JIA and psoriatic arthritis Up to 30% of children testing positive for ANAs have no underlying rheumatic disease
Double-stranded DNA (dsDNA)	SLE	60-70	High specificity for SLE; associated with lupus nephritis
Smith (Sm)	SLE	20-30	Highly specific for SLE; associated with lupus nephritis
Smooth muscle (Sm)	Autoimmune hepatitis	—	—
Pm-Scl (polymyositis-scleroderma)	Sclerodermatomyositis	—	—
SSA (Ro)	SLE, Sjögren syndrome	25-30	Associated with neonatal lupus syndrome, subacute cutaneous lupus, thrombocytopenia
SSB (La)	SLE, Sjögren syndrome	25-30	Usually coexists with anti-SSA antibody
Ribonuclease protein (RNP)	MCTD, SLE	30-40	Suggestive of MCTD unless meets criteria for SLE
Histone	Drug-induced lupus, SLE	—	—
Centromere	Limited cutaneous systemic sclerosis	70	Nonspecific for systemic sclerosis
Topoisomerase I (Scl-70)	Systemic sclerosis	—	Rare in childhood
Antineutrophil cytoplasmic antibodies (ANCAs)	Vasculitis	—	—
Cytoplasmic (cANCAs)/PR3-ANCA		—	cANCAs associated with granulomatosis with polyangiitis (Wegener), cystic fibrosis
Perinuclear (pANCAs)/MPO-ANCA		—	pANCAs associated with microscopic polyangiitis, polyarteritis nodosa, SLE, inflammatory bowel disease, cystic fibrosis, primary sclerosing cholangitis, Henoch-Schönlein purpura, Kawasaki disease, Churg-Strauss syndrome
Anticitrullinated protein (ACPA); also called anti–cyclic citrullinated protein (anti-CCP)	RF-positive JIA	50-90	Specific for JIA (RF+), may be positive before RF

MCTD, Mixed connective tissue disease; MPO-ANCA, antimyeloperoxidase; PR3-ANCA, antiproteinase 3; RF, rheumatoid factor; SLE, systemic lupus erythematosus.
Adapted from Aggerwal A. Clinical application of tests used in rheumatology. *Indian J Pediatr* 2002;69:889–892.

For initial workup of rheumatic disease, a CBC with differential, alanine transaminase/aspartate transaminase (ALT/AST), albumin, BUN/creatinine, urinalysis, creatine phosphokinase/lactate dehydrogenase (CPK/LDH), and inflammatory markers (sedimentation rate and CRP) are recommended. Further appropriate testing depends on clinical concern (see Table 194.4).

One essential laboratory test for rheumatic disease assessment is the *complete blood count* (CBC), because it yields many diagnostic clues. Elevated WBC count is compatible with malignancy, infection, systemic JIA, and vasculitis. Leukopenia can be postinfectious, especially viral, or caused by SLE or malignancy. Lymphopenia is more specific for SLE than is leukopenia. Platelets are acute-phase reactants and are therefore elevated with inflammatory markers. Exceptions are a bone marrow–occupying malignancy, such as leukemia or neuroblastoma, SLE, and early Kawasaki disease. **Anemia** is nonspecific and may be caused by any chronic illness, but hemolytic anemia (positive Coombs test result) may point to SLE or MCTD. Rheumatoid factor (RF) is present in <10% of children with JIA and thus has poor sensitivity as a diagnostic tool; RF may be elevated by infections such as endocarditis, tuberculosis, syphilis, and viruses (parvovirus B19, hepatitis B and C, mycoplasma), as well as primary biliary cirrhosis and malignancies. In a child with chronic arthritis, RF serves as a prognostic indicator.

Inflammatory markers (erythrocyte sedimentation rate, CRP, ferritin, procalcitonin) are nonspecific and are elevated in infections, malignancies, and rheumatic diseases (Table 194.5). Their levels may also be normal in rheumatic diseases such as arthritis, scleroderma, and dermatomyositis. The advantages of a CRP include rapid response to inflammatory stimuli, wide range of clinically relevant values, the fact that it is unaffected by age or gender, it is precise and reproducible, and it can be measured on stored sera. Sedimentation rates have classically been used as markers of inflammation, but they can be affected by anemia, red cell morphology, and drugs such as intravenous immunoglobulin (IVIG); they require a fresh blood sample; and they are slow to respond to clinical changes. Inflammatory marker measurements in general are more useful in rheumatic diseases for following response to treatment than as diagnostic tests.

Muscle enzymes include AST, ALT, CPK, aldolase, and LDH, any of which may be elevated in JDM and in other diseases causing muscle breakdown. Muscle-building supplements, medications, and extreme physical activity may also cause muscle breakdown and enzyme elevations. AST, ALT, and aldolase may also be elevated in liver disease, and a γ-glutamyltransferase (GGT) measurement may help differentiate muscle or liver source.

The use of an antinuclear antibody (ANA) measurement as a screening test is *not* recommended because it has low specificity. A positive ANA test result may be induced by infection, especially EBV infection, endocarditis, and parvovirus B19 infection. The ANA test result is also positive in up to 30% of normal children, and ANA level is

Table 194.4 Evaluation Based on Suspected Diagnosis of Rheumatic Disease

SUSPECTED RHEUMATIC DISEASE(S)	INITIAL EVALUATION	FURTHER EVALUATION	SUBSPECIALTY EVALUATION
Systemic lupus erythematosus (SLE) Mixed connective tissue disease (MCTD)	CBC, ESR, ANA, ALT, AST, CPK, creatinine, albumin, total protein, urinalysis, BP, thyroid profile	If ANA test result is positive: anti-SSA (Ro), anti-SSB (La), anti-Smith, and anti-RNP Abs; anti-dsDNA Ab, C3, C4, Coombs, spot urine protein/creatinine ratio, CXR	Antiphospholipid Abs, lupus anticoagulant, anti–β_2-glycoprotein, echocardiogram; consider renal biopsy, PFTs, bronchoscopy with lavage, HRCT of chest; consider lung biopsy
Juvenile dermatomyositis (JDM)	CBC, CPK, ALT, AST, LDH, aldolase, ANA; check gag reflex	Consider MRI of muscle	Consider electromyography and possible muscle biopsy, PFTs, swallowing study, serum neopterin
Juvenile idiopathic arthritis (JIA)	CBC, ESR, creatinine, ALT, AST, consider anti–streptolysin O/anti–DNAase B for streptococcus-induced arthritis, Epstein-Barr virus titers, Lyme titer, parvovirus B19 titer, plain radiograph of joints	Consider Ab titers to unusual infectious agents, purified protein derivative, RF, ANA, HLA-B27, anti-CCP	MRI
Granulomatosis with polyangiitis (Wegener granulomatosis)	CBC, ANCA, AST, ALT, albumin, creatinine, ESR, urinalysis, CXR, BP	Spot urine protein/creatinine ratio, anti–myeloperoxidase and anti–proteinase-3 Abs, PFTs	Bronchoscopy with lavage, HRCT chest; consider lung and kidney biopsies
Sarcoidosis	CBC, electrolytes, AST, ALT, albumin, creatinine, calcium, phosphorous, ACE, BP	CXR, PFTs	Consider testing for Blau syndrome in infants (see Chapter 200); HRCT of chest; consider renal and lung biopsy
Localized scleroderma	Skin biopsy, CBC, ESR		Serum IgG, ANA, RF, single-stranded DNA Ab, antihistone Ab, CPK
Systemic scleroderma	ANA, CBC, ESR, BP, AST, ALT, CPK, creatinine, CXR	Anti-Scl70, PFTs	HRCT of chest, echocardiogram, upper GI radiography series

Ab, Antibody; ACE, angiotensin-converting enzyme (normally elevated in childhood; interpret with caution); ALT, alanine transaminase; ANA, antinuclear antibody; anti-dsDNA Ab, anti–double-stranded DNA antibody; AST, aspartate transaminase; BP, blood pressure; CBC, complete blood count; CCP, cyclic citrullinated protein; CPK, creatine phosphokinase; CXR, chest x-ray; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; HRCT, high-resolution CT; LDH, lactate dehydrogenase; PFTs, pulmonary function tests; RF, rheumatoid factor; RNP, ribonucleoprotein.

Table 194.5 Conditions Associated with Elevated C-Reactive Protein Levels

NORMAL OR MINOR ELEVATION (<1 mg/dL)
Vigorous exercise
Common cold
Pregnancy
Gingivitis
Seizures
Depression
Insulin resistance and diabetes
Several genetic polymorphisms
Obesity
MODERATE ELEVATION (1-10 mg/dL)
Myocardial infarction
Malignancies
Pancreatitis
Mucosal infection (bronchitis, cystitis)
Most systemic autoimmune diseases
Rheumatoid arthritis
Influenza and adenovirus infections
MARKED ELEVATION (>10 mg/dL)
Acute bacterial infection (80–85%)
Major trauma, surgery
Systemic vasculitis
MIS-C

MIS-C, Multisystem inflammatory syndrome in children.
From Firestein GS, Budd RC, Gabriel SE, et al., eds. *Kelley & Firestein's Textbook of Rheumatology*, 10th ed. Philadelphia: Elsevier; 2017, Table 57-4, p. 849.

increased in those with a first-degree relative with a known rheumatic disease. In the majority of children with a positive ANA without signs of a rheumatic disease on initial evaluation, autoimmune disease does not develop over time, so this finding does not necessitate referral to a pediatric rheumatologist. A positive ANA test result is found in many rheumatic diseases, including JIA, in which it serves as a predictor of the risk for inflammatory eye disease (see Chapter 196). Once a positive ANA test result is discovered in a child, the need for specific autoantibody testing is directed by the presence of clinical signs and symptoms (see Table 194.3).

IMAGING STUDIES

Plain radiographs are useful in evaluation of arthralgias and arthritis, as they offer reassurance in benign pain syndromes and their findings may be abnormal in malignancies, osteomyelitis, and long-standing chronic juvenile arthritis. Musculoskeletal ultrasound can be useful in evaluation of synovitis and joint effusion. MRI findings are abnormal in inflammatory myositis and suggest the optimal site for biopsy. *MRI is more sensitive than plain radiographs in detecting the presence of early erosive arthritis and demonstrates increased joint fluid, synovial enhancement, and sequela of trauma with internal joint derangement.* MRI is also helpful in ruling out infection or malignancy. Cardiopulmonary evaluation is suggested for diseases commonly affecting the heart and lung, including SLE, systemic scleroderma, MCTD, JDM, and sarcoid, as clinical manifestations may be subtle. This evaluation, which may include echocardiogram, pulmonary function tests, and high-resolution CT of the lungs along with consideration of bronchoalveolar lavage, is generally performed by a pediatric rheumatologist to whom the patient is referred (see Table 194.4).

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Chapter 195

Treatment of Rheumatic Diseases

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Both nonpharmacologic and pharmacologic interventions are often necessary to meet the desired goals of disease management. Optimal disease management requires family-centered care delivered by a multidisciplinary team of healthcare professionals providing medical, psychological, social, and school support. Rheumatologic conditions most often follow a course marked by flares and periods of remission, although some children have unremitting disease. The goals of treatment are to control disease, relieve discomfort, avoid or limit drug toxicity, prevent or reduce organ damage, and maximize the physical function and quality of life of affected children. Nonpharmacologic therapy is an important adjunct to medical management of rheumatic diseases (see Chapter 93). A key predictor of long-term outcome is early recognition of rheumatic disease with referral to a rheumatology team experienced in the specialized care of affected children.

PEDIATRIC RHEUMATOLOGY TEAMS AND PRIMARY CARE PHYSICIANS

The multidisciplinary pediatric rheumatology team offers coordinated services for children and their families (Table 195.1). General principles of treatment include prompt initiation of appropriate pharmacologic treatment, monitoring for disease complications and adverse medication effects, and coordination of subspecialty care and rehabilitation services with effective communication of clinical information. Psychosocial support encompasses patient- and family-centered chronic illness care, including support of self-management, alliance with community resources, partnerships with schools, resources for dealing with the financial burdens of disease, and connection with advocacy groups. Planning for transition to adult care providers needs to start in adolescence. Central to effective care is partnering with the primary care provider, who helps coordinate care, monitor compliance with treatment plans, ensure appropriate immunizations, monitor for medication toxicities, and identify disease exacerbations and concomitant infections. Communication between the primary care provider and subspecialty team permits timely intervention when needed.

THERAPEUTICS

A key principle of pharmacologic management of rheumatic diseases is that *early disease control,* striving for induction of remission, leads to less tissue and organ damage with improved short- and long-term outcomes. Medications are chosen from broad therapeutic classes based on diagnosis, disease severity, anthropometrics, and adverse effect profile. Given the relative rarity of pediatric rheumatic diseases, many drugs used do not have U.S. Food and Drug Administration (FDA) indications in these conditions. Therapeutic agents used for treatment of childhood rheumatic diseases have various mechanisms of action, but all suppress inflammation (Table 195.2). *Both biologic and nonbiologic disease-modifying antirheumatic drugs (DMARDs) directly affect the immune system* and should be prescribed by specialists. Live vaccines are contraindicated in patients taking immunosuppressive glucocorticoids or DMARDs. A negative test result for tuberculosis (purified protein derivative and/or QuantiFERON-TB Gold) should be verified and the patient's immunization status updated, if possible, before such treatment is initiated. Killed vaccines are not contraindicated, and annual injectable influenza vaccine is recommended.

Nonsteroidal Antiinflammatory Drugs

NSAIDs are prescribed to decrease both the pain and the acute and chronic inflammation associated with arthritis, pleuritis, pericarditis, uveitis, and cutaneous vasculitis, but they are not disease modifying. NSAID antiinflammatory effects require regular administration at adequate doses based on weight (mg/kg) or body surface area (mg/m^2) for longer periods than needed for analgesia alone. The mean time to achieve antiinflammatory effect in juvenile idiopathic arthritis (JIA) is 4-6 weeks of consistent administration. NSAIDs work primarily by inhibiting the enzyme cyclooxygenase (COX), which is critical in the production of *prostaglandins,* a family of substances that promote inflammation. Two types of COX receptors have been demonstrated; *selective* COX-2 inhibitors such as celecoxib and meloxicam inhibit receptors responsible for promoting inflammation, with potential for fewer gastrointestinal (GI) adverse effects. Clinical trials in children with JIA found that celecoxib and meloxicam were similar in effectiveness and tolerability to the *nonselective* NSAID naproxen.

The most frequent adverse effects of NSAIDs in children are nausea, decreased appetite, and abdominal pain. Gastritis or ulceration (oral or gastric) occurs less frequently in children. Less common adverse effects (≤5% of children undergoing long-term NSAID therapy) include mood change, concentration difficulty that can simulate attention-deficit disorder, sleepiness, irritability, headache, tinnitus, alopecia, anemia, elevated liver enzyme values, proteinuria, and hematuria. Certain agents (indomethacin) have a higher risk of toxicity than others (ibuprofen); naproxen has an intermediate risk. These NSAID-associated adverse effects reverse quickly once the medication is stopped. Additional rare NSAID-specific adverse reactions may also occur. Aseptic meningitis has been associated with ibuprofen, primarily in patients with lupus. Naproxen is more likely than other NSAIDs to cause a unique skin reaction called **pseudoporphyria**, which is characterized by small, hypopigmented depressed scars occurring in areas of minor skin trauma, such as fingernail scratches. Pseudoporphyria is more likely to occur in fair-skinned individuals and on sun-exposed areas. If pseudoporphyria develops, the inciting NSAID should be discontinued because scars can persist for years or may be permanent. NSAIDs should be used cautiously in patients with dermatomyositis or systemic vasculitis because of an increased frequency of GI ulceration with these disorders. *Salicylates have been supplanted by other NSAIDs because of the relative frequency of salicylate hepatotoxicity and the association with Reye syndrome.*

The response to NSAIDs varies greatly among individual patients, but overall, 40–60% of children with JIA experience improvement in their arthritis with NSAID therapy. Patients may try several different NSAIDs for 6-week trials before finding one that demonstrates clinical benefit. NSAIDs with longer half-lives or sustained-release formulations allow for once- or twice-daily dosing and improve compliance. Laboratory monitoring for toxicity includes a complete blood count (CBC), serum creatinine, liver function tests (LFTs), and urinalysis every 6-12 months, although guidelines for frequency of testing are not established.

Nonbiologic Disease-Modifying Antirheumatic Drugs

Methotrexate

Methotrexate (MTX), an antimetabolite, is a cornerstone of therapy in pediatric rheumatology because of its sustained effectiveness and relatively low toxicity over prolonged periods of treatment. The mechanism of action of low-dose MTX in arthritis is complex but is believed to result from the inhibition of folate-dependent processes by MTX polyglutamates, primarily their effect on the enzyme 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase, leading to an increase of extracellular adenosine and, consequently, cyclic adenosine monophosphate (cAMP), which inhibits the production of proinflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β and their downstream effects on lymphocyte activation and proliferation.

MTX has a central role in the treatment of arthritis. The response to oral MTX (10 mg/m^2 once a week) is better than the response to placebo (63% vs 36%). Children who show no response to standard doses of MTX often do show response to higher doses (15-30 mg/m^2/wk). Subcutaneous (SC) administration of MTX is similar in absorption and pharmacokinetic properties to intramuscular (IM) injection, with less pain. MTX is typically used in the treatment of juvenile dermatomyositis as a steroid-sparing agent, with efficacy in 70% of patients. It has also been used successfully at a dosage of 10-20 mg/m^2/wk in patients with systemic lupus erythematosus (SLE) to treat arthritis, serositis, and rash.

Because of the lower dose used in treating rheumatic diseases, MTX is well tolerated by children, with toxicity being milder and

Table 195.1 Multidisciplinary Treatment of Rheumatic Diseases in Childhood

Accurate diagnosis and education of family	Pediatric rheumatologist Pediatrician Nurse • Disease-related education • Medication administration (injection teaching) • Safety monitoring Social worker • Facilitation of school services • Resource identification (community, government, financial, advocacy groups, vocational rehabilitation)
Physical medicine and rehabilitation	Physical therapy • Addressing deficits in joint or muscle mobility, limb-length discrepancies, gait abnormalities, and weakness Occupational therapy • Splinting to reduce joint contractures/deformities and lessen stress on joints; adaptive devices for activities of daily living
Consultant team	Ophthalmology • Eye screening for uveitis • Screening for medication-related ocular toxicity (hydroxychloroquine, glucocorticoids) Nephrology Orthopedics Dermatology Gastroenterology
Physical and psychosocial growth and development	Nutrition • Addressing undernourishment from systemic illness and obesity/overnourishment from glucocorticoids School integration • Individualized educational plan (IEP) or 504 plan Peer-group relationships Individual and family counseling
Coordination of care	Involvement of patient and family as active team members Communication among healthcare providers Involvement of school (school nurse) and community (social worker) resources

qualitatively different from that observed with treatment of neoplasms. Adverse effects include elevated liver enzyme values (15%); GI toxicity (13%); stomatitis (3%); headache (1–2%); and leukopenia, interstitial pneumonitis, rash, and alopecia (<1%). Hepatotoxicity observed among adults with rheumatoid arthritis (RA) treated with MTX has raised concern about similar problems in children. Analysis of liver biopsy specimens in children with JIA undergoing long-term MTX treatment has revealed occasional mild fibrosis but no evidence of even moderate liver damage. Patients receiving MTX should be counseled to avoid alcohol, smoking, and pregnancy. *Folic acid* (1 mg daily) is given as an adjunct to minimize adverse effects. Lymphoproliferative disorders have been reported in adults treated with MTX, primarily in association with Epstein-Barr virus (EBV) infection. Regression of lymphoma may follow withdrawal of MTX.

Monitoring laboratory tests for MTX toxicity include CBC and LFTs at regular intervals, initially every 8-12 weeks for the first 3-6 months of treatment, then every 12 weeks, with more frequent intervals after dosing adjustments or in response to abnormal values.

Hydroxychloroquine

Hydroxychloroquine sulfate is an antimalarial drug important in the treatment of SLE and dermatomyositis, particularly cutaneous manifestations of disease and to reduce lupus flares. It is not indicated to treat JIA because of lack of efficacy. The most significant potential adverse effect is *retinal toxicity,* which occurs rarely but results in irreversible color blindness or loss of central vision. Complete ophthalmologic examinations, including assessment of peripheral vision and color fields, are conducted at baseline and every 6-12 months to screen for retinal toxicity. Retinal toxicity is rare (1/5,000 patients) and is associated with weight-based dosing exceeding 6.5 mg/kg/day; therefore recommended dosing is 5 mg/kg/day, not to exceed 400 mg/day. Other potential adverse effects include rash, skin discoloration, gastric irritation, bone marrow suppression, central nervous system (CNS) stimulation, and myositis.

Leflunomide

Leflunomide is a DMARD approved for treatment of RA and also offers an alternative to MTX for treatment of JIA. MTX outperformed leflunomide for treatment of JIA in a randomized trial (at 16 weeks, 89% of patients receiving MTX achieved a 30% response rate vs 68% of those receiving leflunomide), although both drugs were effective. Dosing is oral, once daily, and weight based: 10 mg for children 10 to <20 kg, 15 mg for children 20-40 kg, and 20 mg for children >40 kg. Adverse reactions include paresthesias and peripheral neuropathy, GI intolerance, elevated liver transaminases and hepatic failure, cytopenias, alopecia, and teratogenesis. Leflunomide has a long half-life, and in cases in which discontinuation of the agent is required, a drug elimination protocol with cholestyramine may be indicated. Avoidance of pregnancy is essential. Laboratory tests (e.g., CBC, LFTs) are monitored every 4 weeks for the first 6 months of treatment, then every 8-12 weeks.

Sulfasalazine

Sulfasalazine is used to treat children with polyarticular JIA, oligoarticular JIA, and the peripheral arthritis and enthesitis associated with juvenile ankylosing spondylitis. In JIA, sulfasalazine 50 mg/kg/day (adult maximum: 3,000 mg/day, divided bid) achieves greater improvement in joint inflammation, global assessment parameters, and laboratory parameters than placebo. More than 30% of sulfasalazine-treated patients withdraw from the treatment because of adverse effects, primarily GI irritation and skin rashes. Sulfasalazine is associated with severe systemic hypersensitivity reactions, including Stevens-Johnson syndrome. Sulfasalazine is generally considered contraindicated in children with active systemic JIA because of increased hypersensitivity reactions. Sulfasalazine should not be used in patients with sulfa or salicylate hypersensitivity or porphyria.

Monitoring laboratory tests for sulfasalazine toxicity include CBC, LFTs, serum creatinine/blood urea nitrogen (BUN), and urinalysis, every other week for the first 3 months of treatment, monthly for 3 months, then every 3 months.

Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is an immunosuppressive drug approved by the FDA for organ transplant rejection. MMF is used primarily for treatment of lupus, uveitis, and autoimmune skin manifestations. In adult clinical trials, MMF was noninferior to cyclophosphamide for induction therapy of lupus nephritis, with a potential for fewer adverse effects (infection, gonadal toxicity). Dosing is based on body surface area (BSA): 600 mg/m^2 orally twice daily, with maximum dosage limits varying by formulation and BSA. The most common adverse reaction is GI intolerance; infections, cytopenias, and secondary malignancies are also reported.

Glucocorticoids

Glucocorticoids are given through oral, intravenous (IV), ocular, topical, and intraarticular administration as part of treatment of rheumatic disease. Oral corticosteroids are foundational treatment for moderate to severe lupus, dermatomyositis, and most forms of vasculitis; their long-term use is associated with many well-described, dose-dependent complications, including linear growth suppression, cushingoid features, osteoporosis, avascular necrosis, hypertension, impaired glucose tolerance, mood disturbance, and increased infection risk. Glucocorticoids should be tapered to the lowest effective dose over time and DMARDs introduced as steroid-sparing agents.

Table 195.2 Therapeutics for Childhood Rheumatic Diseases*

CLASSIFICATION	THERAPEUTIC†	DOSE	INDICATION†	ADVERSE REACTIONS	MONITORING
Nonsteroidal antiinflammatory drugs (NSAIDs)‡	Etodolac[a]	PO once-daily dose: 20-30 kg: 400 mg 31-45 kg: 600 mg 46-60 kg: 800 mg >60 kg: 1,000 mg	JIA Spondyloarthropathy Pain Serositis Cutaneous vasculitis Uveitis	GI intolerance (abdominal pain, nausea), gastritis, hepatitis, tinnitus, anemia, pseudoporphyria, aseptic meningitis, headache, renal disease	CBC, LFTs, BUN/creatinine, urinalysis at baseline, then every 6-12 mo
	Ibuprofen[a]	40 mg/kg/day PO in 3 divided doses Max 2,400 mg/day			
	Naproxen[a]	15 mg/kg/day PO in 2 divided doses Max 1,000 mg/day			
	Celecoxib[a]	10-25 kg: 50 mg PO bid >25 kg: 100 mg PO bid			
	Meloxicam[a]	0.125 mg/kg PO daily Max 7.5 mg			
Disease-modifying antirheumatic drugs (DMARDs)	Methotrexate[a]	10-20 mg/m^2/wk (0.35-0.65 mg/kg/wk) PO 20-30 mg/m^2/wk (0.65-1 mg/kg/wk) SC; higher doses better absorbed by SC injection	JIA Uveitis	GI intolerance (nausea, vomiting), hepatitis, myelosuppression, mucositis, teratogenesis, lymphoma, interstitial pneumonitis	CBC, LFTs at baseline, monthly ×3, then every 8-12 wk
	Leflunomide	PO once daily: 10 to <20 kg: 10 mg 20-40 kg: 15 mg >40 kg: 20 mg	JIA	Hepatitis, hepatic necrosis, cytopenias, mucositis, teratogenesis, peripheral neuropathy	CBC, LFTs, at baseline, monthly ×6, then every 8-12 wk
	Hydroxychloroquine	5 mg/kg PO daily; do not exceed 5 mg/kg/daily Max 400 mg daily	SLE JDMS Antiphospholipid antibody syndrome	Retinal toxicity, GI intolerance, rash, skin discoloration, anemia, cytopenias, myopathy, CNS stimulation, death (overdose)	Ophthalmologic screening every 6-12 mo
	Sulfasalazine[a]	30-50 mg/kg/day in 2 divided doses Adult max 3 g/day	Spondyloarthropathy, JIA	GI intolerance, rash, hypersensitivity reactions, Stevens-Johnson syndrome, cytopenias, hepatitis, headache	CBC, LFTs, BUN/creatinine, urinalysis at baseline, every other wk ×3 mo, monthly ×3, then every 3 mo
Janus kinase inhibitor	Tofacitinib[a]	Oral solution (1 mg/mL) Use for ≥2 yr and ≥10 kg; 10 to <20 kg: 3.2 mg twice daily 20 to <40 kg: 4 mg twice daily ≥40 kg: 5 mg twice daily **or** Immediate-release tablet (5 mg), 5 mg twice daily	Polyarticular JIA	Infection, headache, increased HDL, cytopenias, potential increased malignancy risk, potential increased thrombosis risk	CBC, LFTs at baseline, then every 3 mo; lipids 4-8 wk after initiation, then periodically

Table 195.2 Therapeutics for Childhood Rheumatic Diseases —cont'd

CLASSIFICATION	THERAPEUTIC†	DOSE	INDICATION†	ADVERSE REACTIONS	MONITORING
Tumor necrosis factor (TNF)-α antagonists	Adalimumab[a]	SC once every other wk: 10 to <15 kg: 10 mg 15 to <30 kg: 20 mg ≥30 kg: 40 mg	JIA Spondyloarthropathy Psoriatic arthritis Uveitis	Injection site reaction, infection, rash, cytopenias, lupus-like syndrome, potential increased malignancy risk	TB test; anti-dsDNA, CBC
	Etanercept[a]	0.8 mg/kg SC once weekly (max 50 mg/dose) or 0.4 mg/kg SC twice weekly (max 25 mg/dose)	JIA	Injection site reactions, infections, rash, demyelinating disorders, cytopenias, potential increased malignancy risk	TB test; CBC
	Golimumab[a]	80 mg/m^2 IV at 0 and 4 wk, then every 8 wk	Polyarticular JIA Spondyloarthropathy Psoriatic arthritis	Infusion reactions, hepatitis, potential increased malignancy risk	TB test; anti-dsDNA, LFTs
	Infliximab	5-10 mg/kg IV every 4-8 wk	JIA Spondyloarthropathy Uveitis Sarcoidosis	Infusion reactions, hepatitis, potential increased malignancy risk	TB test; anti-dsDNA, LFTs
Modulate T-cell activation	Abatacept[a]	IV every 2 wk ×3 doses, then monthly for ≥6 yr of age: <75 kg: 10 mg/kg 75-100 kg: 750 mg >100 kg: 1,000 mg SC once weekly: 10 to <25 kg: 50 mg ≥25 to <50 kg: 87.5 mg ≥50 kg: 125 mg	JIA	Infection, headache, potential increased malignancy risk	
Anti-CD20 (B-cell) antibody	Rituximab	575 mg/m^2, max 1,000 mg, IV on days 1 and 15	SLE	Infusion reactions, lymphopenia, reactivation hepatitis B, rash, serum sickness, arthritis, PML	CBC, BMP; consider monitoring quantitative IgG
Anti-BLyS antibody	Belimumab[e]	10 mg/kg IV every 2 wk ×3 doses, then every 4 wk	SLE	Infusion reactions, infection, depression	
Interleukin (IL)-1 antagonist	Anakinra	1-2 mg/kg/daily Adult max 100 mg	Systemic JIA CAPS	Injection site reactions, infection	CBC
	Canakinumab[b]	Given SC every 8 wk (CAPS) every 4 wk (systemic JIA): 15-40 kg: 2 mg/kg (up to 3 mg/kg if needed) >40 kg: 150 mg	CAPS Systemic JIA	Injection site reaction, infection, diarrhea, nausea, vertigo, headache	
		IV: <30 kg: 10 mg/kg/dose every 4 wk ≥30 kg: 8 mg/kg/dose every 4 wk; maximum dose: 800 mg/dose SC: <30 kg: 162 mg/dose once every 3 wk ≥30 kg: 162 mg/dose once every 2 wk	Polyarticular JIA		

Continued

Table 195.2 Therapeutics for Childhood Rheumatic Diseases —cont'd

CLASSIFICATION	THERAPEUTIC†	DOSE	INDICATION†	ADVERSE REACTIONS	MONITORING
IL-6 antagonist	Tocilizumab[a]	≥2 yr and ≥30 kg: 8 mg/kg/dose every 2 wk ≥2 yr and ≤30 kg: 12 mg/kg/dose every 2 wk	Systemic JIA	Infusion reactions, elevated LFTs, elevated lipids, thrombocytopenia, infections	CBC, LFTs, platelet count, serum lipid profile
Intravenous immune globulin	IVIG[c]	1,000-2,000 mg/kg IV infusion For JDMS, give monthly	Kawasaki disease JDMS SLE	Infusion reaction, aseptic meningitis, renal failure	Serum creatinine, BUN, IgG level
Cytotoxic	Cyclophosphamide	0.5-1 g/m^2 IV (max 1.5 g) monthly for 6 mo induction, then every 2-3 mo Oral regimen: 1-2 mg/kg/daily; max 150 mg/daily	SLE Vasculitis JDMS Pulmonary hemorrhage	Nausea, vomiting, myelosuppression, mucositis, hyponatremia, alopecia, hemorrhagic cystitis, gonadal failure, teratogenesis, secondary malignancy	CBC
Immunosuppressive	Mycophenolate mofetil	Oral suspension: max 1,200 mg/m^2/day PO (up to 2 g/day) divided bid Capsules: max 1,500 mg/day PO for BSA 1.25-1.5 m^2, 2 g/day PO for BSA >1.5 m^2 divided bid	SLE Uveitis	GI intolerance (diarrhea, nausea, vomiting), renal impairment, neutropenia, teratogenesis, secondary malignancy, PML	CBC, BMP
Glucocorticoids	Prednisone[a,d-f]	0.05-2 mg/kg/day PO given in 1-4 divided doses; max varies by individual (80 mg/daily) Adverse effects are dose dependent; lowest effective dose should be used	SLE JDMS Vasculitis JIA Uveitis Sarcoidosis	Cushing syndrome, osteoporosis, increased appetite, weight gain, striae, hypertension, adrenal suppression, hyperglycemia, infection, avascular necrosis	Blood glucose, potassium Blood pressure
	Methylprednisolone[a,d-g]	0.5-1.7 mg/kg/day or 5-25 mg/m^2/day IM/IV in divided doses every 6-12 hr For severe manifestations: 30 mg/kg/dose (max 1 g) daily for 1-5 days	SLE JDMS Vasculitis Sarcoidosis Localized scleroderma		
	Intraarticular	Dose varies by joint and formulation	JIA	Subcutaneous atrophy, skin hypopigmentation, calcification, infection	
	Prednisolone ophthalmic suspension	1-2 drops into eye up to every hr while awake Needs monitoring by ophthalmologist	Uveitis	Ocular hypertension, glaucoma, nerve damage, cataract, infection	Ophthalmologic exam

*Consult a clinical pharmacology reference for current dosing and monitoring guidelines and complete list of known adverse effects.
†Therapeutics used in practice may not have an FDA-approved indication. Individual therapeutics annotated with FDA-approved indication as follows: *a*, JIA; *b*, CAPS; *c*, Kawasaki disease; *d*, sarcoidosis; *e*, SLE; *f*, uveitis; *g*, dermatomyositis.
‡Many more products are available in this class.
bid, Twice daily; BLys, B-lymphocyte stimulator; BMP, basic metabolic panel; BSA, body surface area; BUN, blood urea nitrogen; CAPS, cryopyrin-associated periodic syndrome; CBC, complete blood count; CNS, central nervous system; dsDNA, double-stranded DNA; GI, gastrointestinal; IM, intramuscular(ly); IV, intravenous(ly); IVIG, intravenous immune globulin; JDMS, juvenile dermatomyositis; JIA, juvenile idiopathic arthritis; LFTs, liver function tests; PML, progressive multifocal leukoencephalopathy; PO, by mouth; SC, subcutaneous(ly); SLE, systemic lupus erythematosus; TB, tuberculosis

Intravenous corticosteroids have been used to treat severe, acute manifestations of systemic rheumatic diseases such as SLE, dermatomyositis, and vasculitis. The IV route allows for higher doses to obtain an immediate, profound antiinflammatory effect. Methylprednisolone 10-30 mg/kg/dose up to a maximum of 1 g, given over 1 hour daily for 1-5 days is the IV preparation of choice. Although generally associated with fewer adverse effects than oral corticosteroids, IV steroids are associated with significant and occasionally life-threatening toxicities, such as cardiac arrhythmia, acute hypertension, hypotension, hyperglycemia, shock, pancreatitis, and avascular necrosis.

Ocular corticosteroids are prescribed by ophthalmologists as ophthalmologic drops or injections into the soft tissue surrounding the globe (sub–Tenon capsule injection) for active uveitis. Long-term ocular corticosteroid use leads to cataract formation and glaucoma. Current ophthalmologic management with methotrexate and biologic therapy, especially TNF inhibitors, have significantly decreased the frequency of eye complications of JIA-associated uveitis.

Intraarticular corticosteroids are frequently used as initial therapy for children with oligoarticular JIA or as bridge therapy while awaiting efficacy of a DMARD in polyarticular disease. Most patients have significant clinical improvement within 3 days. Duration of response depends on steroid preparation used, joint affected, and arthritis subtype; the anticipated response rate to knee injection is 60–80% at 6 months. Intraarticular administration may result in subcutaneous atrophy and hypopigmentation of the skin at the injection site, as well as subcutaneous calcifications along the needle track.

JANUS KINASE INHIBITORS

Another effective class of DMARDs is the Janus kinase inhibitors, collectively known as **JAKinibs**. In immune cells, these drugs inhibit intracellular signaling through the JAK-STAT pathway in immune cells by binding to various Janus kinases (in humans, JAK 1, JAK 2, JAK 3, and TYK2), thereby negating the response to extracellular cytokine ligation of immune cell receptors. Inhibition affects lymphocyte activation, function, and survival. Many JAKinibs are currently available, including tofacitinib, baricitinib, ruxolitinib, and upadacitinib. Currently, only tofacitinib has FDA approval in pediatric rheumatic disease.

Tofacitinib is a small-molecule, oral JAKinib of the JAK1, JAK3, and, to a lesser extent, JAK2 enzymes. Tofacitinib has FDA approval for treatment of polyarticular JIA (age ≥2 years and weight ≥10 kg) with twice-daily dosing: 3.2 mg bid for 10-20 kg, 4 mg bid for 20-40 kg, and 5 mg bid for >40 kg. It is available as an oral solution (1 mg/mL) and as oral tablets (5 mg). Adverse reactions include increased risk of serious infections, thrombosis including pulmonary and deep venous/arterial, and gastrointestinal perforations; the most common adverse reactions are upper respiratory infections, diarrhea, and headache.

Biologic Agents

Biologic agents are proteins that have been engineered to target and modulate specific components of the immune system, with the goal of decreasing the inflammatory response. Antibodies have been developed to target specific cytokines such as IL-1 and IL-6 or to interfere with specific immune cell function through depletion of β cells or suppression of T-cell activation (Table 195.3). Biologic agents have increased the therapeutic options for treating rheumatic disease recalcitrant to nonbiologic therapies, and in some cases biologics are first-line interventions. A primary concern is the increased risk of malignancy when biologics are combined with other immunosuppressants.

Tumor Necrosis Factor-α Antagonists

Three TNF antagonists have an FDA indication for treatment of children with moderate to severe polyarticular JIA (etanercept, adalimumab, and golimumab). *Etanercept* is a genetically engineered fusion protein consisting of two identical chains of the recombinant extracellular TNF receptor monomer fused with the Fc domain of human immunoglobulin G_1. Etanercept binds both TNF-α and lymphotoxin-α (formerly called TNF-β) and inhibits their activity. Three fourths of children with active polyarticular JIA that fails to respond to MTX demonstrate response to etanercept after 3 months of therapy. Dosing is 0.8 mg/kg subcutaneously weekly (max 50 mg/dose) or 0.4 mg/kg SC twice weekly (max 25 mg/dose). *Adalimumab* is a fully human anti-TNF monoclonal antibody (mAb) used alone or in combination with MTX. In a placebo-controlled withdrawal-design study, children continuing to receive adalimumab were less likely to experience disease flares (43% vs 71%) even if they were also taking MTX (37% vs 65%). Adalimumab is administered subcutaneously every other week at a dose of 10 mg for children weighing 10 to <15 kg, 20 mg for children weighing 15 to <30 kg, and 40 mg for those weighing ≥30 kg. *Golimumab* is a human mAb that binds to both soluble and transmembrane bioactive forms of TNF. It has FDA approval for use in polyarticular JIA at dosing of 80 mg/m^2 IV with initial doses at 0 and 4 weeks and then every 8 weeks thereafter. Non-FDA approved uses include psoriatic arthritis.

Infliximab, a chimeric mouse-human mAb, was tested in a randomized controlled trial (RCT) for use in JIA but did not achieve study end-points. However, it is FDA approved for pediatric inflammatory bowel disease and has been used "off label" for treatment of polyarticular JIA, uveitis, Behçet syndrome, and sarcoidosis. *Certolizumab pegol*, a pegylated humanized antibody against TNF, is approved by the FDA for RA, psoriatic arthritis, and ankylosing spondylitis in adults and is currently in pediatric trials for treatment of polyarticular JIA.

The most common adverse effects are injection site reactions that diminish over time. TNF blockade is associated with an increased frequency of serious systemic infections, including sepsis, dissemination of latent tuberculosis (TB), and invasive fungal infections in endemic areas. TNF blockade should not be initiated in patients with a history of chronic or frequent recurrent infections. TB testing should be done before initiation of therapy with TNF antagonists. If test results are positive, antitubercular treatment must be administered before anti-TNF treatment can be started. Theoretically, the risk of malignancy increases with TNF-α antagonists. Case reports describe the development of lupus-like syndromes, leukocytoclastic vasculitis, interstitial lung disease, demyelinating syndromes, antibody formation to the drug, rashes, cytopenias, anaphylaxis, serum sickness, and other reactions. The benefit/risk profile appears favorable after a decade of experience with this therapeutic class; the safety of longer-term suppression of TNF function is unknown.

Modulator of T-Cell Activation

Abatacept is a selective inhibitor of T-cell costimulation resulting in T-cell anergy. It is FDA approved for treatment of moderate to severe polyarticular JIA. In a double-blind withdrawal RCT in children whose disease had not responded to DMARDs, 53% of placebo-treated patients vs 20% of abatacept-treated patients experienced disease flares during the withdrawal period. The frequency of adverse events did not differ between the

Table 195.3 Method of Action of Biologic Therapies Studied in Juvenile Idiopathic Arthritis

DRUG	METHOD OF ACTION
Etanercept	Soluble TNF p75 receptor fusion protein that binds to and inactivates TNF-α
Infliximab	Chimeric human/mouse monoclonal antibody that binds to soluble TNF-α and its membrane-bound precursor, neutralizing its action
Adalimumab	A humanized IgG_1 monoclonal antibody that binds to TNF-α
Abatacept	Soluble, fully human fusion protein of the extracellular domain of CTLA-4, linked to a modified Fc portion of the human IgG_1. It acts as a costimulatory signal inhibitor by binding competitively to CD80 or CD86, where it selectively inhibits T-cell activation
Tocilizumab	A humanized anti–human IL-6 receptor monoclonal antibody
Anakinra	An IL-1 receptor antagonist (IL-1RA)

CTLA, Cytotoxic T lymphocyte–associated antigen; IL, interleukin; TNF, tumor necrosis factor.

From Beresford MW, Baildam EM. New advances in the management of juvenile idiopathic arthritis. Part 2. The era of biologicals. *Arch Dis Child Educ Pract Ed.* 2009;94:151–156.

groups. Abatacept is administered IV every other week for three doses (<75 kg: 10 mg/kg/dose; 75-100 kg: 750 mg/dose; >100 kg: 1,000 mg/dose; maximum 1,000 mg/dose at 0, 2, and 4 weeks) and then monthly thereafter. Abatacept administered by SC injection was given FDA approval in March 2017 for children ≥4 years old for treatment of polyarticular JIA at doses given weekly: 50 mg for 10-25 kg, 87.5 mg for ≥25 to <50 kg, and 125 mg for ≥50 kg.

B-Cell Depletion

Rituximab is a chimeric mAb to the antigen CD20, a transmembrane protein on the surface of B-cell precursors and mature B lymphocytes. This antibody induces B-cell apoptosis and causes depletion of circulating and tissue-based B cells. Antibody production is not completely abrogated because plasma cells are not removed. Rituximab has FDA approval for treatment of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) in children greater than 2 years of age. It is approved for treatment of adult RA and may also have a role in treatment of SLE, particularly its hematologic manifestations. Adverse events include serious infusion reactions, cytopenias, hepatitis B virus reactivation, hypogammaglobulinemia, infections, serum sickness, vasculitis, and a rare but fatal side effect, *progressive multifocal leukoencephalopathy*. Resistance to rituximab may develop over time in patients being treated for lymphoma.

Belimumab is a human mAb to B-lymphocyte stimulator **(BLys)** that negatively affects B-cell proliferation, differentiation, and long-term survival by inhibiting binding of BLys to its receptors on B cells. It is FDA approved for treatment of pediatric SLE in children age 5 years and older. For this indication, it is given as an IV infusion (10 mg/kg) every 2 weeks for the first three doses, then every 4 weeks thereafter. Side effects associated with belimumab include increased risk of serious infections, allergic (hypersensitivity) reactions, and changes in mood.

Interleukin-1 Antagonists

Anakinra, a recombinant form of the human IL-1 receptor antagonist, competitively inhibits binding of IL-1α and IL-1β to the natural receptor, interrupting the cytokine proinflammatory cascade. Anakinra has been approved for RA in adults. In meta-analyses of treatments for RA, anakinra was outperformed by TNF-α antagonists but has a special niche in pediatric rheumatology for treatment of systemic JIA (sJIA) and other autoinflammatory syndromes, such as cryopyrin-associated periodic syndrome (CAPS). The medication is dosed SC, 1-2 mg/kg, once daily. An IL-1β mAb, *canakinumab,* is FDA approved for use in CAPS, dosed SC every 8 weeks, and sJIA, dosed SC every 4 weeks. Adverse reactions include significant injection site reactions and increased bacterial infections.

Interleukin-6 Receptor Antagonist

Tocilizumab is an anti–IL-6 receptor antibody binding to both soluble and membrane-associated receptors. Tocilizumab has FDA approval for treatment of sJIA and polyarticular JIA. Adverse reactions include transaminase and lipid elevations. Tocilizumab is given as an IV infusion every 2 weeks (sJIA) to 4 weeks (polyarticular JIA), and SC for polyarticular JIA 162 mg every 3 weeks for those <30 kg and every 2 wk for ≥30 kg.

Intravenous Immune Globulin

Intravenous immunoglobulin (IVIG) is thought to be beneficial in various clinical conditions. IVIG significantly improves the short- and long-term natural history of Kawasaki disease. Open studies have supported benefit for juvenile dermatomyositis, lupus-associated thrombocytopenia, and polyarticular JIA. IVIG is given as 1-2 g/kg/dose, administered once monthly. It has been occasionally associated with severe, systemic allergy-like reactions and postinfusion aseptic meningitis (headache, stiff neck) (Table 195.4).

Table 195.4 Predisposing Factors for Immunoglobulin-Induced Adverse Effects

ADVERSE EFFECT	PREDISPOSING FACTORS
Flulike symptoms	High dose, rapid infusion rate, accompanying infection, previous adverse effects
Dermatologic adverse effects	High dose, rapid infusion rate, accompanying infection, male patients with chronic inflammatory demyelinating polyneuropathy
Arrhythmia and hypotension	History of heart disease
Transfusion-related acute lung injury	Rapid infusion rate
Thrombotic events	High dose, rapid infusion rate, advanced age, being bedridden, diabetes mellitus, hypertension, dyslipidemia, prior/current thrombosis, preexisting atherosclerotic disease, elevated serum viscosity, oral contraceptive use, hereditary hypercoagulable state, idiopathic thrombocytopenic purpura
Aseptic meningitis	High dose
Renal impairment	Rapid infusion rate, advanced age, renal insufficiency, nephrotic syndrome, diabetes mellitus, dehydration, sepsis paraproteinemia, nephrotoxic drugs, hemolysis, sucrose-containing preparations
Hemolysis	High dose, rapid infusion rate, non-O blood group, underlying inflammatory state

From Guo Y, Tian X, Wang X, Xiao Z. Adverse effects of immunoglobulin therapy. *Frontiers Immunol.* 2018;9:1299, Table 2.

Cytotoxics

Cyclophosphamide

Cyclophosphamide requires metabolic conversion in the liver to its active metabolites, which alkylate the guanine in DNA, leading to immunosuppression by inhibition of the S2 phase of mitosis. The subsequent decrease in numbers of T and B lymphocytes results in diminished humoral and cellular immune responses. Cyclophosphamide infusions (500-1,000 mg/m^2) given monthly for 6 months, then every 3 months for 12-18 months, have been shown to reduce the frequency of renal failure in patients with lupus and diffuse proliferative glomerulonephritis. Open trials suggest efficacy in severe CNS lupus. Oral cyclophosphamide (1-2 mg/kg/day) is effective as induction treatment of severe antineutrophilic cytoplasmic antibody (ANCA)–associated vasculitis and other forms of systemic vasculitis, as well as interstitial lung disease or pulmonary hemorrhage associated with rheumatic disease.

Cyclophosphamide is a potent cytotoxic drug associated with significant toxicities. Potential short-term adverse effects include nausea, vomiting, anorexia, alopecia, mucositis, hemorrhagic cystitis, and bone marrow suppression. Long-term complications include an increased risk for sterility and cancer, especially leukemia, lymphoma, and bladder cancer. In adult women with lupus treated with IV cyclophosphamide, 30–40% become infertile; the risk of ovarian failure appears to be significantly lower in adolescent and premenarchal girls. Ovarian suppression with an inhibitor of gonadotropin-releasing hormone to preserve fertility is currently being studied.

Other Drugs

Azathioprine is sometimes used to treat ANCA-associated vasculitis after induction therapy or to treat SLE. *Cyclosporine* has been used occasionally in the treatment of dermatomyositis on the basis of uncontrolled studies and is helpful in the treatment of macrophage activation syndrome complicating sJIA (see Chapter 207). Case reports describe the successful use of *thalidomide,* or its analog *lenalidomide,* as treatment for sJIA, inflammatory skin disorders, and Behçet disease.

Several drugs commonly used in the past to treat arthritis are no longer part of standard treatment, including salicylates, gold compounds, and D-penicillamine.

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Chapter 196

Juvenile Idiopathic Arthritis

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Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children and one of the more common chronic illnesses of childhood. JIA represents a heterogeneous group of disorders sharing the clinical manifestation of arthritis. The etiology and pathogenesis of JIA are largely unknown, and the genetic component is complex, making clear distinction among various subtypes difficult. As a result, several classification schemes exist, each with its own limitations. The former classification of the **American College of Rheumatology (ACR)** uses the term *juvenile rheumatoid arthritis* and categorizes the disease into three onset types (Table 196.1). Attempting to standardize nomenclature, the **International League of Associations for Rheumatology (ILAR)** proposed a different classification using the term *juvenile idiopathic arthritis* (Table 196.2), inclusive of all subtypes of chronic juvenile arthritis. We refer to the ILAR classification criteria; see Chapter 197 for enthesitis-related arthritis (ERA) and psoriatic JIA (Tables 196.3 and 196.4).

EPIDEMIOLOGY

The worldwide incidence of JIA ranges from 0.8 to 22.6 per 100,000 children per year, with prevalence ranges from 7 to 401 per 100,000. These wide-ranging numbers reflect population differences, particularly environmental exposure and immunogenetic susceptibility, along with variations in diagnostic criteria, difficulty in case ascertainment, and lack of population-based data. An estimated 300,000 U.S. children have arthritis, including 100,000 with a form of JIA. **Oligoarthritis** is the most common subtype (40–50%), followed by **polyarthritis** (25–30%) and **systemic JIA** (5–15%) (see Table 196.4). More females than males are affected in both oligoarticular (3:1) and polyarticular (5:1) JIA but are equally affected in systemic JIA (sJIA). The peak age at onset is 2-4 years for oligoarticular disease. Age of onset has a bimodal distribution in polyarthritis, with peaks at 2-4 years and 10-14 years. sJIA occurs throughout childhood, with a peak at 1-5 years.

ETIOLOGY

The etiology and pathogenesis of JIA are not completely understood, although both immunogenetic susceptibility and an external trigger are considered necessary. Twin and family studies suggest a substantial role for genetic factors. JIA is a complex genetic trait in which multiple genes may affect disease susceptibility. Variants in major histocompatibility complex (MHC) class I and class II regions have indisputably been associated with different JIA subtypes. Non-HLA candidate loci are also associated with JIA, including polymorphisms in the genes encoding protein tyrosine phosphatase nonreceptor 22 (PTPN22), tumor necrosis factor (TNF)-α, macrophage inhibitory factor, interleukin (IL)-6 and its receptor, and IL-1α. Possible nongenetic triggers include bacterial and viral infections, enhanced immune responses to bacterial or mycobacterial heat shock proteins, abnormal reproductive hormone levels, and joint trauma.

Table 196.1 Criteria for the Classification of Juvenile Rheumatoid Arthritis

Age at onset: <16 yr
Arthritis (swelling or effusion, or the presence of two or more of the following signs: limitation of range of motion, tenderness or pain on motion, increased heat) in one or more joints
Duration of disease: ≥6 wk
Onset type defined by type of articular involvement in the first 6 mo after onset:
Polyarthritis: five or more inflamed joints
Oligoarthritis: four or fewer inflamed joints
Systemic-onset disease: arthritis with rash and a characteristic quotidian fever
Exclusion of other forms of juvenile arthritis

Adapted from Cassidy JT, Levison JE, Bass JC, et al. A study of classification criteria for a diagnosis of juvenile rheumatoid arthritis. *Arthritis Rheum*. 1986;29:274–281.

PATHOGENESIS

JIA is an autoimmune disease associated with alterations in both humoral and cell-mediated immunity. T lymphocytes have a central role, releasing proinflammatory cytokines favoring a type 1 helper T-lymphocyte response. Studies of T-cell receptor expression confirm recruitment of T lymphocytes specific for synovial non–self-antigens. B-cell activation, immune complex formation, and complement activation also promote inflammation. Inheritance of specific cytokine alleles may predispose to upregulation of inflammatory networks, resulting in systemic disease or more severe articular disease.

sJIA is characterized by dysregulation of the innate immune system with a lack of autoreactive T cells and autoantibodies. It therefore may be more accurately classified as an **autoinflammatory disorder**, which may transition to an autoimmune process once actual arthritis develops (Fig. 196.1). The IL-1 family of cytokines is key to disease pathogenesis, which is strongly supported by the marked responsiveness to IL-1 inhibitors. IL-18 in particular is a central driver, and serum IL-18 levels are markedly elevated in children with sJIA.

All these immunologic abnormalities cause inflammatory synovitis, characterized pathologically by villous hypertrophy and hyperplasia with hyperemia and edema of the synovial tissue. Vascular endothelial hyperplasia is prominent and is characterized by infiltration of mononuclear and plasma cells with a predominance of T lymphocytes (Fig. 196.2). Advanced and uncontrolled disease leads to pannus formation and progressive erosion of articular cartilage and contiguous bone (Figs. 196.3 and 196.4).

CLINICAL MANIFESTATIONS

Arthritis must be present ≥6 weeks to make a diagnosis of any JIA subtype. Arthritis is defined by intraarticular swelling or the presence of two or more of the following signs: limitation in range of motion (ROM), tenderness or pain on motion, and warmth. Initial symptoms may be subtle or acute and often include morning stiffness with a limp or gelling after inactivity. Easy fatigability and poor sleep quality may be present. Involved joints are often swollen, warm to the touch, and uncomfortable on movement or palpation with reduced ROM, but usually are not erythematous. Arthritis in large joints, especially knees, initially accelerates linear growth and causes the affected limb to be longer, resulting in a discrepancy in limb lengths. Continued inflammation stimulates rapid and premature closure of the growth plate, resulting in shortened bones.

Oligoarthritis is defined as involving four or fewer joints within the first 6 months of disease onset, and often only a single joint is involved (see Table 196.4). It predominantly affects the large joints of the lower extremities, such as the knees and ankles (Fig. 196.5). Isolated involvement of upper-extremity large joints is less common. Those in whom disease never develops in four or more joints are regarded as having **persistent oligoarticular JIA**, whereas evolution of disease in five or more joints after 6 months changes the classification to **extended oligoarticular JIA** and is associated with a worse prognosis. Isolated involvement of the hip is *almost never* a presenting sign and suggests ERA (see Chapter 197) or a nonrheumatic cause. The presence of a positive antinuclear antibody (ANA) test confers increased risk for asymptomatic anterior uveitis, requiring periodic slit-lamp examination (Table 196.5). ANA positivity may also be correlated with younger age at disease onset, females, asymmetric arthritis, and fewer involved joints over time.

Table 196.2 International League of Associations for Rheumatology Classification of Juvenile Idiopathic Arthritis (JIA)

CATEGORY	DEFINITION	EXCLUSIONS
Systemic JIA	Arthritis in one or more joints with, or preceded by, fever of ≥2 wk in duration that is documented to be daily (quotidian*) for at least 3 days and accompanied by one or more of the following: 1. Evanescent (nonfixed) erythematous rash 2. Generalized lymph node enlargement 3. Hepatomegaly or splenomegaly or both 4. Serositis†	a. Psoriasis or a history of psoriasis in patient or first-degree relative b. Arthritis in an HLA-B27–positive male beginning after the sixth birthday c. Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with IBD, Reiter syndrome, or acute anterior uveitis, or history of one of these disorders in a first-degree relative d. Presence of IgM RF on at least two occasions at least 3 mo apart
Oligoarthritis	Arthritis affecting one to four joints during the first 6 mo of disease; two subcategories are recognized: 1. Persistent oligoarthritis—affecting four or fewer joints throughout the disease course 2. Extended oligoarthritis—affecting five or more joints after the first 6 mo of disease	a, b, c, d (above) *plus* e. Presence of systemic JIA in the patient
Polyarthritis (RF negative)	Arthritis affecting five or more joints during the first 6 mo of disease; a test for RF is negative	a, b, c, d, e
Polyarthritis (RF positive)	Arthritis affecting five or more joints during the first 6 mo of disease; two or more tests for RF at least 3 mo apart during the first 6 mo of disease are positive	a, b, c, e
Psoriatic arthritis	Arthritis and psoriasis or arthritis and at least two of the following: 1. Dactylitis‡ 2. Nail pitting§ and onycholysis 3. Psoriasis in first-degree relative	b, c, d, e
Enthesitis-related arthritis	Arthritis and enthesitis¶ or arthritis or enthesitis with at least two of the following: 1. Presence of or history of sacroiliac joint tenderness or inflammatory lumbosacral pain, or both** 2. Presence of HLA-B27 antigen 3. Onset of arthritis in a male >6 yr old 4. Acute (symptomatic) anterior uveitis 5. History of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with IBD, Reiter syndrome, or acute anterior uveitis in first-degree relative	a, d, e
Undifferentiated arthritis	Arthritis that fulfills criteria in no category or two or more of the above categories	

**Quotidian fever* is defined as a fever that rises to 39°C (102.2°F) once daily and returns to 37°C (98.6°F) between fever peaks.
†*Serositis* refers to pericarditis, pleuritis, or peritonitis or some combination of the three.
‡*Dactylitis* is swelling of one or more digit(s), usually in an asymmetric distribution, that extends beyond the joint margin.
§A minimum of two pits on any one or more nails at any time.
¶*Enthesitis* is defined as tenderness at the insertion of a tendon, ligament, joint capsule, or fascia to bone.
***Inflammatory lumbosacral pain* refers to lumbosacral pain at rest with morning stiffness that improves on movement.
IBD, Inflammatory bowel disease; RF, rheumatoid factor.
From Firestein GS, Budd RC, Harris ED Jr, et al., eds. *Kelley's Textbook of Rheumatology,* 8th ed. Philadelphia: Saunders; 2009.

Table 196.3 Characteristics of ACR and ILAR Classifications of Childhood Chronic Arthritis

PARAMETER	ACR (1977)	ILAR (1997)
Term	Juvenile rheumatoid arthritis (JRA)	Juvenile idiopathic arthritis (JIA)
Minimum duration	≥6 wk	≥6 wk
Age at onset	<16 yr	<16 yr
Four or fewer joints in first 6 mo after presentation	Pauciarticular	Oligoarthritis: Persistent: four or fewer joints for course of disease Extended: four or more joints after 6 mo
Four or more joints in first 6 mo after presentation	Polyarticular	Polyarthritis, RF negative Polyarthritis, RF positive
Fever, rash, arthritis	Systemic onset	Systemic
Other categories included	Exclusion of other forms	Psoriatic arthritis Enthesitis-related arthritis Undifferentiated: Fits no other category Fits more than one category
Inclusion of psoriatic arthritis, inflammatory bowel disease, ankylosing spondylitis	No (see Chapter 197)	Yes

ACR, American College of Rheumatology; ILAR, International League of Associations for Rheumatology; RF, rheumatoid factor.

Table 196.4 Overview of Main Features of Subtypes of Juvenile Idiopathic Arthritis (JIA)

ILAR SUBTYPE	PEAK AGE AT ONSET (yr)	FEMALE:MALE RATIO	% OF ALL JIA CASES	ARTHRITIS PATTERN	EXTRAARTICULAR FEATURES	LABORATORY INVESTIGATIONS	NOTES ON THERAPY
Systemic arthritis	1-5	1:1	5-15	Polyarticular, often affecting knees, wrists, and ankles; also fingers, neck, and hips	Daily fever; evanescent rash; pericarditis; pleuritis	Anemia; WBC ↑↑; ESR ↑↑; CRP ↑↑; ferritin ↑; platelets ↑↑ (normal or ↓ in MAS)	Less responsive to standard treatment with MTX and anti-TNF agents; consider IL-1 or IL-6 inhibitors in resistant cases or as first-line therapy
Oligoarthritis	2-4	3:1	40-50 (but ethnic variation)	Knees ++; ankles, fingers +	Uveitis in 30% of cases	ANA positive in 60%; other test results usually normal; may have mildly ↑ ESR/CRP	NSAIDs and intraarticular corticosteroids; MTX occasionally required
Polyarthritis:							
RF negative	2-4 and 10-14	3:1 and 10:1	20-35	Symmetric or asymmetric; small and large joints; cervical spine; temporomandibular joint	Uveitis in 10%	ANA positive in 40%; RF negative; ESR ↑ or ↑↑; CRP ↑ or normal; mild anemia	Standard therapy with MTX and NSAIDs; then, if nonresponsive, anti-TNF agents or other biologics, including abatacept, indicated as first-line therapy
RF positive	9-12	9:1	<10	Aggressive symmetric polyarthritis	Rheumatoid nodules in 10%; low-grade fever	RF positive; ESR ↑↑; CRP ↑/ normal; mild anemia	Long-term remission unlikely; early aggressive therapy is warranted
Psoriatic arthritis	2-4 and 9-11	2:1	5-10	Asymmetric arthritis of small or medium-sized joints	Uveitis in 10%; psoriasis in 50%	ANA positive in 50%; ESR ↑; CRP ↑ or normal; mild anemia	NSAIDs and intraarticular corticosteroids; MTX, anti-TNF agents
Enthesitis-related arthritis	9-12	1:7	5-10	Predominantly lower limb joints affected; sometimes axial skeleton (but less than in adult, ankylosing spondylitis)	Acute anterior uveitis; association with reactive arthritis and inflammatory bowel disease	80% of patients positive for HLA-B27	NSAIDs and intraarticular corticosteroids; consider sulfasalazine as alternative to MTX; anti-TNF agents

ILAR, International League of Associations for Rheumatology; ANA, antinuclear antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MAS, macrophage activation syndrome; MTX, methotrexate; NSAIDs, nonsteroidal antiinflammatory drugs; RF, rheumatoid factor; TNF, tumor necrosis factor; WBC, white blood cell count.
From Firestein GS, Budd RC, Harris ED Jr, et al., eds. *Kelley's Textbook of Rheumatology*, 8th ed. Philadelphia: Saunders; 2009.

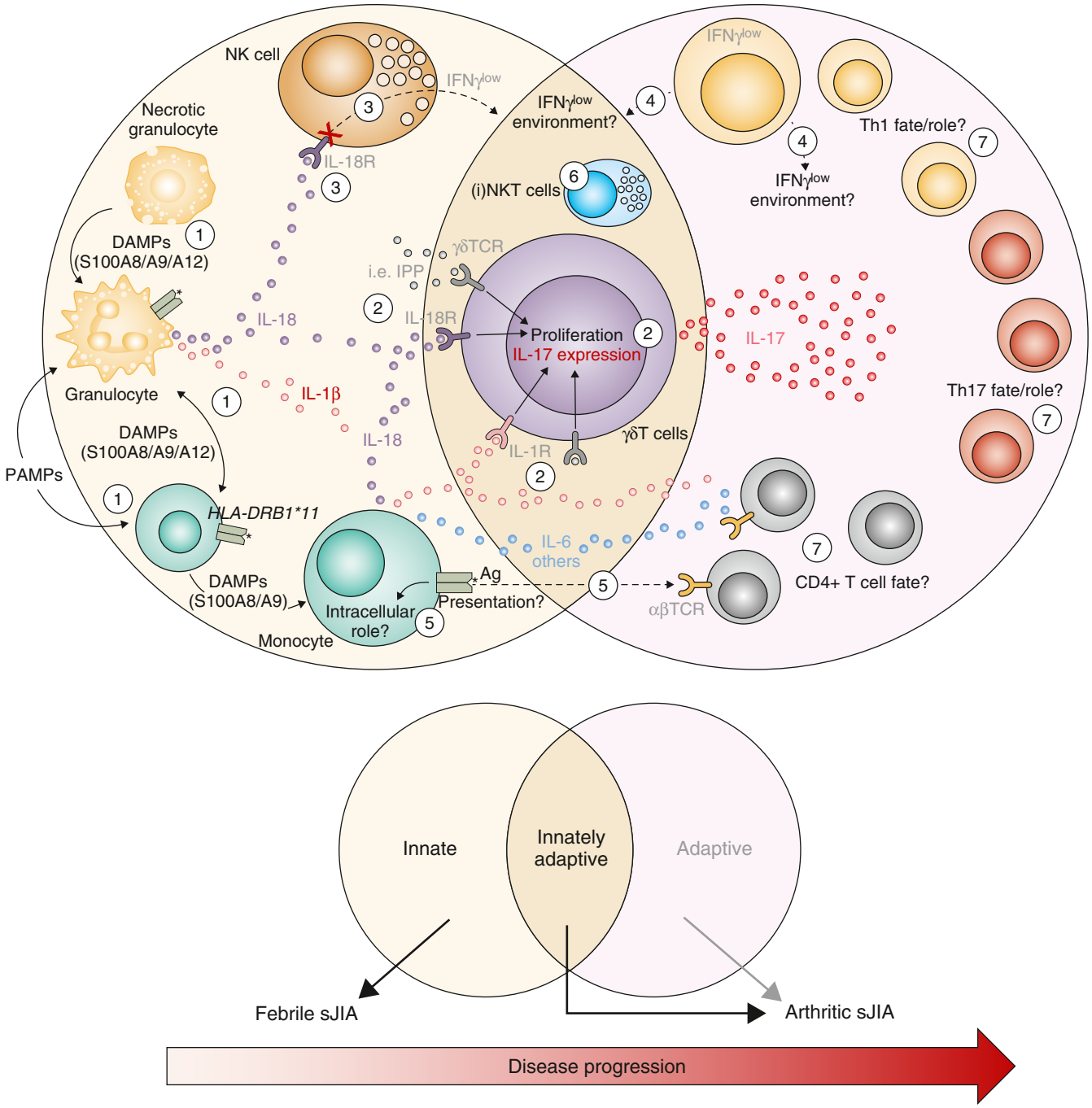

Fig. 196.1 Innately adaptive or truly autoimmune: a pathophysiologic model for disease progression in systemic juvenile idiopathic arthritis (sJIA). Innate immune cells, such as myeloid cells (granulocytes, monocytes) and natural killer (NK) cells, are relevant during the acute febrile phase of systemic JIA. *(1)* Myeloid cells release interleukin-1 (IL-1) family cytokines (IL-1β, IL-18) and other proinflammatory cytokines, which can either be triggered by infection (pathogen- associated molecular patterns [PAMPs]) or result from pattern-recognition receptor activation by damage-associated molecular patterns (DAMPs) released from stressed or necrotic cells. *(2)* Together with γδ T-cell receptor (γδ TCR) activation by endogenous ligands (i.e., isopentenyl pyrophosphate [IPP]) or bacterial ligands, IL-1 and IL-18 can trigger IL-17 expression from γδ T cells, while *(3)* IL-18 fails to trigger interferon-γ (IFNγ) expression from NK cells because of a defective IL-18 receptor (IL-18R). *(4)* Similarly, systemic JIA Th1 cells express only low levels of IFNγ. Both cell types may contribute to hypophysiologic IFNγ levels, potentially promoting IL-17 expression in disease. Although a genetic association or alterations in frequencies have been reported, the pathomechanistic roles of *(5)* HLA- DRB1*11 (whether antigen [Ag] presentation or intracellular function) or *(6)* invariant NKT (iNKT) and *(7)* CD4+ T cells in disease progression are yet largely unclear. Thus current data imply that innately adaptive immune cells bridging innate and adaptive immunity, rather than classic B or T lymphocytes, play a central role in promoting disease progression in systemic JIA. *(From Kessel C, Hedrich CM, Foeil D. Innately adaptive or truly autoimmune: is there something unique about systemic juvenile idiopathic arthritis?* Arth Rheumatol. *2020;72:210–219, Fig. 2, p. 214)*

Polyarthritis is characterized by inflammation of five or more joints in both upper and lower extremities (Figs. 196.6 and 196.7). Rheumatoid factor (RF)–positive polyarthritis resembles the characteristic symmetric presentation of adult rheumatoid arthritis. **Rheumatoid nodules** on the extensor surfaces of the elbows, spine, and over the Achilles tendons, although unusual, are associated with a more severe course and almost exclusively occur in RF-positive individuals (Fig. 196.8). **Micrognathia** reflects chronic temporomandibular joint

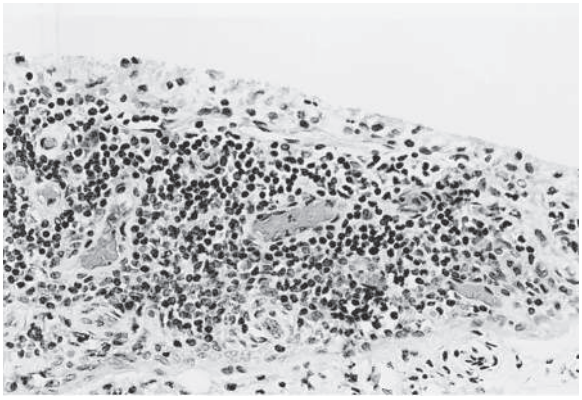

Fig. 196.2 Synovial biopsy specimen from a 10-yr-old child with oligoarticular juvenile idiopathic arthritis. There is a dense infiltration of lymphocytes and plasma cells in the synovium.

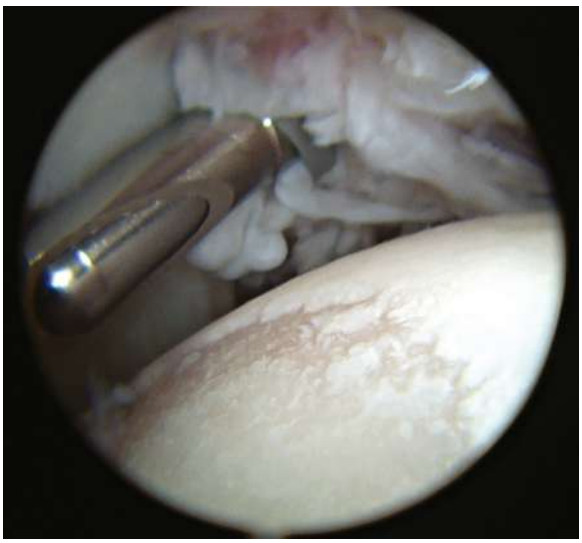

Fig. 196.3 Arthroscopy in the shoulder of a child with juvenile idiopathic arthritis showing pannus formation and cartilage erosions. *(Courtesy Dr. Alison Toth.)*

disease (Fig. 196.9). Cervical spine involvement (Fig. 196.10), manifesting as decreased neck extension, occurs with a risk of atlantoaxial subluxation and neurologic sequelae. Hip disease may be subtle, with findings of decreased or painful ROM on examination (Fig. 196.11).

Systemic JIA is characterized by arthritis (may not be evident on initial presentation), fever, rash, and prominent visceral involvement, including hepatosplenomegaly, lymphadenopathy, and serositis (pericarditis). The characteristic fever, defined as spiking temperatures to ≥39°C (102.2°F), occurs on a daily or twice-daily basis for at least 2 weeks, with a rapid return to normal or subnormal temperatures (Fig. 196.12). The fever is often present in the evening and is frequently accompanied by a characteristic faint, erythematous, macular rash. The evanescent **salmon-colored lesions**, classic for sJIA, are linear or circular and are usually distributed over the trunk and proximal extremities (Fig. 196.13). The classic rash is nonpruritic and migratory with lesions lasting <1 hour. **Koebner phenomenon**, a cutaneous hypersensitivity in which classic lesions are brought on by superficial trauma, is often present. Heat can also evoke rash. Fever, rash, hepatosplenomegaly, and lymphadenopathy are present in >70% of affected children. Without arthritis, the **differential diagnosis** includes the episodic fever (autoinflammatory) syndromes (see Chapter 204), infection (endocarditis, rheumatic fever, brucellosis, multisystem inflammatory syndrome in children [MIS-C]), other rheumatic disorders (systemic lupus erythematosus [SLE], vasculitis syndromes, serum sickness, Kawasaki

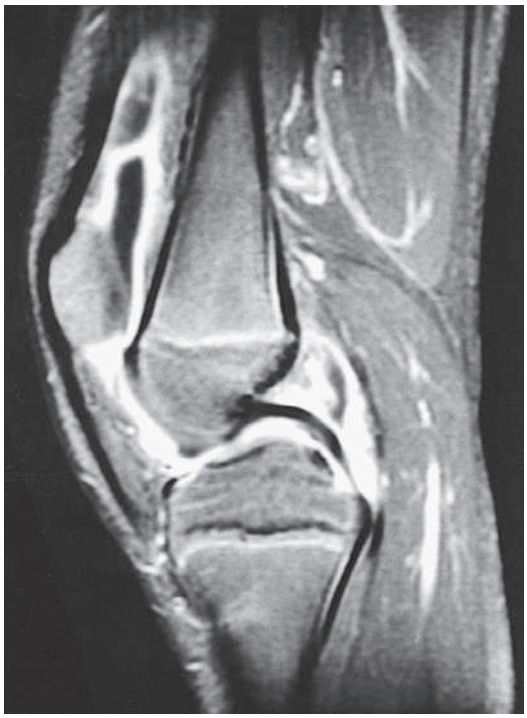

Fig. 196.4 MRI with gadolinium of a 10-yr-old child with juvenile idiopathic arthritis (same patient as in Fig. 196.2). The dense white signal in the synovium near the distal femur, proximal tibia, and patella reflects inflammation. MRI of the knee is useful to exclude ligamentous injury, chondromalacia of the patella, and tumor.

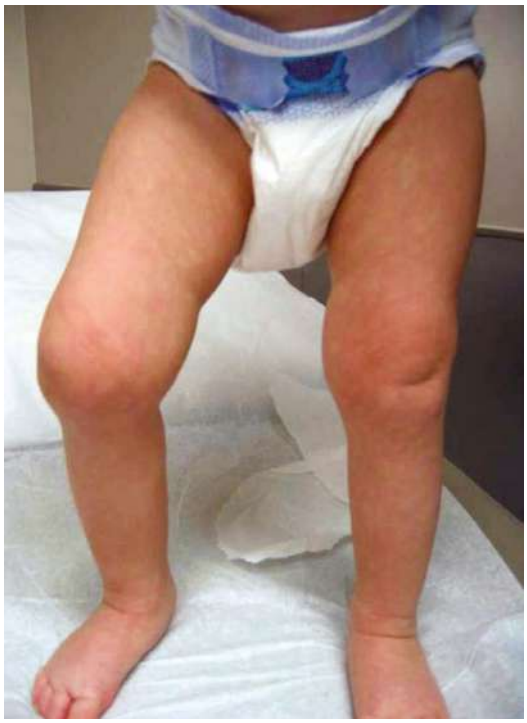

Fig. 196.5 Oligoarticular juvenile idiopathic arthritis with swelling and flexion contracture of the right knee.

disease, sarcoidosis, Castleman disease), inflammatory bowel disease, hemophagocytic lymphohistiocytosis syndromes, and malignancy (leukemia, neuroblastoma, lymphoma). Some children initially present with only systemic features and evolve over time, but definitive

Table 196.5 Frequency of Ophthalmologic Examination in Patients with Juvenile Idiopathic Arthritis

REFERRAL
- Patients should be referred at the time of diagnosis, or suspicion, of JIA

INITIAL SCREENING EXAMINATION
- Should occur as soon as possible and no later than 6 wk from referral
- Symptomatic ocular patients should be seen within a week of referral

ONGOING SCREENING
- Screening at 2-monthly intervals from onset of arthritis for 6 mo
- Followed by 3-4 monthly screening for time outlined below

OLIGOARTICULAR JIA, PSORIATIC ARTHRITIS, AND ENTHESITIS-RELATED ARTHRITIS IRRESPECTIVE OF ANA STATUS, ONSET UNDER 11 YR

AGE AT ONSET (YR)	LENGTH OF SCREENING (YR)
<3	8
3-4	6
5-8	3
9-10	1

POLYARTICULAR, ANA-POSITIVE JIA, ONSET <10 YR

AGE AT ONSET (YR)	LENGTH OF SCREENING (YR)
<6	5
6-9	2

Polyarticular, ANA-negative JIA, onset <7 yr
5-yr screening for all children
Systemic JIA and rheumatoid factor–positive polyarticular JIA
- Uveitis risk very low; however, diagnostic uncertainty in the early stages and overlap of symptoms may mean initial screening is indicated

All categories, onset >11 yr
- 1-yr screening for all children

After stopping immunosuppression (e.g., methotrexate)
- Two-monthly screening for 6 mo, then revert to previous screening frequency as above

After discharge from screening
- Patients should receive advice about regular self-monitoring by checking vision uniocularly once weekly and when to seek medical advice
- Screening may need to continue indefinitely in situations where a young person may be unable to detect a change in vision or be unwilling to seek re-referral
- Annual check by optometrist as a useful adjunct

Data from Clarke SLN, Sen ES, Ramanan AV. Juvenile idiopathic arthritis-associated uveitis. *Pediatr Rheumatol*. 2016;14:27.

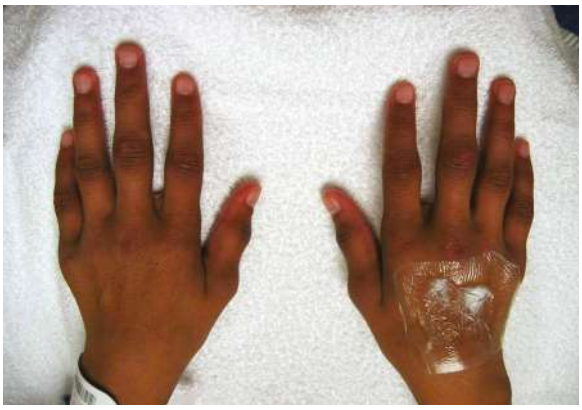

Fig. 196.6 Hands and wrists of a child with polyarticular juvenile idiopathic arthritis, rheumatoid factor negative. Notice the symmetric involvement of the wrists, metacarpophalangeal joints, and proximal and distal interphalangeal joints. In this photograph, there is cream with occlusive dressing on the patient's right hand in preparation for placement of an intravenous line for administration of a biologic agent.

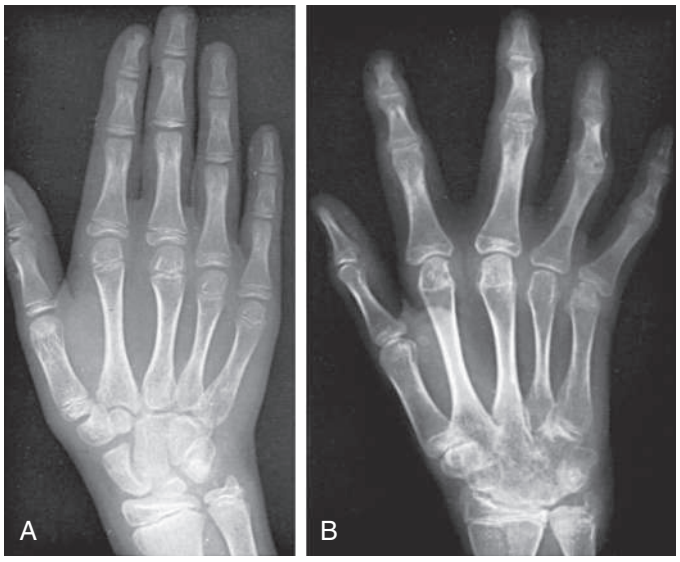

Fig. 196.7 Progression of joint destruction in a child with polyarticular juvenile idiopathic arthritis, rheumatoid factor positive, despite doses of corticosteroids sufficient to suppress symptoms in the interval between radiographs. **A,** Radiograph of the hand at onset. **B,** Radiograph taken 4 years later, showing a loss of articular cartilage and destructive changes in the distal and proximal interphalangeal and metacarpophalangeal joints as well as destruction and fusion of wrist bones.

diagnosis requires the presence of arthritis. Arthritis may affect any number of joints, but the course is classically polyarticular; may be very destructive; and can include hip, cervical spine, and temporomandibular joint involvement.

Macrophage activation syndrome (MAS; see Chapter 207) is a rare but potentially fatal complication of sJIA that can occur at any time (onset, medication change, active or remission) during the disease course. It is also referred to as *secondary hemophagocytic syndrome* or *hemophagocytic lymphohistiocytosis* (HLH) (see Chapter 556.2). There is increasing evidence that sJIA/MAS and HLH share similar functional defects in granule-dependent cytotoxic lymphocyte activity. In addition, sJIA-associated MAS and HLH share genetic variants in approximately 35% of patients with sJIA/MAS. MAS classically manifests as acute onset of high-spiking fevers, lymphadenopathy, hepatosplenomegaly, and encephalopathy. Laboratory evaluation shows thrombocytopenia and leukopenia with elevated liver enzymes, lactate dehydrogenase, ferritin, and triglycerides. Patients may have purpura and mucosal bleeding, as well as elevated fibrin split product values and prolonged prothrombin and partial thromboplastin times. The ESR falls because of hypofibrinogenemia and hepatic dysfunction, a feature useful in distinguishing MAS from a flare of systemic disease (Table 196.6). An international consensus panel developed a set of classification criteria for sJIA-associated MAS, including hyperferritinemia (>684 ng/mL) and any two of the following: thrombocytopenia (≤181 × 10^9/L), elevated liver enzymes (aspartate transaminase >48 U/L), hypertriglyceridemia (>156 mg/dL), and hypofibrinogenemia (≤360 mg/dL) (see Table 196.6). These criteria apply to a febrile patient suspected of sJIA *and* in the absence of disorders such as immune-mediated thrombocytopenia, infectious hepatitis, familial hypertriglyceridemia, or visceral leishmaniasis. *A relative change in laboratory values is likely more relevant in making an early diagnosis than are absolute normal values.* A bone marrow aspiration and biopsy may be helpful in diagnosis, but

Fig. 196.8 Rheumatoid nodules overlying bony prominences in an adolescent with rheumatoid factor–positive polyarthritis. *(From Rosenberg AM, Oen KG. Polyarthritis. In: Cassiday JT, Petty RE, Laxer RM, et al., eds.* Textbook of Pediatric Rheumatology, 6th ed. *Philadelphia: Saunders; 2011: Fig 15-5, p. 257.)*

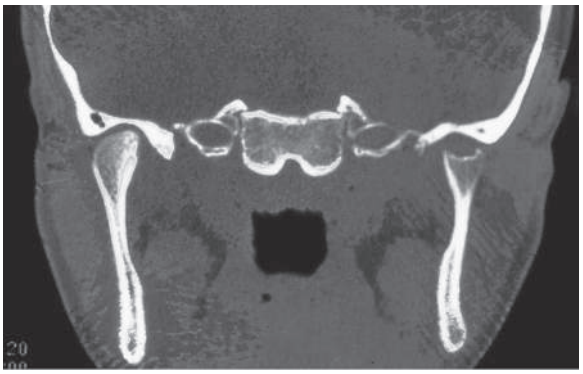

Fig. 196.9 CT scan of the temporomandibular joint of a child with juvenile idiopathic arthritis exhibiting destruction on the right.

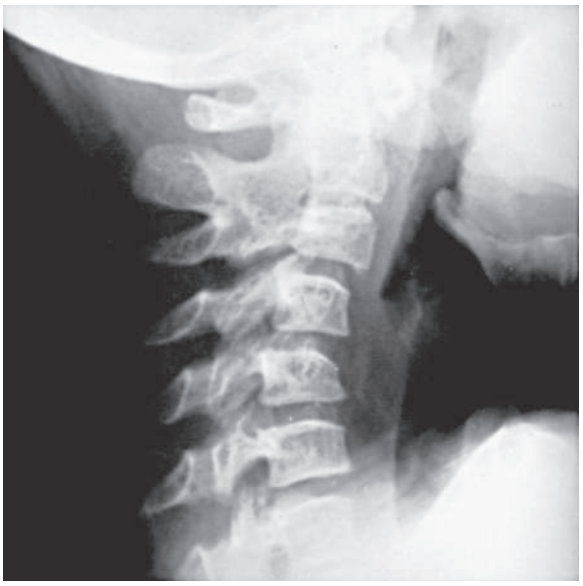

Fig. 196.10 Radiograph of the cervical spine of a child with active juvenile idiopathic arthritis showing fusion of the neural arch between joints C2 and C3, narrowing and erosion of the remaining neural arch joints, obliteration of the apophyseal space, and loss of the normal lordosis.

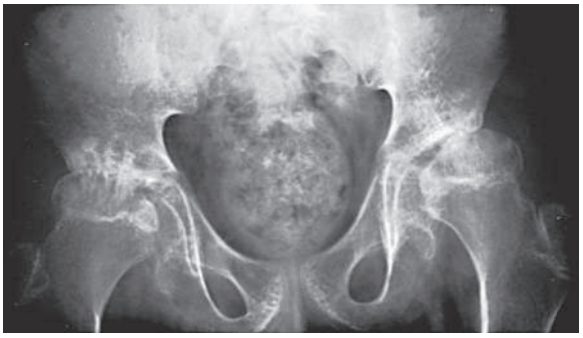

Fig. 196.11 Severe hip disease in 13-yr-old male with active systemic juvenile idiopathic arthritis. Radiograph shows destruction of the femoral head and acetabula, joint space narrowing, and subluxation of left hip. The child had received corticosteroids systemically for 9 years.

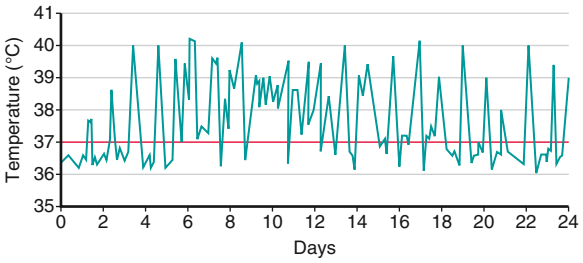

Fig. 196.12 High-spiking intermittent fever in a 3-yr-old child with systemic juvenile idiopathic arthritis. *(From Ravelli A, Martini A. Juvenile idiopathic arthritis.* Lancet *2007;369:767–778.)*

evidence of hemophagocytosis is not always evident. Emergency treatment with high-dose intravenous methylprednisolone, cyclosporine, or anakinra may be effective. Severe cases may require therapy similar to that for primary HLH (see Chapter 556.2).

An inflammatory lung disease has also recently been recognized as a rare but life-threatening complication in children with sJIA. Children can present with little to no respiratory symptoms; acute clubbing can be an early indicator. The predominant pathology is pulmonary alveolar proteinosis and/or endogenous lipoid pneumonia. Compared with children without lung disease, children with sJIA and lung disease are younger at diagnosis, have a history of MAS, have higher serum IL-18 levels, and have higher exposure and adverse reaction rates to cytokine inhibitors. Given the more severe disease course, lung disease in children with sJIA requires a high index of suspicion and prompt evaluation.

Bone mineral metabolism and skeletal maturation are adversely affected in children with JIA, regardless of subtype. Children with JIA have decreased bone mass (osteopenia), which appears to be associated with increased disease activity. Increased levels of cytokines such as TNF-α and IL-6, both key regulators in bone metabolism, have deleterious effects on bone both within the joint and systemically in the axial and appendicular bones. Abnormalities of skeletal maturation become most prominent during the pubertal growth spurt.

DIAGNOSIS

JIA is a clinical diagnosis without any diagnostic laboratory tests. The meticulous clinical exclusion of other diseases and many mimics is therefore essential. Laboratory studies, including tests for ANA and RF,

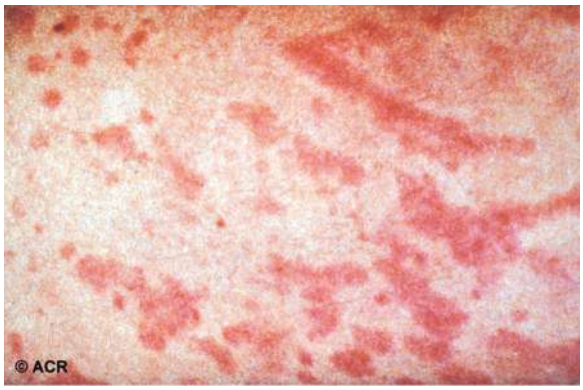

Fig. 196.13 The rash of systemic juvenile idiopathic arthritis is salmon-colored, macular, and nonpruritic. Individual lesions are transient and occur in crops over the trunk and extremities. *(From American College of Rheumatology.* Clinical Slide Collection on the Rheumatic Diseases. *Atlanta, GA: ACR. Copyright 1991, 1995, 1997.)*

Table 196.6 Macrophage Activation Syndrome (MAS)

LABORATORY FEATURES*
1. Cytopenias
2. Abnormal liver function tests
3. Coagulopathy (hypofibrinogenemia)
4. Decreased erythrocyte sedimentation rate
5. Hypertriglyceridemia
6. Hyponatremia
7. Hypoalbuminemia
8. Hyperferritinemia
9. Elevated sCD25 and sCD163
CLINICAL FEATURES*
1. Nonremitting fever
2. Hepatomegaly
3. Splenomegaly
4. Lymphadenopathy
5. Hemorrhages
6. Central nervous system dysfunction (headache, seizures, lethargy, coma, disorientation)
HISTOPATHOLOGIC FEATURES*
1. Macrophage hemophagocytosis in the bone marrow aspirate
2. Increased CD163 staining of the bone marrow
PROPOSED CRITERIA FOR MAS IN SJIA†
1. Serum ferritin >684 ng/mL *and*
2. Any two of the following:
• Thrombocytopenia (≤181 × 10^9/L)
• Elevated liver enzymes (aspartate transaminase >48 U/L)
• Hypertriglyceridemia (>156 mg/dL)
• Hypofibrinogenemia (≤360 mg/dL)

*From Ravelli A, Grom A, Behrens E, Cron R. Macrophage activation syndrome as part of systemic juvenile idiopathic arthritis: Diagnosis, genetics, pathophysiology and treatment. *Genes Immun.* 2012;13:289–298.

†From Ravelli A, Minoia F, Davì S, et al. 2016 Classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation collaborative initiative. *Arthritis Rheumatol.* 2016;68:566–576.

are only supportive or prognostic, and their results may be normal in patients with JIA (see Tables 196.1, 196.3, and 196.4).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for arthritis is broad, and a careful, thorough investigation for other underlying etiology is imperative (Table 196.7). History, physical examination, laboratory tests, and radiography may help exclude other possible causes. Arthritis can be a presenting manifestation for any of the multisystem rheumatic diseases of childhood, including SLE (see Chapter 199), juvenile dermatomyositis (see Chapter 200), sarcoidosis (see Chapter 209), and the vasculitic syndromes (see Chapter 210). In scleroderma (see Chapter 201), limited ROM caused by sclerotic skin overlying a joint may be confused with sequelae from chronic inflammatory arthritis. **Acute rheumatic fever** is characterized by exquisite joint pain and tenderness, remittent fever, and migratory polyarthritis. **Autoimmune hepatitis** can also be associated with an acute arthritis.

Many infections are associated with arthritis, and a recent history of infectious symptoms may help make a distinction. Viruses, including parvovirus B19, rubella, Epstein-Barr virus, hepatitis B virus, and HIV, can induce a transient arthritis. Arthritis may follow enteric infections (see Chapter 198). **Lyme disease** should be considered in children with oligoarthritis living in or visiting endemic areas (see Chapter 268). Although a history of tick exposure, preceding flulike illness, and subsequent rash should be sought, these are not always present. Monoarticular arthritis unresponsive to antiinflammatory treatment may be the result of chronic mycobacterial or other infection, such as *Kingella kingae,* and the diagnosis is established by synovial fluid analysis (polymerase chain reaction [PCR]) or biopsy. Acute onset of fever and a painful, erythematous, hot joint suggests septic arthritis (see Chapter 726). Isolated hip pain with limited ROM suggests suppurative arthritis, osteomyelitis (see Chapter 725), toxic synovitis, Legg-Calvé-Perthes disease, slipped capital femoral epiphysis, and chondrolysis of the hip (see Chapter 719).

Lower-extremity arthritis and tenderness over insertion of ligaments and tendons, especially in a male child, suggest ERA (see Chapter 197). **Psoriatic arthritis** can manifest as limited joint involvement in an unusual distribution (e.g., small joints of the hand and ankle) years before the onset of cutaneous disease. **Inflammatory bowel disease** may manifest as oligoarthritis, usually affecting joints in the lower extremities, as well as gastrointestinal symptoms, elevations in ESR, and microcytic anemia.

Many conditions present solely with arthralgia (i.e., joint pain). Hypermobility may cause joint pain, especially in the lower extremities. Growing pains should be suspected in a child age 4-12 years complaining of leg pain in the evening with normal investigative studies and no morning symptoms. Nocturnal pain that awakens the child also alerts to the possibility of a malignancy. An adolescent with missed school days may suggest a diagnosis of fibromyalgia (see Chapter 211.3).

Children with **leukemia** or **neuroblastoma** may have joint or bone pain resulting from malignant infiltration of the bone, synovium, or more often the bone marrow, sometimes months before demonstrating lymphoblasts on peripheral blood smear. Physical examination may reveal no tenderness, a deeper pain with palpation of the bone, or pain out of proportion to exam findings. Malignant pain often awakens the child from sleep and may cause cytopenias. Because platelets are an acute-phase reactant, a high ESR with leukopenia and a low-normal platelet count may also be a clue to underlying leukemia. In addition, the characteristic quotidian fever of sJIA is absent in malignancy. Bone marrow examination is necessary for diagnosis. Some diseases, such as cystic fibrosis, diabetes mellitus, and the glycogen storage diseases, have associated arthropathies. Swelling that extends beyond the joint can be a sign of lymphedema or IgA vasculitis (formerly Henoch-Schönlein purpura; see Chapter 210.1). A peripheral arthritis indistinguishable from JIA occurs in the humoral immunodeficiencies (see Chapter 165), such as common variable immunodeficiency and X-linked agammaglobulinemia. Skeletal dysplasias associated with a degenerative arthropathy are diagnosed from their characteristic radiologic abnormalities.

Systemic onset of JIA often presents as a fever of unknown origin (see Chapter 222). Important considerations in the differential diagnosis include infections (endocarditis, brucellosis, cat-scratch disease, Q fever, mononucleosis), autoinflammatory disease (see Chapter 204), malignancy (leukemia, lymphoma, neuroblastoma), and HLH.

Table 196.7 Conditions Causing Arthritis or Extremity Pain

RHEUMATIC AND INFLAMMATORY DISEASES
Juvenile idiopathic arthritis
Systemic lupus erythematosus
Juvenile dermatomyositis
Polyarteritis nodosa
Scleroderma
Sjögren syndrome
Behçet disease
Overlap syndromes
Antineutrophilic cytoplasmic antibody (ANCA)–associated vasculitis
Sarcoidosis
Kawasaki syndrome
IgA vasculitis (formerly Henoch-Schönlein purpura)
Chronic recurrent multifocal osteomyelitis

SERONEGATIVE SPONDYLOARTHROPATHIES
Juvenile ankylosing spondylitis
Inflammatory bowel disease
Psoriatic arthritis
Reactive arthritis associated with urethritis, iridocyclitis, and mucocutaneous lesions

INFECTIOUS ILLNESSES
Bacterial arthritis (septic arthritis, *Staphylococcus aureus, Kingella kingae,* pneumococcal, gonococcal, *Haemophilus influenzae*)
Lyme disease
Viral illness (parvovirus, rubella, mumps, Epstein-Barr, hepatitis B, chikungunya)
Fungal arthritis
Mycobacterial infection
Spirochetal infection
Endocarditis

REACTIVE ARTHRITIS
Acute rheumatic fever
Reactive arthritis (postinfectious caused by *Shigella, Salmonella, Yersinia, Chlamydia,* post-streptococcal, or meningococcus)
Serum sickness
Toxic synovitis of the hip
Postimmunization

IMMUNODEFICIENCIES
Hypogammaglobulinemia
Immunoglobulin A deficiency
Common variable immunodeficiency disease (CVID)
Human immunodeficiency virus (HIV)

CONGENITAL AND METABOLIC DISORDERS
Gout
Pseudogout
Mucopolysaccharidoses
Thyroid disease (hypothyroidism, hyperthyroidism)
Hyperparathyroidism
Vitamin C deficiency (scurvy)
Hereditary connective tissue disease (Marfan syndrome, Ehlers-Danlos syndrome)
Fabry disease
Farber disease
Fucosidosis
Amyloidosis (familial Mediterranean fever)

BONE AND CARTILAGE DISORDERS
Trauma
Patellofemoral syndrome
Hypermobility syndromes
Osteochondritis dissecans
Avascular necrosis (including Legg-Calvé-Perthes disease)
Hypertrophic osteoarthropathy
Slipped capital femoral epiphysis
Osteolysis
Benign bone tumors (including osteoid osteoma)
Langerhans cell histiocytosis
Rickets
Idiopathic multicentric osteolysis
Camptodactyly-arthropathy-coxa vara-pericarditis syndrome
Progressive pseudorheumatoid dysplasia
Pachydermodactyly

NEUROPATHIC DISORDERS
Peripheral neuropathies
Carpal tunnel syndrome
Charcot joints

NEOPLASTIC DISORDERS
Leukemia
Neuroblastoma
Lymphoma
Bone tumors (osteosarcoma, Ewing sarcoma)
Histiocytic syndromes
Synovial tumors

HEMATOLOGIC DISORDERS
Hemophilia
Hemoglobinopathies (including sickle cell disease)

MISCELLANEOUS DISORDERS
Autoinflammatory diseases
Recurrent multifocal osteomyelitis
Pigmented villonodular synovitis
Plant-thorn synovitis (foreign body arthritis)
Myositis ossificans
Eosinophilic fasciitis
Tendinitis (overuse injury)
Raynaud phenomenon
Hemophagocytic syndromes

PAIN SYNDROMES
Fibromyalgia
Growing pains
Depression (with somatization)
Complex regional pain syndrome

LABORATORY FINDINGS

Hematologic abnormalities often reflect the degree of systemic or articular inflammation, with elevated white blood cell (WBC) and platelet counts and a microcytic anemia. Inflammation may also cause elevations in ESR and CRP, although it is not unusual for both to be normal in children with JIA.

Elevated ANA titers are present in 40–85% of children with oligoarticular or polyarticular JIA but are rare with sJIA. ANA seropositivity is associated with increased risk of **chronic uveitis** in JIA. Approximately 5–15% of patients with polyarticular JIA are seropositive for RF. Anti–cyclic citrullinated peptide antibody, as with RF, is a marker of more aggressive disease. Both ANA and RF seropositivity can occur in association with transient events, such as viral infection.

Children with sJIA usually have striking elevations in inflammatory markers and WBC and platelet counts. Hemoglobin levels are low, typically 7-10 g/dL, with indices consistent with anemia of chronic disease. The ESR is usually high, except in MAS. Although immunoglobulin levels tend to be high, ANA and RF are uncommon. Ferritin values are typically elevated and can be markedly increased in MAS (>10,000 ng/mL). In the setting of MAS, all cell lines have the potential to decline precipitously because of the consumptive process. A low or normal WBC count and/or platelet count in a child with active sJIA should raise concerns for MAS.

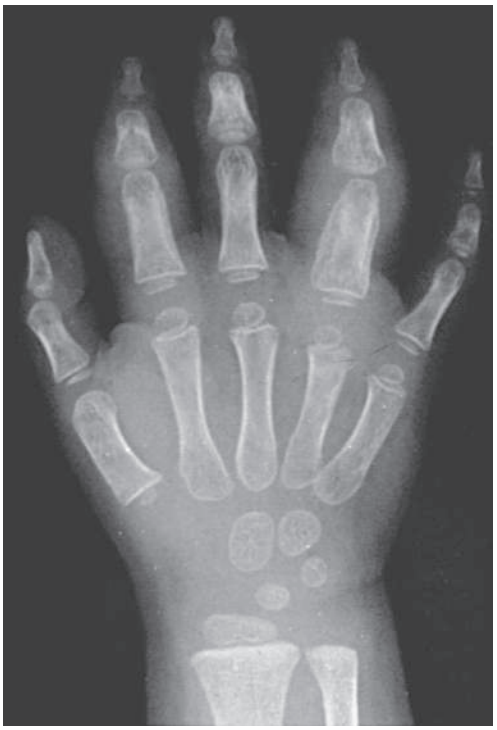

Fig. 196.14 Early (6 month duration) radiographic changes of juvenile idiopathic arthritis. Soft tissue swelling and periosteal new bone formation appear adjacent to the second and fourth proximal interphalangeal joints.

Early radiographic changes of arthritis include soft tissue swelling, periarticular osteopenia, and periosteal new-bone apposition around affected joints (Fig. 196.14). Continued active disease may lead to subchondral erosions, loss of cartilage with varying degrees of bony destruction, and fusion. Characteristic radiographic changes in the cervical spine, most frequently in the neural arch joints at C2-C3 (see Fig. 196.10), may progress to atlantoaxial subluxation. MRI is more sensitive than radiography to detect early changes (Fig. 196.15).

TREATMENT

The goals of treatment are to achieve disease remission, prevent or halt joint damage, and foster normal growth and development. All children with JIA need individualized treatment plans, and management is tailored according to disease subtype and severity, presence of poor prognostic indicators, and response to medications. Disease management also requires monitoring for potential medication toxicities (see Chapter 195).

Children with oligoarthritis often show partial response to nonsteroidal antiinflammatory drugs (NSAIDs), with improvement in inflammation and pain (Table 196.8). Those who have no or partial response after 4-6 weeks of treatment with NSAIDs or who have functional limitations such as joint contracture or leg-length discrepancy benefit from injection of intraarticular corticosteroids. *Triamcinolone hexacetonide* is a long-lasting preparation that provides a prolonged response. A substantial fraction of patients with oligoarthritis show no response to NSAIDs and injections and therefore require treatment with *disease-modifying antirheumatic drugs (DMARDs),* including conventional synthetic DMARDs (csDMARDs) like methotrexate, and, if no response, biologic DMARDs (bDMARDs) like TNF inhibitors.

NSAIDs alone rarely induce remission in children with polyarthritis or sJIA. *Methotrexate* is the oldest and least toxic of the csDMARDs available for adjunctive therapy. It may take 6-12 weeks to see the effects of methotrexate. Failure of methotrexate monotherapy warrants the addition of a bDMARD. bDMARDs that inhibit proinflammatory cytokines, such as TNF-α, IL-1, and IL-6, demonstrate excellent disease control. TNF-α antagonists (e.g., *etanercept, adalimumab, golimumab*) are used to treat children with an inadequate response to methotrexate, poor prognostic factors, or severe disease onset. Early aggressive therapy with a combination of methotrexate and a TNF-α antagonist may result in earlier achievement of clinically inactive disease. *Abatacept,* a selective inhibitor of T-cell activation, and *tocilizumab,* an IL-6

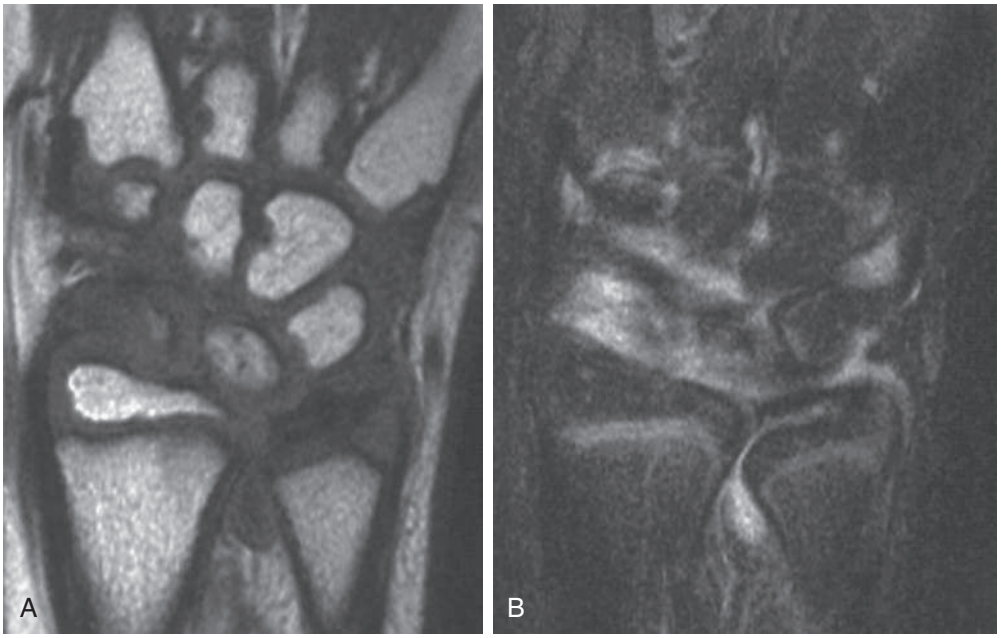

Fig. 196.15 MRI of the wrist in a child with wrist arthritis. **A,** Multiple erosions of carpal bones. **B,** After administration of gadolinium contrast agent, uptake is consistent with active synovitis.

Table 196.8 Pharmacologic Treatment of Juvenile Idiopathic Arthritis (JIA)

TYPICAL MEDICATIONS	TYPICAL DOSES	JIA SUBTYPE	SIDE EFFECT(S)
NONSTEROIDAL ANTIINFLAMMATORY DRUGS			
Naproxen	15 mg/kg/day PO divided bid (maximum dose 500 mg bid)	Polyarthritis Systemic Oligoarthritis	Gastritis, renal and hepatic toxicity, pseudoporphyria
Ibuprofen	40 mg/kg/day PO divided tid (maximum dose 800 mg tid)	Same as above	Same as above
Meloxicam	0.125 mg/kg PO once daily (maximum dose 15 mg daily)	Same as above	Same as above
DISEASE-MODIFYING ANTIRHEUMATIC DRUGS			
Methotrexate	0.5-1 mg/kg PO or SC weekly (maximum dose 25 mg/wk)	Polyarthritis Systemic Persistent or extended oligoarthritis	Nausea, vomiting, oral ulcerations, hepatic toxicity, blood count dyscrasias, immunosuppression, teratogenicity
Sulfasalazine	Initial 12.5 mg/kg PO daily; increase by 10 mg/kg/day Maintenance: 40-50 mg/kg divided bid (maximum dose 2 g/day)	Polyarthritis	GI upset, allergic reaction, pancytopenia, renal and hepatic toxicity, Stevens-Johnson syndrome
Leflunomide*	10-20 mg PO daily	Polyarthritis	GI upset, hepatic toxicity, allergic rash, alopecia (reversible), teratogenicity (needs washout with cholestyramine)
BIOLOGIC AGENTS			
Anti–Tumor Necrosis Factor-α			
Etanercept	0.8 mg/kg SC weekly or 0.4 mg/kg SC twice weekly (maximum dose 50 mg/wk)	Polyarthritis Systemic Persistent or extended oligoarthritis	Immunosuppressant, concern for malignancy, demyelinating disease, lupus-like reaction, injection site reaction
Infliximab*	3-10 mg/kg IV q4-8wk	Same as above	Same as above, infusion reaction
Adalimumab	10 to <15 kg: 10 mg SC every other week 15 to <30 kg: 20 mg SC every other week >30 kg: 40 mg SC every other week	Same as above	Same as above
Golimumab	80 mg/m^2 IV wk 0 and 4 and then q8 wk	Same as above	Same as above
Anticytotoxic T-Lymphocyte–Associated Antigen-4 Immunoglobulin			
Abatacept	<75 kg: 10 mg/kg/dose IV q4wk 75-100 kg: 750 mg/dose IV q4wk >100 kg: 1,000 mg/dose IV q4wk SC once weekly: 10 to <25 kg: 50 mg ≥25 to <50 kg: 87.5 mg ≥50 kg: 125 mg	Polyarthritis	Immunosuppressant, concern for malignancy, infusion reaction
Anti-CD20			
Rituximab*	750 mg/m^2 IV 2 wk × 2 (maximum dose 1,000 mg)	Polyarthritis	Immunosuppressant, infusion reaction, progressive multifocal encephalopathy
Interleukin-1 Inhibitors			
Anakinra*	1-2 mg/kg SC daily	Systemic	Immunosuppressant, GI upset, injection site reaction
Canakinumab	4 mg/kg/dose SC q4wk (maximum dose 300 mg)	Systemic	Immunosuppressant, headache, GI upset, injection site reaction
Rilonacept*	2.2 mg/kg/dose SC weekly (maximum dose 160 mg)	Systemic	Immunosuppressant, allergic reaction, dyslipidemia, injection site reaction
Interleukin-6 Receptor Antagonist			
Tocilizumab	<30 kg: 12 mg/kg/dose IV q2wk (maximum dose 800 mg) 162 mg SC q2wk ≥30 kg: 8 mg/kg/dose IV q2wk (maximum dose 800 mg) 162 mg SC weekly	Systemic	Immunosuppressant, hepatic toxicity, dyslipidemia, cytopenias, GI upset, infusion reaction
	<30 kg: 10 mg/kg/dose IV q4wk (maximum dose 800 mg) 162 mg SC q3wk ≥30 kg: 8 mg/kg/dose IV q4wk 162 mg SC q2wk	Polyarthritis	
Janus Kinase Inhibitors			
Tofacitinib	10 to <20 kg: 3.2 mg PO bid 20 to <40 kg: 4 mg PO bid ≥ 40 kg = 5 mg PO bid	Polyarthritis	Immunosuppressant, GI perforation, thrombosis

*Not indicated by the U.S. Food and Drug Administration for use in JIA as of 2021.

receptor antagonist, have demonstrated efficacy in and are approved for treatment of polyarticular JIA (see Table 196.8).

TNF inhibition is not as effective for the systemic symptoms found in sJIA. When systemic symptoms dominate, systemic corticosteroids are started, followed by the initiation of IL-1 or IL-6 antagonist therapy, which often induces a dramatic and rapid response. Patients with severe disease activity may go directly to anakinra. *Canakinumab,* an IL-1β inhibitor, and tocilizumab are Food and Drug Administration (FDA)–approved treatments for sJIA in children older than 2 years (see Table 196.8). Standardized consensus guiding therapy for sJIA provide four treatment plans based on glucocorticoids, methotrexate, anakinra, or tocilizumab, with optional glucocorticoid use in the latter three plans as clinically indicated.

With the use of DMARDs, the use of systemic corticosteroids can often be avoided or minimized. Systemic corticosteroids are recommended only for management of severe systemic illness, for *bridge therapy* during the wait for therapeutic response to a DMARD, and for control of uveitis. Steroids impose risks of severe toxicities, including Cushing syndrome, growth retardation, and osteopenia, and they do not prevent joint destruction.

Small molecule drugs, including Janus kinase (JAK) inhibitors, are an alternative to csDMARDs and bDMARDs. Oral JAK inhibitors (tofacitinib, ruxolitinib) inhibit JAK signaling pathways involved in immune activation and inflammation. *Tofacitinib* is FDA approved for children older than 2 years with polyarticular JIA.

Management of JIA must include periodic slit-lamp ophthalmologic examinations to monitor for asymptomatic uveitis (Figs. 196.16 and 196.17; see Table 196.4). Optimal treatment of uveitis requires collaboration between the ophthalmologist and rheumatologist; initial management may include mydriatics and corticosteroids used topically, systemically, or through periocular injection. DMARDs allow for a decrease in exposure to steroids, and methotrexate and TNF-α inhibitors (adalimumab and infliximab) are effective in treating severe uveitis.

Dietary evaluation and counseling to ensure appropriate calcium, vitamin D, protein, and caloric intake are important for children with JIA. Physical therapy and occupational therapy are invaluable adjuncts to any treatment program. A social worker and nurse clinician can be important resources for families to recognize stresses imposed by a chronic illness, to identify appropriate community resources, and to aid compliance with the treatment protocol.

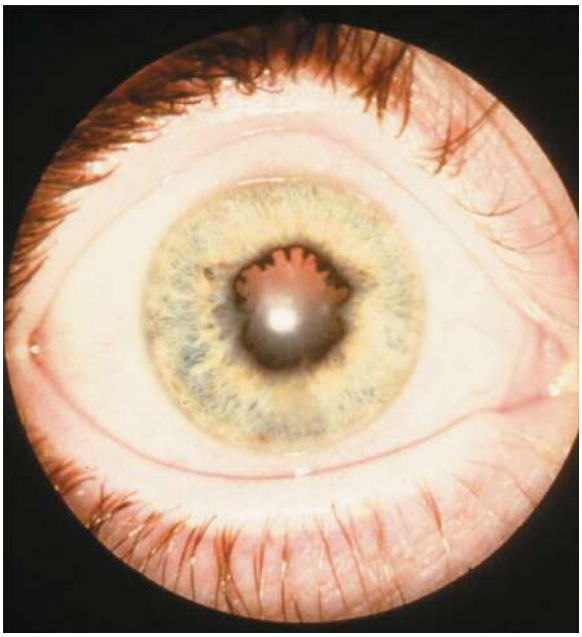

Fig. 196.16 Chronic anterior uveitis demonstrating posterior synechiae and absence of significant scleral inflammation. *(From Firestein GS, Budd RC, Gabriel SE, et al., eds.* Kelley & Firestein's Textbook of Rheumatology, 10th ed. *Philadelphia: Elsevier; 2017: Fig. 107-5, p. 1838.)*

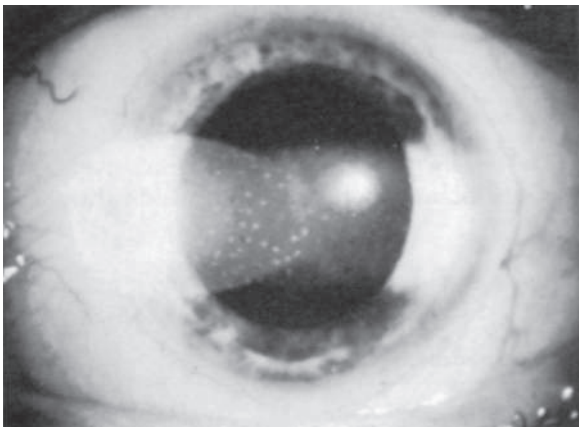

Fig. 196.17 Slit-lamp examination shows "flare" in the fluid of the anterior chamber (caused by increased protein content) and keratic precipitates on the posterior surface of the cornea, representing small collections of inflammatory cells. *(Courtesy Dr. H.J. Kaplan. From Petty RE, Rosenbaum JT. Uveitis in juvenile idiopathic arthritis. In Cassidy JT, Petty RE, Laxer RM, et al., eds.* Textbook of Pediatric Rheumatology, *6th ed. Philadelphia: Saunders; 2011: Fig. 20-3, p. 309.)*

PROGNOSIS

Although the course of JIA in an individual child is unpredictable, some prognostic generalizations can be made on the basis of disease type and course. Studies analyzing management of JIA in the pre–TNF-α era indicate that up to 50% of JIA patients had active disease persisting into early adulthood, often with severe limitations of physical function.

Children with persistent oligoarticular disease fare well, with a majority achieving disease remission. Those with extended oligoarticular disease have a poorer prognosis. Children with oligoarthritis, particularly females who are ANA positive and with onset of arthritis before 6 years of age, are at greatest risk for development of chronic uveitis. There is no association between the activity or severity of arthritis and uveitis. Persistent, uncontrolled anterior uveitis (see Fig. 196.16) can cause posterior synechiae, cataracts, glaucoma, and band keratopathy, with resultant blindness. Morbidity can be averted with early diagnosis and implementation of systemic therapy.

The child with polyarticular JIA often has a more prolonged course of active joint inflammation and requires early and aggressive therapy. Predictors of severe and persistent disease include young age at onset, RF seropositivity or rheumatoid nodules, presence of anti–cyclic citrullinated peptide antibodies, and many affected joints. Disease involving the hip and hand/wrist is also associated with a poorer prognosis and may lead to significant functional impairment.

sJIA is often the most difficult to control in terms of both articular inflammation and systemic manifestations. Poorer prognosis is related to polyarticular distribution of arthritis, fever lasting >3 months, and increased inflammatory markers, such as platelet count and ESR, for >6 months. IL-1 and IL-6 inhibitors have changed the management and improved the outcomes for children with severe and prolonged systemic disease.

Orthopedic complications include leg-length discrepancy and flexion contractures, particularly of the knees, hips, and wrists. Discrepancies in leg length can be managed with a shoe lift on the shorter side to prevent secondary scoliosis. Joint contractures require aggressive medical control of arthritis, often in conjunction with intraarticular corticosteroid injections, appropriate splinting, and stretching of the affected tendons. Popliteal cysts may require no treatment if they are small or respond to intraarticular corticosteroids in the anterior knee.

Psychosocial adaptation may be affected by JIA. Studies indicate that, compared with controls, a significant number of children with JIA have problems with lifetime adjustment and employment. Disability not directly associated with arthritis may continue into young adulthood in as many as 20% of patients, together with continuing chronic pain syndromes at a similar frequency. Psychological complications, including problems with school attendance and socialization, may respond to counseling by mental health professionals.

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Chapter 197

Ankylosing Spondylitis and Other Spondyloarthritides

Pamela F. Weiss

The diseases collectively referred to as *spondyloarthritides* include ankylosing spondylitis (AS), arthritis associated with inflammatory bowel disease (IBD) or psoriasis, and reactive arthritis after gastrointestinal (GI) or genitourinary (GU) infections (Table 197.1 and Table 197.2). **Spondyloarthritis** is more common in adults, but all forms can present during childhood with varying symptoms and signs. Many children with spondyloarthritis are classified in the **juvenile idiopathic arthritis (JIA)** categories of **enthesitis-related arthritis (ERA)** or psoriatic arthritis. Children and adolescents with spondyloarthritis who may not meet JIA criteria include arthritis associated with IBD, juvenile ankylosing spondylitis (JAS), and reactive arthritis.

EPIDEMIOLOGY

JIA is diagnosed in 90 per 100,000 U.S. children every year (see Chapter 196). ERA accounts for 10–20% of JIA and has a mean age at onset of 12 years. In India, ERA is the most common category of JIA, accounting for 35% of cases. Unlike other JIA categories, males are affected more often than females, accounting for 60% of ERA cases. AS occurs in 0.2–0.5% of adults, with approximately 15% of cases beginning in childhood. These disorders can be familial, largely as a result of the influence of human leukocyte antigen (HLA)-B27, which is found in 90% of JAS and 50% of ERA patients compared to 7% of healthy individuals. Approximately 20% of children with ERA have a family history of HLA-B27–associated disease, such as reactive arthritis, AS, or IBD with sacroiliitis.

ETIOLOGY AND PATHOGENESIS

Spondyloarthritides are complex diseases in which susceptibility is largely genetically determined. Only 30% of heritability has been defined, with HLA-B27 responsible for two thirds of the total, and >100 additional genetic loci accounting for only one third. Genes that influence interleukin (IL)-23 responses (e.g., *CARD9, IL23R, JAK2, TYK2, STAT3*) and the function of HLA-B27 *(ERAP1)* are particularly important. Unusual properties of HLA-B27, such as its tendency to misfold and form abnormal cell surface structures, may have a role. Infection with certain GI or GU pathogens can trigger reactive arthritis (see Table 197.2 and Chapter 198). Altered gut microbiota and an abnormal immune response to normal microbiota may also play a role in pathogenesis. Inflamed joints and entheses in spondyloarthritis contain T and B cells, macrophages, osteoclasts, proliferating fibroblasts, and osteoblasts, with activation of the IL-23/IL-17 pathway. Bone loss and osteoproliferation in and around vertebral bodies and facet joints in long-standing AS contribute to significant morbidity.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Clinical manifestations that help distinguish spondyloarthritis from other forms of juvenile arthritis include arthritis of the axial skeleton (sacroiliac joints or spine) and hips, enthesitis (inflammation at the site of a tendon, ligament, or joint capsule attachment to bone), symptomatic eye inflammation (acute anterior uveitis), and GI inflammation (even in the absence of IBD) (Table 197.3, but see also Table 197.1).

Enthesitis-Related Arthritis

Children fulfill classification criteria for ERA if they have *either* arthritis and enthesitis *or* arthritis or enthesitis with at least two of the following characteristics: (1) sacroiliac joint tenderness or inflammatory lumbosacral pain, (2) presence of HLA-B27, (3) onset of arthritis in a male older than 6 years, (4) acute anterior uveitis, and (5) a family history of an HLA-B27–associated disease (ERA, sacroiliitis with IBD, reactive arthritis, or acute anterior uveitis) in a first-degree relative. Patients with psoriasis (or a family history of psoriasis in a first-degree relative), a positive–rheumatoid factor (RF) test result, or systemic arthritis are excluded from this group. During the first 6 months of disease the arthritis is typically

Table 197.1 Overlapping Characteristics of the Spondyloarthritides*

CHARACTERISTIC	JUVENILE ANKYLOSING SPONDYLITIS	JUVENILE PSORIATIC ARTHRITIS	INFLAMMATORY BOWEL DISEASE	REACTIVE ARTHRITIS
Enthesitis	+++	+	+	++
Axial arthritis	+++	++	++	+
Peripheral arthritis	+++	+++	+++	+++
HLA-B27 positive	+++	+	++	+++
Antinuclear antibody positive	–	++	–	–
Rheumatoid factor positive	–	–	–	–
SYSTEMIC DISEASE				
Eyes	+	+	+	+
Skin	–	+++	+	+
Mucous membranes	–	–	+	+
Gastrointestinal tract	–	–	++++	+++

*Frequency of characteristics: –, absent; +, <25%; ++, 25–50%; +++, 50–75%; ++++, ≥75%.
From Petty RE, Laxer RM, Lindsley CB, et al., eds. *Textbook of Pediatric Rheumatology,* 8th ed. Philadelphia: Elsevier; 2021.

Table 197.2 Etiologic Microorganisms of Reactive Arthritis

PROBABLE	POSSIBLE
Chlamydia trachomatis	*Neisseria gonorrhoeae*
Shigella species	*Mycoplasma fermentans*
Salmonella enteritidis	*Mycoplasma genitalium*
Salmonella typhimurium	*Ureaplasma urealyticum*
Yersinia enterocolitica	*Escherichia coli*
Yersinia pseudotuberculosis	*Cryptosporidium*
Campylobacter jejuni and *coli*	*Entamoeba histolytica*
	Giardia lamblia
	Brucella abortus
	Clostridium difficile
	Streptococcus pyogenes
	Chlamydia pneumoniae
	Chlamydia psittaci

From Kim PS, Klausmeier TL, Orr DP. Reactive arthritis: a review. *J Adolesc Health.* 2009;44:309–315, Table 2, p. 311.

Table 197.3 Assessment in SpondyloArthritis International Society (ASAS) Classification Criteria for Spondyloarthritis (SpA)

AXIAL SpA		PERIPHERAL SpA
In patients with ≥3 months back pain and age at onset <45 years		In patients with peripheral symptoms ONLY
Sacroiliitis on imaging* *plus* one or more SpA feature(s)	***or*** **HLA-B27** *plus* two or more other SpA features	**Arthritis** *or* **enthesitis** *or* **dactylitis** *plus*
SpA features • Inflammatory back pain (IBP) • Arthritis • Enthesitis (heel) • Uveitis • Dactylitis • Psoriasis • Crohn disease/ulcerative colitis • Good response to NSAIDs • Family history for SpA • HLA-B27 • Elevated CRP		One or more SpA feature(s): • Uveitis • Psoriasis • Crohn disease/ulcerative colitis • Preceding infection • HLA-B27 • Sacroiliitis on imaging* *or* Two or more other SpA features: • Arthritis • Enthesitis • Dactylitis • IBP ever • Family history for SpA

*Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA. Definite radiographic sacroiliitis according to modified NY criteria.
CRP, C-reactive protein; NSAIDs, nonsteroidal antiinflammatory drugs.
Adapted from Rudwaleit M, van der Heijde D, Landewé R, et al. The development of Assessment of Spondyloarthritis International Society classification criteria for axial spondyloarthritis. Part II. Validation and final selection. *Ann Rheum Dis.* 2009;68(6):777–783; and The Assessment of Spondyloarthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Ann Rheum Dis.* 2011;70(1):25–31.

Table 197.4 Symptoms Characteristic of Inflammatory Back Pain

Pain at night with morning stiffness (and improvement on arising)
No improvement with rest
Improvement with exercise
Insidious onset
Good response to nonsteroidal antiinflammatory drugs

asymmetric and involves fewer than four joints, most frequently the knees, ankles, and hips. Inflammation of the small joints of the foot, or *tarsitis*, is highly suggestive of ERA. Enthesitis is typically symmetric and affects the lower limbs. Up to 40% of children develop clinical or radiographic evidence of sacroiliac joint arthritis as part of their disease; approximately 20% have evidence of sacroiliac joint arthritis at diagnosis. When the sacroiliac or other axial joints are involved, children may experience **inflammatory back pain** (Table 197.4), hip pain, and alternating buttock pain. Patients may also experience pain with palpation of the lower back or with pelvic compression. The risk of sacroiliac joint arthritis is highest in children who are HLA-B27 positive and have an elevated C-reactive protein (CRP). Untreated sacroiliitis may, but does not always, evolve into AS; additional risk factors for progression are unclear.

Psoriatic Arthritis

Psoriatic arthritis accounts for approximately 5% of JIA. Common clinical features of psoriatic arthritis are nail pitting (Fig. 197.1), onycholysis, and dactylitis (sausage-like swelling of fingers or toes).

Children fulfill classification criteria for psoriatic arthritis if they have arthritis and psoriasis *or* arthritis and at least two of the following: (1) dactylitis, (2) nail pitting or onycholysis, and (3) psoriasis in a first-degree relative. The presence of psoriasis aids in diagnosis but is not required. Disease onset peaks during the preschool and early adolescent years. Children with onset during the preschool years are more often female, antinuclear antibody (ANA) positive, and at risk for asymptomatic ocular inflammation. Disease onset during adolescence is equally common among males and females. In the majority

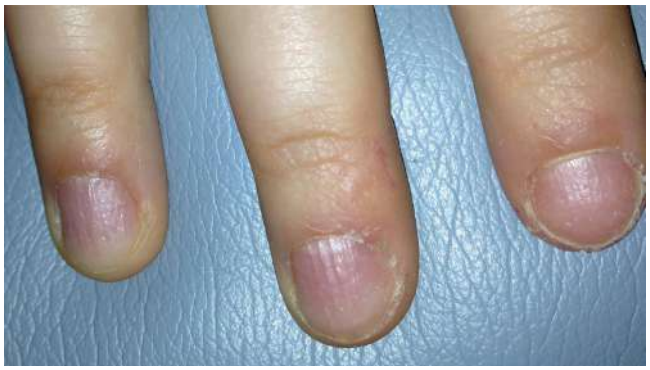

Fig. 197.1 Nail pitting in a 9-year-old with JPsA. (*From Srinivasalu H, Sikora KA, Colbert RA. Recent updates in juvenile spondyloarthritis. Rheum Dis Clin N Am. 2021;47:565–583, Fig. 2, p. 569.*)

of children, the arthritis is asymmetric and affects four or fewer joints at presentation. Large (knees and ankles) and small (fingers and toes) joints may be involved. Although distal interphalangeal joint involvement is uncommon, it is highly suggestive of the diagnosis. Enthesitis is detectable in ~20–75% of patients and seems to be more frequent in those who present at an older age (Table 197.5, Fig. 197.2). Axial (sacroiliac) and root (hip) joints may be affected in up to 30% of children; the risk of axial arthritis is highest in those who are HLA-B27 positive.

Table 197.5 Entheseal Sites Studied in Historical JSpA Cohorts

ENTHESEAL SITES	PERCENTAGE
Insertion of infrapatellar tendon on patella	27-44
Achilles tendon	21-74
Interosseous ligaments of the sacroiliac joint	30.3
Plantar fascia insertion to calcaneus	12-39
Tibial tuberosity	23-30
Quadriceps insertion to upper poles of patella	22-46
Second MTP	21
Third MTP	16
First MTP	14
Greater trochanter	14
Iliac crest	14

JSpA, Juvenile spondyloarthritis; MTP, metatarsophalangeal.
From Srinivasalu H, Sikora KA, Colbert RA. Recent updates in juvenile spondyloarthritis. *Rheum Dis Clin N Am.* 2021;47:565–583, Table 1, p. 567.

Juvenile Ankylosing Spondylitis

JAS frequently begins with oligoarthritis and enthesitis. The arthritis occurs predominantly in the lower extremities and often involves the hips. In comparison to adult-onset AS, axial disease and inflammatory back pain are less frequent at disease onset, whereas enthesitis and peripheral arthritis are more common. AS is diagnosed according to the modified New York (NY) criteria if there is sufficient radiographic evidence of sacroiliitis (sacroiliitis of grade 2 or greater bilaterally or at least grade 3 unilaterally) and if the patient meets at least one clinical criterion involving inflammatory back pain, limitation of motion in the lumbar spine (Fig. 197.3), or limitation of chest expansion. JAS is present if the patient is <16 years old. Juvenile-*onset* AS is frequently used to describe adult AS when the symptoms began before 16 years of age but full criteria were not met until later.

To fulfill the modified NY criteria for AS, patients must have radiographic changes in the sacroiliac joints and clinical sequelae of axial disease. Because radiographic sacroiliitis can take many years to develop in adults and even longer in children, and clinical sequelae may lag further behind, criteria to identify preradiographic axial spondyloarthritis were developed by the **Assessment of SpondyloArthritis International Society**. To meet criteria for axial spondyloarthritis (SpA), patients must have at least 3 months of back pain and sacroiliitis on imaging (acute inflammation on MRI or definite radiographic sacroiliitis by NY criteria) plus one feature of SpA (inflammatory back pain, arthritis, enthesitis [heel], uveitis, dactylitis, psoriasis, Crohn disease/ulcerative colitis, good response to nonsteroidal antiinflammatory drugs [NSAIDs], family history for SpA, HLA-B27, or elevated CRP). Alternatively, patients can fulfill axial SpA criteria if they are HLA-B27 positive and have at least two SpA features. These criteria have low sensitivity and specificity in the pediatric population but, in the absence of alternative pediatric criteria, may be useful as a guide to evaluating preradiographic axial SpA.

Arthritis with Inflammatory Bowel Disease

The presence of erythema nodosum, pyoderma gangrenosum, oral ulcers, abdominal pain, diarrhea, fever, weight loss, or anorexia in a child with chronic arthritis should raise suspicion of IBD. Two patterns of arthritis complicate IBD. **Polyarthritis** affecting large and small joints is most common and often reflects the activity of the intestinal inflammation. Less frequently, **arthritis of the axial skeleton**, including the sacroiliac joints, occurs. As with psoriatic arthritis, the presence of HLA-B27 is a risk factor for the development of axial disease. The severity of axial involvement is independent of the activity of the GI inflammation.

LABORATORY FINDINGS

Laboratory evidence of systemic inflammation with elevation of the erythrocyte sedimentation rate (ESR) and/or CRP value is variable in most spondyloarthritides and may or may not be present at the onset of disease. RF and ANAs are absent, except in children with psoriatic arthritis, as many as 50% of whom are ANA positive. HLA-B27 is present in approximately 90% of children with JAS, compared with 7% of healthy individuals, but is less frequent in ERA and other SpA types.

Imaging

Conventional radiographs detect chronic bony changes and damage but not active inflammation and are unreliable in the assessment of pediatric disease. Early radiographic changes in the sacroiliac joints include indistinct margins and erosions. **Sclerosis** typically starts on the iliac side of the joint (Fig. 197.4). Peripheral joints may exhibit periarticular **osteoporosis**, with loss of sharp cortical margins in areas of enthesitis, which may eventually show erosions or bony spurs (enthesophytes). Squaring of the corners of the vertebral bodies and syndesmophyte formation resulting in the classic "bamboo spine" characteristic of advanced AS are rare in early disease, particularly in childhood. CT, like radiographs, can detect chronic bony changes but not active inflammation and has the disadvantage of more radiation exposure. The gold standard for early visualization of sacroiliitis is evidence of bone marrow edema adjacent to the joint on MRI with fluid-sensitive sequences such as short-T1 inversion recovery (STIR) (Figs. 197.5 and 197.6). Gadolinium does not add value to the study of the sacroiliac joints if STIR is used. MRI will reveal abnormalities before the plain radiograph. Whole

Anatomic region	Enthesitis exam
Foot and ankle	Achilles tendon insertion to calcaneus Plantar fascia insertion to calcaneus Plantar fascia insertion to metatarsal heads Plantar fascia insertion to base of fifth metatarsal
Knee	Quadriceps tendon insertion to patella (2 and 10 o'clock) Infrapatellar ligament insertion to patella (6 o'clock) and tibial tuberosity
Pelvis	Hip extensor insertion at greater trochanter of femur Sartorius insertion at anterior superior iliac spine Posterior superior iliac spine Abdominal muscle insertions to iliac crest Gracilis and adduction insertion to pubis symphysis Hamstrings insertion to ischial tuberosity
Spine	5th lumbar spinous process
Upper extremity	Common flexor insertion at medial epicondyle of humerus Common extensor insertion at lateral epicondyle of humerus Supraspinatus insertion into greater tuberosity of humerus
Chest	Costosternal junctions (1st and 7th)

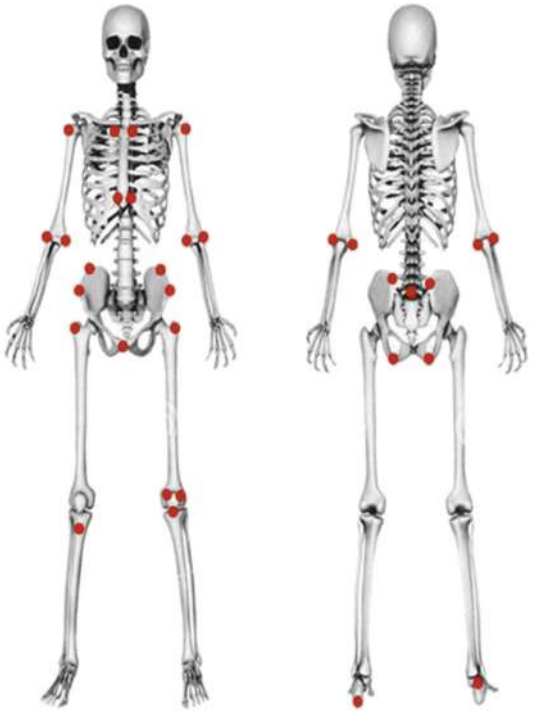

Fig. 197.2 Anatomic sites for assessment of enthesitis in ERA and JAS. (*From Petty RE, Laxer RM, Lindsley CB, et al., eds. Textbook of Pediatric Rheumatology, 8th ed. Philadelphia: Elsevier; 2021: Fig. 20.1, p. 254.*)

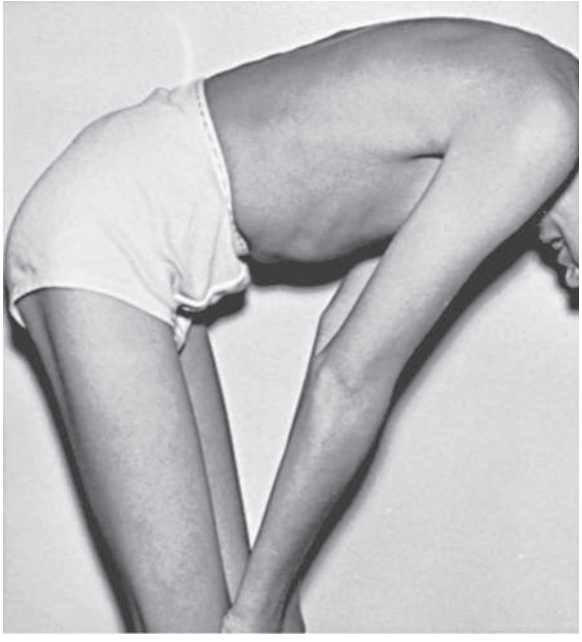

Fig. 197.3 Loss of lumbodorsal spine mobility in a boy with ankylosing spondylitis. The lower spine remains straight when the patient bends forward.

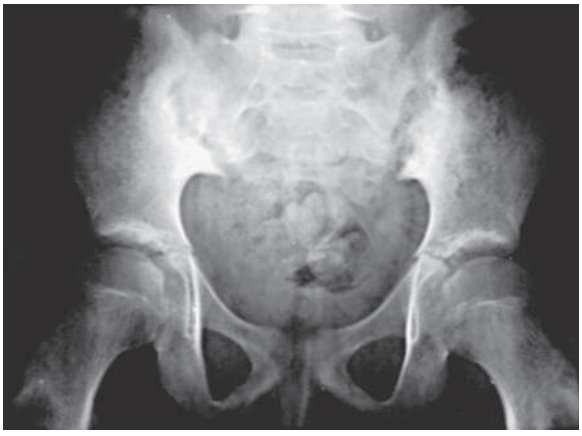

Fig. 197.4 Well-developed sacroiliitis in a boy with ankylosing spondylitis. Both sacroiliac joints show extensive sclerosis, erosion of joint margins, and apparent widening of the joint space.

body MRI may also be used to evaluate the axial skeleton in adults with early disease because it can detect vertebral lesions in addition to sacroiliac changes.

DIFFERENTIAL DIAGNOSIS

The onset of arthritis after a recent history of diarrhea or symptoms of urethritis or conjunctivitis may suggest **reactive arthritis** (see Chapter 198). Lower back pain can be caused by strain, infectious arthritis of the sacroiliac joint, osteomyelitis of the pelvis or spine, chronic nonbacterial osteomyelitis (CNO) of the pelvis or spine, osteoid osteoma of the posterior elements of the spine, pelvic muscle pyomyositis, or malignancies. In addition, mechanical conditions such as spondylolysis, spondylolisthesis, and Scheuermann disease should be considered. Back pain secondary to **fibromyalgia** usually affects the soft tissues of the upper back in a symmetric pattern and is associated with well-localized tender points and sleep disturbance (see Chapter 211.3). Legg-Calvé-Perthes disease (avascular necrosis of the femoral head), slipped capital femoral epiphysis, and chondrolysis may also manifest as pain over the inguinal ligament and loss of internal rotation of the hip joint, but without other SpA features, such as involvement of other entheses and/or joints. Radiography and MRI are critical for distinguishing these conditions.

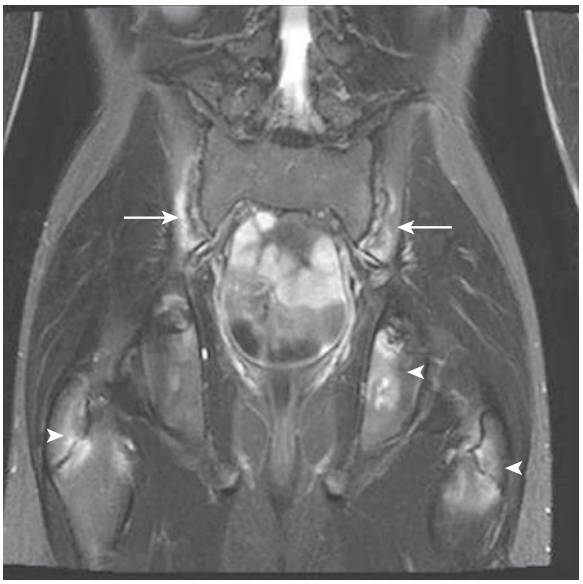

Fig. 197.5 Coronal MRI (STIR) of the pelvis in a 14-year-old boy with ERA (HLA-B27 positive). Fluid and pathology appear bright, spinal fluid also appears bright. Increased signal abnormality is observed around bilateral triradiate cartilages and greater trochanteric apophyses *(arrowheads),* common areas of involvement for ERA. Also, signal abnormality appears on the iliac side of the sacroiliac joints bilaterally around more curvilinear, dark, sclerotic subchondral areas representing erosions and sacroiliitis *(arrows).* (*From Tse SM, Laxer RM. New advances in juvenile spondyloarthritis. Nat Rev Rheumatol. 2012;10;8:269–279.*)

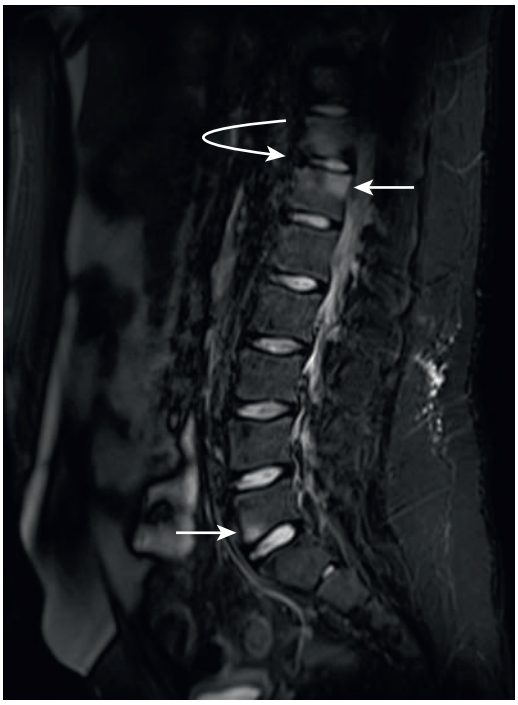

Fig. 197.6 Short T1 inversion recovery image from whole body MRI of a 15-yr-old boy with HLA-B27–negative JSpA. The MRI shows active corner inflammatory lesions of vertebral end plates at multiple levels *(straight arrows)* and more chronic-appearing discovertebral unit changes *(curved arrow).* (*From Srinivasalu H, Sikora KA, Colbert RA. Recent updates in juvenile spondyloarthritis. Rheum Dis Clin N Am. 2021;47:565–583, Fig. 7, p. 574.*)

TREATMENT

The goals of therapy are to control inflammation, minimize pain, preserve function, and prevent ankylosis (fusion of adjacent bones) using a combination of antiinflammatory medications, physical therapy, and education. Treatment regimens for SpA include monotherapy or combination therapy with NSAIDs, disease-modifying antirheumatic drugs (DMARDs), or biologic agents. NSAIDs, such as naproxen (15-20 mg/kg/day), are frequently used to help relieve symptoms and may slow the progression of structural damage (syndesmophyte formation and growth) if used continually. With relatively mild monoarticular disease, intraarticular corticosteroids (e.g., triamcinolone acetonide/hexacetonide) may also help to control peripheral joint inflammation. DMARDs such as sulfasalazine (up to 50 mg/kg/day; maximum 3 g/day) or methotrexate (10 mg/m^2) may be beneficial for peripheral arthritis, but these medications have not been shown to improve axial disease in adults. For axial arthritis, it is typically necessary to add a biologic therapy. Tumor necrosis factor (TNF) inhibitors (e.g., etanercept, infliximab, adalimumab) have been efficacious in reducing symptoms and improving function in adults with AS. It remains unclear whether TNF inhibitors have an impact on structural damage in established AS, underscoring the need for earlier recognition and better therapies. Drugs that target IL-17 (secukinumab/ixekizumab), IL-23/IL-12 (ustekinumab), and the JAK/STAT pathway (tofacitinib/upadacitinib) reduce clinical disease activity in adults with AS.

Physical therapy and low-impact exercise should be included in the treatment program for all children with spondyloarthritis. Exercise to maintain range of motion in the back, thorax, and affected joints should be instituted early in the disease course. Custom-fitted insoles and heel cups are particularly useful in the management of painful entheses around the feet, and the use of pillows to position the lower extremities while the child is in bed can be helpful.

PROGNOSIS

Observational studies suggest that ongoing disease activity for >5 years in juvenile spondyloarthritis predicts disability. Disease remission occurs in <20% of children with spondyloarthritis 5 years after diagnosis. Factors associated with disease progression include tarsitis, HLA-B27 positivity, hip arthritis within the first 6 months, and disease onset after age 8. Important questions, such as which patients with ERA will go on to have JAS/AS, have yet to be addressed. Outcomes for JAS compared with adult-onset AS suggest that hip disease requiring replacement is more common in children but axial disease is more severe in adults.

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Chapter 198

Reactive and Postinfectious Arthritis

Pamela F. Weiss

In addition to causing arthritis by means of direct microbial infection (i.e., septic arthritis; see Chapter 726), microbes activate innate and adaptive immune responses, which can lead to the generation and deposition of immune complexes and antibody or T-cell–mediated cross-reactivity with self. Furthermore, microbes may influence the immune system in ways that promote immune-mediated inflammatory diseases such as systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), juvenile idiopathic arthritis (JIA), and spondyloarthritis. **Reactive arthritis** and **postinfectious arthritis** are defined as joint inflammation caused by a sterile inflammatory reaction after a recent infection. The term *reactive arthritis* is used to refer to arthritis that occurs after enteropathic or urogenital infections and *postinfectious arthritis* to describe arthritis that occurs after infectious illnesses not classically considered in the reactive arthritis group, such as infection with group A streptococcus or viruses. In some patients, nonviable components of the initiating organism have been demonstrated in affected joints, and the presence of viable, yet nonculturable, bacteria within the joint remains an area of investigation.

The course of reactive arthritis is variable and may remit or progress to a chronic spondyloarthritis, including ankylosing spondylitis (see Chapter 197). In postinfectious arthritis, the pain or joint swelling is usually transient, lasting <6 weeks, and does not necessarily share the typical spondyloarthritis pattern of joint involvement. The distinction between postinfectious arthritis and reactive arthritis is not always clear, either clinically or pathophysiologically.

PATHOGENESIS

Reactive arthritis typically follows enteric infection with Salmonella species, *Shigella flexneri, Yersinia enterocolitica, Campylobacter jejuni,* or genitourinary (GU) tract infection with *Chlamydia trachomatis*. *Escherichia coli* and *Clostridium difficile* are also causative enteric agents, although less common (see Table 197.2). Acute **rheumatic fever** caused by group A streptococcus (see Chapters 229 and 229.1), arthritis associated with infective endocarditis (see Chapter 486), and the tenosynovitis associated with *Neisseria gonorrhoeae* are similar in some respects to reactive arthritis.

Approximately 75% of patients with reactive arthritis are HLA-B27 positive. Incomplete elimination of bacteria and bacterial products, such as DNA, has been proposed as a factor in reactive arthritis. A relationship with clinical characteristics of specific infectious disorders is not present. In postinfectious arthritis, several viruses (rubella, varicella-zoster, herpes simplex, cytomegalovirus) have been isolated from the joints of patients. Antigens from other viruses (e.g., hepatitis B, adenovirus) have been identified in immune complexes from joint tissue.

Patients with reactive arthritis who are HLA-B27 positive have an increased frequency of acute and symptomatic uveitis and other extraarticular features. In addition, HLA-B27 is a risk factor for persistent gastrointestinal (GI) inflammation after enteric infections, even after resolution of the initial infection, and significantly increases the risk that the individual will develop chronic spondyloarthritis. Nevertheless, reactive arthritis also occurs in HLA-B27–negative patients, emphasizing the importance of other genes in disease susceptibility.

CLINICAL MANIFESTATIONS AND DIFFERENTIAL DIAGNOSIS

Symptoms of reactive arthritis begin approximately 3 days to 6 weeks after infection. The classic triad of arthritis, urethritis, and conjunctivitis is relatively uncommon in children. The arthritis is typically asymmetric and oligoarticular, with a predilection for the lower extremities. Dactylitis may occur, and enthesitis is common, affecting as many as 90% of patients (Fig. 198.1). Cutaneous manifestations can occur and may include circinate balanitis, ulcerative vulvitis, erythematous oral macules or plaques or erosions, erythema nodosum, paronychia, painful erosions or pustules on fingertips, and keratoderma blennorrhagica, which is similar in appearance to pustular psoriasis (Fig. 198.2). Systemic symptoms may include fever, malaise, and fatigue. Less common features may include conjunctivitis, optic neuritis, aortic valve involvement, sterile pyuria, and polyneuropathy. Early in the disease course, markers of inflammation—erythrocyte sedimentation rate (ESR), C-reactive protein, and platelets—may be greatly elevated. The clinical manifestations may last for weeks to months.

Familiarity with other causes of postinfectious arthritis is vital when a diagnosis of reactive arthritis is being considered. Numerous viruses are associated with postinfectious arthritis and may result in particular patterns of joint involvement (Table 198.1). Rubella and hepatitis B virus typically affect the small joints, whereas mumps and varicella often involve large joints, especially the knees. **Hepatitis B arthritis–dermatitis syndrome** is characterized by urticarial rash and a symmetric migratory polyarthritis resembling that of serum sickness. Rubella-associated arthropathy may follow natural rubella infection and, infrequently, rubella immunization. It typically occurs in young women, with an increased frequency with advancing age, and is uncommon in preadolescent children and in males. Arthralgia of the knees and hands usually begins within 7 days of onset of the rash or 10-28 days after immunization. Parvovirus B19, which is responsible for erythema infectiosum (fifth disease), can cause arthralgia, symmetric

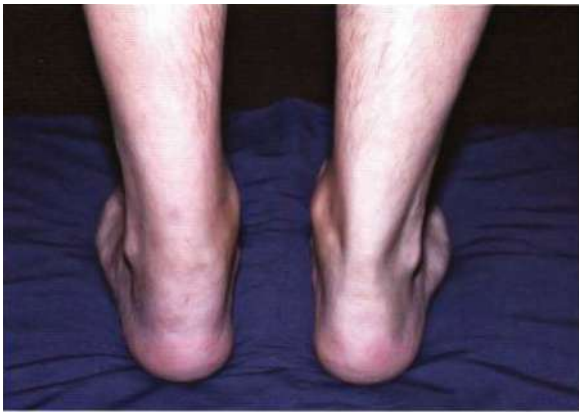

Fig. 198.1 Enthesitis—swelling of the posterior aspect of the left heel and lateral aspect of the ankle. *(Courtesy Dr. Nora Singer, Case Western Reserve University and Rainbow Babies' Hospital.)*

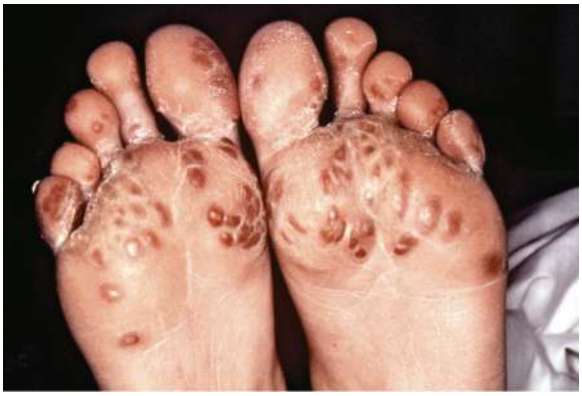

Fig. 198.2 Keratoderma blennorrhagica. *(Courtesy Dr. MF Rein and the Centers for Disease Control and Prevention Public Health Image Library, 1976. Image #6950.)*

Table 198.1 Viruses Associated with Arthritis

TOGAVIRUSES	HERPESVIRUSES
RUBIVIRUS	Epstein-Barr
Rubella	Cytomegalovirus
ALPHAVIRUSES	Varicella-zoster
Ross River	Herpes simplex
Chikungunya	PARAMYXOVIRUSES
O'nyong-nyong	Mumps
Mayaro	FLAVIVIRUS
Sindbis	Zika virus
Ockelbo	HEPADNAVIRUS
Pogosta	Hepatitis B
ORTHOPOXVIRUSES	ENTEROVIRUSES
Variola virus (smallpox)	Echovirus
Vaccinia virus	Coxsackievirus B
Parvoviruses	CORONAVIRUSES
ADENOVIRUSES	SARS-CoV-2
Adenovirus 7	

Adapted from Infectious arthritis and osteomyelitis. In: Petty RE, Laxer RM, Lindsley CB, et al., eds. *Textbook of Pediatric Rheumatology,* 8th ed. Philadelphia: Elsevier; 2021.

joint swelling, and morning stiffness, particularly in adult women and less frequently in children. Arthritis occurs occasionally during cytomegalovirus infection and may occur during varicella infections but is rare after Epstein-Barr virus infection. Varicella may also be complicated by suppurative arthritis, usually secondary to group A streptococcus infection. HIV is associated with an arthritis that resembles psoriatic arthritis more than JIA (see Chapter 196).

Poststreptococcal arthritis may follow infection with either group A or group G streptococcus. It is typically oligoarticular, affecting lower-extremity joints, and mild symptoms can persist for months. Poststreptococcal arthritis differs from rheumatic fever, which typically manifests with painful migratory polyarthritis of brief duration. Because valvular lesions have occasionally been documented by echocardiography after the acute illness, some clinicians consider poststreptococcal arthritis to be an incomplete form of acute rheumatic fever (see Chapter 229.1). Certain HLA-DRB1 types may predispose children to development of either poststreptococcal arthritis (HLA-DRB1*01) or acute rheumatic fever (HLA-DRB1*16).

Transient synovitis (toxic synovitis), another form of postinfectious arthritis, typically affects the hip, often after an upper respiratory tract infection (see Chapter 719.2). Males 3-10 years of age are most often affected and have acute onset of severe pain in the hip (groin), with referred pain to the thigh or knee, lasting approximately 1 week. ESR and white blood cell count are usually normal. Radiologic or ultrasound examination may confirm widening of the joint space secondary to an effusion. Aspiration of joint fluid is often necessary to exclude septic arthritis and typically results in dramatic clinical improvement. The trigger is presumed to be viral, although responsible microbes have not been identified.

Nonsuppurative arthritis has been reported in children, usually adolescent males, in association with severe truncal acne. Patients often have fever and persistent infection of the pustular lesions. **Pyogenic (sterile) arthritis, pyoderma gangrenosum, and acne (cystic) syndrome**, an autosomal dominant disorder caused by a pathogenic variant in the *PSTPIP1* gene, is a difficult-to-treat but rare autoinflammatory disorder that has responded to anakinra or anti–tumor necrosis factor antibody therapy in a few patients (see Chapter 710). Recurrent episodes of erosive arthritis begin in childhood; cystic acne and the painful ulcerating lesions of pyoderma gangrenosum begin during adolescence. Recurrent episodes may also be associated with a sterile myopathy and may last for several months.

Infective endocarditis can be associated with arthralgia, arthritis, or signs suggestive of vasculitis, such as Osler nodes, Janeway lesions, and Roth spots. Postinfectious arthritis, perhaps because of immune complexes, also occurs in children with *N. gonorrhoeae, Neisseria meningitidis, Haemophilus influenzae* type b, and *Mycoplasma pneumoniae* infections.

DIAGNOSIS

A recent GU or GI infection may suggest the diagnosis of reactive arthritis, but there is no diagnostic test. A complete blood count, acute-phase reactants, complete metabolic panel, and urinalysis may be helpful to exclude other etiologies. Although stool or urogenital tract cultures can be performed in an attempt to isolate it, the triggering organism is not typically found at the time arthritis presents. Imaging findings are nonspecific or normal. Documenting previous streptococcal infection with antibody testing (anti-streptolysin O and anti-DNAse B) may help to diagnose postinfectious arthritis. Serum sickness associated with the antibiotic treatment of preceding infection must be excluded.

Because the preceding infection can be remote or mild and often not recalled by the patient, it is also important to rule out other causes of arthritis. Acute and painful arthritis affecting a single joint suggests septic arthritis, mandating joint aspiration. Osteomyelitis may cause pain and an effusion in an adjacent joint but is more often associated with focal bone pain and tenderness at the site of infection. Arthritis affecting a single joint, particularly the knee, may also be secondary to Lyme disease in endemic areas. The diagnosis of postinfectious arthritis is often established by exclusion and after the arthritis has resolved. Arthritis associated with GI symptoms or abnormal liver function test results may be triggered by infectious or autoimmune hepatitis. Arthritis or spondyloarthritis may occur in children with IBD, such as Crohn disease or ulcerative colitis (see Chapters 382.1 and 382.2). Parvovirus infection, macrophage activation (hemophagocytic) syndrome, and leukemia should be strongly considered when two or more blood cell lines are low or progressively decrease in a child with arthritis. Persistent arthritis (>6 weeks) suggests the possibility of a chronic rheumatic disease, including JIA (see Chapter 196) and SLE (see Chapter 199).

TREATMENT

Specific treatment is unnecessary for most cases of reactive or postinfectious arthritis. Nonsteroidal antiinflammatory drugs (NSAIDs) are often needed for management of pain and functional limitation. Unless ongoing *Chlamydia* infection is suspected, attempts to treat the offending organism are not warranted. If swelling or arthralgia recurs, further evaluation may be necessary to exclude active infection or evolving rheumatic disease. Intraarticular corticosteroid injections may be given for refractory or severely involved joints once acute infection has been ruled out. Systemic corticosteroids or disease-modifying antirheumatic drugs (DMARDs) are rarely indicated but may be considered for chronic disease. Participation in physical activity should be encouraged, and physical therapy may be needed to maintain normal function and prevent muscle atrophy. For postinfectious arthritis caused by streptococcal disease, current recommendations include penicillin prophylaxis for at least 1 year. Long-term prophylaxis is often recommended, but the duration is controversial and may need to be individualized.

COMPLICATIONS AND PROGNOSIS

Postinfectious arthritis after viral infections usually resolves without complications unless it is associated with involvement of other organs, such as **encephalomyelitis**. Children with reactive arthritis after enteric infections occasionally experience IBD months to years after onset. Both **uveitis** and **carditis** have been reported in children diagnosed with reactive arthritis. Reactive arthritis, especially after bacterial enteric infection or GU tract infection with *C. trachomatis,* has the potential for evolving to chronic arthritis, particularly spondyloarthritis (see Chapter 197). The presence of HLA-B27 or significant systemic features increases the risk of chronic disease.

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Chapter 199

Systemic Lupus Erythematosus

Rebecca E. Sadun and Stacy P. Ardoin

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by multisystem inflammation and the presence of circulating autoantibodies directed against self-antigens. SLE occurs in both children and adults, disproportionately affecting females of reproductive age. Although nearly every organ may be affected, most commonly involved are the skin, joints, kidneys, blood-forming cells, blood vessels, and the central nervous system. Systemic signs of inflammation such as fever and lymphadenopathy can also be seen. Compared with adults, children and adolescents with SLE have more severe disease and more widespread organ involvement.

ETIOLOGY

The pathogenesis of SLE remains largely unknown, but several factors likely influence risk and severity of disease, including genetics, hormonal milieu, and environmental exposures.

A genetic predisposition to SLE is suggested by the association with specific genetic variants, including congenital deficiencies of C1q, C2, and C4, as well as several polymorphisms (e.g., interferon regulatory factor 5 and protein tyrosine phosphatase N22) and familial clustering of SLE or other autoimmune disease (Table 199.1). In addition, certain human leukocyte antigen (HLA) types (including HLA-B8, HLA-DR2, and HLA-DR3) occur with increased frequency in patients with SLE. Although SLE clearly has a genetic component, its occurrence is sporadic in families and its concordance is incomplete (estimated at 2–5% among dizygotic twins and 25–60% among monozygotic twins), suggesting nonmendelian genetics and involvement of epigenetic and environmental factors. Patients with SLE often have family members—especially mothers and sisters—with SLE or various other autoimmune diseases.

Because SLE preferentially affects females, especially during their reproductive years, it is suspected that hormonal factors are important in pathogenesis. Of individuals with SLE, 90% are female, making female sex the strongest risk factor for SLE. Estrogens are likely to play a role in SLE, and both in vitro and animal model studies suggest that estrogen exposure promotes B-cell autoreactivity. Estrogen-containing oral contraceptives do not appear to induce flares in quiescent SLE, though the risk of flares may be increased in postmenopausal women receiving hormone replacement.

Environmental exposures that may trigger the development of SLE remain largely unknown; certain viral infections (including Epstein-Barr virus) may play a role in susceptible individuals, and ultraviolet light exposure is known to trigger SLE disease activity. Environmental influences also may induce epigenetic modifications to DNA, increasing the risk of SLE and drug-induced lupus; in mouse models, drugs such as procainamide and hydralazine can promote lymphocyte hypomethylation, causing a lupus-like syndrome.

EPIDEMIOLOGY

The reported prevalence of SLE in children and adolescents (1-6/100,000) is lower than that in adults (20-70/100,000). Prevalence of SLE is highest among patients of African, Asian, Hispanic, Native American, and Pacific Island ancestry for both adult and pediatric populations. SLE predominantly affects females, with a reported 2-5:1 ratio before puberty, 9:1 ratio during reproductive years, and return to near-prepubertal ratios in the postmenopausal period. Childhood SLE is rare before 5 years of age and is usually diagnosed in adolescence, with a median age at diagnosis of 11-12 years. Up to 20% of all individuals with SLE are diagnosed before age 16 years. Pediatric-onset SLE (pSLE) is defined as onset of symptoms before age 16 or 18 years.

PATHOLOGY

Histologic features most suggestive of SLE include findings in the kidney and skin. Renal manifestations of SLE are classified histologically according to the criteria of the International Society of Nephrology (see Chapter 560.2). The finding of diffuse proliferative glomerulonephritis (class IV) significantly increases the risk for renal morbidity. Renal biopsies are helpful to establish the diagnosis of SLE and to stage disease. Immune complexes are commonly found with "full house" deposition of immunoglobulin and complement. The characteristic **discoid rash** depicted in Figure 199.1D is characterized on biopsy by hyperkeratosis, follicular plugging, and infiltration of mononuclear cells into the dermal-epidermal junction. The histopathology of photosensitive rashes can be nonspecific, but immunofluorescence examination of both affected and nonaffected skin may reveal deposition of immune complexes within the dermal-epidermal junction. This finding is called the *lupus band test,* which is specific for SLE.

PATHOGENESIS

A hallmark of SLE is the generation of *autoantibodies* directed against self-antigens, particularly nucleic acids. These intracellular antigens are ubiquitously expressed but are usually inaccessible and cloistered within the cell. During cell necrosis or *apoptosis,* the antigens are released. SLE skin cells are highly susceptible to damage from ultraviolet light, and the resulting cell death leads to release of cell contents, including nucleic antigens. Individuals with SLE may have impaired apoptosis or impaired ability to clear cell debris, causing prolonged exposure to nucleic antigens in the bloodstream and increased opportunity for recognition by immune cells, leading to B-cell stimulation and autoantibody production. Circulating autoantibodies form *immune complexes* and deposit in tissues, leading to local complement activation, initiation of a proinflammatory cascade, and, ultimately, tissue damage. Antibodies to **double-stranded DNA** (dsDNA) can form immune complexes, deposit in glomeruli, and initiate inflammation leading to glomerulonephritis. However, many individuals with SLE have circulating antibodies to dsDNA yet do not have nephritis, suggesting that autoantibodies are not the only pathway leading to end-organ damage in SLE.

Both the innate and adaptive arms of the immune system have been implicated in the dysregulation of the immune system seen in SLE. High levels of interferon-α production by plasmacytoid dendritic cells promote expression of other proinflammatory cytokines and chemokines, maturation of monocytes into myeloid dendritic cells, promotion of autoreactive B and T cells, and loss of self-tolerance. Nearly 85% of patients with SLE exhibit this cytokine profile, known as the *type I interferon signature*. Other cytokines with increased expression in SLE include interleukin (IL)-1, IL-2, IL-6, IL-10, IL-12, IL-17, and IL-21; anti–tumor necrosis factor-α; interferon-γ; and *B-lymphocyte stimulator (BLyS)*, also known as *B-cell–activating factor (BAFF)*. Both B and T cells demonstrate functional impairments in SLE. In active SLE, B-cell populations have impaired tolerance and increased autoreactivity, enhancing B cells' ability to produce autoantibodies after exposure to self-antigen. In addition, cytokines such as BLyS/BAFF may promote abnormal B-cell number and function. T-cell abnormalities in SLE include increased numbers of memory T cells and decreased number and function of T-regulatory cells. SLE T cells display aberrant signaling and increased autoreactivity. As a result, they are resistant to attrition by normal apoptosis pathways. In addition, a neutrophil signature can be identified in 65% of adult SLE patients and has recently been recognized as a potential biomarker for active lupus nephritis.

Table 199.1 Reviewed Proteins and Genes Associated with Monogenic Forms of Systemic Lupus Erythematosus and Lupus-Like Phenotypes

PROTEIN	GENE	INHERITANCE	MECHANISM	FEMALE-TO-MALE PATIENT RATIO	ASSOCIATED SYMPTOMS
C1q	*C1QA, C1QB, C1QC*	Autosomal recessive	Complement deficiency	1:1	SLE (cutaneous, renal, CNS, arthritis, ANA), young age onset, recurrent bacterial infections
C1r/s	*C1R, C1S*	Autosomal recessive	Complement deficiency	1:1	SLE (fever, cutaneous, arthritis, renal, ANA, ENA), recurrent infections, encapsulated bacteria, Hashimoto thyroiditis
C2	*C2*	Autosomal recessive	Complement deficiency	7:1	SLE (cutaneous, arthritis), young age onset, type 1 diabetes
C3	*C3*	Autosomal recessive	Complement deficiency	1:1	Recurrent sinopulmonary infections, lupus-like syndrome, glomerulonephritis
C4	*C4A, C4B*	Autosomal recessive	Complement deficiency	1:1	SLE (severe photosensitive rash, renal, ANA, Ro), young age onset
TREX1/DNASE III	*TREX1*	Autosomal dominant (FCL), autosomal recessive and dominant (AGS)	Abnormal DNA clearance leading to IFN activation	Likely 1:1	FCL, AGS, SLE
MDA5	*IFIH1*	Autosomal dominant	Activation of IFN production	Likely 1:1	AGS, SLE, FCL, IgA deficiency
SAMHD1	*SAMHD1*	Autosomal recessive and dominant	Abnormal DNA or RNA clearance leading to IFN production	Likely 1:1	AGS, SLE, FCL, photosensitivity
RNaseH2	*RNASH2*	Autosomal dominant and recessive	Abnormal RNA clearance leading to IFN production	Likely 1:1	AGS, SLE
ADAR1	*ADAR1*	Mainly autosomal dominant	Abnormal RNA clearance leading to IFN production	Likely 1:1	AGS, SLE
STING	*TMEM173*	Autosomal dominant	Activation of IFN production	1:1	SAVI, FCL, SLE
DNase I	*DNASE1*	Autosomal dominant	Abnormal DNA clearance-break intolerance	Likely 1:1	SLE (dsDNA), adolescent onset, Sjögren syndrome
DNase 1-like-3	*DNASE1L3*	Autosomal recessive	Abnormal DNA clearance-break intolerance	1:2	SLE (hypocomplementemia, dsDNA, cANCA, renal), HUVS
DNASE2	*DNASE2*	Possible autosomal recessive	Abnormal DNA clearance	1:1	Neonatal-onset cytopenias, hepatosplenomegaly, arthritis, nephritis
Protein kinase C-delta	*PRKCD*	Autosomal recessive; dominant	Disrupts B-cell proliferation and apoptosis, NK-cell activity	1:1	Early onset SLE nephritis, lymphoproliferation autoimmunity
Ras/MAPK Pathway	*KRAS GoF*	Somatic mutation	Altered cell proliferation, differentiation, apoptosis	Likely 1:1	Pancytopenia, autoantibodies, arthritis, hepatosplenomegaly, pericarditis
Noonan syndrome	*NRAS GoF*	Somatic mutation	Altered cell proliferation, differentiation apoptosis	Likely 1:1	Chilblain lupus, pancytopenia, autoantibodies

AGS, Aicardi-Goutières syndrome; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; CNS, central nervous system; dsDNA, double-stranded DNA; ENA, extractable nuclear antigen antibody; FCL, familial chilblain lupus; GOF, gain of function; HUVS, hypocomplementemic urticarial vasculitis syndrome; IFN, interferon; IgA, immunoglobulin A; SAVI, STING-associated vasculopathy with onset in infancy; SLE, systemic lupus erythematosus.

Modified from Hiraki LT, Silverman ED. Genomics of systemic lupus erythematosus: insights gained by studying monogenic young-onset systemic lupus erythematosus. *Rheum Dis Clin N Am.* 2017;43:415–434, Table 1, p. 417.

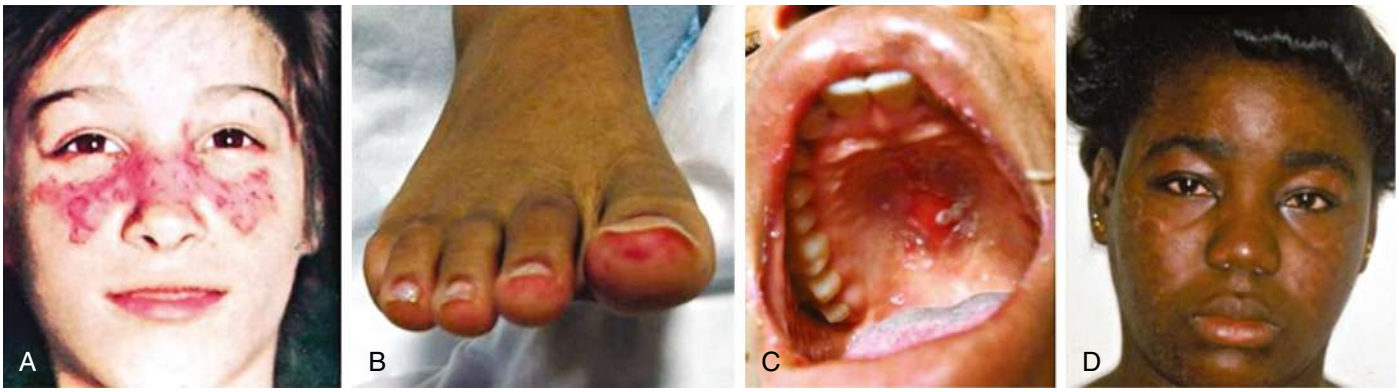

Fig. 199.1 Mucocutaneous manifestations of SLE. A, Malar rash. B, Vasculitic rash on toes. C, Oral mucosal ulcers. D, Discoid rash in malar distribution.

Table 199.2 Potential Clinical Manifestations of Systemic Lupus Erythematosus

TARGET ORGAN	POTENTIAL CLINICAL MANIFESTATIONS
Constitutional	Fatigue, anorexia, weight loss, fever, lymphadenopathy
Musculoskeletal	Arthritis, myositis, tendonitis, arthralgias, myalgias, avascular necrosis, osteoporosis
Skin	Malar rash, discoid (annular) rash, photosensitive rash, cutaneous vasculitis (petechiae, palpable purpura, digit ulcers, gangrene, urticaria), livedo reticularis, periungual capillary abnormalities, Raynaud phenomenon, alopecia, oral and nasal ulcers, panniculitis, chilblains, alopecia
Renal	Hypertension, proteinuria, hematuria, edema, nephrotic syndrome, renal failure
Cardiovascular	Pericarditis, myocarditis, conduction system abnormalities, Libman-Sacks endocarditis
Neurologic	Seizures, psychosis, cerebritis, stroke, transverse myelitis, depression, cognitive impairment, headaches, migraines, pseudotumor, peripheral neuropathy (mononeuritis multiplex), chorea, optic neuritis, cranial nerve palsies, acute confusional states, dural and cerebral venous sinus thrombosis
Pulmonary	Pleuritis, interstitial lung disease, pulmonary hemorrhage, pulmonary hypertension, pulmonary embolism
Hematologic	Immune-mediated cytopenias (hemolytic anemia, thrombocytopenia or leukopenia), anemia of chronic inflammation, hypercoagulability, thrombocytopenic thrombotic microangiopathy, macrophage activation syndrome
Gastroenterology	Hepatosplenomegaly, pancreatitis, vasculitis affecting bowel, protein-losing enteropathy, peritonitis
Ocular	Retinal vasculitis, scleritis, episcleritis, papilledema, dry eyes, optic neuritis

CLINICAL MANIFESTATIONS

Any organ system can be involved in SLE, so the potential clinical manifestations are myriad (Table 199.2). The presentation of SLE in childhood or adolescence differs somewhat from that seen in adults. The most common presenting complaints of children with SLE include fever, fatigue, hematologic abnormalities, arthralgia, and arthritis. Arthritis is usually present in the first year of diagnosis; arthritis may be painful or painless swelling, often with stiffness in the morning, and is usually a **symmetric polyarthritis** affecting large and small joints. Tenosynovitis is often present, but joint erosions or other radiographic changes are rare.

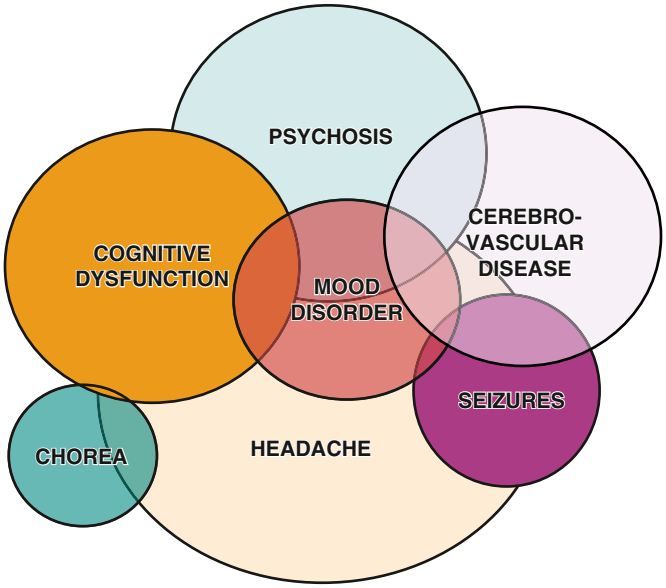

Fig. 199.2 Overlapping neuropsychiatric symptoms in pediatric SLE. Patients with pediatric SLE most commonly have more than one neuropsychiatric symptom—in particular for seizures. (*From Silverman E, Eddy A. Systemic lupus erythematosus. In Cassidy JT, Petty RE, Laxer RM, et al., eds. Textbook of Pediatric Rheumatology, 6th ed. Philadelphia: Saunders; 2011: Fig. 21-17, p. 329.*)

Renal disease in SLE is often asymptomatic, underscoring the need for careful monitoring of blood pressure and urinalyses; in adolescents, SLE can present with **nephrotic syndrome** and/or **renal failure**, with the predominant symptoms being edema, fatigue, changes in urine color, and nausea/vomiting. Because SLE symptoms and findings may develop serially over several years and not all be present simultaneously, the diagnosis may require longitudinal follow-up. SLE is often characterized by periods of flare and disease quiescence but may follow a more smoldering disease course. The **neuropsychiatric complications** of SLE may occur with or without apparently active SLE, posing a particularly difficult diagnostic challenge in adolescents, who are already at high risk for mood disorders (Fig. 199.2). Long-term complications of SLE and its therapy, including accelerated atherosclerosis and osteoporosis, become clinically evident in early to middle adulthood. SLE is a disease that evolves over time in each affected individual, and new manifestations arise even many years after diagnosis.

Table 199.3 Comparison of 1997 American College of Rheumatology and 2012 Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria for Systemic Lupus Erythematosus*

	1997 ACR CRITERIA*	2012 SLICC CRITERIA*
CLINICAL CRITERIA Acute cutaneous lupus	• Malar rash†	• Malar rash, bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, photosensitive lupus rash, or subacute cutaneous lupus†
Chronic cutaneous lupus	• Discoid rash	• Classic discoid rash, hypertrophic (verrucous) lupus, lupus panniculitis (profundus), mucosal lupus, lupus erythematous tumidus, chilblains lupus, or discoid lupus/lichen planus overlap
Mucosal ulcers	• Oral or nasal ulcers	• Oral (palate, buccal, tongue) or nasal ulcers
Other cutaneous	• Photosensitivity	• Nonscarring alopecia
Arthritis	• Nonerosive arthritis in ≥ two peripheral joints	• Synovitis in ≥ two peripheral joints
Serositis	• Pleuritis or pericarditis	• Pleurisy or pericardial pain ≥1 day, pleural effusion or rub, pericardial effusion or rub, or ECG evidence of pericarditis
Renal	• Persistent proteinuria representing > 500 mg/24 hr or cellular casts	• Urine protein/creatinine ratio representing >500 mg protein/24 hr or red blood cell casts
Neurologic	• Seizure or psychosis	• Seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, or acute confusional state
Hematologic	• Hemolytic anemia, leukopenia (<4,000/mm^3, lymphopenia (<1,500/mm^3), or thrombocytopenia (<100,000/mm^3)	• Hemolytic anemia • Leukopenia (<4,000/mm^3) or lymphopenia (<1,000/mm^3) • Thrombocytopenia (<100,000/mm^3)
IMMUNOLOGIC	• Positive anti-double-stranded antibody or positive anti-Smith antibody • Positive antiphospholipid antibody (false-positive rapid plasma reagin test, positive lupus anticoagulant test result, or elevated anticardiolipin antibody level [IgG or IgM]) • Positive ANA	• Positive anti-double-stranded DNA antibody • Positive anti-Smith antibody • Positive antiphospholipid antibody (false-positive rapid plasma regain test, positive lupus anticoagulant test, medium to high titer anticardiolipin antibody level [IgA, IgG, IgM], or positive anti-B2-glycoprotein I antibody [IgA, IgG, IgM]) • Low C3, C4, or Ch50 level • Positive direct Coombs test (in the absence of hemolytic anemia) • Positive ANA

*For the 1997 ACR Criteria, the presence of 4 of 11 cumulative criteria establishes the classification of SLE. For the 2012 SLICC criteria, the presence of 4 cumulative criteria also establishes the classification of SLE; however, at least 1 clinical criterion and at least 1 immunologic criterion are required. In addition, the presence of biopsy-proven lupus nephritis with positive ANA or anti–double-stranded DNA satisfies the 2012 SLICC criteria. For both sets of classification criteria, all items must be attributable to lupus and not an alternate cause (e.g., medication side effect).

†Each bullet point counts as a single criterion whether 1 or more definitions are satisfied.

Adapted from Hochberg MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus, *Arthritis Rheum* 1997;40:1725; and from Petri M, et al: Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus, *Arthritis Rheum* 2012;64:2677-2686.

DIAGNOSIS

The diagnosis of SLE requires a comprehensive clinical and laboratory assessment revealing characteristic multisystem disease and excluding other etiologies, including infection and malignancy. Classification criteria for SLE were developed to identify appropriate subjects for clinical trials but are often used as guideposts for SLE diagnosis. Over the past several decades, SLE classification criteria have undergone serial updates. Both the **American College of Rheumatology (ACR) 1997 Revised Classification**

Entry criterion
Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

If absent, do not classify as SLE
If present, apply additive criteria

Additive criteria

- **Do not count a criterion if there is a more likely explanation than SLE.**
- **Occurrence of a criterion on at least one occasion is sufficient.**
- **SLE classification requires at least one clinical criterion and ≥10 points.**
- **Criteria need not occur simultaneously.**
- **Within each domain, only the highest weighted criterion is counted toward the total score.***

Clinical domains and criteria	Weight
Constitutional	
Fever	2
Hematologic	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Neuropsychiatric	
Delirium	2
Psychosis	3
Seizure	5
Mucocutaneous	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous OR discoid lupus	4
Acute cutaneous lupus	6
Serosal	
Pleural or pericardial effusion	5
Acute pericarditis	6
Musculoskeletal	
Joint involvement	6
Renal	
Proteinuria >0.5 g/24hr	4
Renal biopsy class II or V lupus nephritis	8
Renal biopsy class III or IV lupus nephritis	10

Immunology domains and criteria	Weight
Antiphospholipid antibodies	
Anti-cardiolipin antibodies OR Anti-β2GP1 antibodies OR Lupus anticoagulant	2
Complement proteins	
Low C3 OR low C4	3
Low C3 AND low C4	4
SLE-specific antibodies	
Anti-dsDNA antibody† OR Anti-Smith antibody	6

Total score:

Classify as systemic lupus erythematosus with a score of 10 or more if entry criterion fulfilled.

Fig. 199.3 Classification criteria for systemic lupus erythematosus (SLE). *Additional criteria items within the same domain will not be counted. †In an assay with ≥90% specificity against relevant disease controls. (*From Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus.* Arthritis Rheum. *2019;71[9]:1400–1412.*)

Criteria for SLE and the **2012 Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria** (Table 199.3) are validated in childhood onset SLE populations, with the SLICC Criteria achieving higher sensitivity and the 1997 ACR Criteria achieving better specificity. In both the 1997 ACR and 2012 SLICC Criteria, a positive antinuclear antibody (ANA) test result is not required for the diagnosis of SLE; however, ANA-negative lupus is extremely rare. The ANA test is very sensitive for SLE (95-99%) but is not very specific (~50%). The ANA may become positive many years before a diagnosis of SLE is established; however, most asymptomatic ANA-positive patients will never develop SLE. More recently, the **2019 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) SLE Classification Criteria** (Fig. 199.3) provided a different approach by requiring a positive antinuclear antibody (ANA) test result at a titer ≥1:80. Allthough the 2019 EULAR/ACR criteria have excellent sensitivity and specificity in the adult SLE population, they are still being validated in pediatric populations.

Anti-dsDNA and anti-Smith antibodies are specific for SLE (~98%) but not as sensitive (40–65%) as the ANA. **Hypocomplementemia** was not included in earlier classification criteria, but has been added to the two most recent classification criteria. The 2012 SLICC Criteria also added as criteria nonscarring alopecia, additional cutaneous and neurologic manifestations, and a positive direct Coombs test in the absence of hemolytic anemia.

Table 199.4 Main Differential Diagnoses of SLE (SLE Mimickers)

OTHER CONNECTIVE TISSUE DISEASES
Sjögren (SSA+), dermatomyositis (rash), mixed connective tissue disease
INFECTIOUS DISEASES
Endocarditis; hepatitis A, B, C, E; parvovirus B19; HIV; EBV; CMV; Lyme; disseminated gonococcal arthritis; toxoplasmosis; histoplasmosis; mycobacterial diseases; tinea faciei; visceral leishmaniasis; Whipple disease
HEMATOLOGIC MALIGNANCIES
Hodgkin lymphoma, myelodysplastic syndromes, angioimmunoblastic T-cell lymphoma
SOLID TUMORS AND PARANEOPLASTIC SYNDROMES
Thymoma, carcinoma of the lung, breast, and ovary with paraneoplastic syndromes
OTHER DISEASES
Meigs and Pseudo-Meigs syndrome Multiple sclerosis Castleman disease Interferonopathies (monogenic SLE) Still disease (and other autoinflammatory diseases) Evans syndrome (with primary immune deficiency) Complement deficiency Hypocomplementemic urticarial vasculitis Schizophrenia and other psychoses Kikuchi disease IgG4-related disease Chilblains (cold-induced) Ackerman syndrome and erythema elevatum diutinum with polyarthritis Drug-induced lupus and drug-induced polyarthritis Graft-versus-host disease Systemic manifestations of atrial myxoma Prolidase deficiency

From Chasset F, Richez C, Martin T, et al. Rare diseases that mimic systemic lupus erythematosus (lupus mimickers). *Joint Bone Spine*. 2019;86:165–171, Table 1, p. 166 Copyright Elsevier Masson SAS.

DIFFERENTIAL DIAGNOSIS

Multiorgan disease is the hallmark of SLE, and given its wide array of potential clinical manifestations, SLE is in the differential diagnosis of many clinical scenarios, including unexplained fevers, joint pain or arthritis, rash, cytopenias, nephritis, nephrotic syndrome, pleural or pericardial effusions or other cardiopulmonary abnormalities, and new-onset psychosis or seizures. For patients ultimately diagnosed with pediatric SLE, the initial differential diagnosis often includes infections (sepsis, Epstein-Barr virus, parvovirus B19, endocarditis), malignancies (leukemia and lymphoma), poststreptococcal glomerulonephritis, other rheumatologic conditions (juvenile idiopathic arthritis, vasculitides), and drug-induced lupus (Table 199.4).

Drug-induced lupus refers to the presence of SLE manifestations triggered by exposure to specific medications, including hydralazine, minocycline, many anticonvulsants, sulfonamides, antiarrhythmic agents, and other drugs (Table 199.5). In individuals prone to SLE, these agents may act as a trigger for true SLE, but more commonly these agents provoke a reversible lupus-like syndrome. Unlike SLE, drug-induced lupus affects males and females equally. A genetic predisposition toward slow drug acetylation may increase the risk of drug-induced lupus. Circulating **antihistone antibodies** are often present in drug-induced SLE; these antibodies are only detected in up to 20% of individuals with SLE. Hepatitis, which is rare in SLE, is more common in drug-induced lupus. Individuals with drug-induced lupus are less likely to demonstrate antibodies to dsDNA, hypocomplementemia, and significant renal or neurologic disease. In contrast to SLE, manifestations of drug-induced lupus typically resolve after withdrawal of the offending medication; however, complete recovery may take several months to years, requiring treatment, often with hydroxychloroquine, NSAIDs, and/or corticosteroids.

Table 199.5 Medications Associated with Drug-Induced Lupus

DEFINITE ASSOCIATION
Minocycline, procainamide, hydralazine, isoniazid, penicillamine, diltiazem, interferon-α, methyldopa, chlorpromazine, etanercept, infliximab, adalimumab
PROBABLE ASSOCIATION
Phenytoin, ethosuximide, carbamazepine, sulfasalazine, amiodarone, quinidine, rifampin, nitrofurantoin, β blockers, lithium, captopril, interferon-γ, hydrochlorothiazide, glyburide, docetaxel, penicillin, tetracycline, statins, gold, valproate, griseofulvin, gemfibrozil, propylthiouracil

Table 199.6 Autoantibodies Commonly Associated with Systemic Lupus Erythematosus (SLE)

ANTIBODY	CLINICAL ASSOCIATION
Anti–double-stranded DNA (anti-dsDNA)	Correlates with disease activity, especially nephritis, in some with SLE
Anti-Smith antibody (anti-Sm)	Specific for the diagnosis of SLE
Anti-ribonucleoprotein antibody (anti-RNP)	Increased risk for Raynaud phenomenon, interstitial lung disease, and pulmonary hypertension
Anti-Ro antibody (anti-SSA) Anti-La antibody (anti-SSB)	Associated with sicca syndrome May suggest diagnosis of Sjögren syndrome Increased risk of neonatal lupus in offspring (congenital heart block) May be associated with cutaneous and pulmonary manifestations of SLE May be associated with isolated discoid lupus
Antiphospholipid antibodies (including lupus anticoagulant and anti-cardiolipin or anti-beta-2 glycoprotein antibodies)	Increased risk for venous and arterial thrombotic events
Antihistone antibodies	Present in a majority of patients with drug-induced lupus May be present in SLE

LABORATORY FINDINGS

A positive ANA test is present in 95–99% of individuals with SLE. The ANA has poor specificity for SLE, as up to 20% of healthy individuals also have a positive ANA test result, making the ANA a poor screen for SLE when used in isolation. After diagnosis, ANA titers are not reflective of disease activity; therefore repeat ANA testing in SLE patients is not helpful. Antibodies to dsDNA are specific for SLE, and in many individuals, anti-dsDNA levels correlate with disease activity, particularly in those with significant nephritis. Anti-Smith antibody, although found specifically in patients with SLE, does not correlate with disease activity. Serum levels of total hemolytic complement (CH_{50}), C3, and C4 are typically decreased in active disease and often improve with treatment. Table 199.6 lists autoantibodies

found in SLE along with their clinical associations. Hypergammaglobulinemia is a common but nonspecific finding. Inflammatory markers, particularly the erythrocyte sedimentation rate, are often elevated in active disease. C-reactive protein (CRP) correlates less well with disease activity; significantly elevated CRP values often reflect infection, whereas chronic mild elevation of CRP may indicate increased cardiovascular risk.

Antiphospholipid antibodies, which increase clotting risk, can be found in up to 66% of children and adolescents with SLE. The primary antiphospholipid antibodies are lupus anticoagulant, anticardiolipin, and anti–beta-2 glycoprotein antibodies. When an arterial or venous clotting event occurs in the presence of an antiphospholipid antibody, **antiphospholipid antibody syndrome** is diagnosed. Antiphospholipid antibody syndrome can occur in the context of SLE (secondary) or independent of SLE (primary) (see Chapter 528). Rarely, antiphospholipid antibodies can result in catastrophic antiphospholipid syndrome, a condition in which clots affect three or more organs/tissues simultaneously; this condition has a very high mortality rate.

TREATMENT

Treatment of SLE is tailored to the individual and is based on specific disease manifestations and medication tolerability. For all patients, sunscreen and avoidance of prolonged direct sun exposure and other ultraviolet light may help control disease and should be reinforced at every visit with the patient. **Hydroxychloroquine is recommended for all individuals with SLE when tolerated.** In addition to treating mild SLE manifestations such as rash and mild arthritis, hydroxychloroquine prevents SLE flares, improves lipid profiles, and may have a beneficial impact on mortality and renal outcomes. Potential toxicities include retinal pigmentation that leads to vision impairment; therefore *annual ophthalmology exams are recommended for patients taking hydroxychloroquine, including automated visual field testing and spectral-domain optical coherence tomography (SD-OCT)*. Given that risk factors for ocular toxicity include duration of use and dose, hydroxychloroquine in SLE should not be prescribed at doses greater than 5 mg/kg to a maximum of 400 mg daily.

Corticosteroids are a treatment mainstay for significant manifestations of SLE and work quickly to improve acute deterioration; side effects often limit patient adherence, especially in adolescence, and potential toxicities are worrisome. It is important to limit the dose and length of exposure to corticosteroids whenever possible. Potential consequences of corticosteroid therapy include growth disturbance, weight gain, striae, acne, hyperglycemia, hypertension, cataracts, avascular necrosis, and osteoporosis. The optimal dosing of corticosteroids in children and adolescents with SLE remains unknown; **severe disease is often treated with high doses of intravenous methylprednisolone (e.g., 30 mg/kg/day to a maximum of 1,000 mg for each of 3 days, sometimes followed by a period of weekly pulses) and/or high doses of oral prednisone** (often starting at **1 mg/kg/day).** As disease manifestations improve, corticosteroid dosages are gradually tapered over months. For most patients it is necessary to introduce a steroid-sparing immunosuppressive medication in order to limit cumulative steroid exposure.

Steroid-sparing immunosuppressive agents for the treatment of pediatric SLE include methotrexate, leflunomide, azathioprine, mycophenolate mofetil, tacrolimus, cyclophosphamide, rituximab, and belimumab. Methotrexate, leflunomide, and azathioprine are often used to treat persistent moderate disease, including arthritis, significant cutaneous or hematologic involvement, and pleural disease. Cyclophosphamide, mycophenolate mofetil, and azathioprine are appropriate for the treatment of lupus nephritis, whereas mycophenolate mofetil and rituximab are often used for the treatment of significant hematologic manifestations, including severe leukopenia, hemolytic anemia, or thrombocytopenia.

Cyclophosphamide, usually administered intravenously, is reserved for the most severe, potentially life-threatening SLE manifestations, such as renal, neurologic, and cardiopulmonary disease. Although cyclophosphamide is highly effective in controlling disease, the potential toxicities are significant, including cytopenias, infection, hemorrhagic cystitis, premature gonadal failure, and increased risk of future malignancy. Attention to adequate hydration can attenuate the risk of hemorrhagic cystitis. Fortunately, young females are at much lower risk of gonadal failure than older women, and the use of gonadotropin-releasing hormone agonists, such as leuprolide acetate, may help prevent gonadal failure.

The Childhood Arthritis Rheumatology Research Alliance (CARRA) has developed a consensus treatment plan for induction therapy of newly diagnosed proliferative lupus nephritis (class III and IV) that is specific to the pSLE population; the treatment plan is considered necessary for class III and IV lupus nephritis but also appropriate for certain patients with other classes of lupus nephritis. The CARRA treatment plan advises 6 months of induction therapy with either cyclophosphamide (given per the National Institutes of Health [NIH] protocol as 500-1,000 mg/m^2 IV monthly) or mycophenolate mofetil (dosed as 600 mg/m^2 bid up to 1,500 mg bid), used in combination with one of three standardized glucocorticoid regimens. For patients who fail to achieve a partial response in 6 months, it is appropriate to switch agents. For adult-weight adolescents, the cyclophosphamide dosing regimen used in the Euro-Lupus Nephritis Trial can be considered in lieu of the previous 6-month therapy in an effort to reduce toxicity from cyclophosphamide exposure. Per this protocol, a fixed dose of 500 mg is given every 2 weeks for 3 months; in adults, this regimen is althought to reduce adverse effects while maintaining comparable efficacy for lupus nephritis, though this regimen has not been studied specifically in pediatric lupus. It should be noted that oral medication adherence is very poor in pSLE, and this must be taken into consideration when weighing the benefits of an IV infusion versus a twice daily oral medication such as mycophenolate mofetil. After the 6-month induction therapy, maintenance therapy for lupus nephritis consists of quarterly IV cyclophosphamide (dosed 500-1,000 mg/m^2 once every 3 months), mycophenolate, or azathioprine, with mycophenolate generally being the preferred agent. Maintenance therapy is typically continued for a minimum of 30 months after the completion of induction therapy, but in many circumstances, it is continued longer.

Calcineurin inhibitors such as tacrolimus are often adjunct therapy in the treatment of refractory lupus nephritis. Voclosporin, Food and Drug Administration (FDA)–approved for adults with lupus nephritis, awaits pediatric study. Clinical trial data on the use of rituximab in SLE with treatment-resistant glomerulonephritis has been largely disappointing, but post hoc analysis from the LUNAR study suggests there may be benefit for subpopulations of SLE patients. The FDA has approved the use of belimumab, a monoclonal antibody against BLyS/BAFF, for the treatment of lupus in adults and children; when added to standard SLE therapy, belimumab improves markers of disease activity in renal and nonrenal lupus. Belimumab has been shown to improve renal outcomes in adults, and while it is not used as monotherapy to treat lupus nephritis, it can be used in addition to standard therapy to help achieve renal remission without substantial increase in risk of infectious complications. Anifrolumab (a monoclonal antibody to the interferon-α receptor), achieved 2021 FDA approval for treatment of adult nonrenal SLE, and studies in lupus nephritis and pediatric lupus are forthcoming. Several novel therapies are in the pipeline for the treatment of SLE and lupus nephritis, including Janus kinase inhibitors.

Given the lifelong nature of SLE, optimal care of children and adolescents with this disease also involves preventive practices. Owing to the enhanced risk of atherosclerosis in SLE, attention to cholesterol levels, smoking status, body mass index, blood pressure, and other traditional cardiovascular risk factors is warranted. Even though the Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) study failed to support placing all children with SLE on a statin, post hoc analyses suggest that statins can be considered for primary prevention of atherosclerotic disease in certain clinical circumstances, particularly pubertal patients with an elevated CRP.

Table 199.7 Morbidity in Childhood Lupus

Renal	Hypertension, dialysis, transplantation
Central nervous system	Organic brain syndrome, seizures, psychosis, neurocognitive dysfunction
Cardiovascular	Atherosclerosis, myocardial infarction, cardiomyopathy, valvular disease
Immune	Recurrent or severe infection, functional asplenia, malignancy
Musculoskeletal	Osteopenia, compression fractures, avascular necrosis
Ocular	Cataracts, glaucoma, retinal detachment, blindness
Endocrine	Diabetes, obesity, growth failure, infertility, fetal wastage

From Cassidy JT, Petty RE, Laxer RM, et al., eds. *Textbook of Pediatric Rheumatology*, 6th ed. Philadelphia: Saunders; 2011.

SLE patients with antiphospholipid antibody syndrome (antiphospholipid antibodies and a history of arterial or venous clot or pregnancy morbidity) are treated with long-term anticoagulation to prevent thrombotic events; for SLE patients who are antiphospholipid antibody positive without a history of clots, many pediatric rheumatologists prescribe aspirin 81 mg daily.

For all SLE patients, adequate intake of calcium and vitamin D is necessary to prevent future osteoporosis, particularly as vitamin D levels are lower in pSLE patients compared with age-matched healthy controls. It is worth noting recent studies suggest a link between hypovitaminosis D and SLE susceptibility and also offer an emerging role for vitamin D in immunomodulation.

Infections, particularly pneumococcal disease, commonly complicate SLE, so routine immunization is recommended, including the annual influenza vaccination, SARS-CoV-2 vaccination, and vaccination against human papilloma virus (HPV). In addition, pSLE patients age 6 or older should receive a dose of PPSV23 at least 8 weeks after completing all recommended pneumococcal vaccine series with PCV13 or PCV15. Many of the immunosuppressant medications used in SLE contraindicate administration of live vaccines. Prompt attention to febrile episodes should include an evaluation for serious infections. Because pSLE patients are at high risk for developing anxiety and depression, screening for depression is important. Peer support and cognitive-behavioral therapy interventions reduce pain and enhance resilience in pSLE.

Pregnancy can worsen SLE, and obstetric complications are common. In addition, many medications used to treat SLE are teratogenic. As a consequence, it is important to counsel adolescent girls about these risks and facilitate access to appropriate contraceptive options. Hydroxychloroquine is recommended throughout pregnancy for all SLE patients, whereas other medications may need to be adjusted.

COMPLICATIONS

Within the first several years of diagnosis, the most common causes of death in individuals with SLE include infection and complications of glomerulonephritis and neuropsychiatric disease (Table 199.7). Over the long term, the most common causes of mortality are atherosclerosis and malignancy. The increased risk of premature atherosclerosis in SLE is not explained by traditional risk factors and is partly a result of the chronic immune dysregulation and inflammation associated with SLE. Increased malignancy rates may be caused by immune dysregulation and exposure to medications with carcinogenic potential. Potential lupus emergencies are noted in Table 199.8.

Table 199.8 A Summary of Signs and Symptoms Indicative of Lupus Emergencies

SIGNS/SYMPTOMS	DIFFERENTIAL CONSIDERATIONS
Fever	Evaluate for infection Consider disease flare Consider macrophage activation syndrome
Thrombosis/hemoptysis	May be arterial or venous Evaluate for antiphospholipid syndrome
Chest pain	Pleurisy, pericarditis, pulmonary infarction/embolus
Dyspnea	Pneumonitis, alveolar hemorrhage, pleural effusions, congestive heart failure
Headache	Vascular headaches, meningitis, thrombus, cerebrovascular accident, hypertensive crisis
Altered mental status	Cerebritis, hypertensive crisis, macrophage activation syndrome, stroke, thrombotic thrombocytopenic purpura, and atypical hemolytic uremic syndrome
Rash	Vasculitis lesions, palpable purpura, infarction
Icterus	Autoimmune hemolysis Autoimmune hepatitis
Petechiae	Thrombotic thrombocytopenia purpura
Seizure	Cerebritis, infection, metabolic causes, hypertensive crisis

From Harry O, Yasin S, Brunner H. Childhood-onset systemic lupus erythematosus: a review and update. *J Pediatr.* 2018;196:22–30, Table IV.

PROGNOSIS

SLE disease severity is higher in childhood-onset SLE compared with adult-onset SLE. Fortunately, advances in the diagnosis and treatment of SLE have led to dramatically improved survival over the past 50 years. The 5-year and 10-year survival rates for pSLE are 99% and 97%, respectively, in high-income countries, although these survival rates are 85% and 79%, respectively, in low- and middle-income countries. Infection contributes significantly to mortality in pediatric lupus. In addition, early in the disease course, lupus nephritis, lupus cerebritis, and complications such as macrophage activation syndrome are primary causes of mortality, whereas later in the disease course, atherosclerosis and malignancy become larger contributors to mortality. Given their long burden of disease, children and adolescents with SLE face high risks of future morbidity and mortality from the disease and its complications, as well as medication side effects. Because pSLE is a complex, chronic disease with a high risk for morbidity and mortality, optimal care for children and adolescents with SLE includes treatment by pediatric rheumatologists in a multidisciplinary clinic with access to a full complement of pediatric subspecialists. Furthermore, because SLE is a lifelong disease, it is critically important to ensure an appropriate transition to an adult model of care, which helps avoid interruptions in rheumatology care.

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199.1 Neonatal Lupus

Deborah M. Friedman, Jill P. Buyon, Rebecca E. Sadun, and Stacy P. Ardoin

Neonatal lupus erythematosus (NLE), an entity distinct from SLE, is one of the few rheumatic disorders manifesting in the neonate. NLE is not an autoimmune disease of the fetus, but instead results from passively acquired autoimmunity, when maternal immunoglobulin G autoantibodies cross the placenta and enter the fetal circulation. In contrast to SLE, neonatal lupus is not characterized by ongoing immune dysregulation, although infants with neonatal lupus may be at some increased risk for development of future autoimmune disease. The vast majority of NLE cases are associated with maternal anti-Ro (also known as SSA), anti-La antibodies (also known as SSB), or anti-RNP autoantibodies.

Despite the clear association with maternal autoantibodies, their presence alone is not sufficient to cause disease, as only ~2% of offspring born to mothers with anti-Ro and anti-La antibodies develop neonatal lupus. Increasing evidence supports the observation that generally high maternal anti-Ro titers are necessary for fetal clinical disease. In the prospective evaluation of fetuses with autoimmune-associated congenital heart block followed in the PR Interval and Dexamethasone Evaluation (PRIDE) study, the median anti-Ro titer for pregnancies resulting in heart block was 5 times as high as the median anti-Ro titer in unaffected pregnancies. Another group identified heart block in 8% of cases with very high anti-Ro antibody titers, with no cases among women with low or moderate titers.

Siblings of infants with NLE have a 15–20% chance of developing NLE. Neonatal lupus seems to be independent of the maternal health because many mothers are asymptomatic and only identified to have anti-Ro/anti-La antibodies subsequent to the diagnosis of NLE. Roughly half of the infants with NLE are born to the mothers with a defined rheumatic disease such as Sjogren syndrome or SLE.

Clinical manifestations of neonatal lupus include a characteristic annular or macular rash typically affecting the face (especially the periorbital area), trunk, and scalp (Fig. 199.4). The rash can be present at birth but more often appears within the first 6-8 weeks of life, after exposure to ultraviolet light, and typically lasts 3-4 months. Infants may also have cytopenias and hepatitis, each occurring in ~25% of cases, but the most concerning complication is congenital heart block.

Conduction system abnormalities range from prolongation of the PR interval to complete heart block, with development of progressive cardiomyopathy in the most severe cases. The noncardiac manifestations of neonatal lupus are usually reversible, whereas third-degree congenital heart block is permanent. Conduction system abnormalities can be detected in utero by fetal echocardiogram beginning at 16 weeks of gestational age. Neonatal lupus cardiac disease has a mortality rate of ~20%. Cardiac NLE can manifest as heart block, cardiomyopathy, valvular dysfunction, and endocardial fibroelastosis. Fetal bradycardia from heart block can lead to hydrops fetalis.

In vitro studies suggest that during cardiac development via apoptosis, Ro and La antigens may be exposed on the surface of cardiac cells in the proximity of the atrioventricular node, making the antigens accessible to maternal autoantibodies. Binding incites a local immune response, resulting in fibrosis within the conduction system and more extensive disease in fatal cases. In the skin, exposure to ultraviolet light results in cell damage and the subsequent exposure of Ro and La antigens, inducing a similar local inflammatory response that produces the characteristic rash.

Although the scant clinical trial data have been mixed, fluorinated corticosteroids (dexamethasone or betamethasone), intravenous immunoglobulin (IVIG) at 1-2 g/kg maternal weight, plasmapheresis, hydroxychloroquine, and terbutaline (combined with steroids) have been used in pregnant women with anti-Ro or anti-La antibodies to prevent occurrence or progression of fetal cardiac abnormalities.

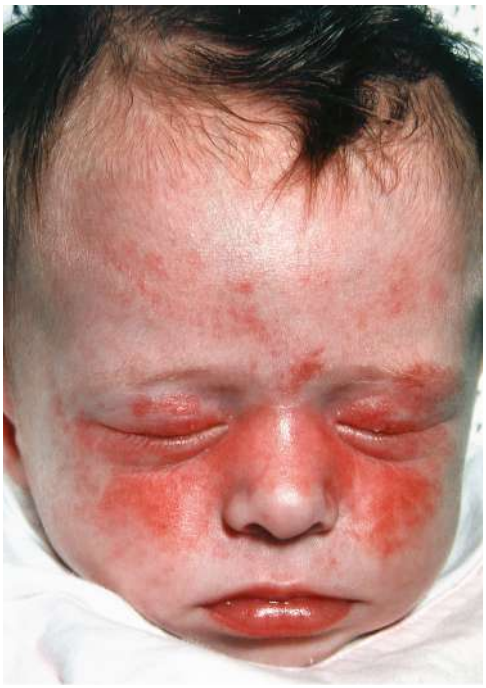

Fig. 199.4 Neonatal lupus syndrome. Typical rash, often photosensitive with a malar distribution, appearing as annular plaques with erythema and scaling. (*From Pain C, Beresford MW. Neonatal lupus syndrome.* Paediatr Child Health. *2007;17:223–227.*)

Most encouraging are retrospective cohort studies suggesting maternal treatment with hydroxychloroquine may reduce the frequency and recurrence of congenital heart block. In a multicenter, single-arm, open-label clinical trial assessing the efficacy of hydroxychloroquine to prevent recurrent autoantibody-associated congenital heart block, hydroxychloroquine treatment reduced the risk of recurrent heart block compared to historical controls by over 50%, from 17.5% to less than 8% of pregnancies.

Significant conduction system abnormalities after birth are treated with cardiac pacing and occasionally IVIG and steroids, whereas severe cardiomyopathy may require cardiac transplantation. If the conduction defect is not addressed, affected children are at risk for exercise intolerance, arrhythmias, and death. With cardiac pacing, however, children with conduction system disease in the absence of cardiomyopathy have an excellent prognosis. In a long-term follow-up study of 239 subjects enrolled in the Research Registry for Neonatal Lupus, 22% of subjects had cardiac dysfunction in the first year of life. Cardiac dysfunction often regressed; nevertheless, some dysfunction did appear later in childhood. Risk factors for cardiac dysfunction were being male or of low socioeconomic status and having low fetal heart rates, a longer period of pacing, or extranodal cardiac disease. In a Swedish cohort of 119 children with congenital heart block, 16.8% developed cardiomyopathy ± congestive heart failure. Congenital heart block increased the risk of cerebral infarctions and infections. Pacemaker treatment was associated with decreased risk of developing cerebral infarction but increased risk of infection and cardiomyopathy.

Noncardiac manifestations are typically transient and are conservatively managed, often with supportive care alone. Topical steroids can be used to treat moderate to severe NLE rash. Cytopenias may improve over time but severe cases occasionally require IVIG. Supportive care is usually appropriate for hepatic and neurologic manifestation. When the neonate clears maternal autoantibodies over the first 6 months of life, these inflammatory manifestations gradually resolve.

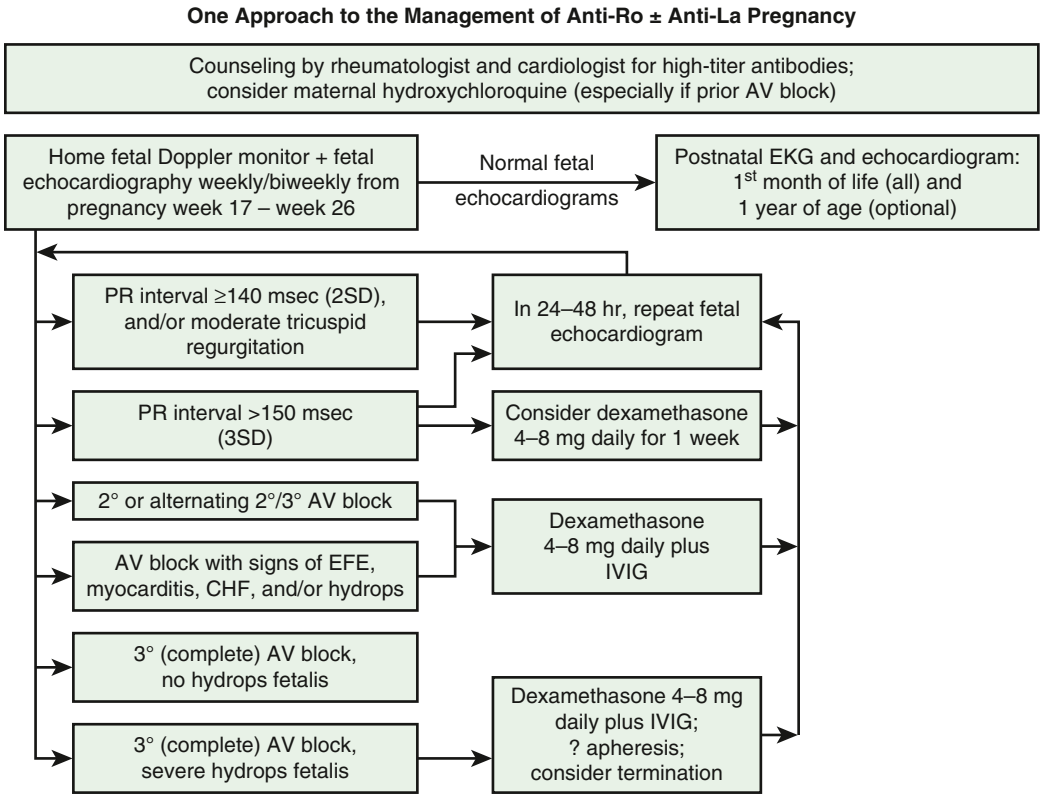

Fig. 199.5 Suggested algorithm for the management of anti-Ro ± anti-La pregnancy. All such pregnancies should include counseling and serial fetal echocardiograms.

Because maternal autoantibodies begin to gain access to the fetus through the placenta via FcRn at about 12 weeks gestation, all pregnant women with circulating anti-Ro and/or anti-La antibodies, or those with a history of offspring with neonatal lupus or congenital heart block, are generally advised to be monitored by a pediatric cardiologist, with screening fetal echocardiography performed weekly or biweekly from 17-26 weeks of gestation. The period of greatest vulnerability is usually 18-24 weeks. If fetal bradycardia is found during routine in utero monitoring in a mother never evaluated for the putative antibodies and if fetal echocardiography confirms a conduction defect, screening for maternal anti-Ro and anti-La antibodies is warranted. In pregnancies at risk for congenital heart block, maternal home monitoring of fetal heart rate using a handheld fetal heart rate monitor 2-3 times daily allows for accurate and early detection of heart rate abnormalities.

A proposed management algorithm is presented in Figure 199.5.

A multicenter retrospective study concluded that *maternal treatment* with dexamethasone and/or intravenous gamma globulin should be initiated in all cases of anti-SSA/Ro antibody cardiac manifestations, including significant first-degree or any higher atrioventricular block, isolated endocardial fibroelastosis, or sinus bradycardia. However, other studies suggest that treatment should be individualized to fetuses at high risk and not universally instituted for isolated complete third-degree block, which is generally considered immutable.

The negative predictive value of antibody titers to identify pregnancies at low risk of fetal atrioventricular block has also been studied. Excluding women with previously affected children, leveraging samples obtained from anti-SSA/Ro exposed pregnancies with and without fetal atrioventricular block, no case of heart block developed among subjects with anti-Ro52 and anti-Ro60 titers of <110 arbitrary units per milliliter using the multiplex bead assay of the Associated Regional and University Pathologists Laboratories (n=141). Applying these 100% negative predictive value thresholds, approximately 50% of the anti-Ro/SSA antibody pregnancies that ultimately had no fetal atrioventricular block could be excluded from surveillance.

Emerging data suggest that not all mothers with anti-SSA/Ro antibodies require surveillance. Based on review of the literature, the Society for Maternal-Fetal Medicine published guidelines that recommended "…that serial fetal echocardiograms for assessment of the PR interval not be routinely performed in patients with anti-SSA/SSB antibodies outside of a clinical trial setting" but rather that, "Doppler assessment of fetal heart rate during routine prenatal visits can be used to screen for fetal complete heart block. Once complete heart block develops, management is expectant, with weekly ultrasound examinations recommended to assess for hydrops."

Guidelines in this domain continue to evolve as new data advances our approach to risk stratification

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Chapter 200

Juvenile Dermatomyositis

Jeffrey A. Dvergsten and Ann M. Reed

Juvenile dermatomyositis (JDM) is the most common of the *juvenile idiopathic inflammatory myopathies (JIIMs),* representing up to 85% of all patients with these rare vasculopathic diseases. It is characterized by proximal muscle weakness and distinctive rashes of the face and extensor joint surfaces.

EPIDEMIOLOGY

The incidence of JDM is approximately 3 cases/1 million children/yr, with an incidence similar in White and Black non-Hispanics and an apparent lower incidence in Hispanics. The peak age of onset is 7 years with a second peak of onset in late adulthood (45-64 years); however, adult-onset dermatomyositis appears to be a distinctly separate entity, both in prognosis and etiology. In the United States the ratio of females to males with JDM is 2:1. Multiple cases of myositis in a single family are rare, but familial autoimmune disease may be increased in families with children who have JDM when compared to families of children without autoimmune disease. Reports of seasonal association have not been confirmed, although clusters of cases may occur.

ETIOLOGY

A precise understanding of the etiology and pathogenesis of JDM remains elusive; many factors that affect elements of innate and adaptive immunity have been identified as contributing to onset and perpetuation of disease. Evidence suggests that the etiology of JDM is multifaceted, with a genetic predisposition influenced by an environmental factor triggering events leading to disease pathogenesis.

Genetic factors that are associated with increased susceptibility to JDM include human leukocyte antigen (HLA) alleles DRB1*0301, DQA1*0501, and DQA1*0301. Additionally, HLA-DQA1*0501 is found on maternal cells present in blood and tissue samples of children with JDM, an example of maternal microchimerism, which has been proposed to play an etiologic role in JDM by creating an immune response comparable to graft-versus-host disease (GVHD). Other polymorphisms implicated in JDM include those affecting cytokine genes such as the tumor necrosis factor (TNF)-α promoter and the variable-number tandem repeats of the interleukin (IL)-1 receptor antagonist A1 gene. An increase in TNF-α may be associated with persistent immune activation leading to a longer disease course. The IL-1 receptor antagonist A1 allele is associated with the development of JIIM in White but not in Black persons, in whom the A3 allele, instead, is a possible risk factor. Environmental factors may also play a contributing role, with geographic and seasonal clustering reported. Short-term increases in ultraviolet (UV) index before the onset of disease have been reported; however, no clear theory of etiology has emerged. A history of infection in the 3 months before disease onset is usually reported; multiple studies have failed to produce a causative organism. Constitutional signs and upper respiratory symptoms predominate, but one third of patients report preceding gastrointestinal (GI) symptoms. Group A streptococcus, upper respiratory infections, GI infections, coxsackievirus B, toxoplasma, enteroviruses, parvovirus B19, and multiple other organisms have been postulated as possible pathogens in the etiology of JDM. Despite these concerns, results of serum antibody testing and polymerase chain reaction amplification of the blood and muscle tissue for multiple infectious diseases have not been revealing.

PATHOGENESIS

JDM and related immune myositis syndromes are believed to be an autoimmune vasculopathic inflammatory disease affecting capillaries of multiple organs, but most notably, the skin, muscles, and GI tract (Table 200.1). Pathogenic mechanisms are both immune and nonimmune with cellular and soluble constituents of the innate and adaptive immune systems and pathways of cellular injury involved. Type I interferons (IFNs), principally α and β, are cytokines of the innate immune system that play a significant role in the pathogenesis of JDM by modulating several immune mechanisms, including upregulation of major histocompatibility complex (MHC) class I molecules on muscle cells; induction of proinflammatory cytokine, chemokine, and adhesion molecule production; and supporting cytotoxic effects of innate and adaptive immune cells. Plasmacytoid dendritic cells (pDCs) play an important role in JDM and are principal producers of type I IFN upon activation of Toll-like receptor (TLR) 9 on their surface by viruses. Cells involved in the inflammatory cascade include monocytes/macrophages (CD14), T-cell subsets (CD4, CD8, Th17), natural killer (NK) cells (CD56), and dendritic cells (DCs). MHC class I upregulation induces endoplasmic reticulum (ER) stress, which results in the degradation of contractile proteins; additional downstream effects of type I IFN include autoantibody production and B-cell proliferation. Galectin-9 and CXCL10 (IP-10) are two IFN-related proteins that have been validated as sensitive and specific peripheral biomarkers of disease activity in JDM.

CLINICAL MANIFESTATIONS

Children with JDM present with either rash, insidious onset of weakness, or both. Fevers, dysphagia or dysphonia, arthritis, muscle tenderness, and fatigue are also commonly reported at diagnosis (Tables 200.2 and 200.3). Certain myositis-specific antibodies are associated with different phenotypic patterns of disease (Fig. 200.1).

Rash develops as the first symptom in 50% of patients and appears concomitant with weakness only 25% of the time. Children often exhibit extreme photosensitivity to UV light exposure with generalized erythema in sun-exposed areas. If seen over the chest and neck, this erythema is known as the **shawl sign**. Erythema is also commonly seen over the knees and elbows. The characteristic **heliotrope rash** is a blue-violet discoloration of the eyelids that may be associated with periorbital edema (Fig. 200.2). Facial erythema crossing the nasolabial folds is also common, in contrast to the malar rash without nasolabial involvement typical of systemic lupus erythematosus (SLE). Classic **Gottron papules** are bright-pink or pale, shiny, thickened, or atrophic plaques over the metacarpal phalangeal joints, proximal interphalangeal joints, and distal interphalangeal joints and occasionally on the knees, elbows, small joints of the toes, and ankle malleoli (Fig. 200.3). The rash of JDM is sometimes mistaken for eczema or psoriasis. Rarely, a thickened erythematous and scaly rash develops in children over the palms (known as **mechanic's hands**) and soles along the flexor tendons, which is associated with anti–Jo-1 antibodies.

Evidence of small vessel inflammation is often visible in the nail folds and gums as individual capillaries display changes including loops, thickening, tortuosity, or loss (Fig. 200.4C). Telangiectasias may be visible to the naked eye but are more easily visualized under capillaroscopy or with another magnifier (e.g., ophthalmoscope). Severe vascular inflammation causes cutaneous ulcers on toes, fingers, axillae, or epicanthal folds.

Early in disease, weakness associated with JDM is often insidious and difficult to differentiate from fatigue. It is typically symmetric, affecting proximal muscles such as the neck flexors, shoulder girdle, and hip flexors. Parents may report difficulty climbing stairs, combing hair, and getting out of bed. Examination reveals inability to perform a sit-up, head lag in a child after infancy, and **Gower sign** (use of hands climbing on thighs to help stand from a sitting position). Patients with JDM may roll to the side rather than sit straight up from lying to compensate for truncal weakness. Approximately half of children exhibit muscle tenderness because of muscle inflammation.

Esophageal and respiratory muscles are also affected, resulting in aspiration or respiratory failure. It is essential to assess for dysphonia or nasal speech, palatal elevation with gag, dysphagia, and gastroesophageal reflux by means of history and physical examination. If any of these are abnormal, a swallow study should be pursued. Respiratory muscle weakness can be a medical emergency and lead to respiratory failure.

Table 200.1 Clinical Associations: Myositis-Specific Antibodies (MSA) and Myositis-Associated Antibodies (MAA) in Juvenile-Onset Myositis (JOM)

AUTOANTIBODY	TARGET AUTOANTIGEN	PREVALENCE (%) IN PATIENTS WITH JOM	CLINICAL ASSOCIATIONS
Common myositis-specific autoantibodies are found in 45–55% of patients with juvenile-onset myositis			
Anti-Mi2	Nucleosome remodeling deacetylase complex (NuRD)	3–4	• "Classic" dermatomyositis • Responds well to standard therapies • Favorable prognosis
Anti-TIF1g (p155/140, TRIM33)	Transcriptional intermediary factor 1 gamma (TIF1-γ)	18–35	• Severe cutaneous disease • Rashes in photoexposed pattern • Chronic disease course • Lipodystrophy
Anti-NXP2 (p140, MJ)	Nuclear matrix protein 2 (NXP2)	15–22	• Calcinosis • More severe muscle disease • Gastrointestinal bleeding, ulcers, and dysphagia • Worse disease outcome and functional status
Anti-MDA5 (CADM-140)	Melanoma differentiation–associated gene 5 (MDA5)	6	• More common in East Asia, where associated with clinically amyopathic myositis, rapidly progressive interstitial lung disease, and a high mortality rate • In White populations associated with mild muscle disease, interstitial lung disease, arthritis, and ulceration
Rare but clinically important myositis-specific autoantibodies are found in 5–8% of patients with juvenile-onset myositis antisynthetases (Jo-1, PL12, PL7, OJ, EJ, KS, Zo, and Ha)			
ANTISYNTHETASES			• Antisynthetase syndrome: myositis, interstitial lung disease, fever, mechanic's hands, Raynaud phenomenon, and arthritis • Occurs in older children • Increased mortality
- Jo-1	- Histidyl	2–3	
- PL12	- Alanyl	2–3	
- PL7	- Threonyl	2–3	
- OJ	- Isoleucyl	2–3	
- EJ	- Glycyl	2–3	
- KS	- Asparaginyl	2–3	
- Zo	- Phenylalanyl	2–3	
- Ha	- Tyrosyl	2–3	
Anti-SRP	Signal recognition particle (SRP)	2	• Necrotizing autoimmune myositis • Severe weakness, muscle necrosis, high CK • Cardiac involvement • Occurs in older children • No rash • May be refractory to standard treatment
Anti-HMGCR	HMGCR	1	• Necrotizing autoimmune myositis, muscle necrosis, high CK, dysphagia, no statin exposure
Anti-SAE	Small ubiquitin-like modifier–activating enzyme (SAE)	1	• Initially amyopathic disease with muscle involvement occurring later
Myositis-associated autoantibodies are found in 16–20% of patients with juvenile-onset myositis. Some may occur in conjunction with a myositis-specific autoantibody.			
Anti-PmScl	Exosome-associated PM- Scl-75; PM-Scl-100; C1D	5	• Overlap syndromes
Anti-U1RNP	U1RNP	2	• Overlap syndromes
Anti-Ro52	Ro52	5	• Overlap syndromes • May be found in conjunction with other MSA, particularly antisynthetases

Common MSAs are present in 45–55% of the U.S. pediatric population with juvenile-onset myositis. Rare MSAs are present in 5–8%. Myositis-associated autoantibodies (MAAs) are found in 16–20% of juvenile-onset myositis, with or without an accompanying MSA.

CK, Creatine kinase; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme reductase; MDA, melanoma differentiation-associated; NuRD, nucleosome remodeling deacetylase; SAE, small ubiquitin-like modifier–activating enzyme; SRP, signal recognition particle; TIF, transcriptional intermediary factor.

Modified from Pachman LM, Khojah AM. Advances in juvenile dermatomyositis: myositis specific antibodies aid in understanding disease heterogeneity. *J Pediatr*. 2018;195:16–27.

Table 200.2 Diagnostic Criteria for Juvenile Dermatomyositis

Classic rash	Heliotrope rash of the eyelids Gottron papules
Plus three of the following:	
Weakness	Symmetric Proximal
Muscle enzyme elevation (≥1)	Creatine kinase Aspartate transaminase Lactate dehydrogenase Aldolase
Electromyographic changes	Short, small polyphasic motor unit potentials Fibrillations Positive sharp waves Insertional irritability Bizarre, high-frequency repetitive discharges
Muscle biopsy	Necrosis Inflammation

Data from Bohan A, Peter JB. Polymyositis and dermatomyositis (second of two parts). *N Engl J Med.* 1975;292:403–407.

Table 200.3 Clinical Features of Juvenile Dermatomyositis During Disease Course

FEATURE	%
Muscle weakness	90-100
Dysphagia or dysphonia	13-40
Muscle atrophy	10
Muscle pain and tenderness	30-75
Skin lesions	85-100
Heliotrope rash of eyelids	66-95
Gottron papules	57-95
Erythematous rash of malar/facial area	42-100
Periungual (nail fold) capillary changes	80-90
Photosensitive rash	5-42
Ulcerations	22-30
Calcinosis	12-30
Lipodystrophy	11-14
Raynaud phenomenon	2-15
Arthritis and arthralgia	22-58
Joint contractures	26-27
Fever	16-65
Gastrointestinal signs and symptoms	8-37
Restrictive pulmonary disease	4-32
Interstitial lung disease	1-7
Cardiac involvement	0-3

From Rider LG, Lindsley CB, Cassidy JT. Juvenile dermatomyositis. In: Cassidy JT, Petty RE, Laxer RM, et al., eds. *Textbook of Pediatric Rheumatology,* 6th ed. Philadelphia: Saunders; 2011: Table 24.20, p. 410.

Children with respiratory muscle weakness do *not* manifest typical symptoms of impending respiratory failure with increased work of breathing, instead demonstrating hypercarbia rather than hypoxemia. Evaluation of respiratory muscle function by negative inspiratory force (NIF) measurement can be performed in the clinic or at the bedside.

DIAGNOSIS

Diagnosis of dermatomyositis requires the presence of a characteristic rash and at least three signs of muscle inflammation and weakness (see Table 200.2). Diagnostic criteria developed in 1975 predate the use of MRI and have not been validated in children. Diagnosis is often delayed because of the insidious nature of disease onset.

Electromyography (EMG) shows signs of myopathy (increased insertional activity, fibrillations, sharp waves) and muscle fiber necrosis (decreased action potential amplitude and duration). Nerve conduction studies are typically normal unless severe muscle necrosis and atrophy are present. It is important that EMG be performed in a center with experience in pediatric EMG and its interpretation. **Muscle biopsy** is typically indicated when the diagnosis is in doubt or for grading disease severity (see Fig. 200.4A). Biopsy of involved muscle reveals focal necrosis and phagocytosis of muscle fibers, fiber regeneration, endomysial proliferation, inflammatory cell infiltrates and vasculitis, and tubuloreticular inclusion bodies within endothelial cells. Findings of lymphoid structures and vasculopathy may portend more severe disease.

Some children present with classic rash but no apparent muscle weakness or inflammation; this variation is called **amyopathic JDM** or **dermatomyositis sine myositis**. It is unclear whether these children have isolated skin disease or mild undetected muscle inflammation, risking progression to more severe muscle involvement with long-term sequelae such as calcinosis and lipodystrophy if untreated.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis depends on the presenting symptoms. If the presenting complaint is solely weakness without rash or atypical disease, other causes of myositis or myopathy should be considered, including polymyositis, infection-related myositis (influenza A and B, coxsackievirus B, and other viral illnesses), muscular dystrophies (e.g., Duchenne, Becker), myasthenia gravis, Guillain-Barré syndrome, endocrinopathies (hyperthyroidism, hypothyroidism, Cushing syndrome, Addison disease, parathyroid disorders), mitochondrial myopathies, TNF receptor–associated periodic syndrome (TRAPS), and metabolic disorders (glycogen and lipid storage diseases). Infections associated with prominent muscular symptoms include trichinosis, *Bartonella* infection, toxoplasmosis, staphylococcal pyomyositis, and SARS-CoV-2. Blunt trauma and crush injuries may lead to transient rhabdomyolysis with myoglobinuria. Myositis in children may also be associated with vaccinations, drugs, growth hormone, and GVHD. The rash of JDM may be confused with dyshidrotic eczema, psoriasis, erythema nodosa, malar rash from SLE, capillary telangiectasias from Raynaud phenomenon, and other rheumatic diseases. Muscle inflammation is also seen in children with SLE, juvenile idiopathic arthritis, mixed connective tissue disease, inflammatory bowel disease, and antineutrophil cytoplasmic antibody–positive vasculitides. Necrotizing immune-mediated myopathies are characterized by muscle necrosis without lymphocytic infiltration. Antibodies to signal recognition particle (SRP) or 3-hydr oxy-3-methylglutaryl-coenzyme A (HMG-CoA) distinguish the two types from each other and from JDM. Table 200.4 compares other juvenile idiopathic inflammatory myositis disorders: JDM, juvenile polymyositis, and juvenile connective tissue myositis.

LABORATORY FINDINGS

Elevated serum levels of muscle-derived enzymes (creatine kinase [CK], aldolase, aspartate transaminase, alanine transaminase [ALT], lactate dehydrogenase) reflect muscle inflammation. Not all enzyme levels rise with inflammation in a specific individual; ALT is usually elevated on initial presentation, whereas CK level may be normal.

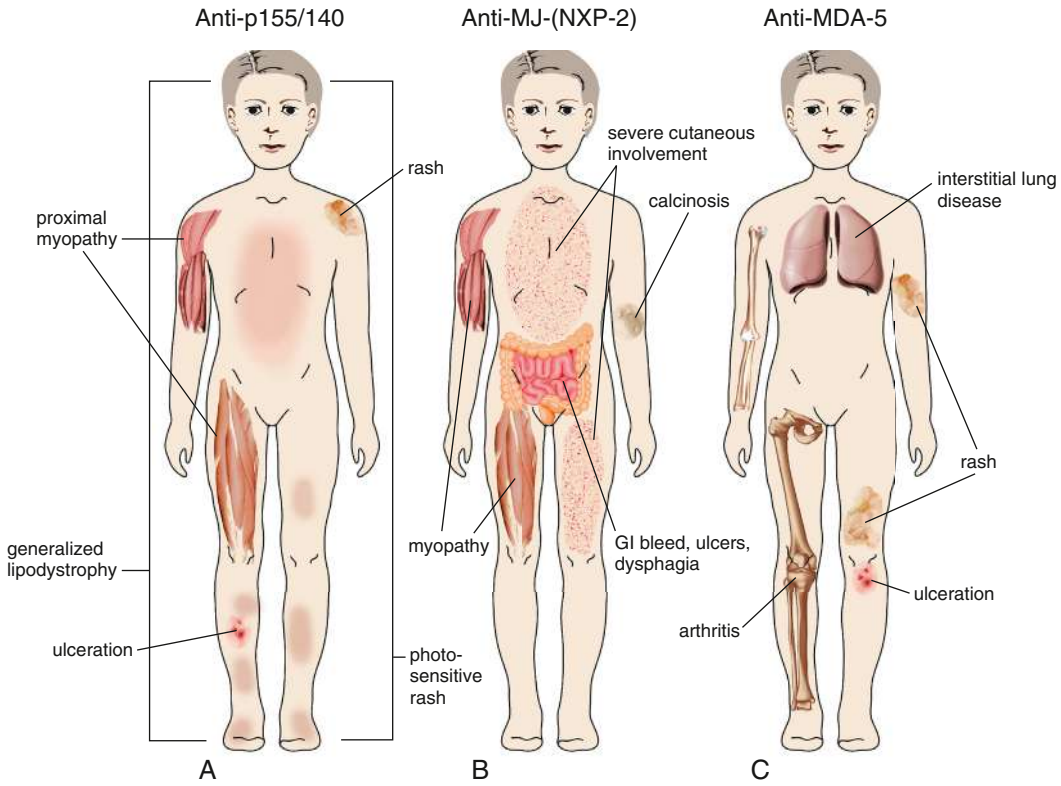

Fig. 200.1 Phenotypes associated with the three most common myositis specific antibodies in children with myositis: anti-p155/140, anti-MJ, and antiMDA-5. **A,** Anti-p155/140, present in 18–30% of idiopathic juvenile inflammatory myopathies, displays an extensive photosensitive rash that ulcerates, a chronic disease course, and generalized lipodystrophy. **B,** Fifteen to twenty-three percent of children positive for anti-MJ (nuclear matrix protein 2 in the United Kingdom) may have disease onset at a younger age and have dysphonia, muscle cramps, atrophy, and contractures, with increased weakness, and they are more likely to develop calcifications and gastrointestinal symptoms; their rash often spares the truncal area. **C,** Anti–MDA-5 is increased in the Japanese population (33%) vs the United Kingdom (6%) and is associated with inflammatory lung disease, oral and cutaneous ulcers, arthritis, and a milder form of muscle involvement. GI, gastrointestinal. *(Modified from Rider LG, Nistala K. The juvenile idiopathic inflammatory myopathies: Pathogenesis, clinical and autoantibody phenotypes, and outcomes.* J Intern Med. *2016;280:24–38, Fig 3.)*

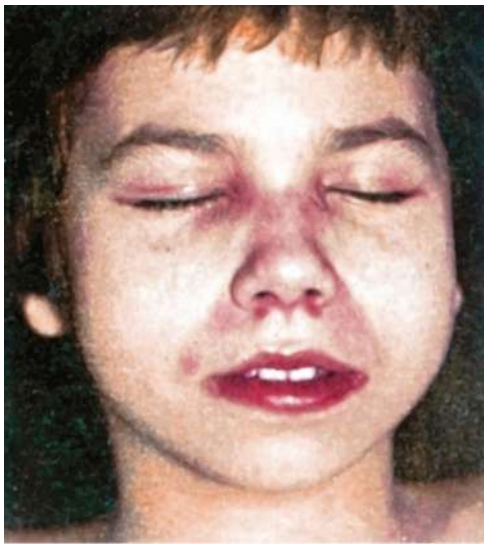

Fig. 200.2 The facial rash of juvenile dermatomyositis. There is erythema over the bridge of the nose and malar areas with violaceous (heliotropic) discolorations of the upper eyelids.

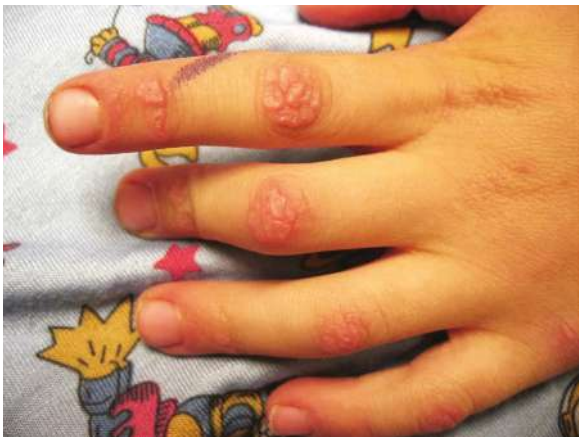

Fig. 200.3 The rash of juvenile dermatomyositis. The skin over the metacarpal and proximal interphalangeal joints may be hypertrophic and pale red (Gottron papules).

The erythrocyte sedimentation rate (ESR) is often normal, and the rheumatoid factor (RF) test result is typically negative. There may be anemia consistent with chronic disease. Antinuclear antibody (ANA) is present in >80% of children with JDM. Serologic testing results are divided into two groups: **myositis-associated antibodies (MAAs)** and **myositis-specific antibodies (MSAs)** (see Table 200.1). MAAs are associated with JDM but are not specific and can be seen in both overlap conditions and other rheumatic diseases. The presence of MAAs such as SSA, SSB, Sm, ribonucleoprotein (RNP), and double-stranded (ds) DNA may increase the likelihood of overlap disease or connective tissue myositis. Antibodies to Pm/Scl identify a small, distinct subgroup of myopathies with a protracted disease course, often complicated by pulmonary interstitial fibrosis and cardiac involvement. MSAs are specific for myositis and are identified in

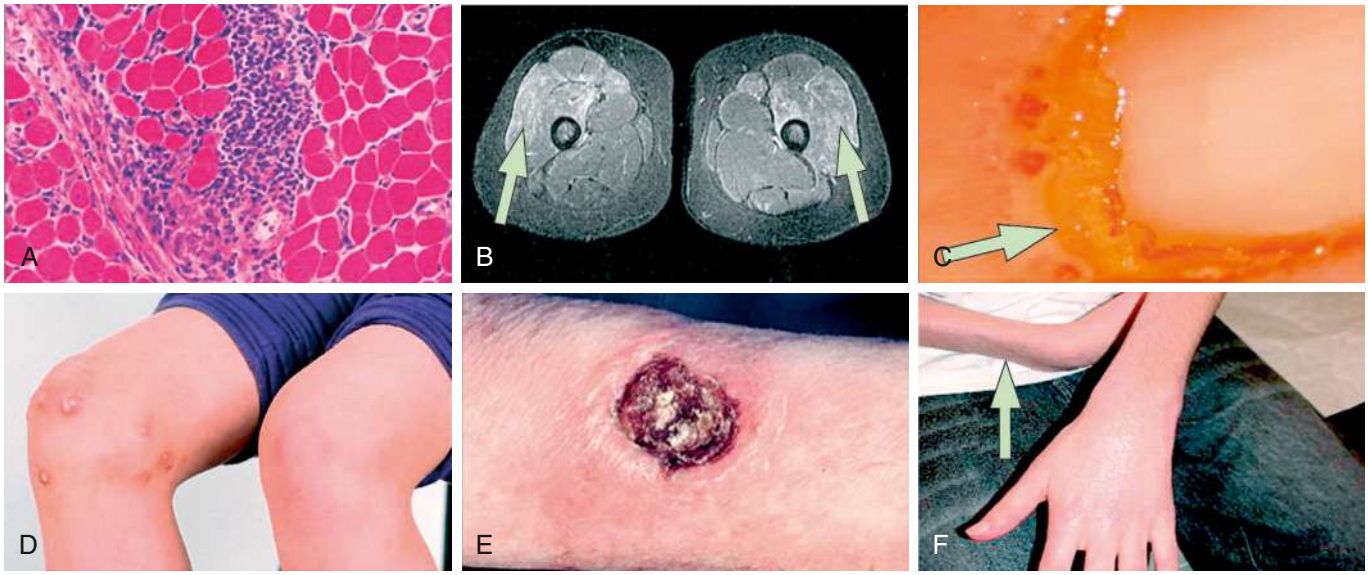

Fig. 200.4 Features of juvenile dermatomyositis. **A,** Perivascular and perifascicular inflammatory infiltrates with necrotic fibers, perifascicular atrophy, and regeneration in a muscle biopsy. **B,** MRI is a sensitive indicator of myositis. Inflamed areas appear bright on short-tau inversion recovery–weighted images *(arrows).* **C,** Capillaries are most often abnormal when viewed at the nail fold. Typical changes of dilation with adjacent dropout *(arrow)* are seen. **D,** About 30% of juvenile dermatomyositis (JDM) patients have dystrophic calcinosis. **E,** Cutaneous ulceration with central necrosis, crust, and surrounding erythema at the elbow of 10-year-old boy with severe JDM. **F,** Lipoatrophy of the forearm *(arrow)* in a boy with JDM. *(From Feldman BM, Rider LG, Reed AM, Pachman LM. Juvenile dermatomyositis and other idiopathic inflammatory myopathies of childhood.* Lancet. *2008;371:2201–2212, Fig. 3, p. 2205.)*

approximately 40–60% of children with JIM. These antibodies suggest a diagnosis of myositis, and their presence may define distinct clinical subsets and may predict prognosis. Anti-TIF-1-γ antibodies are reported in 23–30% of children with JDM and are associated with photosensitive rashes, ulceration, and lipodystrophy. Unlike in adults, this antibody is not associated with malignancy in children with JDM. Anti-NXP2 antibodies are reported in 12–23% of children with JDM and are associated with cramps, muscle atrophy, contractures, and dysphonia. Anti-**MDA5** antibodies are found in approximately 7% of children with JDM and may predict the development of interstitial lung disease (ILD). Because certain MSAs have defined clinical phenotypes in JDM and IFN-related biomarkers that may correlate with disease activity, there is interest in assessing IFN signature by MSA type.

Radiographic studies aid both diagnosis and medical management. MRI using T2-weighted images and fat suppression (see Fig. 200.4B) identifies active sites of disease, reducing sampling error and increasing the sensitivity of muscle biopsy and EMG, results of which are nondiagnostic in 20% of cases if the procedures are not directed by MRI. Extensive rash and abnormal MRI findings may be found despite normal serum levels of muscle-derived enzymes. Muscle biopsy often demonstrates evidence of disease activity and chronicity that is not suspected from the levels of the serum enzymes alone.

A contrast swallow study may document palatal dysfunction and risk of aspiration. Pulmonary function testing detects a restrictive defect consistent with respiratory weakness and reduced diffusion capacity of carbon monoxide from alveolar fibrosis associated with other connective tissue diseases. Serial measurement of vital capacity or negative inspiratory force can document changes in respiratory weakness, especially in an inpatient setting. **Calcinosis** is seen easily on radiographs, along the fascial planes, and within muscles (see Figs. 200.4D and E and Fig. 200.5).

TREATMENT

The aid of an experienced pediatric rheumatologist is invaluable in outlining an appropriate course of treatment for a child with JDM. Before the advent of corticosteroids, one third of patients spontaneously improved; a third had a chronic, lingering course; and a third died from the disease. Corticosteroids have altered the course of the disease, lowering morbidity and mortality. Methotrexate decreases the length of treatment with corticosteroids, thereby reducing morbidity from steroid toxicity. Intravenous (IV) gamma globulin is frequently used as an adjunct for the treatment of severe disease and can be given at 2 g/kg (maximum 70 g) every 2 weeks for three doses, then every 4 weeks as needed. The efficacy and safety have been reported in open-label studies. In the 2010 **Childhood Arthritis and Rheumatology Research Alliance (CARRA)** treatment utilization report, IVIG was used most frequently for initial treatment of severe disease and treatment of refractory disease. It is also a steroid-sparing agent. Consensus treatment plans for guiding treatment of children with JDM are available from CARRA online through PubMed and Figure 200.6.

Corticosteroids remain the mainstay of treatment. In a clinically stable child without debilitating weakness, oral prednisone at 2 mg/kg/day (maximum 60 mg daily) is recommended. Children with GI involvement may have decreased absorption of oral corticosteroids and require IV administration. In more severe cases with respiratory or oropharyngeal weakness, high-dose pulse methylprednisolone is used (30 mg/kg/day for 3 days, maximum dose 1 g/day) with ongoing weekly or monthly IV dosing along with daily oral corticosteroids as needed. Corticosteroid dosage is slowly tapered over 12 months, after indicators of inflammation (muscle enzymes) normalize and strength improves.

Weekly oral, IV, or subcutaneous methotrexate (the lesser of 1 mg/kg or 15 mg/m^2) is often used as a steroid-sparing agent in JDM. The concomitant use of methotrexate halves the cumulative dosage of steroids needed for disease control. Risks of methotrexate include immunosuppression, blood count dyscrasias, chemical hepatitis, pulmonary toxicity, nausea/vomiting, and teratogenicity. *Folic acid is typically given with methotrexate starting at a dose of 1 mg daily to reduce toxicity and side effects of folate inhibition (oral ulcers, nausea, anemia).* Children who are taking immunosuppressive medications such as methotrexate should avoid live-virus vaccination, although inactivated influenza vaccination is recommended yearly. An international trial found the combination of methotrexate plus corticosteroids to perform better than corticosteroids alone and with fewer side effects than corticosteroids plus cyclosporine A.

Hydroxychloroquine has little toxicity risk and is used as a secondary disease-modifying agent to reduce rash and maintain remission.

Table 200.4 Frequency of Manifestations of Juvenile Dermatomyositis (JDM), Juvenile Polymyositis (JPM), and Overlap Myositis

	FREQUENCY AT ONSET (%)		
MANIFESTATION	**JDM**	**JPM**	**OVERLAP MYOSITIS**
Progressive proximal muscle weakness	82-100	100	100
Easy fatigue	80-100	85	84
Gottron papules	57-91	0	74-80
Heliotrope rash	66-87	0	40-59
Erythematous rash of malar/facial area	42-100	0-6	20-51
Periungual nailfold capillary changes	35-91	33	67-80
Muscle pain or tenderness	25-83	61-66	55
Weight loss	33-36	52	53
Falling episodes	40	59	29
Arthritis	10-65	0-45	69-80
Fever	16-65	0-41	0-49
Lymphadenopathy	8-75	0-12	20-22
Dysphagia or dysphonia	15-44	39	40
Joint contractures	9-55	17-42	57-60
V- or shawl-sign rashes	19-29	3-6	8-14
Dyspnea on exertion	5-43	17-42	40
Gastrointestinal symptoms	5-37	9-33	6-53
Photosensitive rashes	5-51	0-6	22-40
Raynaud phenomenon	9-28	0-24	41-60
Edema	11-34	15	20
Gingivitis	6-30	9	0-37
Cutaneous ulceration	5-30	3	20-22
Calcinosis	3-34	6	24
Cardiac involvement	2-13	36	19
Interstitial lung disease	5	15	26
Lipodystrophy	4-14	3	0-6
Gastrointestinal bleeding or ulceration	3-4	3	4-10

From Rider LG, Lindsley CB, Miller FW. Juvenile Dermatomyositis. In: Petty RE, Laxer RM, Lindsley CB, Wedderburn L, eds. *Textbook of Pediatric Rheumatology,* 7th ed. Philadelphia: Elsevier; 2016: Table 26.4.

Typically, it is administered at doses of 4-6 mg/kg/day orally in either tablet or liquid form. Ophthalmologic follow-up one time per year to monitor for rare retinal toxicity is recommended. Other side effects include hemolysis in patients with glucose-6-phosphate deficiency, GI intolerance, and skin/hair discoloration.

The use of **rituximab** in a trial of steroid-dependent patients with resistant inflammatory myopathies, including JDM, did not meet the primary study end-point showing a difference in time to improvement between individuals given rituximab at baseline or at 8 weeks, but overall, 83% of all patients met the definition of improvement in the trial. Additionally, rituximab was noted to have a significant steroid-sparing effect.

Other medications used to treat severe refractory disease include mycophenolate mofetil, cyclosporine, and cyclophosphamide. Given the strong type I IFN signal in JDM and that these cytokines activate intracellular signaling through the Janus kinase (JAK)/signal transducers and activators of transcription (STAT) pathway, consideration of JAK inhibitors, including *tofacitinib,* baricitinib, and ruxolitinib, as potential therapeutic candidates has been bolstered by case reports and case series that report generally promising results with these drugs in off-label treatment of JDM.

Children with pharyngeal weakness may need nasogastric or gastrostomy feedings to avoid aspiration, whereas those with GI vasculitis require full bowel rest. Rarely, children with severe respiratory weakness require ventilator therapy and even tracheostomy until the respiratory weakness improves.

Physical therapy and **occupational therapy** are integral parts of the treatment program, initially for passive stretching early in the disease course and then for direct reconditioning of muscles to regain strength and range of motion. Therapy may improve muscle strength measures and cardiovascular fitness. Bed rest is not indicated, because weight bearing improves bone density and prevents contractures. Social work and psychology services may facilitate adjustment to the frustration of physical impairment in a previously active child and aid with sleep disturbances associated with rheumatic disease.

All children with JDM should avoid sun exposure and apply high–sun protection factor (SPF) sunscreen daily, even in winter and on cloudy days. Vitamin D and calcium supplements are indicated for all

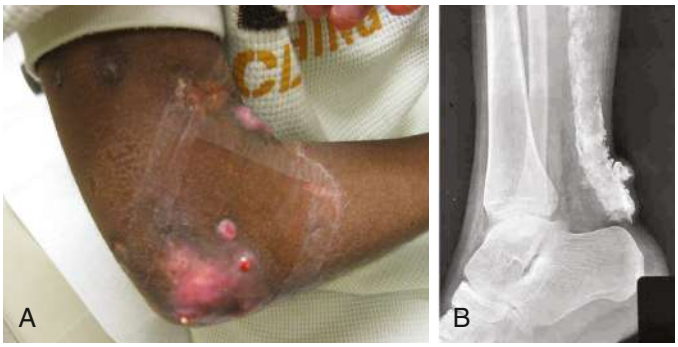

Fig. 200.5 Calcifications in dermatomyositis. A, Skin effects of calcification. B, Radiographic evidence of calcification.

MODERATE JDM
Plan 1 Methotrexate[a] 15 mg/m^2 or 1 mg/kg weekly AND Prednisone[b] 2 mg/kg/d for 4 wk then decrease by 20%
Plan 2 *Plan 1* AND IV methylprednisolone 30 mg/kg for 3 d, then weekly[c]
Plan 3 *Plan 2* AND IVIG 2 g/kg[d] q2wk × 3 doses then monthly
SKIN PREDOMINANT JDM
Plan 1 Hydroxychloroquine 5 mg/kg/d[e]
Plan 2 *Plan 1* AND Methotrexate[a] 15 mg/m^2 or 1 mg/kg weekly
Plan 3 *Plan 2* AND Prednisone[b] 2 mg/kg/d for 4 wk then decrease by 20%
SKIN RESISTANT JDM
Plan 1 IVIG 2 g/kg[d] q2wks × 3 doses then monthly
Plan 2 *Plan 1* AND Mycophenolate mofetil[f] BID 10 mg/kg/dose OR 600 mg/m^2
Plan 3 Cyclosporine 3 mg/kg[g]

Fig. 200.6 Recommended consensus treatment plans from CARRA for JDM patients with moderate, skin-predominant, and skin-resistant disease. IV, intravenous; IG, immunoglobulin. [a]Lesser of 15 mg/m^2 or 1 mg/kg (max 40 mg), [b]max 60 mg, [c]optional, [d]max 70 g, [e]max 400 mg, [f]max 1,500 mg bid, [g]higher doses based on toxicity, efficacy. *(From Kim H, Huber AM, Kim S. Updates on juvenile dermatomyositis from the last decade: classification to outcomes.* Rheum Dis Clin N Am. *2021;47:669–690, Fig. 1, p. 679.)*

children undergoing long-term corticosteroid therapy to reduce drug-induced osteopenia and osteoporosis.

COMPLICATIONS

Most complications from JDM are related to prolonged and severe weakness from muscle atrophy to cutaneous calcifications and scarring or atrophy to lipodystrophy. Secondary complications from medical treatments are also common. Children with acute and severe weakness are at risk for aspiration pneumonia and respiratory failure and occasionally require nasogastric feeding and mechanical ventilation until weakness improves. Rarely, **vasculitis** of the GI tract develops in children with severe JDM. Crampy abdominal pain and occult GI bleeding may indicate bowel wall vasculitis and lead to ischemia, GI bleeding, and perforation if not treated with complete bowel rest and aggressive treatment for the underlying inflammation. Surgery should be avoided, if possible, because the GI vasculitis is diffuse and not easily amenable to surgical intervention. Contrast-enhanced CT may show dilation or thickening of the bowel wall, intraluminal air, or evidence of bowel necrosis.

Involvement of the cardiac muscle with pericarditis, myocarditis, and conduction defects with arrhythmias has been reported, as has reduced diastolic and systolic function related to ongoing disease activity.

Lipodystrophy and **calcinosis** are thought to be associated with long-standing or undertreated disease (see Fig. 200.4D-F). Dystrophic deposition of calcium phosphate, hydroxyapatite, or fluoroapatite crystals occurs in subcutaneous plaques or nodules, resulting in painful ulceration of the skin with extrusion of crystals or calcific liquid. Calcification is found in up to 40% of large cohorts of children with JDM. Pathologic calcifications may be related to severity of disease and prolonged delay to treatment and potentially to genetic polymorphisms of TNF-α-308. Calcium deposits tend to form in subcutaneous tissue and along muscle. Some ulcerate through the skin and drain a soft calcific liquid, and others manifest as hard nodules along extensor surfaces or embedded along muscle. Draining lesions serve as a nidus for cellulitis or osteomyelitis. Nodules cause skin inflammation that may mimic cellulitis. Spontaneous regression of calcium deposits may occur, but there is no evidence-based recommendation for treatment of calcinosis. Some experts recommend aggressive treatment of underlying myositis. Others have recommended bisphosphonates, TNF inhibitors, and sodium thiosulfate, but no evidence-based trials have been conducted for this condition.

Lipodystrophy manifests in 10–40% of patients with JDM and can be difficult to recognize. Lipodystrophy results in progressive loss of subcutaneous and visceral fat, typically over the face and upper body, and may be associated with a metabolic syndrome similar to polycystic ovarian syndrome with insulin resistance, hirsutism, acanthosis, hypertriglyceridemia, and abnormal glucose tolerance. Lipodystrophy may be generalized or localized.

Children receiving prolonged corticosteroid therapy are prone to complications such as cessation of linear growth, weight gain, hirsutism, adrenal suppression, immunosuppression, striae, cushingoid fat deposition, mood changes, osteoporosis, cataracts, avascular necrosis, and steroid myopathy. Families should be counseled on the effects of corticosteroids and advised to use medical alert identification and to consult a nutritionist regarding a low-salt, low-fat diet with adequate vitamin D and calcium supplementation.

An association with malignancy at disease onset is observed in adults with dermatomyositis but very rarely in children.

PROGNOSIS

The mortality rate in JDM has decreased since the advent of corticosteroids, from 33% to currently approximately 1%; little is known about the long-term consequences of persistent vascular inflammation. The period of active symptoms has decreased from about 3.5 years to <1.5 years with more aggressive immunosuppressive therapy; the vascular, skin, and muscle symptoms of children with JDM generally respond well to therapy. At 7 years of follow-up, 75% of patients have little to no residual disability, but 25% continue to have chronic weakness and 40% have chronic rash. Up to one-third may need long-term medications to control their disease. Children with JDM appear able to repair inflammatory damage to vasculature and muscle, but there is some emerging concern about long-term effects on cardiovascular risk.

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Chapter 201

Scleroderma and Raynaud Phenomenon

Heather A. Van Mater and C. Egla Rabinovich

Juvenile scleroderma encompasses a range of conditions unified by the presence of fibrosis of the skin. Juvenile scleroderma is divided into two major categories, **juvenile localized scleroderma** (**JLS**, also known as **morphea**), which is largely limited to the skin, and **juvenile systemic sclerosis (JSSc)**, with multisystem organ involvement. Localized disease is the predominant type seen in pediatric populations (>95%), but systemic sclerosis is associated with mortality and severe multiorgan morbidity.

ETIOLOGY AND PATHOGENESIS

The etiology of scleroderma is unknown, but the mechanism of disease appears to be a combination of a vasculopathy, autoimmunity, immune activation, and fibrosis. Triggers, including trauma, infection, and, possibly, subclinical graft versus host reaction from persistent maternal cells *(microchimerism)*, injure vascular endothelial cells, resulting in increased expression of adhesion molecules. These molecules entrap platelets and inflammatory cells, resulting in vascular changes with manifestations such as Raynaud phenomenon and pulmonary hypertension. Inflammatory cells infiltrate the area of initial vascular damage, causing further vascular damage and resulting in thickened artery walls and reduction in capillary numbers. Macrophages and other inflammatory cells then migrate into affected tissues and secrete cytokines that induce fibroblasts to reproduce and synthesize excessive amounts of collagen, resulting in fibrosis and subsequent lipoatrophy and dermal fibrosis, with loss of sweat glands and hair follicles. In late stages the entire dermis may be replaced by compact collagen fibers.

Autoimmunity is believed to be a key process in the pathogenesis of both localized and systemic scleroderma, given the high percentage of affected children with autoantibodies (Table 201.1). Children with localized disease often have a positive antinuclear antibody (ANA) test result (42%), and 47% of this subgroup have antihistone antibodies. Children with JSSc have higher rates of ANA positivity (80.7%) and may have anti–Scl-70 antibody (34%, antitopoisomerase I). The relationship between specific autoantibodies and the various forms of scleroderma is not well understood, and all antibody test results may be negative, especially in JLS.

CLASSIFICATION

Localized scleroderma is distinct from systemic scleroderma and rarely progresses to systemic disease. The category of JLS includes several subtypes differentiated by both the distribution of the lesions and the depth of involvement (Tables 201.2 and 201.3). Up to 15% of children have a combination of two or more subtypes.

EPIDEMIOLOGY

Juvenile scleroderma is rare, with an estimated prevalence of 1 in 100,000 children. Localized scleroderma (LS) is much more common than systemic sclerosis (SSc) in children, by a 10:1 ratio, with **linear scleroderma** being the most common subtype. LS is predominantly a pediatric condition, with 65% of patients diagnosed before age 18 years. After age 8 years the female/male ratio for both LS and SSc is approximately 3:1, whereas in patients younger than 8 years, the prevalence is equal.

CLINICAL MANIFESTATIONS

Localized Scleroderma

The onset of scleroderma is generally insidious, and manifestations vary according to disease subtype. The initial skin manifestations of localized disease usually include erythema or a bluish hue seen around an area of waxy induration; subtle erythema may be the only presenting

Table 201.1 Clinical Subtypes of Systemic Sclerosis: Associated Organ Manifestations and Autoantibody Association

SUBTYPE	ORGAN SYSTEM	ORGAN SYSTEM FEATURES	ANTIBODY ASSOCIATION
Diffuse cutaneous (dc)	Skin	Thickness proximal to elbows and knees Rapid progressive thickening	Topoisomerase (Scl-70) RNA Polymerase III U3-RNP (fibrillarin)
	Cardiac	Congestive heart failure Conduction abnormalities	
	Renal	Scleroderma renal crisis	
	Pulmonary	Interstitial lung disease	
Limited cutaneous (lc)	Skin	Thickness limited to distal extremities (and face) Restricted and nonprogressive thickening	Centromere Th/To
	Gastrointestinal	Esophageal dysmotility GI strictures Malabsorption	
	Pulmonary	Pulmonary arterial hypertension	
Overlap syndrome	Skin	Either dcSSc or lcSSc pattern Skin manifestations of other CTD, such as Gottron papules (DM) and malar rash (SLE)	PM-Scl U1-RNP Ku
	Musculoskeletal	Arthritis	
		Myositis	
	Cardiac	Can have any of the dcSSc or lcSSc manifestations Additional organ involvement in association with other CTD feature, such as lupus nephritis	
	Renal		
	Pulmonary		
	Gastrointestinal		

CTD, Connective tissue disease; DM, dermatomyositis; PM-Scl, polymyositis-scleroderma antibody; SLE, systemic lupus erythematosus; U1-RNP, U1 ribonucleoprotein antibody.
From Petty RE, Laxer RM, Lindsley CB, et al., eds. *Textbook of Pediatric Rheumatology,* 8th ed. Philadelphia: Elsevier; 2021: Table 27.3, p. 382.

Table 201.2 Classification of Pediatric Scleroderma (Morphea)

LOCALIZED SCLERODERMA
Plaque morphea
Confined to dermis, occasionally superficial panniculus
Well-circumscribed circular area of induration, often a central waxy, ivory-colored area surrounded by a violaceous halo; unilateral
Generalized morphea
Involves dermis primarily, occasionally panniculus
Defined as confluence of individual morphea plaques or lesions in three or more anatomic sites; more likely to be bilateral
Bullous morphea
Bullous lesions that can occur with any of the subtypes of morphea
Linear scleroderma
Linear lesions can extend through the dermis, subcutaneous tissue, and muscle to underlying bone; more likely unilateral
Limbs/trunk:
One or more linear streaks of the extremities or trunk
Flexion contracture occurs when lesion extends over a joint; limb-length discrepancies
En coup de sabre:
Involves the scalp and/or face; lesions can extend into the central nervous system, resulting in neurologic sequelae, most commonly seizures and headaches
Parry-Romberg syndrome:
Hemifacial atrophy without a clearly definable en coup de sabre lesion; can also have neurologic involvement
Deep Morphea
Involves deeper layers, including panniculus, fascia, and muscle; more likely to be bilateral
Subcutaneous morphea:
Primarily involves the panniculus or subcutaneous tissue
Plaques are hyperpigmented and symmetric
Eosinophilic fasciitis:
Fasciitis with marked blood eosinophilia
Fascia is the primary site of involvement; typically involves extremities
Classic description is "peau d'orange," or orange peel texture, but early disease manifests as edema (see Fig. 201.2)
Morphea profunda:
Deep lesion extending to fascia and sometimes muscle, but may be limited to a single plaque, often on the trunk
Disabling pansclerotic morphea of childhood:
Generalized full-thickness involvement of skin on the trunk, face, and extremities, sparing fingertips and toes
SYSTEMIC SCLEROSIS
Diffuse
Most common type in childhood
Symmetric thickening and hardening of the skin (sclerosis) with fibrous and degenerative changes of viscera
Limited
Rare in childhood
Previously known as CREST (calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia) syndrome

Table 201.3 Provisional Criteria for Classification of Juvenile Systemic Sclerosis (JSSc)

MAJOR CRITERION (REQUIRED)*
Proximal skin sclerosis/induration of the skin proximal to metacarpophalangeal or metatarsophalangeal joints
MINOR CRITERIA (AT LEAST TWO REQUIRED)
Cutaneous: Sclerodactyly
Peripheral vascular: Raynaud phenomenon, nail fold capillary abnormalities (telangiectasias), digital tip ulcers
Gastrointestinal: Dysphagia, gastroesophageal reflux
Cardiac: Arrhythmias, heart failure
Renal: Renal crisis, new-onset arterial hypertension
Respiratory: Pulmonary fibrosis (high-resolution CT/radiography), decreased diffusing capacity for carbon monoxide, pulmonary arterial hypertension
Neurologic: Neuropathy, carpal tunnel syndrome
Musculoskeletal: Tendon friction rubs, arthritis, myositis
Serologic: Antinuclear antibodies—SSc-selective autoantibodies (anticentromere, antitopoisomerase I [Scl-70], antifibrillarin, anti-PM/Scl, antifibrillin, or anti-RNA polymerase I or III)

*Diagnosis requires at least one major and at least two minor criteria.
From Zulian F, Woo P, Athreya BH, et al. The Pediatric Rheumatology European Society/American College of Rheumatology/European League against Rheumatism provisional classification criteria for juvenile systemic sclerosis. *Arthritis Rheum.* 2007;57:203–212.

sign (Fig. 201.1). Edema and erythema are followed by indurated, hypopigmented or hyperpigmented atrophic lesions (Fig. 201.2). LS varies in size from a few centimeters to the entire length of the extremity, with varying depth. Patients may present with arthralgias, synovitis, or flexion contractures (Fig. 201.3). Children also experience limb-length discrepancies as a result of growth impairment caused by involvement of muscle and bone. Children with **en coup de sabre** may have symptoms unique to central nervous system (CNS) involvement, such as seizures, hemifacial atrophy, ipsilateral uveitis, and learning/behavioral changes (Fig. 201.4). Up to 25% of children with LS have extracutaneous manifestations, most frequently arthritis (47%) in linear disease and neurologic symptoms (17%) associated with en coup de sabre.

Systemic Scleroderma

SSc is a severe disease in children, starting with an insidious onset followed by a prolonged course characterized by periods of remission and exacerbation, commonly resulting in chronic disability and death, with a 5-year mortality rate of 7.5%.

The **skin manifestations** of SSc include an early phase of edema that spreads proximally from the dorsum of the hands and fingers and includes the face. An eventual decrease in edema is followed by induration and fibrosis of skin, ultimately resulting in loss of subcutaneous fat, sweat glands, and hair follicles. Later, atrophic skin becomes shiny and waxy in appearance. As lesions spread proximally, flexion contractures develop at the elbows, hips, and knees associated with secondary muscle weakness and atrophy. In the face, this process results in a small oral stoma with decreased mouth aperture. Skin ulceration over pressure points, such as the elbows, may be associated with subcutaneous calcifications. Severe **Raynaud phenomenon** (RP; Fig. 201.5) causes ulceration of the fingertips with subsequent loss of tissue pulp and tapered fingers **(sclerodactyly)** (Fig. 201.6). Resorption of the distal tufts of the distal phalanges may occur **(acroosteolysis)**. Hyperpigmented postinflammatory changes surrounded by atrophic depigmentation give a salt-and-pepper appearance to skin. Over years, remodeling of lesions sometimes results in focal improvement in skin thickening.

Pulmonary disease is the most common visceral manifestation of SSc and includes both arterial and interstitial involvement (alveolitis). Symptoms range from asymptomatic disease to exercise intolerance, dyspnea at

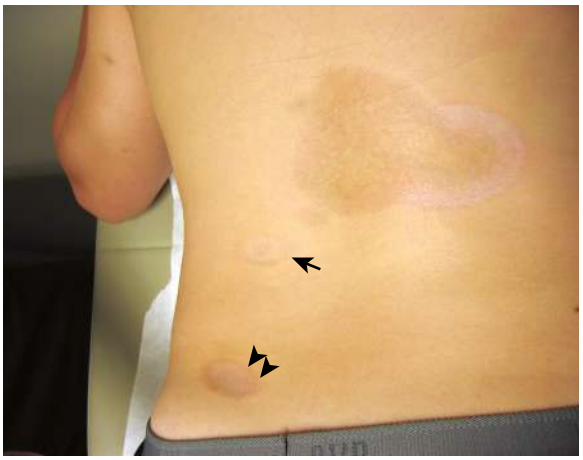

Fig. 201.1 Child with generalized morphea. Note the active circular lesion *(arrowheads)* with a surrounding rim of erythema. The largest lesion has areas of postinflammatory hyperpigmentation and depression with an area of erythema on the right. The small lesion *(arrow)* demonstrates depression caused by lipoatrophy.

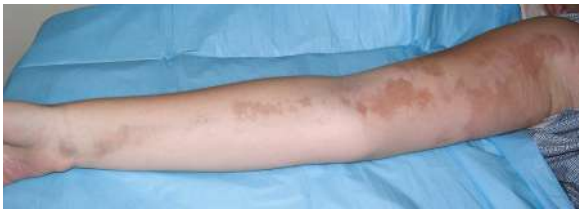

Fig. 201.2 Inactive linear scleroderma demonstrating hyperpigmented lesion with areas of normal skin (skip lesions).

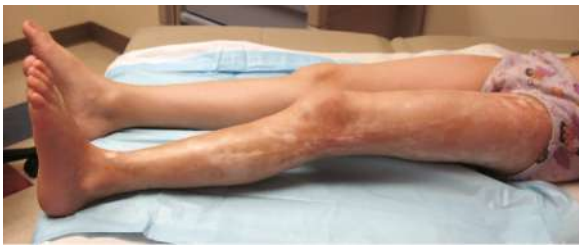

Fig. 201.3 Child with untreated linear scleroderma resulting in knee contracture, immobility of ankle, chronic skin breakdown of scar on the lateral knee, and areas of hypopigmentation and hyperpigmentation. The affected leg is 1 cm shorter.

rest, and right-sided heart failure. **Pulmonary arterial hypertension** is a poor prognostic sign, developing because of lung disease or independently as part of the vasculopathy. Clinical manifestations of pulmonary arterial hypertension in children appear late in the course, are subtle, and include cough and dyspnea on exertion. Pulmonary evaluation should include pulmonary function tests (PFTs) such as diffusion capacity of carbon monoxide (DLco), bronchoalveolar lavage (BAL), and high-resolution chest computed tomography (HRCT). PFTs reveal decreased vital capacity and decreased DLco, whereas neutrophilia or eosinophilia on BAL suggests active alveolitis. Chest CT is much more sensitive than chest radiographs, which are often normal, showing typical basilar ground-glass abnormalities, reticular linear opacities, nodules, honeycombing, and mediastinal adenopathy.

Gastrointestinal tract disease is seen in 25% of children with SSc. Common manifestations include esophageal and intestinal dysmotility resulting in dysphagia, reflux, dyspepsia, gastroparesis, bacterial overgrowth, dilated bowel loops and pseudoobstruction, and dental caries, as well as malabsorption and failure to thrive. **Renal** arterial disease can cause chronic or severe episodic hypertension; unlike adult disease, renal

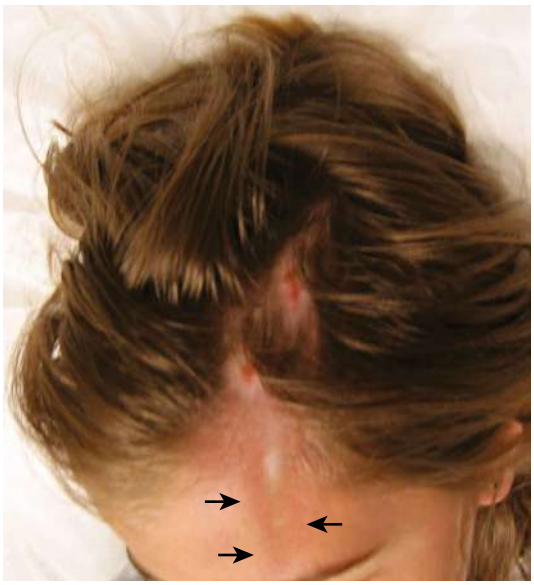

Fig. 201.4 Child with en coup de sabre lesion on scalp extending down to forehead. Before treatment, the skin on the scalp was bound down with chronic skin breakdown. Note the area of hypopigmentation extending down the forehead *(arrows)*.

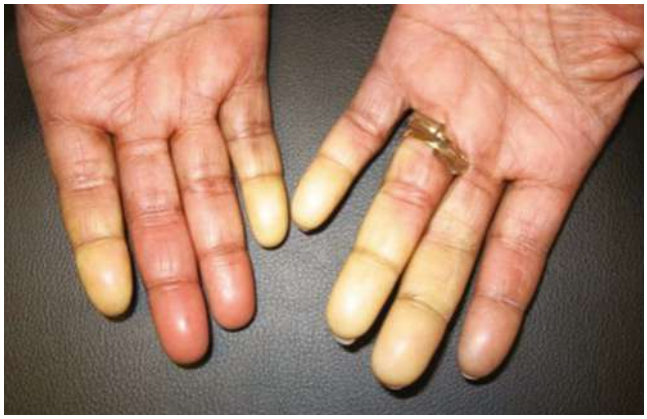

Fig. 201.5 Active Raynaud phenomenon with well-demarcated pallor at the fingertips in a patient with scleroderma. *(From Firestein GS, Budd RC, Gabriels SE, et al., eds.* Firestein & Kelley's Textbook of Rheumatology, *11th ed. Philadelphia: Elsevier; 2021: Fig. 89.2, p. 1507.)*

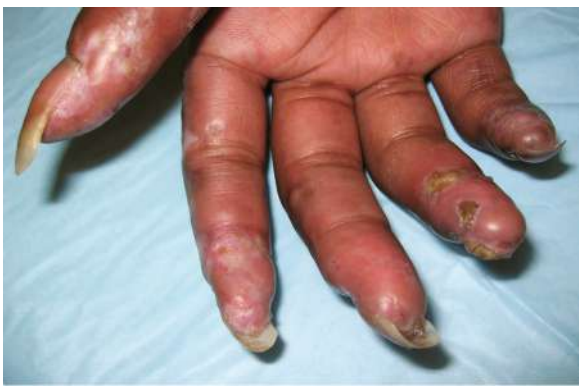

Fig. 201.6 Sclerodactyly and finger ulcerations in a patient with systemic sclerosis who is poorly compliant with treatment.

crisis is rare. **Cardiac** fibrosis is associated with arrhythmias, ventricular hypertrophy, and decreased cardiac function. Mortality from JSSc is usually a result of cardiopulmonary disease. A scoring system helps identify the severity of the multiorgan involvement (Table 201.4).

Table 201.4 Medsger Systemic Sclerosis Severity Scale*

ORGAN SYSTEM	0 (NORMAL)	1 (MILD)	2 (MODERATE)	3 (SEVERE)	4 (END STAGE)
General	Wt loss <5% Hct 37%+ Hb 12.3+ g/dL	Wt loss 5–10% Hct 33–37% Hb 11.0-12.2 g/dL	Wt loss 10–15% Hct 29–33% Hb 9.7-10.9 g/dL	Wt loss 15–20% Hct 25–29% Hb 8.3-9.6 g/dL	Wt loss 20%+ Hct 25% Hb <8.3 g/dL
Peripheral vascular	No RP; RP not requiring vasodilators	RP requiring vasodilators	Digital pitting scars	Digital tip ulcerations	Digital gangrene
Skin	TSS 0	TSS 1-14	TSS 15-29	TSS 30-39	TSS 40+
Joint/tendon	FTP 0-0.9 cm	FTP 1.0-1.9 cm	FTP 2.0-3.9 cm	FTP 4.0-4.9 cm	FTP 5.0+ cm
Muscle	Normal proximal muscle strength	Proximal weakness, mild	Proximal weakness, moderate	Proximal weakness, severe	Ambulation aids required
Gastrointestinal tract	Normal esophagogram; normal small bowel series	Distal esophageal hypoperistalsis; small bowel series abnormal	Antibiotics required for bacterial overgrowth	Malabsorption syndrome; episodes of pseudoobstruction	Hyperalimentation required
Lung	DLCO 80%+ FVC 80%+ No fibrosis on radiograph sPAP <35 mm Hg	DLCO 70–79% FVC 70–79% Basilar rales; fibrosis on radiograph sPAP 35-49 mm Hg	DLCO 50–69% FVC 50–69% sPAP 50-64 mm Hg	DLCO <50% FVC <50% sPAP 65+ mm Hg	Oxygen required
Heart	ECG normal LVEF 50%+	ECG conduction defect LVEF 45–49%	ECG arrhythmia LVEF 40–44%	ECG arrhythmia requiring therapy LVEF 30–40%	CHF LVEF <30%
Kidney	No history of SRC with serum creatinine <1.3 mg/dL	History of SRC with serum creatinine <1.5 mg/dL	History of SRC with serum creatinine 1.5-2.4 mg/dL	History of SRC with serum creatinine 2.5-5.0 mg/dL	History of SRC with serum creatinine >5.0 mg/dL or dialysis required

*If two items are included for a severity grade, only one is required for the patient to be scored as having disease of that severity level.
CHF, Congestive heart failure; DLCO, diffusing capacity for carbon monoxide, % predicted; ECG, electrocardiogram; FTP, fingertip-to-palm distance in flexion; FVC, forced vital capacity, % predicted; Hb, hemoglobin; Hct, hematocrit; LVEF, left ventricular ejection fraction; RP, Raynaud phenomenon; sPAP, estimated pulmonary artery pressure by Doppler echo; SRC, scleroderma renal crisis; TSS, total skin score; Wt, weight.
Modified from Medsger TA Jr, Bombardieri S, Czirjak L, et al. Assessment of disease severity and prognosis, *Clin Exp Rheumatol*. 2003;21(3 Suppl 29):S51, Table 1, p. S-43.

Raynaud Phenomenon

Raynaud phenomenon is the most frequent initial symptom in pediatric SSc, present in 70% of affected children months to years before other manifestations and seen in nearly all over the course of the disease. RP refers to the classic triphasic sequence of blanching, cyanosis, and erythema of the digits induced by cold exposure and/or emotional stress (see Fig. 201.5). RP is typically independent of an underlying rheumatic disease (Raynaud disease) but can result from rheumatic diseases such as scleroderma, systemic lupus erythematosus (SLE), and mixed connective tissue disease (Fig. 201.7). The color changes are brought about by (1) initial arterial vasoconstriction, resulting in hypoperfusion and pallor (blanching), (2) venous stasis (cyanosis), and (3) reflex vasodilation caused by the factors released from the ischemic phase (erythema). The color change is classically reproduced by immersing the hands in iced water and reversed by warming. During the blanching phase, there is inadequate tissue perfusion in the affected area, associated with pain and paresthesias and resulting in ischemic damage only when associated with a rheumatic disease. The blanching usually affects the distal fingers but may also involve thumbs, toes, ears, and tip of the nose. The affected area is usually well demarcated and uniformly white. *Digital ulcers* associated with RP are indicative of underlying rheumatic disease.

Raynaud disease often begins in adolescence and is characterized by symmetric occurrence, the absence of digital ulcers, tissue necrosis and gangrene, and the lack of manifestations of an underlying rheumatic disease. Children have normal nail fold capillaries (absence of periungual telangiectasias). RP should be distinguished from acrocyanosis and chilblains. **Acrocyanosis** is a vasospastic disorder resulting in cool, painless, bluish discoloration in the hands and feet despite normal tissue perfusion. It may be exacerbated by stimulant medications used to treat attention-deficit disorder. **Chilblains** is a condition with episodic color changes and the development of nodules related to severe cold exposure and spasm-induced vessel and tissue damage; it has been associated with SLE and is also referred to as *lupus pernio*, but the majority of children with chilblains do not have lupus.

DIAGNOSIS

The diagnosis of JLS is based on the distribution and depth of characteristic lesions. Biopsy is helpful to confirm the diagnosis. The diagnosis of JSSc requires proximal sclerosis/induration of the skin and the presence of 2 of 20 minor criteria (see Table 201.3).

DIFFERENTIAL DIAGNOSIS

The most important condition to differentiate from JLS is JSSc. Contractures and synovitis from juvenile arthritis can be differentiated from those caused by LS by the absence of skin changes. Other conditions to consider include chemically induced scleroderma-like disease, diabetic cheiroarthropathy, pseudoscleroderma, and scleredema. **Pseudoscleroderma** comprises a group of unrelated diseases characterized by patchy or diffuse cutaneous fibrosis without the other manifestations of scleroderma. These include phenylketonuria, syndromes of premature aging, and localized idiopathic fibrosis. **Scleredema** is a transient, self-limited disease of both children and adults that has sudden onset after a febrile illness (especially streptococcal infections) and is characterized by patchy sclerodermatous lesions on the neck and shoulders and extending to the face, trunk, and arms.

Laboratory Findings

No laboratory studies are diagnostic of either localized or systemic scleroderma. Although the results of complete blood counts, serum chemistry analyses, and urinalysis are normal, children may have elevated erythrocyte sedimentation rate, eosinophilia, or hypergammaglobulinemia, all of which normalize with treatment. Elevations of muscle enzymes, particularly aldolase, can be seen with muscle

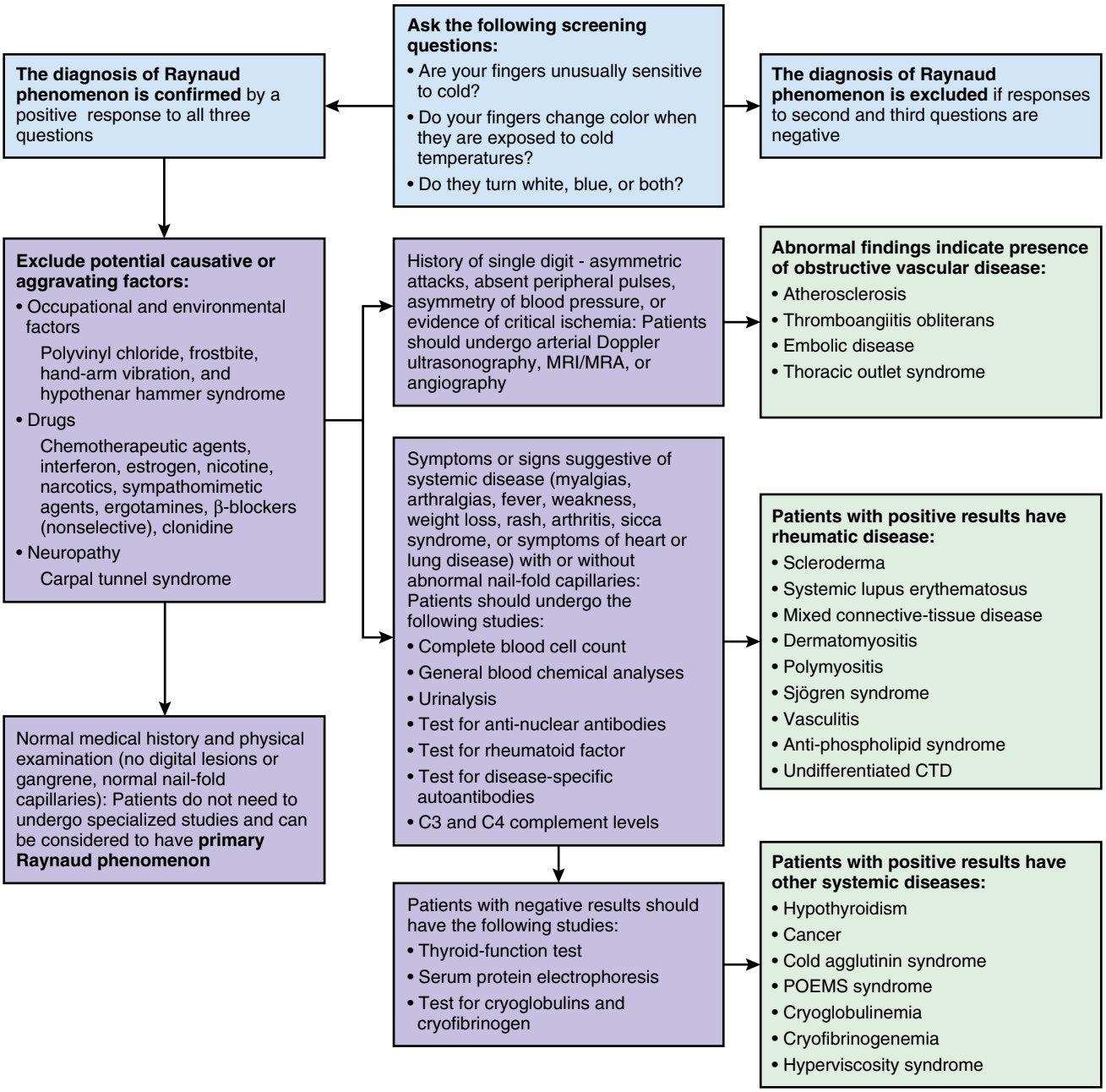

Fig. 201.7 Diagnostic algorithm for Raynaud phenomenon. CTD, Connective tissue disease; MRA, magnetic resonance angiography; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes. *(From Firestein GS, Budd RC, Gabriel SE, et al., eds.* Kelley & Firestein's Textbook of Rheumatology*, 10th ed. Philadelphia: Elsevier; 2017: Fig 84-3.)*

involvement. Patients with JSSc may have anemia, leukocytosis, and eosinophilia and autoantibodies (ANA, anti–Scl-70). Imaging studies delineate the affected area and can be used to follow disease progression. MRI is useful in en coup de sabre and Parry-Romberg syndrome (facial hemiatrophy) for determination of CNS or orbital involvement. Infrared thermography uses the temperature variation between areas of active and inactive cutaneous disease to help differentiate active disease from damage. The role of ultrasound to examine lesion activity is evolving. HRCT, PFTs, echocardiography, and manometry are useful tools for diagnosing and monitoring visceral involvement in JSSc.

TREATMENT

Treatment for scleroderma varies according to the subtype and severity. **Superficial morphea may benefit from topical corticosteroids or ultraviolet therapy.** For lesions involving deeper structures, systemic therapy is recommended. A combination of *methotrexate* and *corticosteroids* is effective in treating JLS by preventing lesion extension and resulting in significant skin softening and improved range of motion of affected joints. The Childhood Arthritis and Rheumatology Research Alliance (CARRA) consensus treatment plans for JLS include (1) weekly subcutaneous (SC) methotrexate at 1 mg/kg (maximum dose 25 mg); (2) weekly SC methotrexate (1 mg/kg; max 25 mg) *plus* either 3 months of high-dose intravenous (IV) corticosteroids (30 mg/kg; max 1,000 mg) for 3 consecutive days a month *or* weekly corticosteroids at the same dose for 3 months; or (3) high-dose daily oral corticosteroids (2 mg/kg/day, max 60 mg) with a slow taper over 48 weeks (Fig. 201.8). *Mycophenolate mofetil* (MMF) and abatacept have shown promise as second-line agents for recalcitrant

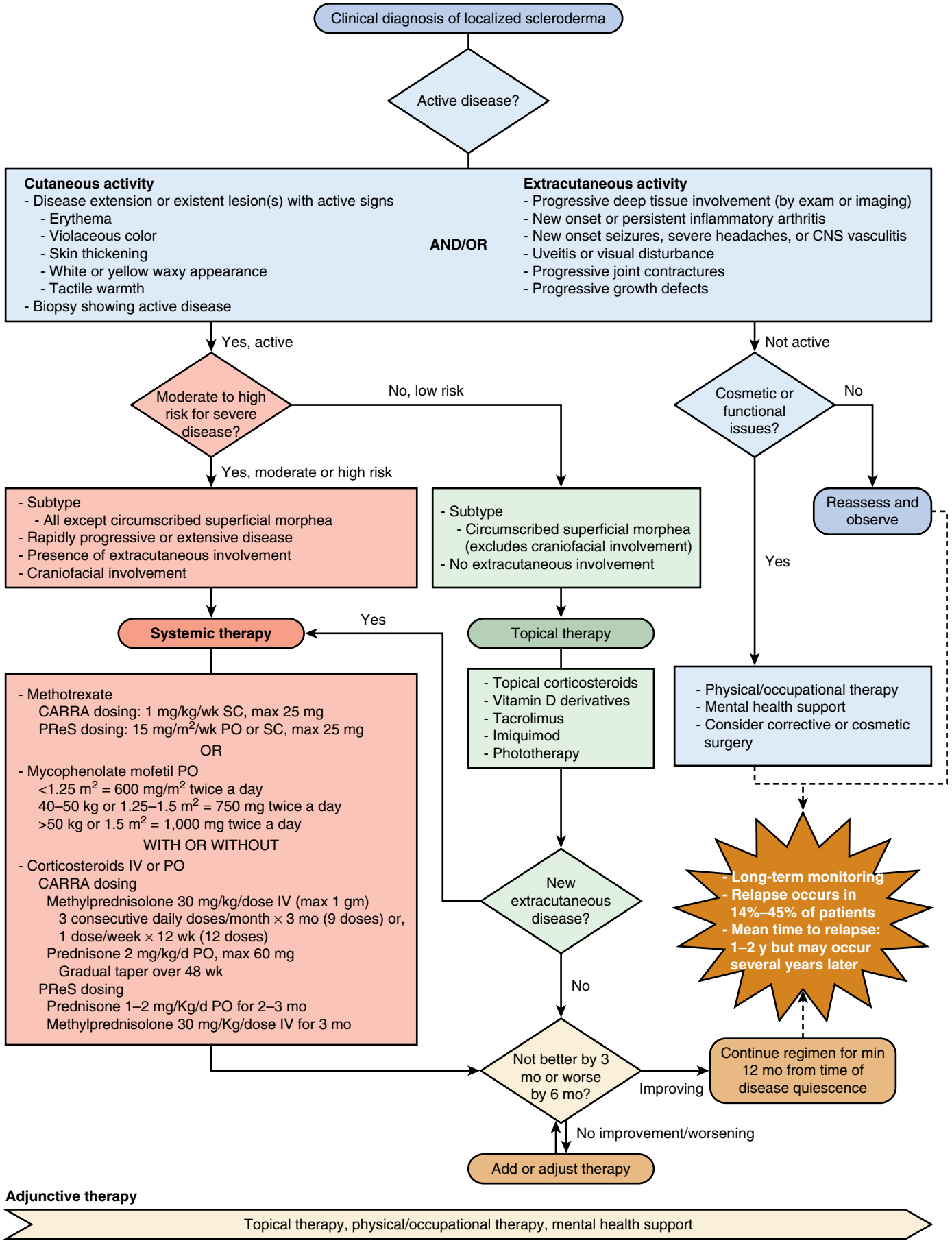

Fig. 201.8 LS treatment recommendations. This algorithm outlines factors to consider when deciding upon treatment and CARRA- and PReS-recommended treatments. Careful and long-term monitoring for both cutaneous and extracutaneous activity is important. The algorithm is based upon the authors' experiences and not intended to serve as prescriptive instructions. CARRA, Childhood Arthritis and Rheumatology Research Alliance; IV, intravenous; max, maximum; min, minimum; PO, by mouth; PReS, Pediatric Rheumatology European Society; SC, subcutaneous. *(From Vasquez-Canizares N, Li SC. Juvenile localized scleroderma – updates and differences from adult-onset disease.* Rheum Dis Clin N Am. *2021;47:737–755, Fig. 5, p. 749.)*

disease. Physical and occupational therapy are important adjuncts to pharmacologic treatment. Eosinophilic fasciitis often responds well to corticosteroids and methotrexate. Close follow-up is necessary in JLS given high rates of relapse—up to 40%.

Treatments for JSSc target specific disease manifestations (Tables 201.5 and 201.6). RP is treated with cold avoidance, and pharmacologic interventions are reserved for severe disease. Calcium channel blockers (nifedipine 30-60 mg sustained-release form daily; amlodipine 2.5-10 mg daily) are the most common pharmacologic interventions. Additional potential therapies for RP include losartan, prazosin, bosentan, and sildenafil. Angiotensin-converting enzyme (ACE) inhibitors (captopril, enalapril) are recommended for hypertension associated with renal disease. Methotrexate or MMF may be beneficial for skin manifestations. Cyclophosphamide and MMF are used to treat pulmonary alveolitis and prevent fibrosis. Corticosteroids should be used cautiously in SSc because of an association with renal crisis. Adults with SSc have been successfully treated with high-dose cyclophosphamide, antithymocyte globulin, and autologous stem cell transplantation. Systemic sclerosis–associated interstitial lung disease has been managed with nintedanib, a tyrosine kinase inhibitor, which has antiinflammatory and antifibrotic effects. Nintedanib combination therapy with MMF is also effective as an initiation therapy or when escalation of therapy is needed.

The treatment of RP begins with avoiding cold stimuli, using hand and foot warmers, and avoiding carrying bags by their handles (impairs circulation). Nifedipine (10-20 mg three times daily—adult dose) reduces, but does not eliminate, the number and severity of episodes. Side effects include headache, flushing, and hypotension. Topical nitrates may result in digital vasodilation and may reduce the severity of an episode.

PROGNOSIS

JLS is ultimately generally self-limited, with the initial inflammatory stage followed by a period of stabilization and then softening, for an average disease duration of 3-5 years, although there are reports of active disease lasting up to 20 years. Prolonged disease activity is associated primarily with linear and deep disease subtypes. JLS, especially linear and deep subtypes, can result in significant morbidity, disfigurement, and disability as a result of joint contractures, muscle atrophy, limb shortening, facial asymmetry, and hyperpigmentation and hypopigmentation. Death from an en coup de sabre lesion with progressive neurologic decline has been reported.

JSSc has a more variable prognosis. Although many children have a slow, insidious course, others demonstrate a rapidly progressive form with early organ failure and death. Skin manifestations reportedly soften years after disease onset. Overall, the prognosis of JSSc is better than that of the adult form, with 5-, 10-, and 15-year survival rates, respectively, in children of 89%, 80–87%, and 74–87%. The most common cause of death is heart failure caused by myocardial and pulmonary fibrosis.

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Table 201.5 Organ-Specific Treatment of Systemic Sclerosis

MANIFESTATION	FIRST-LINE	SECOND-LINE	VERY SEVERE
Raynaud phenomenon	Calcium channel blockers*	PDE-5 inhibitors† Fluoxetine Angiotensin II receptor antagonists‡ Topical nitrates§	Prostacyclins (iloprost)¶ Sympathectomy Botulism toxin Fat grafting
Digital ulcers	PDE-5 inhibitors†	Endothelin receptor antagonists#	Prostacyclins (iloprost)
Pulmonary hypertension	PDE-5 inhibitors† Endothelin receptor antagonists	Prostacyclins (epoprostenol)¶ Riociguat	
Interstitial lung disease	Cyclophosphamide Mycophenolate mofetil Corticosteroids	Rituximab	Hematopoietic stem cell transplantation
Skin	Methotrexate Mycophenolate mofetil Corticosteroids (low dose)	Abatacept Immune globulin	Cyclophosphamide Rituximab
Renal crisis	ACE inhibitors**		
Musculoskeletal	NSAIDs Hydroxychloroquine Methotrexate Corticosteroids (low dose)	Rituximab Abatacept Tocilizumab	

*Calcium channel blockers (nifedipine, amlodipine).
†PDE-5 inhibitors (sildenafil, tadalafil).
‡Angiotensin receptor antagonists (losartan).
§Topical nitrates (glyceryl trinitrate).
¶Prostacyclins (iloprost, epoprostenol).
#Endothelin receptor antagonist (bosentan, ambrisentan, macitentan).
**ACE inhibitors (captopril, enalapril).
ACE, Angiotensin converting enzyme; NSAIDs, nonsteroidal antiinflammatory drugs; PDE-5, phosphodiesterase-5.
From Petty RE, Laxer RM, Lindsley CB, et al., eds. *Textbook of Pediatric Rheumatology,* 8th ed. Philadelphia: Elsevier; 2021: Table 27.8, p. 395.

Table 201.6 Treatment of Gastrointestinal Manifestations of Juvenile SSc

ORGAN	MANIFESTATION	TREATMENT
Oral	Buccal, lingual fibrosis Tooth decay Mandibular resorption Gingival recession Dysphagia	Dental hygiene Fluoride treatments every 3 months Dental sealant Soft foods, small portions, adequate fluids Gingival mucosa grafting Dietary restriction (low sugar, soft foods)
Esophageal	Dysmotility Reflux Constriction	Metoclopramide, erythromycin Weight loss; small, frequent meals; avoid eating 3 hr before bed; raise head of bed 6 inches Avoid tight clothes, heavy lifting, bending Proton pump inhibitors, H2 blockers Dilatation
Stomach	GAVE (watermelon stomach) Fructose intolerance	Metoclopramide Erythromycin* Octreotide
Small intestines	Bacterial overgrowth Bezoars Malabsorption leading to malnutrition Pseudoobstruction	FODMAP diet Vitamin supplementation Low-residue, elemental diet Metoclopramide Antibiotics Octreotide
Colon	Fibrosis of lymphatics Ischemia	Erythromycin Metamucil High-fiber diet
Anorectal	Internal anal sphincter atrophy	Biofeedback Pelvic floor exercises Sacral nerve stimulation

*Side effects of erythromycin can be avoided by using low doses (rather than antibiotic-level doses).
FODMAP, Fermentable oligosaccharides, disaccharides, monosaccharides, and polyol; GAVE, gastric antrum vascular ectasia; SSc, systemic sclerosis.
From Petty RE, Laxer RM, Lindsley CB, et al., eds. *Textbook of Pediatric Rheumatology,* 8th ed. Philadelphia: Elsevier; 2021: Table 27.9, p. 398.

Chapter 202

Behçet Disease

Seza Ozen

Behçet disease (BD) is classified as a primary *multisystem variable vessel vasculitis* because of the involvement of any size and type (arterial, venous) of blood vessel. BD is probably underdiagnosed in children as a result of the heterogeneity in clinical features, the large spectrum of differential diseases, and lack of specific tests. Originally described with recurrent oral ulcerations, uveitis, and skin abnormalities, the BD spectrum is much broader.

EPIDEMIOLOGY

BD has a high prevalence in countries along the *Silk Road,* extending from Japan to the Eastern Mediterranean. It is increasingly recognized among people of European ancestry as well. BD has a prevalence of 5-7 per 100,000 adults. The increased disease recognition might have had a role in the rising prevalence of BD as well as the migrations of the 20th century. Prevalence in children is probably not more than 10% of the adult counterparts in Eastern Mediterranean countries; boys and girls are equally affected. A family history of BD is present in approximately 20% of the cases. Onset in children is usually 8-12 years of age. Newborns of affected mothers have demonstrated symptoms of BD.

ETIOLOGY AND PATHOGENESIS

The etiology of BD is unknown. It is a polygenic disorder with autoinflammatory features. The autoinflammatory nature of BD is suggested by its episodic nature, the prominent innate immune system activation, the absence of identifiable autoantibodies, and the coassociation with the *MEFV* gene. However, there is evidence supporting the role of the adaptive immune system as well. BD has also been considered to be an MHC-I-opathy because of the strong association with HLA-B51. Genetic contribution to BD is evident through this well-known association with HLA-B5101, the familial cases, the sibling and twin recurrence rate, the specific frequency of the disease among people along the Silk Road, evidence for genetic anticipation, and genome-wide analysis. Genome-wide analysis studies among Turkish and Japanese BD patients confirm the marked association with HLA-B5101. Other significant associations include interleukin (IL)-10 and IL-23R/IL-12Rβ_2 genes. Other possible susceptibility loci demonstrate associations with *STAT4* (a transcription factor in a signaling pathway related to cytokines such as IL-12, type I interferons, and IL-23) and *ERAP1* (an endoplasmic reticulum–expressed

aminopeptidase that functions in the processing of peptides onto major histocompatibility complex class I).

An infectious agent may be responsible for inducing the aberrant innate immune system attacks in the genetically predisposed host. A number of infectious agents have been implicated and include streptococci and herpes simplex virus type 1. A microbiome study in BD proposed a distinct salivary signature.

BD has some genetic and immune similarities to periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis (PFAPA) syndrome and recurrent aphthous stomatitis, suggesting a spectrum of these disorders.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The course of BD is characterized by exacerbations and remissions. There is marked heterogeneity in disease manifestations.

The mean age of the first symptom is between 8 and 12 years. The most frequent initial symptom is a *painful* **oral ulcer** (Fig. 202.1). The oral ulcers are often recurrent, may be single or multiple, range from 2 to 10 mm, and may be in any location in the oral cavity. They are often very painful. The oral ulcers last 3-10 days and heal without scarring. In contrast, the genital ulcers heal with scars. Genital scars are noted in 60–85% of the patient, usually occur after puberty, and are seen on the labia, scrotum, penis, or anal area.

Another key feature of BD that has significant morbidity is the bilateral eye involvement seen in 30–60% of pediatric patients. The main symptoms of **anterior uveitis** are blurred vision, redness, periorbital or global pain, and photophobia. Although it is often in the form of panuveitis, anterior uveitis may be seen in females. Uveitis in general is more common in males. Vitritis and retinal vasculitis are the most prominent features of *posterior* involvement. Complications of uveitis include blindness (unusual with treatment), glaucoma, and cataracts. Retinal vasculitis, retinal detachment, and retrobulbar neuritis (optic neuritis) are less common eye manifestations of BD.

The skin lesions are the third most common symptom of BD. They range from erythema nodosum (seen in approximately 50% of patients) to papulopustular acneiform lesions (85%), folliculitis, purpura, and ulcers. Pathergy (seen in 50%) is another skin feature associated with BD and is a pustular reaction occurring 24-48 hours after a sterile needle puncture or saline injection; it is not pathognomonic of BD.

The vasculitis of BD involves both arteries and veins, thrombosis and aneurysm formation, occlusions, or stenosis in arteries of any size. In children, deep venous thrombosis of the lower limbs is the most frequent vasculitic feature. If the hepatic vein is thrombosed, Budd-Chiari syndrome may occur. Pulmonary artery aneurysms are the most severe feature of pediatric BD, associated with the highest mortality. Coronary artery aneurysms may confuse BD with Kawasaki or multisystem inflammatory syndrome in children (MIS-C) disease. Microvascular involvement may be noted in the nail bed capillaries.

Central nervous system (CNS) manifestations (approximately 10%) in children include meningoencephalitis (headache, meningismus, cerebrospinal fluid pleocytosis), encephalomyelitis, pseudotumor cerebri, dural sinus thrombosis, and organic psychiatric disorders (psychosis, depression, dementia). Dural sinus thrombosis is the most common CNS manifestation in children.

Gastrointestinal (GI) involvement (seen in 10–30%) manifests with abdominal pain, diarrhea, and intestinal ulcerations, most often in the ileocecal region. Gastrointestinal BD may be difficult to distinguish from inflammatory bowel disease. Oligoarticular arthritis/arthralgia is present in >50% of patients and can be recurrent, but is nondeforming. Other rare manifestations include orchitis, renal vasculitis, glomerulonephritis, or amyloidosis and cardiac involvement.

The International Study Group for Behçet Disease (ISG) criteria used to be the most widely used and require the presence of oral ulcers (at least 3 times per year) along with two other major features, including genital ulcers, a positive pathergy test, uveitis, and the characteristic skin lesions. If only one of the criteria is present along with oral ulcerations, the term *incomplete* or *partial Behçet disease* is applied. The revised International Criteria for Behçet Disease (ICBD) have been reported to have a much better performance than the 1990 ISG criteria.

Additional classification criteria for children have been suggested by the use of an international prospective observational cohort. According to these criteria, BD is diagnosed when three of the following criteria are present: recurrent oral aphthosis, genital ulcers, skin involvement (necrotic folliculitis, acneiform lesions, erythema nodosum), ocular involvement, neurologic involvement, and vascular involvement (venous thrombosis, arterial thrombosis, arterial aneurysm). These criteria performed better than the ISG criteria in the pediatric cohort (Table 202.1).

There are no specific laboratory tests. Acute-phase reactants are often mildly elevated. The diagnosis relies on the constellation of symptoms and excluding other causes.

Hughes-Stovin syndrome is characterized by thrombophlebitis and multiple bronchial or pulmonary artery aneurysms. This vasculitic

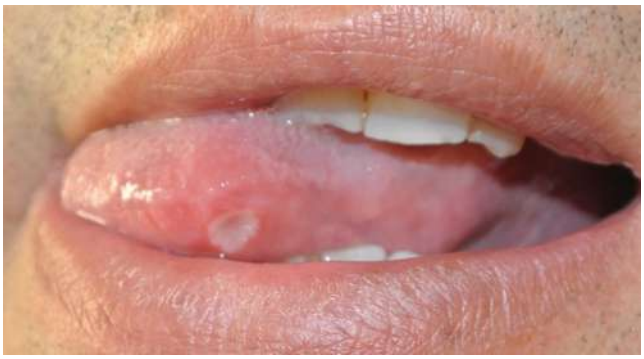

Fig. 202.1 A deep aphthous ulcer in a patient with Behçet disease.

Table 202.1 Consensus Classification of Pediatric Behçet Disease

ITEM	DESCRIPTION
Recurrent oral aphthosis	At least three attacks/year
Genital ulceration or aphthosis	Typically with scar
Skin involvement	Necrotic folliculitis, acneiform lesions, erythema nodosum
Ocular involvement	Anterior uveitis, posterior uveitis, retinal vasculitis
Neurologic signs	With the exception of isolated headaches
Vascular signs	Venous thrombosis, arterial thrombosis, arterial aneurysm

From Koné-Paut I, Shahram F, Darce-Bello M, et al, for PEDBD group. Consensus classification criteria for paediatric Behçet's disease from a prospective observational cohort: PEDBD. *Ann Rheum Dis.* 2016;75:958–964.

process is regarded as a clinical variant of BD (partial or incomplete) but without ulcerations.

TREATMENT AND PROGNOSIS

Azathioprine is highly recommended to treat inflammatory eye disease. Anti–tumor necrosis factor (TNF) treatment and interferon (IFN)-α should be considered for refractory eye disease. For oral and genital ulcers, topical treatment and colchicine are recommended (sucralfate, corticosteroids). **Apremilast**, an oral phosphodiesterase-4 inhibitor, is effective in treating the oral ulcers of BD. In patients without major organ involvement, colchicine significantly improves oral and genital ulcers, skin features, and disease activity. There is no evidence-based treatment for GI disease, but 5-ASA derivatives, corticosteroids, azathioprine, and anti-TNF agents have been recommended. For CNS disease and venous thrombosis, corticosteroids, azathioprine, and anti-TNF agents are recommended. Patients treated with anti-TNF drugs have had persistent responses in 90%, 89%, 100%, and 91% of patients with resistant mucocutaneous, ocular, GI, and CNS involvement, respectively. There is no consensus about the benefit of anticoagulation in the management of vein thrombosis in BD.

In patients with pulmonary arterial or cardiac involvement, cyclophosphamide is typically used initially.

Mortality in children with BD is low except for the pulmonary aneurysms. However, BD is a chronic disease associated with significant morbidity. Early diagnosis and effective treatment improve the outcome of BD.

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Chapter 203

Sjögren Syndrome

C. Egla Rabinovich

Sjögren syndrome is a chronic, inflammatory autoimmune disease characterized by progressive lymphocytic and plasma cell infiltration of the exocrine glands, especially salivary and lacrimal (parotid being prototypical), with potential for systemic manifestations. It is rare in children and has classic symptoms of dry eyes **(keratoconjunctivitis sicca)** and dry mouth **(xerostomia)**.

EPIDEMIOLOGY

Sjögren syndrome typically manifests at 35-45 years of age, with 90% of cases among females, but it is underrecognized in children because symptoms often start in childhood. The mean age at diagnosis in children is 9-10 years; 75% are female. The disease can occur as an isolated disorder, referred to as **primary** Sjögren syndrome **(sicca complex)**, or as a **secondary** Sjögren syndrome in association with other rheumatic disorders, such as systemic lupus erythematosus (SLE), scleroderma, or mixed connective tissue disease, which usually precedes the associated autoimmune disease by years.

ETIOLOGY AND PATHOGENESIS

The etiology of Sjögren syndrome is complex and includes genetic predisposition and possibly an infectious trigger. Lymphocytes and plasma cells infiltrate salivary glands, forming distinct periductal and periacinar foci that become confluent and may replace epithelial structure. Several genes regulating apoptosis influence the chronicity of lymphocytic infiltration.

CLINICAL MANIFESTATIONS

International classification criteria have been developed for the diagnosis of Sjögren syndrome in adult patients, but these criteria apply poorly to children. Although diagnostic criteria in children have been proposed, they have not been validated (Table 203.1). Recurrent parotid gland enlargement and parotitis are the most common manifestations in children (>70%), whereas **sicca syndrome** (dry mouth, painful mucosa, halitosis, widespread dental caries) predominates in adults. Children tend to have a higher prevalence of systemic symptoms, including fevers and adenopathy, compared to adults. In a cross-sectional study of children with Sjögren syndrome, manifestations included recurrent parotitis (72%), sicca symptoms (38%), polyarthritis (18%), vulvovaginitis (12%), hepatitis (10%), Raynaud phenomenon (10%), fever (8%), renal tubular acidosis (9%), lymphadenopathy (8%), and central nervous system (CNS) involvement (5%).

Table 203.1 Proposed Pediatric Criteria for Diagnosis of Sjögren Syndrome (SS)

JUVENILE SS
CLINICAL SYMPTOMS
1. Recurrent parotitis or parotid enlargement
2. Recurrent conjunctivitis (nonallergic and noninfectious)
3. Recurrent vaginitis
4. Systemic: fever of unknown origin, arthralgias, hypokalemic paralysis, or abdominal pain
OBJECTIVE
5. Ocular dryness (ocular staining or a Schirmer test)
6. Abnormal sialography
7. Elevated serum amylase
8. Leukopenia or elevated ESR
9. Hyperimmunoglobulinemia (polyclonal)
10. Renal tubular acidosis
SEROLOGY
11. At least one of anti-SSA, anti-SSB, high titer ANA (speckled pattern), RF
HISTOPATHOLOGY
12. Lymphocytic infiltration of salivary glands or other organs
DIAGNOSIS OR CLASSIFICATION REQUIREMENTS
13. Diagnosis requires at least 4 of 12 items

Modified from Yokogawa N, Lieberman SM, Sherry DD, Vivino FB. Features of childhood Sjögren's syndrome in comparison to adult Sjögren's syndrome: considerations in establishing child-specific diagnostic criteria. *Clin Exper Rheumatol.* 2016;34:343–351, Table 1.

Subjective symptoms of xerostomia complaints are relatively rare in juvenile cases, perhaps indicating that Sjögren syndrome is a slowly progressive disease; however, increased dental caries is seen clinically in children. Serologic markers (antinuclear antibodies [ANAs], antibodies to Ro [SSA] and La [SSB]) and articular manifestations are significantly more common in adults. Reported frequencies of ANAs and SSA and SSB antibodies in children are 78%, 75%, and 65%, respectively, with rheumatoid factor present in 67%. Additional clinical manifestations from a variety of organ involvement patterns include a decreased sense of smell; hoarseness; chronic otitis media; leukocytoclastic vasculitis (purpura); and internal organ exocrine disease involving the lungs (diffuse interstitial lymphocytosis), pancreas, hepatobiliary system, gastrointestinal tract, kidneys (renal tubular acidosis), musculoskeletal (arthritis and arthralgia), hematologic (cytopenias), peripheral nervous system (sensory and autonomic neuropathy), and CNS (optic neuritis, transverse myelitis, meningoencephalitis).

Nonexocrine disease manifestations of Sjögren syndrome may be related to inflammatory vascular disease (skin, muscle and joints, serosal surfaces, CNS, peripheral nervous system), noninflammatory vascular disease (Raynaud phenomenon), mediator-induced disease (hematologic cytopenias, fatigue, fever), and autoimmune endocrinopathy (thyroiditis).

DIAGNOSIS

Clinical presentation of recurrent **parotitis** and/or recurrent parotid gland swelling in a child or adolescent is characteristic and should raise the suspicion for Sjögren syndrome. The diagnosis is based on clinical features supported by biopsy of salivary or parotid glands demonstrating foci of lymphocytic infiltration, the current gold standard for diagnosis. Children are more likely to have normal minor salivary gland but abnormal parotid gland biopsies. Supporting laboratory abnormalities include cryoglobulinemia, elevated erythrocyte sedimentation rate, hypergammaglobulinemia, positive rheumatoid factor, and presence of SSA and SSB antibodies. The Schirmer test detects abnormal tear production (≤5 mm of wetting of a filter paper strip in 5 minutes). Special dyes (e.g., fluorescein, Lissamine green) detects damaged ocular epithelial conjunctival and corneal cells. Imaging studies, including MRI, technetium (^{99m}Tc) scintigraphy, parotid ultrasound, and sialography, are useful in the diagnostic evaluation for Sjögren syndrome (Fig. 203.1).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of Sjögren syndrome in children includes **juvenile recurrent parotitis**, characterized by intermittent *unilateral* parotid swelling typically lasting only a few days; it is frequently associated with fever and may undergo remission with puberty. Unlike in Sjögren syndrome, there is a male predominance, juvenile recurrent parotitis is seen in the younger children (3-6 years), and there is a lack of focal lymphocytic infiltrates on biopsy. Other conditions in the differential diagnosis include eating disorders, infectious parotitis (mumps, streptococcal and staphylococcal infections, Epstein-Barr virus, cytomegalovirus, HIV, parainfluenza, influenza enterovirus), and local trauma to the buccal mucosa. Rarely, polycystic parotid disease, tumors, and sarcoidosis may present with recurrent parotid swelling.

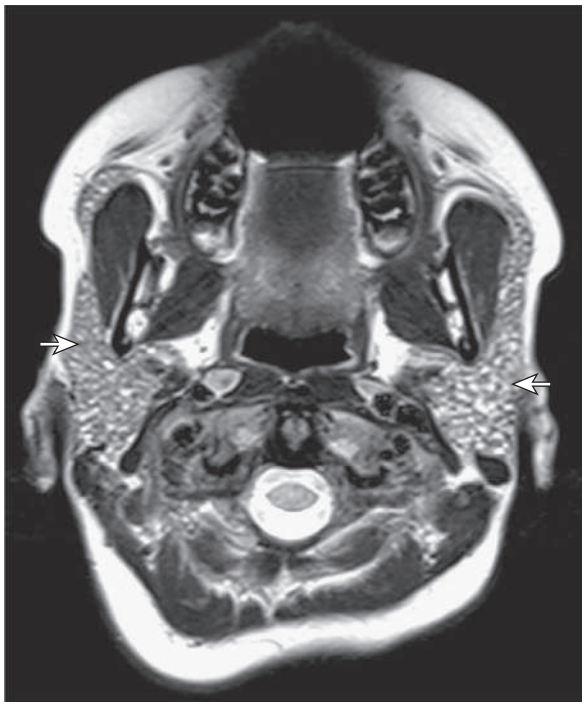

Fig. 203.1 T2-weighted MRI of a child with Sjögren syndrome showing parotitis *(arrows)*.

In these conditions, sicca complex, rash, arthralgia, and ANAs are usually absent.

TREATMENT

Symptomatic treatment of Sjögren syndrome includes the use of artificial tears, massage of the parotids, oral lozenges, and fluids to limit the damaging effects of decreased secretions. Corticosteroids, nonsteroidal antiinflammatory drugs, and hydroxychloroquine are among the more commonly used agents for treatment, with reports of methotrexate and etanercept used for treatment of arthritis. Stronger immunosuppressive agents, such as cyclosporine and cyclophosphamide, are reserved for severe manifestations (e.g., lung involvement) and life-threatening complications.

COMPLICATIONS AND PROGNOSIS

The symptoms of Sjögren syndrome develop and progress slowly. Diminished salivary flow typically remains constant for years. Because monoclonal B-lymphocyte disease originates chiefly from lymphocytic foci within salivary glands or from parenchymal internal organs, there is increased risk for mucosa-associated lymphoid tissue lymphoma. Maternal Sjögren syndrome can be an antecedent to neonatal lupus syndrome (see Chapter 199.1).

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Chapter 204

Hereditary Periodic Fever Syndromes and Other Systemic Autoinflammatory Diseases

James W. Verbsky

The hereditary periodic fever syndromes are a group of monogenic diseases that present with recurrent bouts of fever and associated pleural and/or peritoneal inflammation, arthritis, and various types of skin rash. A number of identifiable disorders present with recurrent episodes of inflammation, although fevers *may not* be a common feature. Therefore the term **autoinflammatory diseases** is used to include all diseases that present with seemingly unprovoked episodes of inflammation, without the high-titer autoantibodies or antigen-specific T cells typically seen in autoimmune diseases. Whereas autoimmune diseases are disorders of the *adaptive* immune system, driven by B- and T-lymphocyte effector cells, autoinflammatory diseases largely represent disorders of the phylogenetically more primitive *innate* immune system, mediated by myeloid effector cells and germline-encoded receptors. Autoinflammatory diseases exhibit episodic or persistent inflammation characterized by an acute-phase response with elevation of the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum amyloid A (AA). In some patients, untreated autoinflammatory disorders over time will lead to AA amyloidosis (see Chapter 206).

It is important to note that autoinflammatory disorders are rare, whereas fever in childhood caused by innocuous illness is very common. The approach to a child with fevers should include a detailed history, physical examination, and limited laboratory investigations to rule out other conditions that lead to fevers, including autoimmune disorders and malignancies (Table 204.1). If there is evidence of recurrent infections with fevers, an immune deficiency could be considered and evaluated. If the workup is reassuring, the inflammatory episodes resolve, and the child is otherwise well without unusual physical findings, observation is often warranted because these episodes are likely to resolve as the child's immune system matures.

CLASSIFICATION OF AUTOINFLAMMATORY DISORDERS

Because of the rapidly expanding number of autoinflammatory disorders and their varied clinical presentation, it can be difficult to group these disorders in a meaningful manner. Some autoinflammatory disorders present with prominent fevers and are known as **hereditary periodic fever syndromes**. These include two disorders with an *autosomal recessive* mode of inheritance: familial Mediterranean fever (**FMF**; MIM249100) and hyperimmunoglobulinemia D (hyper-IgD) with periodic fever syndrome (**HIDS**; MIM260920). Hereditary periodic fever syndromes with an *autosomal dominant* mode of inheritance include tumor necrosis factor (TNF) receptor–associated periodic syndrome (**TRAPS**; MIM191190) and a spectrum of disorders known as the *cryopyrin-associated periodic syndromes* **(CAPS)** or *cryopyrinopathies*. From mildest to most severe, CAPS include familial cold autoinflammatory syndrome (**FCAS1**; MIM120100), Muckle-Wells syndrome (**MWS**; MIM191100), and neonatal-onset multisystem inflammatory disease (**NOMID**; MIM607115) (also known as *chronic infantile neurologic cutaneous and articular syndrome* [**CINCA**]) (Table 204.2).

A variety of mendelian *autoinflammatory disorders* may or may not exhibit prominent fevers and are not considered periodic fever syndromes, but do have continuous or repeated episodes of spontaneous inflammation with unique clinical characteristics. These include the syndrome of pyogenic arthritis with pyoderma gangrenosum and acne (**PAPA**; MIM604416), deficiency of the interleukin-1 (IL-1) receptor antagonist (**DIRA**; MIM612852), **Blau syndrome** caused by pathogenic variants in *NOD2* (also known as *early-onset sarcoidosis;* MIM186580), autoinflammation with phospholipase $C\gamma_2$-associated antibody deficiency and immune dysregulation (**APLAID**; MIM614878), and deficiency of adenosine deaminase-2 (**DADA2**). Other disorders include congenital sideroblastic anemia with B-cell immunodeficiency, periodic fevers, and developmental delay **(SIFD)** caused by biallelic pathogenic variants of the *TRNT1* gene (MIM616084), autoinflammation with infantile enterocolitis caused by pathogenic variants in *NLRC4* (**AIFEC**; MIM616060), familial cold autoinflammatory syndrome type 2 caused by pathogenic variants in *NLRP12* (**FCAS2**; MIM611762), **CARD14** (MIM607211), and deficiency in IL-36 receptor antagonist (**DITRA**; 614204) (see Table 204.2).

In addition to the previous autoinflammatory disorders, a variety of disorders are characterized by inappropriate *interferon expression:* the **interferonopathies**. Type 1 interferons (e.g., IFN-α, IFN-β) are cytokines expressed by many cells in response to viral infections (see Table 204.2 and Chapter 205). Disorders that result in spontaneous interferon production and inflammatory manifestations include STING-associated vasculopathy of infancy (**SAVI**; MIM615934) and chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (**CANDLE**; MIM256040).

There are also a number of autoinflammatory disorders with a complex mode of inheritance. These include the syndrome of periodic fever with aphthous stomatitis, pharyngitis, and adenitis **(PFAPA)** and chronic recurrent multifocal osteomyelitis (**CRMO**; MIM259680). Other genetically complex disorders that are sometimes considered

Table 204.1 Differential Diagnosis of Periodic Fever

HEREDITARY
See Table 204.2
NONHEREDITARY
A. Infectious
   1. Hidden infectious focus (e.g., aortoenteric fistula, lung sequestration)
   2. Recurrent infection/reinfection (e.g., chronic meningococcemia, immune deficiency)
   3. Specific infection (e.g., Whipple disease, malaria)
B. Noninfectious inflammatory disorders
   1. Adult-onset Still disease
   2. Systemic-onset juvenile idiopathic arthritis
   3. Periodic fever, aphthous stomatitis, pharyngitis, and adenitis
   4. Schnitzler syndrome
   5. Behçet syndrome
   6. Crohn disease
   7. Sarcoidosis
   8. Orofacial granulomatosis (Melkersson-Rosenthal syndrome)
C. Neoplastic
   1. Lymphoma (e.g., Hodgkin disease, angioimmunoblastic lymphoma)
   2. Solid tumor (e.g., pheochromocytoma, myxoma, colon carcinoma)
   3. Hemophagocytic lymphohistiocytosis
D. Vascular (e.g., recurrent pulmonary embolism)
E. Hypothalamic
F. Psychogenic periodic fever
G. Ectodermal dysplasia
H. Factitious or fraudulent

Adapted from Simon A, van der Meer JWM, Drenth JPH. Familial autoinflammatory syndromes. In Firestein GS, Budd RC, Gabriel SE, et al., eds. *Kelley's Textbook of Rheumatology*, 9th ed. Philadelphia: Saunders; 2012: Table 97-2.

Table 204.2 The Monogenic Autoinflammatory Diseases

	Mechanism	Disease	Gene	Inheritance	Clinical presentation	Targeted therapy
Inflammasomopathies and other IL-1 family conditions	Pyrin activation	FMF	*MEFV*	AR or AD	Fever, pain, (abdominal, chest, joint), rash	IL-1, colch.
		PAAND	*MEFV*	AD	Fever, myalgia, myositis, rash, abscesses	IL-1, colch.
		MKD	*MVK*	AR	Fever, pain (abdominal, extremity), vomiting, rash	IL-1
		PAPA	*PSTPIP1*	AD	Pyoderma gangrenosum, arthritis	IL-1, TNF
		Hz/Hc	*PSTPIP1*	AD	Rash, FTT, hepatosplenomegaly, neutropenia	IL-1, TNF
		PFIT	*WDR1*	AR	Fever, infection, oral inflammation, perianal ulceration	IL-18
	Cryopyrin activation	FCAS	*NLRP3*	AD	Cold urticaria, extremity pain, conjunctivitis, fever	IL-1
		MWS	*NLRP3*	AD	Urticarial rash, extremity pain, hearing loss, conjunctivitis, fever	IL-1
		NOMID	*NLRP3*	AD	CNS inflammation, urticaria, knee arthropathy, fever	IL-1
		Majeed's	*LPIN2*	AR	Osteomyelitis, fevers, rash, dyserythropoietic anemia	IL-1
	NLRC4 activation	AIFEC	*NLRC4*	AD	Enterocolitis, rash, arthritis, fever	IL-1, IL-18
		FCAS/ NOMID	*NLRC4*	AD	Cold urticaria, extremity pain, fever, CNS disease	IL-1
	NLRP12 activation	FCAS	*NLRP12*	AD	Cold urticaria, extremity pain, fever	TNF, IL-1
	NLRP1 activation	NAIAD	*NLRP1*	AD	Ocular, laryngeal, skin dyskeratosis, fever, arthritis	IL-1, TNF
	Receptor antagonist deficiency	DIRA	*IL1RN*	AR	Pustular rash, osteomyelitis, periostitis, fever,	IL-1
		DITRA	*IL36RN*	AR	Pustular psoriasis, fever, malaise	TNF, IL-17/12/23?
Type I interferonopathies	Nucleic acid processing and degradation	Aicardi-Goutières syndrome	*TREX1, ADAR1, RNASEH2A/B/C, SAMHD1, IFIH1*	AR (AD: *IFIH1*)	Fever, neurologic decline, encephalopathy, cerebral calcification, chilblains, autoantibodies	JAK, RTI?
		Monogenic SLE	*DNASE1/2/1L3, complements*	AR (AD: *DNASE1*)	Autoantibodies, cytopenias, glomerulonephritis, skin rash, oral ulcers, arthritis	JAK?
	Nucleic acid sensing	SMS	*IFIH1, DDX58a*	AD	Calcification of aorta / cardiac valves, osteopenia, acro-osteolysis, dental anomalies	JAK?
		SAVI	*TMEM137*	AD	Chilblain's rash, small vessel vasculitis, arthritis, ILD	JAK
	Proteasome	CANDLE / PRAAS, PRAID	*PSMB4, PSMA3, PSMB8, POMP, PSMG2, PSMB9, PSMB10*	Digenic, AR (AD: POMP)	Fever, joint contractures, annular plaques, eyelid swelling, hepatosplenomegaly, lipodystrophy, FTT, developmental delay, anemia	JAK
	IFN signaling	AGS-like	*USP18, ISG15, STAT2*	AR	Skin ulcerations, seizures, hydrocephalus, cerebral calcifications, respiratory failure	JAK
	Other	SPENCD	*ACP5*	AR	Skeletal dysplasia, short stature, cerebral calcification, cytopenias, autoantibodies	?
NF-κB and/or aberrant TNF activity	Dysregulation of NFκB signaling	HA20	*TNFAIP3*	AD	Oral, gastrointestinal and genital ulcerations, fever, arthritis, recurrent infection	TNF, IL-1, JAK?
		RELA haploinsuf.	*RELA*	AD	Oral and gastrointestinal ulcerations, cytopenias, lymphoproliferative disease	TNF
		ORAS	*OTULIN*	AR	Fever, panniculitis, diarrhea, arthritis, FTT	TNF
		LUBAC deficiency	*HOIL1, HOIP*	AR	Fever, recurrent infection, FTT, hepatosplenomegaly, amylopectin-like deposits in muscles	TNF?
	Dysregulation of TNF	Blau	*NOD2*	AD	Granulomatous dermatitis, uveitis, polyarticular arthritis	TNF
		TRAPS	*TNFRSF1A*	AD	Episodic fever, abdominal pain, headache, conjunctivitis, painful centrifugal rash	IL-1, TNF
		DADA2	*ADA2*	AR	Systemic vasculitis, fever, rash, stroke, cytopenias, hypogammaglobulinemia	TNF, HSCT
		CRIA	*RIPK1*	AD	Fever, lymphadenopathy, hepatosplenomegaly	IL-6?
Other mechanisms	Golgi-ER transport	COPA	*COPA*	AD	Arthritis, ILD, diffuse alveolar hemorrhage, autoantibodies	IL-17? JAK?
	Intracellular calcium signaling	PLAID	*PLCG2*	AD	Cold urticaria, atopy, granulomatous dermatitis, hypogammaglobulinemia, infection, autoantibodies	?
		APLAID	*PLCG2*	AD	Blistering skin lesions, ILD, bronchiolitis, eye inflammation, enterocolitis, immunodeficiency	?
	tRNA biogenesis	SIFD	*TRNT1*	AR	Fever, developmental delay, seizures, microcytic anemia hypogammaglobulinemia	TNF
	Lipid metabolism? ER stress?	LACC1 deficiency	*LACC1/FAMIN*	AR	Fever, systemic JIA, oligoarticular/polyarticular JIA	?
	Cytokine dysregulation	VEO-IBD	*IL-10, IL10RA, IL10RB*	AR	Early-onset colitis, FTT	HSCT, IL-1?
	Actin assembly	ARPC1B deficiency	*ARPC1B*	AR	Platelet abnormalities, bleeding, recurrent infection, small vessel vasculitis, eczema, arthritis	?
	Actin polymerization	CDC42 deficiency	*CDC42*	AR	Neurodevelopmental defects, facial dysmorphism cytopenias, recurrent infection, fever, rash	IL-1

For definitions of abbreviations and acronyms, see next page

Continued

Presented is a simplified representation of disease mechanism classification, causative gene, heritability, major clinical manifestations, and typical treatment options for a representative range of monogenic autoinflammatory diseases.
AD, Autosomal dominant; AIFEC, autoinflammation with infantile enterocolitis; APLAID, autoinflammation and PLAID; AR, autosomal recessive; CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; CNS, central nervous system; CRIA, cleavage-resistant RIPK1-induced autoinflammatory syndrome; DADA2, deficiency of adenosine deaminase 2; DIRA, deficiency of IL-1 receptor antagonist; ER, endoplasmic reticulum; FAMIN, fatty acid metabolism-immunity nexus; FTT, failure to thrive; Haploinsuf., haploinsufficiency; *HSCT*, hematopoietic stem cell transplant; HOIL1, heme-oxidized IRP2 ubiquitin ligase 1; HOIP, HOIL1-interacting protein; Hz/Hc, hyperzincemia/hypercalprotectinemia; ILD, interstitial lung disease; JIA, juvenile idiopathic arthritis; LACC1, laccase domain-containing 1; MWS, Muckle-Wells syndrome; NOMID, neonatal-onset multisystem inflammatory disease; ORAS, OTULIN-related autoinflammatory syndrome; PAAND, pyrin-associated autoinflammation with neutrophilic dermatosis; PAPA, pyogenic arthritis, pyoderma gangrenosum and acne; PFIT, periodic fever, immunodeficiency, and thrombocytopenia; PLAID, PLCG2-associated antibody deficiency and immune dysregulation; PLCG2, phospholipase C gamma 2; PRAAS, proteasome-associated autoinflammatory syndrome; PRAID, POMP-related autoinflammation and immune dysregulation disease; RTI, reverse-transcriptase inhibitor; SAVI, STING-associated vasculopathy of infancy; SIFD, sideroblastic anemia with B-cell immunodeficiency, periodic fevers, and developmental delay; SLE, systemic lupus erythematosus; SMS, Singleton-Merten syndrome; SPENCD, spondyloenchondrodysplasia; tRNA, transfer ribonucleic acid; VEO-IBD, very early onset inflammatory bowel disease. From Nigrovic PA, Lee PY, Hoffman HM. Monogenic autoinflammatory disorders: Conceptual overview, phenotype, and clinical approach. *J Allergy Clin Immunol*. 2020;146(5):925–937, Fig. 3.

autoinflammatory include **systemic-onset juvenile idiopathic arthritis** (see Chapter 196), **Behçet disease** (see Chapter 202), and **Crohn disease** (see Chapter 382.2).

Distinguishing autoinflammatory disorders from one another can be difficult because their presentations can be variable and have significant overlap. Some disorders have characteristic fever patterns (Fig. 204.1), whereas others have characteristic skin findings that can aid in a diagnosis (Table 204.3). Others can have characteristic physical features or organ involvement. Some of these disorders have bone involvement (Table 204.4). Other clinical features can also be helpful, such as ethnicity, age of onset, triggers, laboratory testing, and response to therapies (Table 204.5). Genetic panels are often used to screen for most, if not all, of these defects in a single test, rather than individual genetic assessment based on clinical findings.

AUTOINFLAMMATORY DISEASES WITH PERIODIC OR PROMINENT FEVERS

The first descriptions of autoinflammatory disorders focused on genetic diseases that presented with prominent fevers: the periodic fever syndromes.

Familial Mediterranean Fever

FMF is a recessively inherited autoinflammatory disease usually characterized by recurrent, short-lived (1-3 days), self-limited episodes of fever, serositis, monoarticular or pauciarticular arthritis, or an erysipeloid rash, sometimes complicated by AA amyloidosis. Most patients with FMF present with symptoms in childhood, with 90% presenting before age 20. Clinical features of FMF may include fever, serositis presenting as pleuritic chest pain or severe abdominal pain, arthritis, and rash. The pleural pain is typically unilateral, whereas the abdominal pain (sterile peritonitis) can be generalized or localized to one quadrant, similar to other forms of peritonitis. FMF-associated arthritis occurs primarily in the large joints, may be accompanied by large, neutrophil-rich effusions, and is usually nonerosive and nondestructive. The hallmark cutaneous finding is an erysipeloid erythematous rash that overlies the ankle or dorsum of the foot (Fig. 204.2). Other clinical findings include scrotal pain caused by inflammation of the tunica vaginalis testis, febrile myalgia, exercise-induced myalgia (particularly common in children), and an association with various forms of vasculitis, including Henoch-Schönlein purpura, in as many as 5% of pediatric patients. FMF episodes may be triggered by stress, menses, or infections. Between flares, patients are generally symptom free but may have persistent elevation of their inflammatory markers. The attack frequency can vary from weekly to one to two flares per year. Table 204.6 lists the diagnostic criteria for FMF.

FMF is caused by autosomal recessive pathogenic variants in *MEFV,* a gene encoding a 781–amino acid protein denoted *pyrin* (Greek for "fever"). Pyrin is expressed in granulocytes, monocytes, and dendritic cells (DCs) and in peritoneal, synovial, and dermal fibroblasts. The N-terminal—approximately 90 amino acids of pyrin—is the prototype for a motif (the PYRIN domain) that mediates protein-protein interactions and is found in >20 different human proteins that regulate inflammation and apoptosis. Many of the FMF-associated pathogenic variants in pyrin are found at the C-terminal B30.2 domain of pyrin, encoded by exon 10 of *MEFV.* More than 50 such FMF pathogenic variants are listed in an online database (https://infevers.umai-montpellier.fr/web/), almost all of which are missense substitutions. Homozygosity for the M694V pathogenic variant may be associated with an earlier age of onset, arthritis, and an increased risk of amyloidosis. The substitution of glutamine for glutamic acid at residue 148 (E148Q) is considered either a mild pathogenic variant or a functional polymorphism in the pyrin protein. The carrier frequency of FMF pathogenic variants among several Mediterranean populations is very high, suggesting the possibility of a heterozygote advantage.

FMF occurs primarily among ethnic groups of Mediterranean ancestry, most frequently in people of Jewish, Turkish, Armenian, Arab, or Italian descent. Because of a higher frequency of the M694V pathogenic variant, FMF is more severe and more readily recognized in the Sephardic (North African) than the Ashkenazi (East European) Jewish population. With the advent of genetic testing, pathogenic variant–positive FMF has been documented worldwide, although at lower frequency than in the Mediterranean basin and Middle East.

Through PYRIN-domain interactions, pyrin can activate caspase-1, the enzyme that converts the 31-kDa pro–IL-1β molecule into the biologically active 17-kDa IL-1β, which is a major mediator of fever and inflammation. Pyrin works to sense changes in Rho-GTPases, which can occur due to certain bacterial toxins, thus acting as a sensor of bacterial invasion. FMF pathogenic variants lead to a gain-of-function activation of caspase-1 and IL-1β–dependent inflammation, with a gene-dosage effect. These results may explain why as many as 30% of heterozygous carriers of FMF pathogenic variants have biochemical evidence of inflammation.

Prophylactic daily oral colchicine decreases the frequency, duration, and intensity of FMF flares. This regimen also prevents the development of systemic AA amyloidosis. Colchicine is generally well tolerated and safe in children, with the most common side effects being diarrhea and other gastrointestinal (GI) complaints. Some patients develop lactose intolerance while taking colchicine. GI side effects can be minimized by initiating therapy at a low dose (for young children, 0.3 mg/day) and slowly titrating upward. A dose-related transaminitis may also be observed; bone marrow suppression is rarely seen at the dosages prescribed for FMF. Pediatric patients may require doses of colchicine similar to those needed in adults (1-2 mg/kg/day), reflecting that children metabolize the drug more rapidly than adults. It is not always possible to find a tolerated dose of colchicine at which all symptoms are suppressed, but approximately 90% of patients have a marked improvement in disease-related symptoms. A small percentage of FMF patients are either unresponsive to or intolerant of therapeutic doses of colchicine. Based on the role of pyrin in IL-1β activation, reports have demonstrated the safety and effectiveness of the IL-1 inhibitors *rilonacept, anakinra, and canakinumab* in FMF.

Amyloidosis is the most serious complication of FMF, and in its absence FMF patients may live a normal life span (see Chapter 206). Amyloidosis may develop when serum AA, an acute-phase reactant found at extremely high levels in the blood during FMF attacks, is cleaved to produce a 76–amino acid fragment that misfolds and deposits ectopically, usually in the kidneys, GI tract, spleen, lungs, testes, thyroid, and adrenals. Rarely, cardiac amyloidosis may develop; macroglossia and amyloid neuropathy are generally not seen with the amyloidosis of FMF. The most common presenting sign of AA amyloidosis is proteinuria. The diagnosis is then usually confirmed by rectal or renal biopsy. In a small number of case reports, mostly from the Middle East, amyloidosis may actually precede overt FMF attacks, presumably because of subclinical inflammation. Risk factors for the development of amyloidosis in FMF include homozygosity for the

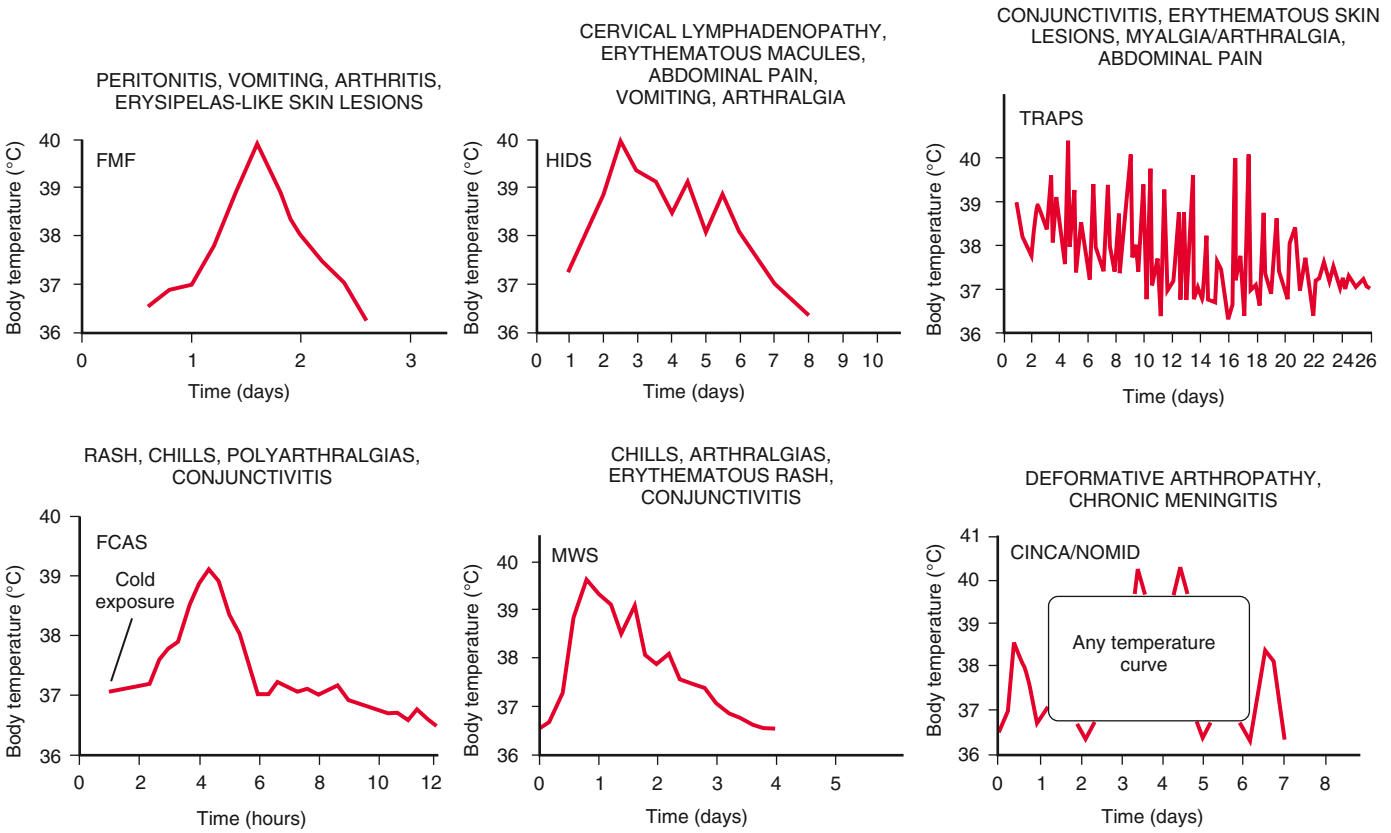

Fig. 204.1 Characteristic patterns of body temperature during inflammatory attacks in the familial autoinflammatory syndromes. Interindividual variability for each syndrome is considerable, and even for the individual patient, the fever pattern may vary greatly from episode to episode. Note the different time scales on the *x* axes. CINCA/NOMID, Chronic infantile neurologic cutaneous and articular syndrome/neonatal-onset multisystemic inflammatory disease; FCAS, familial cold autoinflammatory syndrome; HIDS, hyper-IgD syndrome; MWS, Muckle-Wells syndrome; TRAPS, tumor necrosis factor receptor–associated periodic syndrome. (*From Simon A, van der Meer JWM, Drenth JPH. Familial autoinflammatory syndromes. In Firestein GS, Budd RC, Gabriel SE, et al., eds. Kelley's Textbook of Rheumatology, 9th ed. Philadelphia: Saunders; 2012: Fig. 97-1.*)

M694V *MEFV* pathogenic variant, polymorphisms of the serum AA gene (encoding AA), noncompliance with colchicine treatment, male gender, and a positive family history of AA amyloid. For unclear reasons, country of origin is also a major risk factor for amyloidosis in FMF, with patients raised in the Middle East having a much higher risk than genotypically identical patients raised in the West. Aggressive lifelong suppression of the acute-phase reactants should be the goal in patients with FMF amyloidosis, and documented cases show this may result in resorption of amyloid deposits. The natural history of untreated amyloidosis in FMF is the inexorable progression to renal failure, often within 3-5 years.

Hyperimmunoglobulinemia D with Periodic Fever Syndrome

HIDS, also known as **mevalonate kinase deficiency**, occurs primarily in patients of Northern European descent. HIDS is recessively inherited and caused by pathogenic variants of *MVK*, a gene that encodes mevalonate kinase (MVK). The clinical features of HIDS generally appear within the first 6 months of life. Febrile attacks last 3-7 days, with abdominal pain often accompanied by diarrhea, nausea, and vomiting. Other clinical manifestations include cervical lymphadenopathy, diffuse macular rash, aphthous ulcers, headaches, and occasional splenomegaly (Figs. 204.3-204.5). Arthritis or arthralgia can be present in an oligoarticular or polyarticular pattern. Inflammatory bowel disease–like illness and Kawasaki disease–like presentation have also been reported. Attacks are often precipitated by intercurrent illness, immunizations, and surgery. Families frequently recount flares around the time of birthdays, holidays, and family vacations. The symptoms of HIDS may persist for years but tend to become less prominent in adulthood. Patients with HIDS usually have a normal life span. Unlike FMF and TRAPS, the incidence of AA amyloidosis is quite low. Complete MVK deficiency results in mevalonic aciduria that presents with severe developmental delay, ataxia, myopathy, cataracts, and failure to thrive (see Chapter 105).

MVK is expressed in multiple tissues and catalyzes the conversion of mevalonic acid to 5-phosphomevalonic acid in the biosynthesis of cholesterol and nonsterol isoprenoids. Patients with HIDS-associated pathogenic variants have greatly reduced, but not absent, MVK enzymatic activity. HIDS patients usually have low-normal serum cholesterol levels, but the deficiency of isoprenoids may cause increased IL-1β production by reduced geranylgeranylation of Rho GTPases resulting in pyrin activation. Temperature elevation may further exacerbate this process by more complete inhibition of MVK activity, leading to a possible positive feedback loop.

The diagnosis of HIDS may be confirmed either by two pathogenic variants in *MVK* (approximately 10% of patients with seemingly typical disease have only a single identifiable pathogenic variant) or by elevated levels of mevalonate in the urine. HIDS-associated pathogenic variants are distributed throughout the MK protein, but the two most common pathogenic variants are the substitution of isoleucine for valine at residue 377 (V377I), a variant that is quite common in the Dutch population, and the substitution of threonine for isoleucine at residue 268 (I268T). The eponymous elevation in serum IgD levels *is not* universally present, especially in young children; IgA levels can also be elevated. Conversely, serum IgD levels may be increased in other autoinflammatory disorders and in some chronic infections. During attacks, leukocytosis and increased serum levels of acute-phase reactants and proinflammatory cytokines are frequently present. Table 204.7 lists diagnostic criteria for HIDS.

Standards for the **treatment** of HIDS are evolving. Very few patients respond to colchicine, and milder disease courses may respond to nonsteroidal antiinflammatory drugs (NSAIDs). Corticosteroids can be beneficial during attacks, but long-term use is not recommended. Reports have shown efficacy in the use of the TNF-α blocker *etanercept* and the IL-1 blockers *anakinra and canakinumab*.

Table 204.3 Clinical Grouping of Autoinflammatory Diseases by Skin Manifestations

NEUTROPHILIC URTICARIA (THE CRYOPYRINOPATHIES)

Recurrent fever attacks of short duration (typically <24 hr)

- CAPS/FCAS: familial cold autoinflammatory syndrome
- CAPS/MWS: Muckle-Wells syndrome
- FCAS2/NLRP12

Continuous low-grade fever

- CAPS/NOMID: neonatal-onset multisystem inflammatory disease (NOMID)/chronic infantile neurologic cutaneous and articular syndrome (CINCA)

GRANULOMATOUS SKIN LESIONS AND MINIMAL OR LOW-GRADE FEVER ATTACKS

- Blau syndrome/early-onset sarcoidosis (pediatric granulomatous arthritis)

PUSTULAR SKIN RASHES AND FEVER

With inflammatory bone disease

- DIRA: deficiency of interleukin-1 receptor agonist
- Majeed syndrome

With pyogenic arthritis

- PAPA: pyogenic arthritis, pyoderma gangrenosum, and acne syndrome

Without other organ involvement

- DITRA: deficiency of interleukin-36 receptor antagonist
- CAMPS: CARD14-mediated psoriasis

ATYPICAL NEUTROPHILIC DERMATOSIS WITH HISTIOCYTIC-LIKE INFILTRATE

- CANDLE: proteasome-associated autoinflammatory syndromes

LIVEDO RETICULARIS, VASCULOPATHY WITH ULCERATIONS

- SAVI; STING-associated vasculopathy, infantile onset

LIVEDO RACEMOSA, VASCULITIS WITH ULCERATIONS

- ADA2; adenosine deaminase-2 deficiency

CAPS, Cryopyrin-associated periodic syndromes.
Modified from Almeida de Jesus A, Goldbach-Mansky R. Monogenic autoinflammatory diseases: Concept and clinical manifestations. *Clin Immunol.* 2013;147:155–174, Table 1.

Tumor Necrosis Factor Receptor–Associated Periodic Syndrome

TRAPS is characterized by recurrent fevers and localized inflammation and is inherited in an autosomal dominant manner. TRAPS has a number of distinguishing clinical and immunologic features. It was first recognized in patients of Irish descent and denoted *familial Hibernian fever* to draw a contrast with FMF, but the current nomenclature was proposed when pathogenic variants in *TNFRSF1A* were discovered not only in the original Irish family but also in families from a number of other ethnic backgrounds. *TNFRSF1A* encodes the 55-kDa receptor (denoted p55, TNFR1, or CD120a) for TNF-α that is widely expressed on a number of cell types. A second 75-kDa receptor is largely restricted to leukocytes.

Patients with TRAPS typically present within the first decade of life with flares that occur with variable frequency but of often substantially longer duration than FMF or HIDS flares. The febrile episodes of TRAPS last at least 3 days and can persist for weeks. There may be pleural and peritoneal involvement. At times, patients present with signs of an acute abdomen; on exploration such patients have *sterile peritonitis,* sometimes with adhesions from previous episodes. Patients may also have nausea and frequently report constipation at the onset of flares that progresses to diarrhea by the conclusion. Ocular signs include periorbital edema and conjunctivitis. TRAPS patients may also experience severe myalgia, and on imaging, the muscle groups may have focal areas of edema. Many rashes can be seen in TRAPS patients, but the most common is an erythematous macular rash that on biopsy contains superficial and deep perivascular infiltrates of mononuclear cells. Patients often report that the rash migrates distally on a limb during its course with an underlying myalgia and can resemble cellulitis. Other rashes include erythematous annular patches and a serpiginous rash (Fig. 204.6). Approximately 10–15% of patients with TRAPS may develop AA amyloidosis; the presence of cysteine pathogenic variants and a positive family history are risk factors for this complication. If amyloidosis does not develop, TRAPS patients have a normal life expectancy. Table 204.8 lists diagnostic criteria.

Almost all the TRAPS-associated pathogenic variants are in the extracellular domain of the TNFR1 protein, with about one third involving the substitution of another amino acid for a highly conserved cysteine residue, thus disrupting disulfide bonds and leading to protein misfolding. A number of other missense pathogenic variants not involving cysteine residues have been shown to have a similar effect on TNFR1 protein folding. Misfolded TNFR1 aggregates intracellularly and leads to constitutive signaling through mitogen-activated protein kinases or nuclear factor (NF)-κB, resulting in the release of proinflammatory cytokines such as IL-6, IL-1β and TNF-α.

Colchicine is generally not effective in TRAPS. For relatively mild disease, NSAIDs may suffice. For more severe disease with infrequent attacks, corticosteroids at the time of an attack may be effective, but it is not unusual for steroid requirements to increase over time. Etanercept is often effective in reducing the severity and frequency of flares, but longitudinal follow-up of TRAPS patients treated with etanercept indicates waning efficacy with time. Of note, treatment of TRAPS with anti-TNF-α monoclonal antibodies has sometimes led to a paradoxical worsening of disease. Clinical responses to the IL-1 blockers *anakinra* and *canakinumab* and to *tocilizumab,* a monoclonal anti-IL6 antibody, have been favorable in TRAPS patients.

Cryopyrin-Associated Periodic Fever Syndrome

CAPS represents a spectrum of clinical disorders, including **familial cold autoinflammatory syndrome**, **Muckle-Wells syndrome**, and **neonatal-onset multisystem inflammatory disorder**. Although three separate clinical diagnoses have been defined, it should be emphasized that the **cryopyrinopathies** are really a *continuum* of disease severity. This spectrum of illness is caused by pathogenic variants in *NLRP3* (formerly known as *CIAS1*), which encodes a protein called **cryopyrin**; >100 disease-associated *NLRP3* pathogenic variants have been enumerated on the *Infevers* online database. Advances in next-generation sequencing have also permitted the identification of symptomatic individuals with somatic *NLRP3* mosaicism.

NLRP3 is a PYRIN domain-containing protein that is strongly expressed in myeloid cells and to a lesser degree in other tissues. It is a part of a macromolecular complex termed the *NLRP3 inflammasome* that activates pro–IL-1β to its mature form in response to a variety of endogenous danger-associated molecular patterns and pathogen-associated molecular patterns (PAMPs). Patients with cryopyrinopathies have *gain-of-function pathogenic variants* in *NLRP3* that result in constitutive or easily triggered activation of the NLRP3 inflammasome.

The cryopyrinopathies are characterized by persistent or recurrent bouts of inflammation and an urticaria-like rash that develops early in infancy (Fig. 204.7). Histopathologic examination reveals a perivascular neutrophilic infiltrate without the mast cells or mast cell degranulation seen with true urticaria. In patients with FCAS, febrile attacks generally begin 1-3 hours after generalized cold exposure. FCAS patients also experience polyarthralgia of the hands, knees, and ankles, and conjunctivitis may also develop during attacks. FCAS episodes are self-limited and generally resolve within 24 hours. AA amyloidosis rarely occurs in FCAS. Table 204.9 lists the diagnostic criteria for FCAS.

In contrast to FCAS, the febrile episodes of MWS do not require cold exposure but are characterized by the same urticarial-like rash seen in FCAS (Fig. 204.8). Many MWS patients also develop progressive sensorineural hearing loss, and untreated, approximately 30% of MWS patients develop AA amyloidosis. NOMID exhibits the most severe symptoms and presents in the neonatal period with a diffuse, urticarial rash, daily fevers, and dysmorphic features (Fig. 204.9). Significant joint deformities, particularly of the knees, may develop because of bony overgrowth of the epiphyses of the long bones (Fig. 204.10). NOMID patients also develop chronic aseptic meningitis, leading to increased intracranial pressure, optic disc edema, visual impairment, progressive sensorineural hearing loss, and intellectual disability (Fig. 204.11).

Table 204.4 Autoinflammatory Bone Disorders

	CRMO	MAJEED SYNDROME	DIRA	CHERUBISM	CMO AND LUPO MICE
Ethnicity	Worldwide, but mostly European	Arabic	European, Puerto Rican, Arabic	Worldwide	Occurs in various backgrounds
Fever	Uncommon	Common	Uncommon	No	Not assessed
Sites of osseous involvement	Metaphyses of long bones > vertebrae, clavicle, sternum, pelvis, others	Similar to CRMO	Anterior rib ends, metaphyses of long bones, vertebrae, others	Mandible > maxilla Rarely ribs	Vertebrae hind > forefeet
Extraosseous manifestations	PPP, psoriasis, IBD, others	Dyserythropoietic anemia, Sweet syndrome, HSM, growth failure	Generalized pustulosis, nail changes, lung disease, vasculitis	Cervical lymphadenopathy	Dermatitis, extramedullary hematopoiesis, splenomegaly
Family history of inflammatory disorders	Psoriasis, PPP, arthritis, IBD, others	Psoriasis in some obligate carriers	No known associations	No known associations	Heterozygotes normal
Inheritance	Not clear	Autosomal recessive	Autosomal recessive	Autosomal dominant; incomplete penetrance	Autosomal recessive
Gene defect	Unknown	*LPIN2*	*IL1RN*	*SH3BP2* >> *PTPN11*	*Pstpip2*
Protein name	?	Lipin2	IL-1Ra	SH3BP2	PSTPIP2 (MAYP)
Protein function	?	Fat metabolism: (PAP enzyme activity), ↑ message to oxidative stress, ? role in mitosis	Antagonist of IL-1 receptor	↑ Myeloid cell response to M-CSF and RANKL, ↑ TNF-α expression in macrophages	Macrophage proliferation, macrophage recruitment to sites of inflammation, cytoskeletal function
Cytokine abnormalities	↑ serum TNF-α	Not tested	↑ IL-1α, IL-1β, MIP-1α, TNF-α, IL-8, IL-6 ex vivo monocyte assay; skin reveals ↑ IL-17 staining	↑ serum TNF-α in mouse model	Cmo: ↑ serum IL-6, MIP-1α, TNF-α, CSF-1, IP-10 Lupo: ↑ serum MIP-1α, IL-4, RANTES, TGF-β

CRMO, Chronic recurrent multifocal osteomyelitis; CSF, colony-stimulating factor; CMO, chronic multifocal osteomyelitis; DIRA, deficiency of interleukin-1 receptor antagonist; HSM, hepatosplenomegaly; IBD, inflammatory bowel disease; IL, interleukin; IL-1Ra, interleukin-1 receptor antagonist; IP-10, interferon-inducible protein-10; Lupo, mouse model; M-CSF, macrophage colony-stimulating factor; MIP-1α, macrophage inflammatory protein-1α; PAP, phosphatidate phosphatase; PPP, palmar-plantar pustulosis; PSTPIP2, proline-serine-threonine phosphatase interacting protein; RANKL, receptor activator of nuclear factor-κB ligand; RANTES, regulated on activation, normal T cell expressed and secreted; SH3BP2, SH3-binding protein 2; TGF, transforming growth factor; TNF-α, tumor necrosis factor alpha.

From Ferguson PJ, Laxer RM. Autoinflammatory bone disorders. In Cassidy JT, Petty RE, Laxer RM, et al., eds. *Textbook of Pediatric Rheumatology,* 6th ed. Philadelphia: Saunders; 2011: Table 44-2.

Targeted therapy with anakinra (a recombinant IL-1R antagonist) *has been life changing for NOMID patients,* not only controlling fever and rash but also preventing end-organ damage. Anakinra, rilonacept, and canakinumab are all effective in both FCAS and MWS; they are approved by the U.S. Food and Drug Administration (FDA) for both conditions. Aggressive IL-1 blockade has resulted in attenuation of amyloidosis in the cryopyrinopathies.

OTHER MENDELIAN AUTOINFLAMMATORY DISEASES

Syndrome of Pyogenic Arthritis with Pyoderma Gangrenosum and Acne

PAPA syndrome is a rare autosomal dominant disorder caused by pathogenic variants in *PSTPIP1,* a gene that encodes the cytoskeletal proline serine threonine phosphatase–interacting protein-1 (PSTPIP1). The PSTPIP1 protein interacts with a number of immunologically important molecules, including CD2, Wiskott-Aldrich syndrome protein (WASP), and pyrin. PAPA-associated *PSTPIP1* pathogenic variants greatly increase its affinity to pyrin and cause increased IL-1β production.

Clinical manifestations of PAPA syndrome begin in early childhood with recurrent episodes of sterile, pyogenic arthritis that leads to erosions and joint destruction, and it appears to develop spontaneously or after minor trauma. Fever is not a dominant feature. Cutaneous manifestations tend to develop in adolescence, at which time patients are prone to developing severe cystic acne (see Chapter 710). Additionally, PAPA patients commonly develop ulcerating pyoderma gangrenosum lesions (Fig. 204.12), and some develop pathergy reactions.

The treatment of PAPA syndrome may involve the use of corticosteroids, IL-1 antagonists, and TNF-α inhibitors, sometimes in combination. The joint manifestations of PAPA appear to respond to IL-1 blockade, whereas the cutaneous manifestations seem to respond more favorably to TNF-α blockade. Local measures, such as joint aspiration and drainage and intensive wound care, are also important in the care of PAPA patients, as is pain management for cutaneous disease. Caution should be taken when prescribing sulfonamides because some PAPA patients develop pancytopenia.

Deficiency of Interleukin-1 Receptor Antagonist

DIRA is an autosomal recessive autoinflammatory disease that is distinct from the cryopyrinopathies. DIRA typically presents in the neonatal period with systemic inflammation and a neutrophilic pustulosis, sterile multifocal osteomyelitis, widening of the anterior ends of the ribs, periostitis, and osteopenia (Figs. 204.13 and 204.14). Although fever is not a prominent clinical feature, patients do have greatly elevated acute-phase reactants. Multiorgan failure and pulmonary interstitial fibrosis can occur and can be fatal.

DIRA is caused by loss-of-function pathogenic variants in *IL1RN,* encoding the IL-1R antagonist. Because of the lack of antagonistic activity, the cells are hyperresponsive to IL-1β stimulation. Numerous treatments for DIRA have been tried, including NSAIDs, glucocorticoids,

Table 204.5 Clues That May Assist in the Diagnosis of Autoinflammatory Syndromes

AGE OF ONSET	
At birth	NOMID, DIRA, MWS
Infancy and first year of life	HIDS, FCAS, NLRP12
Toddler	PFAPA
Late childhood	PAPA
Most common of autoinflammatory syndromes to have onset in adulthood	TRAPS, DITRA
Variable (mostly in childhood)	All others
ETHNICITY AND GEOGRAPHY	
Armenians, Turks, Italian, Sephardic Jews	FMF
Arabs	FMF, DITRA (Arab Tunisian)
Dutch, French, German, Western Europe	HIDS, MWS, NLRP12
United States	FCAS
People of West African origin	TRAPS
Eastern Canada, Puerto Rico	DIRA
Worldwide	All others
TRIGGERS	
Vaccines	HIDS
Cold exposure	FCAS, NLRP12
Stress, menses	FMF, TRAPS, MWS, PAPA, DITRA
Minor trauma	PAPA, MWS, TRAPS, HIDS
Exercise	FMF, TRAPS
Pregnancy	DITRA
Infections	All, especially DITRA
ATTACK DURATION	
<24 hr	FCAS, FMF
1-3 days	FMF, MWS, DITRA (fever)
3-7 days	HIDS, PFAPA
>7 days	TRAPS, PAPA
Almost always "in attack"	NOMID, DIRA
INTERVAL BETWEEN ATTACKS	
3-6 wk	PFAPA, HIDS
>6 wk	TRAPS
Mostly unpredictable	All others
Truly periodic	PFAPA, cyclic neutropenia
USEFUL LABORATORY TESTS	
Acute-phase reactants must be normal between attacks	PFAPA
Urine mevalonic acid in attack	HIDS
IgD >100 mg/dL	HIDS
Proteinuria (amyloidosis)	FMF, TRAPS, MWS, NOMID
RESPONSE TO THERAPY	
Corticosteroid dramatic	PFAPA
Corticosteroid partial	TRAPS, FCAS, MWS, NOMID, PAPA*
Colchicine	FMF, PFAPA (30% effective)
Cimetidine	PFAPA (30% effective)
Etanercept	TRAPS, FMF arthritis
Anti–IL-1 dramatic	DIRA (anakinra), FCAS, MWS, NOMID, PFAPA
Anti–IL-1 mostly	TRAPS, FMF
Anti–IL-1 partial	HIDS, PAPA

*For intraarticular corticosteroids.
DIRA, Deficiency of IL-1 receptor antagonist; DITRA, deficiency of IL-36 receptor antagonist (generalized pustular psoriasis); FCAS, familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; HIDS, hyper-IgD syndrome; IL, interleukin; MWS, Muckle-Wells syndrome; NLRP, nucleotide oligomerization domain–like receptor family, pyrin domain; NOMID, neonatal-onset multisystem inflammatory disorder; PAPA, pyogenic sterile arthritis, pyoderma gangrenosum, acne syndrome; PFAPA, periodic fever, aphthous stomatitis, pharyngitis, adenitis; TRAPS, tumor necrosis factor receptor–associated periodic syndrome.
From Hashkes PJ, Toker O. Autoinflammatory syndromes. *Pediatr Clin North Am*. 2012;59:447–470, Table 2.

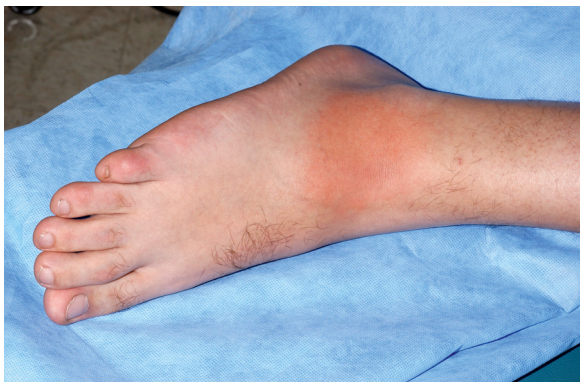

Fig. 204.2 Characteristic erysipeloid erythema associated with familial Mediterranean fever. This rash appears during a flare and overlies the ankle or dorsum of the foot.

intravenous immunoglobulin (IVIG), methotrexate, cyclosporine, and etanercept. However, *anakinra is the treatment of choice*, essentially replacing the lost protein and resulting in a rapid clinical response. Anakinra is dosed daily, with the dose titrated to achieve a normal CRP. There are now longer-acting anti–IL-1 agents, canakinumab and rilonacept, which are effective and require less frequent dosing than anakinra.

Blau Syndrome

Blau syndrome is a rare autosomal dominant disorder that manifests as early-onset (<5 years of age) granulomatous arthritis, uveitis, and rash. The arthritis may affect the ankles and wrists and may lead to flexion contractures of the fingers and toes (camptodactyly). **Early-onset sarcoidosis** presents with a similar clinical picture, sometimes with visceral involvement, and both conditions are caused by pathogenic variants in the caspase recruitment domain protein 15 (CARD15), also known as *nucleotide-binding oligomerization domain-2 protein* (NOD2). NOD2

Table 204.6 Diagnostic Criteria for Familial Mediterranean Fever (FMF)*

MAJOR CRITERIA
1. Typical attacks† with peritonitis (generalized)
2. Typical attacks with pleuritis (unilateral) or pericarditis
3. Typical attacks with monoarthritis (hip, knee, ankle)
4. Typical attacks with fever alone
5. Incomplete abdominal attack

MINOR CRITERIA
1. Incomplete attacks‡ involving chest pain
2. Incomplete attacks involving monoarthritis
3. Exertional leg pain
4. Favorable response to colchicine

*Requirements for a diagnosis of FMF are one or more major criteria or two or more minor criteria.
†Typical attacks are defined as recurrent (three or more of the same type), febrile (≥38°C), and short (lasting between 12 hr and 3 days).
‡Incomplete attacks are defined as painful and recurrent attacks not fulfilling the criteria for a typical attack.
From Livneh A, Langevitz P, Zemer D, et al. Criteria for the diagnosis of familial Mediterranean fever. *Arthritis Rheum.* 1997;40:1879–2045.

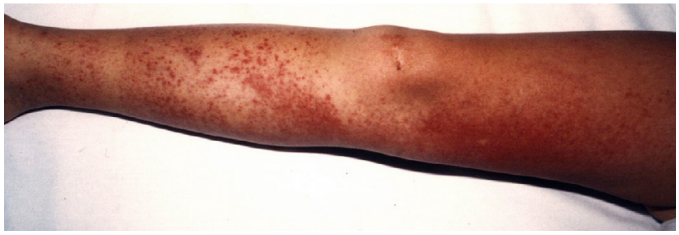

Fig. 204.4 Petechiae on the leg of a hyper-IgD syndrome patient during a febrile attack. (*From Simon A, van der Meer JWM, Drenth JPH. Familial autoinflammatory syndromes. In Firestein GS, Budd RC, Gabriel SE, et al., eds. Kelley's Textbook of Rheumatology, 9th ed. Philadelphia: Saunders; 2012: Fig. 97-7.*)

Table 204.7 Diagnostic Indicators of Hyper-IgD Syndrome

AT TIME OF ATTACKS
1. Elevated erythrocyte sedimentation rate and leukocytosis
2. Abrupt onset of fever (≥38.5°C)
3. Recurrent attacks
4. Lymphadenopathy (especially cervical)
5. Abdominal distress (e.g., vomiting, diarrhea, pain)
6. Skin manifestations (e.g., erythematous macules and papules)
7. Arthralgias and arthritis
8. Splenomegaly

CONSTANTLY PRESENT
1. Elevated IgD (above upper limit of normal) measured on two occasions at least 1 mo apart*
2. Elevated IgA (≥2.6 g/L)

SPECIFIC FEATURES
1. Pathogenic variants in mevalonate kinase gene
2. Decreased mevalonate kinase enzyme activity

*Extremely high serum concentrations of IgD are characteristic but not obligatory.
From Firestein GS, Budd RC, Gabriel SE, et al. (eds): *Kelley & Firestein's Textbook of Rheumatology*, 10th ed. Philadelphia: Elsevier, 2017: Table 97-4, p. 1674.

is an intracellular sensor of bacterial products in DCs, myelomonocytic cells, and Paneth cells. Pathogenic variants in the NACHT oligomerization domain of this protein cause Blau syndrome/early-onset sarcoidosis, whereas variants primarily in the leucine-rich repeat domain are associated with susceptibility to **Crohn disease**. Corticosteroids have been the mainstay of therapy for Blau syndrome, but are limited by side effects. Methotrexate, cyclosporin, and mycophenolate have all been

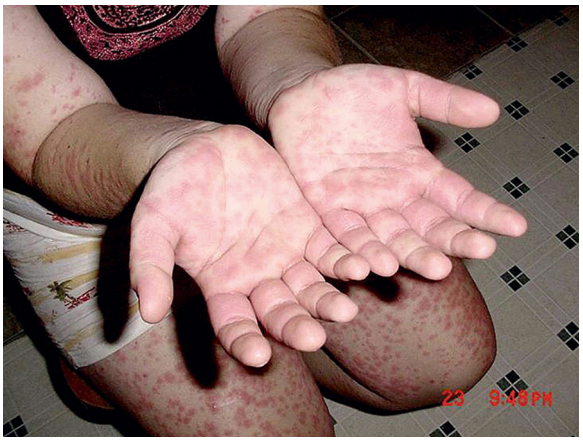

Fig. 204.3 Polymorphic rash on the hands, arms, and legs of a patient with hyper-IgD syndrome (HIDS). (*From Takada K, Aksentijevich I, Mahadevan V, et al. Favorable preliminary experience with etanercept in two patients with the hyperimmunoglobulinemia D and periodic fever syndrome. Arthritis Rheum 2003;48:2646.*)

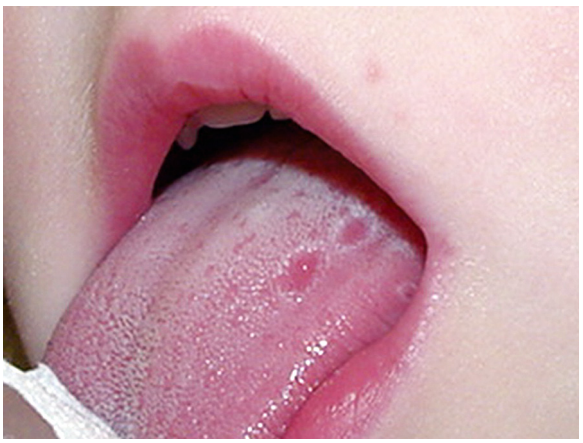

Fig. 204.5 Aphthous ulceration detected on the tongue of a patient with hyper-IgD syndrome. (*Courtesy Dr. K. Antila, North Carelian Central Hospital, Joensuu, Finland; from Simon A, van der Meer JWM, Drenth JPH. Familial autoinflammatory syndromes. In Firestein GS, Budd RC, Gabriel SE, et al., eds. Kelley's Textbook of Rheumatology, 9th ed. Philadelphia: Saunders; 2012: Fig. 97-8.*)

tried with variable results. TNF-α inhibitors have been reported to be beneficial; IL-1 antagonism has shown variable effects.

Autoinflammation with Phospholipase Cγ$_2$–Associated Antibody Deficiency and Immune Dysregulation

APLAID is a dominantly inherited disorder characterized by recurrent blistering skin lesions, bronchiolitis, arthralgia, ocular inflammation, enterocolitis, absence of autoantibodies, and immunodeficiency. Rash is the first manifestation of APLAID, which is described as a full-body epidermolysis bullosa–like eruption. Over time, this rash changes to recurrent plaques and vesiculopustular lesions that are triggered by heat and sunlight. Colitis also presents in childhood before age 5 years. Ocular manifestations begin before age 1 year and include corneal ulcerations and erosions as well as cataracts. Immune manifestations include markedly decreased class-switched memory B cells, resulting in low IgM and IgA.

Patients with APLAID show a gain-of-function missense variant or deletion of the autoinhibitory region of phospholipase Cγ$_2$ (PLCγ$_2$), leading to increased activity of downstream mediators and stimulation of lymphocytes. Despite the enhanced signaling, the resulting populations of immune cells have poor function. Interestingly, a different pathogenic variant in the PLCγ$_2$ complex leads to a syndrome known

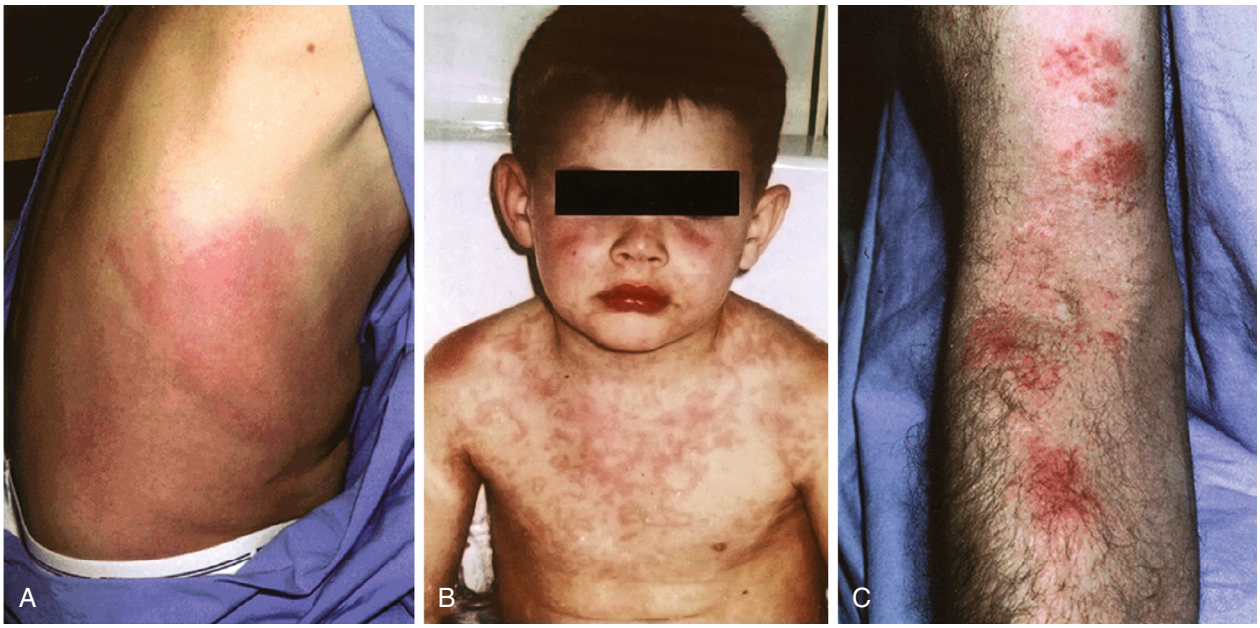

Fig. 204.6 Cutaneous manifestations of tumor necrosis factor receptor–associated periodic syndrome. **A,** Right flank of a patient with the T50M pathogenic variant. **B,** Serpiginous rash involving the face, neck, torso, and upper extremities of a child with the C30S pathogenic variant. **C,** Erythematous, macular patches with crusting on the flexor surface of the right arm of a patient with the T50M pathogenic variant. (*From Hull KM, Drewe, Aksentijevich I, et al. The TNF receptor-associated periodic syndrome [TRAPS]: Emerging concepts of an autoinflammatory syndrome, Medicine (Baltimore). 2002;81:349–368.*)

Table 204.8 Diagnostic Indicators of Tumor Necrosis Factor Receptor–Associated Periodic Syndrome (TRAPS)

1. Recurrent episodes of inflammatory symptoms spanning >6-mo duration (several symptoms generally occur simultaneously)
   a. Fever
   b. Abdominal pain
   c. Myalgia (migratory)
   d. Rash (erythematous macular rash occurs with myalgia)
   e. Conjunctivitis or periorbital edema
   f. Chest pain
   g. Arthralgia or monoarticular synovitis
2. Episodes last >5 days on average (although variable)
3. Responsive to glucocorticosteroids but not colchicine
4. Affects family members in autosomal dominant pattern (although may not always be present)
5. Any ethnicity may be affected

From Hull KM, Drewe E, Aksentijevich I, et al. The TNF receptor-associated periodic syndrome (TRAPS): emerging concepts of an autoinflammatory disorder. *Medicine (Baltimore).* 2002;81:349–368.

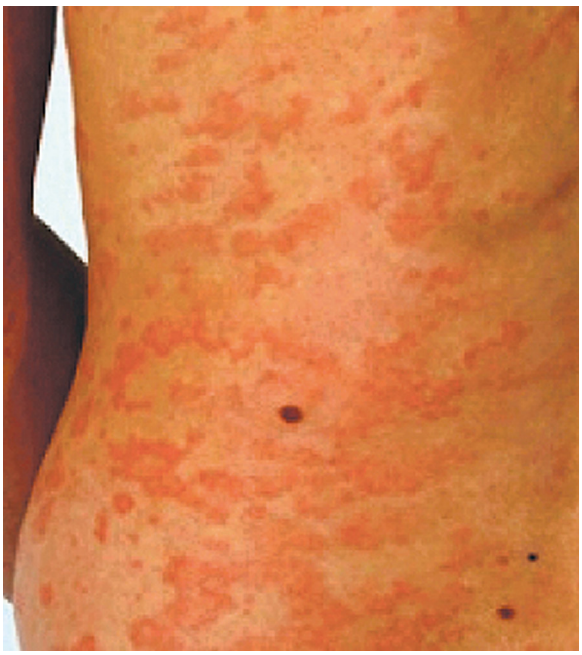

Fig. 204.7 Urticarial-like rash. Inflammatory clinical manifestations and organ damage in the IL-1–mediated diseases; in neonatal-onset multisystem inflammatory disease (NOMID), which is the severe form of cryopyrin-associated periodic syndromes (CAPS); and deficiency of IL-1 receptor antagonist (DIRA). This rash is not truly urticarial and occurs due to neutrophil infiltrates into the skin. (*From Jesus AA, Goldbach-Mansky R. IL-1 blockade in autoinflammatory syndromes. Annu Rev Med. 2014;65:223–244, Fig. 2.*)

as **PLCγ_2-associated antibody deficiency and immune dysregulation (PLAID)**, characterized by cold-induced urticaria, hypogammaglobulinemia with resulting susceptibility to infection, and autoimmunity.

Because of the low number of affected patients described, there are no agreed treatment regimens for APLAID. Patients have been treated with NSAIDs, and corticosteroids can be effective, but side effects limit their long-term use. TNF-α inhibitors and IL-1 inhibitors have been used with some success.

Deficiency of Adenosine Deaminase 2 (DADA2)

DADA2 is an autoinflammatory disorder caused by loss-of-function pathogenic variants in *CECR1,* encoding adenosine deaminase 2. DADA2 presents with recurrent fevers and a spectrum of *vascular* manifestations that includes livedo racemosa, early-onset ischemic lacunar strokes, and systemic vasculitis of medium-size vessels similar to **polyarteritis nodosa**. The lacunar strokes, typically affecting the deep brain nuclei and the brainstem, transpire before age 5 years and typically occur during inflammatory episodes. The livedoid rash is also a prominent feature during inflammatory episodes, and biopsies demonstrate a predominance of neutrophils and macrophages as well as vasculitis in medium-sized vessels. Acute-phase

Table 204.9 Diagnostic Criteria for Familial Cold Autoinflammatory Syndrome (FCAS)

1. Recurrent intermittent episodes of fever and rash that primarily follow generalized cold exposures
2. Autosomal dominant pattern of disease inheritance
3. Age of onset <6 mo
4. Duration of most attacks <24 hr
5. Presence of conjunctivitis associated with attacks
6. Absence of deafness, periorbital edema, lymphadenopathy, and serositis

From Hoffman HM, Wanderer AA, Broide DH. Familial cold autoinflammatory syndrome: phenotype and genotype of an autosomal dominant periodic fever. *J Allergy Clin Immunol*. 2001;108:615–620.

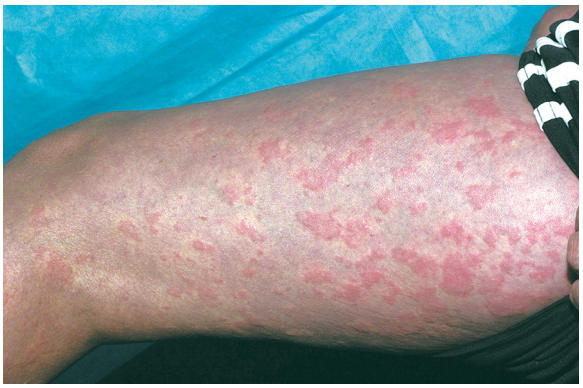

Fig. 204.8 Urticarial-like skin rash in a patient with Muckle-Wells syndrome. (*Courtesy Dr. D.L. Kastner, National Institutes of Health, Bethesda, Maryland; from Simon A, van der Meer JWM, Drenth JPH. Familial autoinflammatory syndromes. In Firestein GS, Budd RC, Gabriel SE, et al., eds. Kelley's Textbook of Rheumatology, 9th ed. Philadelphia: Saunders; 2012: Fig. 97-14.*)

reactants are typically elevated. Other features include ophthalmologic involvement, various degrees of lymphopenia, hypogammaglobulinemia, hepatosplenomegaly, portal hypertension, and pancytopenia due to bone marrow aplasia. Patients may meet criteria for polyarteritis nodosa and can exhibit digit necrosis and Raynaud phenomenon.

ADA2 is produced primarily by monocytes and macrophages, is found in plasma, and appears to act as a growth and differentiation factor for a subset of inflammatory macrophages. Numerous antiinflammatories have been tried in patients with DAD2, including glucocorticoids and cyclophosphamide. TNF-α inhibitors (etanercept or adalimumab) are the mainstay of treatment, and anecdotal reports have shown a benefit with anakinra. Macrophages and monocytes are the main sources of ADA2, raising the possibility of bone marrow transplant to achieve a permanent cure.

Sideroblastic Anemia with Immunodeficiency, Fevers, and Developmental Delay

SIFD is a syndrome characterized by systemic inflammation, fevers, enteritis, and sideroblastic anemia and caused by biallelic pathogenic variants in *TRNT1*. SIFD presents in infancy with fever, elevated inflammatory markers, gastroenteritis, and anemia. Bone marrow biopsies demonstrate ringed sideroblasts. Other features include hypogammaglobulinemia, B-cell lymphopenia, developmental delay, and variable neurodevelopmental degeneration, seizures, and sensorineural hearing loss. Brain imaging was notable for cerebellar atrophy, delayed white matter myelination, and decreased perfusion. Other isolated clinical features include nephrocalcinosis, aminoaciduria, ichthyotic skin, cardiomyopathy, and retinitis pigmentosa. TRNT1 is an RNA polymerase that is necessary for maturation of cytosolic and mitochondrial transfer RNAs by the addition of two cytosines and one adenosine to the transfer RNA (tRNA) ends.

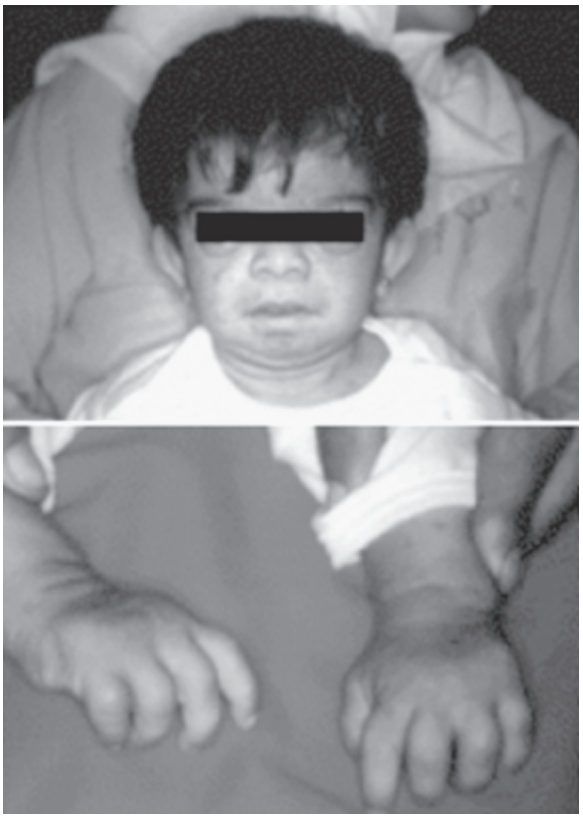

Fig. 204.9 A 3-yr-old female with NOMID/CINCA disease. Note the markedly deformed hands, rash, frontal bossing, and large head. (*From Padeh S. Periodic fever syndromes. Pediatr Clin North Am. 2005;52:577–560.*)

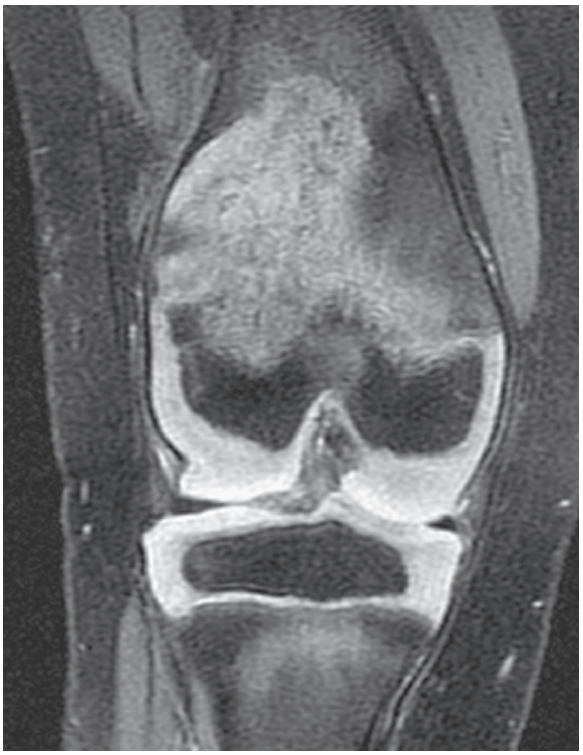

Fig. 204.10 Metaphyseal bone overgrowth. Inflammatory clinical manifestations and organ damage in the IL-1–mediated diseases; in NOMID, the severe form of CAPS; and DIRA. (*From Jesus AA, Goldbach-Mansky R. IL-1 blockade in autoinflammatory syndromes. Annu Rev Med. 2014;65:223–244, Fig. 2C.*)

Symptomatic treatment with regular blood transfusions and immunoglobulin replacement therapy is the mainstay of SIFD therapy. Iron overload from the transfusion often requires chelation therapy. Anakinra relieved the febrile episodes in one patient but did not alter the other clinical manifestations. Patients with SIFD have a high mortality rate. One patient underwent hematopoietic bone marrow transplantation at 9 months of age that resulted in correction of the hematologic and immunologic abnormalities.

Deficiency of Interleukin-36 Receptor Antagonist

DITRA is characterized by episodes of diffuse erythematous pustular rash (generalized pustular psoriasis), fevers, general malaise, and systemic inflammation. Attacks can be triggered by events such as infections, pregnancy, or menstruation or can occur randomly. The underlying genetic etiology has been determined to be autosomal recessive pathogenic variants in the *IL36RN* gene, which encodes an IL-36R antagonist. IL-36 is related to and acts similarly to an IL-1R antagonist, preventing production of inflammatory cytokines such as IL-8. Interestingly, the rash of DITRA is similar to the rash of DIRA (IL-1R deficiency; see earlier), but DITRA is largely skin limited. DITRA has been treated with various modalities, including vitamin A analogs, cyclosporine, methotrexate, and TNF-α inhibitors. The use of anakinra has been described in case reports and results in alleviation of the symptoms.

Familial Cold Autoinflammatory Syndrome Type 2

Pathogenic variants in *NLRP12* lead to a periodic fever syndrome characterized by fevers >40°C, arthralgias, and myalgias lasting from 2 to 10 days. This disorder is named FCAS2 because these episodes can be precipitated by cold. Clinical findings may include an urticarial-like rash, abdominal pain and vomiting, aphthous ulcers, and lymphadenopathy. As with MWS, sensorineural hearing loss and optic neuritis have been described. NALP12 is a member of the CATERPILLAR family of proteins, which are important in innate immunity. Similar to toll-like receptors (TLRs) that act to recognize PAMPs, NLRP12 also senses PAMPs and can lead to the activation of the inflammasome and

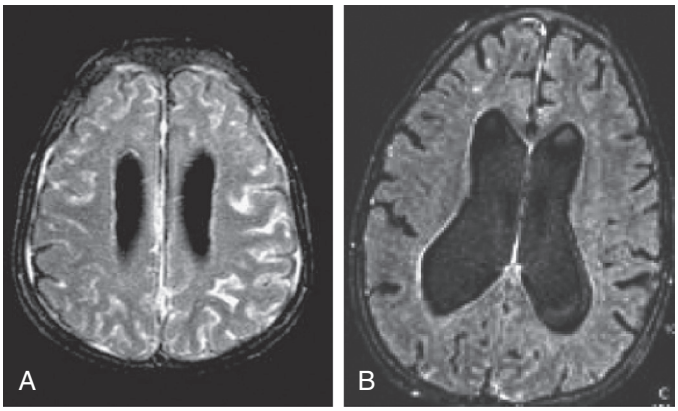

Fig. 204.11 A, Leptomeningeal enhancement. B, Hydrocephalus and cerebral atrophy. Inflammatory clinical manifestations and organ damage in the IL-1–mediated diseases, NOMID (severe form of CAPS) and DIRA. (*From Jesus AA, Goldbach-Mansky R. IL-1 blockade in autoinflammatory syndromes. Annu Rev Med. 2014;65:223–244, Fig. 2G,H.*)

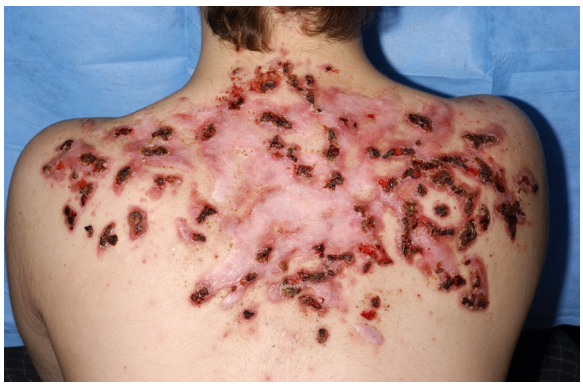

Fig. 204.12 Pyoderma gangrenosum lesions in a patient with PAPA syndrome and the A230T pathogenic variant in *PSTPIP1*. Note the diffuse scarring indicative of prior lesions on his upper back.

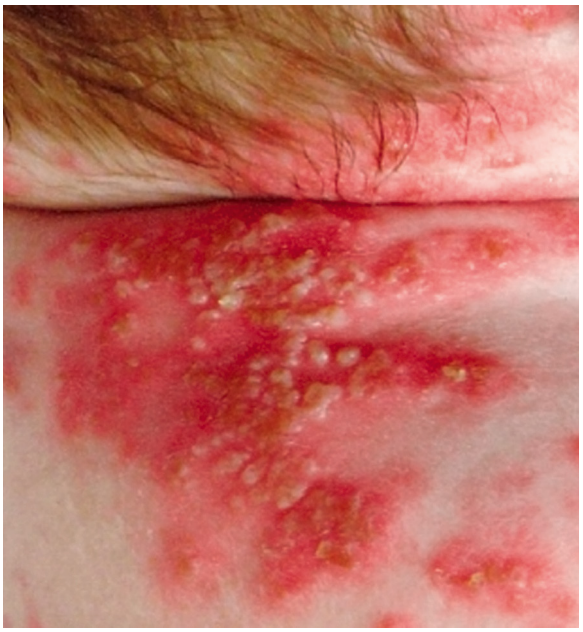

Fig. 204.13 Pustular rash. Inflammatory clinical manifestations and organ damage in the IL-1–mediated diseases, NOMID (severe form of CAPS) and DIRA. This can also be seen in deficiency of the IL-36 receptor antagonist (DITRA). (*From Jesus AA, Goldbach-Mansky R. IL-1 blockade in autoinflammatory syndromes. Annu Rev Med 2014;65:223–244, Fig. 2B.*)

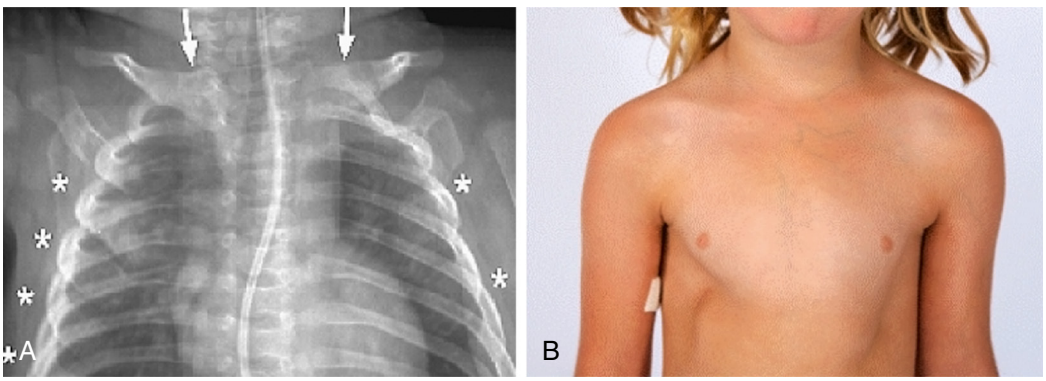

Fig. 204.14 A, Widening of multiple ribs *(asterisks)* and clavicles *(arrows)* in DIRA osteomyelitis. B, Chest deformity. Inflammatory clinical manifestations and organ damage in the IL-1-mediated diseases NOMID and DIRA. (*From Jesus AA, Goldbach-Mansky R. IL-1 blockade in autoinflammatory syndromes. Annu Rev Med. 2014;65:223–244, Fig. 2E,F.*)

generation of IL-1β. Treatment of *NALP12* pathogenic variants was difficult until the advent of anti–IL-1 agents (e.g., anakinra), which are the preferred treatment for FCAS2 and result in remarkable resolution of symptoms. Colchicine can be partially effective, and systemic glucocorticoids can reduce the duration of the attacks.

Autoinflammation with Enterocolitis

A disorder caused by pathogenic variants in *NLRC4* was described with neonatal-onset enterocolitis, fever, and inflammatory episodes. Inflammatory markers are typically elevated, including CRP and ferritin. **Macrophage activation syndrome**, characterized by pancytopenia, hypertriglyceridemia, and coagulopathies, is common during acute flares, which can be precipitated by emotional and physical stress. Recurrent myalgias with febrile episodes often occur as well. This disorder is caused by gain-of-function missense pathogenic variants in NOD-like receptor C4 (NLRC4), which normally aids in the activation of the inflammasome. The resulting protein leads to constitutive production of IL-1. The mainstay of treatment is anti–IL-1 agents such as anakinra, canakinumab, and rilonacept. Before their diagnosis, patients with *NLRC4* pathogenic variants had been treated with colchicine and oral glucocorticoids, with varying success.

Majeed Syndrome

Majeed syndrome is an autosomal recessive disorder caused by pathogenic variants in the *LPIN2* gene (see Table 204.4). The clinical manifestation of Majeed syndrome begin in childhood with recurrent fevers, sterile osteomyelitis, congenital dyserythropoietic anemia (CDA), neutrophilic dermatosis, failure to thrive, and hepatomegaly. Treatment of Majeed syndrome has included NSAIDs, corticosteroids, and IL-1R antagonists. How pathogenic variants in *LPIN2* lead to an autoinflammatory disorder is not known.

NF-κB Disorders

Although the majority of the previous autoinflammatory disorders involve the IL-1 pathway, a variety of newer disorders that affect the NF-κB signaling has been discovered. NF-κB consists of several transcription factors that are sequestered in the cytoplasm bound to the inhibitory proteins IκBα, and when activated, these inhibitors are degraded via the ubiquitin pathway allowing for the nuclear translocation of NF-κB and gene transcription. Several autoinflammatory disorders have been linked to the NF-κB pathway. **Otulipenia** is an autoinflammatory disorder that presents in infancy with episodes of recurrent fevers, joint swelling, painful nodular red rash, GI inflammation/diarrhea, and failure to thrive. Biopsies of rash will show a neutrophilic dermatosis and small/medium vessel vasculitis. Otulipenia is due to autosomal recessive variants in the *FAM105B* gene that encode otulin, a protein that inhibits deubiquitination of this pathway resulting in constitutional activation of NF-κB. Effective treatment with anti-TNF therapy has been described, with less success with other agents. Another related autoinflammatory disorder has been described that is caused by haploinsufficiency in the *TNFAIP3* gene, which encodes the A20 protein. This is autosomal dominantly inherited and also affects deubiquitination. Patients with this disorder present as familial Behçet disease with systemic inflammation, oral and genital ulcers, uveitis, and fevers.

Interferonopathies

See Chapter 205.

GENETICALLY COMPLEX AUTOINFLAMMATORY DISEASES

Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis

PFAPA is the most common recurrent fever syndrome in children. It usually presents between ages 2 and 5 years with recurring episodes of fever, malaise, exudative-appearing tonsillitis with negative throat cultures, cervical lymphadenopathy, oral aphthae, and, less often, headache, abdominal pain, and arthralgia. The episodes last 4-6 days, regardless of antipyretic or antibiotic treatment, and often occur with clocklike regularity on 3- to 6-week cycles. Findings during the episodes may include mild hepatosplenomegaly, mild leukocytosis, and elevated acute-phase reactants. Both the frequency and the intensity of the episodes diminish with increasing age. The etiology and pathogenesis of PFAPA remain unknown.

Most patients show dramatic response to a single oral dose of prednisone (0.6-2.0 mg/kg), although this approach does not prevent recurrence and may actually shorten the interval between flares. Cimetidine at 20-40 mg/kg/day is reported to be effective at preventing recurrences in approximately one third of cases. Small series have shown that anakinra may be effective during a flare, but because corticosteroids are effective, this may not be a cost-effective approach. Colchicine may extend the time between flares. Complete resolution has been reported after tonsillectomy, although medical management should be the first approach.

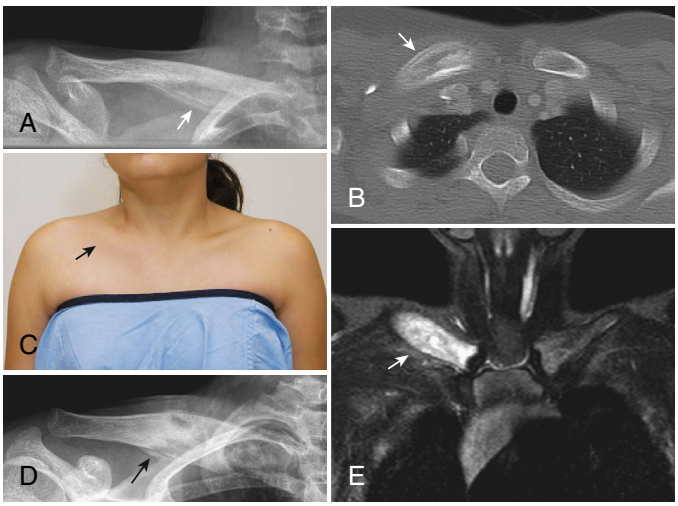

Fig. 204.15 Clavicular involvement in chronic recurrent multifocal osteomyelitis. Adolescent female with unilateral clavicular involvement. **A,** Plain radiograph of the right clavicle at presentation reveals widening of the medial two-thirds, with associated periosteal reaction. **B,** Corresponding CT scan of the right clavicle demonstrates expansion of the medial right clavicle with areas of increased sclerosis accompanied by a surrounding periosteal reaction *(arrow)*. **C,** Flare of disease 18 months later showing further clavicular enlargement (clinical photo). **D,** Plain radiograph of the right clavicle at that time demonstrates marked interval sclerosis and thickening. **E,** MRI at the same time shows increased signal intensity on fat-suppressed contrast-enhanced T1-weighted images of the right medial clavicle consistent with continued inflammation. (*Images courtesy Dr. Paul Babyn, University of Saskatchewan and Saskatchewan Health Authority, Saskatchewan, Canada.*)

Chronic Recurrent Multifocal Osteomyelitis

CRMO is a form of inflammatory bone disease most frequently seen in children (see Table 204.4). Histologically and radiologically, CRMO is virtually indistinguishable from infectious osteomyelitis (Fig. 204.15). Patients typically present with bone pain and may also have fever, soft tissue swelling, and elevated acute-phase reactants. Cultures are sterile. Typically involved bones include the distal femur, proximal tibia or fibula, spine, and pelvis. Both metaphyseal and epiphyseal lesions may occur; premature physeal closure may develop. Less frequently involved bones include the clavicle and mandible. The differential diagnosis includes infectious osteomyelitis, histiocytosis, and malignancy (neuroblastoma, lymphoma, leukemia, Ewing sarcoma). **SAPHO** (synovitis, acne, pustulosis, hyperostosis, and osteitis) may be an adult equivalent to CRMO. The etiology of sporadic CRMO is unknown. CRMO is seen in Majeed syndrome (see earlier), in association with inflammatory bowel disease, and with inflammatory skin disease such as palmoplantar pustulosis. Initial therapy includes NSAIDs. Second-line treatments include corticosteroids, TNF inhibitors, and bisphosphonates.

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Chapter 205

Interferonopathies

Sara E. Sabbagh and James W. Verbsky

Type I interferonopathies refer to a group of inherited autoinflammatory disorders that are characterized by dysregulation of the type I interferon (IFN) pathway (Table 205.1). Type I interferonopathies were recognized when a report described the phenotypic overlap between Aicardi-Goutières syndrome (AGS) encephalopathy, congenital viral infections, and monogenic systemic lupus erythematosus (SLE). The clinical similarities of these diseases stimulated the theory of a shared pathologic mechanism. Pathogenic variants involved in type I IFN signaling were identified to be causative for AGS and monogenic forms of SLE. Several other novel monogenic disorders with aberrant IFN signaling have been identified.

Type I IFNs are ubiquitously expressed inflammatory polypeptides that are induced by microbial and viral nucleic acids. During viral replication, accumulation of viral nucleic acids is sensed by several different cellular mechanisms, which leads to downstream IFN production (Fig. 205.1). Type I IFNs are released from the cell and bind to IFN receptors (IFNRs) through autocrine and paracrine action. The IFNR then activates signal translation through Janus kinase/signal transducers and activators of transcription (JAK-STAT) pathways, which promotes the expression of IFN-simulated genes (ISGs), which stops cell replication and protein translation of the infected cell. There are several molecular mechanisms that lead to altered regulation of IFN signaling: (1) loss-of-function variants of genes that encode enzymes responsible for DNA or DNA-RNA hybrid molecule degradation; (2) variants that lead to constitutive activation or reduction of the activation threshold of intracytosolic nucleic acid sensors; (3) gain-of-function variants of positive IFN signaling regulators; (4) loss-of-function variants of negative IFN signaling regulators; and (5) proteasomal dysfunction leading to the unfolded protein response and downstream IFN pathway activation. Examples of these altered molecular mechanisms and the associated

Table 205.1 Mutated Gene, Protein Function, Pattern of Inheritance, and Main Symptoms of Known Type 1 Interferonopathies

DISEASE	GENE	PROTEIN FUNCTION	INHERITANCE	SYMPTOMS
Aicardi-Goutières syndrome (AGS) type 1	*TREX-1*	3′-5′ DNA exonuclease	AR and AD	Classical AGS
AGS2	*RNASEH2B*	Components of RNase H2 complex. Removes ribonucleotides from RNA-DNA hybrids	AR	Classical AGS
AGS3	*RNASEH2C*			Classical AGS
AGS4	*RNASEH2A*			Classical AGS with dysmorphic features
AGS5	*SAMHD1*	Restricts the availability of cytosolic deoxynucleotides	AR	Mild AGS, mouth ulcer, deforming arthropathy, cerebral vasculopathy with early-onset stroke
AGS6	*ADAR*	Deaminates adenosine to inosine in endogenous dsRNA, preventing recognition by MDA5 receptor	AR and AD	Classical AGS, bilateral striatal necrosis
AGS7	*IFIH1*	Cytosolic receptor for dsRNA	AD	Classic or mild AGS, asymptomatic
Retinal vasculopathy with cerebral leukodystrophy (RVCL)	*TREX-1*	3′-5′ DNA exonuclease	AD	Adult-onset loss of vision, stroke, motor impairment, cognitive decline, Raynaud, and liver involvement
Spondyloenchondrodysplasia (SPENCD)	*ACP5*	Lysosomal phosphatase activity	AR	Spondyloenchondrodysplasia, immune disregulation, and in some cases combined immunodeficiency
STING-associated vasculopathy with onset in infancy (SAVI)	*TMEM173*	Transduction of cytoplasmic DNA-induced signal	AD	Systemic inflammation, cutaneous vasculopathy, pulmonary inflammation
Proteasome-associated autoinflammatory syndrome (PRAAS)	*PSMB8*	Part of the proteasome complex	AR	Autoinflammation, lipodystrophy, dermatosis, hyperimmunoglobulinemia, joint contractures, short stature
ISG15 deficiency	*ISG15*	Stabilizes USP18, a negative regulator of type 1 interferon	AR	Brain calcifications, seizures, mycobacterial susceptibility
Singleton-Merten syndrome (SMS)	*IFIH1*	Cytosolic receptor for dsRNA	AD	Dental dysplasia, aortic calcifications, skeletal abnormalities, glaucoma, psoriasis
Atypical SMS	*DDX58*	Cytosolic receptor for dsRNA	AD	Aortic calcifications, skeletal abnormalities, glaucoma, psoriasis
Trichohepatoenteric syndrome (THES)	*SKIV2L*	RNA helicase	AR	Severe intractable diarrhea, hair abnormalities (trichorrhexis nodosa), facial dysmorphism, immunodeficiency in most cases

From Volpi S, Picco P, Caorsi R, Candotti F, Gattorno M. Type I interferonopathies in pediatric rheumatology. *Pediatr Rheumatol Online J.* 2016;14(1):35.

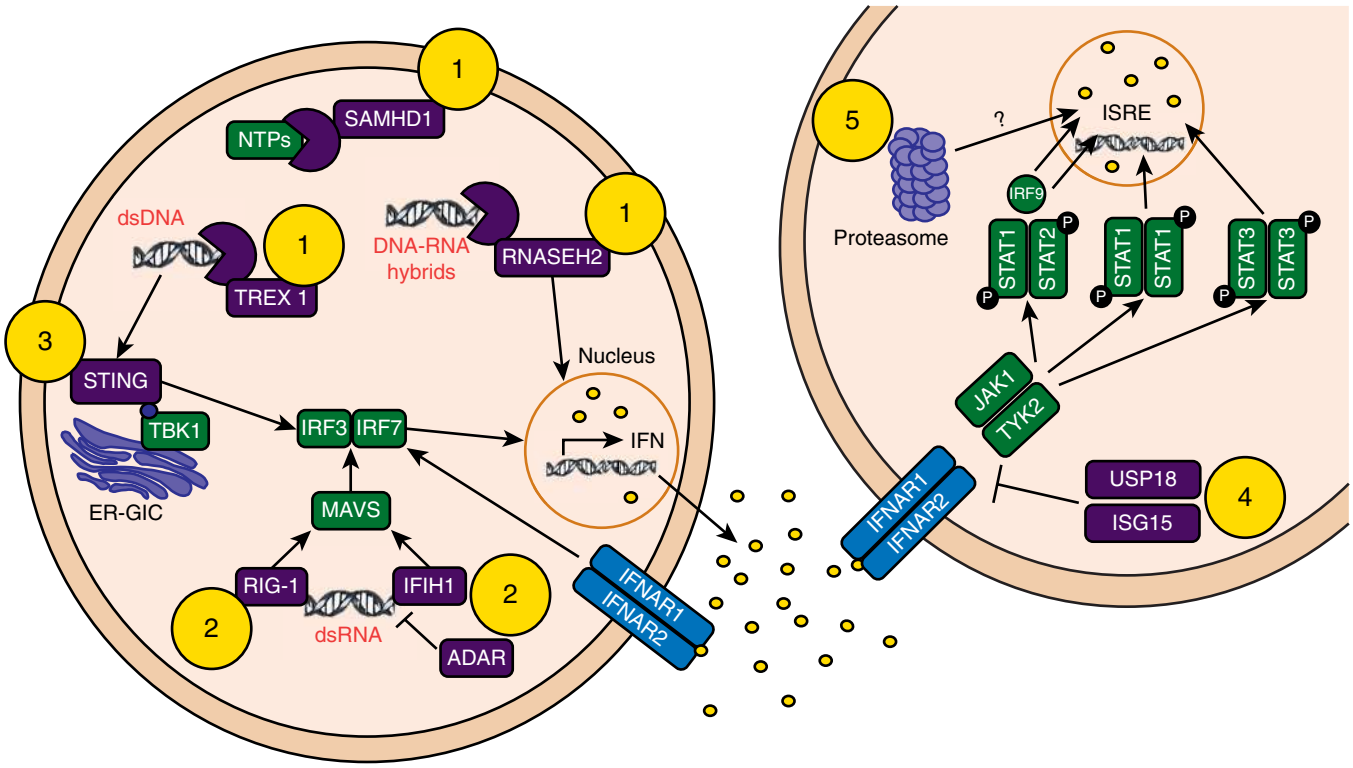

Fig. 205.1 Schematic representation of various pathways affected in genetic interferonopathies. *Purple rectangle*s indicate variant proteins in type I interferonopathies. Numbered *yellow circles* indicate the common mechanistic defect. *1.* Loss-of-function pathogenic variants of genes that encode enzymes responsible for DNA or DNA-RNA hybrid molecule degradation. *2.* Pathogenic variants that lead to constitutive activation or reduction of activation threshold of intracytosolic nucleic acid sensors. *3.* Gain-of-function pathogenic variants of positive IFN signaling regulators; *4.* Loss-of-function pathogenic variants of negative IFN signaling regulators; and *5.* Proteasomal dysfunctional leading to the unfolded protein response and downstream IFN pathway activation. STING: stimulator of interferon genes; SAMHD1: SAM domain and HD domain deoxynucleoside triphosphate triphosphohydrolase 1; NTPs: nucleoside triphosphates; TREX1: DNA 3′ repair exonuclease 1; ISG15: interferon-stimulated gene 15; MAVS: mitochondrial antiviral-signaling protein; RIG-I: retinoic acid-inducible gene I; TBK1: TANK-binding kinase 1; USP18: ubiquitin-specific peptidase 18; RNASEH2, ribonuclease H domain 2; IFIH1: IFN-induced helicase C domain-containing protein 1; ADAR: RNA adenosine deaminase; IRF3: interferon regulatory factor 3; IRF7: interferon regulatory factor 7; IRF9: interferon regulatory factor 9; ERGIC: endothelial reticulum–Golgi intermediate compartment; IFNAR: interferon-α receptor; ISGF3: the transcriptional activator induced by interferon-α; ISRE: interferon-sensitive response element; JAK1: Janus kinase 1; TYK2: tyrosine kinase 2; STAT: signal transducer and activator of transcription. P indicates phosphorylation.

genetic variants are depicted in Figure 205.1. Each genetic variant that leads to dysregulation of IFN signaling is causative of a unique clinical syndrome or subtype of a clinical syndrome that has been classified as a type I interferonopathy. Despite some disease heterogeneity, interferonopathies have a characteristic clinical phenotype, which may include recurrent fevers, early onset of skin vasculopathy with chilblains, livedo reticularis, panniculitis, lipodystrophy, interstitial lung disease with fibrosis, and encephalopathic CNS involvement (Fig. 205.2 and Table 205.2).

AUTOINFLAMMATORY INTERFERONOPATHIES

Aicardi-Goutières Syndrome

AGS is a clinically heterogeneous disease with a spectrum of associated phenotypes. AGS is characterized by an early-onset progressive encephalopathy with basal ganglia calcifications, leukoencephalopathy, and cerebral atrophy with elevated type I IFN cerebrospinal fluid (CSF) levels and CSF pleocytosis. Cutaneous features, seen in about 30% of patients, include chilblains, or cold-induced acral dermatosis of the digits and auricles secondary to peripheral inflammatory vasculopathy. Other common manifestations include thrombocytopenia, hepatosplenomegaly, transaminitis, psoriasis, interstitial lung disease, and intermittent fever. Most frequently, AGS has an infantile onset in which patients develop abrupt irritability, sterile pyrexias, and developmental regression within the first few months of life. Neurologic symptoms may include limb hypertonia with truncal hypotonia, dystonia, excessive startle, abnormal eye movements, epileptic seizures, and slowing of head growth. *RNASEH2B* variants are commonly seen in this context; however, variants of any associated AGS-related genes may present with this clinical scenario. AGS may also present prenatally with a striking similarity to transplacentally acquired infections (pseudo-TORCH), with onset of disease in utero. At birth, patients may have irritability, feeding difficulties, jitteriness, microcephaly, abnormal movements, epileptic seizures, thrombocytopenia, anemia, and liver dysfunction. This presentation is most frequently associated with *TREX1* pathogenic variants and leads to profound developmental sequelae and increased risk of death in infancy. In both clinical presentations, neuroimaging shows a highly characteristic pattern of diffuse abnormal white matter, intracranial calcifications, swelling of temporal or frontal lobes, and cerebral atrophy, similar to radiologic findings seen in congenital infections. Patients may also develop autoimmunity, including type 1 diabetes mellitus, hypothyroidism, hypergammaglobulinemia, and hemolytic anemia. Rarely, AGS can have a later onset with abrupt profound neurologic regression after an extended period of normal development.

There are seven recognized genetic variants and corresponding disease subtypes of AGS (AGS 1-7), all of which are responsible for RNA/DNA degradation or detection, resulting in type I

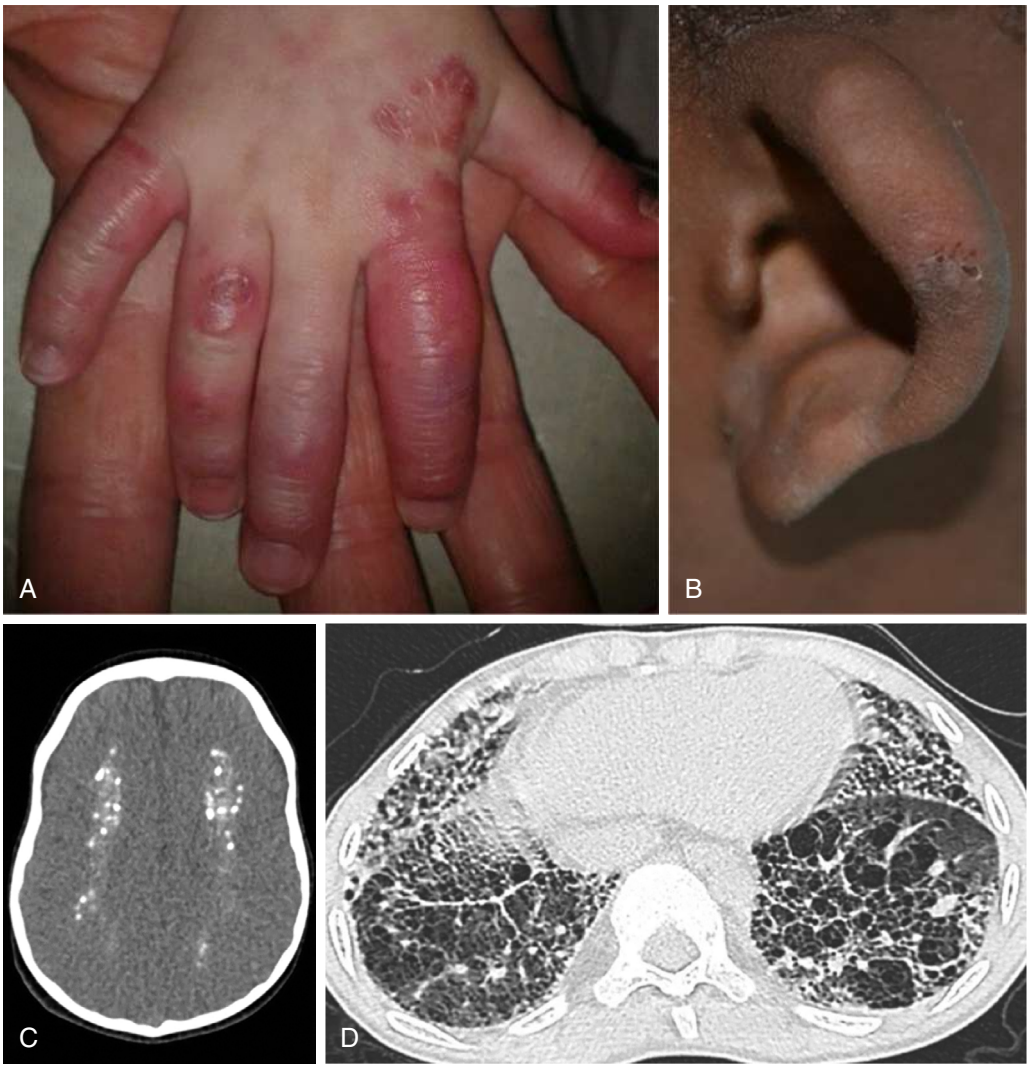

Fig. 205.2 Characteristic clinical phenotypes of interferonopathies. Chilblain lesions typical of monogenic type I interferonopathies, seen most frequently on the toes, fingers (A), ears (B), and nose. The lesions are generally worse in the cold months. C, Representative brain CT scan of intracranial calcifications seen in a patient with Aicardi-Goutières syndrome due to *TREX1* homozygous pathogenic variants. D, Chest CT scan of a SAVI patient (performed at the age of 12.5 years) showing evidence of interstitial lung disease (interlobular septal thickening, intralobular lines, cystic lesions, and some ground-glass lesions) and fibrosis (honeycombing). *(Modified from Melki I, Fremond ML. Type I interferonopathies: from a novel concept to targeted therapeutics.* Curr Rheum Reports. *2020;22:32, Fig. 1.)*

IFN production and upregulation of ISGs. These include variants of *3′-5′ DNA exonuclease-TREX1* **(AGS1)**; ribonucleases including *RNASEH2B* **(AGS2)**, *RNASEH2C* **(AGS3)**, and *RNASEH2A* **(AGS4)**; SAM and HD domain-containing deoxynucleoside *triphosphate triphosphohydrolase 1-SAMHD1* **(AGS5)**; adenosine deaminase acting on *RNA 1-ADAR1* **(AGS6)**; and IFN-induced helicase C domain–containing protein-*IFIH1* **(AGS7)**. The majority of AGS subtypes are autosomal recessive; however, heterozygous gain-of-function variants can also occur in AGS1 and AGS6, and variants causing AGS7 are autosomal dominant.

There are several manifestations that are strongly associated with distinct AGS subtypes. Bilateral striatal necrosis with severe dystonia is associated with variants in *ADAR1* (AGS6), and spastic paraparesis has been associated with variants in *ADAR1* (AGS6), *IFIH1* (AGS7), and *RNASEH2B* (AGS2). Variants involving *SAMHD1* (AGS5) have the most variable phenotype with cutaneous involvement, glaucoma, progressive contractures, stroke, and cerebral aneurysms. Beyond the phenotype diversity between different AGS variants, there are descriptions of marked intrafamilial variation in siblings harboring identical homozygous variants, which raises questions regarding how environmental factors influence disease expression and penetrance.

Spondyloenchondrodysplasia

Spondyloenchondrodysplasia (SPENCD) is a rare autosomal recessive disorder best characterized as a skeletal dysplasia with sclerosis, enchondromas, short stature, platyspondyly, and irregularity of vertebral end plates. Patients may also develop intracranial calcifications, spasticity, and a spectrum of autoimmunity that bears resemblance to SLE, including hemolytic anemia, thrombocytopenia, glomerulonephritis, malar rash, myositis, antiphospholipid syndrome, and autoantibody positivity. Patients have also developed hypothyroidism, Raynaud phenomenon, Sjögren syndrome, and vitiligo. SPENCD is caused by variants of the *ACP5* gene on chromosome 19p13, which encodes tartrate-resistant acid phosphatase (TRAP). Loss of TRAP expression impairs inactivation of osteopontin (Opn), a protein involved in bone metabolism and Th1 differentiation, via signaling through TLR9 in plasmacytoid dendritic cells (pDCs). Increased levels of Opn thus leads to increased IFN-α production.

STING-Associated Vasculopathy with Onset in Infancy

STING-associated vasculopathy with onset in infancy (SAVI) is a rare disorder that presents with systemic inflammation, fevers, and elevated inflammatory markers in the first months of life.

Table 205.2 Suggestive Features of Type I Interferonopathies

Familial history	Several affected individuals, even if phenotypic spectrum might be variable within the same family
Age of onset	• Young age at onset, in favor of monogenic disease • Later onset also reported
Neurologic phenotypes	**Clinical signs:** • Spasticity, spastic paraparesis • Acute or subacute dystonia • Encephalopathy with seizures and progressive microcephaly • Cortical blindness • Variable developmental delay • Ataxia • Psychosis • Vascular neurologic disease (Moyamoya)/strokes • Rare demyelinating or multifocal neuropathies **Lumbar puncture:** • Meningitis (inconstant) • Elevated pterins/neopterins in the CSF • Elevated IFN-α activity or protein in the CSF **Morphologic imaging features:** • CT scans: ICC, basal ganglia calcifications or progressive cerebral atrophy • Cerebral MRI: leukoencephalopathy, white matter rarefaction, delayed myelination, bilateral striatal necrosis, deep white matter cysts, or intracranial aneurysms
Cutaneous features	• Chilblains/FCL; necrotizing vasculitis of fingers, toes, helix, cheeks, and nose, telangiectasia, cutaneous ulcerations • Livedo reticularis • Panniculitis, violaceous periorbital rash • Lentigines • Psoriasis • Nail dystrophy, sparse hair
Failure to thrive/short stature	• Secondary to osseous dysplasia (ACP5) • Secondary to the inflammatory status (TMEM173)
Systemic inflammation and immune features	• Recurrent fevers • Autoimmune features/SLE/autoantibodies (not necessarily specific) • Inconstant immune deficiency • Elevated IFN I pathway in whole blood/serum/plasma
Hematologic	• AI anemia, dyserythropoiesis • Thrombocytopenia or thrombocytosis • Malignancies (chronic lymphocytic leukemia, cutaneous T cell lymphoma, *SAMHD1*)
Lung features	• Interstitial lung disease (isolated or not) • Lung fibrosis • Intraalveolar hemorrhage • Macrophagic alveolitis
Vascular features	• Calcification of the aorta or blood vessels
Musculoskeletal features	• Joint pain, arthritis • Contractures and joint retractions • Jaccoud arthropathy, tendon rupture • Muscle weakness and pain/myositis • Calcinosis • X-rays: acro-osteolysis, wide medullar cavities phalange, deforming arthropathies/joint subluxation with conserved interarticular space, calcinosis
Ophthalmologic features	• Glaucoma • Papillary edema[a]
Kidney features	• Lupus nephritis
Gastrointestinal features	• VEO-IBD (very severe protein-losing enteropathy)
Dental anomalies	• Retained primary teeth[b] • Early loss of permanent teeth

[a]Reported in one SAVI patient treated with JAK1/2 inhibitor.
[b]Data not published.
Ab, Autoantibodies; AI, autoimmune; CSF, cerebrospinal fluid; CT, computerized tomography; FCL, familial chilblain lupus; ICC, intracranial calcifications; IFN, interferon; IFN I, type I interferon; MRI, magnetic resonance imaging; SLE, systemic lupus erythematosus; VEO-IBD, very-early-onset inflammatory bowel disease.
From Melki I, Fremond ML. Type I interferonopathies: From a novel concept to targeted therapeutics. *Curr Rheum Reports.* 2020;22:3, Table 2.

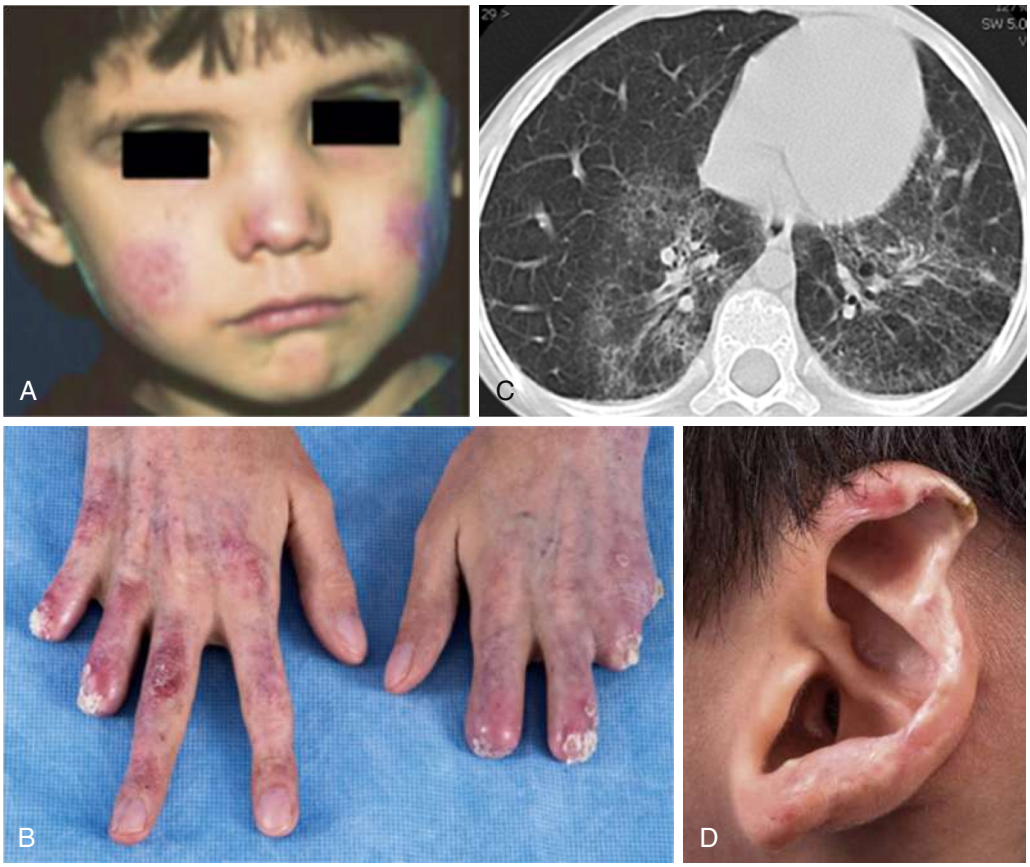

Fig. 205.3 Clinical manifestations of stimulator of interferon genes (STING)–associated vasculopathy with onset in infancy (SAVI). **A,** Typical facial distribution of telangiectatic lesions on the nose and cheeks with atrophy and scarring of the skin with loss of deep tissue of the nose. **B,** Violaceous, scaling, atrophic plaques on both hands and progressive autoamputations of several fingers. **C,** Hilar lymphadenopathy and bilateral interstitial infiltrates on high-resolution computed tomography (CT) image. **D,** Ulcerated lesions on the pinna of the ear with scales and crusts. *(Courtesy Dr. Raphaela Goldbach-Mansky. From Petty RE, Laxer RM, Lindsley CB, et al., eds.* Textbook of Pediatric Rheumatology, *8th ed. Philadelphia: Elsevier; 2021: Fig. 39.11, p. 541.)*

Cutaneous involvement is characterized by vasculopathic rashes in acral areas (Fig. 205.3). These lesions present as violaceous plaques or nodules on the face, ears, or nose or as distal ulceration and may become necrotic. Lesional skin biopsy reveals leukocytoclastic vasculitis, microthrombotic angiopathy, neutrophilia, and occasional immune complex deposition. As STING is expressed in alveolar macrophages, type 2 pneumocytes, and bronchial epithelium, patients with SAVI also develop pulmonary complications. Paratracheal adenopathy, interstitial lung disease, and lung fibrosis have been described to a variable extent. Patients may also develop myositis, arthritis, arthralgia, oral ulcers, aphthosis, and nasal septum perforation. Low-titer autoantibodies (e.g., antinuclear antibody, anticardiolipin antibodies, and antibodies against β2 glycoprotein I) may be seen. Notably, the presence of antineutrophil cytoplasmic antibodies (cANCA) may lead to misdiagnosis of childhood granulomatosis with polyangiitis. SAVI is caused by a dominant gain-of-function variant in *TMEM173,* which encodes the stimulator of interferon genes (STING). Working as both a direct cytosolic DNA sensor and as an adaptor protein in type I IFN signaling, STING mediates the production of IFN-α/β.

Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature/ Proteasome-Associated Autoinflammatory Syndromes

Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome is a rare autoinflammatory disease caused by abnormal functioning of the proteasome-immunoproteasome. CANDLE presents in early infancy with fevers, systemic inflammation, and cutaneous involvement including neutrophilic dermatosis, annular erythema, violaceous eyelid swelling, and erythema nodosum–like panniculitis. Histology reveals a characteristic mononuclear interstitial infiltrate, which includes "immature" neutrophils in the dermis. Lipodystrophy, usually of the face, trunk, and upper limbs, begins in early childhood. Arthralgias, without radiographic evidence of arthritis, are common in children, and severe joint contractures may develop into adulthood. Acute attacks of inflammatory myositis, aseptic meningitis, sterile epididymitis, conjunctivitis, nodular episcleritis, parotitis, pneumonitis, nephritis, carditis, and otitis have been reported. Autoimmunity can occur, including Coombs-positive hemolytic anemia and hypothyroidism. Most commonly, CANDLE is due to loss-of-function variants in the *PSMB8* gene, which encodes the proteasome β5i subunit. More recently, variants in other genes encoding other proteasome-immunoproteasome subunits or the regulatory protein POMP have been discovered in patients with CANDLE syndrome. The defective proteasome function may lead to an accumulation of damaged proteins, resulting in cellular stress and type 1 IFN upregulation.

ISG15 Deficiency/USP18 Deficiency

Ubiquitin-like protein IFN stimulated gene-15 *(ISG15)* deficiency has only been reported in a few individuals and leads to a phenotype similar to AGS, with intracranial calcifications and seizures. ISG15 is an IFN-induced protein that that plays a central role in the host antiviral response, although, in humans, ISG15 deficiency does not cause an increased susceptibility to viral infection. Rather, the absence of intracellular ISG15 prevents the accumulation of ubiquitin-specific peptidase 18 (USP18), a potent negative regulator of IFN-α/β signaling, which results in an unchecked IFN-α/β

response. Notably, loss-of-function recessive variants of USP18 have been reported in five patients, all of whom had neonatal demise soon after birth owing to the dysregulation of type 1 IFN responses.

Singleton-Merten Syndrome

Singleton-Merten syndrome (SMS) is an autosomal dominant disorder characterized by early-onset severe aortic and valvular calcification, dental anomalies, acro-osteolysis, osteoporosis, and glaucoma. There is a broad spectrum of disease with variable expressivity, and patients have been reported to have an SLE or AGS phenotype. SMS is caused by gain-of-function variants in *IFIH1* and *DDX58,* which encode retinoic acid–inducible gene-I (RIG-I)–like receptor family members melanoma differentiation-associated gene 5 *(MDA5)* and *RIG-I,* respectively. MDA5 and RIG-I are cytosolic pattern recognition receptors that detect viral RNA and promote type I and III IFN expression. The phenotype variability of SMS suggests that other genetic and/or environmental factors may influence the clinical presentation.

X-Linked Reticulate Pigmentary Disorder

X-linked reticulate pigmentary disorder (XLPDR) is an X-linked dominant disorder that manifests in the first few months of life in affected males with recurrent pneumonia, bronchiectasis, diarrhea, and failure to thrive. Diffuse skin hyperpigmentation occurs in early childhood, and distinct facial features develop. Female carriers typically exhibit only pigmentary changes along the lines of Blaschko. Hypohidrosis, corneal scarring, enterocolitis, and urethral strictures can develop. The defect in XLPDR is in an intron of the *POLA1* gene, which encodes the catalytic subunit of DNA polymerase-a. Although this defect does not affect DNA replication, it does appear to increase IFN production and IFN-induced genes as well as NF-κB–induced genes in response to dsDNA, cytosolic dsRNA, and TNF-α.

DNAse II Deficiency

Deoxyribonucleases (DNAses) degrade double-stranded DNA molecules and exist in several forms. DNAse II degrades DNA contained in lysosomes, and recently deficiency of DNAse II was shown to cause a form of monogenic SLE. This autosomal recessive disease presents with severe anemia, thrombocytopenia, and hepatosplenomegaly at birth that may resolve over time. In childhood patients may then develop membranoproliferative glomerulonephritis, arthropathy, lipodystrophy, chilblain-like vasculitis, and hypogammaglobulinemia. Laboratory testing shows high titer ANA and dsDNA antibodies and high levels of serum IFNs and IFN-stimulated gene expression. In addition to DNAse II, there are two extracellular DNAses (DNAse1 and DNAse1L3) that do cause a monogenic form of SLE. Although these are likely to exhibit high IFN signatures, no data are available on these two diseases, and thus they are not classically considered interferonopathies.

AUTOIMMUNE INTERFERONOPATHIES

Systemic Lupus Erythematosus

There were descriptions of increased levels of IFN in the serum of patients with SLE. Further rationale for IFN contributing to SLE pathogenesis was supported by observational studies of patients who developed a lupuslike disease with autoantibody formation after treatment with IFN-α. Several groups showed that the majority of patients with SLE have an increased expression of type I IFN–regulated genes and that active SLE could be distinguished by an IFN-induced gene expression pattern. Many clinical features of SLE are associated with increased production of IFN, and a high IFN signature has been correlated with cytopenia, autoantibody formation, and cutaneous disease activity. There are a large number of possible inducers of IFN production in SLE. Neutrophil extracellular TRAP formation, transposable elements, and immune complexes have all been associated with IFN production in SLE patients. From a genetic standpoint, over 100 risk loci have been associated with SLE, many of which encode proteins with functions linked to type I IFN production or response. There are also several *rare* forms of monogenic SLE that are due to pathogenic variants involving type I IFN signaling. Monogenic forms of SLE, including loss-of-function variants in *DNAse II, DNASE1L3,* and *DNASE1,* are classically grouped under the umbrella of interferonopathies and are characterized by typical SLE clinical manifestations with autoantibody formation and immune complex deposition (see Chapter 199). Success of targeting the IFN pathway has been documented in SLE, and multicenter phase 3 randomized placebo-controlled trials are currently underway in extrarenal disease.

Juvenile Dermatomyositis

Dermatomyositis has become recognized as a disease partly driven by aberrant IFN signaling. An elevated IFN signature was first discovered in muscle tissue and later identified in peripheral blood cells of patients with adult and juvenile-onset dermatomyositis (DM, JDM). Subsequently, multiple studies have shown an association between type I IFN in the circulation and disease activity in myositis. Targeting the IFN pathway has shown success in treatment of DM and JDM, and there are several ongoing clinical trials evaluating small-molecule Janus kinase (JAK) inhibitors for the treatment of dermatomyositis.

Therapeutics Targeting the Interferon Pathway

Treatments for interferonopathies has been historically empiric. Numerous immunosuppressive medications, including corticosteroids and a variety of biologics, have been tried in case reports with variable results. However, because interferonopathies have a common pathway involving IFN signaling, the use of small-molecule JAK inhibitors (JAKinibs) has gained interest as a targeted therapy for these disorders. Signaling through the IFN pathway involves JAKs that phosphorylate signal transducers and activators of transcription (STAT) proteins that then dimerize and enter the nucleus to drive transcription of IFN-stimulated genes. JAKinibs block activation of JAK proteins and have been used to treat various autoimmune diseases. There is Food and Drug Administration (FDA) approval of several JAKinibs, including tofacitinib, baricitinib, and upadacitinib, for the treatment of rheumatoid arthritis; tofacitinib is also approved for the treatment of psoriatic arthritis, ulcerative colitis, and polyarticular juvenile idiopathic arthritis. Clinical trials are underway to test the utility of JAKinibs in interferonopathies.

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Chapter 206

Amyloidosis

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Amyloidosis is the result of extracellular deposition of insoluble, fibrous amyloid proteins in various body tissues. It may be caused by a hereditary abnormality in an amyloidogenic protein or occur as a result of chronic inflammation associated with some infectious and rheumatologic diseases.

ETIOLOGY

Amyloidosis is a result of protein misfolding. These misfolded proteins aggregate and form insoluble fibrils that can affect the normal function of several vital organs. In the amyloidosis nomenclature, a distinction is made between amyloidosis that develops from pathogenic gene variants in the amyloid fibril proteins **(hereditary amyloidoses)** and amyloidosis associated with genetic mutation in nonamyloid proteins. The hereditary amyloidoses include diseases caused by pathogenic variants in the genes for transthyretin and apolipoprotein A and usually do not present in childhood. However, children may be affected by **amyloid A (AA) amyloidosis**, which develops in patients with chronic inflammatory states. It is estimated that approximately 45% of all amyloid cases worldwide are AA amyloidosis. In the past, chronic infectious diseases such as tuberculosis, malaria, leprosy, and chronic osteomyelitis accounted for most cases of AA amyloidosis. Since the development of effective treatments for these infections, other causes of AA have become more common.

Individuals with chronic inflammatory rheumatic diseases, such as **rheumatoid arthritis (RA)**, **juvenile idiopathic arthritis (JIA)**, and **ankylosing spondylitis**, as well as **hereditary autoinflammatory diseases**, have an increased risk for the development of AA amyloidosis. AA amyloidosis has also been associated with sarcoidosis, cystic fibrosis, Crohn disease, malignancies (mesothelioma and Hodgkin disease), intravenous drug use disorders, and HIV infection. Approximately 6% of AA amyloidosis cases have no identified disease association.

EPIDEMIOLOGY

Only AA amyloidosis affects children in appreciable numbers. The factors that determine the risk for amyloidosis as a complication of inflammation are not clear. Many individuals with long-standing inflammatory disease do not demonstrate tissue amyloid deposition, but some children with relatively recent onset of disease may develop amyloid. In developed countries, before therapy with disease-modifying antirheumatic drugs (DMARDs) and biologic agents was available, **rheumatoid arthritis** was the most common inflammatory disease associated with AA amyloidosis. Patients who had a long history of severe and poorly controlled disease with extraarticular manifestations were at the greatest risk of developing amyloidosis, and the median time from first symptoms of their rheumatic condition to the diagnosis of amyloidosis was 212 months. The use of DMARDs and biologic therapy has resulted in a sustained decline in the number of new cases of RA-associated amyloidosis.

JIA may be associated with AA amyloidosis, with the highest prevalence occurring in patients with systemic JIA, followed by those with polyarticular disease. AA amyloidosis has been observed in JIA patients as soon as 1 year after diagnosis. Before the availability of DMARDs and biologics, the prevalence of AA amyloidosis in JIA patients ranged from 1% to 10%. Higher prevalence was seen in Northern European patients, especially Polish patients, who had a prevalence of 10.6%; a lower prevalence was observed in North American patients. The reasons for this discrepancy are not completely understood, although it is speculated that selection bias, genetic background, and tendency toward earlier, more aggressive therapy in North Americans may have played a role. As with RA, the occurrence of new amyloid cases in patients with JIA has significantly decreased in the past 20 years because of the increased efficacy of treatment with DMARDs and biologics.

The **hereditary autoinflammatory diseases** define a group of illnesses characterized by attacks of seemingly unprovoked recurrent inflammation without significant levels of either autoantibodies or antigen-specific T cells, which are typically found in patients with autoimmune diseases. These attacks often appear to be initiated by stress, immunizations, or trauma. Common findings of autoinflammatory diseases include fevers, cutaneous rashes, arthritis, serositis, and ocular involvement. The inflammatory attacks are accompanied by intense elevations in inflammatory markers (erythrocyte sedimentation rate and C-reactive protein) and high levels of serum amyloid A (SAA). Amyloidosis AA is associated with some, but not all, hereditary autoinflammatory diseases.

Familial Mediterranean fever (FMF) is the most common of the Mendelian autoinflammatory diseases and is seen most frequently in the Armenian, Arab, Turkish, and Sephardic Jewish populations. FMF is an autosomal recessive disease that results from pathogenic variants in the *MEFV* gene, which encodes the pyrin protein. *MEFV* pathogenic variants affecting the M680 and M694 amino acid residues are associated with early onset of symptoms, severe disease, and an increased risk of AA amyloidosis. Patients residing in Armenia, Turkey, and Arab countries have an increased risk of developing AA amyloidosis compared with patients with the same *MEFV* mutations living in North America. While one might assume that FMF patients who have frequent, severe attacks would be at the highest risk for the development of AA amyloidosis, this is not always the case. Some patients with a history of frequent attacks never develop amyloidosis, whereas others develop amyloidosis at an early age.

Tumor necrosis factor receptor–associated periodic syndrome (TRAPS) is associated with pathogenic variants in the *TNFRSF1A* gene, which encodes the 55-kDa tumor necrosis factor (TNF) receptor protein (TNFR1). It is estimated that 14–25% of untreated patients with TRAPS will develop AA amyloidosis. The risk of amyloidosis appears to be greater among patients with cysteine pathogenic variants or the T50M pathogenic variant. These cysteine residues normally create disulfide bonds within the protein, and disruption of these bonds by amino acid substitutions is thought to interfere with protein folding.

Pathogenic variants in the *NLRP3* (NLR family pyrin domain containing 3) gene encoding the NLRP3 or cryopyrin protein cause three clinically distinct diseases or cryopyrinopathies: **familial cold autoinflammatory syndrome (FCAS**, or ***NLRP3*-AID mild)**, **Muckle-Wells syndrome (MWS**, or ***NLRP3*-AID moderate**), and **neonatal-onset multisystem inflammatory disease (NOMID**, or ***NLRP3*-AID severe)**, also known as **chronic infantile neurologic cutaneous and articular (CINCA) syndrome**. Pathogenic variants in *NLRP3* are inherited in an autosomal dominant fashion or as de novo variants in patients with the most severe disease. A few patients have been found to carry somatic variants in *NLRP3*.

FCAS is the least severe of the cryopyrinopathies and is rarely associated with AA amyloidosis. MWS presents with fevers, myalgias, arthralgias, urticarial-like rash, and progressive sensorineural hearing loss. AA amyloidosis is quite common in MWS, affecting up to one third of the patients. NOMID/CINCA is the most severe cryopyrinopathy. NOMID patients have not developed AA amyloidosis as often as MWS patients, but this may be attributable to the fact that before the availability of effective treatments, 20% of NOMID patients died before reaching adulthood.

Mevalonate kinase deficiency (MKD) – mild (**formally known as Hyper-IgD syndrome**, or **HIDS**) is an autoinflammatory disease that presents in early childhood with high fevers, abdominal pain, lymphadenopathy, and occasional rash. MVK-mild is an autosomal recessive disease that involves loss-of-function variants in the *MVK* gene that encodes the mevalonate kinase enzyme. Patients with MVK-mild retain a low level of enzyme activity, whereas patients with MVK-severe **(mevalonic aciduria)** have severe *MVK* variants that completely abolish enzyme activity, causing recurrent fevers, dysmorphic features, and developmental delays. Inflammatory markers are high during

MVK-mild attacks and may remain elevated between attacks. AA amyloidosis is rare in patients with MVK-mild but has been reported, most often associated with the V377I/I268T genotype.

Although seen less frequently than in the hereditary periodic fever syndromes, AA amyloidosis occurs in an estimated 1% of U.S. patients and up to 3% of Northern European patients with **Crohn disease**. Conversely, AA amyloidosis in patients with ulcerative colitis is extremely rare, with an estimated prevalence of 0.07%. Patients with Crohn disease and AA usually have a long-standing history of aggressive, poorly controlled disease, although there are reports of amyloidosis in patients with well-controlled inflammatory markers.

Thirty-six proteins have been identified as being amyloidogenic in humans, but most of these rarely cause disease during childhood. **Transthyretin-related hereditary amyloidosis** is an autosomal dominant disorder with variable penetrance and onset in the second to third decades of life. Manifestations include familial amyloidotic polyneuropathy, familial amyloid cardiomyopathy, nephropathy, and ocular disease.

PATHOGENESIS

The deposition of AA amyloid fibrils is a result of a prolonged inflammatory state that leads to misfolding of the AA amyloid protein and deposition into tissues. The precursor protein of the fibrils in AA amyloidosis is an apolipoprotein called **serum amyloid A**. SAA is expressed by three different genes on chromosome 11p15.1. SAA1 and SAA2 are two isoforms that are acute-phase reactants synthesized by the liver. SAA is produced in response to proinflammatory cytokines, such as interleukin (IL)-1, IL-6, and TNF-α, and can increase more than 1,000-fold during inflammation.

It has been speculated that SAA has a role as a chemoattractant and in lipid metabolism. Supporting this theory is the finding that amyloid deposition occurs initially in organs that are major sites of lipid and cholesterol metabolism, such as the kidney, liver, and spleen. Approximately 80% of secreted SAA1 and SAA2 is bound to lipoproteins. Usually SAA secreted by the liver is completely degraded by macrophages. The secreted SAA protein is 104 amino acids in length and is primarily secreted in an α-helix structure. For reasons not completely understood, patients with AA amyloidosis have incomplete degradation and accumulation of intermediate SAA products. In these patients, SAA is transferred to the lysosome where the c-terminal portion of the 104–amino acid SAA protein is cleaved, allowing the remaining 66-76 amino acid proteins to fold into a β-pleated sheet configuration. These cleaved fragments polymerize, form fibrils that are deposited in the extracellular space, and bind proteoglycans and other proteins such as serum amyloid P. These fibrils are resistant to proteolysis and deposit in organ tissues.

CLINICAL MANIFESTATIONS

Although organ involvement may vary, AA amyloidosis most frequently affects the kidneys; 90% of patients have some degree of renal involvement. Unexplained proteinuria may be the presenting feature in some patients. Nephrotic syndrome and renal failure may develop if the underlying inflammatory condition is not well-controlled. Patients with higher SAA levels have a significantly higher risk of death than those with lower SAA levels. Gastrointestinal (GI) involvement is seen in approximately 20% of patients and usually manifests as chronic diarrhea, GI bleeding, abdominal pain, and malabsorption. When biopsied, the testes are frequently discovered to be involved (87%). Relatively uncommon findings associated with AA amyloidosis include anemia, amyloid goiter, hepatomegaly, splenomegaly, adrenal involvement, and pulmonary involvement. The heart, tongue, and skin are rarely involved.

DIAGNOSIS

The diagnosis of amyloidosis is established by a biopsy demonstrating amyloid fibril proteins in affected tissues. The tissues tested may include kidney, rectum, abdominal fat pad, and gingiva. Amyloid deposits are composed of seemingly homogeneous eosinophilic material that stains with Congo red dye and demonstrates the pathognomonic "apple-green birefringence" in polarized light. Tissue staining and genetic testing are useful for diagnosing transthyretin amyloidosis.

LABORATORY FINDINGS

In the United States, specific laboratory testing is not commercially available for AA amyloid, but SAA levels are available in some other countries and can be monitored to guide response to treatment.

TREATMENT

There is no established therapy for AA amyloidosis, and thus the primary approach is aggressive management of the underlying inflammatory or infectious disease. As newer therapies are developed to treat the underlying conditions, emerging evidence shows that the incidence of AA amyloidosis is decreasing. **Colchicine** is effective not only in controlling the attacks of FMF but also in preventing the development of amyloidosis associated with FMF. AA amyloidosis associated with other autoinflammatory diseases and chronic rheumatic diseases does not respond to colchicine. Biologic agents against proinflammatory cytokines used to treat RA, JIA, spondyloarthropathies, and the hereditary autoinflammatory diseases appear to decrease the risk of developing AA amyloidosis and may even reverse the deposition of amyloid.

The class of medications referred to as the **TNF inhibitors** have been paramount in the management of RA and other autoimmune diseases, and there are reports documenting the effectiveness of anti-TNF agents in blunting the progression of amyloidosis. Adverse effects of anti-TNF medications include reactivation of tuberculosis and hepatitis B, and thus screening should be performed before instituting therapy. Caution should be used in prescribing anti-TNF agents to patients with a history of heart failure or demyelinating disease, because their use may cause exacerbations of underlying cardiac and neurologic diseases.

The IL-1 pathway is the target of three biologic medications used in autoimmune and autoinflammatory diseases. The available IL-1 antagonists are **anakinra** (IL-1 receptor antagonist), **rilonacept** (soluble IL-1 receptor decoy), and **canakinumab** (long-acting fully humanized IgG_1 anti–IL-1β monoclonal antibody). **A trial of canakinumab in patients with colchicine-resistant FMF, MKD, and TRAPS showed that it was effective in controlling and preventing flares.** The various IL-1 inhibitors have been successful at slowing the progression of AA amyloidosis, and in some cases treatment results in regression of amyloid proteinuria.

Tocilizumab, an anti–IL-6 receptor antibody, has been shown to attenuate experimental AA amyloid and to reverse AA amyloidosis complicating JIA and RA. A trial using **eprodisate disodium** in AA amyloid patients failed to meet its primary end-point of reducing progression to end-stage renal disease and was halted in 2016.

Transthyretin amyloidosis has been treated with liver transplantation, which removes the source of mutated transthyretin molecules, and several medications that inhibit the synthesis of the mutated protein, stabilize tetramers of the protein, or disrupt fibrils.

PROGNOSIS

End-stage renal failure is the underlying cause of death in 40–60% of patients with amyloidosis. According to a large-scale study of 374 patients with AA amyloidosis, the factors associated with a poor prognosis include older age, a lower albumin serum level, end-stage renal disease at baseline, and prolonged serum elevation of SAA. An elevated SAA value was the most powerful risk factor for end-stage renal disease and death from AA amyloidosis.

PREVENTION

The primary means of preventing AA amyloidosis is treatment of the underlying inflammatory or infectious disease, resulting in decreases in the level of SAA protein and the risk of amyloid deposition. Although the period of latency between the onset of inflammation from the underlying disease and the initial clinical signs of AA amyloidosis may vary and is often prolonged, progression of the amyloid depositions can be rapid.

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Chapter 207

Macrophage Activation Syndrome

Rebecca Trachtman and Edward M. Behrens

Macrophage activation syndrome (MAS) is a potentially fatal complication of rheumatic diseases thought to be caused by excessive activation and expansion of macrophages and T cells. These events lead to an overwhelming inflammatory reaction, involving fever, hepatosplenomegaly, lymphadenopathy, cytopenias, liver dysfunction, and coagulopathy resembling disseminated intravascular coagulation (DIC). Extreme hyperferritinemia is a characteristic laboratory feature that separates MAS from primary disease flare.

Inflammatory infiltrates composed predominantly of T lymphocytes and hemophagocytic macrophages are commonly seen in the bone marrow; they are also found in the liver, spleen, or lymph nodes. These hemophagocytic macrophages can infiltrate most organs in the body. Both the systemic and local inflammation can cause severe organ damage, which can be life-threatening and progress to multiple organ failure. The abundance of tissue macrophages exhibiting hemophagocytic activity in inflammatory lesions in MAS suggests that MAS is related to a group of histiocytic disorders collectively known as *hemophagocytic lymphohistiocytosis* (HLH).

EPIDEMIOLOGY

Although MAS can occur in many rheumatic diseases, it is seen most frequently in systemic juvenile idiopathic arthritis (SJIA) and in its adult equivalent, adult-onset Still disease (AOSD). The reasons for this association remain unclear; elevated interleukin (IL)-18 may be a causative factor. Approximately 7–17% of patients with SJIA develop severe disease, whereas more mild subclinical MAS may be seen in as many as 30% of patients with SJIA.

Systemic lupus erythematosus (SLE) and Kawasaki disease are other rheumatologic conditions in which MAS occurs somewhat more frequently than in other rheumatic diseases. In SLE, MAS occurs in approximately 1–9% of patients.

MAS most often occurs subsequent to the onset of rheumatologic disease; MAS has also been known to occur at the initial presentation of a rheumatic illness. Approximately 23% of episodes of MAS have occurred at the onset of SJIA. MAS typically occurs in the setting of active primary rheumatic disease. However, it can occur despite good control of underlying rheumatic disease. Many cases occur in the setting of infections and/or modifications in drug therapy. Both of these triggers are possibly related to subsequent active rheumatic disease.

PATHOPHYSIOLOGY AND OTHER HYPERINFLAMMATORY SYNDROMES

The exact mechanisms behind MAS remain unclear; however, much has been extrapolated from the pathogenesis of primary HLH (pHLH). Consistent with parallels to pHLH, in MAS there is an abundance of interferon-gamma (IFN-γ)–producing $CD8^+$ T cells in inflammatory lesions. Further suggesting a role for T-cell–mediated inflammation, cyclosporine A, a therapeutic agent that acts predominantly on T cells, is very effective in the treatment of the majority of MAS patients. CXCL9, a biomarker of IFN-γ activity, is also elevated in patients during an MAS episode. Cytotoxic function appears to be impaired in certain subsets of SJIA patients, perhaps specifically in those at risk for MAS, although this finding has been inconsistent. Some studies have demonstrated an enrichment of heterozygous pathogenic variants in known pHLH genes in MAS populations, suggesting that *hypomorphic* lesions in cytolytic pathways may result in disease.

Translational studies in SJIA patients suggest that elevated serum IL-18 is a risk factor for the development of SJIA/MAS. A common link to the "IFN-γ-centric" models is that IL-18 is perhaps most noted for its ability to stimulate IFN-γ production by T cells and natural killer cells. In the case of MAS caused by activating pathogenic variants in the *NLRC4* gene, IL-18 has been shown to be highly elevated, and case reports of IL-18 blockade leading to resolution of both disease and IFN-γ activity suggest a causal link.

Cytokine Storm

A "cytokine storm" is the common pathophysiologic state in many hyperinflammatory diseases. There is increasing interest in the relative roles of cytokines in MAS pathophysiology, and the similarities and differences to HLH, multisystem inflammatory syndrome in children (MIS-C) related to SARS-CoV-2 virus, and sepsis.

HLH

MAS belongs to a group of hemophagocytic disorders, which includes HLH. The current classification of histiocytic disorders distinguishes primary, or familial, HLH and secondary, or reactive, HLH (see Chapter 556.2). Clinically, they may be difficult to distinguish from each other. pHLH is a constellation of rare autosomal recessive immune disorders linked to genetic defects in various genes all affecting the cytolytic pathway. The clinical symptoms of pHLH usually become evident within the first months of life. Secondary HLH tends to occur in older children or adults. It may be associated with an identifiable infectious episode, most often Epstein-Barr virus (EBV) or cytomegalovirus (CMV) infection. However, when EBV-associated HLH occurs as part of a genetic syndrome, such as the X-linked proliferative disorders, it is more properly considered pHLH. The group of secondary hemophagocytic disorders also includes malignancy-associated HLH. Some consider MAS to be a form of secondary HLH, whereas others make a distinction and prefer the moniker "Rheuma-HLH" to separate MAS from other secondary HLH conditions. The distinction between primary and secondary HLH is becoming less distinct because of other genetic causes, some of which are associated with less severe and more distinct clinical presentations. Some of these may present later in life because heterozygous or compound heterozygous pathogenic variants in cytolytic pathway genes that confer a partial dominant negative effect on the cytolytic function.

The exact relationship between HLH and MAS is an area of extensive investigation, and some rheumatologists believe that MAS should be categorized as secondary HLH occurring in a setting of a rheumatic disease (or MAS-HLH). Although there are multiple attempts to try to standardize the nomenclature for these various syndromes, at this point, best practice would be to use the term *primary HLH* for cases with known molecular diagnoses or a clear genetic component. For secondary cases, there is not yet a prescribed specific terminology, but inclusion of known secondary causes can add clarity to the specific syndromes being described (e.g., SJIA-MAS, EBV-HLH).

Multisystem Inflammatory Syndrome in Children (MIS-C)

Children may develop a postinfectious hyperinflammatory syndrome after SARS-CoV-2 virus exposure that bears some resemblance to MAS. Approximately 4-8 weeks after infection, children developed multiorgan dysfunction, frequently involving persistent fever, abdominal pain, and rash, and sometimes accompanied by abnormal cardiac function or hypotension. Laboratory evaluation is significant for elevation of markers of inflammation and sometimes hyperferritinemia, coagulopathy, and liver dysfunction. Similar to MAS, this phenomenon occurred after infectious trigger, and cytokine storm has been invoked in multiple studies, especially involving IL-18, IL-10, IL-6, and the IFN-γ–induced CXCL9.

CLINICAL AND LABORATORY MANIFESTATIONS

The clinical findings in overt MAS are dramatic and often evolve rapidly. High persistent fever, hepatosplenomegaly, generalized lymphadenopathy, liver dysfunction, and changes in mental status are common. Coagulopathy resembling DIC can be associated with hemorrhagic

skin rashes ranging from mild petechiae to extensive ecchymotic lesions. These can progress to epistaxis and hematemesis secondary to upper gastrointestinal bleeding. Mental status changes, seizures, and coma are the most common manifestations of CNS disease. Cerebrospinal fluid examination in these patients usually reveals pleocytosis with mildly elevated protein. Deterioration in renal function has been noted in several series and may be associated with particularly high mortality. Pulmonary infiltrates can occur, and hemophagocytic macrophages can be found in bronchoalveolar lavage fluid.

These clinical symptoms are associated with notable laboratory features. A precipitous fall in at least two of three blood cell lines (leukocytes, erythrocytes, or platelets) is one of the early findings, caused in part by increased destruction of cells by phagocytosis and consumption at inflammatory sites. Decreasing erythrocyte sedimentation rate (ESR) despite persistently high CRP is another characteristic laboratory feature. This parallels hypofibrinogenemia, likely secondary to fibrinogen consumption and liver dysfunction. Prolonged prothrombin and partial thromboplastin times, fibrin degradation products, and moderate deficiency of vitamin K–dependent clotting factors are usually present as well. Liver involvement is common in MAS, and most patients develop marked hepatomegaly, and sometimes mild jaundice. Liver function tests frequently reveal high serum transaminase activity and mildly elevated levels of serum bilirubin. Serum ammonia levels are typically normal or only mildly elevated. Additional laboratory findings in MAS include hypertriglyceridemia, hypoalbuminemia, and elevated lactate dehydrogenase (LDH).

Perhaps the most striking laboratory change in MAS is the elevation of serum ferritin. Although diagnostic/classification criteria set levels of 500 ng/mL and 684 ng/mL as cutoffs for HLH and SJIA-MAS respectively, levels are often greater than 10,000 ng/mL. The reasons for this elevated ferritin are not clear and are likely multifactorial. Although extremely high ferritin is often a good serologic marker of HLH and MAS, high levels are not pathognomonic and can be seen in a wide variety of conditions. Thus ferritin needs to be interpreted in the context of the other features of the disease to support a diagnosis. Further, serum ferritin is usually 60–80% glycosylated, whereas intracellular ferritin is not glycosylated. In hemophagocytic syndromes, the percentage of glycosylated ferritin in the serum is low, typically below 20%; assessment of glycosylated ferritin may also be a useful tool for MAS diagnosis.

It has been recognized that as many as one third of patients with active SJIA may have mild subclinical MAS. These patients typically have moderate hyperferritinemia, highly increased CRP, moderately decreased hemoglobin, and relatively low platelet counts. These patients may also have mild hepatosplenomegaly and mildly elevated liver enzymes. Serum fibrinogen tends to remain in the normal range despite highly increased CRP.

DIAGNOSIS

Recognition of MAS is crucial, but early diagnosis is often difficult. There is no single clinical or laboratory feature that is specific for MAS, including hemophagocytosis, and many clinical features of MAS overlap with those seen in the underlying rheumatic diseases. The MAS clinical presentation also overlaps with sepsis-like syndromes associated with infection. This is further complicated by the fact that MAS may also be triggered by a flare of the underlying rheumatic disease or infection. In a patient with active underlying rheumatologic disease, persistent fevers and decrease in ESR and platelet count in combination with increasing serum ferritin and persistently high CRP should raise suspicion for impending MAS. Increasing liver enzymes, aspartate aminotransferase in particular, is another characteristic laboratory change. The diagnosis of MAS might be confirmed by bone marrow biopsy, with the presence of increased hemophagocytosis. However, demonstration of hemophagocytosis may be limited by sampling error, particularly at the early stages of the syndrome. In such cases, additional staining of the bone marrow with anti-CD163 antibodies may be helpful. Features consistent with MAS include massive expansion of highly activated histiocytes. The diagnosis of MAS is supported by elevated levels of soluble IL2Rα and soluble CD163 in serum.

Table 207.1 The Classification Criteria for Macrophage Activation Syndrome in Systemic Juvenile Idiopathic Arthritis

A *febrile* patient with *known or suspected systemic juvenile idiopathic arthritis* is classified as having macrophage activation syndrome if the following criteria are met:
Ferritin >684 ng/mL and any two of the following:
Platelet count ≤181 × 10^9/L
Aspartate aminotransferase >48 U/L
Triglycerides >156 mg/dL
Fibrinogen ≤360 mg/dL

Evidence is mounting that IFN-γ is the pivotal cytokine in MAS; however, peripheral measurement of IFN-γ can be difficult because of retention in tissues. Therefore the IFN-induced chemokine CXCL9 may be a more reliable serum biomarker of MAS. Although substantial elevation in the serum levels of soluble IL2Rα receptors and CXCL9 in an SJIA patient is highly suggestive of MAS, these assessments remain nonspecific, and elevation can be associated with some malignancies and viral infections, such as viral hepatitis.

Striking clinical similarities between MAS and HLH have led some to advocate for the use of the HLH-2004 diagnostic guidelines developed by the HLH Study Group of the International Histiocyte Society (see Chapter 556.2). However, the application of the HLH diagnostic criteria to SJIA patients with suspected MAS is problematic, both because there is significant overlap with common features of active rheumatic disease and because SJIA patients may reach some of the criteria only later in the clinical course. NK function testing as a means to assess cytotoxic activity is problematic, as defects in this pathway are only variably associated with SJIA and MAS.

Criteria for the diagnosis of MAS complicating SJIA are noted in Table 207.1. In cross-validation analyses, the criteria revealed a sensitivity of 0.72-0.76 and a specificity 0.97-0.99. It should be noted that these criteria were developed for classification for studies and trials and were not optimized for clinical diagnostic purposes. One limitation of the MAS classification criteria is that background treatment with biologics might modify the clinical presentation of MAS. Although IL-1 and IL-6 inhibitors effectively control the disease in the majority of SJIA patients, they do not provide full protection against MAS and may impede diagnosis. Furthermore, the MAS classification criteria are less likely to classify tocilizumab-treated patients as having MAS compared with historical controls or canakinumab-treated patients.

DIFFERENTIAL DIAGNOSIS

It is most important to distinguish MAS from a flare of an underlying rheumatologic disease and from intercurrent infection. Further, one must consider other clinical entities associated with hyperferritinemia, hepatic dysfunction, coagulopathy, cytopenias, or encephalopathy, specifically DIC, thrombotic thrombocytopenic purpura (TTP), and malignancy-associated HLH. Some other important differential diagnoses include sepsis and drug reactions; a thorough infectious workup is necessary for the majority of MAS patients. Hyperferritinemia is not specific for hemophagocytic syndromes and may be observed in various liver and kidney diseases, hematologic malignancies, or conditions requiring chronic blood transfusions.

TREATMENT

MAS is still associated with high mortality rates; therefore prompt recognition and initiation of immediate therapeutic intervention are critical. To achieve rapid reversal of coagulation abnormalities and cytopenias, most clinicians start with intravenous methylprednisolone pulse therapy (30 mg/kg for three consecutive days) followed by 2 to 3 mg/kg/day in four divided doses.

If response to glucocorticoids is not satisfactory, cyclosporine A (2-7 mg/kg/day) is usually added to the treatment regimen based on several reports describing the rapid resolution of MAS features in response to this medication. Cyclosporine is preferentially used orally, and careful monitoring for toxicity is required, especially if it is administered intravenously. In many patients, administration of cyclosporine A not only provides rapid control of symptoms but also avoids excessive use of steroids. Case reports support the use of tacrolimus as an alternative to cyclosporine A, as it is often effective and has a desirable safety profile.

There is also reported efficacy with the use of anakinra for MAS. Because MAS episodes may be triggered by disease flare, biologics that neutralize IL-1 could extinguish the underlying inflammation driving the cytokine storm. There are several case reports and two case series of anakinra treatment for MAS with promising results, particularly when used in higher doses. However, in established SJIA, continuous treatment with standard doses of anti–IL-1 and anti-IL-6 biologic therapies does not absolutely protect against MAS even if the underlying disease responds well to the treatment. In the phase 3 clinical trial of canakinumab, IL-1 blockade did not confer full protection from MAS even in patients with fully controlled SJIA. These results suggest that IL-1 inhibition effectively treats MAS in many patients, but does not completely prevent the occurrence of MAS, particularly in the setting of viral infection in treated subjects.

Intravenous immune globulin treatment has been successful in virus-associated reactive HLH. Rituximab—a treatment that depletes B lymphocytes, the main type of cells harboring EBV virus—has been successfully used in EBV-induced lymphoproliferative disease and could be considered in EBV-driven MAS.

If MAS remains active despite the use of corticosteroids, anakinra, and cyclosporine A, the HLH-2004 treatment protocol developed by the HLH Study Group of the International Histiocyte Society may be considered. In addition to steroids and cyclosporine A, this protocol includes etoposide (or VP16), a podophyllotoxin derivative that inhibits DNA synthesis by forming a complex with topoisomerase II and DNA. However, this protocol is limited by the toxicity of etoposide and its likelihood of causing kidney and liver damage. In addition, severe bone marrow suppression, overwhelming infection, and death have been reported. The use of lower doses of etoposide (50-100 mg/m^2 range rather than 150 mg/m^2, as suggested by the HLH-2004 protocol) has been advocated by some groups.

It has also been suggested that antithymocyte globulin (ATG) might be a safer alternative to etoposide, particularly in patients with renal and hepatic impairment. ATG depletes both CD4$^+$ and CD8$^+$ T cells through complement-dependent cell lysis. Mild depletion of monocytes is noted in some patients as well. Although this treatment was tolerated well in reported cases, infusion reactions are frequently reported with the use of ATG, and adequate laboratory and supportive medical resources must be readily available if this treatment is used. Occasional reports describe successful use of cyclophosphamide to control MAS, mainly in patients with SLE.

The monoclonal antibody tocilizumab is very effective in treating SJIA. However, in a phase 3 clinical trial of tocilizumab in SJIA, several patients developed MAS. Similar to canakinumab, at the time of MAS presentation, underlying SJIA in most of these patients was well controlled. Furthermore, tocilizumab can cause normalization of some of the laboratory parameters of MAS, without actually altering the course of MAS activity itself, providing false reassurance of disease control.

In a patient with an inflammasomopathy caused by gain-of-function pathogenic variants in *NLRC4,* administration of the recombinant IL-18BP resulted in rapid and sustained improvement, including the resolution of all MAS-like features. It remains unclear whether a similar therapeutic intervention might be effective in MAS as well. Based on their essential roles in transmitting cytokine-induced signals, particularly from IFN-γ, the JAK/STAT pathways have become a target for pharmacologic manipulation in inflammatory diseases. Ruxolitinib, a potent inhibitor of JAK1 and JAK2, has been shown to ameliorate the disease-influencing patterns of JAK/STAT-dependent gene expression in animal models of pHLH, but it remains to be determined whether this treatment will be routinely effective in patients with MAS.

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Chapter 208

Kawasaki Disease

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Kawasaki disease (KD), formerly known as *mucocutaneous lymph node syndrome* and *infantile polyarteritis nodosa,* is an acute febrile illness of childhood seen worldwide, with the highest incidence occurring in Asian children. KD is a systemic inflammatory disorder manifesting as a vasculitis with a predilection for the coronary arteries. Approximately 20–25% of untreated children develop **coronary artery abnormalities (CAAs)**, including aneurysms, whereas <5% of children treated with intravenous immunoglobulin (IVIG) develop CAA. Nonetheless, KD is the leading cause of acquired heart disease in children in most developed countries, including the United States and Japan.

ETIOLOGY

The cause of KD remains unknown. Certain epidemiologic and clinical features support an infectious origin, including the young age-group affected; epidemics with wavelike geographic spread of illness; the self-limited nature of the acute febrile illness; and the clinical features of fever, rash, enanthem, conjunctival injection, and cervical lymphadenopathy. Further evidence of an infectious trigger includes the infrequent occurrence of the illness in infants <3 months old, possibly the result of protective maternal antibodies, and the rarity of cases in adults, possibly the result of prior exposures with subsequent immunity. Furthermore, the number of hospitalizations per year for KD significantly decreased during the COVID-19 pandemic, both in Japan and the United States, possibly due to low circulating causative viruses. However, there are also features that are not consistent with an infectious origin; it is unusual to have multiple cases present at the same time within a family or daycare center. Furthermore, no single infectious etiologic agent has been successfully identified, despite an exhaustive search. Other environmental triggers such as airborne toxins and climate shifts have also been speculated to play a role.

Genetic factors clearly influence the pathogenesis of KD, as evidenced by the higher risk of KD in Asian children regardless of country of residence and in siblings and children of individuals with a history of KD. The concordance rate among identical twins is approximately 13%. Linkage studies and genome-wide association studies (GWAS) have identified significant potential associations between polymorphisms in the *ITPKC* gene, a T-cell regulator, with increased susceptibility to KD and more severe disease. Other candidate genes for KD identified by GWAS include *CASP3, BLK,* and *FCGR2A*. Lastly, multiple alleles in different human leukocyte antigen (HLA) regions have been reported to influence risk for KD.

EPIDEMIOLOGY

For the majority of patients, KD is a disease of early childhood, and nearly all epidemiologic studies show a higher susceptibility to KD in males. Large database studies suggest that the hospitalization rate for KD in the United States has been mostly stable over time, although the proportion of hospitalizations complicated by "KD shock syndrome" has increased over time. In 2017, the Kids' Inpatient Database estimated 19.3 hospitalizations/100,000 children <4 years of age. Children of Asian/Pacific Islander descent had the highest rates of KD among all racial groups.

In other countries, such as the United Kingdom, South Korea, and Japan, the rate of KD seems to be increasing. In Japan, nationwide surveys have been administered every 2 years to monitor trends in KD incidence. In 2018 the highest recorded rate thus far of 359 per 100,000 children ages 0-4 years was described, with the highest rate in young children ages 9-11 months. Fortunately, the proportion of Japanese

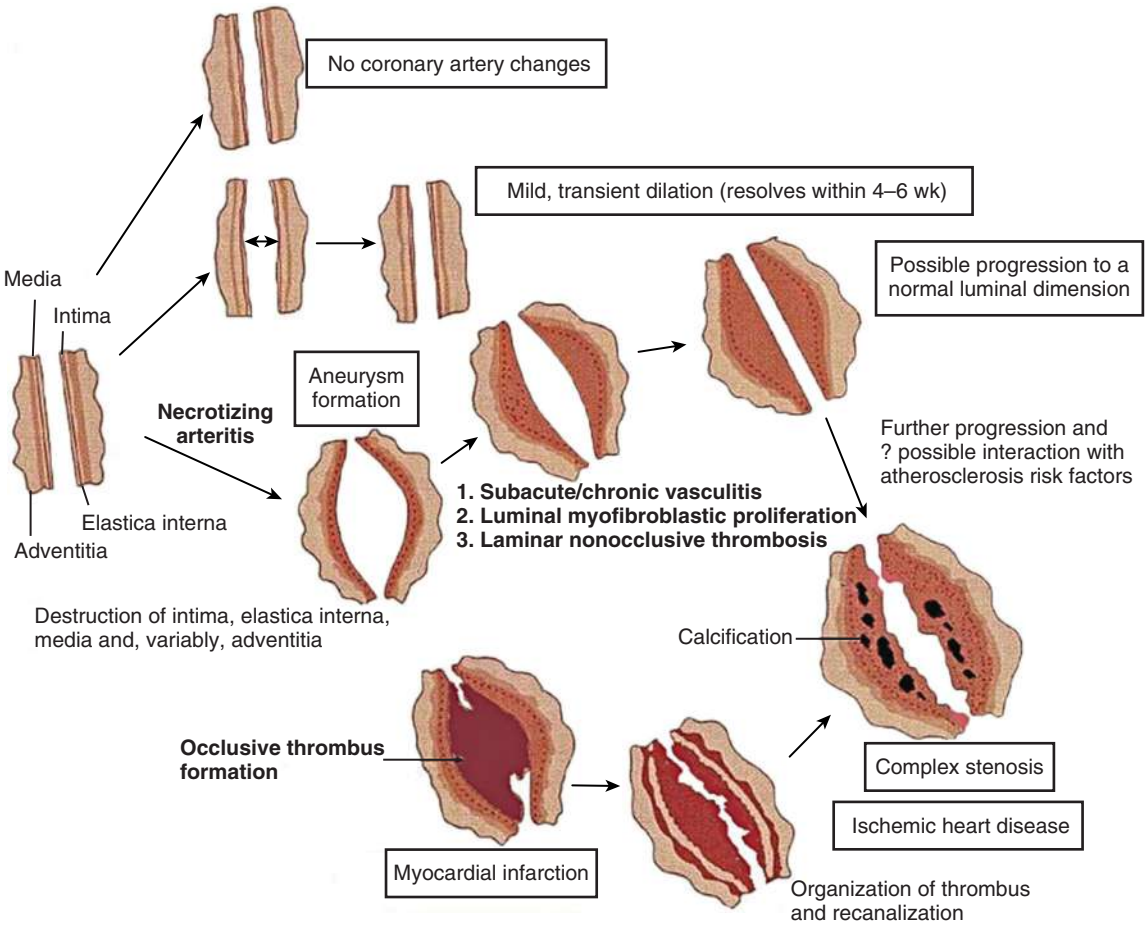

Fig. 208.1 Natural history of coronary artery abnormalities. *(Modified from Kato H. Cardiovascular complications in Kawasaki disease: coronary artery lumen and long-term consequences. Prog Pediatr Cardiol. 2004;19:137–145.)*

patients with coronary aneurysms and myocardial infarction has decreased over time, at 2.6% for the former in the most recent survey.

Several risk-stratification models have been constructed to determine which patients with KD are at highest risk for CAA. Predictors of poor outcome across several studies include young age; being male; persistent prolonged fever; poor response to IVIG; and laboratory abnormalities, including neutrophilia, thrombocytopenia, transaminitis, hyponatremia, hypoalbuminemia, elevated levels of N-terminal brain natriuretic protein, and elevated C-reactive protein (CRP) levels. Asian, Pacific Islander, and Hispanic ethnicity are also risk factors for CAA. Three risk scores for IVIG resistance, which refers to incomplete response to the first treatment, have been constructed by Japanese researchers; of these, the **Kobayashi score** is the most widely used and has high sensitivity and specificity. Unfortunately, when applied to non-Japanese populations, these scores do not appear to be as accurate in identifying children at risk for IVIG resistance and CAA. Body surface area (BSA)–adjusted coronary artery dimensions on initial echocardiography are good predictors of CAA development. In a North American cohort, coronary artery *z* scores ≥2.0 are predictive of CAA development; similar findings have been reported in Japanese cohorts as well. Accordingly, coronary artery *z* scores at initial presentation are useful imaging biomarkers that can be used to guide adjunctive therapy for high-risk patients.

PATHOLOGY

KD is a vasculitis that predominantly affects medium-size arteries. The coronary arteries are most often involved, although other arteries (e.g., axillary, subclavian, femoral, popliteal, brachial) can also develop dilation. A three-phase process to the arteriopathy of KD has been described. The first phase is a neutrophilic necrotizing arteritis occurring in the first 2 weeks of illness that begins in the endothelium and moves through the coronary wall. Saccular aneurysms may form from this arteritis. The second phase is a subacute/chronic vasculitis driven by lymphocytes, plasma cells, and eosinophils, which may last weeks to years and results in fusiform aneurysms. The vessels affected by the subacute/chronic vasculitis then develop smooth muscle cell myofibroblasts, which may cause diminution of internal lumen dimension and progressive stenosis in the third phase. Thrombi may form in the lumen and obstruct blood flow (Fig. 208.1).

CLINICAL MANIFESTATIONS

Fever is characteristically high (≥38.3°C [101°F]), persistent, and unresponsive to antipyretics. The duration of fever without treatment is generally 1-2 weeks but may be as short as 5 days or may persist for 3-4 weeks. In addition to fever, the **five principal clinical criteria** of KD are (1) bilateral *nonexudative* conjunctival injection with limbal sparing; (2) erythema of the oral and pharyngeal mucosa with strawberry tongue and red, cracked lips; (3) edema (induration) and erythema of the hands and feet; (4) rash of various forms (maculopapular, urticarial, erythema multiforme–like, scarlatiniform, and rarely, micropustular or psoriatic-like); and (5) nonsuppurative cervical lymphadenopathy, usually unilateral, with node size >1.5 cm (Table 208.1 and Figs. 208.2-208.5). Superficial perineal desquamation is common in the acute phase. Periungual desquamation of the fingers and toes begins 2-3 weeks after the onset of illness and may progress to involve the entire hand and foot (Fig. 208.6).

Additional symptoms other than the principal clinical criteria are common in the 10 days before diagnosis of KD, which may be explained in part by the finding that up to a third of patients with KD have confirmed, concurrent infections. Gastrointestinal (GI)

Table 208.1 Clinical and Laboratory Features of Kawasaki Disease

EPIDEMIOLOGIC CASE DEFINITION (CLASSIC CLINICAL CRITERIA)*

Fever persisting at least 5 days†

Presence of at least four principal features:
- Changes in extremities
  - Acute: erythema of palms, soles; edema of hands, feet
  - Subacute: periungual peeling of fingers, toes in wk 2 and 3
- Polymorphous exanthem
- Bilateral bulbar conjunctival injection without exudate
- Erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa
- Cervical lymphadenopathy (>1.5 cm diameter), usually unilateral

Exclusion of other diseases with similar findings‡

These features do not have to occur concurrently.

OTHER CLINICAL AND LABORATORY FINDINGS

Cardiovascular System
- Myocarditis, pericarditis, valvular regurgitation, cardiogenic shock
- Coronary artery abnormalities
- Aneurysms of medium-sized noncoronary arteries
- Peripheral gangrene
- Aortic root enlargement

Respiratory System
- Peribronchial and interstitial infiltrates on chest radiograph
- Pulmonary nodules

Musculoskeletal System
- Arthritis, arthralgias (pleocytosis of synovial fluid)

Gastrointestinal Tract
- Diarrhea, vomiting, abdominal pain
- Hepatitis, jaundice
- Hydrops of gallbladder
- Pancreatitis
- Parotitis

Central Nervous System
- Extreme irritability
- Aseptic meningitis (pleocytosis of cerebrospinal fluid)
- Facial nerve palsy
- Sensorineural hearing loss

Genitourinary System
- Urethritis/meatitis, hydrocele

Other Findings
- Desquamating rash in groin
- Retropharyngeal phlegmon
- Anterior uveitis by slit-lamp examination
- Erythema, induration at bacille Calmette-Guérin inoculation site

LABORATORY FINDINGS IN ACUTE KAWASAKI DISEASE
- Leukocytosis with neutrophilia and immature forms
- Elevated erythrocyte sedimentation rate
- Elevated C-reactive protein
- Elevated nitrogen-terminal pro B-type natriuretic peptide (NT-proBNP)
- Anemia
- Abnormal plasma lipids
- Hypoalbuminemia
- Hyponatremia
- Thrombocytosis after wk 1§
- Sterile pyuria
- Elevated serum transaminase
- Elevated serum γ-glutamyl transpeptidase
- Pleocytosis of cerebrospinal fluid
- Leukocytosis in synovial fluid

*Patients with fever at least 5 days and fewer than four principal criteria can be diagnosed with Kawasaki disease when coronary artery abnormalities are detected by two-dimensional echocardiography or angiography.

†In the presence of four or more principal criteria, particularly when redness and swelling of the hands and feet are present, Kawasaki disease diagnosis can be made on day 4 of illness. Experienced clinicians who have treated many patients with Kawasaki disease may establish a diagnosis before day 4 in rare cases.

‡See the differential diagnosis (Table 208.3).

§Rarely infants present with thrombocytopenia and disseminated intravascular coagulation.

From McCrindle BW, Rowley A, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *Circulation*. 2017;135(17):e927–e999.

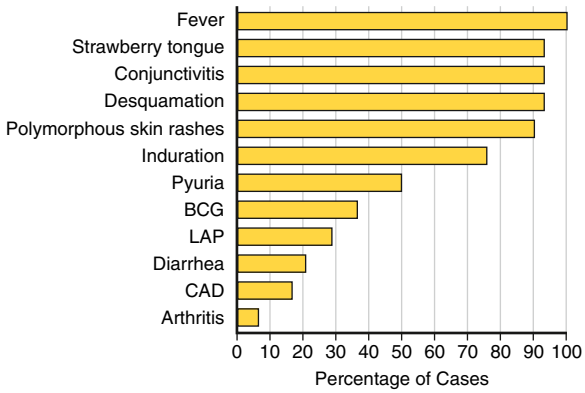

Fig. 208.2 Clinical symptoms and signs of Kawasaki disease. Summary of clinical features from 110 cases of Kawasaki disease seen in Kaohsiung, Taiwan. LAP, Lymphadenopathy in head and neck area; BCG, reactivation of bacille Calmette-Guérin inoculation site; CAD, coronary artery dilation, defined by an internal diameter >3 mm. *(From Wang CL, Wu YT, Liu CA, et al. Kawasaki disease: infection, immunity and genetics. Pediatr Infect Dis J. 2005;24:998–1004.)*

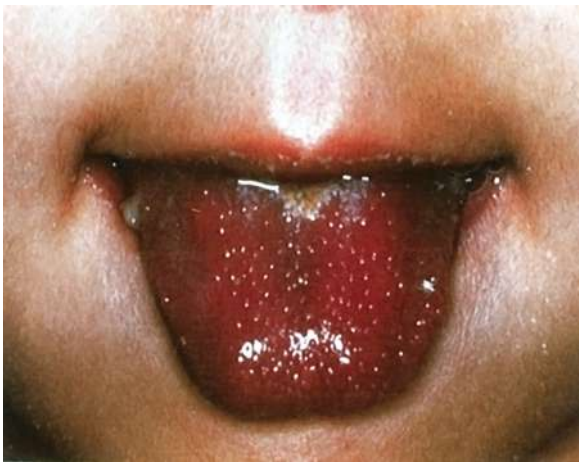

Fig. 208.3 Kawasaki disease. Strawberry tongue in patient with mucocutaneous lymph node syndrome. *(Courtesy Tomisaku Kawasaki, MD. From Hurwitz S. Clinical Pediatric Dermatology, 2nd ed. Philadelphia: Saunders; 1993.)*

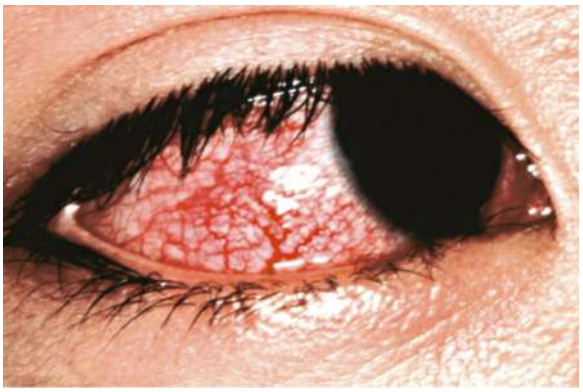

Fig. 208.4 Kawasaki disease. Congestion of bulbar conjunctiva in a patient with mucocutaneous lymph node syndrome. *(Courtesy Tomisaku Kawasaki, MD. From Hurwitz S. Clinical Pediatric Dermatology, 2nd ed. Philadelphia: Saunders; 1993.)*

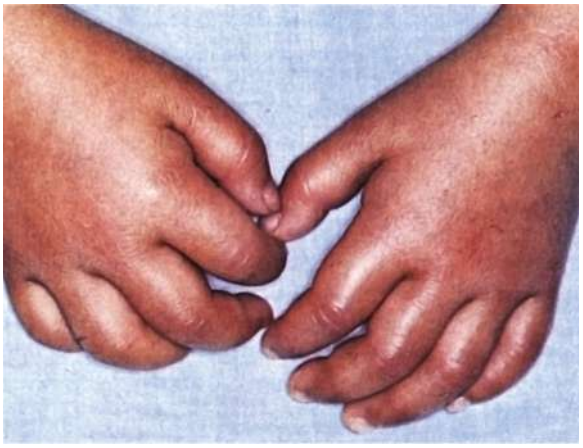

Fig. 208.5 Kawasaki disease. Indurative edema of the hands in a patient with mucocutaneous lymph node syndrome. *(Courtesy Tomisaku Kawasaki, MD. From Hurwitz S. Clinical Pediatric Dermatology, 2nd ed. Philadelphia: Saunders; 1993.)*

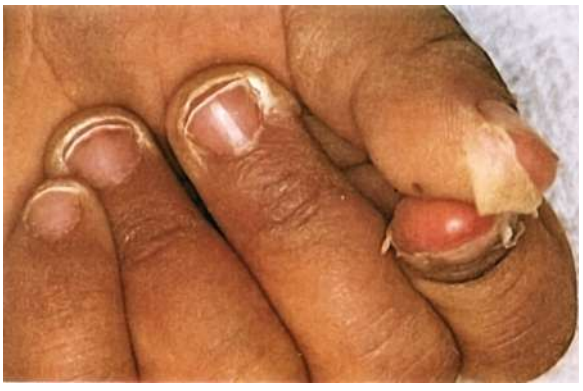

Fig. 208.6 Kawasaki disease. Desquamation of the fingers in a patient with mucocutaneous lymph node syndrome. *(Courtesy Tomisaku Kawasaki, MD. From Hurwitz S. Clinical Pediatric Dermatology, 2nd ed. Philadelphia: Saunders; 1993.)*

symptoms (vomiting, diarrhea, or abdominal pain) occur in >60% of patients, and at least one respiratory symptom (rhinorrhea or cough) occurs in 35%. Other clinical findings can include significant irritability that is especially prominent in infants and likely caused by aseptic meningitis, mild hepatitis, hydrops of the gallbladder, urethritis and meatitis with sterile pyuria, uveitis, and arthritis. Arthritis may occur early in the illness or may develop in the second or third week. Small or large joints may be affected, and the arthralgias may persist for several weeks. Patients previously vaccinated with bacillus Calmette-Guerin (BCG) may show reactivation at the inoculation site. Clinical features that are *not consistent* with KD include exudative/purulent conjunctivitis; exudative pharyngitis; generalized lymphadenopathy; discrete oral lesions (e.g., ulceration); splenomegaly; and bullous, petechial, or vesicular rashes.

Cardiac involvement is the most important manifestation of KD. Myocarditis may occur in patients with acute KD and may manifest as tachycardia disproportionate to fever, along with diminished left ventricular systolic function. Occasionally, patients with KD present in cardiogenic shock **(KD shock syndrome)**, with hypotension and greatly diminished left ventricular function. In addition, KD shock syndrome may manifest with thrombocytopenia, a high band count, and a high CRP. Case series of KD shock syndrome indicate that these patients may be at higher risk for coronary artery dilation. Pericarditis with a small pericardial effusion can also occur during the acute illness. Mitral regurgitation of at least mild severity is evident on echocardiography in 10–25% of patients at presentation but diminishes over time, except among rare patients with coronary aneurysms and ischemic heart disease. Up to 25% of untreated patients develop CAA by Japanese Ministry of Health criteria in the second to third week of illness; initially these are usually asymptomatic and detected by echocardiography. Almost all the morbidity and mortality in KD occur in patients with **large or giant coronary artery aneurysms**, defined by the 2017 American Heart Association (AHA) scientific statement on the diagnosis and treatment of KD as having a *z* score ≥10 or an absolute dimension of ≥8 mm. Specifically, large or giant aneurysms are associated with the greatest risk of later thrombosis or stenosis, angina, and myocardial infarction (Figs. 208.7 and 208.8A). Rupture of a giant aneurysm is a rare complication that generally occurs in the first month after illness onset and may present as hemopericardium with tamponade. Axillary, popliteal, iliac, or other systemic medium-sized muscular arteries may also become aneurysmal, but always in the setting of giant coronary aneurysms (see Fig. 208.8B); these usually regress.

Occasionally KD presents initially with only fever and lymphadenopathy **(node-first KD)**. This presentation may be confused with bacterial or viral cervical lymphadenitis and may delay the diagnosis and treatment. Persistence of high fever, lack of response to antibiotics, and subsequent development of other signs of KD suggest the diagnosis. Children with node-first KD tend to be older (4 vs 2 years) and have more days of fever and higher CRP levels. In addition to cervical adenopathy, many node-first patients had retropharyngeal and peritonsillar inflammation on CT scans (Fig. 208.9). Patients with node-first KD have a higher incidence of coronary aneurysms. Patients with infectious adenitis usually respond to antibiotics; they may have abscesses noted on imaging studies (ultrasonography or CT).

KD can be divided into three clinical phases. The **acute febrile phase** is characterized by fever and the other acute signs of illness and usually lasts 1-2 weeks. The **subacute phase** is associated with desquamation, thrombocytosis, development of CAA, and the highest risk of sudden death in patients who develop aneurysms; it generally lasts 3 weeks. The **convalescent phase** begins when all clinical signs of illness have disappeared and continues until the erythrocyte sedimentation rate (ESR) returns to normal, typically 6-8 weeks after the onset of illness.

LABORATORY AND RADIOLOGY FINDINGS

There is no diagnostic test for KD, but patients usually have characteristic laboratory findings. The leukocyte count is often elevated, with a predominance of neutrophils and immature forms. Normocytic, normochromic anemia is common. The platelet count is generally normal in the first week of illness and rapidly increases by the second to third week of illness, sometimes exceeding 1 million/mm^3. An elevated ESR or CRP value is universally present in the acute phase of illness. The ESR may remain elevated for weeks, in part from the effect of IVIG. Sterile pyuria, mild elevations of the hepatic transaminases, hyperbilirubinemia, and cerebrospinal fluid pleocytosis may also be present. KD is unlikely if the ESR, CRP, and platelet counts are normal after 7 days of fever.

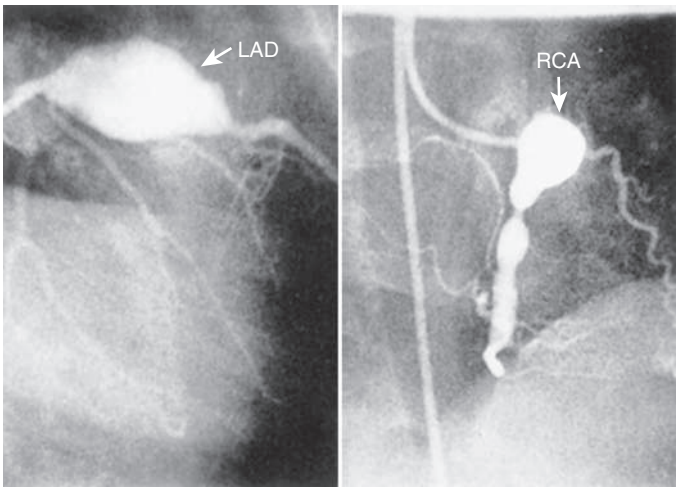

Fig. 208.7 Coronary angiograms in 6-yr-old boy with Kawasaki disease. *Left,* Giant aneurysm of the left anterior descending coronary artery (LAD) with obstruction. *Right,* Giant aneurysm of the right coronary artery (RCA) with an area of severe narrowing. *(From Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease. Pediatrics. 2004;114:1708–1733.)*

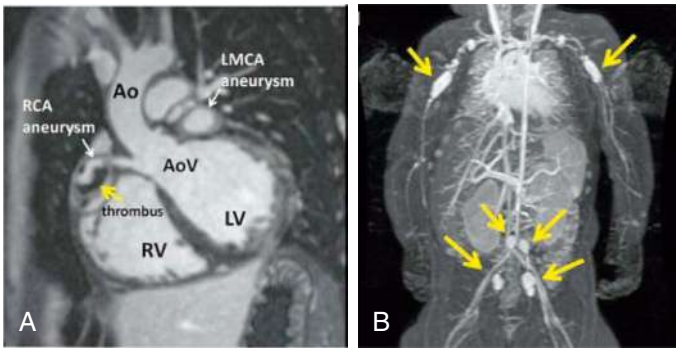

Fig. 208.8 MRI of coronary and peripheral artery aneurysms in Kawasaki disease. **A,** Image of left ventricular outflow tract showing a giant right coronary artery (RCA) aneurysm with nonocclusive thrombus *(yellow arrow)* and a giant left main coronary artery (LMCA) aneurysm. Ao, Aorta; AoV, aortic valve; LV, left ventricle; RV, right ventricle. **B,** Aneurysms in the axillary and subclavian arteries and the iliac and femoral arteries *(arrows). (From McCrindle BW, Rowley A, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. Circulation 2017;135[17]:e927–e999, Fig. 2G and H, p. e935.)*

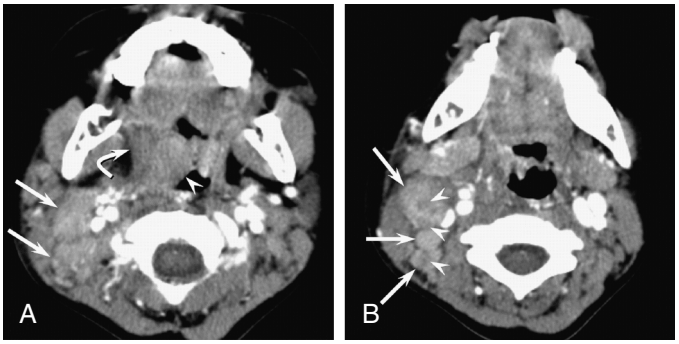

Fig. 208.9 Contrast-enhanced CT in 3-yr-old boy with Kawasaki disease. **A,** Right-sided cervical lymphadenopathy *(arrows),* peritonsillar hypodense area *(curved arrow),* and swelling of right palatine tonsil *(arrowhead).* **B,** Right-sided cervical lymphadenopathy with perinodal infiltration *(arrows)* and intranodal focal low attenuation *(arrowheads). (From Kato H, Kanematsu M, Kato Z, et al. Computed tomographic findings of Kawasaki disease with cervical lymphadenopathy. J Comput Assist Tomogr. 2012;36[1]:138–142, Fig. 1, p. 139.)*

Two-dimensional echocardiography is the most useful test to monitor for development of CAA. Although frank aneurysms are rarely detected in the first week of illness, coronary arteries are commonly dilated. Coronary artery dimensions, adjusted for BSA (*z* scores), may increase over the first 6 weeks of illness, and higher *z* scores at the time of diagnosis are the strongest risk factor for the presence of coronary aneurysms 2-8 weeks after illness onset. Children with non-KD febrile illnesses also have mildly increased *z* scores compared with nonfebrile controls, but to a lesser degree than patients with KD. Aneurysms have been defined with the use of absolute dimensions by the Japanese Ministry of Health and are classified as small (≤4 mm internal diameter [ID]), medium (>4 to ≤8 mm ID), or giant (>8 mm ID). Some experts believe that a *z* score–based system for classification of aneurysm size may be more discriminating, because it adjusts the coronary dimension for BSA. The AHA *z* score classification system is noted in Table 208.2.

Echocardiography should be performed at diagnosis and again after 1-2 weeks of illness. If the results are normal, a repeat study should be performed 6-8 weeks after onset of illness. If results of either of the initial studies are abnormal or the patient has recurrent fever or symptoms, more frequent echocardiography or other studies may be necessary. In patients in whom CAA has not developed in the first 4-6 weeks of illness, the patient may be discharged from cardiology care, although follow-up through 12 months may be considered. Children and families should be counseled regarding healthy diet and the importance of exercise at regular primary care visits. For patients with CAA, the type of testing and the frequency of cardiology follow-up visits are tailored to the patient's coronary artery status (see Table 208.2).

DIAGNOSIS

The diagnosis of KD is based on the presence of characteristic clinical signs. For **classic KD**, the diagnostic criteria require the presence of fever for at least 5 days and at least four of five of the other principal characteristics of the illness (see Table 208.1). The diagnosis of KD should be made within 10 days, and ideally within 7 days, of fever onset to improve coronary artery outcomes. In **incomplete KD**, patients have persistent fever but fewer than four of the five characteristic clinical signs. In patients with incomplete KD, laboratory and echocardiographic data can assist in the diagnosis (Fig. 208.10). Incomplete cases occur most frequently in infants, who also have the highest likelihood of development of CAA. Ambiguous cases should be referred to a center with experience in the diagnosis of KD. Establishing the diagnosis with prompt initiation of treatment is essential to prevent potentially devastating coronary artery disease. For this reason, it is recommended that *any infant age ≤6 months with fever for ≥7 days and signs of systemic inflammation without explanation undergo echocardiography to assess the coronary arteries.*

DIFFERENTIAL DIAGNOSIS

Adenovirus, measles, and scarlet fever lead the list of common childhood infections that mimic KD (Table 208.3). Children with **adenovirus** typically have exudative pharyngitis and exudative conjunctivitis, allowing differentiation from KD. A common clinical problem is the differentiation of **scarlet fever** from KD in a child who is a group A streptococcal carrier. Patients with scarlet fever typically have a rapid clinical response to appropriate antibiotic therapy. Such treatment for 24-48 hours with clinical reassessment generally clarifies the diagnosis. Furthermore, ocular findings are quite rare in group A streptococcal pharyngitis and may assist in the diagnosis of KD.

Features of **measles** that distinguish it from KD include exudative conjunctivitis, Koplik spots, rash that begins on the face and hairline and behind the ears, and leukopenia. **Cervical lymphadenitis** can be the initial diagnosis in children who are ultimately recognized to have KD. Less common infections such as Rocky Mountain spotted fever and leptospirosis are occasionally confused with KD. **Rocky Mountain spotted fever** is a potentially lethal bacterial infection, and appropriate antibiotics should not be withheld if the diagnosis is under consideration. Its distinguishing features include pronounced myalgias and headache at onset, centripetal rash, and petechiae on the palms and soles. **Leptospirosis** can also be an illness of considerable severity. Risk factors include exposure to water contaminated

Table 208.2 Classification of Coronary Artery Dilation or Aneurysms (after AHA Guidance with Modification)

CLASSIFICATION OF RISK LEVEL	DESCRIPTION OF CORONARY ARTERIES	FOLLOW-UP INTERVAL	IMAGING REQUIRED TO ASSESS FOR INDUCIBLE ISCHEMIA (STRESS ECHO OR STRESS MRI)	PSP	REGIONAL SPECIALIST KAWASAKI DISEASE CLINIC
1	No involvement at any time point (*z* score<2)	2 wk 6 wk 6 mo 12 mo Discharge if normal at 12 mo	None	No	No—annual cardiac and general health review with GP recommended*
2	Dilation only (2< *z* score ≤2.5): resolves within 1 year	2 wk 6 wk 6 mo 12 mo Discharge if normal at 12 mo	None	No	No—annual cardiac and general health review with GP recommended*
3	Small aneurysm (2.5≤ *z* score <5): (a) current or persistent (b) decreased to normal or *z* score <2.5	2 wk 6 wk 6 mo 12 mo Annual review	Coronary angiography (preferably CT) at 12 mo as baseline Consider stress imaging for inducible myocardial ischemia every 2 years Imaging (echo) for coronary surveillance annually	Yes	Yes
4	Medium aneurysm (5 ≤*z* score <10): (a) persistent aneurysm (b) decreased to normal or *z* score <2.5	2 wk 6 wk 6 mo 12 mo Annual review	Coronary angiography (preferably CT) at 12 mo as baseline Consider stress imaging for inducible myocardial ischemia annually Imaging (echo, CT,† or MRI) for coronary thrombus surveillance annually	Yes	Yes
5	Giant aneurysm (*z* score ≥10 or ≥8 mm): (a) persistent giant aneurysm (b) persistent aneurysm (but regressed to medium or small aneurysms) (c) regressed to normal dimensions	2 wk 6 wk 3 mo 6 mo 9 mo 12 mo Then every 6 mo	Coronary angiography (preferably CT) at 6-12 mo as baseline Consider stress imaging for inducible myocardial ischemia annually Imaging (echo, CT,† or MRI) for coronary thrombus surveillance every 6 mo	Yes	Yes

*GP review should include clinical examination, blood pressure measurement, general health discussion, and advice on avoidance of cardiovascular risk factors and lifestyle choices, including maintaining a healthy weight, reducing the risk of diabetes, avoiding smoking, and taking regular exercise. This provides the opportunity to discuss any parent or patient questions and concerns.

†CT should not be used repeatedly if possible. Use MRI or ultrasound where possible to reduce radiation exposure.

ADP, Adenosine diphosphate; AHA, American Heart Association; FBC, full blood count; GP, general practitioner; PSP, person-specific protocol.

From McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: A scientific statement for health professionals from the American Heart Association [published correction appears in *Circulation*. 2019 Jul 30;140(5):e181-e184]. *Circulation*. 2017;135(17):e927–e999.).

with urine from infected animals. The classic description of leptospirosis is of a biphasic illness with a few asymptomatic days between an initial period of fever and headache and a late phase with renal and hepatic failure. In contrast, patients with KD have consecutive days of fever at diagnosis and rarely have renal or hepatic failure.

Drug hypersensitivity reactions, including Stevens-Johnson syndrome, share some characteristics with KD. Drug reaction features such as the presence of oral ulcerations and a normal or minimally elevated ESR are not seen in KD. **Systemic juvenile idiopathic arthritis** (sJIA) is also characterized by fever and rash, but physical findings include diffuse lymphadenopathy and hepatosplenomegaly. Arthritis may or may not be present in the initial illness. Fevers typically show a quotidian or double-quotidian pattern, in contrast to the unremitting fevers seen in KD. Laboratory findings may include coagulopathy, elevated fibrin degradation product values, and hyperferritinemia. Interestingly, there are reports of children with sJIA who have echocardiographic evidence of CAA. Coronary aneurysms have also been reported in Behçet disease, primary cytomegalovirus infection, granulomatosis with polyangiitis, lupus, infantile polyarteritis nodosa, hyper-IgE syndrome, hyper-IgD syndrome (mevalonic aciduria), and meningococcemia.

Children with KD may present with **Kawasaki disease shock syndrome,** with a clinical picture similar to that of toxic shock syndrome or of the multisystem inflammatory syndrome in children associated with COVID-19 (MIS-C; see Chapter 311). Features of **toxic shock syndrome** that are not usually seen in KD include renal insufficiency, coagulopathy, pancytopenia, and myositis. With COVID-19 disease, some children developed a KD-like illnesses presenting in cardiogenic shock. **multisystem inflammatory syndrome in children (MIS-C)**, also known as *pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2* (PIMS-TS), occurs 2-6 weeks after infection with SARS-CoV-2. The initial infection may be asymptomatic. Children with MIS-C may show conjunctival injection, oropharyngeal changes, and rashes similar to that seen in KD. CAAs have also been described in MIS-C, but the risk of CAA in MIS-C does not strictly correlate with criteria for incomplete or complete KD. Furthermore, patients are often older and have a greater degree of myocardial dysfunction as compared with KD; distinguishing laboratory features include greater hyperferritinemia, more pronounced cytopenias, and elevated D-dimer in MIS-C (Table 208.4).

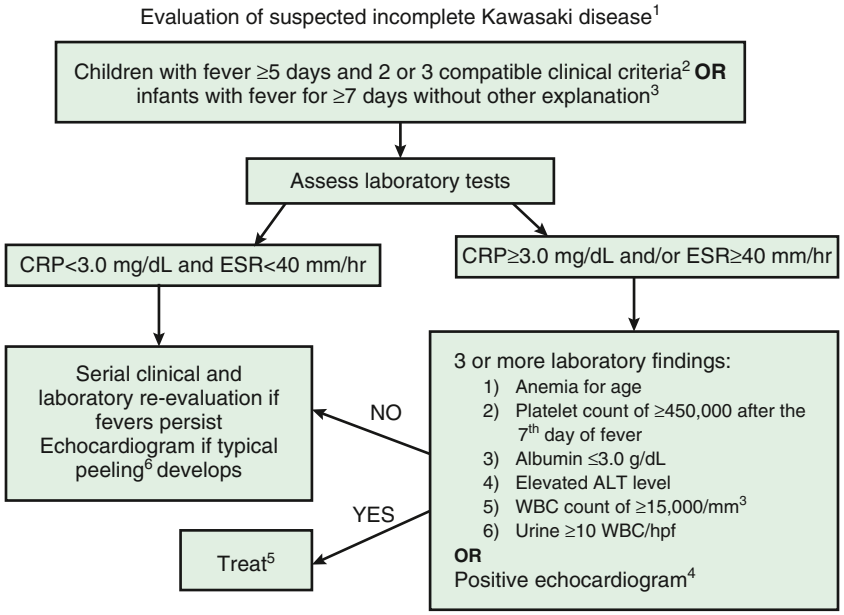

Fig. 208.10 Algorithm for the evaluation of suspected incomplete Kawasaki disease (KD). [1]In the absence of a gold standard for diagnosis of KD, this algorithm cannot be evidence based, but rather represents the informed opinion of the expert committee. Consultation with an expert should be sought any time assistance is needed. [2]Clinical findings of KD are listed in Table 208.1. Characteristics suggesting that another diagnosis should be considered include exudative conjunctivitis, exudative pharyngitis, ulcerative intraoral lesions, bullous or vesicular rash, generalized adenopathy, and splenomegaly. [3]Infants ≤6 months of age are most likely to develop prolonged fever without other clinical criteria for KD; these infants are at particularly high risk of developing coronary artery abnormalities. [4]Echocardiography is considered positive for purposes of this algorithm if any of three conditions are met: *z* score of left anterior descending coronary artery or right coronary artery ≥2.5; coronary artery aneurysm is observed; or three or more other suggestive features exist, including decreased left ventricular function, mitral regurgitation, pericardial effusion, or *z* scores in the left anterior descending coronary artery or right coronary artery of 2-2.5. [5]If the echocardiogram is positive, treatment should be given within 10 days of fever onset or after the 10th day of fever in the presence of clinical and laboratory signs (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR]) of ongoing inflammation. [6]Typical peeling begins under the nail beds of fingers and toes. ALT, Alanine transaminase; WBC, white blood cell. *(From McCrindle BW, Rowley A, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: A scientific statement for health professionals from the American Heart Association. Circulation. 2017;135:e927–e999, Fig. 2, p. e937.)*

Table 208.3 Differential Diagnosis of Kawasaki Disease

VIRAL INFECTIONS*
Adenovirus
Enterovirus
Measles
Epstein-Barr virus
Cytomegalovirus
BACTERIAL INFECTIONS
Scarlet fever
Rocky Mountain spotted fever
Leptospirosis
Bacterial cervical lymphadenitis ± retropharyngeal phlegmon
Meningococcemia
Urinary tract infection
RHEUMATOLOGIC DISEASE
Systemic-onset juvenile idiopathic arthritis
Behçet disease
Rheumatic fever
Polyarteritis nodosa
Takayasu arteritis
OTHER
Multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19
Toxic shock syndromes
Serum sickness
Staphylococcal scalded skin syndrome
Macrophage activation syndrome (may also complicate Kawasaki disease)
Hemophagocytic lymphohistiocytosis
Drug hypersensitivity reactions
Stevens-Johnson syndrome
Aseptic meningitis
Autoinflammatory diseases

*Detection of a virus does not exclude Kawasaki disease in the presence of the principal clinical features (see Table 208.1).

Table 208.4 Comparing and Contrasting Multisystem Inflammatory Syndrome in Children (MIS-C) with Kawasaki Disease

MIS-C	KAWASAKI DISEASE
Mean age 8-12 years	Mean age <5 years
Fever >24 hr	Fever >5 days
GI symptoms common (severe abdominal pain) (50–90%)	GI complaints not common (~20%)
Myocarditis/myocardial dysfunction (left ventricular dysfunction)	Myocardial function normal/ mildly reduced*
Coronary artery dilation or aneurysms (25–50%)	Coronary artery abnormalities such as aneurysms common if untreated
Hypotension	Normal BP*
Renal involvement more common	Renal involvement rare
Proinflammatory state common	Proinflammatory state common
Lymphopenia common	Lymphopenia not common
Thrombocytopenia	Thrombocytosis
Elevated ferritin	Ferritin usually normal

*Except in Kawasaki shock syndrome (~5%).
GI, Gastrointestinal.
Modified from Naka F, Melnick L, Gorelik M, et al. A dermatologic perspective on multisystem inflammatory syndrome in children. *Clin Dermatol*. 2021;39(1):163–168, Table 5.

TREATMENT

Patients with acute KD should be treated with 2 g/kg of IVIG as a single infusion, usually administered over 10-12 hours within 10 days of disease onset, and ideally as soon as possible after diagnosis (Table 208.5).

In addition, moderate-dose (30-50 mg/kg/day divided every 6 hours) aspirin should be administered until the patient is afebrile, then lowered to antiplatelet doses (3-5 mg/kg/day). Other NSAIDs should *not* be given during therapy with aspirin because they may block aspirin's antiplatelet effect. The mechanism of action of IVIG in KD is likely multifaceted, but treatment results in defervescence and resolution of clinical signs of illness in approximately 85% of patients. Using Japanese Ministry of Health criteria, the prevalence of coronary disease is 20–25% in children treated with aspirin alone and falls to <5% in those treated with IVIG and aspirin within the first 10 days of illness. In children diagnosed after the 10th day of fever, IVIG should still be offered to patients with persistent fever, abnormal dimensions of the coronary arteries, or signs of systemic inflammation. Low-dose aspirin is continued for its antithrombotic effect until 6-8 weeks after illness onset and is then discontinued in patients who have had normal echocardiography findings throughout the course of their illness. Patients with CAA continue with aspirin therapy longer and may require anticoagulation, depending on the degree of coronary dilation (see later).

Glucocorticoids have been used as primary therapy with the first dose of IVIG in hopes of improving coronary outcomes. A North American trial using a single pulse dose of intravenous methylprednisolone (30 mg/kg) with IVIG as primary therapy did not improve coronary outcomes. However, a trial in Japan using the Kobayashi score to identify high-risk children demonstrated improved coronary outcomes with a regimen of methylprednisolone/prednisolone (2 mg/kg/day, divided every 12 hours) plus IVIG as primary therapy. Furthermore, a systematic review and meta-analysis of 16 comparative studies demonstrated that early treatment with glucocorticoids improved coronary artery outcomes in children with KD. These data suggest that primary glucocorticoid therapy in addition to standard of care (IVIG plus aspirin) may be helpful in children at *high risk* for CAA. Fewer data are available to support the use of TNF alpha inhibitors for prevention of coronary artery aneurysms.

IVIG-resistant KD (nonresponders) occurs in approximately 15% of patients and is defined by persistent or recrudescent fever 36 hours after completion of the initial IVIG infusion. Patients with IVIG resistance are at increased risk for CAA. Therapeutic options for the child with IVIG resistance include a second dose of IVIG (2 g/kg), a tapering course of glucocorticoids, infliximab, or possibly anakinra (Table 208.6). For the most severely affected patients with enlarging coronary aneurysms, additional therapies such as cyclosporine or cyclophosphamide may be administered, with consultation from specialists in pediatric rheumatology and cardiology.

Table 208.5 Treatment of Kawasaki Disease

ACUTE STAGE
Standard risk: Intravenous immune globulin 2 g/kg over 10-12 hr
and
Aspirin 30-50 mg/kg/day divided every 6 hr orally until patient is afebrile for at least 48 hr
High risk for coronary artery abnormalities:* Intravenous immune globulin and aspirin as above, *plus* methylprednisolone 2 mg/kg/d IV divided q12hr until afebrile, then prednisolone orally until CRP normalized, then taper over 2-3 wk
CONVALESCENT STAGE
Aspirin 3-5 mg/kg once daily orally until 6- after illness onset if normal coronary findings throughout course

*High risk for coronary artery abnormalities is defined as age <6 months or baseline left anterior descending (LAD) or right circumflex artery (RCA) z-score greater than or equal to 2.5.

COMPLICATIONS

Acute KD is complicated in 1–2% of patients by macrophage activation syndrome (MAS; see Chapter 207), a syndrome of life-threatening hyperinflammation on the spectrum of hemophagocytic lymphohistiocytosis. MAS may mimic MIS-C. These patients may present with hyperferritinemia, coagulopathy, thrombocytopenia, and shock, warranting more aggressive immunosuppressive therapy.

In all phases of KD, patients with giant coronary aneurysms may experience myocardial infarction, angina, and sudden death due to thrombosis. For this reason, aspirin is continued indefinitely in children with coronary aneurysms (Table 208.7). When aneurysms are moderate-sized, dual antiplatelet therapy (e.g., aspirin and clopidogrel) is sometimes administered. For those with large or giant aneurysms, anticoagulation with warfarin or low-molecular-weight heparin is added to aspirin. For acute thrombosis that occasionally occurs in an aneurysmal or stenotic coronary artery, thrombolytic therapy may be lifesaving. In very rare circumstances of severe, giant aneurysms, rupture can occur.

Long-term follow-up of patients with CAAs is tailored to the past (i.e., worst-ever) and current coronary status, with a schedule of testing recommended in the 2017 AHA scientific statement on KD (see Table 208.2). Testing may include echocardiography, assessment for inducible ischemia, advanced imaging (CT, MRI, or invasive angiography), physical activity counseling, and cardiovascular risk factor assessment and management. Patients with coronary artery stenosis and inducible ischemia may be managed with coronary artery bypass grafting (CABG) or catheter

Table 208.6 Treatment Options for IVIG-Resistant Patients with Kawasaki Disease*

AGENT	DESCRIPTION	DOSE
MOST FREQUENTLY ADMINISTERED		
IVIG: second infusion	Pooled polyclonal IG	2 g/kg IV
IVIG + methylprednisolone/ prednisolone	IVIG + glucocorticoid	IVIG: 2 g/kg IV + methylprednisolone 2 mg/kg/d IV divided every 12 hr until afebrile, then oral prednisolone 2 mg/kg/d divided twice daily
Infliximab	Monoclonal antibody against TNF-α	Single infusion: 5-10 mg/kg IV
ALTERNATIVE TREATMENTS		
Anakinra	Recombinant IL-1β receptor antagonist	2-8 mg/kg/day given by subcutaneous injection or IV infusion
Cyclosporine	Inhibitor of calcineurin-NFAT pathway	IV: 3 mg/kg/d divided every 12 hr PO: 4-8 mg/kg/d divided every 12 hr Adjust dose to achieve trough 50-150 ng/mL; 2 hr peak level 300-600 ng/mL
Cyclophosphamide	Alkylating agent blocks DNA replication	10-15 mg/kg IV, 1 or 2 doses
Plasma exchange	Replaces plasma with albumin	1-5 cycles

*IVIG resistance is defined as persistent or recrudescent fever at least 36 hr and <7 days after completion of first IVIG infusion. The top three treatments have been most frequently used, although no comparative effectiveness trial has been performed. Pulsed high-dose corticosteroid treatment is not recommended. The alternative treatments have been used in a limited number of patients with KD.

CRP, C-reactive protein; IG, immunoglobulin; IL, interleukin; IV, intravenous(ly); IVIG, intravenous immune globulin; NFAT, nuclear factor of activated T cells; PO, oral; TNF, tumor necrosis factor.

Table 208.7 Anticoagulation for Coronary Artery Abnormalities in Kawasaki Disease

LONG TERM THERAPY
Small aneurysms: Aspirin 3-5 mg/kg/d
Medium aneurysms: Aspirin +/- clopidogrel 1 mg/kg/d (max 75 mg/d)
Giant aneurysms: Aspirin + anticoagulation with warfarin, low molecular weight heparin, or direct oral anticoagulants (e.g. apixaban)
ACUTE CORONARY THROMBOSIS
Prompt fibrinolytic therapy with tissue plasminogen activator or other thrombolytic agent under the supervision of a pediatric cardiologist

interventions, including percutaneous transluminal coronary rotational ablation, directional coronary atherectomy, and stent implantation.

Patients undergoing long-term aspirin therapy should receive annual influenza vaccination to reduce the risk of Reye syndrome. A different antiplatelet agent can be substituted for aspirin during the 6 weeks after varicella vaccination. IVIG may interfere with the immune response to live virus vaccines as a result of a specific antiviral antibody, so the measles-mumps-rubella and varicella vaccinations should generally be deferred until 11 months after IVIG administration. Nonlive vaccinations do not need to be delayed.

PROGNOSIS

The vast majority of patients with KD return to normal health; timely treatment reduces the risk of coronary aneurysms to <5%. Acute KD recurs in 1–3% of cases. Published fatality rates are very low, generally <1%. The prognosis for patients with CAA depends on the severity of coronary disease; therefore recommendations for follow-up and management are stratified according to coronary artery status. A 6-week echocardiogram may be unnecessary in patients with normal coronary artery measurements at baseline and at 2 weeks of illness, as these children very rarely develop new abnormalities over time. Overall, ~50% of CAAs remodel to normal lumen diameter by 1-2 years after the illness, with smaller aneurysms being more likely to regress. Intravascular ultrasonography has demonstrated that regressed aneurysms are associated with marked myointimal thickening and abnormal vascular function. Giant aneurysms are less likely to regress to normal lumen diameter and are more likely to lead to thrombosis or stenosis. Bypass grafting may be required if there is inducible ischemia; it is best accomplished with the use of arterial grafts, which grow with the child and are more likely than venous grafts to remain patent over the long term. Heart transplantation has been required in rare cases where revascularization is not feasible because of distal coronary stenoses, distal aneurysms, or severe ischemic cardiomyopathy. A study from Japan reported outcomes in adult patients with a history of KD and giant aneurysms. These patients required multiple cardiac and surgical procedures, but the 30-years survival rate approached 90%.

The long-term outcomes of children who have had KD and never had coronary artery abnormalities, based upon reliable echocardiograms performed early in the course of disease, appear to be similar to those in the normative population. Although studies of endothelial dysfunction in children with a history of KD and normal coronary dimensions have produced conflicting results, reassuring data suggest that the standardized mortality ratio among adults in Japan who had KD in childhood without aneurysms is indistinguishable from that of the general population. All children with a history of KD should be counseled regarding a heart-healthy diet, adequate amounts of exercise, tobacco avoidance, and intermittent lipid monitoring. Among children with coronary aneurysms, the AHA recommends treatment thresholds for risk factors for atherosclerotic heart disease that are lower than those for the normal population.

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Chapter 209

Sarcoidosis

Laura Cannon and Eveline Y. Wu

Sarcoidosis is a rare multisystem granulomatous disease of unknown etiology. There appears to be two distinct, age-dependent patterns of disease among children with sarcoidosis. The clinical features in older children are similar to those in adults (pediatric-onset adult sarcoidosis), with frequent systemic features (fever, weight loss, malaise), pulmonary involvement, and lymphadenopathy. In contrast, early-onset sarcoidosis manifesting in children <4 years of age is characterized by the triad of rash, uveitis, and polyarthritis.

ETIOLOGY

The etiology of sarcoidosis remains obscure but likely results from exposure of a genetically susceptible individual to one or more unidentified antigens. This exposure initiates an exaggerated immunologic response that ultimately leads to the formation of granulomas. The human major histocompatibility complex is located on chromosome 6, and specific human leukocyte antigen (HLA) class I and class II alleles are associated with disease phenotype. Genetic polymorphisms involving various cytokines and chemokines may also have a role in development of sarcoidosis. Familial clustering supports the contribution of genetic factors to sarcoidosis susceptibility. Environmental and occupational exposures are also associated with disease risk. There are positive associations between sarcoidosis and agricultural employment, occupational exposure to insecticides, and moldy environments typically associated with microbial bioaerosols.

Blau syndrome is an autosomal dominant, familial form of sarcoidosis and is typified by the early onset of granulomatous inflammation involving the skin, eyes, and joints. Pathogenic genetic variants in the *CARD15/NOD2* gene have been found in affected family members and appear to be associated with development of sarcoidosis. Similar genetic variants have been found in individuals with a sporadic **early-onset sarcoidosis (EOS)** (rash, uveitis, arthritis), suggesting that this nonfamilial form and Blau syndrome are genetically and phenotypically identical (see Chapter 204).

EPIDEMIOLOGY

A nationwide patient registry of childhood sarcoidosis in Denmark estimated the annual incidence to be 0.22-0.27 per 100,000 children. The incidence increases with age, and peak onset occurs at 20-39 years. The most common age of reported childhood cases is 13-15 years. In comparison, an international registry and Spanish cohort of Blau syndrome and EOS reported the mean age of disease onset as 30 months and 36 months, respectively. There is no clear gender predilection in any form of childhood sarcoidosis. The majority of U.S. childhood sarcoidosis cases are reported in the southeastern and southcentral states.

PATHOLOGY AND PATHOGENESIS

Noncaseating, epithelioid granulomatous lesions are a cardinal feature of sarcoidosis. Activated macrophages, epithelioid cells, and multinucleated giant cells, as well as $CD4^+$ T lymphocytes, accumulate and become tightly packed in the center of the granuloma. The causative agent that initiates this inflammatory process is unknown. The periphery of the granuloma contains a loose collection of monocytes, $CD4^+$ and $CD8^+$ T lymphocytes, and fibroblasts. The interaction between the macrophages and $CD4^+$ T lymphocytes is important in the formation and maintenance of the granuloma. The activated macrophages secrete high levels of tumor necrosis factor (TNF)-α and other proinflammatory mediators. The $CD4^+$ T lymphocytes differentiate into type 1 helper T cells and release interleukin (IL)-2 and interferon (IFN)-γ, promoting proliferation of lymphocytes. Granulomas may heal or resolve with complete preservation of the parenchyma. In approximately 20% of the

lesions, the fibroblasts in the periphery proliferate and produce fibrotic scar tissue, leading to significant and irreversible organ dysfunction.

The sarcoid macrophage is able to produce and secrete 1,25-$(OH)_2$-vitamin D, or *calcitriol,* an active form of vitamin D typically produced in the kidneys. The hormone's natural functions are to increase intestinal absorption of calcium and bone resorption and decrease renal excretion of calcium and phosphate. An excess of calcitriol may result in hypercalcemia and hypercalciuria in patients with sarcoidosis.

CLINICAL MANIFESTATIONS

Sarcoidosis is a multisystem disease, and granulomatous lesions may occur in any organ of the body. The clinical manifestations depend on the extent and degree of granulomatous inflammation and are extremely variable. Children may present with nonspecific symptoms, such as fever, weight loss, and general malaise. In adults and older children, pulmonary involvement is most frequent, with infiltration of the thoracic lymph nodes and lung parenchyma. Isolated bilateral hilar adenopathy on chest radiograph is the most common finding (Fig. 209.1), but parenchymal infiltrates and miliary nodules may also be seen (Figs. 209.2, 209.3, and 209.4). Patients with lung involvement are usually found to have restrictive changes on pulmonary function testing. Symptoms of pulmonary disease are seldom severe and generally consist of a dry, persistent cough.

Extrathoracic lymphadenopathy and infiltration of the liver, spleen, and bone marrow also occur often (Table 209.1). Infiltration of the liver and spleen typically leads to isolated hepatomegaly and splenomegaly, respectively, but actual organ dysfunction is rare. Cutaneous disease, such as plaques, nodules, erythema nodosum in acute disease, or lupus pernio in chronic sarcoidosis, appears in one quarter of cases and is usually present at onset. Red-brown to purple maculopapular lesions <1 cm on the face, neck, upper back, and extremities are the most common skin finding (Fig. 209.5). Papulonodular granulomatous lesions have been reported to develop in cosmetic (eyebrows) and decorative tattoos (tattoo sarcoidosis). Ocular involvement is frequent and has variable manifestations, including anterior or posterior uveitis, conjunctival granulomas, eyelid inflammation, and orbital or lacrimal gland infiltration. The arthritis in sarcoidosis can be confused with **juvenile idiopathic arthritis** (JIA). Central nervous system (CNS) involvement is rare in early childhood but may manifest as seizures, cranial nerve involvement, intracranial mass lesions, and hypothalamic dysfunction (Fig. 209.6). Kidney disease occurs infrequently in children but typically manifests as renal insufficiency, proteinuria, transient pyuria, or microscopic hematuria caused by early monocellular infiltration or granuloma formation in kidney tissue. Only a small fraction of children have hypercalcemia or hypercalciuria. Sarcoid granulomas can also infiltrate the heart and lead to cardiac arrhythmias and, rarely, sudden death. Other

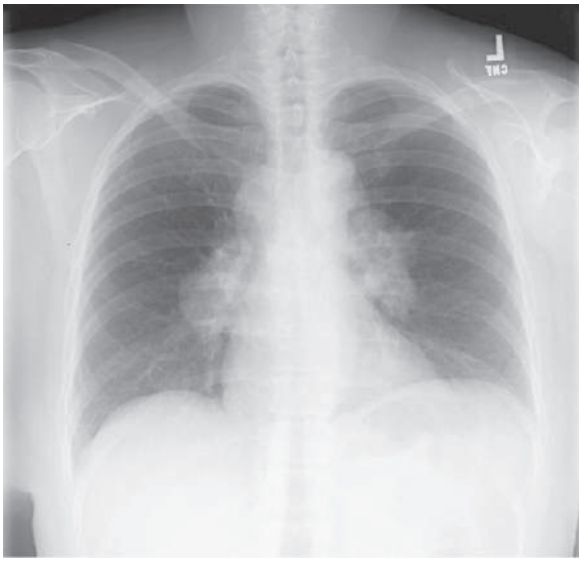

Fig. 209.1 Sarcoidosis. Chest radiograph demonstrating stage I disease with enlarged mediastinal and hilar lymph nodes. *(From Iannuzzi M. Sarcoidosis. In Goldman L, Schafer AI, eds. Goldman's Cecil Medicine, 24th ed. Philadelphia: Saunders; 2012: Fig. 95-1, p. 582.)*

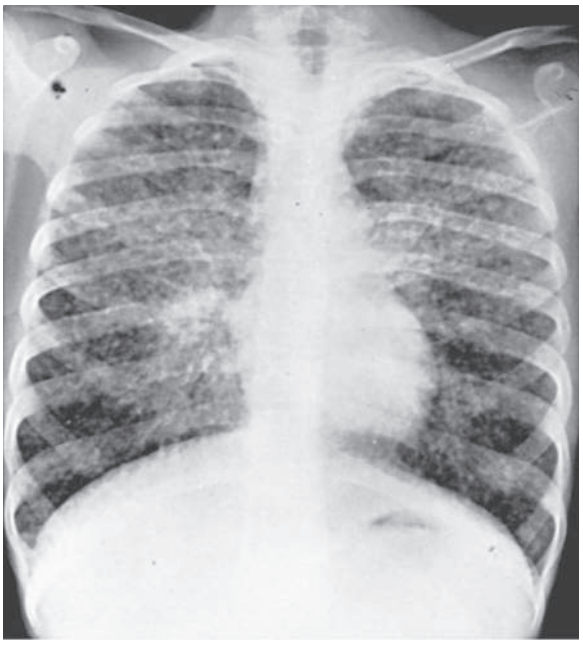

Fig. 209.2 Sarcoidosis. Chest radiograph of 10-year-old girl showing widely disseminated peribronchial infiltrates, multiple small nodular densities, hyperaeration of the lungs, and hilar lymphadenopathy.

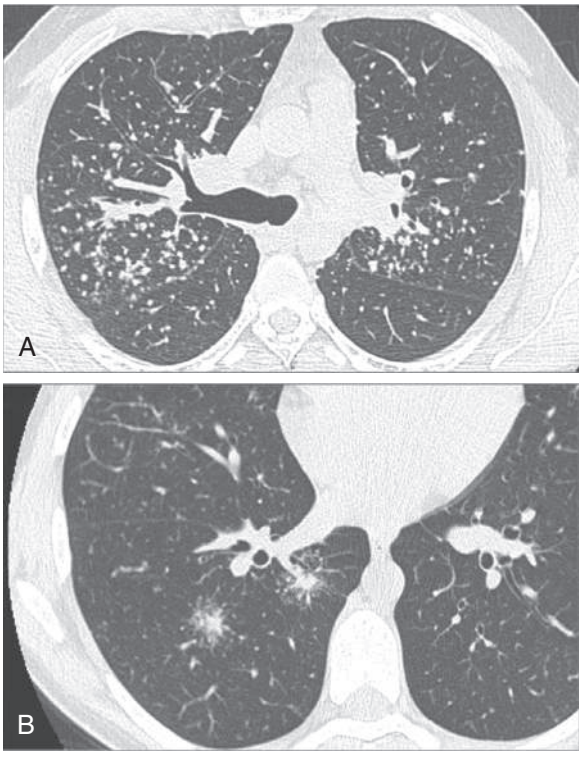

Fig. 209.3 Typical features of lung sarcoidosis on CT. **A,** Usual perilymphatic distribution of micronodules with fissural spreading. **B,** Typical nodules with irregular margins and satellite micronodules known as the *galaxy sign. (From Valerye D, Prasse A, Nunes H, et al. Sarcoidosis. Lancet. 2014;383:1155–1167, Fig. 2, p. 1158.)*

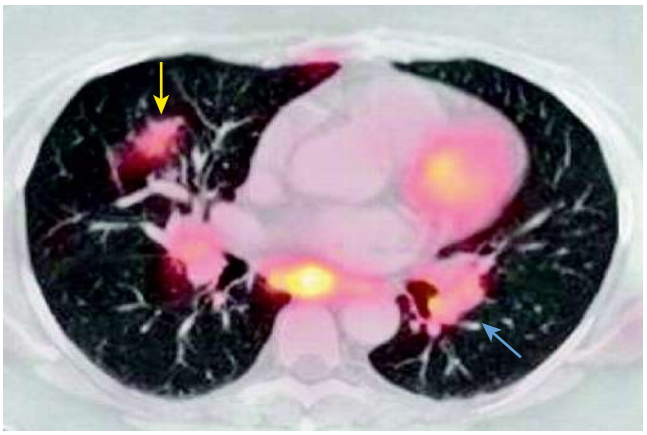

Fig. 209.4 Confluent parenchymal lung nodules and mediastinal and bilateral hilar lymphadenopathy with increased FDG uptake in a female with biopsy-proven sarcoidosis. PET/CT shows confluent parenchymal lung nodules *(yellow arrow)* and mediastinal and bilateral hilar lymphadenopathy *(blue arrow)*. These abnormalities show increased FDG uptake on fused PET/CT. *(Modified from Prabhakar HB, Rabinowitz CB, Gibbons FK, et al. Imaging features of sarcoidosis on MDCT, FDG PET, and PET/CT. AJR Am J Roentgenol. 2008;190:S1–S6, Fig. 6, p. S4.)*

rare sites of disease involvement include blood vessels of any size, the gastrointestinal tract, parotid gland, muscles, bones, and testes.

In contrast to the variable clinical presentation of sarcoidosis in older children, **Blau syndrome and EOS** (NOD2-associated sarcoidosis) classically manifest as the triad of uveitis, arthritis, and rash (see Chapter 204). **Infantile-onset panniculitis with uveitis and systemic granulomatosis** is an uncommon manifestation of sarcoidosis.

LABORATORY FINDINGS

There is no single standard laboratory test diagnostic of sarcoidosis. Anemia, leukopenia, and eosinophilia may be seen. Other nonspecific findings include hypergammaglobulinemia and elevations in acute-phase reactants, including ESR and CRP. Hypercalcemia and/or hypercalciuria occur in only a small proportion of children with sarcoidosis. Angiotensin-converting enzyme (ACE) is produced by the epithelioid cells of the granuloma, and *its serum value may be elevated, but this finding lacks diagnostic sensitivity and specificity*. ACE levels are estimated to be elevated in >50% of children with sarcoidosis. In addition, ACE values may be difficult to interpret because reference values for serum ACE are age dependent. Fluorodeoxyglucose–positron emission tomography (FDG-PET) (with either CT or MRI) can help identify nonpulmonary (lymph nodes, bone, cardiac, liver, spleen) sites for a diagnostic evaluation or biopsy (Fig. 209.7).

DIAGNOSIS

Definitive diagnosis ultimately requires demonstration of the characteristic noncaseating granulomatous lesions in a biopsy specimen (usually taken from the most readily available affected organ) and exclusion of other known causes of granulomatous inflammation. Skin and transbronchial lung biopsies have higher yield, greater specificity, and fewer associated adverse events than biopsy of mediastinal lymph nodes or liver. Additional diagnostic testing includes chest radiography, pulmonary function testing with measurement of diffusion capacity, hepatic enzyme measurements, and renal function assessment. Ophthalmologic slit-lamp examination is essential because ocular inflammation is frequently present and may be asymptomatic in sarcoidosis, and vision loss is a sequela of untreated disease.

Bronchoalveolar lavage may be used to assess for disease activity, and the fluid typically reveals an excess of lymphocytes with an increased $CD4^+/CD8^+$ ratio of 2-13:1. In addition to flexible bronchoscopy with transbronchial biopsy, endosonographic-guided intrathoracic node aspiration has been valuable in obtaining tissue to assess for noncaseating granulomas.

Table 209.1 Sarcoidosis: Extrapulmonary Localizations

	SYMPTOMS
Skin	Papules, nodules, plaques, scar sarcoidosis, lupus pernio, subcutaneous sarcoidosis, granuloma annulare, lip granulomas, vitiligo, erythema nodosum, Lofgren syndrome*
Peripheral lymphadenopathy	Mostly cervical or supraclavicular; inguinal, axillary, epitrochlear, or submandibular lymph node sites also possible; painless and mobile
Eye	Anterior, intermediate, or posterior uveitis; retinal vascular change; conjunctival nodules; lacrimal gland enlargement
Liver	Often symptom free; abnormal liver function tests in 20–30% of patients; hepatomegaly; rarely hepatic insufficiency, chronic intrahepatic cholestasis, or portal hypertension
Spleen	Splenomegaly; rarely, pain or pancytopenia; very rarely, splenic rupture
Heart	Atrioventricular or bundle branch block; ventricular tachycardia or fibrillation; congestive heart failure; pericarditis; impairment of sympathetic nerve activity; sudden death
Nervous system	Facial nerve palsy, optic neuritis, leptomeningitis, diabetes insipidus, hypopituitarism, seizures, cognitive dysfunction, deficits, hydrocephalus, psychiatric manifestations, spinal cord disease, polyneuropathy, small-fiber neuropathy
Kidney	Rare symptoms; increased creatinine sometimes associated with hypercalcemia; nephrocalcinosis; kidney stones
Parotitis	Symmetric parotid swelling; Heerfordt syndrome when associated with uveitis, fever, and facial palsy
Nose	Nasal stuffiness, nasal bleeding, crusting, anosmia
Larynx	Hoarseness, breathlessness, stridor, dysphagia
Bones	Often asymptomatic; hands and feet classically most involved, also large bones and axial skeleton
Skeletal muscles	Proximal muscle weakness, amyotrophy, myalgia, intramuscular nodules
Genitourinary tract	All organs can be involved, including breast, uterus, epididymis, and testicle
Gastrointestinal tract	Most often symptom free, but the esophagus, stomach, small intestine, and colon can be involved

*Lofgren syndrome: acute arthritis, erythema nodosum, and hilar adenopathy.
Adapted from Valerye D, Prasse A, Nunes H, et al. Sarcoidosis. *Lancet.* 2014;383:1155–1167, Table 1.

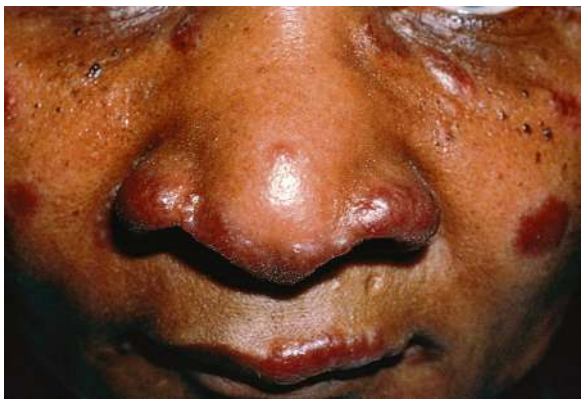

Fig. 209.5 Sarcoidosis nodules on the face. *(From Shah BR, Laude TA. Atlas of Pediatric Clinical Diagnosis. Philadelphia: Saunders; 2000.)*

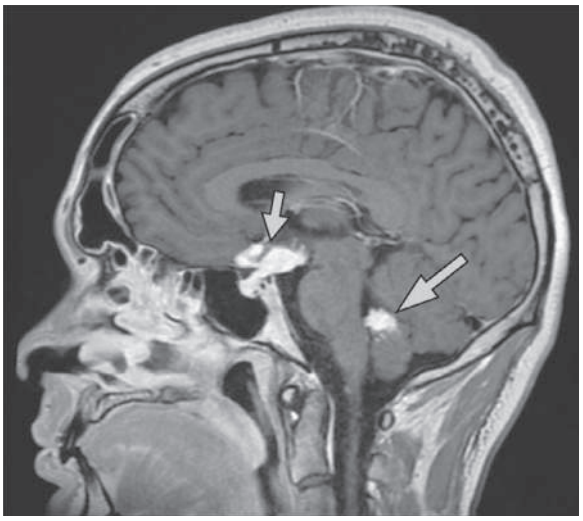

Fig. 209.6 Neurologic involvement in sarcoidosis. Typical involvement of hypothalamus, pituitary gland, and optic chiasm seen on a sagittal gadolinium-enhanced T1-weighted sequence MRI *(small arrow)*. Abnormal nodular enhancement of the fourth ventricle is seen *(large arrow)*. *(Modified from Valerye D, Prasse A, Nunes H, et al. Sarcoidosis. Lancet. 2014;383:1155–1167, Fig. 3D, p. 1160.)*

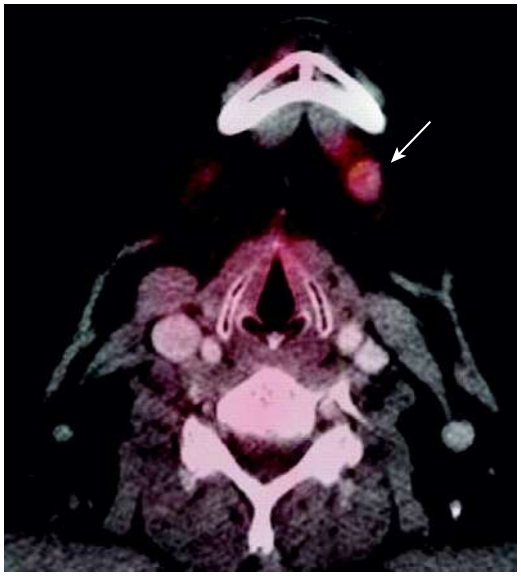

Fig. 209.7 Palpable submental lymph node with FDG uptake. Axial fused contrast-enhanced PET/CT image shows enlarged left submental lymph node *(arrow)* with increased FDG uptake. Lesion was biopsied and was consistent with sarcoidosis. *(From Prabhakar HB, Rabinowitz CB, Gibbons FK, et al. Imaging features of sarcoidosis on MDCT, FDG PET, and PET/CT. AJR Am J Roentgenol. 2008;190:S1–S6, Fig. 5, p. S3.)*

DIFFERENTIAL DIAGNOSIS

Because of its protean manifestations, the differential diagnosis of sarcoidosis is extremely broad and depends largely on the initial clinical manifestations. **Granulomatous infections**, including tuberculosis, cryptococcosis, pulmonary mycoses (histoplasmosis, blastomycosis, coccidioidomycosis), brucellosis, tularemia, and toxoplasmosis, must be excluded. Other causes of granulomatous inflammation are granulomatosis with polyangiitis (formerly Wegener granulomatosis), hypersensitivity pneumonia, chronic berylliosis, and other occupational exposures to metals. Localized granulomatous lesions of the head and neck may be due to **orofacial granulomatosis (Melkersson-Rosenthal syndrome)**. Other granulomatous lesions involving the head, neck, and orofacial regions are noted in Table 209.2. Immunodeficiencies that may manifest with granulomatous lesions include common variable immunodeficiency, selective IgA deficiency, chronic granulomatous disease, ataxia telangiectasia, and severe combined immunodeficiency. Granulomas of the lung, skin, or lymph nodes have been reported in patients treated with anti-TNF agents. Lymphoma should be ruled out in cases of hilar or other lymphadenopathy. Sarcoid arthritis may mimic JIA. Evaluation for endocrine disorders is needed in the setting of hypercalcemia or hypercalciuria.

Table 209.2 Granulomatous Disorders with Head and Neck Manifestations

AUTOIMMUNE
GPA (Wegener granulomatosis)
Churg-Strauss syndrome
Behçet disease
INFECTIOUS
Tuberculosis
Cat-scratch fever
Syphilis
Leprosy
Fungal (blastomycosis, histoplasmosis)
Actinomycosis
IDIOPATHIC/INFLAMMATION
Sarcoidosis
Orofacial granulomatosis (Melkersson-Rosenthal syndrome)
HEREDITARY
CGD
OTHER DISEASES WITH SECONDARY GRANULOMATOUS MANIFESTATIONS
Relapsing polychondritis
LCH
SLE
Rheumatoid arthritis
Chemical exposure (e.g., cocaine, talc, beryllium)

CGD, chronic granulomatous disease; GPA, Granulomatosis with polyangiitis; LCH, Langerhans cell histiocytosis; SLE, systemic lupus erythematosus.
Modified from Nwawka OK, Nadgir R, Fujita A, Sakai O. Granulomatous disease in the head and neck: Developing a differential diagnosis. *RadioGraphics.* 2014;34(5):1240–1256, Table 1.

TREATMENT

Treatment should be based on disease severity and the number and type of organs involved. *Corticosteroids are the mainstay of treatment for most acute and chronic disease manifestations.* The optimal dose and duration of corticosteroid therapy in children have not been established. Induction treatment typically begins with oral prednisone or prednisolone (1-2 mg/kg/day up to 40 mg daily) for 8-12 weeks until manifestations improve. Corticosteroid dosage is then gradually decreased over 6-12 months to the minimal effective maintenance dose (e.g., 5-10 mg/day) that controls symptoms, or discontinued if symptoms resolve. *Methotrexate* or *leflunomide* may be effective as a corticosteroid-sparing agent. On the basis of the role of TNF-α in the formation of granulomas, there is rationale for the use of TNF-α antagonists. Results of small clinical trials showed modest effects with *infliximab* and *adalimumab* treatment of selected disease manifestations (CNS, lupus pernio, pulmonary, ocular), whereas etanercept does not appear to be particularly effective. Other therapeutics used for sarcoidosis manifestations include topical corticosteroids (eye), inhaled corticosteroids (lung), azathioprine (CNS), cyclophosphamide (cardiac, CNS), hydroxychloroquine (skin), mycophenolate mofetil (CNS, skin), thalidomide or its analogs (skin), and nonsteroidal antiinflammatory drugs (joints).

PROGNOSIS

The prognosis of childhood sarcoidosis is not well defined. The disease may be self-limited with complete recovery or may persist with a progressive or relapsing course. Outcome is worse in the setting of

multiorgan or CNS involvement. Most children requiring treatment experience considerable improvement with corticosteroids, although a significant number have morbid sequelae, mainly involving the lungs and eyes. Children with early-onset sarcoidosis have a poorer prognosis and generally experience a more chronic, progressive disease course. The greatest morbidity is associated with ocular involvement, including cataract formation, development of synechiae, and loss of visual acuity or blindness. Long-term systemic treatment may be required for the eye disease. Progressive polyarthritis may result in joint destruction. The overall mortality rate in older children with sarcoidosis is low.

Serial pulmonary function tests and chest radiographs are useful in following the course of lung involvement. Monitoring for other organ involvement should also include electrocardiogram with consideration of an echocardiogram, urinalysis, renal function tests, and measurements of hepatic enzymes and serum calcium. Other potential indicators of disease activity include inflammatory markers and serum ACE, although changes in ACE level do not always correlate with other indicators of disease status. Given the frequency of asymptomatic eye disease and the ocular morbidity associated with pediatric sarcoidosis, all patients should have an ophthalmologic examination at presentation with monitoring at regular intervals, perhaps every 3-6 months, as recommended in children with JIA.

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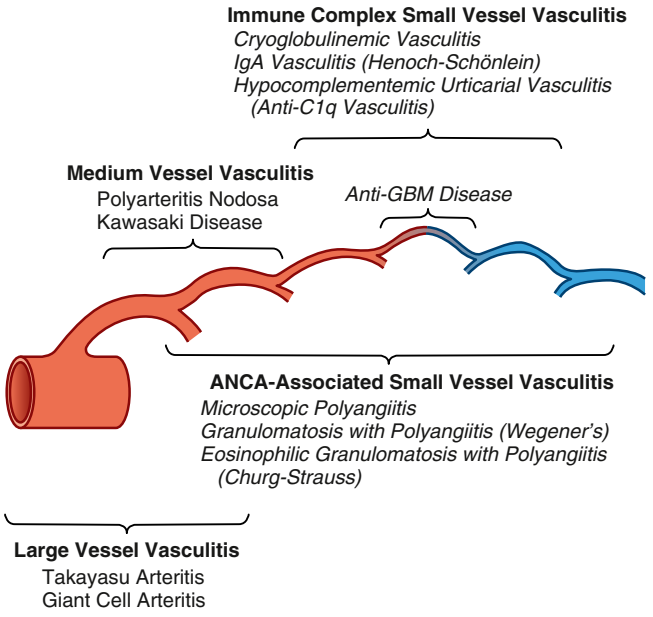

Fig. 210.1 Distribution of vessel involvement in large, medium, and small vessel vasculitis. There is substantial overlap with respect to arterial involvement, and all three major categories of vasculitis can affect any size artery. Large vessel vasculitis affects large arteries more often than other vasculitides. Medium vessel vasculitis predominantly affects medium arteries. Small vessel vasculitis predominantly affects small vessels, but medium arteries and veins may be affected, although immune complex small vessel vasculitis rarely affects arteries. Not shown is *variable vessel vasculitis*, which can affect any type of vessel, from aorta to veins. The diagram depicts (from *left* to *right*) aorta, large artery, medium artery, small artery/arteriole, capillary, venule, and vein. ANCA, Antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane. *(From Jennette JC, Falk RJ, Bacon PA, et al. 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum. 2013;65:1–11, Fig. 2, p. 4.)*

Chapter 210

Vasculitis Syndromes

Vidya Sivaraman, Edward C. Fels, and Stacy P. Ardoin

INTRODUCTION

Childhood vasculitis encompasses a broad spectrum of diseases that share inflammation of the blood vessels as the central pathophysiology. The pathogenesis of the vasculitides is generally idiopathic. Some forms of vasculitis are associated with infectious agents and medications, whereas others may occur in the setting of preexisting autoimmune or autoinflammatory diseases. The pattern of vessel injury provides insight into the form of vasculitis and serves as a framework to delineate the different vasculitic syndromes. The distribution of vascular injury includes *small vessels* (capillaries, arterioles, and postcapillary venules), *medium vessels* (renal arteries, mesenteric vasculature, and coronary arteries), and *large vessels* (the aorta and its proximal branches) (Fig. 210.1). Additionally, some forms of small vessel vasculitis are characterized by the presence of **antineutrophil cytoplasmic antibodies (ANCAs)**, whereas others are associated with **immune complex** deposition in affected tissues. A combination of clinical features, histologic appearance of involved vessels, and laboratory data is used to classify vasculitis (Tables 210.1-210.4). A nomenclature system from the 2012 International Chapel Hill Consensus Conference (see Table 210.1) has proposed using the pathologic diagnosis rather than eponyms for vasculitis nomenclature. For example, Henoch-Schönlein purpura would be referred to as IgA vasculitis. Additionally, the classification criteria endorsed by the European League Against Rheumatism (EULAR), Pediatric Rheumatology International Trial Organization (PRINTO), and Pediatric Rheumatology European Society (PRES) have been validated in childhood vasculitis (see Table 210.2).

Childhood vasculitis varies from a relatively benign and self-limited disease such as Henoch-Schönlein purpura (IgA vasculitis) to catastrophic disease with end-organ damage, as seen in granulomatosis with polyangiitis (formerly Wegener granulomatosis). Vasculitis generally manifests as a heterogeneous multisystem disease. Although some features, such as purpura, are easily identifiable, others, such as hypertension secondary to renal artery stenosis or glomerulonephritis, can be subtler. Ultimately, the key to recognizing vasculitis relies heavily on *pattern recognition*. Demonstration of vessel injury and inflammation on biopsy or vascular imaging is required to confirm a diagnosis of vasculitis.

Clues to the diagnosis of a vasculitis disorder are noted in Table 210.3, and a broad diagnostic approach is noted in Table 210.5.

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210.1 Henoch-Schönlein Purpura (IgA Vasculitis)

Vidya Sivaraman, Edward C. Fels, and Stacy P. Ardoin

Henoch-Schönlein purpura (**HSP**) is the most common vasculitis of childhood and is characterized by leukocytoclastic vasculitis and immunoglobulin A deposition in the small vessels in the skin, joints, gastrointestinal tract, and kidney. HSP is also referred to as **IgA vasculitis**, based on the presence of vasculitis with predominance of IgA deposits affecting small vessels.

Table 210.1 2012 Chapel Hill Consensus Conference on Nomenclature of Systemic Vasculitis

LARGE VESSEL VASCULITIS (LVV)*	
Giant cell (temporal) arteritis (GCA)	Granulomatous arteritis of the aorta and its major branches with a predilection for the extracranial branches of the carotid artery *Often involves the temporal artery* *Usually occurs in patients older than 50 yr of age and often associated with polymyalgia rheumatica*†
Takayasu arteritis (TAK)	Granulomatous inflammation of the aorta and its major branches *Usually occurs in patients much younger than 50 yr of age*
MEDIUM VESSEL VASCULITIS (MVV)*	
Polyarteritis nodosa (PAN)	Necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules and not associated with ANCAs
Kawasaki disease (KD)	Arteritis involving large, medium-sized, and small arteries associated with mucocutaneous lymph node syndrome *Coronary arteries are often involved* *Aorta and veins may be affected* *Usually occurs in children*
SMALL VESSEL VASCULITIS (SVV)*	
ANCA-associated vasculitis (AAV)	
Granulomatosis with polyangiitis (Wegener) (GPA)	Granulomatous inflammation involving the respiratory tract associated with necrotizing vasculitis affecting small- to medium-sized vessels *Necrotizing glomerulonephritis is common*
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)	Eosinophilic and granulomatous inflammation involving the respiratory tract accompanied by necrotizing vasculitis affecting small to medium-sized vessels associated with asthma and eosinophilia
Microscopic polyangiitis (MPA)	Necrotizing vasculitis with few or no immune deposits, affecting small vessels *Necrotizing arteritis involving small and medium-sized arteries may be present* *Necrotizing glomerulonephritis is common* *Pulmonary capillaritis often occurs*
Immune Complex Small Vessel Vasculitis	
IgA vasculitis (Henoch-Schönlein) (IgAV)	Vasculitis characterized by immunoglobin A–dominant immune deposits affecting small vessels *Typically involves skin, gut, and glomeruli. Arthralgias and arthritis are common*
Cryoglobulinemic vasculitis (CPV)	Vasculitis with cryoglobulin immune deposits affecting small vessels associated with cryoglobulinemia *Skin and glomeruli are often involved*
Anti–glomerular basement membrane (anti-GBM) disease	Vasculitis affecting pulmonary and renal capillaries with deposition of anti–glomerular basement membrane antibodies
Hypocomplementemic urticarial vasculitis	Associated with anti-Clq antibodies *Affects kidney, joints, lungs, and eyes*
VARIABLE VESSEL VASCULITIS (VVV)	
Behçet disease (BD)	Affects arteries and veins with thrombosis, arteritis, and arterial aneurysms *Oral and/or genital aphthous ulcers and can involve skin, eyes, joints, and central nervous system*
Cogan syndrome (CS)	Affects small, medium, or large arteries; aortitis, aortic, and mitral valvulitis
SINGLE-ORGAN VASCULITIS (SOV)	
Cutaneous leukocytoclastic angiitis	Vasculitis Isolated cutaneous leukocytoclastic angiitis without systemic vasculitis or glomerulonephritis
Cutaneous arteritis	Cutaneous vasculitis not associated with systemic vasculitis
Primary central nervous system vasculitis	CNS vasculitis not associated with systemic vasculitis
Isolated aortitis	Aortitis not associated with systemic vasculitis
Others	
VASCULITIS ASSOCIATED WITH SYSTEMIC DISEASE	
Lupus vasculitis	
Rheumatoid vasculitis	
Sarcoid vasculitis	
Others	
VASCULITIS ASSOCIATED WITH PROBABLE ETIOLOGY	
Hepatitis C–associated cryoglobulinemia vasculitis	
Hepatitis B–associated vasculitis	
Syphilis-associated vasculitis	
Drug-associated immune complex vasculitis	
Drug-associated ANCA associated vasculitis	
Cancer-associated vasculitis	
Others	

*Large vessels: aorta and its larger branches directed toward major anatomic regions; medium vessels: renal, hepatic, coronary, and mesenteric arteries; small vessels: venules, capillaries, arterioles, and intraparenchymal distal arteries and arterioles.
†Essential components are in normal type; *italicized type* represents usual, but not essential, components.
Adapted from Jennette JC, Falk RJ, Bacon P, et al. *Arthritis Rheum*. 2013;65(1):1–11.

Table 210.2 EULAR/PRES Classification of Childhood Vasculitis

I. PREDOMINANTLY LARGE-SIZED VESSEL VASCULITIS
- Takayasu arteritis

II. PREDOMINANTLY MEDIUM-SIZED VESSEL VASCULITIS
- Childhood polyarteritis nodosa
- Cutaneous polyarteritis
- Kawasaki disease

III. PREDOMINANTLY SMALL-SIZED VESSEL VASCULITIS

A. Granulomatous
- Wegener granulomatosis*
- Churg-Strauss syndrome*

B. Nongranulomatous
- Microscopic polyangiitis
- Henoch-Schönlein purpura
- Isolated cutaneous leukocytoclastic vasculitis
- Hypocomplementemic urticarial vasculitis

IV. OTHER VASCULITIDES
- Behçet disease
- Vasculitis secondary to infection (including hepatitis B–associated polyarteritis nodosa), malignancies, and drugs (including hypersensitivity vasculitis)
- Vasculitis associated with connective tissue diseases
- Isolated vasculitis of the central nervous system
- Cogan syndrome
- Unclassified

*This classification predated the removal of eponyms and histopathologic subclassification by the CHCC 2012.

From Ozen S, Ruperto N, Dillon MJ, Bagga A, Barron K, Davin JC, et al. EULAR/PReS endorsed consensus criteria for the classification of childhood vasculitides. *Ann Rheum Dis.* 2006;65:936–941.

Table 210.3 Features that Suggest a Vasculitic Syndrome

CLINICAL FEATURES
- Fever, weight loss, fatigue of unknown origin
- Skin lesions (palpable purpura, fixed urticaria, livedo reticularis, nodules, ulcers)
- Neurologic lesions (headache, mononeuritis multiplex, focal central nervous system lesions)
- Arthralgia or arthritis, myalgia, or myositis, serositis
- Hypertension, hematuria, renal failure
- Pulmonary infiltrates or hemorrhage
- Myocardial ischemia, arrhythmias

LABORATORY FEATURES
- Increased erythrocyte sedimentation rate or C-reactive protein level
- Leukocytosis, anemia, thrombocytosis
- Eosinophilia
- Antineutrophil cytoplasmic antibodies
- Elevated factor VIII–related antigen (von Willebrand factor)
- Cryoglobulinemia
- Circulating immune complexes
- Hematuria

From Petty RE, Laxer RM, Lindsley CB, Wedderburn LR. *Textbook of Pediatric Rheumatology,* 7th ed. Philadelphia: Saunders; 2016.

EPIDEMIOLOGY

HSP occurs worldwide and affects all ethnic groups. The incidence is estimated at 14-20 per 100,000 children per year and affects males more than females, with a 1.2-1.8:1 male/female ratio. Approximately 90% of HSP cases occur in children, usually between ages 3 and 10 years. HSP is distinctly less common in adults, who often have severe and chronic complications. HSP is more common in the winter and spring and is unusual in summer months. Many cases of HSP follow a documented upper respiratory infection.

PATHOLOGY

Skin biopsies demonstrate **leukocytoclastic vasculitis** of the dermal capillaries and postcapillary venules. The inflammatory infiltrate includes neutrophils and monocytes. Renal histopathology typically shows endocapillary proliferative glomerulonephritis, ranging from a focal segmental process to extensive crescentic involvement. In all tissues, immunofluorescence identifies IgA deposition in walls of small vessels (Fig. 210.2), accompanied to a lesser extent by deposition of C3, fibrin, and IgM.

PATHOGENESIS

The exact pathogenesis of HSP remains unknown. Given the seasonality of HSP and the frequency of preceding upper respiratory infections, infectious triggers such as group A β-hemolytic streptococcus, *Staphylococcus aureus, Mycoplasma,* and adenovirus have been suspected. The common finding of deposition of IgA, specifically IgA_1, suggests that HSP is a disease mediated by IgA and IgA immune complexes. HSP occasionally clusters in families, suggesting a genetic component. HLA-B34 and HLA-DRB1*01 alleles have been linked to HSP nephritis. Patients with familial Mediterranean fever, hereditary periodic fever syndromes, and complement deficiencies are at increased risk for developing HSP, suggesting that genetically determined immune dysregulation may contribute.

CLINICAL MANIFESTATIONS

The hallmark of HSP is its **rash**: palpable purpura starting as pink macules or wheals and developing into petechiae, raised purpura, or larger ecchymoses. Occasionally, bullae and ulcerations develop. The skin lesions are usually symmetric and occur in gravity-dependent areas (lower extremities), the extensor aspect of the upper extremities, or on pressure points (buttocks) (Figs. 210.2 and 210.3). The skin lesions often evolve in groups, typically lasting 3-10 days, and may recur up to 4 months after initial presentation. Subcutaneous edema localized to the dorsa of the hands and feet, periorbital area, lips, scrotum, or scalp is also common.

Musculoskeletal involvement, including arthritis and arthralgias, is common, occurring in up to 75% of children with HSP. The arthritis tends to be self-limited and oligoarticular, with a predilection for large joints such as the knees and ankles, and does not lead to deformities. Periarticular swelling and tenderness without erythema or effusions are common. The arthritis usually resolves within 2 weeks but can recur.

Gastrointestinal (GI) manifestations occur in up to 80% of children with HSP and include abdominal pain, vomiting, diarrhea, paralytic ileus, and melena. Intussusception, mesenteric ischemia, and intestinal perforation are rare but serious complications. Endoscopic evaluation is usually not needed but may identify vasculitis of the intestinal tract.

Renal involvement occurs in up to 30% of children with HSP, manifesting as microscopic hematuria, proteinuria, hypertension, frank nephritis, nephrotic syndrome, and acute or chronic renal failure. However, progression to end-stage renal disease (ESRD) is uncommon in children (1–2%) (see Chapter 560.3). Renal manifestations can be delayed for several months after the initial illness, so close follow-up with serial urinalyses and blood pressure monitoring is necessary.

Neurologic manifestations of HSP, caused by hypertension (posterior reversible encephalopathy syndrome) or central nervous system (CNS) vasculitis, may also occur, including intracerebral hemorrhage, seizures, headaches, depressed level of consciousness, cranial or peripheral neuropathies, and behavior changes. Other, less common potential manifestations of HSP are inflammatory eye disease, carditis, pulmonary hemorrhage, orchitis, and testicular torsion.

DIAGNOSIS

The diagnosis of HSP is clinical and often straightforward when the typical rash is present. However, in at least 25% of cases, the rash appears after other manifestations, making early diagnosis challenging.

Table 210.4 Clinicopathologic Characteristics of Vasculitides in Childhood

SYNDROME	FREQUENCY	VESSELS AFFECTED	CHARACTERISTIC PATHOLOGY
POLYARTERITIS			
Polyarteritis nodosa	Rare	Medium-size and small muscular arteries and sometimes arterioles	Focal segmental (often near bifurcations); fibrinoid necrosis; gastrointestinal, renal microaneurysms; lesions at various stages of evolution
Kawasaki disease	Common	Coronary and other muscular arteries	Thrombosis, fibrosis, aneurysms, especially of coronary vessels
LEUKOCYTOCLASTIC VASCULITIS			
Henoch-Schönlein purpura (IgA vasculitis)	Common	Arterioles and venules, often small arteries and veins	Leukocytoclasis; mixed cells, eosinophils, IgA deposits in affected vessels
Hypersensitivity angiitis	Rare	Arterioles and venules	Leukocytoclastic or lymphocytic, varying eosinophils, occasionally granulomatous; widespread lesions at same stage of evolution
GRANULOMATOUS VASCULITIS			
Granulomatosis with polyangiitis (Wegener granulomatosis)	Rare	Small arteries and veins, occasionally larger vessels	Upper and lower respiratory tract, necrotizing granulomata glomerulonephritis
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)	Rare	Small arteries and veins, often arterioles and venules	Necrotizing extravascular granulomata; lung involvement; eosinophilia
GIANT CELL ARTERITIS			
Takayasu arteries	Uncommon	Large arteries	Granulomatous inflammation, giant cells; aneurysms, dissection
Temporal arteritis	Rare	Medium-size and large arteries	Granulomatous inflammation, giant cell arteries

Adapted from Cassidy JT, Petty RE. *Textbook of Pediatric Rheumatology,* 6th ed. Philadelphia: Saunders; 2011.

Table 210.6 summarizes the EULAR/PRES classification criteria for HSP. Most patients are afebrile.

The **differential diagnosis** for HSP depends on specific organ involvement, but usually includes other small vessel leukocytoclastic vasculitides (Table 210.7), infections, acute poststreptococcal glomerulonephritis, hemolytic-uremic syndrome, coagulopathies, and other acute intraabdominal processes. Additional disorders in the differential include papular-purpuric glove and sock syndrome, systemic lupus erythematosus (SLE), other vasculitides (urticarial, hypersensitivity), and thrombocytopenia.

Infantile acute hemorrhagic edema (AHE), an isolated cutaneous leukocytoclastic vasculitis that affects infants <2 years of age, resembles HSP clinically. AHE manifests as fever; tender edema of the face, scrotum, hands, and feet; and ecchymosis (usually larger than the purpura of HSP) on the face and extremities (Fig. 210.4). The trunk is spared, but petechiae may be seen in mucous membranes. The patient usually appears well except for the rash. The platelet count is normal or elevated, and the urinalysis results are normal. The younger age, nature of the lesions, absence of other organ involvement, and a biopsy may help distinguish infantile AHE from HSP.

LABORATORY FINDINGS

No laboratory finding is diagnostic of HSP. Common but nonspecific findings include leukocytosis, thrombocytosis, mild anemia, and elevations of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). *The platelet count is normal in HSP*. Occult blood is frequently found in stool specimens. Serum albumin levels may be low because of renal or intestinal protein loss. Autoantibody testing such as antinuclear antibody (ANA) is not useful diagnostically except to exclude other diseases. Serum IgA values are often elevated but are not routinely measured. Assessment of renal involvement with blood pressure, urinalysis, and serum creatinine is necessary.

Ultrasound is often used in the setting of GI complaints to look for bowel wall edema or the rare occurrence of an associated intussusception. Barium enema can also be used to both diagnose and treat intussusception. Although often unnecessary in typical HSP, biopsies of skin and kidney can provide important diagnostic information, particularly in atypical or severe cases, and characteristically show leukocytoclastic vasculitis with IgA deposition in affected tissues.

TREATMENT

Treatment for mild and self-limited HSP is *supportive,* with an emphasis on ensuring adequate hydration, nutrition, and analgesia. Corticosteroids are most often used to treat significant GI involvement or other life-threatening manifestations. Glucocorticoids such as oral prednisone (1-2 mg/kg/day), or in severe cases, intravenous (IV) methylprednisolone for 1-2 weeks, followed by taper, reduce abdominal and joint pain but do not alter the overall prognosis. Corticosteroids are not routinely recommended for prevention of complications such as nephritis. Rapid tapering of corticosteroids may lead to a flare of HSP symptoms. Although few data are available to demonstrate efficacy, intravenous immunoglobulin (IVIG) and plasma exchange are sometimes used for severe disease. In some patients, chronic HSP renal disease is managed with a variety of immunosuppressants, including azathioprine, cyclophosphamide, cyclosporine, and mycophenolate mofetil. ESRD develops in <5% of children with HSP nephritis.

COMPLICATIONS

Acutely, serious GI involvement, including intussusception and intestinal perforation, imparts significant morbidity and mortality. Renal disease is the major long-term complication, occurring in 1–2% of children with HSP. Renal disease can develop up to 6 months after diagnosis but rarely does so if the initial urinalysis findings are normal. Therefore, it is recommended that children with HSP undergo serial monitoring of blood pressure and urinalysis for at least 6 months after diagnosis to monitor for development of nephritis.

PROGNOSIS

Overall, the prognosis for childhood HSP is excellent, and most children experience an acute, self-limited course lasting on average 4 weeks. However, 15–60% of children with HSP experience one or more recurrences, typically within 4-6 months of diagnosis. With each relapse, symptoms are usually milder than at presentation. Children

Table 210.5 Recommendations on the Diagnosis of Rare Pediatric Systemic Vasculitides

RECOMMENDATION

1. In any pediatric patient with ongoing or a history of unexplained systemic inflammation, the diagnosis of systemic vasculitis should be considered and referral to a pediatric rheumatologist should be made, particularly in the presence of unexplained organ involvement.
2. Clinical features combined with laboratory evidence of inflammation that suggest a vasculitic syndrome warranting referral to a pediatric rheumatologist are included in the following nonexhaustive list:
   - Pyrexia of unknown origin
   - Vasculitic skin rash
   - PNS or CNS involvement
   - Unexplained arthritis, myalgia, serositis
   - Unexplained pulmonary, gastrointestinal, cardiovascular, or renal disease
3. When vasculitis is suspected, the diagnosis is often difficult and differential diagnoses are broad. The general workup for diagnosis of a specific vasculitic syndrome should include tissue histology, imaging, and determination of ANCA.
4. In every patient in whom a specific vasculitic syndrome is suspected, basic screening investigations, along with blood pressure measurement, should include:
   - Hematology and acute-phase reactants:
     - Full blood count, ESR, CRP, clotting, prothrombotic screen (if patchy ischemia of digits or skin)
     - Peripheral blood smear
   - Basic biochemistry:
     - Renal function, liver function, CPK, LDH
     - Urine dipstick test of urine with UA:UC ratio or UP:UC ratio
   - Infection:
     - Routine pediatric infection screen
     - Anti–streptolysin O antibody titer (ASOT) and/or anti–DNase b
     - VZV antibody status
   - Immunologic tests:
     - ANA, ENA antibodies, ANCA, antiphospholipid antibodies
     - Immunoglobulins IgG/IgA/IgM/IgE
     - Complement (C3, C4)
     - RF (if nephritis or interstitial lung disease)
     - GBM antibody
   - Radiologic/other:
     - CXR
     - Doppler abdominal ultrasound scan
     - ECG; echocardiography
     - Digital clinical photography of lesions
5. When considering a specific vasculitic syndrome, depending on presenting symptoms, tests with specific indications should be considered:
   - The following may be useful if blood pressure abnormalities:
     - Four limb blood pressure measurements
     - 24-hr ambulatory blood pressure monitor
   - The following may be useful if evidence/suspicion of specific organ involvement:
     - CT (e.g., thorax, abdomen, brain)
     - MRI
     - MRI/MRA of aorta and major branches
     - Selective contrast visceral arteriography
     - Tissue biopsy (e.g., skin, nasal or sinus, kidney, sural nerve, lung, liver, gut, temporal artery, brain)
     - Nail fold capillaroscopy
     - Possible bone/joint involvement: radiograph of suspected sites
     - Eye symptoms: ophthalmology screen
     - Pulmonary symptoms: V/Q scan
     - Renal involvement: Tc-99m DMSA scan
     - Peripheral vascular symptoms: ultrasound scan Doppler of peripheral arteries
     - Neuropathy: nerve conduction studies
     - Cerebral involvement: MRI/MRA of brain and cerebral contrast angiography
     - Organ-specific autoantibodies (e.g., ASCAs, brain/neuronal specific autoantibodies)
     - Cryoglobulins or cryoprecipitants (technical expertise required), particularly if skin involved predominantly at peripheral sites
   - The following may be useful when the differential diagnosis includes malignancy:
     - Lymph node excision biopsy
     - Bone marrow analysis
     - PET-CT
   - The following may be useful when the differential diagnosis includes infection:
     - Tuberculosis screen
     - PCR for viral infection (e.g., CMV, EBV, enterovirus, adenovirus, VZV, HBV, HCV)
     - Serology for HIV, rickettsiae, *Borrelia burgdorferi, Mycoplasma*
     - Viral serology for hepatitis B and C, parvovirus B19
     - Cryoglobulins or cryoprecipitants (technical expertise required)
   - The following may be useful when the differential diagnosis includes autoinflammatory syndromes:
     - DNA analysis for MEFV (familial Mediterranean fever), TNFRSF1A (TNF-α receptor–associated periodic fever syndrome [TRAPS]), MVK (mevalonate kinase deficiency; previously referred to as hyper-IgD syndrome [HIDS]), NLRP3 (cryopyrin-associated periodic syndrome [CAPS]), NOD2 (Crohn/Blau/juvenile sarcoid mutations), ADA2 (deficiency of ADA2), genetic screening for SAVI (TMEM173) and CANDLE (PSMB8, 4, 9, and other proteasome genes if available).
6. In the clinical assessment of suspected systemic vasculitis, a structured multiorgan assessment should take place.
7. For suspected systemic vasculitis, the Pediatric Vasculitis Activity Score (PVAS) may facilitate structured multiorgan assessment. The PVAS can be found here: http://ard.bmj.com/content/72/10/1628.short
8. At diagnosis and in ongoing follow-up of systemic vasculitis, a PVAS score should be performed to assess disease activity.
9. At diagnosis and in ongoing follow-up of systemic vasculitis, a multiorgan assessment of damage should be undertaken.
10. There is no currently validated tool to assess pediatric vasculitis damage. This is an ongoing unmet need. The PVDI, while unvalidated, can be assessed here: https://ard.bmj.com/content/73/Suppl_2/696.4

PNS, Peripheral nervous system; PVAS, pediatric vasculitis activity score; PVDI, pediatric vasculitis damage index; CNS, central nervous system; CPK, creatine phosphokinase; LDH, lactate dehydrogenase; UA:UC, urine albumin to urinary creatinine ratio; UP:UC, urine protein to urinary creatinine ratio; VZV, varicella-zoster virus; CXR, chest x-ray; ECG, electrocardiogram; MRA, magnetic resonance angiography; V/Q, ventilation/perfusion; DMSA, dimercaptosuccinic acid; ASCA, anti–*Saccharomyces cerevisiae* antibodies; SAVI, STING-associated vasculitis of infancy; CANDLE, chronic atypical neutrophilic dermatosis lipodystrophy and elevated temperature.

Modified from de Graeff N, Groot N, Brogan P, et al. European consensus-based recommendations for the diagnosis and treatment of rare paediatric vasculitides – the SHARE initiative. *Rheumatology*. 2019;58(4):656–671, Table 1.

with a more severe initial course are at higher risk for relapse. The long-term prognosis usually depends on the severity and duration of GI or renal involvement. Chronic renal disease develops in 1–2% of children with HSP, and <5% of those with HSP nephritis go on to have ESRD. The risk of HSP recurrence and graft loss after renal transplantation is estimated at 7.5% after 10 years.

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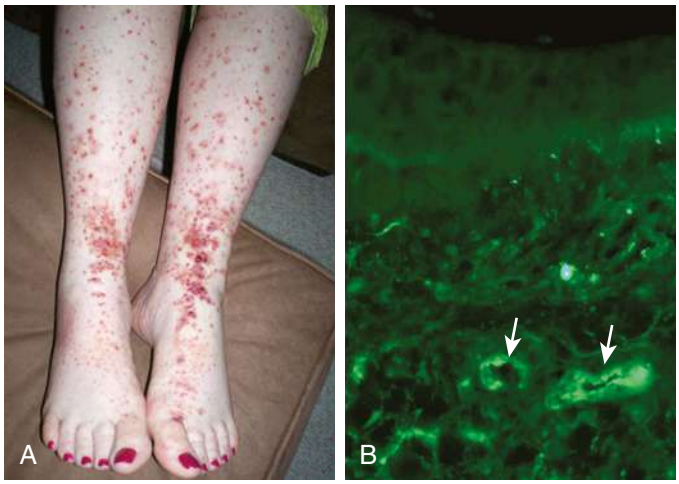

Fig. 210.2 Henoch-Schönlein purpura. **A,** Typical palpable purpura in lower extremities. **B,** Skin biopsy of lesion shows direct immunofluorescence of IgA *(arrows)* within the walls of dermal capillaries.

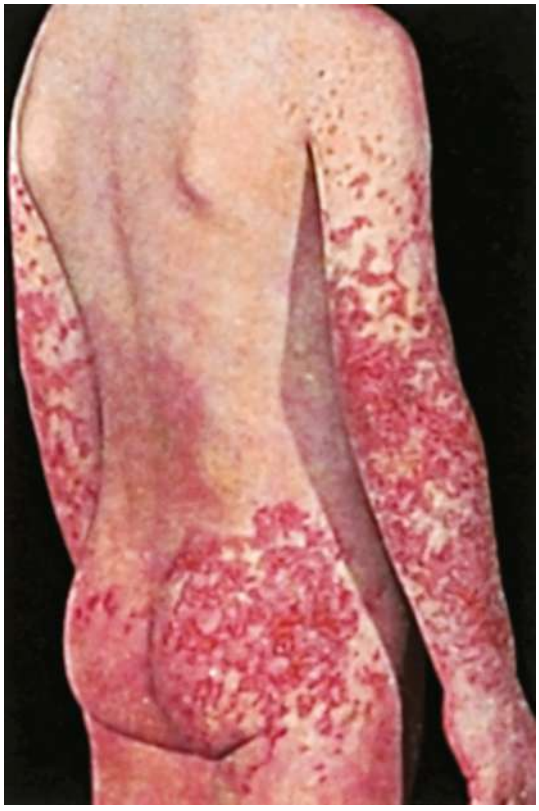

Fig. 210.3 Henoch-Schönlein purpura. *(From Korting GW. Hautkrankheiten bei Kindern und Jungendlichen, 3rd ed. Stuttgart: FK Schattaur Verlag; 1982.)*

Table 210.6 Classification Criteria for Henoch-Schönlein Purpura*

EUROPEAN LEAGUE AGAINST RHEUMATISM/PEDIATRIC RHEUMATOLOGY EUROPEAN SOCIETY CRITERIA†
Palpable purpura (in absence of coagulopathy or thrombocytopenia) and one or more of the following criteria must be present:
• Abdominal pain (acute, diffuse, colicky pain)
• Arthritis or arthralgia
• Biopsy of affected tissue demonstrating predominant IgA deposition
• Renal involvement (proteinuria >0.3 g/24 hr), hematuria, or red cell casts

*Classification criteria are developed for use in research and are not validated for clinical diagnosis.
†Developed for use in pediatric populations only.
Adapted from Ozen S, Pistorio A, Iusan SM, et al. EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II. Final classification criteria. *Ann Rheum Dis.* 2010;69:798–806.

Table 210.7 Conditions Associated with Leukocytoclastic Vasculitis

Immunoglobulin (Ig) A vasculitis (Henoch-Schönlein)
Hypersensitivity vasculitis
Hypocomplementemic urticarial vasculitis
Mixed cryoglobulinemia
Cutaneous polyarteritis
Antineutrophil cytoplasmic antibody (ANCA)–associated small-vessel vasculitis*
Goodpasture syndrome
Rheumatic disorders: systemic lupus erythematosus (SLE), juvenile dermatomyositis, mixed connective tissue disease (MCTD), scleroderma, juvenile idiopathic arthritis (JIA)
Mucha-Habermann disease
Relapsing polychondritis
Köhlmeier-Degos syndrome
Antiphospholipid antibody syndrome
Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome
Malignancy-associated disease
Sweet syndrome
Cronkhite-Canada syndrome
Stevens-Johnson syndrome
Erythema elevatum diutinum
COVID-19/MIS-C

*Leukocytoclastic vasculitis may occur in cutaneous lesions in some patients with ANCA-associated vasculitis and collagen vascular diseases.
Modified from Petty RE, Laxer RM, Lindsley CB, et al., eds. *Textbook of Pediatric Rheumatology,* 8th ed. Philadelphia: Elsevier; 2021: Box 33.1, p. 457.

210.2 Takayasu Arteritis

Vidya Sivaraman, Edward C. Fels, and Stacy P. Ardoin

Takayasu arteritis (TA), also known as *pulseless disease,* is a chronic large vessel vasculitis of unknown etiology that predominantly involves the aorta and its major branches.

EPIDEMIOLOGY

Although TA occurs worldwide and can affect all ethnic groups, the disease is most common in those of Asian descent. Age of onset is typically between 10 and 40 years. Most children are diagnosed as adolescents, on average at age 13 years. Up to 20% of individuals with TA are diagnosed before 19 years. Younger children may be affected, but diagnosis in infancy is rare. TA preferentially affects females, with a reported 2-4:1 female/male ratio in children and adolescents and a 9:1 ratio among adults. Occlusive complications are more common in the United States, Western Europe, and Japan, whereas aneurysms predominate in Southeast Asia and Africa.

PATHOLOGY

TA is characterized by inflammation of the vessel wall, starting in the vasa vasorum. Involved vessels are infiltrated by T cells, natural killer cells, plasma cells, and macrophages. Giant cells and granulomatous inflammation develop in the media. Persistent inflammation damages the elastic lamina and muscular media, leading to blood vessel

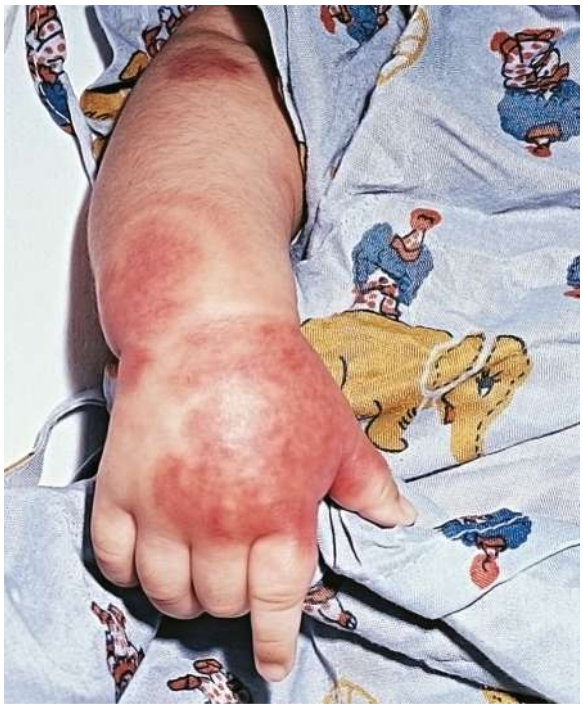

Fig. 210.4 Infantile acute hemorrhagic edema. Typical lesions on the arm of an infant. *(From Eichenfield LF, Frieden IJ, Esterly NB. Textbook of Neonatal Dermatology. Philadelphia: Saunders; 2001.)*

dilation and the formation of aneurysms. Progressive scarring and intimal proliferation can result in stenotic or occluded vessels. The subclavian, renal, and carotid arteries are the most commonly involved aortic branches; pulmonary, coronary, and vertebral arteries may also be affected.

PATHOGENESIS

The etiology of TA remains unknown. The presence of abundant T cells with a restricted repertoire of T-cell receptors in TA vascular lesions points to the importance of cellular immunity and suggests the existence of a specific but unknown aortic tissue antigen. Expression of interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α is reported to be higher in patients with active TA than in patients with inactive TA and in healthy controls. In some patient populations, IL-1 genetic polymorphisms are linked to TA. Some individuals with TA have elevated serum values of antiendothelial antibodies. The increased prevalence of TA in certain ethnic populations and its occasional occurrence in monozygotic twins and families suggest a genetic predisposition to the disease.

CLINICAL MANIFESTATIONS

The diagnosis of TA is challenging because early disease manifestations are often nonspecific. As a result, diagnosis can be delayed for several months, and the time to diagnosis is usually longer in children than in adults. Fever, malaise, weight loss, headache, hypertension, myalgias, arthralgias, dizziness, and abdominal pain are common early complaints in the *prepulseless* phase of the disease. Among children, hypertension and headache are particularly common presenting manifestations and should prompt consideration of TA when present without alternative explanation. Some individuals with TA report no systemic symptoms and instead present with vascular complications. It is only after substantial vascular injury that evidence of hypoperfusion becomes clinically evident. Later manifestations of disease include diminished pulse, asymmetric blood pressure, claudication, Raynaud phenomenon, renal failure, and symptoms of pulmonary or cardiac ischemia. Inflammation can extend to the aortic valve, resulting in valvular insufficiency. Other findings may include pericardial effusion, pericarditis, pleuritis, splenomegaly, and arthritis.

Supradiaphragmatic (aortic arch) disease often manifests with CNS (stroke, transient ischemic attack) and cardiac (heart failure, palpitations) symptoms. **Infradiaphragmatic** (midaortic syndrome) disease may produce hypertension, abdominal bruits, and pain. Most patients have involvement in both areas.

Table 210.8 Proposed Classification Criteria for Pediatric-Onset Takayasu Arteritis

Angiographic abnormalities (conventional, CT, or magnetic resonance angiography) of the aorta or its main branches and at least one of the following criteria:

- Decreased peripheral artery pulse(s) and/or claudication of extremities
- Blood pressure difference between arms or legs of >10 mm Hg
- Bruits over the aorta and/or its major branches
- Hypertension (defined by childhood normative data)
- Elevated acute-phase reactant (erythrocyte sedimentation rate or C-reactive protein)

Adapted from Ozen S, Pistorio A, Iusan SM, et al. EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II. Final classification criteria. *Ann Rheum Dis.* 2010;69:798–806.

DIAGNOSIS

Specific pediatric criteria for TA have been proposed (Table 210.8). The 2022 ACR/ EULAR classification criteria for Takayasu arteritis propose a criterion-based scoring system in adults (Table 210.9). *Radiographic demonstration of large vessel vasculitis is necessary*. A thorough physical examination is required to detect an aortic murmur, diminished or asymmetric pulses, and vascular bruits. Four extremity blood pressures should be measured; >10 mm Hg asymmetry in systolic pressure is indicative of disease.

DIFFERENTIAL DIAGNOSIS

In the early phase of TA, when nonspecific symptoms predominate, the differential diagnosis includes a wide array of systemic infections, autoimmune conditions, and malignancies. Although **giant cell arteritis**, also known as *temporal arteritis,* is a common large vessel vasculitis in older adults, this entity is rare in childhood. Noninflammatory conditions that can cause large vessel compromise include fibromuscular dysplasia, Marfan syndrome, and Ehlers-Danlos syndrome.

LABORATORY FINDINGS

The laboratory findings in TA are nonspecific, and there is no specific diagnostic laboratory test. ESR and CRP values are typically elevated, and other nonspecific markers of chronic inflammation may include leukocytosis, thrombocytosis, anemia of chronic inflammation, and hypergammaglobulinemia. Autoantibodies, including ANA and ANCA, are not useful in diagnosing TA except to help exclude other autoimmune diseases.

Radiographic assessment is essential to establish large vessel arterial involvement. Conventional arteriography of the aorta and major branches, including carotid, subclavian, pulmonary, renal, and mesenteric branches, can identify luminal defects, including dilation, aneurysms, and stenoses, even in smaller vessels such as the mesenteric arteries. Figure 210.5 shows a conventional arteriogram in a child with TA. Although not yet thoroughly validated in TA, magnetic resonance angiography (MRA) and computed tomographic angiography (CTA) also provide important information about vessel wall thickness and enhancement, although they may not image smaller vessels as well as conventional angiography. Positron emission tomography (PET) may detect vessel wall inflammation but has not been studied extensively. Ultrasound with duplex color flow Doppler imaging may identify vessel wall thickening and assesses arterial flow. Echocardiography is recommended to assess for aortic valvular

Table 210.9 2022 American College of Rheumatology/EULAR Classification Criteria for Takayasu Arteritis

Considerations when applying these criteria: • These classification criteria should be applied to classify the patient as having Takayasu arteritis when a diagnosis of medium-vessel or large-vessel vasculitis has been made. • Alternate diagnoses mimicking vasculitis should be excluded before applying the criteria.	
ABSOLUTE REQUIREMENTS	
Age ≤ 60 yr at time of diagnosis	
Evidence of vasculitis on imaging[1]	
ADDITIONAL CLINICAL CRITERIA	
Female sex	+1
Angina or ischemic cardiac pain	+2
Arm or leg claudication	+2
Vascular bruit[2]	+2
Reduced pulse in upper extemity[3]	+2
Carotid artery abnormality[4]	+2
Systolic blood pressure difference in arms ≥20 mm Hg	+1
ADDITIONAL IMAGING CRITERIA	
Number of affected arterial territories (select one)[5]	
One arterial territory	+1
Two arterial territories	+2
Three arterial territories	+3
Symmetric involvement of paired arteries[6]	+1
Abdominal aorta involvement with renal or mesenteric involvement[7]	+3
	*TOTAL:

*Sum the scores for 10 items, if present. A score of ≥ 5 points is needed for the classification of Takayasu arteritis.

[1]Evidence of vasculitis in the aorta or branch arteries must be confirmed by vascular imaging (e.g., computed tomographic/catheter-based/magnetic resonance angiography, ultrasonography, positron emission tomography).

[2]Bruit detected by auscultation of a large artery, including the aorta, carotid, subclavian, axillary, brachial, renal, or iliofemoral arteries.

[3]Reduction or absence of pulse by physical examination of the axillary, brachial, or radial arteries.

[4]Reduction or absence of pulse of the carotid artery or tenderness of the carotid artery.

[5]Number of arterial territories with luminal damage (e.g., stenosis, occlusion, or aneurysm) detected by angiography or ultrasonography from the following nine territories: thoracic aorta, abdominal aorta, mesenteric, left or right carotid, left or right subclavian, left or right renal arteries.

[6]Bilateral luminal damage (stenosis, occlusion, or aneurysm) detected by angiography or ultrasonography in any of the following paired vascular territories: carotid, subclavian, or renal arteries.

[7]Luminal damage (stenosis, occlusion, aneurysm) detected by angiography or ultrasonography involving the abdominal aorta and either the renal or mesenteric arteries.

From Grayson PC, Ponte C, Suppiah R, et al. 2022 American College of Rheumatology/EULAR classification criteria for Takayasu arteritis. Ann Rheum Dis. 2022;81(12):1654–1660. Fig. 1.

involvement. Serial vascular imaging is usually necessary to assess response to treatment and to detect progressive vascular damage.

TREATMENT

Glucocorticoids are the mainstay of therapy, typically starting with high doses (1-2 mg/kg/day of prednisone or methylprednisolone IV) followed by gradual dosage tapering. When TA progresses or recurs, steroid-sparing therapy is often required, usually involving methotrexate or azathioprine. *Cyclophosphamide* is reserved for severe or refractory disease. Results of small case series also suggest that *mycophenolate mofetil* or anti–TNF-α therapy may be beneficial in select patients. Anti–IL-6 therapy with tocilizumab has shown promising results in a small case series

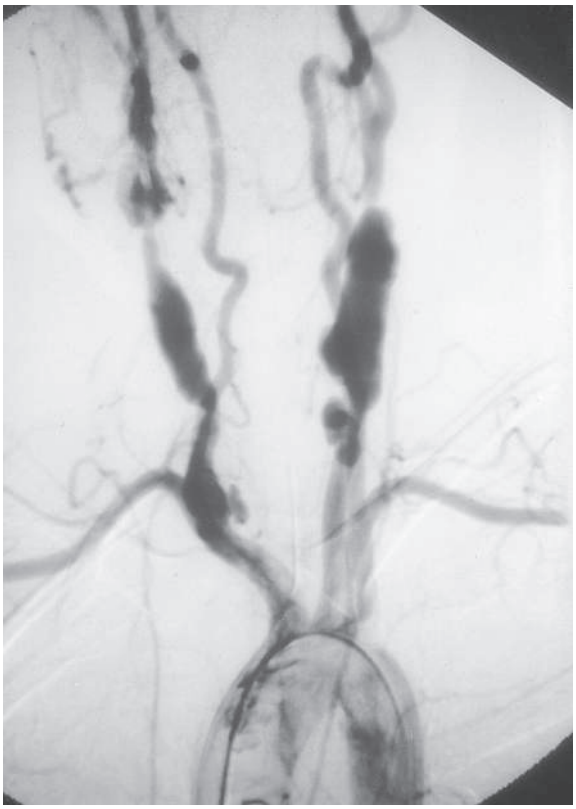

Fig. 210.5 Child with Takayasu arteritis. Conventional angiogram shows massive bilateral carotid dilation, stenosis, and poststenotic dilation.

of children with TA. Antihypertensive medications are often necessary to control blood pressure caused by renovascular disease.

COMPLICATIONS

Progressive vascular damage can result in arterial stenoses, aneurysms, and occlusions, which produce ischemic symptoms and can be organ or life threatening. Potential ischemic complications include stroke, renal impairment or failure, myocardial infarction, mesenteric ischemia, and limb-threatening arterial disease. When these complications occur or are imminent, intervention with *surgical* vascular grafting or catheter-based angioplasty and stent placement may be necessary to restore adequate blood flow. A high rate of recurrent stenosis has been reported after angioplasty and stent placement. Aortic valve replacement may be required if significant aortic insufficiency develops.

PROGNOSIS

Although up to 20% of individuals with TA have a monophasic course and achieve sustained remission, most suffer relapses. Survival for individuals with TA has improved considerably over the decades, although higher mortality rates are reported in children and adolescents. The overall estimated survival for individuals with TA is 93% at 5 years and 87% at 10 years. However, morbidity from vascular complications remains high, particularly when there is evidence of ongoing active inflammation as detected by elevated CRP or ESR. Given the chronic endothelial insult and inflammation, children and adolescents with TA are probably at high risk for accelerated atherosclerosis. Early detection and treatment are critical to optimizing outcomes in TA.

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210.3 Polyarteritis Nodosa and Cutaneous Polyarteritis Nodosa

Vidya Sivaraman, Edward C. Fels, and Stacy P. Ardoin

Polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis affecting small and medium-size arteries. Aneurysms and stenoses form at irregular intervals throughout affected arteries. Cutaneous PAN is limited to the skin.

EPIDEMIOLOGY

PAN is rare in childhood. Males and females are equally affected, and the mean age at presentation is 9 years. The cause is unknown, but the development of PAN after infections, including group A streptococcus and chronic hepatitis B, suggests that PAN may represent a postinfectious autoimmune response. Infections with other organisms, including Epstein-Barr virus, *Mycobacterium tuberculosis*, cytomegalovirus, parvovirus B19, and hepatitis C virus, have also been associated with PAN. There is a possible association between PAN and familial Mediterranean fever.

PATHOLOGY

Biopsies show **necrotizing vasculitis** with granulocytes and monocytes infiltrating the walls of small and medium-size arteries. Involvement is usually segmental and tends to occur at vessel bifurcations. Granulomatous inflammation is not present, and deposition of complement and immune complexes is rarely observed. Different stages of inflammation are found, ranging from mild inflammatory changes to panmural fibrinoid necrosis associated with aneurysm formation, thrombosis, and vascular occlusion.

PATHOGENESIS

Immune complexes are believed to be pathogenic, but the mechanism is poorly understood. It is not known why PAN has a predilection for small and medium-size blood vessels. The inflamed vessel wall becomes thickened and narrowed, impeding blood flow and contributing to end-organ damage characteristic of this disease. Although there is no clear genetic association with PAN, PAN-like vasculitis is a component of three recently described monogenic autoinflammatory conditions.

Deficiency in **adenosine deaminase 2 (DADA2)**, caused by mutations in the *CECR1* gene, causes a familial form of vasculitis with an autosomal recessive inheritance (see Chapter 204).

CLINICAL MANIFESTATIONS

The clinical presentation of PAN is variable but generally reflects the distribution of inflamed vessels. Constitutional symptoms are present in most children at disease onset. Weight loss and severe abdominal pain suggest mesenteric arterial inflammation and ischemia. Renovascular arteritis can cause hypertension, hematuria, or proteinuria, although glomerulonephritis is not typical. Cutaneous manifestations include purpura, livedo reticularis, ulcerations, digital ischemia, and painful nodules (Fig. 210.6). Arteritis affecting the nervous system can result in cerebrovascular accidents, transient ischemic attacks, psychosis, and ischemic motor or sensory peripheral neuropathy **(mononeuritis multiplex)**. Myocarditis or coronary arteritis can lead to heart failure and myocardial ischemia; pericarditis and arrhythmias have also been reported. Arthralgias, arthritis, or myalgias are frequently present. Less common symptoms include testicular pain that mimics testicular torsion, bone pain, and vision loss as a result of retinal arteritis. The pulmonary vasculature is usually spared in PAN.

DIAGNOSIS

The diagnosis of PAN requires demonstration of vessel involvement on biopsy or angiography (Table 210.10). Biopsy of cutaneous lesions shows small or medium vessel vasculitis. Kidney biopsy in patients with renal manifestations may show necrotizing arteritis. Electromyography in children with peripheral neuropathy identifies affected nerves, and sural nerve biopsy may reveal vasculitis. Conventional arteriography is the gold-standard diagnostic imaging study for PAN and reveals areas of aneurysmal dilation and segmental stenosis, the classic "beads on a string" appearance (Fig. 210.7). MRA and CTA, less invasive imaging alternatives, are gaining acceptance but may not be as effective in identifying small vessel disease or in younger children.

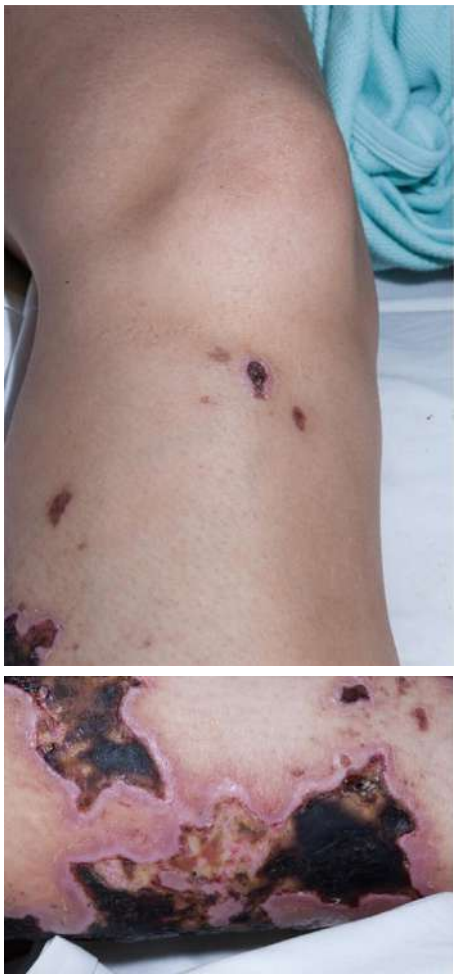

Fig. 210.6 Purpuric and necrotic lesions on the legs of a child with polyarteritis nodosa. *(From Petty RE, Laxer RM, Lindsley CB, et al., eds. Textbook of Pediatric Rheumatology, 8th ed. Philadelphia: Elsevier; 2021: Fig. 34.1, p. 468.)*

DIFFERENTIAL DIAGNOSIS

Early skin lesions may resemble those of HSP, although the finding of nodular lesions and the presence of systemic features help distinguish PAN. Because pulmonary vascular involvement is very rare in PAN, pulmonary lesions suggest ANCA-associated vasculitis or Goodpasture disease. Other rheumatic diseases, including SLE, have characteristic target-organ involvement and associated autoantibodies distinguishing them from PAN. Prolonged fever and weight loss should also prompt consideration of inflammatory bowel disease or malignancy.

Deficiency of DADA2 is a mimic of PAN and should be suspected in the presence of vasculitic rash (Fig. 210.8), hypogammaglobulinemia, cytopenias, and strokes. In addition, **SAVI** (STING-associated vasculopathy with onset in infancy) presents in infancy with ulcerating skin lesions that form eschars, cytopenias, interstitial lung disease, and failure to thrive (see Chapter 204).

LABORATORY FINDINGS

Nonspecific laboratory findings include elevations of ESR and CRP, anemia, leukocytosis, and hypergammaglobulinemia. Abnormal urine sediment, proteinuria, and hematuria indicate renal disease. Laboratory findings may be normal in cutaneous PAN or similar to those of systemic PAN. Elevated hepatic enzyme values may suggest hepatitis B or C infection. Serologic tests for hepatitis (hepatitis B surface antigen and hepatitis C antibody) should be performed in all patients.

Table 210.10 Proposed Classification Criteria for Pediatric-Onset Polyarteritis Nodosa*

CRITERION	FINDINGS
Histopathology	Necrotizing vasculitis in medium or small arteries
Angiographic abnormalities	Angiography showing aneurysm, stenosis, or occlusion of medium or small artery not from noninflammatory cause
Cutaneous findings	Livedo reticularis, tender subcutaneous nodules, superficial skin ulcers, deep skin ulcers, digital necrosis, nail bed infarctions, or splinter hemorrhages
Muscle involvement	Myalgia or muscle tenderness
Hypertension	Systolic or diastolic blood pressure >95th percentile for height
Peripheral neuropathy	Sensory peripheral neuropathy, motor mononeuritis multiplex
Renal involvement	Proteinuria (>300 mg/24 hr equivalent), hematuria or red blood cell casts, impaired renal function (glomerular filtration rate <50% normal)

*The presence of five criteria provides 89.6% sensitivity and 99.6% specificity for the diagnosis of childhood-onset polyarteritis nodosa.
Adapted from Ozen S, Pistorio A, Iusan SM, et al: EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II. Final classification criteria. *Ann Rheum Dis.* 2010;69:798–806.

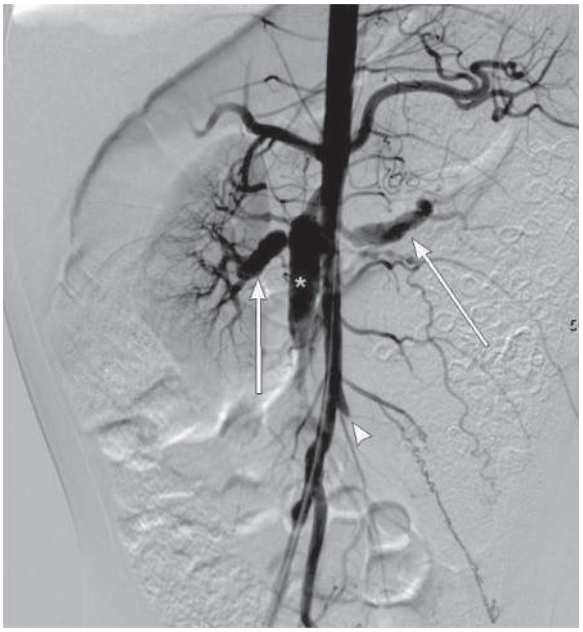

Fig. 210.7 Child with polyarteritis nodosa. Abdominal aortogram shows bilateral renal artery aneurysms *(arrows)*, superior mesenteric artery aneurysm *(asterisk)*, and left common iliac artery occlusion *(arrowhead)*. *(Courtesy Dr. M. Hogan.)*

TREATMENT

Oral *prednisone* (1-2 mg/kg/day) or IV pulse *methylprednisolone* (30 mg/kg/day) are the mainstay of therapy. Oral or IV cyclophosphamide is often used as adjunctive therapy, and plasma exchange may be warranted for life-threatening disease. If hepatitis B is identified, appropriate antiviral therapy should be initiated (see Chapter 406). Most cases of cutaneous PAN can be treated with less intense therapy such as corticosteroids alone, nonsteroidal antiinflammatory drugs (NSAIDs), and methotrexate. Azathioprine, mycophenolate mofetil, IVIG, thalidomide, cyclosporine, and anti-TNF agents such as infliximab have all been reported as successful in the treatment of refractory cutaneous or systemic PAN. If an infectious trigger for PAN is identified, antibiotic prophylaxis can be considered.

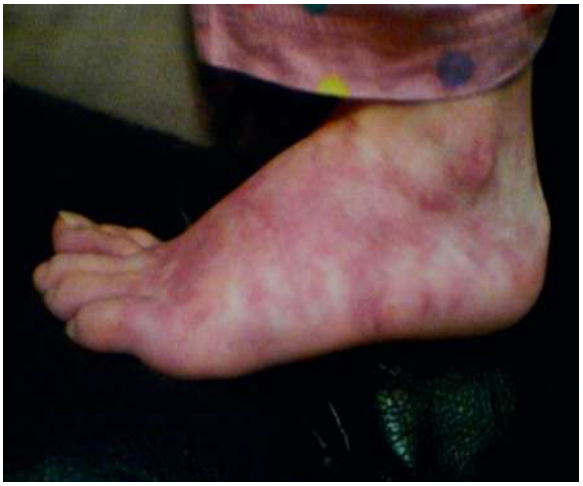

Fig. 201.8 Retiform purpura in a child with deficiency of adenosine deaminase type 2. *(From Petty RE, Laxer RM, Lindsley CB, et al., eds. Textbook of Pediatric Rheumatology, 8th ed. Philadelphia: Elsevier; 2021, Fig. 34.3, p. 469.)*

COMPLICATIONS

Cutaneous nodules may ulcerate and become infected. Hypertension and chronic renal disease may develop from renovascular involvement in PAN. Cardiac involvement may lead to decreased cardiac function or coronary artery disease. Mesenteric vasculitis can predispose to bowel infarction, rupture, and malabsorption. Stroke and rupture of hepatic arterial aneurysm are uncommon complications of this disorder.

PROGNOSIS

The course of PAN varies from mild disease with few complications to a severe, multiorgan disease with high morbidity and mortality. Poor prognostic factors in PAN include elevated serum creatinine, proteinuria, severe GI involvement, cardiomyopathy, and CNS involvement. Early and aggressive immunosuppressive therapy increases the likelihood of clinical remission. Compared with disease in adults, childhood PAN is associated with less mortality. Cutaneous PAN is unlikely to transition to systemic disease. Early recognition and treatment of the disease are important to minimizing potential long-term vascular complications.

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210.4 Antineutrophilic Cytoplasmic Antibody–Associated Vasculitis

Vidya Sivaraman, Edward C. Fels, and Stacy P. Ardoin

The ANCA-associated vasculitides are characterized by small vessel involvement, circulating ANCAs, and a paucity of immune complex deposition in affected tissues, thus the term **pauci-immune vasculitis**. ANCA-associated vasculitis is categorized into three distinct forms: **granulomatosis with polyangiitis (GPA)** (Table 210.11),

Table 210.11 2022 American College of Rheumatology/ EULAR Classification Criteria for Granulomatosis with Polyangiitis

Considerations when applying these criteria:
- These classification criteria should be applied to classify a patient as having granulomatosis with polyangiitis when a diagnosis of small-vessel or medium-vessel vasculitis has been made.
- Alternate diagnoses mimicking vasculitis should be excluded before applying the criteria.

CLINICAL CRITERIA	
Nasal involvement: bloody discharge, ulcers, crusting, congestion, blockage, or septal defect / perforation	+3
Cartilaginous involvement (inflammation of ear or nose cartilage, hoarse voice or stridor, endobronchial involvement, or saddle nose deformity	+2
Conductive or sensorineural hearing loss	+1
LABORATORY, IMAGING, AND BIOPSY CRITERIA	
Positive test for cytoplasmic antineutrophil cytoplasmic antibodies (cANCA) or antiproteinase 3 (anti-PR3) antibodies	+5
Pulmonary nodules, mass, or cavitation on chest imaging	+2
Granuloma, extravascular granulomatous inflammation, or giant cells on biopsy	+2
Inflammation, consolidation, or effusion of the nasal/ paranasal sinuses, or mastoiditis on imaging	+1
Pauci-immune glomerulonephritis on biopsy	+1
Positive test for perinuclear antineutrophil cytoplasmic antibodies (pANCA) or antimyeloperoxidase (anti-MPO) antibodies	–1
Blood eosinophil count ≥ 1×10^9/liter	–4
	*TOTAL:

*Sum the scores for 10 items, if present. A score of ≥ 5 points is needed for the classification of granulomatosis with polyangiitis.
From Robson JC, Grayson PC, Ponte C, et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for granulomatosis with polyangiitis. *Ann Rheum Dis*. 2022;81(3):315–320. Fig. 1.

Table 210.12 Presenting Manifestations (Reported as Percentages) in Children with Granulomatosis with Polyangiitis and Microscopic Polyangiitis from the ARChiVe Cohort (n = 231)

CLINICAL FEATURE	GPA (n = 183)	MPA (n = 48)
CONSTITUTIONAL/GENERAL	88	85
Malaise, fatigue	83	77
Fever	53	52
Weight loss	44	31
RENAL	83	75
Proteinuria	72	69
Hematuria	72	60
Biopsy proven glomerulonephritis	94 (101 of 108)	94 (30 of 32)
Elevated serum creatinine	54	58
PULMONARY	74	44
Hemoptysis/alveolar hemorrhage	42	15
Nodules	54	0
Fixed pulmonary infiltrates	36	0
Oxygen dependency	22	13
Pleurisy	14	8
Requiring ventilation	12	4
EAR, NOSE, THROAT	70	4
Nasal involvement	53	0
Sinusitis	39	0
Otitis/mastoiditis	17	0
Subglottic involvement	10	0
Hearing loss	10	0
Oral ulcers	15	4
MUSCULOSKELETAL	65	52
Arthralgia/arthritis	61*	42
Myalgia, muscle weakness, or myositis	14	19
CUTANEOUS	47	52
Palpable purpura/petechia	27	31
EYES	43	31
Nonspecific red eye	10	2
Conjunctivitis	11	6
Scleritis/episcleritis	8	4
GASTROINTESTINAL	36	58
Nonspecific abdominal pain	22	38
Chronic nausea	12	33
NERVOUS SYSTEM	20	21
Severe headache	11	13
Dizziness	7	4
CARDIOVASCULAR	5	6

*Arthralgias and arthritis at disease onset were not reported separately.
GPA, Granulomatosis with polyangiitis; MPA, microscopic polyangiitis.
From Petty RE, Laxer RM, Lindsley CB, et al., eds. *Textbook of Pediatric Rheumatology*, 8th ed. Philadelphia: Elsevier; 2021: Table 36.2, p. 487.

formerly Wegener granulomatosis; **microscopic polyangiitis (MPA)** (Table 210.12); and **eosinophilic granulomatosis with polyangiitis** (Table 210.13), formerly Churg-Strauss syndrome **(CSS)**. The 2022 ACR/ EULAR classification criteria for adults with GPA, MPA and EGPA employ a criterion-based scoring system for classification of these vasculitides.

EPIDEMIOLOGY

GPA is a necrotizing, granulomatous, small and medium vessel vasculitis that occurs at all ages and targets the upper and lower respiratory tracts and the kidneys. Most cases of GPA occur in adults; the disease also occurs in children with a mean age at diagnosis of 14 years. There is a female predominance of 3-4:1, and pediatric GPA is most prevalent in the White population.

MPA is a small vessel necrotizing vasculitis with clinical features similar to those of GPA, but without granulomas and upper airway involvement. CSS is a small vessel necrotizing granulomatous (allergic granulomatosis) vasculitis associated with a history of refractory asthma and peripheral eosinophilia. MPA and CSS are rare in children, and there does not appear to be a gender predilection in either disease.

PATHOLOGY

Necrotizing vasculitis is the cardinal histologic feature in both GPA and MPA. Kidney biopsies typically demonstrate crescentic glomerulonephritis with little or no immune complex deposition ("pauci-immune"), in contrast to biopsies from patients with SLE. Although granulomatous inflammation is common in GPA and CSS, it is typically not present in MPA. Biopsies showing perivascular eosinophilic infiltrates distinguish CSS from both MPA and GPA.

Table 210.13 American College of Rheumatology Criteria for Classification of Eosinophilic Granulomatosis with Polyangiitis Syndrome

CRITERION*	DESCRIPTION
Asthma	History of wheezing or diffuse high-pitched rales on expiration
Eosinophilia	Eosinophils >10% of differential white blood cell count
History of allergy	History of seasonal allergy (e.g., allergic rhinitis) or documented allergies, including food, contactants, and others (except for drug allergies)
Mononeuropathy or polyneuropathy	Mononeuropathy, multiple mononeuropathies or polyneuropathy (i.e., glove/stocking distribution) attributable to a systemic vasculitis
Pulmonary infiltrates	Migratory or transitory pulmonary infiltrates on radiographs attributable to a systemic vasculitis
Paranasal sinus abnormality	History of acute or chronic paranasal sinus pain or tenderness or radiographic opacification of the paranasal sinuses
Extravascular eosinophils	Biopsy including artery, arteriole, or venule, showing accumulation of eosinophils in extravascular areas

*For classification purposes, a patient is said to have EGPA if at least four of these criteria are present. The presence of any four or more criteria has a sensitivity of 85% and a specificity of 99.7%.

From Petty RE, Laxer RM, Lindsley CB, et al., eds. *Textbook of Pediatric Rheumatology,* 8th ed. Philadelphia: Elsevier; 2021, Fig. 36.7, p. 495.

PATHOGENESIS

The etiology of ANCA-associated vasculitis remains unknown, although neutrophils, monocytes, and endothelial cells are involved in disease pathogenesis. Neutrophils and monocytes are activated by ANCAs, specifically by the ANCA-associated antigens proteinase-3 (PR3) and myeloperoxidase (MPO), and release proinflammatory cytokines such as TNF-α and IL-8. Localization of these inflammatory cells to the endothelium results in vascular damage characteristic of the ANCA vasculitides. Why the respiratory tract and kidneys are preferential targets in GPA and MPA is unknown.

CLINICAL MANIFESTATIONS

The early disease course is characterized by nonspecific constitutional symptoms, including fever, malaise, weight loss, myalgias, and arthralgias. In GPA, upper airway involvement can manifest as sinusitis, nasal ulceration, epistaxis, otitis media, and hearing loss. Lower respiratory tract symptoms in GPA include cough, wheezing, dyspnea, and hemoptysis. Pulmonary hemorrhage can cause rapid respiratory failure. Compared with adults, childhood GPA is more frequently complicated by subglottic stenosis (Fig. 210.9). Inflammation-induced damage to the nasal cartilage can produce a saddle nose deformity (see Fig. 210.9). Ophthalmic involvement includes conjunctivitis, scleritis, uveitis, optic neuritis, and invasive orbital pseudotumor (causing proptosis). Perineural vasculitis or direct compression on nerves by granulomatous lesions can cause cranial and peripheral neuropathies. Hematuria, proteinuria, and hypertension in GPA signal renal disease. Cutaneous lesions include palpable purpura and ulcers. Venous thromboembolism is a rare but potentially fatal complication of GPA. The frequencies of organ system involvement throughout the disease course in GPA are as follows: respiratory tract, 74%; kidneys, 83%; joints, 65%; eyes, 43%; skin, 47%; sinuses, 70%; and nervous system, 20%. Table 210.11 lists the classification criteria for pediatric-onset GPA.

The clinical presentation of MPA closely resembles that of GPA, although sinus disease is less common; systemic features of fever, malaise, weight loss, myalgias, and arthralgias may be dominant. MPA predominantly affects the kidney and lungs; other organ systems include skin, CNS, muscle, heart, and eyes (see Table 210.12).

CSS frequently causes inflammation of the upper and lower respiratory tracts, but cartilage destruction is rare. CSS may initially demonstrate chronic or recurrent rhinitis/sinusitis, nasal polyposis, nonfixed pulmonary lesions, and difficult-to-treat asthma. Eosinophilia (>10% of leukocytes) with pulmonary infiltrates may precede a vasculitic phase. Other organ involvement includes skin, cardiac, peripheral neuropathy, GI tract, and muscle. Renal involvement in CSS is uncommon.

DIAGNOSIS

GPA should be considered in children who have recalcitrant sinusitis, pulmonary infiltrates, and evidence of nephritis. Chest radiography often fails to detect pulmonary lesions, and chest CT may show nodules, ground-glass opacities, mediastinal lymphadenopathy, and cavitary lesions (Fig. 210.10). The diagnosis is confirmed by the presence of c-ANCA with anti-PR3 specificity (PR3-ANCAs) and the finding of necrotizing granulomatous vasculitis on pulmonary, sinus, or renal biopsy. The ANCA test result is positive in approximately 90% of children with GPA, and the presence of anti-PR3 increases the specificity of the test.

In MPA, ANCAs are also frequently present (70% of patients) but are usually p-ANCA with reactivity to MPO (MPO-ANCAs). MPA can be distinguished from PAN by the presence of ANCAs and the tendency for small vessel involvement. The ANCA test result is positive in 50–70% of cases of CSS, and MPO-ANCAs are more common than PR3-ANCAs. In addition, the presence of chronic asthma and peripheral eosinophilia suggests the diagnosis of CSS.

DIFFERENTIAL DIAGNOSIS

ANCAs are absent in other granulomatous diseases, such as sarcoidosis and tuberculosis. **Goodpasture syndrome** is characterized by antibodies to glomerular basement membrane. Medications such as propylthiouracil, hydralazine, and minocycline are associated with drug-induced ANCA (usually perinuclear ANCA) vasculitis. SLE and HSP can manifest as pulmonary hemorrhage and nephritis.

LABORATORY FINDINGS

Nonspecific laboratory abnormalities include elevated ESR and CRP values, leukocytosis, and thrombocytosis, which are present in most patients with an ANCA-associated vasculitis but are nonspecific. Anemia may be caused by chronic inflammation or pulmonary hemorrhage. ANCA antibodies show two distinct immunofluorescence patterns: *perinuclear* (p-ANCA) and *cytoplasmic* (c-ANCA). In addition, ANCAs can be defined by their specificity for PR3 or MPO antigen. GPA is strongly associated with c-ANCAs/anti-PR3 antibodies, whereas 75% of patients with MPA have a positive p-ANCA. There is no clear correlation between ANCA titers and disease activity or relapse.

TREATMENT

When the lower respiratory tract or kidneys are significantly involved, initial induction therapy usually consists of prednisone (oral 2 mg/kg/day oral or IV methylprednisolone 30 mg/kg/day × 3 days) in conjunction with daily oral or monthly IV cyclophosphamide. *Rituximab,* a monoclonal antibody to CD20 on activated B cells, is an option for induction therapy in ANCA-positive vasculitides, although it has been studied primarily in adults. *Plasmapheresis* in conjunction with methylprednisolone has a role in the therapy of patients with severe disease manifestations such as pulmonary hemorrhage or ESRD, with the potential for reducing dialysis dependency. Patients are transitioned to a less toxic maintenance medication (usually methotrexate, azathioprine, or

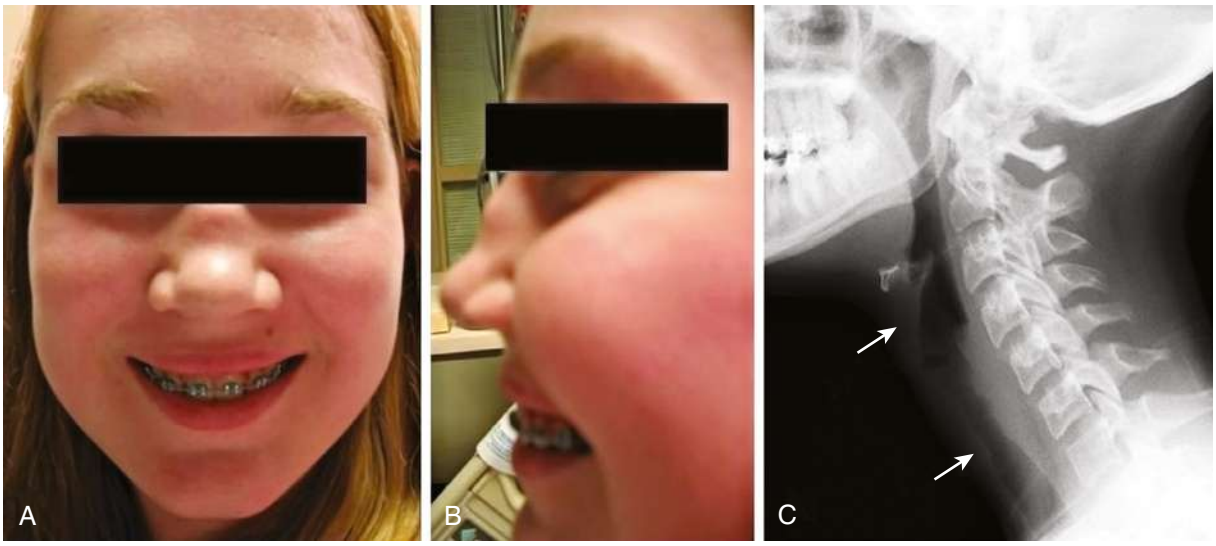

Fig. 210.9 Adolescent with granulomatosis with polyangiitis. **A** and **B**, Anterior and lateral views of saddle nose deformity. **C**, Segment of subglottic posterior tracheal irregularity (between *arrows*) on lateral neck radiograph.

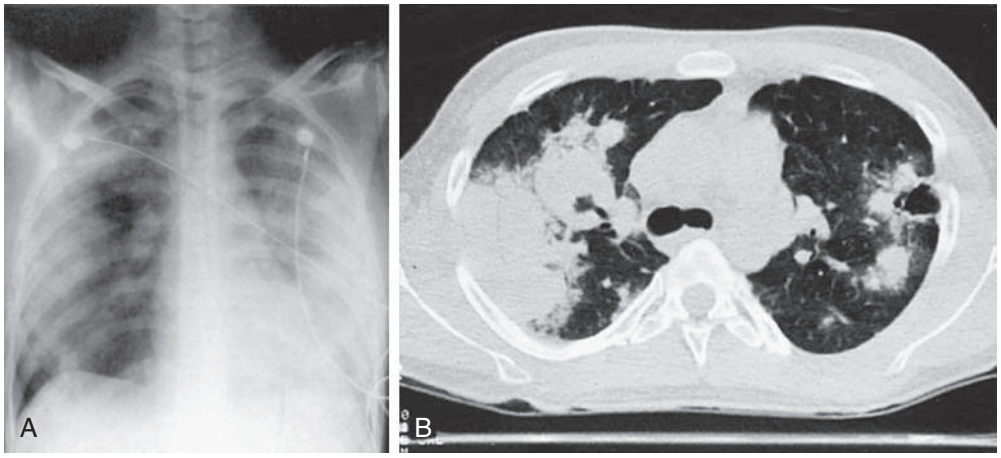

Fig. 210.10 Radiographs of lower respiratory tract disease in granulomatosis with polyangiitis (GPA). **A**, Chest radiograph of 14-yr-old girl with GPA and pulmonary hemorrhage. Extensive bilateral, fluffy infiltrates are visualized. **B**, Chest CT scan in 17-yr-old boy with GPA. Air space consolidation, septal thickening, and a single cavitary lesion are present. (**A** *from Cassidy JT, Petty RE. Granulomatous vasculitis, giant cell arteritis and sarcoidosis. In Textbook of Pediatric Rheumatology, 3rd ed. Philadelphia: Saunders; 1995;* **B** *from Kuhn JP, Slovis TL, Haller JO. Caffey's Pediatric Diagnostic Imaging, 10th ed. Philadelphia: Mosby; 2004.)*

mycophenolate mofetil) within 3-6 months once remission is achieved. The Childhood Arthritis and Rheumatology Research Alliance has published treatment guidelines for the induction and maintenance therapy of children with severe ANCA-associated vasculitides consisting of induction therapy with cyclophosphamide or rituximab and maintenance therapy with rituximab, methotrexate, or azathioprine. Trimethoprim-sulfamethoxazole (one 160 mg/800 mg tablet 3 days/week) is often prescribed both for prophylaxis against *Pneumocystis jirovecii* infection and to reduce upper respiratory bacterial colonization with *S. aureus*, which may trigger disease activity. If disease is limited to the upper respiratory tract, corticosteroids (1-2 mg/kg/day) and methotrexate (0.5-1.0 mg/kg/week) may be first-line treatment. *Avacopan*, a C5a receptor inhibitor, has been shown to be effective in reducing the need for corticosteroids in addition to standard therapy in adults with ANCA-associated vasculitis but has not been studied in children.

Mepolizumab, an anti–IL-5 monoclonal antibody, may have a role in the treatment of eosinophilic granulomatosis with polyangiitis (CSS).

COMPLICATIONS

Upper respiratory tract lesions can invade the orbit and threaten the optic nerve, and lesions in the ear can cause permanent hearing loss. Respiratory complications include potentially life-threatening pulmonary hemorrhage and upper airway obstruction caused by subglottic stenosis. Chronic lung disease secondary to granulomatous inflammation, cavitary lesions, and scarring can predispose to infectious complications. Chronic glomerulonephritis may progress to ESRD in a subset of patients with advanced or undertreated disease.

PROGNOSIS

The course is variable, but disease relapse occurs in up to 60% of patients. Mortality has been reduced with the introduction of cyclophosphamide and other immunosuppressive agents. Compared with adults, children are more likely to develop multiorgan involvement, renal involvement, and subglottic stenosis.

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210.5 Other Vasculitis Syndromes: Hypersensitivity, CNS, and COVID-19 Related

Vidya Sivaraman, Edward C. Fels, and Stacy P. Ardoin

Other vasculitic conditions can occur in childhood; the most common is **Kawasaki disease** (see Chapter 208). **Behçet disease** is a rare form of vasculitis seen in children of Turkish and Mediterranean descent, characterized by the triad of recurrent aphthous stomatitis, genital ulcers, and uveitis (see Chapter 202).

Hypersensitivity vasculitis is a cutaneous vasculitis triggered by medication or toxin exposure. The rash consists of palpable purpura or other nonspecific rash. Skin biopsies reveal characteristic changes of **leukocytoclastic vasculitis** (small vessels with neutrophilic perivascular or extravascular neutrophilic infiltration) (Table 210.14). **Hypocomplementemic urticarial vasculitis** involves small vessels and manifests as recurrent urticaria that resolves over several days but leaves residual hyperpigmentation. This condition is associated with low levels of complement component C1q and systemic findings that include fever, GI symptoms, arthritis, and glomerulonephritis. Some patients with urticarial vasculitis have normal complement levels. **Cryoglobulinemic vasculitis** can complicate mixed essential cryoglobulinemia and is a small vessel vasculitis affecting skin, joints, kidneys, and lungs.

Primary angiitis of the central nervous system represents vasculitis confined to the CNS and requires exclusion of other systemic vasculitides. **Large vessel disease** (angiography positive) may be progressive or nonprogressive and may manifest with focal deficits similar to an occlusive stroke, with hemiparesis, focal gross or fine motor deficits, language disorders, or cranial nerve deficits. Diffuse cognitive, memory, and concentration deficits and behavioral disorders are seen in 30–40% of patients. **Small vessel disease** (angiography negative, biopsy positive) more often results in language problems and diffuse deficits, such as cognitive, memory, behavior, and concentration problems, as well as focal seizures. In both types of cerebral angiitis, patients may have an elevated ESR or CRP and abnormal CSF findings (increased protein, pleocytosis), although these are not consistent findings in all patients. Diagnosis remains a challenge, and brain biopsy is often indicated to confirm the diagnosis and exclude vasculitis mimics such as infections that could worsen with immunosuppressive therapy (Table 210.15).

Table 210.14 Criteria for Diagnosis of Hypersensitivity Vasculitis*

CRITERION	DEFINITION
Age at onset >16yr	Development of symptoms after 16yr of age
Medication at disease onset	Medication that may have been a precipitating factor was taken at the onset of symptoms
Palpable purpura	Slightly elevated purpuric rash over one or more areas; does not blanch with pressure and is not related to thrombocytopenia
Maculopapular rash	Flat and raised lesions of various sizes over one or more areas of the skin
Biopsy, including arteriole and venule	Histologic changes showing granulocytes in a perivascular or extravascular location

*For purposes of classification, a patient is said to have hypersensitivity vasculitis if at least three of these criteria are present. The presence of three or more criteria has a diagnostic sensitivity of 71.0% and specificity of 83.9%. The age criterion is not applicable for children.

Adapted from Calabrese LH, Michel BA, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of hypersensitivity vasculitis. *Arthritis Rheum.* 1990;33:1108–1113, Table 2, p. 1110; and Petty RE, Laxer RM, Lindsley CB, Wedderburn LR. *Textbook of Pediatric Rheumatology,* 7th ed. Philadelphia: Saunders; 2016: Table 38.2, p. 511.

Table 210.15 Differential Diagnosis of Small Vessel Primary Central Nervous System (CNS) Vasculitis in Children

CNS VASCULITIS COMPLICATING OTHER DISEASES

Infections

- Bacterial: *Mycobacterium tuberculosis, Mycoplasma pneumoniae, Streptococcus pneumoniae*
- Viral: Epstein-Barr virus, cytomegalovirus, enterovirus, varicella-zoster virus, hepatitis C virus, parvovirus B19, West Nile virus
- Fungal: *Candida albicans, Actinomyces, Aspergillus*
- Spirochetal: *Borrelia burgdorferi, Treponema pallidum*

Rheumatic and Inflammatory Diseases

- Systemic vasculitis such as granulomatosis with polyangiitis, microscopic polyangiitis, Henoch-Schönlein purpura, Kawasaki disease, polyarteritis nodosa, Behçet disease
- Systemic lupus erythematosus, juvenile dermatomyositis, morphea
- Inflammatory bowel disease
- Autoinflammatory syndromes
- Hemophagocytic lymphohistiocytosis
- Neurosarcoidosis
- Adenosine deaminase-2 deficiency

Other

- Drug-induced vasculitis
- Malignancy-associated vasculitis

NONVASCULITIS INFLAMMATORY BRAIN DISEASES

Demyelinating Diseases

- Multiple sclerosis, acute demyelinating encephalomyelitis (ADEM), optic neuritis, transverse myelitis

Antibody-Mediated Inflammatory Brain Disease

- Anti–NMDA receptor encephalitis, neuromyelitis optica (NMO), antibody-associated limbic encephalitis (antibodies against LGI, AMP, AMP-binding protein), Hashimoto encephalopathy, celiac disease, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)

T-Cell–Associated Inflammatory Brain Disease

- Rasmussen encephalitis

Other

- Febrile infection-related epilepsy syndrome (FIRES)

NONINFLAMMATORY VASCULOPATHIES

- Hemoglobinopathies (sickle cell disease), thromboembolic disease
- Radiation vasculopathy, graft versus host disease
- Metabolic and genetic diseases such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), mitochondrial encephalopathy lactic acidosis and strokelike episodes (MELAS), cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL), Moyamoya disease, Fabry disease
- Malignancy (lymphoma)

Modified from Gowdie P, Twilt M, Benseler SM. Primary and secondary central nervous system vasculitis. *J Child Neurol.* 2012;27:1448–1459.

Table 210.16 Diagnostic Considerations for Other Vasculitis Syndromes

VASCULITIS SYNDROME	APPROACH TO DIAGNOSIS
Hypersensitivity vasculitis	Skin biopsy demonstrating leukocytoclastic vasculitis
Hypocomplementemic urticarial vasculitis	Biopsy of affected tissue demonstrating small vessel vasculitis Low levels of circulating C1q
Cryoglobulinemic vasculitis	Biopsy of affected tissue demonstrating small vessel vasculitis Measurement of serum cryoglobulins Exclusion of hepatitides B and C infections
Primary angiitis of CNS	Conventional, CT, or MRA evidence of CNS vasculitis Consideration of dura or brain biopsy
Nonprogressive angiography-positive CNS vasculitis	Conventional, CT, or MRA evidence of CNS vasculitis
Cogan syndrome	Ophthalmology and audiology evaluations Conventional, CT, or MRA evidence of CNS or aortic vasculitis

Table 210.17 Acral and Nonacral Potential Cutaneous Manifestations of Pediatric COVID-19

ACRAL	NONACRAL
Pernio-like lesions	Urticaria
EM-like lesions	Erythematous patches
Plantar papules	EM-like lesions
Retiform purpura	Vesicles/papulovesicles
Ecchymotic-like lesions	Herpetiform oral eruption
Livedo reticularis	Roseola-like rash
	Maculopapular rash
	Macular eruption
	Lingual papillitis
	Eccrine hidradenitis
	Erythema nodosum
	Petechiae
	Purpura

Modified from Neale H, Hawryluk EB. COVID-19 pediatric dermatology. *Dermatol Clin.* 2021;39:505–519, Table 4, p. 513.

Nonprogressive angiography-positive CNS vasculitis, also known as *transient CNS angiopathy,* represents a more benign variant and can be seen after varicella infection. **Cogan syndrome** is rare in children; its potential clinical manifestations include constitutional symptoms; inflammatory eye disease such as uveitis, episcleritis, or interstitial keratitis; vestibuloauditory dysfunction (vertigo, hearing loss, tinnitus); arthritis; and large vessel vasculitis or aortitis. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy **(CADASIL)** is caused by pathogenic variants in the *NOTCH3* gene and manifests with stroke, mood changes, cognitive decline, and migraines; it is a vasculitis mimic and demonstrates osmophilic granules in cerebral arteries. Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (**CARASIL**) is another mimic of angiitis caused by pathogenic variants in the *HTRA1* gene. It manifests with early-onset hair loss, spasticity, stroke, memory loss, and personality changes.

Identification of these vasculitis syndromes requires a comprehensive history and physical examination. Table 210.16 outlines other diagnostic considerations. Although tailored to disease severity, treatment generally includes prednisone (up to 2 mg/kg/day). Potent immunosuppressive medications, such as cyclophosphamide, are often indicated, particularly in primary angiitis of the CNS to prevent rapid neurologic decline. For hypersensitivity vasculitis, withdrawal of the triggering medication or toxin is indicated if possible.

COVID-19, including multisystem inflammatory syndrome in children (**MIS-C**), has been associated with a variety of cutaneous lesions that resemble vasculitis, vasculopathy, and vasoocclusive etiologies (see Chapter 311) (Table 210.17, Fig. 210.11). Lesions include pernio (chilblain: COVID toes)–like lesions suggestive of a vasculitis. Other cutaneous manifestations include urticarial vasculitis and livedo reticularis–like or livedo racemosa—both resemble a pauci-inflammatory occlusive vasculitis. Sweet syndrome and erythema multiforme–like lesions have also been described. Most cutaneous lesions associated with known COVID-19 or MIS-C do not require a biopsy, but some of those that were biopsied have demonstrated a leukocytoclastic vasculitis.

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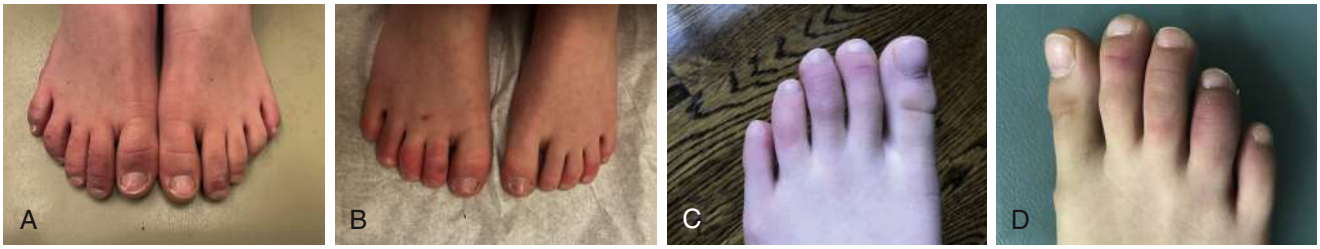

Fig. 210.11 Pernio-like lesions in children. **A,** A child with purpuric papules on the first, second, fourth, and fifth right digits and second proximal left digit. **B,** Digits on the same child appearing with increased erythema. **C,** Right toes of a child appearing with pink and dusky papules and plaques, also involving the child's left digits **(D)**. *(From Neale H, Hawryluk EB. COVID-19 pediatric dermatology. Dermatol Clin. 2021;39:505–519, Fig. 3, p. 511.)*

Chapter 211

Musculoskeletal Pain Syndromes

James J. Nocton

Musculoskeletal pain is a frequent reason for children to visit a healthcare provider and is the most common problem referred to pediatric rheumatology clinics. Prevalence estimates of persistent musculoskeletal pain in community samples range from 10% to 40%. Although inflammatory diseases such as juvenile idiopathic arthritis (JIA) and systemic lupus erythematosus (SLE) are associated with musculoskeletal pain, noninflammatory conditions such as trauma, hypermobility, overuse, and **idiopathic pain syndromes** are much more common causes of musculoskeletal pain in children.

CLINICAL MANIFESTATIONS

Acute and subacute musculoskeletal pain in children is most commonly the result of trauma, overuse, hypermobility, or some combination of these. The history and physical findings of trauma are most often readily apparent, and the pain associated with overuse or hypermobility is most often described as related to activities and improving with rest. The physical examination of children with pain related to overuse, hypermobility, and other mechanical causes of pain does not reveal signs of inflammation such as warmth, swelling, or limited range of motion and most often reveals hypermobility with perhaps mild tenderness over tendons and their insertion points.

Chronic idiopathic musculoskeletal pain syndromes are defined by pain of at least 3 months duration in the absence of objective abnormalities on physical examination or laboratory screening (see Chapter 212). The prevalence of chronic idiopathic musculoskeletal pain syndromes increases with age and is higher in females. These syndromes often persist despite treatment with nonsteroidal antiinflammatory drugs (NSAIDs) and other analgesics. Chronic pain may occur anywhere and is most often diffuse and poorly localized, but may sometimes involve only a single extremity or part of an extremity. Pain may start in one location before potentially developing in other areas over time.

Psychologic and emotional distress, including anxiety, depression, stress, or a combination of these, is quite common in those with chronic idiopathic musculoskeletal pain syndromes. Frequent crying, school and social stress, poor concentration, and excessive worry are often described. Sleep disturbance in children with chronic pain syndromes may include difficulty falling asleep, multiple night awakenings, disrupted sleep-wake cycles with increased daytime sleeping, nonrestorative sleep, and fatigue.

Children who are high achievers, excellent students, mature, and responsible, with high expectations of themselves have a predisposition to the development of pain syndromes in general, including chronic musculoskeletal pain. As a result, headaches and abdominal pain or other gastrointestinal symptoms are also frequently present in those with chronic idiopathic musculoskeletal pain syndromes.

The constellation of chronic pain, psychologic distress, and sleep disturbance often leads to a high degree of functional impairment. Poor school attendance is common, and children may struggle to complete other daily activities relating to self-care and participation in household chores. Decreased physical fitness can also occur, along with changes in gait and posture, as children avoid the use of the area affected by pain. Peer relationships may also be disrupted by decreased opportunities for social interaction because of pain. Loneliness and social isolation characterized by few friends and lack of participation in extracurricular activities are common.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of a musculoskeletal pain syndrome is based primarily on history and physical examination. Children with pain require a thorough clinical history, including a complete social history and review of systems, and a careful, comprehensive physical examination. The specific characteristics of the pain should be defined, evidence of potential systemic disease should be sought, and any additional associated symptoms and signs should be elicited.

The need for laboratory testing and imaging studies should be individualized, depending on the information elicited in the history and discovered with the physical examination. Possible indicators of an inflammatory cause for musculoskeletal pain include objective joint warmth, swelling, limited range of joint motion on physical examination, localized bone tenderness, and muscle weakness; potential indicators of a systemic disease include poor linear growth, weight loss, and constitutional symptoms. The lack of these symptoms and objective abnormalities on physical examination is more suggestive of a noninflammatory cause for pain (Table 211.1). The complete blood count (CBC) and erythrocyte sedimentation rate (ESR) are often abnormal in children whose pain is secondary to a bone or joint infection, rheumatic disease, or a malignancy. Bone tumors, fractures, and other focal pathology resulting from infection, malignancy, or trauma can often be identified through imaging studies, including plain radiographs or MRI.

The presence of chronic, persistent pain, accompanied by psychologic distress, sleep disturbance, and/or functional impairment, in the absence of objective laboratory or physical examination abnormalities, suggests the diagnosis of an **idiopathic musculoskeletal pain syndrome**. Table 211.2 outlines common causes of pediatric musculoskeletal pain according to anatomic location, including **growing pains** (see Chapter 211.1), diffuse **amplified pain syndromes** and chronic widespread pain (see Chapter 211.3), **complex regional pain syndrome** (see Chapter 211.4), localized pain syndromes, low back pain, and chronic overuse-related pain (e.g., Osgood-Schlatter disease). A differential diagnosis of more serious conditions is noted in Table 211.3.

TREATMENT

The primary goal of treatment for acute and subacute musculoskeletal pain related to trauma, hypermobility, overuse, or other mechanical factors is to minimize the discomfort as much as possible and to promote normal activities. Rest, topical analgesics, mechanical joint support to be worn with activities, ice, oral analgesics, and physical therapy may all be used. Education of children and families regarding pain related to these mechanical factors is critical in helping them to understand what to expect. Although it is common for the discomfort related to hypermobility and overuse to be recurrent, the prognosis for these mechanical pains is excellent, and most children learn to manage their discomfort with few, if any, restrictions on activities.

The primary goal of treatment of chronic idiopathic musculoskeletal pain syndromes is to improve function and relieve pain; these outcomes may not occur simultaneously or quickly. Pain may persist even as children resume normal function (e.g., increased school attendance and participation in extracurricular activities). For all children and adolescents with pediatric musculoskeletal pain syndromes whose school attendance has been affected by their symptoms, regular school attendance is a primary initial goal. The dual nature of treatment, targeting both *function* and *pain,* needs to be clearly explained. Children and families need to be supported in disengaging from the sole pursuit of pain relief and embracing the equally imperative goal of improved functioning.

Recommended treatment modalities include physical and/or occupational therapy, pharmacologic interventions, and cognitive-behavioral and/or other psychotherapeutic interventions. The overarching goal of **physical therapy** is to improve children's physical function and should emphasize participation in aggressive but graduated aerobic exercise. **Pharmacologic** interventions should be used judiciously. Low-dose

Table 211.1 Potential Indicators of Inflammatory vs Noninflammatory Causes of Musculoskeletal Pain

CLINICAL FINDING	NONINFLAMMATORY	INFLAMMATORY
Effects of rest vs activity on pain	Relieved by rest and worsened by activity	Present at rest and may be relieved by activity
Time of day pain and/or stiffness occurs	End of the day and nights	Morning*
Objective joint swelling	No	Yes
Joint characteristics	Hypermobile/normal	Stiffness, limited range of motion
Bone tenderness	No	Possible
Muscle strength	Normal	Possible weakness
Gait	Normal	Limp
Growth	Normal growth pattern or weight gain	Poor growth and/or weight loss
Constitutional symptoms	Fatigue without other constitutional symptoms	Possible
Laboratory findings	Normal CBC, ESR, CRP	Abnormal CBC, raised ESR and CRP
Imaging findings	Normal	Effusion, osteopenia, radiolucent metaphyseal lines, joint space loss, bone destruction

*Cancer pain is often severe and worst at night.
CBC, Complete blood count; CRP, C-reactive protein level; ESR, erythrocyte sedimentation rate.
Data from Malleson PN, Beauchamp RD. Diagnosing musculoskeletal pain in children. *CMAJ* 2001;165:183–188.

Table 211.2 Common Musculoskeletal Pain Syndromes in Children by Anatomic Region

ANATOMIC REGION	PAIN SYNDROMES
Shoulder	Impingement syndrome
Elbow	"Little League elbow" Avulsion fractures Osteochondritis dissecans Tennis elbow Panner disease
Arm	Localized hypermobility syndrome Complex regional pain syndrome
Pelvis and hip	Avulsion injuries Legg-Calvé-Perthes syndrome Slipped capital femoral epiphysis Congenital hip dysplasia
Knee	Osteochondritis dissecans Osgood-Schlatter disease Sinding-Larsen syndrome Patellofemoral syndrome Malalignment syndromes
Leg	Growing pains Complex regional pain syndrome Localized hypermobility syndrome Shin splints Stress fractures Compartment syndromes
Foot	Plantar fasciitis Tarsal coalition Stress fractures Achilles tendonitis Juvenile bunion
Spine	Musculoskeletal strain Spondylolisthesis Spondylolysis Scoliosis Scheuermann disease (kyphosis) Low back pain
Generalized	Hypermobility syndrome Diffuse amplified pain syndrome Chronic widespread pain

Adapted from Anthony KK, Schanberg LE. Assessment and management of pain syndromes and arthritis pain in children and adolescents. *Rheum Dis Clin North Am.* 2007;33:625–660, Box 1.

tricyclic antidepressants (amitriptyline 0.1 mg/kg at bedtime; can increase to 0.5 to 2 mg/kg as tolerated) may improve sleep; selective serotonin reuptake inhibitors (sertraline 25-100 mg daily) may help to alleviate symptoms of depression and anxiety if present. **Cognitive-behavioral therapy (CBT)** and/or other psychotherapeutic interventions are designed to teach children and adolescents coping skills for controlling the behavioral, cognitive, and physiologic responses to pain. Specific components often include cognitive restructuring, relaxation, distraction, and problem-solving skills. Parent education and involvement in the psychologic intervention are important to ensure maintenance of progress. More intensive family-based approaches are warranted if barriers to treatment success are identified at the family level. These could include parenting strategies or family dynamics that serve to maintain children's pain complaints, such as overly solicitous responses to the child's pain and maladaptive models for coping with pain.

COMPLICATIONS AND PROGNOSIS

Musculoskeletal pain related to hypermobility and/or overuse may be recurrent and related to specific activities, but is typically mild, does not usually significantly limit activities, and is most often managed symptomatically. Conversely, chronic idiopathic musculoskeletal pain syndromes have a much greater potential to negatively affect development and future role functioning. Worsening pain and the symptoms of depression and anxiety associated with chronic pain can lead to substantial school absences, peer isolation, and developmental delays later in adolescence and early adulthood. Specifically, adolescents with chronic idiopathic musculoskeletal pain syndromes may fail to achieve the level of autonomy and independence necessary for age-appropriate activities, such as attending college, living away from home, and maintaining a job. Fortunately, not all children and adolescents with these syndromes experience this degree of impairment. Factors that contribute to the persistence of pain are increasingly understood and include female gender, pubertal stage at pain onset, older age of pain onset, increased psychologic distress associated with the pain, and greater functional impairment. The likelihood of positive health outcomes is increased with multidisciplinary treatment addressing the pain, the functional disabilities, and the psychologic comorbidities associated with pain.

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Table 211.3 Differential Diagnosis of Idiopathic Musculoskeletal Pain Syndrome

CHANNELOPATHIES
Erythromelalgia: primary (associated with the *SCN9A* gene) or secondary
Paroxysmal extreme pain disorder (*SCN9A* gene)
Small fiber neuropathy (*SCN9A, SCN1OA* genes)
Familial episodic pain syndrome (*SCN11A, TRPA1* genes)
CONNECTIVE TISSUE DISORDERS
Ehlers-Danlos syndrome
Marfan syndrome
IMMUNE/AUTOIMMUNE
Systemic lupus erythematosus
Sarcoidosis
Juvenile idiopathic arthritis
Sjögren syndrome
Familial Mediterranean fever and other autoinflammatory recurrent fever syndromes
Hereditary angioedema
Chronic nonbacterial osteomyelitis
Mononeuritis multiplex associated with vasculitis
METABOLIC/NUTRITION
Fabry disease
Gaucher disease
Porphyria
Mitochondrial neuropathies
Vitamin deficiency (thiamine, B_{12}, C, D)
X-linked adrenoleukodystrophy
OTHER
Guillain-Barré syndrome
Multiple sclerosis
Toxic: lead, arsenic, chemotherapy
HIV
Familial amyloid neuropathy
Complex regional pain syndrome types 1 and 2
Sickle cell anemia
Thalamic stroke
Primary, metastatic, or recurrent malignancy (acute lymphocytic leukemia, neuroblastoma)
Neurofibromatosis
Radiculopathy
Nerve entrapment syndromes
1. Peroneal
2. Suprascapular
3. Anterior, posterior hip
4. Anterior cutaneous nerve (abdominal)

From Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis,* 2nd ed. Philadelphia: Elsevier; 2023: Table 33.2, p. 547.

211.1 Growing Pains (Benign Limb Pain of Childhood)

James J. Nocton

The cause of benign limb pain of childhood, historically referred to as **growing pains**, is unknown. Low pain threshold, overuse, and behavioral causes have been postulated, and it is possible that there are multiple causes for these pains. This pain affects 10–20% of children, with peak incidence between age 4 and 12 years. Benign limb pains of childhood are intermittent and usually bilateral, poorly localized, and predominantly affecting the anterior thigh, shin, and calf. Occasionally, bilateral upper extremity pain may be associated with leg pain. Children typically describe cramping or aching that occurs most often in the late afternoon or evening. Pain may wake the child from sleep, may be severe, and may last a few minutes to hours, but typically resolves quickly with massage or analgesics; pain is nearly always resolved by the following morning (Table 211.4). Pain may often follow a day with increased or excessive physical activity. Physical examination is normal, and gait is not impaired.

Treatment should focus on reassurance, education, and healthy sleep hygiene while preparing parents and children for the possibility that the pain may occur intermittently for years, with eventual resolution. Massage, acetaminophen, or NSAIDs during the episode are nearly always effective.

Restless legs syndrome (RLS), seen more frequently among adolescents and adults, is a sensorimotor disturbance that may be confused with growing pains (see Chapter 31). Often familial, RLS is a difficult-to-control *urge* to move the leg that is exacerbated during rest and at night and is relieved by movement (see Table 211.4). There is significant overlap in the diagnostic features of growing pains and RLS. Moreover, these conditions can be comorbid, and there is a high incidence of RLS in the parents of children with growing pains. RLS appears to be best distinguished from growing pains by the *urge* to move the legs, associated uncomfortable leg sensations that may not be described as painful; worsening with periods of rest; and relief through movement. Iron supplementation may benefit pediatric patients with RLS.

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211.2 Small Fiber Polyneuropathy

James J. Nocton

Some patients with juvenile-onset widespread pain syndromes have evidence of a small fiber polyneuropathy causing dysfunctional or degeneration of small-diameter unmyelinated C fibers and thinly myelinated A delta fibers that mediate nociception and the autonomic nervous system. In addition to pain, these children may have dizziness, postural orthostatic tachycardia syndrome (POTS), constipation and/or gastrointestinal dysmotility, and other symptoms suggestive of dysautonomia (Fig. 211.1).

The diagnosis of small fiber polyneuropathy requires distal leg immunolabeled skin biopsy to identify epidermal nociceptive fibers and autonomic function testing to examine cardiovagal, adrenergic, and sudomotor small fiber function. Genetic testing for pathogenic variants in genes coding for sodium channels may reveal *SCN9A, SCN10A,* or *SCN11A* variants. Some small studies have reported the presence of autoantibodies to trisulfated disaccharide and fibroblast growth factor receptor 3, suggestive of immune-mediated pathogenesis. Other potential etiologies for small fiber neuropathy are noted in Table 211.5; most cases are idiopathic. In addition, other genetic painful neuropathies should be considered (Table 211.6).

Optimal treatment of patients with small fiber polyneuropathy is unknown. Corticosteroids and intravenous immune globulin have been effective in very small numbers of patients.

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211.3 Diffuse Amplified Pain Syndromes

James J. Nocton

Diffuse amplified pain syndrome is more common in children than localized amplified pain. In addition to widespread pain, children frequently have associated chronic fatigue, sleep disturbance, headaches, chronic abdominal pain and gastrointestinal symptoms, stress, anxiety, and/or symptoms of depression (see also Chapter 212). The terms *diffuse amplified pain syndrome, chronic widespread pain syndrome, chronic myofascial pain syndrome,* and *juvenile primary fibromyalgia syndrome* are often used to describe the same constellation of symptoms. Some of these children have findings that fulfill the criteria that have been developed for adult patients with fibromyalgia by either the American College of Rheumatology (Table 211.7) or the Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks-American Pain Society (Table 211.8 and

Table 211.4 Inclusion and Exclusion Criteria for Growing Pains Including Features of Restless Legs Syndromes (RLS)

	INCLUSIONS	EXCLUSIONS	RLS FEATURES
Nature of pain	Intermittent; some pain-free days and nights, deep aching, cramping	Persistent; increasing intensity, pain during the day	Urge to move legs often accompanied by unpleasant sensations in legs, but may not be painful
Unilateral or bilateral	Bilateral	Unilateral	
Location of pain	Anterior thigh, calf, posterior knee—in muscles not the joints	Articular, back, or groin pain	Urge to move and discomfort throughout leg
Onset of pain	Late afternoon or evening	Pain still present next morning	Worse later in day or night but also present at periods of rest or inactivity throughout the day
Physical findings	Normal	Swelling, erythema, tenderness; local trauma or infection; reduced joint range of motion; limping, fever, weight loss, mass	
Laboratory findings	Normal	Objective evidence of abnormalities; increased erythrocyte sedimentation rate or C-reactive protein; abnormal complete blood count, radiography, bone scan, or MRI	

Adapted from Evans AM, Scutter SD. Prevalence of "growing pains" in young children. *J Pediatr*. 2004;145:255–258; and Walters AS, Gabelia D, Frauscher B. Restless legs syndrome (Willis-Ekbom disease) and growing pains: are they the same thing? A side-by-side comparison of the diagnostic criteria for both and recommendations for future research. *Sleep Med*. 2013;14:1247–1252.

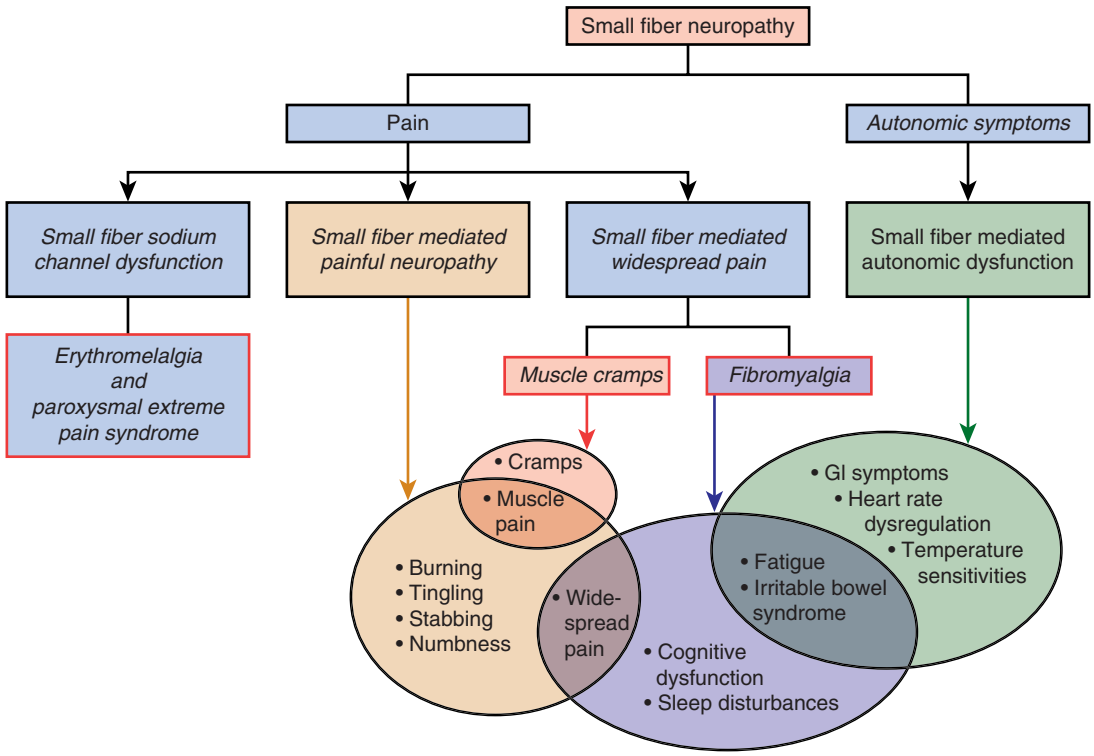

Fig. 211.1 Small fiber neuropathy symptom clusters and neuropathy classifications. *(From Levine TD. Small fiber neuropathy: disease classification beyond pain and burning. J Central Nervous Sys Dis. 2018;10:1–6, Fig. 1, p. 3).*

Fig. 211.2). Separate criteria for the diagnosis of juvenile primary fibromyalgia syndrome in children have been proposed, but these have not been validated (Table 211.9). The evaluation of fibromyalgia tender points has not been useful or diagnostic.

Although the precise cause of diffuse amplified pain is unknown, there is an emerging understanding that the development and maintenance of chronic pain are related both to biologic and psychologic factors. Diffuse amplified pain likely has multifactorial causes and is hypothesized to be an abnormality of central pain processing associated with disordered sleep physiology, enhanced pain perception, disordered mood, and dysregulation of hypothalamic-pituitary-adrenal and other neuroendocrine axes, resulting in lower pain thresholds and increased pain sensitivity. Children and adolescents with diffuse amplified pain often find themselves in a vicious cycle of pain, where symptoms build on one another and contribute to the onset and maintenance of new symptoms.

Diffuse amplified pain has a chronic course that can detrimentally affect child health and development. Adolescents who do not

Table 211.5 Causes of Small Fiber Neuropathy

PRIMARY	SECONDARY
IDIOPATHIC Idiopathic small fiber neuropathy Burning mouth syndrome	METABOLIC Impaired glucose tolerance Diabetes mellitus Rapid glycemic control Vitamin B_{12} deficiency Dyslipidemia Hypothyroidism Chronic kidney disease
HEREDITARY/GENETIC Familial amyloid polyneuropathy Fabry disease Tangier disease Sodium channelopathies (see text)	INFECTIONS HIV Hepatitis C Influenza TOXINS AND DRUGS Antiretrovirals Antibiotics—metronidazole, nitrofurantoin, linezolid Chemotherapy—bortezomib Flecainide Statin Alcohol Vitamin B_6 toxicity IMMUNE MEDIATED Celiac disease Sarcoidosis Sjögren syndrome Rheumatoid arthritis Systemic lupus erythematosus Vasculitis Inflammatory bowel disease Paraneoplastic Monoclonal gammopathy/amyloid

Note that a number of these conditions may present as a small fiber neuropathy and then evolve to include large fibers.
Modified from Themistocleous AC, Ramirez JD, Serra J, Bennett DLH. The clinical approach to small fibre neuropathy and painful channelopathy. *Pract Neurol.* 2014;14:368–379, Table 1.

receive treatment or who are inadequately treated may withdraw from school and the social milieu, complicating their transition to adulthood. **Treatment** of diffuse amplified pain is ideally multidisciplinary. The major goals are to restore function and alleviate pain and to improve comorbid mood and sleep disorders. Treatment strategies include parent/child education, pharmacologic interventions, exercise-based interventions, and psychologic interventions. Graduated **aerobic exercise** is the recommended exercise-based intervention, whereas psychologic interventions should include training in pain coping skills, stress management skills, emotional support, and sleep hygiene. CBT is particularly effective in reducing symptoms of depression in children and adolescents with chronic pain and helps to reduce functional disability.

Drug therapies, although largely unsuccessful in isolation, may include tricyclic antidepressants (amitriptyline 0.1 mg/kg at bedtime; can increase to 0.5 to 2 mg/kg as tolerated), selective serotonin reuptake inhibitors (sertraline 25-100 mg daily), and anticonvulsants. Pregabalin and duloxetine hydrochloride are approved by the U.S. Food and Drug Administration (FDA) for treatment of fibromyalgia in adults (≥18 years of age); however, data regarding the efficacy of these medications in children are limited.

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211.4 Complex Regional Pain Syndrome

James J. Nocton

Complex regional pain syndrome (CRPS) is characterized by chronic, persistent limb pain, often burning in character. **CRPS type 1**, also termed *reflex sympathetic dystrophy*, has no evidence of nerve injury, whereas the less common **CRPS type 2** is associated with a known mechanism of nerve injury. The pain of CRPS is typically extreme and disproportionate to the inciting event. Associated features include **allodynia** (a heightened pain response to normally non-noxious stimuli), **hyperalgesia** (exaggerated pain reactivity to noxious stimuli), swelling of the affected extremity, and indicators of **autonomic dysfunction** (cyanosis, mottling, hyperhidrosis).

There are no diagnostic criteria specifically for pediatric CRPS; in adults, several sets of criteria have been developed (Table 211.10); the clinical utility of these criteria is controversial. The diagnosis of CRPS is clinical and can be made when continuous pain is present that is disproportionate to any potential inciting event with associated allodynia, or hyperalgesia, evidence of edema, skin blood flow abnormalities, or excessive sweating activity, and exclusion of other disorders. Other features that may be present include atrophy of hair or nails, loss of joint mobility, weakness, tremor, and dystonia.

Although many pediatric patients with CRPS present with a history of minor trauma or repeated stress injury (e.g., caused by competitive sports), a significant proportion are unable to identify a precipitating event. Usual age of onset is between 8 and 16 years, and females outnumber males with the disease by as much as 6:1. Childhood CRPS differs from the adult form in that lower extremities, rather than upper extremities, are most often affected. The incidence of CRPS in children is unknown, largely because it is often undiagnosed or diagnosed late. Left untreated, CRPS can have severe consequences for children, including bone demineralization, muscle wasting, and joint contractures.

The **treatment** of CRPS, like that of more diffuse pain syndromes, is ideally multidisciplinary. Aggressive physical therapy (PT) should be initiated as soon as the diagnosis is made, and CBT added as needed. **PT** is recommended three to four times a week, and children may need analgesic premedication at the onset, particularly before PT sessions. PT is initially limited to desensitization and then moves to weight bearing, range of motion, and other functional activities. CBT used as an adjunctive therapy targets psychosocial obstacles to fully participating in PT and provides pain-coping skills training. The goal of both pharmacologic and adjunctive treatments for CRPS is to provide sufficient pain relief to allow the child to participate in aggressive physical rehabilitation. Multiple studies have shown that noninvasive treatments, particularly PT and CBT, are at least as efficacious as nerve blocks in helping children with CRPS achieve resolution of their symptoms.

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211.5 Erythromelalgia

James J. Nocton

Children with erythromelalgia experience episodes of intense burning pain, erythema, edema, and heat, most often in the hands and feet (Fig. 211.3) and less frequently in other locations. Symptoms are most often triggered by exposure to heat or exercise and typically last for hours to days. Erythromelalgia is more common in females during adolescence, and the diagnosis is often delayed for many years. Although many cases are sporadic, an autosomal dominant hereditary form results most often from gain-of-function pathogenic variants of the *SCN9A* gene, which encodes the alpha subunit of the sodium channel $Na_V1.7$ found in nociceptive neurons that transmit pain signals. Age of onset for the

Table 211.6 Clinical Features of Human Disorders Caused by Pathogenic Gene Variants in Ion-Channel Genes that Lead to Altered Pain Perception and Are Inherited in a Mendelian Manner

	GENE (PROTEIN)	TYPE AND EFFECT OF GENE VARIANT	MAIN PHENOTYPE	ADDITIONAL FEATURES
Inherited erythromelalgia	*SCN9A* ($Na_v1.7$)	Heterozygous, activating	Onset by age 20 yr; episodic pain triggered by warmth; feet affected more frequently than hands	Erythema of feet
Paroxysmal extreme pain disorder	*SCN9A* ($Na_v1.7$)	Heterozygous, activating	Onset at birth; episodic pain; sacral region is affected most frequently; face is affected more often than the limbs; physical triggers include defecation	Erythema of the sacrum; tonic attacks
Small-fiber neuropathy	*SCN9A* ($Na_v1.7$)	Heterozygous, activating	Onset at any age but more common in early adulthood; persistent burning pain; feet affected more frequently than hands	Could be autonomic features
Small-fiber neuropathy	*SCN10A* ($Na_v1.8$)	Heterozygous, activating	Persistent burning pain	Could be autonomic features
Familial episodic pain syndrome type I	*TRPA1* (TRPA1)	Heterozygous, activating	Onset at birth or in infancy; episodic chest or arm pain; triggers are hunger and cold	
Familial episodic pain syndrome type III	*SCN11A* ($Na_v1.9$)	Heterozygous, activating	Onset in first decade; episodic hand and foot pain; triggers are intercurrent illness or exercise	

Na_v Sodium ion channel.
Modified from Bennett DLH, Woods CG. Painful and painless channelopathies. *Lancet Neurol*. 2014;13:587–599, Table 1.

Table 211.7 American College of Rheumatology Fibromyalgia Diagnostic Criteria (2016 Revision)

The following three conditions must be met:

1. Widespread Pain Index (WPI) ≥7 and Symptom Severity Scale (SSS) score ≥5 *or* WPI 4-6 and SSS score ≥9.
2. Generalized pain, defined as pain in at least four of five regions, must be present. Jaw, chest, and abdominal pain are not included in generalized pain definition.
3. Symptoms have been generally present for at least 3 mo.

ASCERTAINMENT OF WPI

The WPI is the number of areas in which a patient has had pain over the last week. The score will be between 0 and 19: Left Upper Region: left jaw, left shoulder girdle, left upper arm, left lower arm; Right Upper Region: right jaw, right shoulder girdle, right upper arm, right lower arm; Left Lower Region: left hip (buttock, trochanter), left upper leg, left lower leg; Right Lower Region: right hip (buttock, trochanter), right upper leg, right lower leg; Axial Region: chest, abdomen, upper back, lower back, and neck.

ASCERTAINMENT OF SSS SCORE

The SSS score is the sum of the severity of three symptoms (fatigue, waking unrefreshed, and cognitive symptoms) over the past week (each given a score from 0 to 3) *plus* the sum of the number of the following symptoms the patient has been bothered by that occurred during the previous 6 mo: headaches, pain or cramps in the lower abdomen, and depression (each given a score from 0 to 1). The final score will be between 0 and 12. For fatigue, waking unrefreshed, and cognitive symptoms, the level of severity over the past week is rated using the following scale:

0 = No problem

1 = Slight or mild problems, generally mild or intermittent

2 = Moderate, considerable problems, often present and/or at a moderate level

3 = Severe: pervasive, continuous, life-disturbing problems

- For headaches, pain or cramps in the lower abdomen, and depression, the severity for each is scored as 0 or 1.

Adapted from Wolfe F, Clauw DJ, Fitzcharles MA, et al. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. *Semin Arthritis Rheum*. 2016;46(3):319–329.

Table 211.8 Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks-American Pain Society Pain Taxonomy (AAPT) Fibromyalgia Diagnostic Criteria

Core diagnostic criteria:

1. Musculoskeletal pain defined as 6 or more pain sites from a total of 19 possible sites (see Fig. 211.2)
2. Moderate to severe sleep problems OR fatigue
3. Musculoskeletal pain plus fatigue or sleep problems must have been present for at least 3 mo

NOTE: The presence of another pain disorder or related symptoms does not rule out a diagnosis of fibromyalgia. However, a clinical assessment is recommended to evaluate for any condition that could fully account for the patient's symptoms or contribute to the severity of the symptoms.
Adapted from Arnold LM, Bennett RM, Crofford LJ, et al. AAPT Diagnostic Criteria for Fibromyalgia. *J Pain*. 2019;20:611–628.

familial form ranges from 1 to 16 years. **Secondary** erythromelalgia is associated with many disorders, including myeloproliferative diseases, peripheral neuropathies, frostbite, and rheumatic diseases. The differential diagnosis includes Fabry disease, Raynaud phenomenon or disease, reflex sympathetic dystrophy, and peripheral neuropathies. In contrast to Raynaud phenomenon, the pain in erythromelalgia is relieved by cooling the affected area. Treatment includes avoidance of heat exposure and other precipitating situations and the use of cooling techniques that do not cause tissue damage during attacks. There is no proven reliably efficacious treatment, and NSAIDs, narcotics, anesthetic agents (lidocaine patch), anticonvulsants (oxcarbazepine, carbamazepine, gabapentin), antidepressants, sodium nitroprusside, magnesium, mexiletine, and misoprostol, as well as biofeedback, medical and surgical nerve blocks, and hypnosis have had variable efficacy.

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Widespread Pain Index
(1 point per circle; score range: 0–19 points)

Please indicate if you have had pain or tenderness **during the past 7 days** in the areas shown below.
Fill in the circles on the diagram for each area in which you have had pain or tenderness.

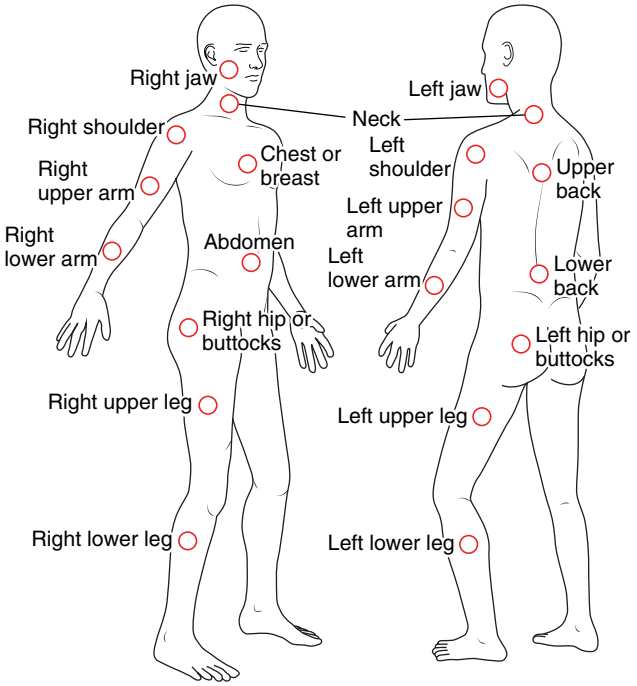

Fig. 211.2 Widespread pain index. *(Modified from Fraix M. Fibromyalgia. In Tallia AF, Scherger JE, Dickey NW (eds). Swanson's Family Medicine Review, 9th ed. Philadelphia: Elsevier, 2022. Fig 47.1.)*

Table 211.9 Suggested Diagnostic Criteria for Juvenile Primary Fibromyalgia Syndrome (JPFS)

MAJOR CRITERIA
1. Generalized musculoskeletal aching at three or more sites for ≥3 mo
2. Absence of an underlying condition/cause
3. Normal laboratory tests
4. Five or more typical tender points*
MINOR CRITERIA
1. Chronic anxiety or tension
2. Fatigue
3. Poor sleep
4. Chronic headaches
5. Irritable bowel syndrome
6. Subjective soft tissue swelling
7. Numbness
8. Pain modulated by physical activities
9. Pain modulated by changes in weather
10. Pain modulated by anxiety/stress

*Thirty-one potential tender points were listed for these criteria when proposed in 1985. JPFS is diagnosed when all major criteria are met, plus three of the minor criteria or when there are four tender points and five minor criteria.
Adapted from Coles M, Weissmann R, Uziel Y. Juvenile primary fibromyalgia syndrome: Epidemiology, etiology, pathogenesis, clinical manifestations and diagnosis. *Pediatr Rheumatol Online J.* 2021;19(1):22.

Table 211.10 Budapest Clinical Diagnostic Criteria for Complex Regional Pain Syndrome

All of the following criteria must be met:

1. Continuing pain, which is disproportionate to any inciting event
2. Must report at least one symptom in each of the following four categories:
   - *Sensory*: Hyperesthesia and/or allodynia
   - *Vasomotor*: Temperature asymmetry, skin color changes, and/or skin color asymmetry
   - *Sudomotor/edema*: Edema, sweating changes, and/or sweating asymmetry
   - *Motor/trophic*: Decreased range of motion, motor dysfunction (tremor, weakness, dystonia) and/or trophic changes (hair, nail, skin)
3. Must display at least one sign at time of evaluation in two or more of the following four categories:
   - *Sensory*: Evidence of hyperesthesia (to pin prick) and/or allodynia (to light touch, temperature sensation, deep somatic pressure, and/or joint movement)
   - *Vasomotor*: Evidence of temperature asymmetry (>1°C), skin color changes, and/or skin color asymmetry
   - *Sudomotor/edema*: Edema, sweating changes, and/or sweating asymmetry
   - *Motor/trophic*: Decreased range of motion, motor dysfunction (tremor, weakness, dystonia) and/or trophic changes (hair, nail, skin)
4. There is no other diagnosis that better explains the signs and symptoms.

Adapted from Harden RN, Bruel S, Stanton-Hicks, et al. Proposed new diagnostic criteria for complex regional pain syndrome. *Pain Med.* 2007;8:326–331.

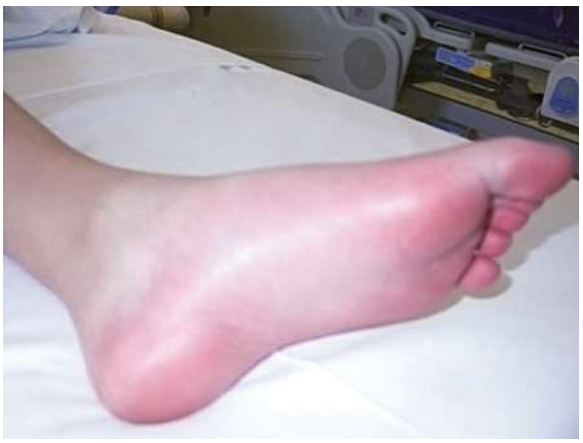

Fig. 211.3 Characteristic redness and edema of the foot associated with erythromelalgia. *(From Pfund Z, Stankovics J, Decsi T, Illes Z. Childhood steroid-responsive acute erythromelalgia with axonal neuropathy of large myelinated fibers: a dysimmune neuropathy? Neuromuscul Disord. 2009;19:49–52, Fig. 1A, p. 50.)*

Chapter 212

Chronic Overlapping Pain Conditions

Thomas C. Chelimsky and Gisela G. Chelimsky

In chronic overlapping pain conditions **(COPCs)**, several painful symptoms affecting different body systems coexist without clear underlying pathophysiology. Other terms for COPCs include **medically unexplained symptoms**, **functional somatic syndromes** (FSS), and **central sensitivity syndromes**. These disorders are probably highly prevalent; for example, two COPCs, irritable bowel syndrome (IBS) and migraine, *each* affect 10–20% of the population. Pediatric COPC studies usually focus on populations with one painful condition (headaches) and their psychiatric comorbidities, rather than somatic comorbidities. The overlap of these disorders with psychiatric conditions has led both the public and the medical specialists to dichotomize these disorders artificially into "physical," by implication, "real" disorders and "psychologic," by implication, "not real" disorders. This classification ignores the unity of brain and body and hinders progress in understanding these disorders. COPC connotes a nonassumptive neutral position, appropriately attributing no assumed pathophysiology to the disorder, in contrast to other terms, such as "medically unexplained syndrome," subtly suggesting a psychologic process, more strongly implied in the term "functional."

PREVALENCE

The prevalence of COPCs is unknown depending on which symptom is being assessed and how much overlap exists across disorders. A large study from 28 countries (about 400,000 participants) found a prevalence of headache of 54%, stomachache 50%, and backache 37%, occurring at least once a month for at least 6 months. Females had a higher prevalence of having all three complaints when compared with males; the prevalence increased with age. These three pain syndromes, headache, stomachache, and backache, frequently coexist.

IBS and chronic abdominal pain affect 6–20% of children and adolescents. Idiopathic musculoskeletal pain affects about 16% of schoolchildren age 5-16 years and is often associated with sleep disturbances, headache, abdominal pain, daytime tiredness, and feeling sad. Migraines present >6 months occur in about 8% of the population (children and adolescents <20 years). Fibromyalgia is present in 1.2–6%. The prevalence of chronic disabling fatigue increases during adolescence from about 1.9% at age 13 to 3% at 18 years. As with most COPCs, fibromyalgia has many comorbid disorders, such as sleep disturbance, fatigue, headache, sore throat, joint pain, and abdominal pain. The American College of Rheumatology definition of fibromyalgia incorporates some of these comorbid conditions.

SYMPTOM/DISORDER OVERLAP

Diagnostic criteria of many of these disorders overlap with one another, making differentiation between two disorders more of a semantic issue rather than a clinical differentiation. **Chronic fatigue syndrome (CFS)**, clinically the most concerning symptom, shares many of the diagnostic criteria with fibromyalgia. Patients with a single pain condition, such as fibromyalgia, CFS, IBS, multiple chemical sensitivity (MCS), headaches, or temporomandibular joint disorder (TMJD), will typically have another disorder. This overlap of symptoms may reflect a shared pathophysiology, possibly a central nervous system (CNS) dysfunction, as was implied in the prior term "central sensitization syndrome." A CNS pathophysiology would also explain the "invisibility" of these disorders to usual screening tools that most often target an end organ.

COPCs also harbor many symptoms that are not strictly "pain," although they may be equally or more disabling. Adolescents seen in a tertiary referral center with a **functional gastrointestinal disorder (FGID)** also manifest dizziness, chronic nausea, chronic fatigue, and sleep disturbance, as well as migraines. Up to 50% of adolescents complain of weekly fatigue, and 15%, daily fatigue. COPCs are studied in their discipline-specific silos rather than collectively as a group.

Migraine headaches are frequently associated with anxiety and depression. **Anxiety** also predicts the persistence of migraine headaches. Sleep disturbance and migraine also interact closely. Poor sleep can trigger a migraine or a migraine cluster; migraine headache itself disturbs sleep. Juvenile fibromyalgia is associated with sleep disturbances such as prolonged sleep latency, frequent awakening, less total sleep time, and periodic limb movements. Adult patients with IBS also have sleep disturbances, correlating with anxiety, depression, and stress.

The *comorbidities* of **hypermobility Ehlers-Danlos (hEDS)** and **postural orthostatic tachycardia syndrome (POTS)** with COPC have been significant. Patients with hEDS may complain of widespread and sometimes debilitating pain with or after activity, severe fatigue, handwriting difficulties, "cracking" of joints, joint swelling, joint dislocation, subluxation, or back pain. The chronic pain reduces exercise tolerance, with poorer quality of life and an ever-worsening cycle because exercise is a key piece of management. Patients with FGID may also have hEDS, fibromyalgia, chronic pain, and higher somatizations scores than those with organic gastrointestinal (GI) disorders.

The diagnosis of pediatric POTS requires an increase in heart rate >40 beats/min in the first 10 minutes of upright tilt test associated with orthostatic symptoms. POTS is also associated with multiple comorbidities, including sleep disruption, chronic pain, Raynaud-like symptoms, GI abnormalities, and less frequently, headaches, syncope, and urinary complaints. Patients with both POTS and hEDS usually have more migraines and syncope than those with POTS alone. The prevalence of comorbid disorders in children with COPC is identical whether they have POTS or hEDS.

PSYCHIATRIC COMORBIDITIES

Many of these disorders have significant psychiatric comorbidities. Juvenile fibromyalgia is associated with anxiety disorders and major mood disorders. Children with medically unexplained symptoms generally have more anxiety and depression than children with other chronic disorders. Other associations include disruptive behaviors, symptom internalization, fearfulness, greater dependency, hyperactivity, and concern about sickness.

PREDISPOSING FACTORS

Female gender and older age (adolescence) increase the risk of COPCs. Certain conditions (e.g., headache) are more common in males or have similar prevalence across genders during childhood, but the prevalence in females increases after puberty. Trauma or posttraumatic stress disorder increases psychologic comorbidities in juvenile fibromyalgia. Some studies suggest that anxiety predisposes to chronic pain. A population-based study following children from 18 months to 14 years of age suggested that maternal psychologic distress in early childhood and depressive and pain complaints in preadolescence increase the risk of recurrent abdominal pain at age 14. Postinfectious IBS is an identifiable risk factor for new-onset anxiety, depression, and sleep disruption in adults. Children with recurrent abdominal pain often have parents with abdominal pain. It is unclear if this association is caused by a common environmental/genetic factor or a learned behavior of the child imitating the parent.

NATURAL HISTORY

The natural history of COPC is not well known. Chronic disabling fatigue in the general adolescent population persists 2-3 years in about 25% of patients, but only 8% of youth affected at age 13 still had the complaints at ages 16 and 18. A meta-analysis suggests that the prognosis of CFS in children is usually good, with a small minority having persistent disabling symptoms. The patient's belief in an underlying

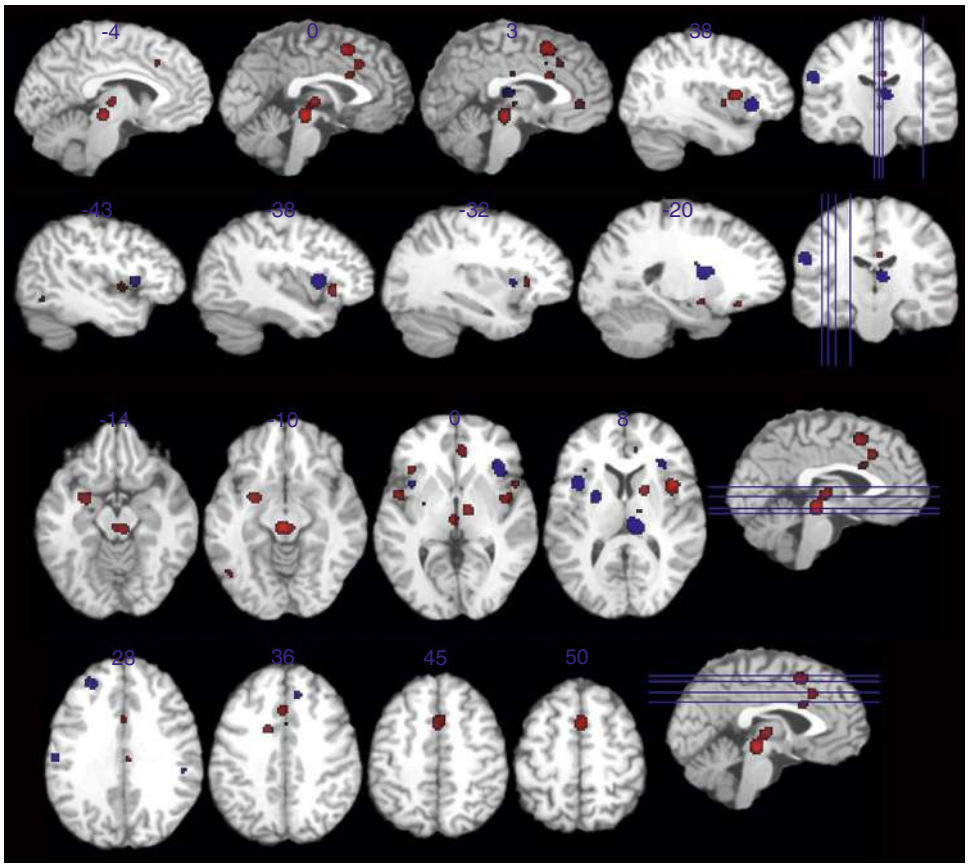

Fig. 212.1 Brain areas demonstrating more *(red)* or less *(blue)* activation in irritable bowel syndrome compared with healthy control in a meta-analysis of rectal distention. *(From Tillisch K, Mayer EA, Labus JS. Quantitative meta-analysis identifies brain regions activated during rectal distension in irritable bowel syndrome. Gastroenterology. 2011;140:91–100, Fig. 3.).*

physical disorder and the presence of psychiatric comorbidities predict a poorer outcome.

In a study of children with FGID, the outcome depended on specific variables. Those who perceived their abdominal pain as more threatening, with high levels of pain catastrophization and little capacity to cope with pain because of reduced activity levels, had a poorer outcome. This "high pain dysfunctional profile" subgroup was predominantly female (70%) with a mean age of 12.2 years. Two thirds of this subgroup still complained of FGID at follow-up vs about one third of those in the other groups. These groups included a "high pain adaptive profile" group with similar pain levels but better adaptive skills and less catastrophization, predominantly slightly younger (11.8 years) females, and a "low pain adaptive profile" group, slightly younger (11.1 years), with equal males and females but less abdominal pain, better coping mechanisms, and less impairment of daily activities. In the high pain dysfunctional profile group, 41% had both FGID and nonabdominal chronic pain at follow-up vs 11% in the high pain adaptive and 17% in the low pain adaptive group. Another study following children ages 4-16.6 years with IBS demonstrated resolution of symptoms in 58%, usually without medication. The differences between these studies may result from the age of the groups, with better outcome in the younger patients, as well as the number of comorbidities and psychologic profile. Similarly, in juvenile fibromyalgia, symptoms are still present 2-6 years later in about 60% of affected children. The psychiatric comorbidities, mainly depression, and controlling family environments are associated with a poor prognosis.

PROPOSED PATHOPHYSIOLOGY

There may be dysfunction in the hypothalamic-hypophyseal-adrenal axis, circadian patterns, autonomic responses, some aspects of CNS processing, the inflammatory immune response, and the musculoskeletal system. Vagal tone measured by heart rate variability is decreased in some children with FGID symptoms and in children with COPCs. Alterations in the autonomic nervous system may affect the immune system and circadian patterns. The stress response may increase muscle tone, which in turn leads to body aches and tension headaches. In fibromyalgia the cortisol response is altered, with lower cortisol levels on awakening and throughout the day. **Orthostatic intolerance** from autonomic abnormalities may also contribute to poor concentration from brain hypoperfusion and blood pooling in the lower extremities.

The pathophysiology has been better studied in myalgic encephalomyelitis (ME)/CFS. ME/CFS has been associated with joint hypermobility, orthostatic intolerance, decreased range of motion, and reduced activity. These patients demonstrate excessive glial activation resulting in neuroexcitation, neuroinflammation, and possibly neurodegeneration. These features may contribute to the cognitive issues and fatigue present in this disorder.

Neuroinflammation and other changes in processing may lead to abnormal descending inhibitory pain pathways, resulting in distal pain and "central sensitization." The malfunction of descending antinociceptive pathways allows pain to spread in the body, associated with increased activity of the nociceptive facilitator pathways. These facilitator pathways are further activated by psychologic factors, such as catastrophization, depression, lack of acceptance, and hypervigilance. Other signals such as pressure, sound, heat, and cold are also aberrantly processed, with activation of areas of the brain that are typically activated only by acute pain stimuli, such as the insula, prefrontal cortex, and anterior cingulate cortex, as well as some regions usually not involved in pain processing.

The neuromechanisms involved in dysregulated brain-gut interactions in patients with FGID include changes in functional connectivity between brain regions associated with nociceptive processing and the somatosensory cortexes. Enhanced sensory processing of the gut homeostasis (homeostatic afferent) and attentive responses to salience stimuli (salience network) as well as changes in certain brain regions are noted in patients with FGID (Fig. 212.1). These alterations affect the perception of pain and may affect the endocrine and autonomic nervous systems. What was once called FGIDs is currently considered disorders of gut-brain interactions. Proposed mechanisms are noted in Figure 212.2. Research investigating the role of the microbiome in regulating microglia, astrocytes, and immune cells may lead to central sensitization and chronic pain.

TREATMENT

In general, *chronic pain should never be treated with opioids*; **cognitive-behavioral therapy (CBT) and a gradually progressive exercise program**

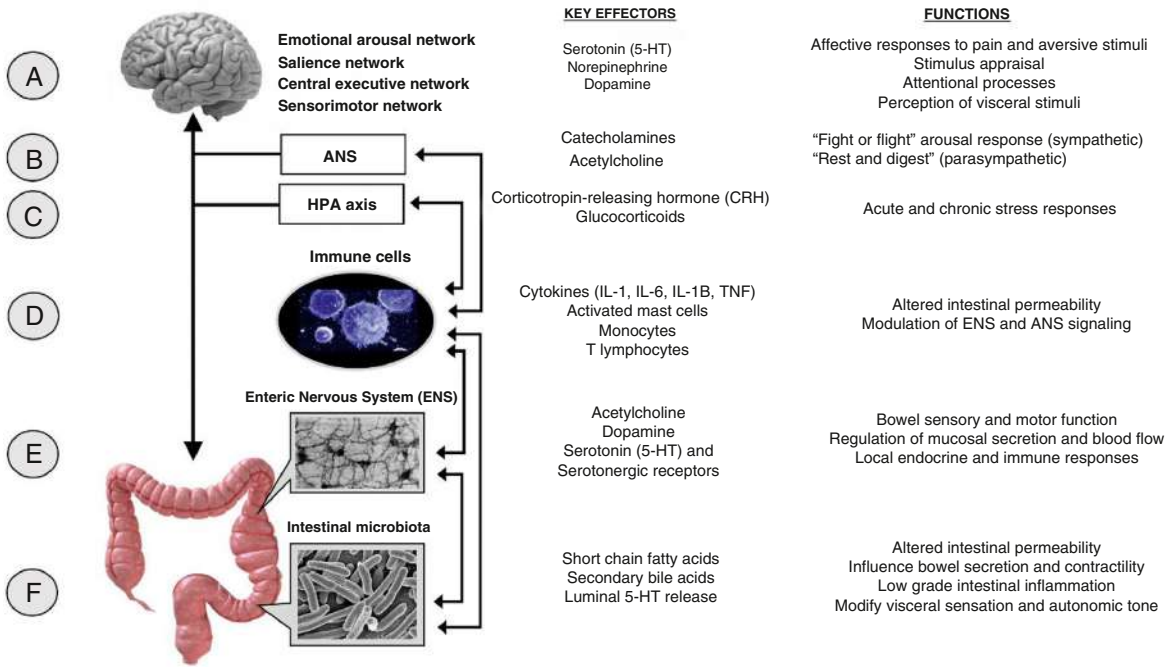

Fig. 212.2 Key effectors and functions of the brain-gut-microbiota axis. ANS, autonomic nervous system; HPA, hypothalamic pituitary axis. *(From Tait C, Sayuk GS. The brain-gut-microbial axis: A framework for understanding functional GI illness and their therapeutic interventions. Eur J Int Med. 2021;84:1–9, Fig. 2.)*

constitute the cornerstones of treatment. The complex comorbid nature of COPCs typically requires a multidisciplinary approach. Because neither CBT nor exercise will have any effect in the absence of full patient engagement and understanding, the team must include the family and the patient, a pain psychologist with experience in CBT, a physical therapist, and the primary care physician. Depending on comorbid conditions, rheumatology, neurology, or gastroenterology may have important roles for symptom management and a possible alternative diagnosis. Depending on the initial symptomatology, the differential diagnosis should include inflammatory bowel disease, celiac disease, juvenile idiopathic arthritis, systemic lupus erythematosus, dermatomyositis, autoinflammatory disorders, Fabry disease, porphyrias, hereditary sensory-autonomic neuropathies, and Ehlers-Danlos syndrome. Red flags suggesting a medical/organic etiology for abdominal pain (Table 212.1), headache (Tables 212.2 and 212.3), and musculoskeletal pain (Table 212.4) must be assessed.

When a thorough evaluation for a structural cause of symptoms is unrevealing, an important next step is patient and family education. This should include the common presentation, the expectation that "markers" for these types of disorders would typically be absent, and the presence of solid management tools with high probability of improvement. Families and patients need to receive encouragement to stop seeking a "magic diagnosis and cure" and to begin the path to full recovery. Without this step, critical patient engagement in the treatment will not occur. In our practice, we sometimes call *functional* disorders a problem of "software," in contrast to *structural* issues that would involve "hardware." We explain that successful management must change the software, not just mask symptoms. Approaches that accomplish such a goal include CBT and a rehabilitative program that may require physical therapy, a vigorous exercise program with interval training, meditation, and/or yoga. Patients are often deconditioned and may need to start with a very low level of physical activity. In addition, their exercise tolerance may be significantly hampered by an orthostatic intolerance syndrome (e.g., POTS). For these reasons, we frequently recommend starting with a *water aerobics* program, which provides several benefits: (1) very low gravitational force, so the patient can be set up for success, working only on conditioning and not simultaneously fighting an orthostatic challenge; (2) builds both limb and core strength; and (3) gentle on joints for those with arthralgias or a hypermobility syndrome. When water is unavailable, we recommend starting with a recumbent exercise program such as a recumbent stationary bike. In both circumstances, we then slowly introduce upright aerobic activities on land over 2-3 months. Strength exercises are also useful. A Cochrane review in adults with painful disorders showed exercise to have minimal side effects and to improve functionality, reduce pain, and improve quality of life. Patients with fibromyalgia who undergo a 3-month multidisciplinary program with twice-weekly physical therapy and CBT benefited in function and physical activity level, and most importantly continued to exercise regularly at 1 year follow-up. Pharmacologic interventions have less impact than nonmedical treatments.

When children are missing school or are homebound, it is important to work closely with the school to encourage reentry. This may require modifying the school schedule initially, starting with fewer hours at school, and providing extra time for homework on days that the children are not feeling well.

Although medications such as tricyclic antidepressants are often added to the treatment, the improvement with these medications for chronic pain is minimal, and the side effects need to be considered. Nonetheless, amitriptyline and anticonvulsants like gabapentin are often used because they help in treating headaches and abdominal pain and improve sleep quality, a critical element to manage any chronic pain condition.

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212.1 Chronic Fatigue Syndrome

Mark R. Magnusson

Chronic fatigue syndrome **(CFS)**, also known as **myalgic encephalomyelitis (ME)**, is a complex, diverse, and debilitating illness characterized by chronic or intermittent fatigue accompanied by select symptoms and occurring in children, adolescents, and adults. The combination of fatigue and other symptoms interferes significantly with daily activities and has no identified medical explanation (Fig. 212.3). The fatigue does not require exertion by the patient, nor does rest relieve it. Some consider **postexertion malaise**, or worsening of

Table 212.1 Red Flags and Clues to an Organic Cause of Abdominal Pain

Age <4 yr old
Localized pain in nonperiumbilical site
Referred pain
Sudden onset of excruciating pain
Crescendo nature of pain
Sudden worsening of pain
Fever (high fever >39.4°C suggests pneumonia, pyelonephritis, dysentery, cholangitis, more than perforation or abscess)
Jaundice
Distention*
Dysphagia
Dysuria
Emesis (especially bilious)
Anorexia
Weight loss, failure to thrive
Positive family history (metabolic disorders, peptic ulcer disease)†
Change in urine or stool color (blood, acholic) or frequency
Vaginal discharge
Menstrual abnormalities (amenorrhea)
Sexual activity
Delayed sexual development (chronic pain)
Anemia
Elevated erythrocyte sedimentation rate
Elevated stool calprotectin
Specific physical findings (hepatomegaly, splenomegaly, absent bowel sounds, adnexal tenderness, palpable mass, involuntary guarding, focal or diffuse tenderness, positive rectal examination results, perianal disease, joint swelling, rashes)

*Consider the five Fs: fat, feces, flatus (aerophagia, obstruction), fluid (ascites, hydronephrosis, cysts), fetus (pregnancy or fetal-like abnormal growth [e.g., tumors]).
†Family history is also positive for chronic pain syndromes (constipation, irritable bowel, dysmenorrhea, and lactase or sucrase deficiency).
Modified from Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Philadelphia: Elsevier; 2023: Table 13.8, p. 229.

Table 212.3 Physical Examination Red Flags for Secondary Headaches

Abnormal vital signs:
Hypertension
Growth failure
Increased head circumference or bulging fontanel
Fever
Meningeal signs with or without fever
Evidence of cranial trauma
Cranial bruit
Frontal bony tenderness
Macrocephaly
Abnormal ophthalmologic findings:
Papilledema
Abnormal ocular movements
Squinting
Pathologic pupillary response
Visual field defects
Abnormal neurologic findings:
Impaired mental status
Cranial nerve palsy
Ataxia
Abnormal gait
Abnormal coordination
Abnormal reflexes
Asymmetric motor or sensory examination
Hemiparesis
Developmental regression
Precocious, delayed, or arrested puberty
Skin findings:
Café-au-lait or ash leaf macules
Petechiae or purpura
Facial hemangioma
Malar rash

From Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Philadelphia: Elsevier; 2023: Table 34.6, p. 553.

Table 212.2 History-Related Red Flags for Secondary Headaches

Quality:
"Thunderclap" rapid-onset headache or the "worst headache of my life"
Recent worsening in severity or frequency
Change in quality
New-onset symptoms consistent with cluster headache
Location:
Unilateral without alteration of sides
Chronic or recurrent occipital headache
Timing:
Awakens from sleep
Occurs in morning or causes morning vomiting
Acute or chronic progressive pattern
Positional or activity-related variations:
Worsened in the recumbent position or when bending over
Headache experienced or worsened with cough or the Valsalva maneuver
Associated neurologic history:
Neurologic dysfunction other than typical aura
Altered sensorium during headache
Sensory deficits or changes in vision, gait, or coordination
Other focal neurologic deficits
Seizures or syncope
Decreased visual acuity
Mental status changes (e.g., confusion or disorientation)
Regression in fine or gross motor developmental skills
Decline in cognition or school performance
Change in mood, behavior, or personality
Associated general history:
Vomiting without nausea and morning/fasting nausea or vomiting
Polyuria or polydipsia
Preschool or younger age
History of head trauma
Neck pain:
Medical comorbidities
History of ventriculoperitoneal shunt
Certain medications
Signs of systemic or localized head/neck infection
Negative family history of primary headache disorders

From Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Philadelphia: Elsevier; 2023: Table 34.5, p. 553.

Table 212.4 Musculoskeletal/Joint Pain Warning Signals Requiring Further Workup

- Arthritis: Erythema, warmth, swelling, pain on palpation
- Pain/stiffness in the morning
- Abnormal radiographic findings
- Pain at rest, relieved by activity
- Pain at night: Worsened by massage, analgesics ineffective
- Refusal to walk
- Extremity atrophy
- Bony tenderness
- Poor growth
- Weight loss
- Fever
- Rash
- Abnormal blood results: Including complete blood count (CBC), C-reactive protein (CRP), erythrocyte sedimentation rate

Modified from Friedrichsdorf SJ, Giordano J, Dakoji KD, et al. Chronic pain in children and adolescents: Diagnosis and treatment of primary pain disorders in head, abdomen, muscles and joints. *Children*. 2016;3:42, Table 3.

the fatigue with additional symptoms after mental or physical exertion and lasting >24 hours, to be characteristic of CFS. A definitive causal agent or process has not been identified, although the differential diagnosis includes infectious, inflammatory, metabolic, genetic, and autoimmune diseases. Our understanding of this condition is largely from studies of adults and adolescents, with limited descriptions of chronic fatiguing illnesses in younger children.

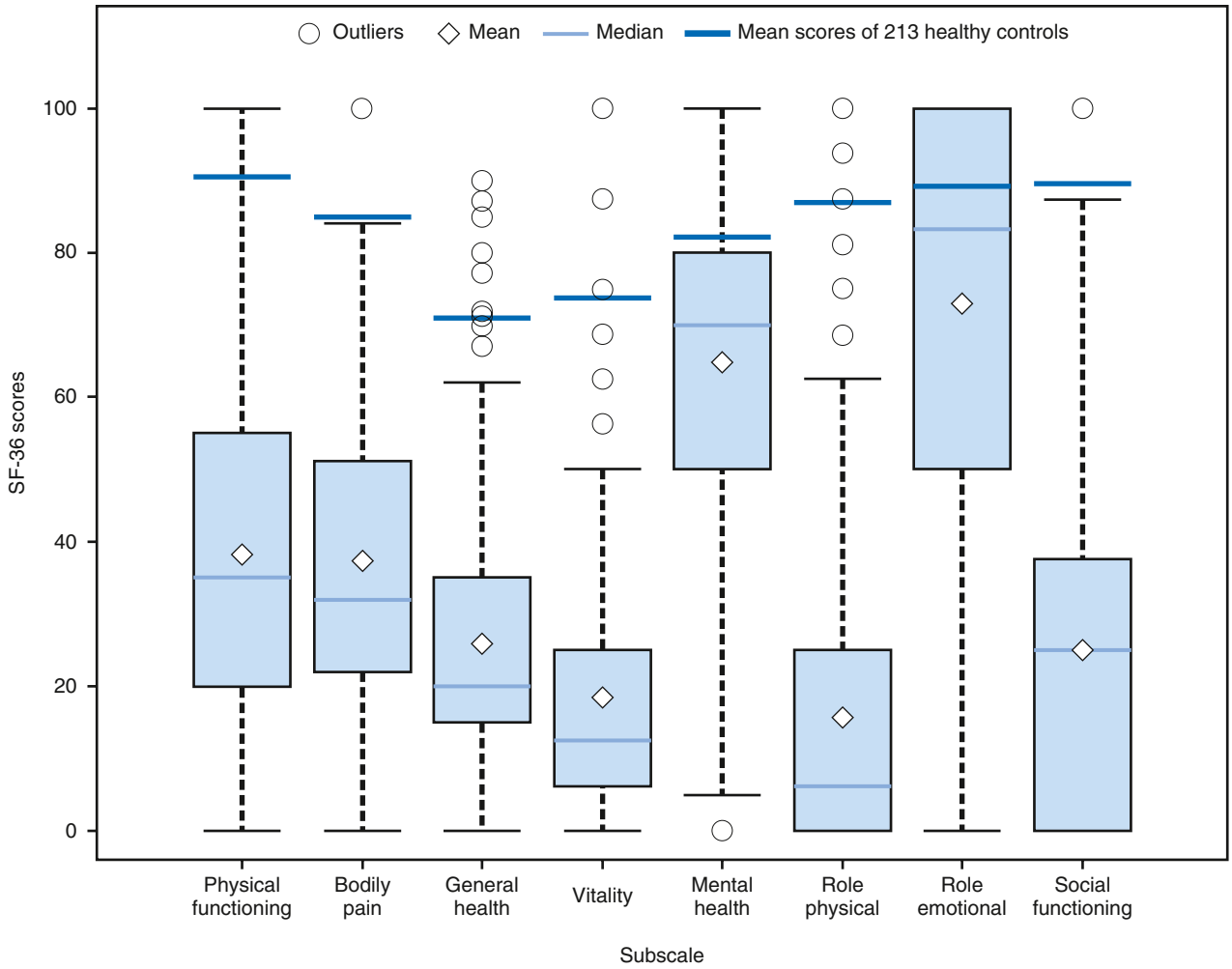

Fig. 212.3 Functional status* of 471 patients enrolled in the CDC Multisite Clinical Assessment† of ME/CFS§—United States, September 2015. *Measured by box plots of scores in the eight subscales of Short-Form Health Survey (SF-36) scores (25th and 75th percentile at *bottom* and *top* of box). SF-36 scores range from 0 to 100, with higher scores indicating better functioning. †https://www.cdc.gov/cfs/programs/clinical-assessment/index.html. §ME/CFS (myalgic encephalomyelitis/chronic fatigue syndrome) patients show significant impairment, particularly in vitality and physical functioning subscale scores, but with preservation of mental health and emotional role functioning. *(From Unger ER, Lin JMS, Brimmer DJ, et al. CDC Grand Rounds: Chronic fatigue syndrome—advancing research and clinical education. MMWR. 2016;65[50–51]:1434–1438.)*

The illness was formally defined in 1988 as *chronic fatigue syndrome* because persistent unexplained fatigue was considered the principal and invariable physical symptom. A variety of other names have been used to describe the illness, including *chronic mononucleosis, chronic Epstein-Barr virus (EBV) infection, postinfection syndrome,* and *immune dysfunction syndrome.* Several case definitions have been developed and are in use in both clinical care and research (Table 212.5).

The Institute of Medicine (IOM) 2015 recommendations apply to all ages and include a special focus on pediatrics. The IOM suggested new diagnostic criteria and a new name, **systemic exertion intolerance disease (SEID)**, to emphasize the postexertion malaise criterion and better understand the illness (Table 212.6).

EPIDEMIOLOGY

Based on worldwide studies, 0.2–2.3% of adolescents or children have CFS. Most epidemiology studies use the 1994 definition. CFS is more prevalent in adolescents than in younger children. The variation in CFS prevalence estimates may result from variations in case definition, study methodology and application, study population composition (specialty vs general practice or general population), and data collection (parent, self-reporting vs clinician evaluation). Gender distribution in children differs from that in adults, with a more equal distribution in children <15 years old, while remaining two-fold to three-fold higher in females 15-18 years old. Few studies have reported the incidence of CFS among children <10 years old. In adolescents in the Netherlands, the pediatrician-diagnosed incidence of CFS/ME was 0.01%, and in the United Kingdom, 0.5%.

PATHOGENESIS

Although the etiology and pathophysiology of CFS are unknown, some patients and clinicians correlate the onset with a recent episode of a viral illness such as infectious mononucleosis (10–12%) (EBV; see Chapter 301). A pathophysiologic relationship of CFS to infection is suggested because the symptoms and biologic markers elicited by the nonspecific innate host responses to infections in general are present in CFS. CFS-like illness after infectious mononucleosis is not predicted by viremia or altered host response to EBV infection, but is associated with the severity of the primary infection. A wide variety of other candidate viral infections have been associated with postinfectious fatigue syndromes, particularly in adolescents and adults. SARS CoV-2/COVID-19 infection has also been implicated, as patients with a history of COVID-19 infection have presented with symptoms similar to patients with ME/CFS, labeled long COVID, post-acute sequalae of SARS CoV-2 infection (PASC), or post–COVID-19 conditions (Table 212.7) (see

Table 212.5 Overview of Current Case Definitions for Systemic Exertion Intolerance Disease (SEID) and Past Definitions of Chronic Fatigue Syndrome or Myalgic Encephalomyelitis

SYMPTOM	SEID	CFS	ME
Fatigue and impairment of daily function	≥6 mo	≥6 mo	≥6 mo
Sudden onset	Yes	Yes	
Muscle weakness			Yes
Muscle pain		Yes	
Postexertional symptoms	Yes	Yes	Yes
Sleep disturbance	Yes		Yes
Memory or cognitive disturbances	Yes		Yes
Autonomic symptoms			Yes
Sore throat		Yes	
Lymph node involvement		Yes	
Cardiovascular symptoms	Yes		
Headaches		Yes	
Arthralgias		Yes	Yes

CFS, Chronic fatigue syndrome; ME, myalgic encephalomyelitis.
Data from Institute of Medicine. *Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Redefining an Illness*. Washington, DC: National Academies Press; 2015; Jason L, Evans M, Porter N, et al. The development of a revised Canadian myalgic encephalomyelitis chronic fatigue syndrome case definition. *Am J Biochem Biotechnol*. 2010;6:120–135; Reeves WC, Wagner D, Nisenbaum R, et al. Chronic fatigue syndrome—a clinically empirical approach to its definition and study. *BMC Med*. 2005;3:19.

Table 212.6 Criteria for Diagnosis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

Patient has each of the following three symptoms at least half the time to at least a moderately severe degree:

- A substantial reduction or impairment in the ability to engage in preillness levels of occupational, educational, social, or personal activities that persists for >6 mo and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest.
- Postexertional malaise*
- Unrefreshing sleep*

Plus at least one of the two following manifestations (chronic, severe):

- Cognitive impairment*
- Orthostatic intolerance

*Frequency and severity of symptoms should be assessed. The diagnosis of ME/CFS should be questioned if patients do not have these symptoms at least half of the time with moderate, substantial, or severe intensity.
From Institute of Medicine. *Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome*. Washington, DC: National Academies Press; 2015.

Table 212.7 WHO Definition of Long (Post)–COVID-19 Condition

- Post–COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 mo from the onset of COVID-19, with symptoms that last for at least 2 mo and cannot be explained by an alternative diagnosis.
- Common symptoms include fatigue, shortness of breath, and cognitive dysfunction and generally have an impact on everyday functioning.
- Symptoms might be new onset after initial recovery from an acute COVID-19 episode or persist from the initial illness.
- Symptoms might also fluctuate or relapse over time; a separate definition might be applicable for children.

Modified from Munblit D, O'Hara ME, Akrami A, et al. Long COVID: Aiming for a consensus. *Lancet Respir Med*. 2022;10(7):632–634.

Chapter 449.1). Similar features have been described in **post–intensive care syndrome.**

Similarities between CFS symptoms and those experienced by patients with autoimmune and other inflammatory disorders suggests primary perturbation of immune function in the pathogenesis of CFS. Hypogammaglobulinemia and hypergammaglobulinemia, immunoglobulin subclass deficiencies, elevated levels of circulating immune complexes, altered helper/suppressor lymphocyte ratios, natural killer cell dysfunction, elevated cytokines, and monocyte dysfunction have been inconsistently reported in adult patients with CFS. These findings have not been consistent among studies. CFS patients as a group differ from healthy controls, but most laboratory values of the immune parameters are not outside the normal range.

Autonomic nervous system (ANS) changes are suggested by the **orthostatic intolerance** (OI) experienced by some patients with CFS. OI syndromes with circulatory dysfunction include **neutrally mediated hypotension** and **POTS** and have been observed in some patients with CFS and could contribute to the syndrome. The pathophysiology of these manifestations among adolescents with CFS is unclear, but in postinfectious states could be associated with unreplenished fluid and electrolyte losses associated with acute infection or immune-mediated injury (autoantibodies directed against ANS).

Because the widespread musculoskeletal pain in CFS is similar to **fibromyalgia**, and because some consider these to be overlapping syndromes, fibromyalgia and CFS may share similarities in pathogenesis. Other hypotheses under investigation for the biologic basis of CFS involve alterations in energy metabolism (e.g., mitochondrion, particularly as related to exercise intolerance and postexertion malaise), alterations in sleep, the stress response, and the hypothalamic-pituitary axis. Understanding CFS has proved so challenging because it likely represents more than one underlying pathophysiology. Current studies and guidelines are attempting to stratify or subgroup patients to address this possibility.

CLINICAL MANIFESTATIONS

The dominant symptom expressed by adolescents and adults is a substantial reduction or impairment in the ability to engage in pre-illness levels of activity, accompanied by fatigue (see Fig. 212.2). In younger children, who often do not spontaneously report symptoms, exertion induces behavioral changes, manifested by a lack of their usual energy and reduced participation in activities. In adolescents, fatigue and postexertion malaise may lead to decreased participation in school, family activities, and social exchange.

Cognitive impairment includes reported difficulties in concentrating, which are common and indicated by reduced participation in school, difficulty keeping up with homework, and a drop in grades. Sleep may be impaired, and nonrestorative sleep is common. Other sleep complaints include difficulty falling asleep and staying asleep, whereas diagnosed sleep disorders, including restless legs syndrome, parasomnias, and sleep apnea, are less common. Myalgia and arthralgia may accompany fatigue and altered sleep. Sore throat and cervical lymph node tenderness can occur but may be part of an inciting illness. Adolescents also have increased reports of headache, abdominal pain, nausea, and sensitivity to light and sound with amplified pain.

Patients diagnosed with CFS in primary care practices are more likely to report abrupt onset of their symptoms, often as part of an initial virus-like illness, whereas gradual onset is more common in those identified in population-based studies. School absenteeism is a major social issue. In one study, two thirds of adolescents missed >2 weeks over a 6-week observation period, and one third required home tutoring. Unlike school phobia, inactivity due to CFS persists on the weekends and during holidays the same as it does during the school week.

Although fatigue and accompanying symptoms are subjective, the magnitude of impairment of each component can be measured by questionnaires addressing pain and function or, in the case of suspected orthostatic instability, by recording routine supine and standing heart rate and blood pressure measurements. Fatigue cannot be dismissed as a minor ailment. It generally manifests as lassitude, profound tiredness, intolerance of exertion with easy fatigability, and general malaise.

Abnormal physical examination findings are conspicuously absent, providing both reassurance and consternation for the patient, family, and physician. The presence of "alarm symptoms" such as weight loss, chest pain with exertion, paresthesia, dry mouth and eyes, fevers, diarrhea, cough, night sweats, and rash is uncommon and warrants consideration of a diagnosis other than CFS.

DIAGNOSIS

There are no pathognomonic signs or diagnostic tests for CFS. The diagnosis is clinically defined based on inclusion and exclusion criteria (Fig. 212.4). The diagnostic criteria are applicable to adults and adolescents >11 years old because of the current requirement for a self-generated history. Whereas duration of symptoms is 3-6 months depending on age, symptom management should not wait until this criterion is met.

CFS is difficult to diagnose in children, who may have difficulty describing their symptoms and articulating their concerns. Sole reliance on parental history can be fraught with confusion because parents may also struggle to interpret their children's symptoms and feelings in providing accurate historical information. A combination of child and parent reporting is most effective. It is important to document the child's activity levels and worsening of symptoms after physical or mental endeavors. Changes in participation in hobbies and family or other social activities can help identify the impact of CFS on function.

The diagnosis of CFS can be established only after other medical and psychiatric causes of fatigue and other symptoms, many of which are treatable, have been excluded. These include medical conditions presenting with chronic symptoms, such as hypothyroidism,

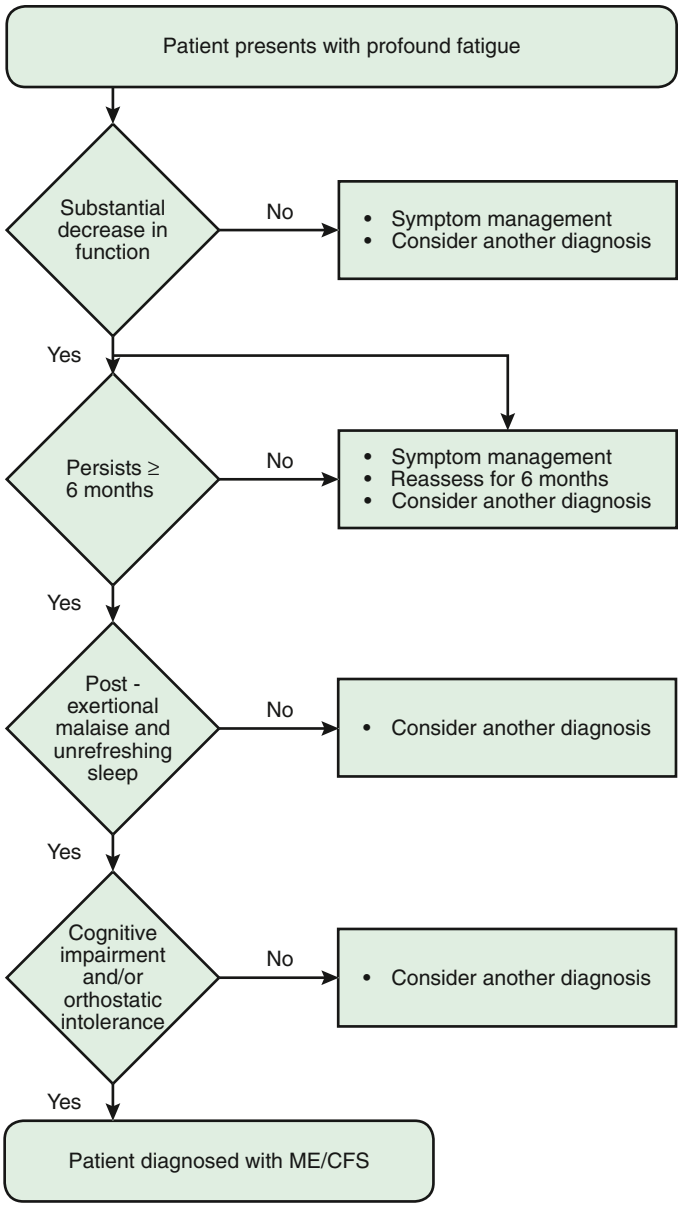

Fig. 212.4 Diagnostic algorithm for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). ANS, autonomic nervous system; HPA, hypothalamic-pituitary axis. *(From Institute of Medicine. Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. Washington, DC: National Academies Press; 2015.)*

adrenal insufficiency, respiratory and food allergies, sleep apnea, narcolepsy, substance abuse, posttraumatic stress disorder, adverse drug reactions, and obesity. A previously diagnosed medical condition with incomplete or uncertain resolution that may explain fatigue needs be considered.

Certain illnesses (e.g., fibromyalgia), amplified pain syndrome, post–COVID-19 condition, post–intensive care syndrome, and depression share similar symptoms with CFS but are not exclusionary diagnoses. These should be considered in the differential diagnosis in select cases. There is concern that CFS might be mistaken for readily identifiable psychiatric disorders such as anxiety and mood disorders, but evidence supports differences in their clinical presentation from CFS. CFS should not be diagnosed in persons with a prior diagnosis of major depressive disorder with psychotic or melancholic features, bipolar affective disorders, schizophrenia

of any subtype, delusional disorders of any subtype, dementia of any subtype, eating disorder of any type, or alcohol or other substance abuse within 2 years before the onset of the chronic fatigue or any time thereafter.

Although evaluation of each patient should be individualized, initial laboratory evaluation should be limited to screening laboratory testing sufficient to provide reassurance of the lack of significant medical illness. Further evaluation should be directed primarily toward excluding treatable illnesses that may be suggested by the history, symptoms, signs, or physical exam findings present in specific patients.

MANAGEMENT

Management of CFS is based on relief of the core and most disruptive symptoms in the individual patient. The diagnostic criterion of 6 months duration of illness should not delay evaluation and symptom management, because these may be initiated as soon as the child or adolescent presents with a CFS-like picture. Problems with sleep can be addressed by encouraging patients to adopt good sleep habits using standard sleep hygiene techniques. It may be beneficial to refer the patient to a sleep medicine specialist for the identification and treatment of sleep disorders and disturbances. Once pain is found not to be related to other specific disease or illness, nonpharmacologic treatment is indicated.

One of the nonpharmacologic approaches to pain management, CBT, may also assist the patient in managing and coping with CFS. Through explanation and changes in perception of the illness, CBT may help patients and their families develop coping skills and provide emotional support. Improved methods of coping may allow some improved function while living with the illness. Comorbid psychiatric conditions such as anxiety require appropriate evaluation and intervention. Guided graded-exercise therapy may be beneficial and added to CBT.

Although the overall goal is to help patients with CFS tolerate activity, children and adolescents with CFS should limit physical or mental efforts that result in aggravated symptoms. Return to school should be initiated gradually and systematically with the goal to return to full-time attendance. Home tutoring, cyber-school, and partial attendance can be interim steps. Parents and clinicians can work with teachers and school administrators to define appropriate expectations for attendance and performance for children with CFS. Because of the crucial importance of learning socialization skills, even brief attendance in school or participation in school activities should be encouraged, remembering that too rapid remobilization usually exacerbates symptoms and should be avoided.

Continued empathy and support by the treating physician are crucial in maintaining a physician-parent-patient relationship that is conducive to managing this illness. Careful attention must be directed to family dynamics to identify and resolve family problems or psychopathology that may be contributing to children's perception of their symptoms.

PROGNOSIS

The natural history of CFS is highly variable, and patients and families understand that the symptoms will wax and wane. Children and adolescents with CFS appear to have a more optimistic outcome than adults, typically with an undulating course of gradual improvement over several years. Overall, a good functional outcome has been reported in up to 80% of patients. Poor prognostic factors include gradual onset, increased school absenteeism, lower socioeconomic status, chronic maternal health problems, and untreated comorbid individual and family psychiatric disorders. Favorable prognostic factors include patient control of the rehabilitation program, with continuing support from health professionals and family members, and improvement in orthostatic intolerance.

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Chapter 213

Miscellaneous Conditions Associated with Arthritis

Angela Byun Robinson and C. Egla Rabinovich

RELAPSING POLYCHONDRITIS

Relapsing polychondritis (RP) is a rare condition characterized by episodic chondritis causing cartilage destruction and deformation of the ears (sparing the earlobes), nose, larynx, and tracheobronchial tree. Antibodies to matrillin-1 and collagen (types II, IX, and XI) are present in approximately 60% of patients with RP, suggesting an autoimmune pathogenesis. Patients may experience arthritis, uveitis, and hearing loss resulting from inflammation near the auditory and vestibular nerves. Children may initially relate episodes of intense erythema over the outer ears. Other dermatologic manifestations may include erythema nodosum, maculopapular rash, and purpura. Cardiac involvement, including conduction defects and coronary vasculitis, has been reported. Severe, progressive, and potentially fatal disease resulting from destruction of the tracheobronchial tree and airway obstruction is unusual in childhood. **Diagnostic criteria** established for adults are useful guidelines for evaluating children with suggestive symptoms (Table 213.1). The clinical course of RP is variable; flares of disease are often associated with elevations of acute-phase reactants and may remit spontaneously. Although seen more often in the adult population, RP may coexist with other rheumatic disease (e.g., systemic lupus erythematosus, Sjögren syndrome, Henoch-Schönlein purpura) in up to 30% of patients. The differential diagnosis includes **ANCA-associated vasculitis** (granulomatosis with polyangiitis) (see Chapter 210.4) and **Cogan syndrome**, which is characterized by auditory nerve inflammation and keratitis but not chondritis. **MAGIC** (mouth and genital ulcers with inflamed cartilage) syndrome has many similarities to Behçet disease (see Chapter 202). A genetic syndrome named vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome is caused by somatic pathogenic variants affecting the *UBA1* gene. Adolescent and adult patients (most are male) with this syndrome may have fevers, myalgia, arthralgia, auricular chondritis, and erythema nodosum. Approximately 50% of patients with VEXAS meet criteria for relapsing polychondritis. Between 5% and 10% of patients originally thought to have RP have pathogenic variants in *UBA1*. Affected patients have a high CRP and ESR in addition to lower platelet counts when compared with patients with only RP.

Many children respond to nonsteroidal antiinflammatory drugs, but some require corticosteroids or other immunosuppressive agents

Table 213.1 Suggested Criteria for Relapsing Polychondritis*

MAJOR
Typical inflammatory episodes of ear cartilage
Typical inflammatory episodes of nose cartilage
Typical inflammatory episodes of laryngotracheal cartilage
MINOR
Eye inflammation (conjunctivitis, keratitis, episcleritis, uveitis)
Hearing loss
Vestibular dysfunction
Seronegative inflammatory arthritis

*The diagnosis is established by the presence of two major or one major and two minor criteria. Histologic examination of affected cartilage is required when the presentation is atypical.

Data from Michet CJ Jr, McKenna CH, Luthra HS, et al. Relapsing polychondritis: Survival and predictive role of early disease manifestations. *Ann Intern Med.* 1986;104:74–78.

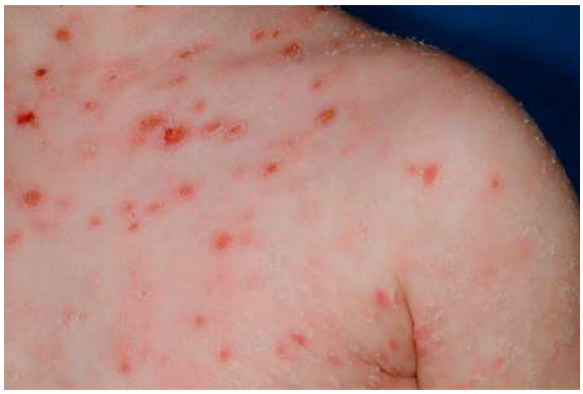

Fig. 213.1 Pityriasis lichenoides et varioliformis acuta (PLEVA). Symmetric, oval and round, reddish brown macular, papular, necrotic, and crusted lesions on the chest of 9-yr-old boy. *(From Paller AS, Mancini AJ, eds.* Hurwitz Clinical Pediatric Dermatology*, 5th ed. Philadelphia: Elsevier; 2016: Fig. 4-33, p. 87.)*

(azathioprine, methotrexate, hydroxychloroquine, colchicine, cyclophosphamide, cyclosporine, and anti–tumor necrosis factor [TNF] agents), as reported in small series and case reports.

MUCHA-HABERMANN DISEASE/PITYRIASIS LICHENOIDES ET VARIOLIFORMIS ACUTA

Pityriasis lichenoides et varioliformis acuta **(PLEVA)** is a benign, self-limited cutaneous vasculitis characterized by episodes of macules, papules, and papulovesicular lesions that can develop central ulceration, necrosis, and crusting (Fig. 213.1). Different stages of development are usually seen at once. **PLEVA fulminans** or febrile ulceronecrotic Mucha-Habermann disease **(FUMHD)** is the severe, life-threatening form of PLEVA. Large, coalescing, ulceronecrotic lesions are seen, accompanied by high fever and elevated ESR. Systemic manifestations can include interstitial pneumonitis, abdominal pain, malabsorption, arthritis, and neurologic manifestations. PLEVA has a male predominance and occurs more frequently in childhood. The diagnosis is confirmed by biopsy of skin lesions, which reveals perivascular and intramural lymphocytic inflammation affecting capillaries and venules in the upper dermis that may lead to keratinocyte necrosis. Phototherapy has been used in some cases of PLEVA. When disease is severe, corticosteroids have been used with questionable effect, and methotrexate has been reported to induce rapid remission in resistant cases. Cyclosporine and anti-TNF agents have also been efficacious in case reports.

SWEET SYNDROME

Sweet syndrome, or **acute febrile neutrophilic dermatosis**, is a rare entity in children. It is characterized by fever, elevated neutrophil count, and raised, tender erythematous plaques and nodules over the face, extremities, and trunk. Skin biopsy reveals neutrophilic perivascular infiltration in the upper dermis. Female predominance is seen in the adult population, whereas gender distribution is equal in children. Established criteria are useful for diagnosis (Table 213.2). Children can also have arthritis, multifocal nonbacterial osteomyelitis, myositis, and other extracutaneous manifestations. Sweet syndrome may be idiopathic or secondary to malignancy (particularly acute myelogenous leukemia), drugs (granulocyte colony-stimulating factor, tretinoin, azathioprine, or trimethoprim-sulfamethoxazole), or rheumatic diseases (Behçet disease, antiphospholipid antibody syndrome, systemic lupus erythematosus). It has also been reported in association with COVID-19, VEXAS, CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature), Majeed syndrome, and deficiency of interleukin-1 receptor antagonist (DIRA) and pyrin associated autoinflammation with neutrophilic dermatosis (PAAND) syndromes (see Chapter 204). **The condition usually responds to treatment with corticosteroids, treatment of underlying disease, or removal of the associated medication.**

HYPERTROPHIC OSTEOARTHROPATHY

Children with chronic disease, especially pulmonary or cardiac disease, can demonstrate clubbing of the terminal phalanges and have associated periosteal reaction and arthritis. These findings characterize the classic presentation of hypertrophic osteoarthropathy (HOA). HOA can be **primary** (idiopathic) or secondary. Although rare, **secondary** HOA is more common in children and is seen in those with chronic pulmonary disease (cystic fibrosis), congenital heart disease, gastrointestinal disease (malabsorption syndromes, biliary atresia, inflammatory bowel disease), and malignancy (nasopharyngeal sarcoma, osteosarcoma, Hodgkin disease). It may precede a diagnosis of cardiopulmonary disease or malignancy. The pathogenesis of secondary HOA is unknown; symptoms often improve if the underlying condition is treated successfully. HOA-related pain can be disabling; in adults, management with bisphosphonates has been reported. Evaluation of children presenting with HOA should include a chest radiograph to evaluate for pulmonary disease or intrathoracic mass. Autosomal recessive pathogenic variants in prostaglandin pathway genes have been described in primary HOA, also described as **pachydermoperiostosis**.

Table 213.2 Diagnostic Criteria for Classic Sweet Syndrome*

MAJOR CRITERIA
Abrupt onset of painful erythematous plaques or nodules
Histopathologic evidence of dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis
MINOR CRITERIA
Pyrexia >38°C
Association with underlying hematologic or visceral malignancy, inflammatory disease, or pregnancy *or* preceded by an upper respiratory or gastrointestinal infection or vaccination
Excellent response to systemic corticosteroids or potassium iodide
Abnormal laboratory values at presentation (three of four):
Erythrocyte sedimentation rate >20 mm/hr
Positive C-reactive protein test result
>8,000 leukocytes/mm^3
>70% neutrophils/mm^3

*The diagnosis is established by the presence of two major criteria plus two of the four minor criteria.

Adapted from Walker DC, Cohen PR. Trimethoprim-sulfamethoxazole-associated acute febrile neutrophilic dermatosis: Case report and review of drug induced Sweet's syndrome. *J Am Acad Dermatol.* 1996;34:918–923.

PLANT THORN SYNOVITIS

A diagnosis of plant thorn synovitis should be considered in children with monoarticular arthritis nonresponsive to antiinflammatory therapy. Acute or chronic arthritis can occur after a plant thorn or other foreign object penetrates a joint. Unlike septic arthritis, children with plant thorn synovitis are usually afebrile. The most common organism seen with plant thorn synovitis is *Pantoea agglomerans,* although cultures are often negative. The initial injury may be unknown or forgotten, making the diagnosis difficult. Ultrasound or MRI can be useful in identifying the foreign body. **Removal of the foreign body using arthroscopy, followed by an antibiotic course, is the accepted therapy.**

PIGMENTED VILLONODULAR SYNOVITIS

Proliferation of synovial tissue is seen in pigmented villonodular synovitis (PVNS). This proliferation is localized or diffuse and can affect the joint, tendon sheath, or bursa. Macrophages and multinucleated giant cells with brownish hemosiderin are present histologically. It is unclear if the etiology of PVNS is inflammatory or neoplastic in nature. Although findings are not pathognomonic, MRI with contrast is a useful diagnostic tool by which PVNS can be seen as a mass or bone erosion. Brown or bloody synovial fluid is seen with arthrocentesis, but the diagnosis is made by tissue biopsy. **Surgical removal of the affected tissue is the therapeutic modality, and with diffuse disease, a total synovectomy is recommended**.

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