Rheumatic Diseases of Childhood

PART XVI

Chapter 153

Evaluation of Suspected Rheumatic Disease

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Rheumatic diseases are defined by the constellation of results of the physical examination, autoimmune marker 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 results may be positive in the absence of disease. Further complicating the 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, 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 a rheumatic disease, 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 on the basis of 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 153-1). 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 a **pain syndrome** (e.g., fibromyalgia). If arthralgia is accompanied by a history of dry skin, hair loss, fatigue, growth disturbance, and/or cold intolerance, testing for **thyroid disease** is merited. Nighttime awakenings because of severe pain along with decreased platelet count or white blood cell count or, alternatively, a very high white blood cell 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 girl presenting with knee pain aggravated by walking up stairs and on patellar distraction likely has **patellofemoral syndrome**. Children ages 3 to 10 yr who have a history of episodic pain that occurs at night 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 age 3 to 10 yr, that is increased with activity and is associated with hyperextensible joints on exam is likely **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 183.1).

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 and/or stiffness after physical inactivity (gelling phenomenon). A diagnosis of chronic juvenile arthritis cannot be made without the finding of arthritis on physical examination (see Chapters 155 and 156), and there are no laboratory tests diagnostic of juvenile rheumatoid arthritis or any other chronic inflammatory arthritis in childhood.

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 commonly present in SLE, vasculitis, and the chronic childhood arthritides. 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 mandated in any child in whom a rheumatic disease is suspected, because many rheumatic diseases have associated subtle physical findings that will 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 153-2; see Fig. 158-1*A*), especially in an adolescent girl. Diffuse facial rash is more indicative of JDM. A hyperkeratotic rash on the face or around the ears of an adolescent African-American girl may represent discoid lupus (see Fig. 158-1*D*). A palpable purpuric rash on the extensor surfaces of the lower extremities points to **Henoch-Schönlein purpura** (see Fig. 167-1*A*). 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 and SLE. Gottron papules (see Fig. 159-2) and heliotrope rashes (see Fig. 159-1) along with erythematous rashes on the elbows and knees are pathognomonic of JDM. Dilated capillary loops in the nail beds (periungual telangiectasias; see Fig. 159-3) 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. 155-12). 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. 158-1*D*); 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 (formally Wegener granulomatosis; see Fig. 167-4) but is also seen in relapsing polychondritis and syphilis.

Table 153-1 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 post-infectious 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 rheumatoid 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.

Table 153-2 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 chronic arthritis of childhood; MCTD associated with diffuse puffiness of hands	Postviral arthritis, reactive arthritis, trauma, infection, Lyme disease, Kawasaki disease, malignancy, overuse syndromes

ANCA, antineutrophilic cytoplasmic antibody; HSP, Henoch-Schönlein purpura; HSV, herpes simplex virus; JDM, juvenile dermatomyositis; MCTD, mixed connective tissue disease; PFAPA, periodic fever, aphthous stomatitis, pharyngitis and adenitis; SLE, systemic lupus erythematosus.

Alopecia can be associated with SLE but is also found in localized scleroderma (see Fig. 160-4) 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 juvenile arthritis. Erythematous conjunctiva may be a result of uveitis or episcleritis associated with juvenile rheumatoid arthritis, 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 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 points to Wegener granulomatosis, microscopic angiitis, or SLE. Pulmonary vascular aneurysms are indicative of Behçet disease.

Arthritis is defined by the presence of intraarticular swelling or 2 or more of the following findings on joint examination: pain on motion, loss of motion, erythema, and heat. Arthritis is present in all of 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, infections such as septic arthritis, Lyme disease, osteomyelitis, viral infections (such as rubella, hepatitis B, parvovirus B19), and postinfectious etiologies such as Epstein-Barr virus, 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, as both of 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 153-3 and 153-4). 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.

One essential laboratory test for rheumatic disease assessment is the complete blood count, as it yields many diagnostic clues. Elevated white blood cell count is compatible with malignancy, infection, systemic JIA, and vasculitis. Leukopenia can be caused by postinfectious, especially viral, etiologies, 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

Table 153-3 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.
Modified from Aggerwal A: Clinical application of tests used in rheumatology, Indian J Pediatr *69:889–892, 2002.*

be caused by any chronic illness, but hemolytic anemia (positive Coombs test result) may point to SLE or MCTD. Rheumatoid factor is present in less than 10% of children with JIA and thus has poor sensitivity as a diagnostic tool; it may be elevated by infections such as endocarditis, tuberculosis, syphilis, viral infections (parvovirus B19, hepatitides B and C, mycoplasma) as well as primary biliary cirrhosis and malignancies. In a child with chronic arthritis, rheumatoid factor serves as a prognostic indicator.

Inflammatory markers (erythrocyte sedimentation rate, C-reactive protein level) are nonspecific and are elevated in infections and malignancies as well as rheumatic diseases. Their levels may also be normal in rheumatic diseases such as arthritis, scleroderma, and dermatomyositis. Inflammatory marker measurements are more useful in rheumatic diseases for following response to treatment than as diagnostic tests. Muscle enzymes include aspartate aminotransferase, alanine aminotransferase, creatinine phosphokinase, aldolase, and lactate dehydrogenase, any of which may be elevated in JDM as well as in other diseases causing muscle breakdown. Muscle-building supplements, medications, and extreme physical activity may also cause muscle breakdown and enzyme elevations. Aspartate aminotransferase, alanine aminotransferase, and aldolase are also elevated secondary to liver disease, and a γ-glutamyltransferase measurement may help differentiate whether the source is muscle or liver.

The use of an antinuclear antibody (ANA) measurement as a screening test is not recommended, as it has low specificity. A positive ANA test result may be induced by infection, especially Epstein-Barr virus infection, endocarditis, and parvovirus B19 infection. The ANA test result is also positive in up to 30% of normal children and the level of ANA is increased in those with a 1st-degree relative with a known rheumatic disease. In the majority of children with a positive ANA test result without signs of a rheumatic disease on initial evaluation, autoimmune disease does not develop disease 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. 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 153-3).

IMAGING STUDIES

Plain radiographs are useful in evaluation of arthralgias and arthritis, as they offer reassurance in benign pain syndromes and their findings are often abnormal in malignancies, osteomyelitis, and long-standing chronic juvenile arthritis. Radionucleotide bone scans help localize areas of abnormality in the patient with diffuse pains caused by osteomyelitis, neuroblastoma, chronic multifocal osteomyelitis, and systemic arthritis. 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. Cardiopulmonary evaluation is suggested for diseases commonly affecting the heart and

Table 153-4 Evaluation Based on Suspected Diagnosis

SUSPECTED RHEUMATIC DISEASE(S)	INITIAL EVALUATION	FURTHER EVALUATION	SUBSPECIALTY EVALUATION
SLE, 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
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
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 159); HRCT of chest; consider renal and lung biopsy
Localized scleroderma	Skin biopsy, CBC, ESR		Serum immunoglobulin G, 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 gastrointestinal radiography series

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

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 153-4).

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Chapter 154

Treatment of Rheumatic Diseases

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Nonpharmacologic as well as 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. A key predictor of long-term outcome consists of early recognition and referral to a rheumatology team experienced in the specialized care of children with rheumatic diseases. Significant differences in outcome are seen 10 yr after disease onset in patients with juvenile idiopathic arthritis (JIA) depending on whether referral to a pediatric rheumatology center was accomplished within 6 mo of onset.

PEDIATRIC RHEUMATOLOGY TEAMS AND PRIMARY CARE PHYSICIANS

The **multidisciplinary pediatric rheumatology team** (Table 154-1) offers coordinated services for children and their families. General principles of treatment include: early recognition of signs and symptoms of rheumatic disease with timely referral to rheumatology for prompt initiation of treatment; monitoring for disease complications and adverse effects of treatment; coordination of subspecialty care and rehabilitation services with communication of clinical information; and child- and family-centered chronic illness care, including self-management support, alliance with community resources, partnership 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 partnership with the primary care provider, who helps coordinate care, monitor compliance with treatment plans, ensure appropriate immunization, monitor for medication toxicities, and

Table 154-1 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, 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 (see Table 155-4) • Screening for medication-related ocular toxicity (hydroxychloroquine, glucocorticoids) Nephrology Orthopedics Dermatology Gastroenterology
Physical and psychosocial growth and development	Nutrition: • Addressing undernourishment from systemic illness, obesity/overnourishment from glucocorticoids School integration: • Individualized Educational Plan (IEP) or 504 plan Peer group relationships Individual and/or 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

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 on the basis of diagnosis, disease severity, anthropometrics, and adverse effect profile. Many drug therapies used do not have U.S. Food and Drug Administration (FDA) indications for pediatric rheumatic diseases given the relative rarity of these conditions. The evidence base may be limited to case series, uncontrolled studies, or extrapolation from use in adults. The exception is JIA, for which there is a growing body of randomized control trial evidence, particularly for newer therapeutics. Therapeutic agents used for treatment of childhood rheumatic diseases (Table 154-2) have various mechanisms of action, but all suppress inflammation. **Both biologic and nonbiologic disease-modifying antirheumatic drugs (DMARDs) directly affect the immune system**. DMARDs 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

Nonsteroidal antiinflammatory drugs (NSAIDs) are prescribed to decrease both the pain and 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 JIA is 4-6 wk 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 celecoxib and meloxicam to be 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 occurs less frequently in children. Less-common adverse effects, occurring in ≤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 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 owing to 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-wk 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 mo, though 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 relative low toxicity over prolonged periods of treatment. The mechanism of action low-dose MTX in arthritis is complex but is believed

Table 154-2 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 divided 3 times daily Max 2400 mg per day			
	Naproxen[a]	15 mg/kg/day PO in 2 divided doses Maximum 1,000 mg per day			
	Celecoxib[a]	10-25 kg: 50 mg PO twice daily >25 kg: 100 mg PO twice daily			
	Meloxicam[a]	0.125 mg/kg, maximum 7.5 mg, PO once daily			
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	5-6 mg/kg PO once daily; do not exceed 6.5 mg/kg/daily Maximum dose 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 divided in twice-daily doses Adult maximum 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
Tumor necrosis factor α (TNF-α) antagonists	Adalimumab[a]	SC once every other wk: 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 (maximum 50 mg/dose) or 0.4 mg/kg SC twice weekly (maximum 25 mg/dose)	JIA	Injection site reactions, infections, rash, demyelinating disorders, cytopenias, potential increased malignancy risk	TB test; CBC
	Infliximab	5-10 mg/kg IV q4-8wk	JIA Spondyloarthropathy Uveitis Sarcoidosis	Infusion reactions, hepatitis, potential increased malignancy risk	TB test; anti-dsDNA, LFTs

*Consult a clinical pharmacology reference for current dosing and monitoring guidelines, and complete list of known adverse effects.

Continued

Table 154-2 Therapeutics for Childhood Rheumatic Diseases—cont'd

CLASSIFICATION	THERAPEUTIC[†]	DOSE	INDICATION[†]	ADVERSE REACTIONS	MONITORING
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	JIA	Infection, headache, potential increased malignancy risk	
Anti-CD20 (B cell) antibody	Rituximab	575 mg/m^2, maximum 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 1 antagonist	Anakinra	1-2 mg/kg/daily Adult maximum 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	
Interleukin-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 immunoglobulin	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 (maximum 1.5 g) monthly for 6-mo induction, then every 2-3 mo Oral regimen: 1-2 mg/kg/daily; maximum 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: maximum 1,200 mg/m^2/day PO (up to 2 g/day) divided twice daily Capsules: maximum 1,500 mg/day PO for BSA 1.25-1.5 m^2, 2 g/day PO for BSA >1.5 m^2 divided twice daily	SLE Uveitis	GI intolerance (diarrhea, nausea, vomiting), renal impairment, neutropenia, teratogenesis, secondary malignancy, PML	CBC, BMP

Table 154-2 Therapeutics for Childhood Rheumatic Diseases—cont'd

CLASSIFICATION	THERAPEUTIC[†]	DOSE	INDICATION[†]	ADVERSE REACTIONS	MONITORING
Glucocorticoids	Prednisone[a,d-f]	0.05-2 mg/kg/day PO given in 1-4 divided doses; maximum 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 q6-12h For severe manifestations: 30 mg/kg/dose (maximum 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

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; Ig, immunoglobulin; IM, intramuscular(ly); IV, intravenous(ly); IVIG, intravenous immunoglobulin; 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.

[†]Therapeutics used in practice may not have a 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 available in this class.

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, which inhibits the production of proinflammatory cytokines including 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, especially in children with polyarticular JIA. 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 or 30 mg/m^2/wk). Subcutaneous administration of MTX is similar in absorption and pharmacokinetic properties to intramuscular injection, with less pain. MTX is commonly used in 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 qualitatively different from that observed with treatment of neoplasms. In 8 published studies including 288 patients with JIA taking MTX, adverse effects included 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 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 and no evidence of even moderate liver damage. Children 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 infection. Regression of lymphoma may follow withdrawal of MTX.

Monitoring laboratory tests for MTX toxicity include CBC and LFTs at regular intervals, initially every 4 wk for the 1st 3 mo of treatment, then every 8-12 wk, 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 mo 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 <6.5 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 stimulation, and myositis.

Leflunomide

Leflunomide is a DMARD approved for treatment of rheumatoid arthritis that offers an alternative to MTX for treatment of JIA. MTX outperformed leflunomide for treatment of JIA in a randomized trial (at 16 wk, 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. Monitoring laboratory tests include CBC, LFTs, every 4 wk for the 1st 6 mo of treatment, then every 8-12 wk.

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) 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 1st 3 mo of treatment, monthly for 3 mo, every 3 mo for 1 yr, then every 6 mo.

Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is an immunosuppressive drug approved by the FDA for organ transplant rejection. In rheumatology, 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 less-adverse effects (infection, gonadal toxicity). Dosing is based on body surface area: 600 mg/m^2 orally twice daily, with maximum dosage limits varying by formulation and body surface area. The most common adverse reaction is GI intolerance. Infections, cytopenias, and secondary malignancies are among other adverse reactions reported.

Glucocorticoids

Glucocorticoids are given through oral, intravenous, ocular, topical, and intraarticular administration as part of treatment of rheumatic disease. Oral steroids are foundational treatment for moderate to severe lupus, dermatomyositis, and most forms of vasculitis; their long-term use is associated with a long list of 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.**

Intravenous steroids have been used to treat severe, acute manifestations of systemic rheumatic diseases such as SLE, dermatomyositis, and vasculitis. The intravenous 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 hr daily for 1-5 days, is the intravenous preparation of choice. Although generally associated with fewer adverse effects than oral steroids, intravenously administered steroids are associated with significant and occasionally life-threatening toxicities, such as cardiac arrhythmia, acute hypertension, hypotension, hyperglycemia, shock, pancreatitis, and avascular necrosis.

Ocular steroids 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 steroid use leads to cataract formation and glaucoma. Current ophthalmologic management has significantly decreased the frequency of blindness as a complication of JIA-associated uveitis.

Intraarticular steroids are being used with increasing frequency 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, with the anticipated response rate to knee injection being between 60% and 80% at 6 mo. 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.

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 B cells or suppression of T-cell activation (Table 154-3). The availability of these agents has dramatically increased the therapeutic options for treating rheumatic disease recalcitrant to nonbiologic therapies and they are, in some instances, becoming first-line interventions. A primary concern regarding biologic therapy is that when use is combined with other immunosuppressants, risk of malignancy may be increased.

Tumor Necrosis Factor-α Antagonists

Currently, 2 TNF antagonists have an FDA indication for treatment of children with moderate to severe polyarticular JIA (etanercept and adalimumab). *Etanercept* is a genetically engineered fusion protein consisting of 2 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

Table 154-3 Summary of Biologic Therapies Studied in Juvenile Idiopathic Arthritis and Their Method of Action

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; Ig, immunoglobulin; IL, interleukin; TNF, tumor necrosis factor.

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

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 mo of therapy. Dosing is 0.8 mg/kg subcutaneous weekly (maximum 50 mg/dose) or 0.4 mg/kg subcutaneously twice a week (maximum 25 mg/dose). Adalimumab is a fully human anti-TNF monoclonal antibody 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 20 mg for children weighing 15-30 kg and 40 mg for those weighing >30 kg.

Infliximab, a chimeric mouse-human monoclonal antibody, was tested in a randomized controlled clinical trial 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. Two additional anti-TNF agents—*golimumab*, a human monoclonal antibody against TNF, and *certolizumab pegol*, a pegylated humanized antibody against TNF—have been approved by the FDA for rheumatoid arthritis in adults and are currently in pediatric trials.

The most common adverse reactions 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, and invasive fungal infections in endemic areas. TNF blockade should not be initiated in subjects with history of chronic or frequent recurrent infections. Tuberculosis should be tested for prior to initiation of therapy with TNF antagonists. If test results are positive, antitubercular treatment must be administered before anti-TNF treatment can be started. There is a theoretically increased risk of malignancy with TNF-α antagonists, and there have been reports of 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, randomized controlled withdrawal trial in children whose disease had not responded to DMARDs, 53% of placebo-treated patients, compared with 20% of abatacept-treated patients, experienced disease flares during the double-blind withdrawal period. The frequency of adverse events did not differ between the groups. Abatacept is administered IV every other week for 3 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 wk) and then monthly thereafter.

B-Cell Depletion

Rituximab is a chimeric monoclonal antibody 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 as plasma cells are not removed. Rituximab is licensed for treatment of B-cell non-Hodgkin lymphoma and is FDA approved for use in adult rheumatoid arthritis and idiopathic thrombocytopenic purpura but does not have a pediatric indication. Rituximab 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 monoclonal antibody to B-lymphocyte stimulator that negatively affects B-cell proliferation, differentiation, and long-term survival. It was FDA-approved in March 2011 for treatment of SLE in adults and studies of long-term safety and efficacy are ongoing. Currently, belimumab is not FDA approved for use in pediatric SLE.

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 rheumatoid arthritis in adults. In meta-analyses of treatments for rheumatoid arthritis, anakinra was outperformed by TNF-α antagonists but has a special niche in pediatric rheumatology for treatment of systemic JIA (SoJIA) and other autoinflammatory syndromes, such as cryopyrin-associated periodic syndromes. The medication is dosed subcutaneously, 1-2 mg/kg, once daily. An IL-1β monoclonal antibody, *canakinumab* is FDA approved for use in cryopyrin-associated periodic syndromes dosed subcutaneously every 8 wk and SoJIA dosed subcutaneously every 4 wk. 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 as well as membrane-associated receptors. Tocilizumab has FDA approval for treatment of SoJIA and polyarticular JIA. Adverse reactions include transaminase and lipid elevations. Tocilizumab is given as an IV infusion every 2 (SoJIA) to 4 (polyarticular JIA) wk.

Intravenous Immunoglobulin

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 allergic–like reactions and post-infusion aseptic meningitis (headache, stiff neck).

Cytotoxics

Cyclophosphamide

Cyclophosphamide requires metabolic conversion in the liver to its active metabolites, which alkylate the guanine in DNA, leading to immunosuppression by the 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 mo, and then every 3 mo for 12-18 mo, have been shown to reduce the frequency of renal failure in patients with lupus and diffuse proliferative glomerulonephritis. Open trials suggest efficacy in severe central nervous system lupus. Oral cyclophosphamide (1-2 mg/kg/day) is effective as induction treatment of severe antineutrophilic cytoplasmic antibody-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. Thirty percent to 40% of adult women with lupus treated with intravenous cyclophosphamide 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 antineutrophilic cytoplasmic antibody-associated vasculitis following 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 SoJIA (see Chapter 155). There are case reports describing the successful use of *thalidomide*, or its analog *lenalidomide,* as treatment for SoJIA, 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 155

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 all 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 schemas exist, each with its own limitations. The former classification scheme of the American College of Rheumatology uses the term *juvenile rheumatoid arthritis* and categorizes the disease into 3 onset types (Table 155-1). Attempting to standardize nomenclature, The International League of Associations for Rheumatology (ILAR) proposed a different classification using the term **JIA** (Table 155-2), inclusive of all subtypes of chronic juvenile arthritis. We refer to the ILAR classification criteria; see Chapter 156 for enthesitis-related arthritis (ERA) and psoriatic JIA (Tables 155-3 and 155-4).

EPIDEMIOLOGY

The worldwide incidence of JIA ranges from 0.8-22.6/100,000 children per year, with prevalence ranges from 7-401/100,000. 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. It is estimated that 300,000 children in the United States 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 155-4). There is no sex predominance in systemic JIA (sJIA), but more girls than boys are affected in both oligoarticular (3:1) and polyarticular (5:1) JIA. The peak age at onset is between 2 and 4 yr for oligoarticular disease. Age of onset has a bimodal distribution in polyarthritis, with peaks at 2-4 yr and 10-14 yr. sJIA occurs throughout childhood with a peak between 1 and 5 yr.

Table 155-1 Criteria for the Classification of Juvenile Rheumatoid Arthritis

Age at onset: <16 yr
Arthritis (swelling or effusion, or the presence of 2 or more of the following signs: limitation of range of motion, tenderness or pain on motion, increased heat) in ≥1 joint
Duration of disease: ≥6 wk
Onset type defined by type of articular involvement in the 1st 6 mo after onset:
Polyarthritis: ≥5 inflamed joints
Oligoarthritis: ≤4 inflamed joints
Systemic-onset disease: arthritis with rash and a characteristic quotidian fever
Exclusion of other forms of juvenile arthritis

Modified from Cassidy JT, Levison JE, Bass JC, et al: A study of classification criteria for a diagnosis of juvenile rheumatoid arthritis, Arthritis Rheum *29:174–181, 1986.*

ETIOLOGY

The etiology and pathogenesis of JIA are not completely understood, though both immunogenetic susceptibility and an external trigger are considered necessary. 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 IL-1α. There is evidence that the IL-6 gene confers susceptibility to sJIA, with increased transmission of the −174G allele in patients older than 5 yr. 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.

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**, more like familial Mediterranean fever, than the other subtypes of JIA. This theory is also supported by work demonstrating similar expression patterns of a phagocytic protein (S100A12) in sJIA and familial Mediterranean fever, as well as the same marked responsiveness to IL-1 inhibitors.

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. 155-1). Advanced and uncontrolled disease leads to pannus formation and progressive erosion of articular cartilage and contiguous bone (Figs. 155-2 and 155-3).

CLINICAL MANIFESTATIONS

Arthritis must be present to make a diagnosis of any JIA subtype. Arthritis is defined by intraarticular swelling or the presence of 2 or more of the following signs: limitation in range of motion, 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 associated. Involved joints are often swollen, warm to touch, and painful on movement or palpation with reduced range of motion, 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.

Table 155-2 International League of Associations for Rheumatology Classification of Juvenile Idiopathic Arthritis (JIA)

CATEGORY	DEFINITION	EXCLUSIONS
Systemic	Arthritis in ≥1 joint with, or preceded by, fever of at least 2 wk in duration that is documented to be daily ("quotidian"*) for at least 3 days and accompanied by ≥1 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 the patient or a 1st-degree relative b. Arthritis in an HLA-B27–positive boy beginning after the 6th birthday c. Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter syndrome, or acute anterior uveitis, or a history of one of these disorders in a 1st-degree relative d. Presence of immunoglobulin M RF on at least 2 occasions at least 3 mo apart
Oligoarthritis	Arthritis affecting 1-4 joints during the 1st 6 mo of disease. Two subcategories are recognized: 1. Persistent oligoarthritis—affecting ≤4 joints throughout the disease course 2. Extended oligoarthritis—affecting >4 joints after the 1st 6 mo of disease	a, b, c, d (above) plus e. Presence of systemic JIA in the patient
Polyarthritis (RF-negative)	Arthritis affecting ≥5 joints during the 1st 6 mo of disease; a test for RF is negative	a, b, c, d, e
Polyarthritis (RF-positive)	Arthritis affecting ≥5 joints during the 1st 6 mo of disease; ≥2 tests for RF at least 3 mo apart during the 1st 6 mo of disease are positive	a, b, c, e
Psoriatic arthritis	Arthritis and psoriasis, or arthritis and at least 2 of the following: 1. Dactylitis‡ 2. Nail pitting§ and onycholysis 3. Psoriasis in a 1st-degree relative	b, c, d, e
Enthesitis-related arthritis	Arthritis and enthesitis,‖ or arthritis or enthesitis with at least 2 of the following: 1. Presence of or a 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 inflammatory bowel disease, Reiter syndrome, or acute anterior uveitis in a 1st-degree relative	a, d, e
Undifferentiated arthritis	Arthritis that fulfills criteria in no category or in ≥2 of the above categories.	

RF, rheumatoid factor.
**Quotidian fever* is defined as a fever that rises to 39°C (102.2°F) once a day and returns to 37°C (98.6°F) between fever peaks.
†*Serositis* refers to pericarditis, pleuritis, or peritonitis, or some combination of the 3.
‡*Dactylitis* is swelling of ≥1 digits, usually in an asymmetric distribution, that extends beyond the joint margin.
§A minimum of 2 pits on any 1 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.
From Firestein GS, Budd RC, Harris ED Jr, et al, editors: Kelley's textbook of rheumatology, *ed 8, Philadelphia, 2009, Saunders.*

Table 155-3 Characteristics of the American College of Rheumatology (ACR) and International League of Associations for Rheumatology (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
≤4 joints in 1st 6 mo after presentation	• Pauciarticular	• Oligoarthritis: a. Persistent: <4 joints for course of disease b. Extended: >4 joints after 6 mo
>4 joints in 1st 6 mo after presentation	• Polyarticular	• Polyarthritis rheumatoid factor–negative • Polyarthritis rheumatoid factor–positive
Fever, rash, arthritis	• Systemic-onset	• Systemic
Other categories included	Exclusion of other forms	• Psoriatic arthritis • Enthesitis-related arthritis • Undifferentiated: a. Fits no other category b. Fits more than 1 category
Inclusion of psoriatic arthritis, inflammatory bowel disease, ankylosing spondylitis	No (see Chapter 156)	Yes

Table 155-4 Overview of the Main Features of the Subtypes of Juvenile Idiopathic Arthritis

INTERNATIONAL LEAGUE OF ASSOCIATIONS FOR RHEUMATOLOGY SUBTYPE	PEAK AGE OF ONSET (Yr)	FEMALE:MALE RATIO	PERCENTAGE 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 steroids; 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 ↑/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 ↑/normal; mild anemia	NSAIDs and intraarticular steroids; 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 intra-articular steroids; consider sulfasalazine as alternative to MTX; anti-TNF agents

ANA, antinuclear antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; JIA, juvenile idiopathic arthritis; MAS, macrophage activation syndrome; MTX, methotrexate; NSAID, nonsteroidal antiinflammatory drug; RF, rheumatoid factor; TNF, tumor necrosis factor; WBC, white blood cell count.

From Firestein GS, Budd RC, Harris ED Jr, et al, editors: Kelley's textbook of rheumatology, *ed 8, Philadelphia, 2009, Saunders.*



Figure 155-1 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.

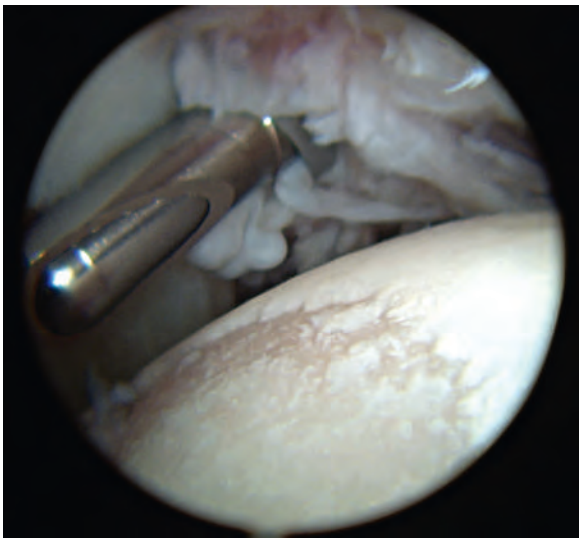


Figure 155-2 Arthroscopy in the shoulder of a child with juvenile idiopathic arthritis showing pannus formation and cartilage erosions. *(Courtesy of Dr. Alison Toth.)*



Figure 155-3 MRI with gadolinium of a 10 yr old child with juvenile idiopathic arthritis (same patient as in Fig. 155-1). 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.



Figure 155-4 Oligoarticular juvenile idiopathic arthritis with swelling and flexion contracture of the right knee.

Oligoarthritis is defined as involving ≤4 joints within the 1st 6 mo of disease onset, and often only a single joint is involved (see Table 155-4). It predominantly affects the large joints of the lower extremities, such as the knees and ankles (Fig. 155-4). Isolated involvement of upper extremity large joints is less common. Those in whom disease never develops in more than 4 joints are regarded as having **persistent oligoarticular JIA**, whereas evolution of disease in more than 4 joints after 6 mo 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 156) or a nonrheumatic cause. The presence of a positive antinuclear antibody (ANA) confers increased risk for asymptomatic anterior uveitis, requiring periodic slit-lamp examination (Table 155-5). ANA positivity may also be correlated with younger age at disease onset, female sex, asymmetric arthritis, and lower number of involved joints over time.

Polyarthritis is characterized by inflammation of ≥5 joints in both upper and lower extremities (Figs. 155-5 and 155-6). 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. 155-7). **Micrognathia** reflects chronic temporomandibular joint disease

Table 155-5 Frequency of Ophthalmologic Examination in Patients with Juvenile Idiopathic Arthritis

TYPE	ANTINUCLEAR ANTIBODY TEST RESULT	AGE AT ONSET (Yr)	DURATION OF DISEASE (Yr)	RISK CATEGORY	EYE EXAMINATION FREQUENCY (Mo)
Oligoarthritis or polyarthritis	+	≤6	≤4	High	3
	+	≤6	>4	Moderate	6
	+	≤6	>7	Low	12
	+	>6	≤4	Moderate	6
	+	>6	>4	Low	12
	–	≤6	≤4	Moderate	6
	–	≤6	>4	Low	12
	–	>6	NA	Low	12
Systemic disease	NA	NA	NA	Low	12

From Cassidy J, Kivlin J, Lindsley C, et al: Section on Rheumatology; Section on Ophthalmology: Ophthalmologic examinations in children with juvenile rheumatoid arthritis, Pediatrics *117:1843–1845, 2006.*



Figure 155-5 Hands and wrists of a girl 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. 155-8). Cervical spine involvement (Fig. 155-9), 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 range of motion on exam (Fig. 155-10).

sJIA is characterized by arthritis, 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 wk, with a rapid return to normal or subnormal temperatures (Fig. 155-11). 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 most commonly distributed over the trunk and proximal extremities (Fig. 155-12). The classic rash is nonpruritic and migratory with lesions lasting <1 hr. **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 syndromes, infection, and malignancy. Some children initially present with only systemic features, and evolve over time, but definitive diagnosis requires 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) 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 507). There is increasing evidence that sJIA/MAS and HLH share similar functional defects in granule-dependent cytotoxic lymphocyte activity. 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 prothromboplastin times. The erythrocyte sedimentation rate (ESR) falls because of hypofibrinogenemia and hepatic dysfunction, a feature useful in distinguishing MAS from a flare of systemic disease (Table 155-6). Although finalized diagnostic criteria for MAS do not currently exist, the features that were decided by an international consensus panel as the most important indicators of MAS include a falling platelet count, extreme hyperferritinemia, evidence of macrophage hemophagocytosis in the bone marrow, increased liver enzymes, falling leukocyte count, persistent, continuous fever ≥38°C (100.4°F), falling ESR, hypofibrinogenemia, and hypertriglyceridemia. *A relative change in laboratory values is likely more relevant in making an early diagnosis than are absolute normal values.* The diagnosis is suggested by clinical criteria and is confirmed by bone marrow biopsy demonstrating hemophagocytosis (Table 155-6). 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 507).

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 within the joint as well as 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, are only supportive or prognostic, and their results may be normal in patients with JIA (see Tables 155-1 to 155-4).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for arthritis is broad and a careful, thorough investigation for other underlying etiology is imperative (Table 155-7). History, physical exam, 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 systemic lupus erythematosus (see Chapter 158), juvenile dermatomyositis (see Chapter 159), sarcoidosis (see Chapter 165), and



Figure 155-6 Progression of joint destruction in a girl with polyarticular juvenile idiopathic arthritis, rheumatoid factor–positive, despite doses of corticosteroids sufficient to suppress symptoms in the interval between the radiographs shown in **A** and **B. A,** Radiograph of the hand at onset. **B,** Radiograph taken 4 yr 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.

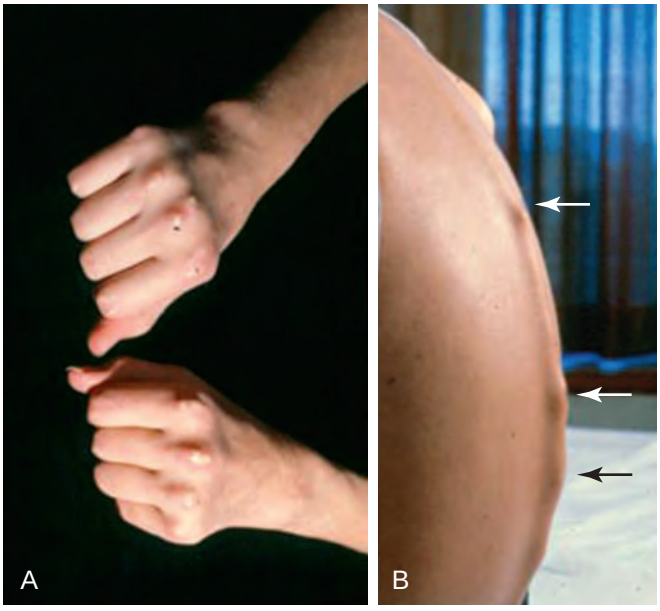


Figure 155-7 Rheumatoid nodules overlying bony prominences in an adolescent with rheumatoid factor–positive polyarthritis. *(From Rosenberg AM, Oen KG: Polyarthritis. In Cassiday JT, Petty RE, Laxer RM, et al, editors:* Textbook of pediatric rheumatology, *ed 6, Philadelphia, 2011, Saunders Elsevier,* Fig. 15-5, *p. 257.)*



Figure 155-8 CT scan of the temporomandibular joint of a patient with juvenile idiopathic arthritis exhibiting destruction on the right.

the vasculitic syndromes (see Chapter 167). In scleroderma (see Chapter 160), limited range of motion as a consequence of 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, a remittent fever, and a 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,



Figure 155-9 Radiograph of the cervical spine of a patient 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.



Figure 155-10 Severe hip disease in a 13 yr old boy with active systemic juvenile idiopathic arthritis. Radiograph shows destruction of the femoral head and acetabula, joint space narrowing, and subluxation of left hip. The patient had received corticosteroids systemically for 9 yr.

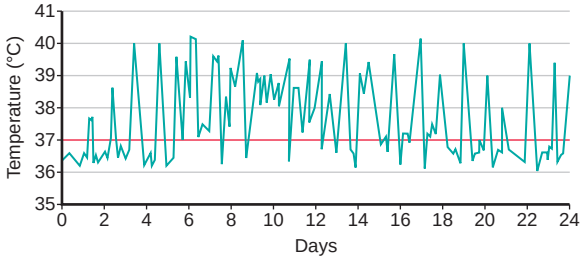


Figure 155-11 High-spiking intermittent fever in a 3 yr old patient with systemic juvenile idiopathic arthritis. *(From Ravelli A, Martini A: Juvenile idiopathic arthritis,* Lancet *369:767–778, 2007.)*

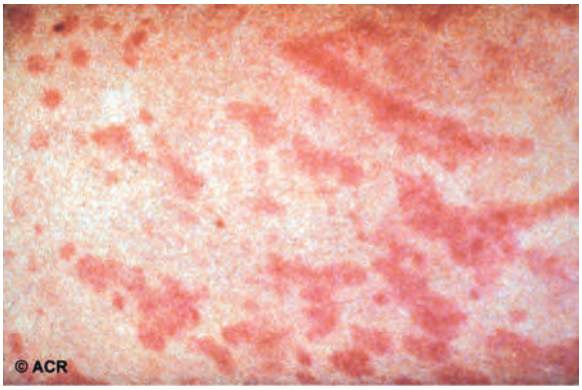


Figure 155-12 The rash of systemic juvenile idiopathic arthritis. The rash is salmon-colored, macular, and nonpruritic. Individual lesions are transient and occur in crops over the trunk and extremities. *(Reprinted from the American College of Rheumatology:* Clinical slide collection on the rheumatic diseases, *Atlanta, copyright 1991, 1995, 1997, ACR. Used with permission of the American College of Rheumatology.)*

Table 155-6 Main Clinical, Laboratory, and Pathologic Features of Macrophage Activation Syndrome

LABORATORY CRITERIA
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 CRITERIA
1. Nonremitting fever
2. Hepatomegaly
3. Splenomegaly
4. Lymphadenopathy
5. Hemorrhages
6. Central nervous system dysfunction (headache, seizures, lethargy, coma, disorientation)
HISTOPATHOLOGIC CRITERIA
1. Macrophage hemophagocytosis in the bone marrow aspirate
2. Increased CD163 staining of the bone marrow

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 *13:289–298, 2012.*

can induce a transient arthritis. Arthritis may follow enteric infections (see Chapter 157). **Lyme disease** (see Chapter 222) should be considered in children with oligoarthritis living in or visiting endemic areas. Although a history of tick exposure, preceding flu-like illness, and subsequent rash should be sought, they 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 or biopsy. Acute onset of fever and a painful, erythematous, hot joint suggests septic arthritis. Isolated hip pain with limited motion raises the possibility of suppurative arthritis (see Chapter 685), osteomyelitis (see Chapter 684), toxic synovitis, Legg-Calvé-Perthes disease, slipped capital femoral epiphysis, and chondrolysis of the hip (see Chapter 678).

Lower-extremity arthritis and tenderness over insertion of ligaments and tendons, especially in a boy, raises the possibility of ERA (see Chapter 156). **Psoriatic arthritis** can manifest as limited joint involvement in an unusual distribution (e.g., small joints of the hand and

Table 155-7 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
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,* pneumococcus, gonococcus, *Haemophilus influenzae*)
Lyme disease
Viral illness (parvovirus, rubella, mumps, Epstein-Barr virus, hepatitis B, Chikungunya virus)
Fungal arthritis
Mycobacterial infection
Spirochetal infection
Endocarditis

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

IMMUNODEFICIENCIES
Hypogammaglobulinemia
Immunoglobulin A deficiency
Human immunodeficiency virus

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
Amyloidosis (familial Mediterranean fever)

BONE AND CARTILAGE DISORDERS
Trauma
Patellofemoral syndrome
Hypermobility syndrome
Osteochondritis dissecans
Avascular necrosis (including Legg-Calvé-Perthes disease)
Hypertrophic osteoarthropathy
Slipped capital femoral epiphysis
Osteolysis
Benign bone tumors (including osteoid osteoma)
Histiocytosis
Rickets

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

PAIN SYNDROMES
Fibromyalgia
Growing pains
Depression (with somatization)
Reflex sympathetic dystrophy
Regional myofascial pain syndromes

ankle) years prior to 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 arthralgias (i.e., joint pain). Hypermobility may cause joint pain, especially in the lower extremities. Growing pains should be suspected in a child between the ages of 4-12 yr complaining of leg pain in the evenings with normal investigative studies and no morning symptoms. Nocturnal pain also alerts to the possibility of a malignancy. An adolescent with missed school days may suggest a diagnosis of fibromyalgia (see Chapter 168).

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 mo 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 (see Chapter 169). Swelling that extends beyond the joint can be a sign of lymphedema or Henoch-Schönlein purpura (see Chapter 515). A peripheral arthritis indistinguishable from JIA occurs in the humoral immunodeficiencies (see Chapter 124), 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 an fever of unknown origin (see Chapter 177). Important considerations in the differential diagnosis include infections (endocarditis, brucellosis, cat scratch disease, Q fever, mononucleosis), autoinflammatory disease (see Chapter 163) malignancy (leukemia, lymphoma, neuroblastoma) and HLH (see Chapter 507.2).

LABORATORY FINDINGS

Hematologic abnormalities often reflect the degree of systemic or articular inflammation, with elevated white blood cell and platelet counts and a microcytic anemia. Inflammation may also cause elevations in ESR and C-reactive protein, 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, like 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 white blood cell and platelet counts. Hemoglobin levels are low, typically in the range of 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 owing to the consumptive process. A low or normal white blood cell count and/or platelet count in a child with active sJIA should raise concerns for MAS.

Early radiographic changes of arthritis include soft tissue swelling, periarticular osteopenia, and periosteal new-bone apposition around affected joints (Fig. 155-13). Continued active disease may lead to subchondral erosions, loss of cartilage, with varying degrees of bony destruction, and fusion. Characteristic radiographic changes in cervical spine, most frequently in the neural arch joints at C2-C3 (see Fig. 155-9) may progress to atlantoaxial subluxation. MRI is more sensitive than radiography to detect early changes (Fig. 155-14).

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



Figure 155-13 Early (6 mo duration) radiographic changes of juvenile idiopathic arthritis. Soft-tissue swelling and periosteal new bone formation appear adjacent to the 2nd and 4th proximal interphalangeal joints.

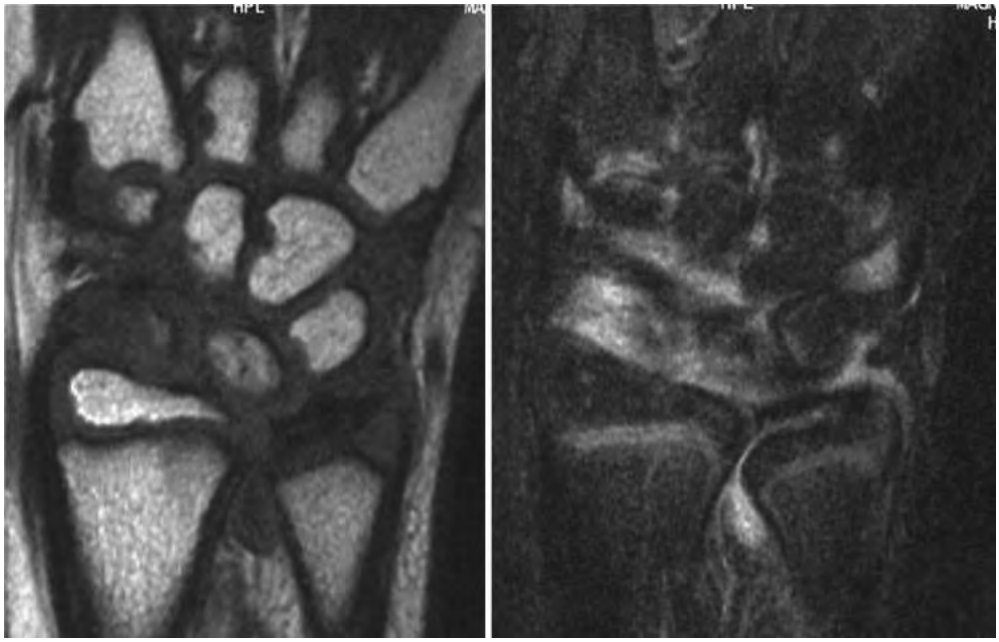


Figure 155-14 MRI of the wrist in a child with wrist arthritis. Image on the *left* shows multiple erosions of carpal bones. Image on the *right,* obtained after administration of gadolinium contrast agent, reveals uptake consistent with active synovitis.

Table 155-8 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	<30 kg: 20 mg SC every other week >30 kg: 40 mg SC every other week	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	Polyarthritis	Immunosuppressant, concern for malignancy, infusion reaction
Anti-CD20			
Rituximab*	750 mg/m2 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 (maximum dose 100 mg/day)	Systemic	Immunosuppressant, GI upset, injection site reaction
Canakinumab	15-40 kg: 2 mg/kg/dose SC q8wk >40 kg: 150 mg SC q8wk	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 q2wk >30 kg: 8 mg/kg/dose q2wk (maximum dose 800 mg)	Systemic Polyarthritis	Immunosuppressant, hepatic toxicity, dyslipidemia, cytopenias, GI upset, infusion reaction

bid, Twice daily; GI, gastrointestinal; IV, intravenous; PO, oral; SC, subcutaneous; tid, 3 times daily.
*Not indicated by the U.S. Food and Drug Administration for use in JIA.

prognostic indicators, and response to medications. Disease management also requires monitoring for potential medication toxicities (see Chapter 154).

Children with oligoarthritis often show partial response to nonsteroidal antiinflammatory drugs (NSAIDs), with improvement in inflammation and pain (Table 155-8). Those who have no or partial response after 4-6 wk 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 minority of patients with oligoarthritis show no response to NSAIDs and injections, and therefore require treatment with disease-modifying antirheumatic drugs (DMARDs), methotrexate, and, if no response, TNF inhibitors.

NSAIDs alone rarely induce remission in children with polyarthritis or sJIA. Methotrexate is the oldest and least toxic of the DMARDs available for adjunctive therapy. It may take 6-12 wk to see the effects of methotrexate. Failure of methotrexate monotherapy warrants the addition of a biologic DMARD. Biologic medications that inhibit proinflammatory cytokines, such as TNF-α, IL-1, and IL-6, demonstrated excellent disease control. TNF-α antagonists (e.g., etanercept, adalimumab) are used to treat children with an inadequate response to methotrexate, with poor prognostic factors, or with 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.

TNF inhibition is not as effective for the systemic symptoms found in sJIA. When systemic symptoms dominate systemic steroids 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, an IL-6 receptor antagonist, are



Figure 155-15 Chronic anterior uveitis, or iridocyclitis, of juvenile idiopathic arthritis. Extensive posterior synechiae have resulted in a small, irregular pupil. A well-developed cataract and early band keratopathy can be seen at the medial and lateral margins of the cornea.

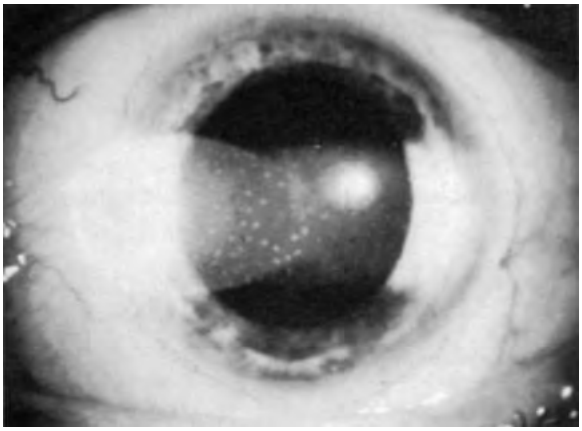


Figure 155-16 A slit-lamp examination shows "flare" in the fluid of the anterior chamber (caused by increased protein content) and keratic precipitates on the posterior surface of the cornea, representing small collections of inflammatory cells. *(Courtesy of Dr. H.J. Kaplan. From Petty RE, Rosenbaum JT: Uveitis in juvenile idiopathic arthritis. In Cassidy JT, Petty RE, Laxer RM, et al, editors,* Textbook of pediatric rheumatology, *ed 6, Philadelphia, 2011, Saunders, Fig. 20-3, p. 309.)*

FDA-approved treatments for sJIA in children older than 2 yr. Standardized consensus treatment plans have been published to guide therapy for sJIA. These outline 4 treatment plans based on glucocorticoids, methotrexate, anakinra, or tocilizumab with optional glucocorticoid use in the latter 3 plans as clinically indicated.

With the advent of newer DMARDs, the use of systemic corticosteroids can often be avoided or minimized. Systemic steroids 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.

Oral Janus kinase (JAK) inhibitors (tofacitinib, ruxolitinib) inhibit JAK signaling pathways involved in immune activation and inflammation. Tofacitinib is FDA approved for adults with rheumatoid arthritis.

Management of JIA must include periodic slit-lamp ophthalmologic examinations to monitor for asymptomatic uveitis (see Table 155-5; Figs. 155-15 and 155-16). Optimal treatment of uveitis requires collaboration between the ophthalmologist and rheumatologist. Initial management of uveitis may include mydriatics and corticosteroids used topically, systemically, or through periocular injection. DMARDs allow for a decrease in exposure to steroids, and methotrexate and antibodies to TNF-α (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.

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 patients with JIA have 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 girls who are ANA-positive and with onset of arthritis earlier than 6 yr 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. 155-15) 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, the presence of anti–cyclic citrullinated peptide antibodies, and large numbers of affected joints. Disease involving the hip and hand and 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 mo, and increased inflammatory markers, such as platelet count and ESR, for >6 mo. 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 corticosteroid injection in the anterior knee.

Psychosocial adaptation may be affected by JIA. Studies indicate that, compared with control subjects, 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 156

Ankylosing Spondylitis and Other Spondyloarthritides

Pamela F. Weiss and Robert A. Colbert

The diseases collectively referred to as **spondyloarthritides** include ankylosing spondylitis (AS), arthritis associated with inflammatory bowel disease (IBD) and psoriasis, and reactive arthritis following gastrointestinal or genitourinary infections (Tables 156-1 and 156-2). Many children with spondyloarthritis are classified in the juvenile idiopathic arthritis (JIA) category of **enthesitis-related arthritis (ERA). Children and adolescents with spondyloarthritis, who may not meet ERA criteria, include arthritis associated with psoriasis or IBD, juvenile AS (JAS), and reactive arthritis.**

EPIDEMIOLOGY

JIA is diagnosed in 90 per 100,000 children in the United States every year (see Chapter 155). ERA accounts for 10-20% of JIA, and has a mean age of onset of 12 yr. 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 HLA-B27, which is found in 90% of JAS and 50% of ERA 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. HLA-B27 is responsible for 23.3% of AS heritability, with genes encoding the interleukin (IL)-23 receptor (*IL23R*), ERAP1 (endoplasmic reticulum aminopeptidase-1), IL-12p40 (*IL12B*), and others having important roles, but together accounting for only approximately 2% of heritability. Infection with certain gastrointestinal or genital pathogens can trigger reactive arthritis (see Chapter 157 and Table 156-2); environmental triggers for other forms of spondyloarthritis have not been identified. Unusual properties of HLA-B27, such as its tendency to misfold and form unusual cell surface structures, may have a role. Inflamed joints and entheses in spondyloarthritides contain T cells, B cells, macrophages, osteoclasts, proliferating fibroblasts and osteoblasts. 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) and hips, enthesitis (inflammation at the site of tendon, ligament, or joint capsule attachment to bone), symptomatic eye inflammation (acute anterior uveitis), and gastrointestinal inflammation (even in the absence of IBD) (see Table 156-1).

Enthesitis-Related Arthritis

Children have ERA if they have *either* arthritis and enthesitis *or* arthritis or enthesitis, with at least 2 of the following characteristics: (1) sacroiliac joint tenderness or inflammatory lumbosacral pain, (2) the presence of HLA-B27, (3) onset of arthritis in a male older than 6 yr,

Table 156-2 Etiologic Microorganisms of Reactive Arthritis

PROBABLE	POSSIBLE
Chlamydia trachomatis	*Neisseria gonorrhoeae*
Shigella flexneri	*Mycoplasma fermentans*
Salmonella enteritidis	*Mycoplasma genitalium*
Salmonella typhimurium	*Ureaplasma urealyticum*
Yersinia enterocolitica	*Escherichia coli*
Yersinia pseudotuberculosis	*Cryptosporidium*
Campylobacter jejuni	*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 *44:309–315, 2009, Table 2, p. 311.*

Table 156-1 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% or more.
From Cassidy JT, Petty RE: Textbook of pediatric rheumatology, *ed 6, Philadelphia, 2011, Elsevier/Saunders.*

(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 1st-degree relative. Patients with psoriasis (or a family history of psoriasis in a 1st-degree relative), a positive rheumatoid factor test result, or systemic arthritis are excluded from this group. During the 1st 6 mo of disease the arthritis is typically asymmetric and involves 4 or fewer joints. The most frequently affected joints are 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 most commonly affects the lower limbs. Up to 40% of children develop clinical or radiographic evidence of sacroiliac joint arthritis as part of their disease. When the sacroiliac or other axial joints are involved, children may experience inflammatory back pain (Table 156-3) and alternating buttock pain. Patients may also experience pain with palpation of the lower back or with pelvic compression. Untreated sacroiliitis may evolve into AS, but risk factors for progression are unclear.

Psoriatic Arthritis

Psoriatic arthritis accounts for approximately 10% of JIA. Common clinical features of psoriatic arthritis are nail pitting (Fig. 156-1), onycholysis, and dactylitis (sausage-like swelling of the fingers or toes).

Children have psoriatic arthritis if they have arthritis and psoriasis *or* arthritis and at least 2 of the following: (1) dactylitis, (2) nail pitting or onycholysis, or (3) psoriasis in a 1st-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–positive, and at risk for asymptomatic ocular inflammation.

Table 156-3 Symptoms Characteristic of Inflammatory Back Pain

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

Disease onset during adolescence is equally common among males and females. In the majority of children, the arthritis is asymmetric and affects 4 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 20-60% of patients and seems to be more frequent in those who present at an older age. 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.

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, while enthesitis and peripheral arthritis are more common. AS is diagnosed according to the modified 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. 156-2), or limitation of chest expansion. JAS is present if the patient is <16 yr old. Juvenile *onset* AS is frequently used to describe adult AS when the symptoms began before 16 yr of age, but full criteria were not met until later.

To fulfill the modified New York criteria for AS, patients must have radiographic changes in the sacroiliac joints as well as 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 pre-radiographic axial spondyloarthritis have been developed by the Assessment of SpondyloArthritis International Society. To meet criteria for axial spondyloarthritis patients must have at least 3 mo of back pain and sacroiliitis on imaging (acute inflammation on MRI or definite radiographic sacroiliitis by the New York criteria) plus 1 feature of spondyloarthritis (i.e., inflammatory back pain, arthritis, enthesitis [heel], uveitis, dactylitis, psoriasis, Crohn disease/ulcerative colitis, good response to nonsteroidal antiinflammatory drugs [NSAIDs], family history for spondyloarthritis, HLA-B27, or elevated C-reactive protein). Alternatively, patients can fulfill axial spondyloarthritis criteria if



Figure 156-1 Nail pitting *(arrowhead)* and "sausage digit" (dactylitis) of the left index finger of a girl with juvenile psoriatic arthritis. *(From Petty RE, Malleson P: Spondyloarthropathies of childhood,* Pediatr Clin North Am *33:1079–1096, 1986.)*

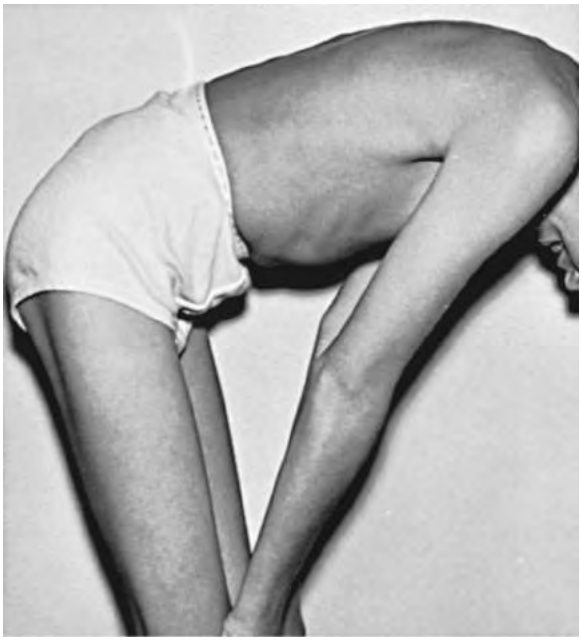


Figure 156-2 Loss of lumbodorsal spine mobility in a boy with ankylosing spondylitis. The lower spine remains straight when the patient bends forward.

they are HLA-B27–positive and have at least 2 features of spondyloarthritis. These criteria have not been validated in the pediatric population but may be useful as a guide to evaluating preradiographic spondyloarthritis.

Arthritis with Inflammatory Bowel Disease

The presence of erythema nodosum, pyoderma gangrenosum, 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, resulting in AS. 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 gastrointestinal inflammation.

LABORATORY FINDINGS

Laboratory evidence of systemic inflammation with elevation of the erythrocyte sedimentation rate and/or C-reactive protein value is variable in most spondyloarthritides and may or may not be present at the onset of disease. Rheumatoid factor and antinuclear antibodies are absent, except in patients with psoriatic arthritis, of which as many as 50% are antinuclear antibody–positive. HLA-B27 is present in ≈90% of children with JAS, compared with ≈7% of healthy individuals but is less frequent in ERA and other types of spondyloarthritis.

Imaging

Conventional radiographs detect chronic bony changes and damage but not active inflammation. Early radiographic changes in the sacroiliac joints include indistinct margins and erosions that can result in joint space widening. Sclerosis typically starts on the iliac side of the joint (Fig. 156-3). 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 is 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 short T1 inversion recovery (STIR) sequences. Gadolinium does not add value to the study if STIR is used. MRI will reveal abnormalities before the plain radiograph. Whole body MRI is also used to evaluate the axial skeleton in adults with early disease as it can detect vertebral lesions in addition to sacroiliac changes.



Figure 156-3 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.

DIFFERENTIAL DIAGNOSIS

The onset of arthritis following a recent history of diarrhea or symptoms of urethritis or conjunctivitis may suggest reactive arthritis (see Chapter 157). Lower back pain can be caused by suppurative arthritis of the sacroiliac joint, osteomyelitis 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 168.1). 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 features of spondyloarthritis, such as involvement of other entheses and/or joints. Radiography or MRI is critical for distinguishing these conditions.

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 spondyloarthritis include monotherapy or combination therapy with NSAIDs, disease-modifying antirheumatic drugs, or biologic agents. NSAIDs, such as naproxen (15-20 mg/kg/day), are frequently used initially and may reduce structural damage (syndesmophyte formation and growth) if used continually. With relatively mild disease, intraarticular corticosteroids (e.g., triamcinolone hexacetonide) may also help to control peripheral joint inflammation. However, for moderate disease and JAS, it is typically necessary to add a second-line agent. Disease-modifying antirheumatic drugs 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. Tumor necrosis factor-α inhibitors (e.g., etanercept, infliximab, adalimumab) have been efficacious in reducing symptoms and improving function in adults with AS, and there is evidence that similar responses are seen in children. It remains unclear whether tumor necrosis factor inhibitors have an impact on structural damage in established AS, underscoring the need for earlier recognition and better therapies.

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 are particularly useful in 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 greater than 5 yr in juvenile spondyloarthritis predicts disability. Disease remission occurs in less than 20% of children with spondyloarthritis 5 yr after diagnosis. Factors associated with disease progression include tarsitis, HLA-B27 positivity, hip arthritis within the 1st 6 mo, 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 157

Reactive and Postinfectious Arthritis

Pamela F. Weiss and Robert A. Colbert

In addition to causing arthritis by means of direct microbial infection (i.e., septic arthritis; see Chapter 685), infection can lead to the generation and deposition of immune complexes as well as antibody or T cell–mediated cross-reactivity with self. Microbes may influence the immune response in ways that indirectly affect susceptibility to immune-mediated inflammatory diseases such as systemic lupus erythematosus, inflammatory bowel disease, juvenile idiopathic arthritis, and spondyloarthritis. **Reactive and postinfectious arthritis** are defined as joint inflammation caused by a sterile inflammatory reaction following a recent infection. We use *reactive arthritis* to refer to arthritis that occurs following 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 cases, 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 156). In **postinfectious arthritis**, the pain or joint swelling is usually transient, lasting less than 6 wk, 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 in terms of pathophysiology.

PATHOGENESIS

Reactive arthritis typically follows enteric infection with *Salmonella* sp., *Shigella flexneri, Yersinia enterocolitica, Campylobacter jejuni*, or genitourinary tract infection with *Chlamydia trachomatis*. *Escherichia coli* and *Clostridium difficile* are also causative enteric agents, although less common (see Table 156-2 in Chapter 156). Although similar in some respects to reactive arthritis, acute rheumatic fever caused by group A streptococcus (see Chapters 183.1 and 438), arthritis associated with infective endocarditis (see Chapter 437), and the tenosynovitis associated with *Neisseria gonorrhoeae* are considered in later chapters.

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 inflammation following 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 2-4 wk following infection. The classic triad of arthritis, urethritis, and conjunctivitis is relatively uncommon in children. The arthritis is typically oligoarticular, with a predilection for lower extremities. Dactylitis may occur, and enthesitis (Fig. 157-1) is common (affects as many as 90% of patients; see Chapter 156). Cutaneous manifestations can occur and may include circinate balanitis, ulcerative vulvitis, oral lesions, erythema nodosum, and keratoderma blennorrhagica, which is similar in appearance to pustular psoriasis (Fig. 157-2). Systemic symptoms may include fever, malaise, and fatigue. Early in the disease course, markers of inflammation—erythrocyte sedimentation rate, C-reactive protein, and platelets—may be markedly 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 (Table 157-1) and may result in particular patterns of joint involvement. Rubella and hepatitis B virus typically affect the small joints, whereas mumps and varicella often involve large joints, especially the knees. The **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



Figure 157-1 Enthesitis—swelling of the posterior aspect of the left heel and lateral aspect of the ankle. *(Courtesy of Nora Singer, Case Western Reserve University and Rainbow Babies' Hospital.)*



Figure 157-2 Keratoderma blennorrhagica. *(Courtesy of Dr. M.F. Rein and The Centers for Disease Control and Prevention Public Health Image Library, 1976. Image #6950.)*

Table 157-1 Viruses Associated with Arthritis

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

Adapted from Cassidy JT, Petty RE: Infectious arthritis and osteomyelitis. In Textbook of pediatric rheumatology, *ed 5, Philadelphia, 2005, Saunders.*

for erythema infectiosum (fifth disease), can cause arthralgia, symmetric 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 juvenile idiopathic arthritis (see Chapter 155).

Poststreptococcal arthritis is a postinfectious arthritis that 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 183.1). 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 678.2). Boys from 3-10 yr of age are most commonly affected and have acute onset of severe pain in the hip (groin), with referred pain to the thigh or knee, lasting approximately 1 wk. The erythrocyte sedimentation rate 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 boys, 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 mutation 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. Recurrent episodes of erosive arthritis begin in childhood, while 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 genitourinary or gastrointestinal 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 the triggering organism, the offending agent 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 in endemic areas. The diagnosis of postinfectious arthritis is often established by exclusion, and after the arthritis has resolved. Arthritis associated with gastrointestinal symptoms or abnormal liver function test results may be triggered by infectious or autoimmune hepatitis. Arthritis or spondyloarthritis may occur in children with inflammatory bowel disease, such as Crohn disease or ulcerative colitis (see Chapter 336). When 2 or more blood cell lines are low or progressively decrease in a child with arthritis, parvovirus infection, macrophage activation (hemophagocytic) syndrome, and leukemia should be strongly considered. Persistent arthritis (>6 wk) suggests the possibility of a chronic rheumatic disease, including juvenile idiopathic arthritis (see Chapters 155 and 156) and systemic lupus erythematosus (see Chapter 158).

TREATMENT

Specific treatment is unnecessary for most cases of reactive or postinfectious arthritis. Nonsteroidal antiinflammatory agents 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 steroid injections may be utilized for refractory or severely involved joints once acute infection has been ruled out. Systemic steroids or disease-modifying anti-rheumatic drugs 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 due to streptococcal disease, current recommendations include penicillin prophylaxis for at least 1 yr. Long-term prophylaxis is often recommended, but the duration is controversial and may need to be individualized.

COMPLICATIONS AND PROGNOSIS

Postinfectious arthritis following 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 inflammatory bowel disease 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 genitourinary tract infection with *C. trachomatis,* has the potential for evolving to chronic arthritis, particularly spondyloarthritis (see Chapter 156). The presence of HLA-B27 or significant systemic features increases the risk of chronic disease.

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Chapter 158

Systemic Lupus Erythematosus

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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. Compared with adults, children and adolescents with SLE have more severe disease and more widespread organ involvement.

ETIOLOGY

The pathogenesis of SLE remains largely unelucidated, 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 abnormalities,** 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. 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 that multiple genes are involved and that epigenetic and nongenetic factors are also important in disease expression.

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 gender 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 aggravate SLE disease activity. Environmental influences also may induce epigenetic modifications to DNA, which increase 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 African-Americans, Asians, Hispanics, Native Americans, and Pacific Islanders for both adult and pediatric populations. SLE predominantly affects females, with reported 2-5:1 ratio prior to puberty, 9:1 ratio during reproductive years, and return to near prepubertal ratios in the postmenopausal period. Childhood SLE is rare before 5 yr of age and is usually diagnosed in adolescence, with a median age at diagnosis of 11-12 yr. Up to 20% of all individuals with SLE are diagnosed prior to age 16 yr.

PATHOLOGY

Histologic features most suggestive of SLE include findings in the kidney and skin, especially the discoid rash. Renal manifestations of SLE are classified histologically according to the criteria of the International Society of Nephrology (see Chapter 514). The finding of diffuse proliferative glomerulonephritis (class IV) significantly increases 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 158-1*D* 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 markedly increased levels of apoptosis or significantly 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 autoantibody production. Circulating autoantibodies form immune complexes and deposit in tissues, leading to local complement activation, initiation of a proinflammatory cascade, and,

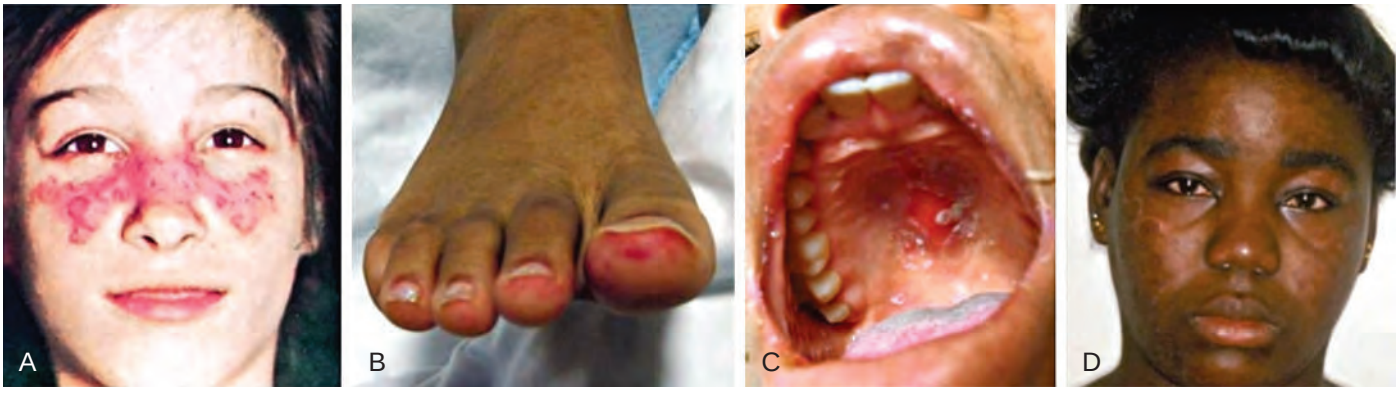


Figure 158-1 Mucocutaneous manifestations of SLE. **A,** Malar rash; **B,** vasculitic rash on toes; **C,** oral mucosal ulcers; **D,** discoid rash in malar distribution.

ultimately, tissue damage. Antibodies to double-stranded DNA can form immune complexes, deposit in glomeruli, and initiate inflammation leading to glomerulonephritis. However, many individuals with SLE have circulating antibodies to double-stranded DNA 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. Many, but not all, 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, IL-21, interferon-γ, B-lymphocyte stimulator (BLyS), and anti–tumor necrosis factor-α.

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 following exposure to self-antigen. In addition, cytokines such as BLyS 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.

CLINICAL MANIFESTATIONS

Any organ system can be involved in SLE, so the potential clinical manifestations are myriad (Table 158-1). The presentation of SLE in childhood or adolescence differs from that 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 1st yr of diagnosis, may be asymptomatic (morning stiffness, painless swelling) but is often a symmetric polyarthritis affecting large and small joints. Tenosynovitis is often present, but radiologic joint changes are very rare. Pediatric lupus may develop in patients previously diagnosed with polyarticular or systemic juvenile idiopathic arthritis (see Chapter 155).

Renal disease in SLE is often asymptomatic, underscoring the need for careful monitoring of blood pressure and urinalyses; in adolescents, SLE often presents 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 be present at one time, the diagnosis may require longitudinal follow up. SLE is often characterized by periods of flare and disease quiescence or 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. 158-2). Long-term complications of SLE and its therapy, including accelerated atherosclerosis and osteoporosis, become clinically evident in young to middle adulthood. SLE is a disease that evolves over time in each affected individual, and new manifestations may arise even many years after diagnosis.

Table 158-1 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 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
Gastroenterology	Hepatosplenomegaly, pancreatitis, vasculitis affecting bowel, protein-losing enteropathy, peritonitis
Ocular	Retinal vasculitis, scleritis, episcleritis, papilledema, dry eyes, optic neuritis

DIAGNOSIS

The diagnosis of SLE requires a comprehensive clinical and laboratory assessment revealing characteristic multisystem disease and excluding other etiologies, including infection and malignancy. Presence of 4 of the 11 **American College of Rheumatology (ACR) 1997 Revised Classification Criteria for SLE** (Table 158-2) simultaneously or cumulatively over time establishes the diagnosis of SLE. Of note, although a positive antinuclear antibody (ANA) test result is not required for the diagnosis of SLE, ANA-negative lupus is extremely rare. Although ANA is very sensitive for SLE (95-99%), it is not very specific (~50%). Antibodies against double-stranded DNA and anti-Smith are specific for SLE (~98%) but not as sensitive (40-65%). Hypocomplementemia, although common in SLE, is not represented among the ACR classification criteria; hypocomplementemia has been added to **updated criteria validated by the Systemic Lupus International Collaborating Clinics (SLICC) in 2012** (Table 158-3). Other differences in the SLICC criteria include addition of nonscarring alopecia, additional cutaneous and neurologic manifestations of lupus, and a positive direct Coombs test in the absence of hemolytic anemia.

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, arthritis, rash, cytopenias, neurologic or cardiopulmonary abnormalities, nephritis, and nephrotic syndrome. 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 (systemic onset juvenile idiopathic arthritis, vasculitides), and drug-induced lupus.

Drug-induced lupus refers to the presence of SLE manifestations triggered by exposure to specific medications, including minocycline, many anticonvulsants, sulfonamides, antiarrhythmic agents, and other drugs (Table 158-4). In individuals prone to SLE, these agents may act as a trigger for true SLE. In others, 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

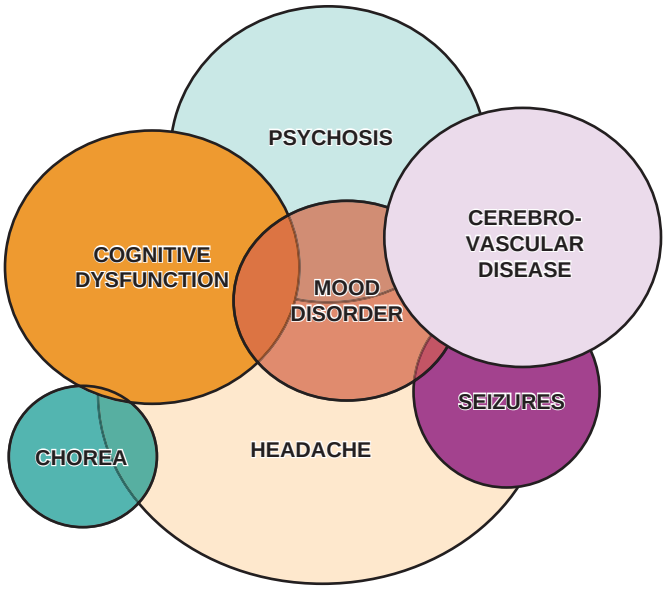


Figure 158-2 Overlapping neuropsychiatric symptoms in pediatric SLE. Patients with pediatric SLE most commonly have more than 1 neuropsychiatric symptom—in particular for seizures. *(From Silverman E, Eddy A: Systemic lupus erythematosus. In Cassidy JT, Petty RE, Laxer RM, et al, editors,* Textbook of pediatric rheumatology, *ed 6, Philadelphia, 2011, Saunders/Elsevier,* Fig. 21-17, *p. 329.)*

Table 158-2 American College of Rheumatology 1997 Revised Classification Criteria for Systemic Lupus Erythematosus*

Malar rash
Discoid rash
Photosensitivity
Oral or nasal ulcers
Arthritis
Nonerosive, ≥2 joints
Serositis
Pleuritis, pericarditis or peritonitis
Renal manifestations†
Consistent renal biopsy
Persistent proteinuria or renal casts
Seizure or psychosis
Hematologic manifestations†
Hemolytic anemia
Leukopenia (<4,000 leukocytes/mm^3)
Lymphopenia (<1,500 leukocytes/mm^3)
Thrombocytopenia (<100,000 thrombocytes/mm^3)
Immunologic abnormalities†
Positive anti–double-stranded or anti-Smith antibody
False-positive rapid plasma regain test result, positive lupus anticoagulant test result, or elevated anticardiolipin immunoglobulin (Ig) G or IgM antibody
Positive antinuclear antibody test result

*The presence of 4 of 11 criteria establishes the diagnosis of SLE. These criteria were developed for classification in clinical trials and not for clinical diagnosis.
†Each of these criteria 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 *40:1725, 1997.*

Table 158-3 Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria for Systemic Lupus Erythematosus*

CLINICAL CRITERIA	IMMUNOLOGIC CRITERIA
Acute cutaneous lupus	**Positive antinuclear antibody**
Malar rash, bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, photosensitive lupus rash, or subacute cutaneous lupus	**Positive double-stranded DNA antibody**
Chronic cutaneous lupus	**Positive anti-Smith antibody**
Classic discoid rash, lupus panniculitis, mucosal lupus, lupus erythematous tumidus, chilblains lupus, discoid lupus/lichen planus overlap	**Antiphospholipid antibody positivity**
Oral or nasal ulcers	Positive lupus anticoagulant, false-positive test for rapid plasma regain, medium to high titer anticardiolipin antibody level (IgA, IgG, IgM), or positive anti–B_2-glycoprotein I antibody (IgA, IgG, IgM)
Nonscarring alopecia	**Low complement**
Synovitis (≥2 joints)	Low C3, C4, or Ch50 level
Serositis	**Positive direct Coombs test** (in the absence of hemolytic anemia)
Pleurisy or pericardial pain ≥1 day, pleural effusion or rub, pericardial effusion or rub, ECG evidence of pericarditis	
Renal	
Presence of red blood cell casts or urine protein/creatinine ratio representing >500 mg protein/24 hours	
Neurologic	
Seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, or acute confusional state	
Hemolytic anemia	
Leukopenia (<4,000/mm^3) or lymphopenia (<1,000/mm^3)	
Thrombocytopenia (<100,000/mm^3)	

*The presence of 4 criteria (including at least 1 clinical and 1 immunologic criterion) establishes the diagnosis of SLE. Biopsy-proven lupus nephritis with positive ANA or anti–double-stranded DNA also satisfies the diagnosis of SLE. These criteria were developed for classification in clinical trials and not for clinical diagnosis.
Adapted from Petri M: Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus, Arthritis Rheum *64(8):2677–2686, 2012.*

Table 158-4 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, beta blockers, lithium, captopril, interferon-γ, hydrochlorothiazide, glyburide, docetaxel, penicillin, tetracycline, statins, gold, valproate, griseofulvin, gemfibrozil, propylthiouracil

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 double-stranded DNA, 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.

LABORATORY FINDINGS

A positive ANA test result is present in 95-99% of individuals with SLE. This test has poor specificity for SLE, as up to 20% of healthy individuals also have a positive ANA test result, making the ANA a poor screening test for SLE. ANA titers are not reflective of disease activity; therefore, repeating ANA titers is not helpful in disease management. Antibodies to double-stranded DNA are more specific for SLE, and in some individuals, anti–double-stranded DNA levels correlate with disease activity, particularly 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; although hypocomplementemia is not included in the ACR classification criteria, it has been added to 2012 SLICC criteria, along with direct Coombs positivity. Table 158-5 lists autoantibodies found in SLE along with their clinical associations. Hypergammaglobulinemia is a common but nonspecific finding. Inflammatory markers, particularly erythrocyte sedimentation rate, are often elevated in active disease. C-reactive protein (CRP) correlates less well with disease activity and acutely elevated CRP values may reflect infection, while 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. Antiphospholipid antibodies can be detected by several means, and laboratory features that point to the presence of these antibodies include the presence of anticardiolipin antibodies, prolonged phospholipid-dependent coagulation test results (partial thromboplastin time, dilute Russell viper-venom time), and a circulating **lupus anticoagulant** (which confirms that a prolonged partial thromboplastin time is not corrected with mixing studies). 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 or independent of SLE (see Chapter 479).

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 (5-7 mg/kg/day up to 400 mg/day) is recommended for all individuals with SLE if 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 and color vision impairment; therefore, ophthalmology exams every 6-12 mo are recommended for patients taking hydroxychloroquine. Nonsteroidal antiinflammatory agents can be useful for management of arthralgias and arthritis; it is important to keep in mind their potential hepatic, renal, and cardiovascular toxicities.

Table 158-5 Autoantibodies Commonly Associated with Systemic Lupus Erythematosus (SLE)

ANTIBODY	CLINICAL ASSOCIATION
Anti–double-stranded DNA	Correlates with disease activity, especially nephritis, in some with SLE
Anti-Smith antibody	Specific for the diagnosis of SLE
Antiribonucleoprotein antibody	Increased risk for Raynaud phenomenon and pulmonary hypertension High titer may suggest diagnosis of mixed connective tissue disorder
Anti-Ro antibody (anti-SSA antibody) Anti-La antibody (anti-SSB antibody)	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 anticardiolipin 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

Corticosteroids are a mainstay for treatment of significant manifestations of SLE and work quickly to improve acute deterioration; side effects often limit patient compliance, especially in adolescence, and potential toxicities are worrisome. It is important to limit 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 for 3 days, followed by weekly pulses) or high doses of oral prednisone (1-2 mg/kg/day). As disease manifestations improve, corticosteroid dosages are gradually tapered over months. It often becomes necessary to introduce steroid-sparing immunosuppressive medications in order to limit cumulative steroid exposure.

Steroid-sparing immunosuppressive agents often used in the treatment of pediatric SLE include methotrexate, leflunomide, azathioprine, mycophenolate mofetil, cyclophosphamide, and belimumab. Methotrexate, leflunomide, and azathioprine are often used to treat persistent moderate disease, including arthritis, significant cutaneous or hematologic involvement, and pleural disease. Intravenous or oral cyclophosphamide 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 girls 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. Clinical trial data on the

use of rituximab in SLE with treatment-resistant glomerulonephritis has been largely disappointing, but results from the LUNAR study suggest there may be benefit for subpopulations of SLE patients. The FDA has approved the use of belimumab (a monoclonal antibody against BLyS, also called B-cell activating factor); when added to standard SLE therapy, belimumab improves multiple markers of disease severity. BLyS levels are elevated in SLE and relate to disease activity. Treatment reduces the number of SLE flares and decreases the dose of prednisone. Side effects include fever, nausea, and diarrhea.

The Childhood Arthritis Rheumatology Research Alliance has developed a consensus treatment plan induction therapy of newly-diagnosed proliferative lupus nephritis that is specific to the pediatric SLE population; these guidelines advise 6 mo of therapy with either cyclophosphamide or mycophenolate mofetil, used in combination with a standardized glucocorticoid regimen. For patients who fail to achieve a partial response in 6 mo it is appropriate to switch agents. Consensus statements for maintenance therapy of lupus nephritis recommend use of mycophenolate mofetil, every 3 mo IV cyclophosphamide or azathioprine for 12 mo after completing induction therapy.

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, ad hoc analyses suggest that statins may be considered for primary prevention of atherosclerotic disease in certain clinical circumstances, particularly pubertal patients with an elevated CRP. For all SLE patients, adequate intake of calcium and vitamin D is necessary to prevent future osteoporosis. Infections commonly complicate SLE, so routine immunization is recommended, as well as annual influenza vaccination and administration of the 23-valent pneumococcal vaccine. Prompt attention to febrile episodes should include an evaluation for serious infections. It should be remembered that pregnancy can worsen SLE, and obstetric complications are more common in SLE. In addition, many of the medications used to treat SLE are teratogenic. As a consequence, it is important to counsel adolescent girls about these risks and appropriate contraceptive options. SLE patients with antiphospholipid antibody syndrome are treated with long-term anticoagulation to prevent thrombotic events.

COMPLICATIONS

Within the 1st several yr of diagnosis, the most common causes of death in individuals with SLE include infection and complications of glomerulonephritis and neuropsychiatric disease (Table 158-6). Over the long-term, the most common causes of mortality also include complications of 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 as well as exposure to medications with carcinogenic potential.

Table 158-6 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 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: Textbook of pediatric rheumatology, *ed 6, Philadelphia, 2011, Elsevier/Saunders.*

PROGNOSIS

The severity of disease in pediatric SLE is notably worse than the typical course for most adult-onset SLE. However, owing to advances in the diagnosis and treatment of SLE, survival has improved dramatically over the past 50 yr. Currently, the 5 yr survival rate for pediatric SLE is ~95%, though the 10 yr survival rate remains ~80-90%. Given their long burden of disease, children and adolescents with SLE face a high risk of future morbidity and mortality from the disease and its complications, especially atherosclerosis and malignancy (see Table 158-6). Given the complex and chronic nature of SLE, it is optimal for children and adolescents with SLE to be treated by pediatric rheumatologists in a multidisciplinary clinic.

Bibliography is available at Expert Consult.

158.1 Neonatal Lupus

Deborah Friedman, Rebecca E. Sadun, Stacy P. Ardoin, and Laura E. Schanberg

Neonatal lupus, an entity distinct from SLE, is one of the few rheumatic disorders manifesting in the neonate. Clinical manifestations of neonatal lupus include a characteristic annular or macular rash typically affecting the face (especially the periorbital area), trunk, and scalp (Fig. 158-3). The rash typically appears within the 1st 6 wk of life after exposure to ultraviolet light and lasts 3-4 mo; however, it can be present at birth. Infants may also have cytopenias and hepatitis, but the most feared complication is congenital heart block. Conduction system abnormalities range from prolongation of the PR interval to complete heart block, with development of progressive



Figure 158-3 Neonatal lupus syndrome. Typical rash, often photosensitive with a malar distribution, appearing as annular plaques with erythema and scaling. *(Reproduced, with written parental permission, from Pain C, Beresford MW: Neonatal lupus syndrome,* Paediatr Child Health *17:223–227, 2007.)*

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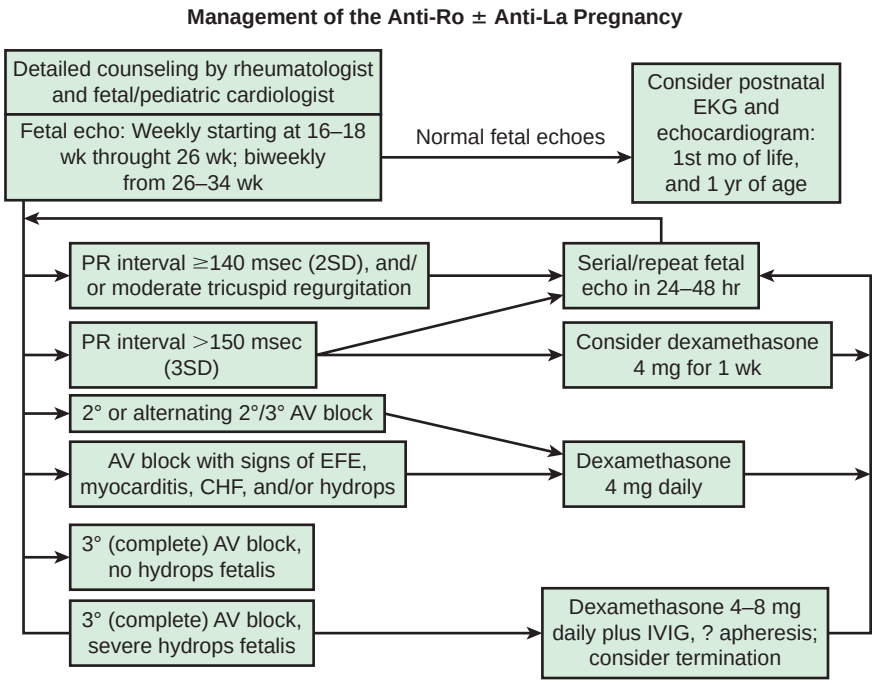


Figure 158-4 Algorithm for the management of the anti-Ro ± anti-La pregnancy. All such pregnancies should include counseling and serial fetal echocardiograms.

cardiomyopathy in the most severe cases. The noncardiac manifestations of neonatal lupus are usually reversible, whereas congenital heart block is permanent. Conduction system abnormalities can be detected in utero by fetal echocardiogram beginning at 16 wk of gestational age.

Neonatal lupus results from the passive transfer of maternal immunoglobulin G autoantibodies to the fetus. The vast majority of neonatal lupus cases are associated with maternal anti-Ro (also known as SSA) and anti-La antibodies (also known as SSB). Despite the clear association with maternal autoantibodies, their presence alone is not sufficient to cause disease, as ~2% of offspring born to mothers with anti-Ro and anti-La antibodies experience congenital heart block.

In vitro studies suggest that during cardiac development, 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 as well as 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, 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, including congenital heart block, endocardial fibroelastosis, and hydrops fetalis. Most encouraging are retrospective cohort studies suggesting maternal treatment with hydroxychloroquine may provide effective prophylaxis against congenital heart block. The mechanisms of action probably involve changes in acidification of endosomes and their interaction with Toll-like receptors. All clinical data on the use of hydroxychloroquine in pregnancy points to safety, and there are ongoing prospective clinical studies examining efficacy in the prevention of neonatal lupus syndrome in pregnant women known to be anti-Ro and/or anti-La positive.

Fluorinated corticosteroids seem to improve cases of hydrops. Significant conduction system abnormalities after birth are treated with cardiac pacing and occasionally intravenous immunoglobulin and steroids, while severe cardiomyopathy may require cardiac transplantation. Transient, noncardiac manifestations are conservatively managed, with topical steroids used occasionally to treat the rash.

Because maternal autoantibodies gain access to the fetus via the placenta at the 16th wk of gestation, all pregnant women with circulating anti-Ro or anti-La antibody (or those with a history of offspring with neonatal lupus or congenital heart block) are monitored by a pediatric cardiologist with regular fetal electrocardiography from 16 wk of gestation until delivery. If fetal bradycardia is found unexpectedly during in utero monitoring, screening for maternal anti-Ro and anti-La antibodies is warranted.

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. A mother who has borne a child with congenital heart block caused by neonatal lupus has an approximately 17% risk of recurrence with future pregnancies. With cardiac pacing, children with conduction system disease in the absence of cardiomyopathy have an excellent prognosis. If the conduction defect is not addressed, affected children are at risk for exercise intolerance, arrhythmias, and death. A proposed management algorithm is presented in Figure 158-4.

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Chapter 159

Juvenile Dermatomyositis

Angela Byun Robinson and Ann M. Reed

Juvenile dermatomyositis (JDM) is the most common inflammatory myositis in children, distinguished by proximal muscle weakness and a characteristic rash. Inflammatory cell infiltrates result in vascular inflammation, the underlying pathology in this disorder.

ETIOLOGY

Evidence suggests that the etiology of JDM is multifactorial, based on genetic predisposition and an unknown environmental trigger. Human

leukocyte antigen (HLA) alleles such as B8, DRB1*0301, DQA1*0501, and DQA1*0301 are associated with increased susceptibility to JDM in selected populations. Maternal microchimerism may play a part in the etiology of JDM by causing graft-versus-host disease or autoimmune phenomena. Persistent maternal cells have been found in blood and tissue samples of children with JDM. An increased number of these maternal cells are positive for HLA-DQA1*0501, which may assist with transfer or persistence of chimeric cells. Specific cytokine polymorphisms in tumor necrosis factor-α promoter and variable number tandem repeats of the interleukin-1 receptor antagonist may increase genetic susceptibility. These polymorphisms are common in the general population. A history of infection in the 3 mo prior to disease onset is commonly 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. Environmental factors may also play a contributing role, with geographic and seasonal clustering reported; however, no clear theory of etiology has emerged.

EPIDEMIOLOGY

The incidence of JDM is approximately 3 cases/1 million children/yr without racial predilection. Peak age of onset is between 4 and 10 yr. There is a second peak of dermatomyositis onset in late adulthood (45-64 yr), but adult-onset dermatomyositis appears to be a distinctly separate entity in prognosis and etiology. In the United States, the ratio of girls to boys 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 than in families of healthy children. Reports of seasonal association have not been confirmed, although clusters of cases may occur.

PATHOGENESIS

Interferon upregulates genes critical in immunoregulation and major histocompatibility complex (MHC) class I expression, activates natural killer cells, and supports dendritic cell maturation. Upregulation of gene products controlled by type I interferons occurs in patients with dermatomyositis, potentially correlating with disease activity and holding promise as clinical biomarkers.

It appears that children with genetic susceptibility to JDM (HLA-DQA1*0501, HLA-DRB*0301) may have prolonged exposure to maternal chimeric cells and/or an unknown environmental trigger. Once triggered, an inflammatory cascade with type I interferon response leads to upregulation of MHC class I expression and maturation of dendritic cells. Overexpression of MHC class I upregulates adhesion molecules, which influence migration of lymphocytes, leading to inflammatory infiltration of muscle. In an autoregulatory feedback loop, muscle inflammation increases the type I interferon response, regenerating the cycle of inflammation. Cells involved in the inflammatory cascade include natural killer cells (CD56), T-cell subsets (CD4, CD8, Th17), monocytes/macrophages (CD14), and plasmacytoid dendritic cells. Neopterin, interferon-inducible protein 10, monocyte chemoattractant protein, myxovirus resistance protein, and von Willebrand factor products, as well as other markers of vascular inflammation may be elevated in patients with JDM who have active inflammation.

Table 159-1 Diagnostic Criteria for Juvenile Dermatomyositis

Classic rash	Heliotrope rash of the eyelids Gottron papules
Plus 3 of the following:	
Weakness	Symmetric Proximal
Muscle enzyme elevation (≥1)	Creatine kinase Aspartate aminotransferase 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

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Table 159-2 Clinical Features of Juvenile Dermatomyositis During the Course of the Disease

FEATURE	%
Muscle weakness	90-100
Dysphagia or dysphonia	13-40
Muscle atrophy	10
Muscle pain and tenderness	30-83
Skin lesions	85-100
Heliotrope rash of eyelids	66-83
Gottron papules	57-91
Erythematous rash of malar/facial area	42-100
Periungual capillary changes	80
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	16-46
Gastrointestinal signs and symptoms	8-22
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, editors, Textbook of pediatric rheumatology, *ed 6, Philadelphia, 2011, Saunders, Table 24-20, p. 410.*

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 159-1 and 159-2).

Rash develops as the first symptom in 50% of cases and appears concomitant with weakness only 25% of the time. Children often exhibit extreme photosensitivity to ultraviolet 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** (Fig. 159-1) is a blue-violet discoloration of the eyelids that may be associated with periorbital edema. Facial erythema crossing the

nasolabial folds is also common, in contrast to the malar rash without nasolabial involvement typical of systemic lupus erythematosus. Classic **Gottron papules** (Fig. 159-2) are bright pink or pale, shiny, thickened or atrophic plaques over the proximal interphalangeal joints and distal interphalangeal joints and occasionally on the knees, elbows, small joints of the toes, and ankle malleoli. 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 nailfolds and gums as individual capillary loops that are thickened, tortuous, or absent (Fig. 159-3). Telangiectasias may be visible to the naked eye but are more easily visualized under capillaroscopy or with use of a magnifier such as an ophthalmoscope. Severe vascular inflammation causes cutaneous ulcers on toes, fingers, axillae, or epicanthal folds.

Weakness associated with JDM is often insidious and difficult to differentiate from fatigue at onset. 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 on thighs to 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 as a result 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, physical exam, and swallow study, if symptoms are present. Respiratory muscle weakness can be a medical emergency and lead to respiratory failure. 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.

Lipodystrophy and **calcinosis** (Fig. 159-4) are thought to be associated with long-standing or undertreated disease. 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. Calcinosis is reported in up to 40% of children with JDM, but the prevalence is thought to be lower in children who are treated early and aggressively. In rare instances, an "exoskeleton" of calcium deposition forms, greatly limiting mobility. 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,



Figure 159-1 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.



Figure 159-2 The rash of juvenile dermatomyositis. The skin over the metacarpal and proximal interphalangeal joints may be hypertrophic and pale red (Gottron papules).

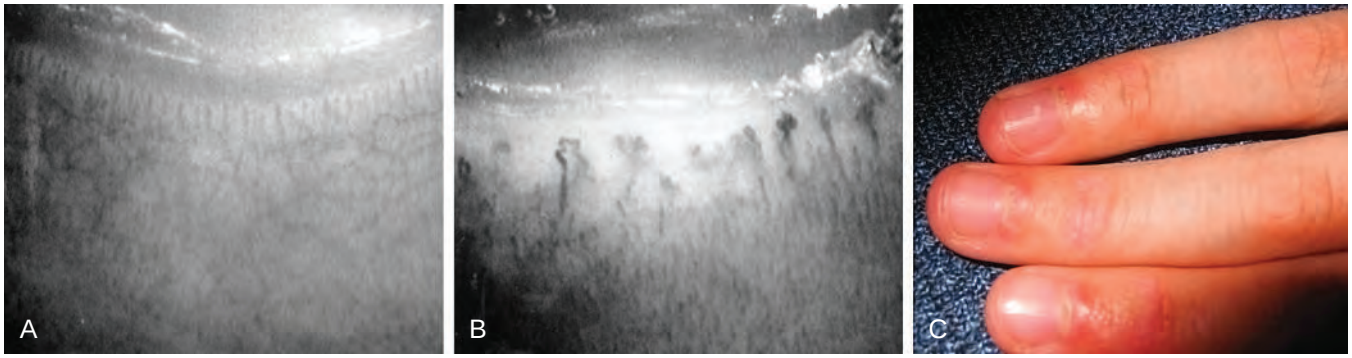


Figure 159-3 Nailfold capillary pattern in rheumatic disease. **A,** Normal nailfold capillary pattern in a healthy child with a homogeneous distribution and uniform appearance of capillary loops. **B,** The nailfold capillary pattern in a child with juvenile dermatomyositis shows dropout of capillary end loops, resulting in a wide band of avascularity. Dilated, tortuous capillaries can also be seen. **C,** Severe periungual telangiectasias may be seen without microscopy.

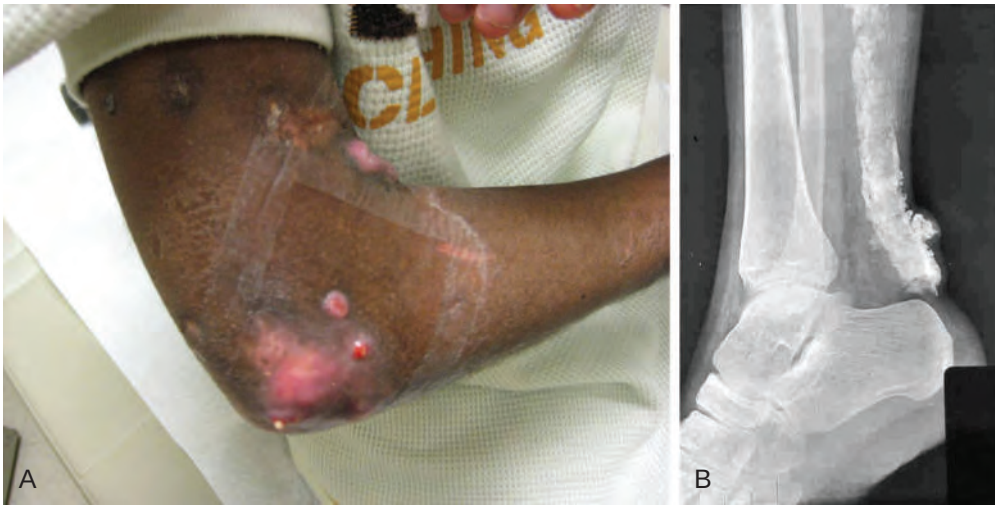


Figure 159-4 Rash and calcifications in dermatomyositis. **A,** Skin effects of calcification. **B,** Radiographic evidence of calcification.

hypertriglyceridemia, and abnormal glucose tolerance. Lipodystrophy may be generalized or localized.

Rarely, vasculitis of the GI tract develops in children with severe JDM, with crampy abdominal pain, pancreatitis, GI bleeding, and potential for intestinal perforation or infarction. Involvement of the cardiac muscle with pericarditis, myocarditis, and conduction defects has been reported. An association with malignancy at disease onset is observed in adults with dermatomyositis but very rarely in children.

DIAGNOSIS

Diagnosis of dermatomyositis requires the presence of characteristic rash as well as at least three signs of muscle inflammation and weakness (see Table 159-1). 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 shows signs of myopathy (increased insertional activity, fibrillations, and sharp waves) as well as 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 electromyography (EMG) be performed in a center with experience in pediatric EMG and its interpretation. Muscle biopsy is typically indicated when diagnosis is in doubt or for grading disease severity. 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 depends on the presenting symptoms. If the presenting complaint is solely weakness without rash or atypical disease, other causes of myopathy should be considered, including polymyositis, infection-related myositis (influenza A and B, coxsackievirus B, and other viral illnesses), muscular dystrophies (Duchenne and Becker as well as others), myasthenia gravis, Guillain-Barré syndrome, endocrinopathies (hyperthyroidism, hypothyroidism, Cushing syndrome, Addison disease, parathyroid disorders), mitochondrial myopathies, and metabolic disorders (glycogen and lipid storage diseases). Infections associated with prominent muscular symptoms include trichinosis, *Bartonella* infection, toxoplasmosis, and staphylococcal pyomyositis. 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 graft-versus-host disease. The rash of JDM may be confused with eczema, dyshidrosis, psoriasis, malar rash from systemic lupus erythematosus, capillary telangiectasias from Raynaud phenomenon, and other rheumatic diseases. Muscle inflammation is also seen in children with systemic lupus erythematosus, juvenile idiopathic arthritis, mixed connective tissue disease, inflammatory bowel disease, and antineutrophil cytoplasmic antibody–positive vasculitides. Table 159-3 compares other juvenile inflammatory myositis disorders.

LABORATORY FINDINGS

Elevated serum levels of **muscle-derived enzymes** (creatine kinase, aldolase, aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase) reflect muscle inflammation. Not all enzyme levels rise with inflammation in a specific individual; alanine aminotransferase is most commonly elevated on initial presentation, whereas the creatine kinase level may be normal. The erythrocyte sedimentation rate is often normal, and the rheumatoid factor test result is typically negative. There may be anemia consistent with chronic disease. Antinuclear antibody is present in >80% of children with JDM. Results of tests for antibodies to SSA, SSB, Sm, ribonucleoprotein, and double-stranded DNA are generally negative. Antibodies to Pm/Scl identify a small, distinct subgroup of myopathies with a protracted disease course, often complicated by pulmonary interstitial fibrosis and/or cardiac involvement. Similar to what is seen in adults, the presence of myositis-specific autoantibodies in JDM such as anti–Jo-1, anti–Mi-2, anti-p155/140, anti-NXP2, and other myositis-specific autoantibodies help define distinct clinical subsets and may predict the development of complications, although differences remain in certain aspects such as malignancy between adults and children.

Radiographic studies aid both diagnosis and medical management. MRI using T2-weighted images and fat suppression (Fig. 159-5) 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 instances 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.

Table 159-3 Phenotypic Characteristics of the Clinical Subgroups of Juvenile Myositis*

CHARACTERISTIC	JDM	JPM	JCTM
Demographics			
Median age at diagnosis (yr)	Youngest (7.4 yr)	Oldest (12.1 yr)	Intermediate (10.2 yr)
Race	Predominantly white (71.2%)	Black (39.4%)	Black or other (49.0%)
Severity at onset	Mild or moderate severity	**Severe or very severe onset**	Mild or moderate severity
Median delay to diagnosis (mo)	4 mo	3.5 mo	Longer delay (7 mo)
Clinical features	Gottron papules Heliotrope rash **Periungual capillary abnormalities** **Malar rash** *Photosensitivity* *Linear extensor erythema*† Cuticular overgrowth Mucous membrane involvement "V-sign" and "shawl-sign" rashes Skin ulcerations Dyspnea on exertion	*Weight loss* Falling episodes Raynaud phenomenon Abnormal PFT Dyspnea on exertion Cardiac abnormalities on EKG or ECHO	Gottron papules Heliotrope rash **Malar rash** **Raynaud phenomenon** **Interstitial lung disease** **Arthralgia** *Linear extensor erythema*† *Mucous membrane involvement* *Arthritis* *Photosensitivity* *Sclerodactyly* *Periungual capillary abnormalities*† Cuticular overgrowth Abdominal pain, GI bleeding Dyspnea on exertion Weight loss
Autoantibodies	Intermediate ANA titer (median, 1:320) *Anti-p155/140*† Anti-MJ Anti-Mi-2	Intermediate ANA titer (median, 1:320) Anti-SRP Anti-aminoacyl-tRNA synthetase (anti–Jo-1)	Highest ANA titer (median, 1:1280) **Anti-U1-RNP** Anti-PM-Sc1 Anti-Ro Anti-SM Anti-La All other U-RNP autoantibodies
Laboratory features	*Lowest CK level (median, 829 U/L)*	**Highest CK level (median, 5027 U/L)** Highest levels of aldolase and ALT	Intermediate CK level (median 1208 U/L)
Outcome	Low mortality (2.4%) Calcinosis (34.0%)	Medium mortality (6.3%) **Frequently hospitalized (71.9%)** Wheelchair use	Highest mortality (14.6%)

ALT, alanine aminotransferase; ANA, antinuclear antibody; CK, creatine kinase; ECHO, echocardiogram; EKG, electrocardiogram; GI, gastrointestinal; JCTM, juvenile myositis overlapping with another autoimmune or connective tissue disease; JDM, juvenile dermatomyositis; JPM, juvenile polymyositis; PFT, pulmonary function test; tRNA, transfer RNA.

*Bold indicates significant in logistic regression; *italics* indicates top variables entered in pruned-down random forest models. Other variables included in this table were significant in univariable analysis to $p \leq 0.01$.

†Removed from logistic regression analyses because variable was either 100% or 0% in 1 of the compared subgroups. Gottron papules and heliotrope rash, which were part of the definition of cases of dermatomyositis, were not entered into multivariable analyses.

Modified from Shah M, Mamyrova G, Targoff IN, et al: The clinical phenotypes of the juvenile idiopathic inflammatory myopathies. Medicine (Baltimore) *92:25–41, 2013, Table 9, p. 36.*

TREATMENT

The aid of an experienced pediatric rheumatologist is invaluable in outlining an appropriate course of treatment for a child with JDM. Prior to the advent of corticosteroids, one-third of patients spontaneously improved, one-third had a chronic, lingering course, and one-third died from the disease. Corticosteroids have altered the course of disease, lowering morbidity and mortality. Methotrexate decreases the length of treatment with corticosteroids, thereby reducing morbidity from steroid toxicity. Intravenous gammaglobulin is frequently used as an adjunct for treatment of severe disease.

Corticosteroids are still the mainstay of treatment. In a clinically stable child without debilitating weakness, oral prednisone at 2 mg/kg/day (maximum 60 mg daily) is usually started. Children with GI involvement have decreased absorption of oral steroids and require intravenous 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 a period of 12 mo, after indicators of inflammation (muscle enzymes) normalize and strength improves.

Weekly oral, intravenous, or subcutaneous methotrexate (the lesser of 1 mg/kg or 15 mg/m^2, maximum 40 mg) is commonly 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, and anemia). Children who are taking immunosuppressive medications such as methotrexate should avoid live-virus vaccination, although inactivated influenza vaccination is recommended yearly.

Hydroxychloroquine has little toxicity risk and is used as a secondary disease-modifying agent to reduce rash and maintain remission. Typically, it is administered at doses between 4 and 6 mg/kg/day orally

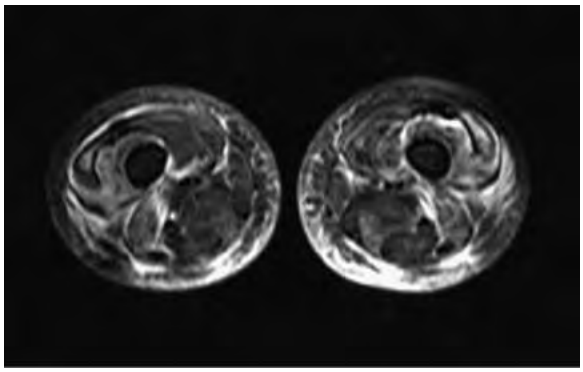


Figure 159-5 MRI using T2-weighting and fat suppression of the proximal muscle of the lower extremities of a child with juvenile dermatomyositis with normal muscle enzyme levels. There is focal inflammatory myopathy. The bright areas reflect the inflammatory response in involved muscle. The darker areas are more normal. Identification of involved areas by MRI directs the location of the muscle biopsy or electromyography.

in either tablet or liquid form. Ophthalmologic follow-up 1-2 times 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 subjects given rituximab at baseline or at 8 wk, but overall, 83% of all subjects met the definition of improvement in the trial. Reports of the use of other biologic agents are based on case reports with mixed results.

Other medications for severe unresponsive disease include intravenous immunoglobulin, mycophenolate mofetil, cyclosporine, and cyclophosphamide. 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 strength muscle 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 sunscreen daily, even in winter and on cloudy days. Vitamin D and calcium supplements are indicated for all children undergoing long-term corticosteroid therapy, in an attempt to reduce osteopenia and osteoporosis from medication.

COMPLICATIONS

Most complications from JDM are related to prolonged and severe weakness, including muscle atrophy, to cutaneous calcifications and scarring or atrophy, and 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. 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. Cardiac involvement by JDM is rare but includes arrhythmias.

Pathologic calcifications may be related to severity of disease and prolonged delay to treatment and potentially to genetic polymorphisms of tumor necrosis factor -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.

Lipodystrophy manifests in 10-40% of patients with JDM and can be difficult to recognize. Fat atrophy may be generalized, partial, or local. Lipodystrophy has been associated with insulin resistance, acanthosis nigricans, dyslipidemia, hypertension, and menstrual irregularity, similar to features seen in polycystic ovarian disease or metabolic syndrome.

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.

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 yr to <1.5 yr with more aggressive immunosuppressive therapy; the vascular, skin, and muscle symptoms of children with JDM generally respond well to therapy. At 7 yr 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.

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Chapter 160

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 2 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 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, 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. 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. Within the category of JLS there are several subtypes that are differentiated by both the distribution of the lesions and the depth of involvement (Table 160-1). Up to 15% of children have a combination of 2 or more subtypes.

Table 160-1 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 3 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. 160-2)
Morphea profunda:
Deep lesion extending to fascia and sometimes muscle, but may be limited to a single plaque, often on trunk
Disabling pansclerotic morphea of childhood:
Generalized full-thickness involvement of skin on the trunk, face and extremities, sparing finger tips 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

EPIDEMIOLOGY

Juvenile scleroderma is rare, with an estimated prevalence of 1/100,000. Localized scleroderma is far more common than 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 yr. After age 8 yr the female:male ratio for both LS and SSc is approximately 3:1, whereas in patients younger than 8 yr there is no sex predilection.

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 sign (Fig. 160-1). Edema and erythema are followed by indurated, hypopigmented or hyperpigmented, atrophic lesions (Fig. 160-2). **LS** varies in size from a few centimeters to the entire length of the extremity, with varying depth. Patients sometimes present with arthralgias, synovitis, or flexion contractures (Fig. 160-3). 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** (Fig. 160-4) may have symptoms unique to central nervous system involvement, such as seizures, hemifacial atrophy, ipsilateral uveitis, and learning/behavioral changes.

Up to 25% of children with LS have extracutaneous manifestations, most commonly arthritis (47%) and neurologic symptoms (17%) associated with en coup de sabre.

Systemic Scleroderma

SSc also has an insidious onset with a prolonged course characterized by periods of remission and exacerbation, ending in either remission or, more commonly, chronic disability and death.

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 causes ulceration of the fingertips with subsequent loss of tissue pulp and tapered fingers (**sclerodactyly**) (Fig. 160-5). Resorption of the distal tufts of the distal phalanges may occur (**acroosteolysis**). Hyperpigmented postinflammatory changes surrounded by atrophic depigmentation gives a



Figure 160-1 Boy 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.



Figure 160-2 Inactive linear scleroderma demonstrating hyperpigmented lesion with areas of normal skin (skip lesions).



Figure 160-3 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.



Figure 160-4 Child with en coup de sabre lesion on scalp extending down to forehead. Prior to treatment the skin on the scalp was bound down with chronic skin breakdown. Note the area of hypopigmentation extending down the forehead *(arrows)*.



Figure 160-5 Sclerodactyly and finger ulcerations in a patient with systemic sclerosis who is poorly compliant with treatment.

salt-and-pepper appearance to skin. Over a period of 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 rest, and right-sided heart failure. **Pulmonary arterial hypertension** is a poor prognostic sign, developing either as a consequence 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 testing, bronchioalveolar lavage, and high-resolution chest CT. Pulmonary function tests reveal decreased vital capacity and decreased diffusion of carbon monoxide capacity, while neutrophilia and/or eosinophilia on bronchioalveolar lavage suggest 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.

Other organ systems include gastrointestinal tract disease, which is seen in 25% of children with the disease. 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 crisis is rare. Cardiac fibrosis is associated with arrhythmias, ventricular hypertrophy, and decreased cardiac function. Mortality from JSSc is most commonly a result of cardiopulmonary disease.

Raynaud Phenomenon

Raynaud phenomenon (RP) is the most frequent initial symptom in pediatric systemic sclerosis, present in 70% of affected children months to years before other manifestations. RP refers to the classic triphasic sequence of blanching, cyanosis, and erythema of the digits induced

Table 160-2 Classification of Raynaud Phenomenon

Isolated Raynaud phenomenon
Occupational Raynaud phenomenon:
Cold injury
Vibrating tools
Polyvinyl chloride exposure
Secondary Raynaud phenomenon:
Systemic sclerosis
Mixed connective tissue disease
Sjögren syndrome
Systemic lupus erythematosus
Polymyositis/dermatomyositis
Rheumatoid arthritis
Arteritis
Antiphospholipid antibody syndrome
Primary biliary cirrhosis
Carpal tunnel syndrome
Cryoglobulinemia
Leukemia
Vasospastic disorders (migraine, Prinzmetal angina)
Infection:
Hepatitis B and C (cryoglobulinemia)
Cytomegalovirus (?)
Obstructive vascular disease:
Thromboangiitis obliterans
Thoracic outlet syndrome (cervical rib)
Metabolic syndrome:
Hypothyroid
Carcinoid syndrome
Drug-induced:
Antimigraine medications
β-Blocker
Bleomycin
Interferons
Ergotamine derivatives

From Firestein GS, Budd RC, Harris ED Jr, et al, editors: Kelley's textbook of rheumatology, *ed 8, vol II, Philadelphia, 2009, Saunders/Elsevier.*

Table 160-3 Provisional Criteria for the Classification of Juvenile Systemic Sclerosis (SSc)

MAJOR CRITERION (REQUIRED)*
Proximal skin sclerosis/induration of the skin proximal to metacarpophalangeal or metatarsophalangeal joints
MINOR CRITERIA (AT LEAST 2 REQUIRED)
Cutaneous: sclerodactyly
Peripheral vascular: Raynaud phenomenon, nailfold 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 computed tomography/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 1 major and at least 2 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 *57:203–212, 2007.*

by cold exposure and/or emotional stress. RP is most commonly independent of an underlying rheumatic disease (**Raynaud disease**), but it can be a consequence of rheumatic diseases such as scleroderma, systemic lupus erythematosus, and mixed connective tissue disease (Table 160-2). 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 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 sometimes 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; this condition has been associated with systemic lupus erythematosus.

DIAGNOSIS

The diagnosis of localized scleroderma 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 as well as the presence of 2 of 20 minor criteria (Table 160-3).

DIFFERENTIAL DIAGNOSIS

The most important condition to differentiate from JLS is JSSc. Contractures and synovitis from juvenile arthritis can be differentiated from those due to linear scleroderma by the absence of skin changes. Other conditions to consider include chemically induced scleroderma-like disease, **diabetic cheiroarthropathy**, **pseudoscleroderma**, and **scleredema**. Pseudoscleroderma is composed of 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

There are no laboratory studies 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 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 for determination of central nervous system or orbital involvement. Infrared thermography utilizes the temperature variation between areas of active and inactive cutaneous disease to help differentiate active disease from damage. The role of ultrasound to look at lesion activity is evolving. High-resolution CT, pulmonary function tests, 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 treatment plan for JLS and includes: (1) weekly subcutaneous methotrexate given at 1/mg/kg weekly (maximum dose: 25 mg); (2) weekly methotrexate as in (1) plus either 3 mo of high-dose intravenous corticosteroids (30 mg/kg, maximum dose: 1,000 mg) for 3 consecutive days a month *or* weekly corticosteroids at the same dose for 3 mo; (3) high daily oral corticosteroids (2 mg/kg/day, maximum: 60 mg) with a slow taper over 48 wk. Mycophenolate mofetil is a second-line agent for recalcitrant disease. Physical and occupational therapy are important adjuncts to pharmacologic treatment. Eosinophilic fasciitis often responds well to corticosteroids and methotrexate.

Treatments for JSSc target specific disease manifestations. RP is treated with cold avoidance with pharmacologic interventions are reserved for severe disease. Calcium channel blockers (nifedipine 30-60 mg of 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 inhibitors (captopril, enalapril) are recommended for hypertension associated with renal disease. Methotrexate or mycophenolate mofetil may be beneficial for skin manifestations. Cyclophosphamide and mycophenolate mofetil are used to treat pulmonary alveolitis and prevent fibrosis. Corticosteroids should be used cautiously in systemic sclerosis because of an association with renal crisis. Adults with systemic sclerosis have been successfully treated with high-dose cyclophosphamide, antithymocyte globulin and autologous stem cell transplantation.

The treatment of RP begins with avoiding cold stimuli, use of hand and foot warmers, and avoiding carrying bags by their handles (impairs circulation). Nifedipine (10-20 mg tid 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

Localized scleroderma is generally self-limited, with initial inflammatory stage followed by a period of stabilization and then softening for an average disease duration of 3-5 yr; however there are reports of active disease lasting up to 20 yr. Prolonged disease activity is associated primarily with linear and deep disease subtypes. Localized scleroderma, 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 hyper- and hypopigmentation. Death from a **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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Chapter 161

Behçet Disease

Seza Özen

Behçet disease (BD) is classified as a primary *variable vessel vasculitis*, emphasizing the involvement of any size and type (arterial, venous) of vessel. BD is also recognized as an autoinflammatory disease. Originally described with recurrent oral ulcerations, uveitis and skin abnormalities, the 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. BD has a prevalence of 5-7 per 100,000 adults, which makes it more frequent than the other vasculitides such as granulomatosis polyangiitis (Wegener disease). The increased disease recognition might have had a role in the rising prevalences as well as the immigrations of the 20th century. Prevalence in children is probably not more than 10% of the adult counterparts in eastern Mediterranean countries. In children, boys and girls are equally affected. Family history of BD is present in approximately 20% of the cases. Onset in children is 8-12 yr of age; newborns of affected mothers have demonstrated symptoms of BD.

ETIOLOGY AND PATHOGENESIS

BD is a polygenic autoinflammatory disorder. Genetic contribution to BD is evident through the 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 the genome wide analysis studies that support the genetic contribution in the pathogenesis. 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-12RB2 genes. Other possible susceptibility loci in a Turkish cohort demonstrate associations in 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 processing of peptides onto major histocompatibility complex class I).

The autoinflammatory nature of the disease is suggested by the episodic nature of the disease, the prominent innate immune system activation, the absence of identifiable autoantibodies and the co-association with the *MEFV* (Mediterranean fever) gene. 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, herpes simplex virus type 1, and parvovirus B19.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The course of BD is characterized by exacerbations and remissions. There is also marked heterogeneity in disease manifestation (Table 161-1).

The mean age of the first symptom is between 8 and 12 yr. The most frequent initial symptom is a painful **oral ulcer** (Fig. 161-1). The oral ulcers are often recurrent, may be single or multiple, range from 2-10 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% of the patients, usually occur after puberty, and are seen on the labia, scrotum, penis, or the anal area.

Another key feature of BD that has significant morbidity is 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. Vitreitis 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** of BD range from erythema nodosum, papulopustular acneiform lesions, folliculitis, purpura, and ulcers. **Pathergy** is also a skin feature that is a pustular reaction occurring 24-48 hr after a sterile needle puncture or saline injection; it is not pathognomonic of BD.

Table 161-1 Criteria of the International Study Group for the Diagnosis of Behçet disease

CRITERION	DESCRIPTION
Recurrent oral ulceration	Minor aphthous, major aphthous, or herpetiform ulceration recurring at least 3 times in one 12 mo period, observed by physician or patient
Plus 2 of the following:	
Recurrent genital ulcers	Aphthous ulceration or scarring observed by physician or patient
Eye lesions	Anterior uveitis, posterior uveitis, cells in vitreous on slit-lamp examination, or retinal vasculitis observed by an ophthalmologist
Skin lesions	Erythema nodosum observed by physician or patient, pseudofolliculitis or papulopustular lesions, or acneiform nodules observed by physician in postadolescent patient not on corticosteroid treatment
Pathergy	Skin reaction to a needle prick observed by physician at 24-48 hr

From International Study Group for Behçet's Disease: Criteria for diagnosis of Behçet's disease, Lancet *335:1070–1080,1990.*



Figure 161-1 Oral aphthous lesion in a girl with Behçet disease. *(From Ozen S, Petty RE: Behçet disease. In Cassidy JT, Petty RE, Laxer RM, et al, editors,* Textbook of pediatric rheumatology, *ed 6, Philadelphia, 2011, Saunders, Fig. 36-1, p. 554.)*

The **vasculitis** of BD involves both arterial or venous thrombosis and aneurysm formation or 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 aneurysms are the most severe feature of pediatric BD, associated with the highest mortality. Coronary artery aneurysms may confuse BD with Kawasaki disease. Microvascular involvement may be noted in the nail bed capillaries.

Central nervous system (CNS) manifestations 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 involvement 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 more than 50% of the patients and can be recurrent, but is nondeforming. Other rare manifestations include orchitis, renal vasculitis, glomerulonephritis, or amyloidosis and cardiac involvement.

DIAGNOSIS

The International Study Group criteria are most widely used and require the presence of oral ulcers (at least 3 times per year) along with 2 other major features, including genital ulcers, a positive pathergy test, uveitis, and the characteristic skin lesions (see Table 161-1). If only 1 of the criteria is present along with oral ulcerations, the term *incomplete* or *partial Behçet disease* is applied. 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.

TREATMENT AND PROGNOSIS

Azathioprine is highly recommended to treat inflammatory eye disease. For oral and genital ulcers topical treatment is recommended (sucralfate, steroids). Colchicine is recommended for erythema nodosum or arthritis in males and females and for genital ulcers in females. There is no evidence-based treatment for gastrointestinal disease, but thalidomide, sulfasalazine, steroids, azathioprine and anti–tumor necrosis factor (TNF) agents have been recommended. For CNS disease and vasculitis, steroids, azathioprine, cyclophosphamide, interferon alpha, and in unresponsive CNS disease anti-TNF agents are suggested. There is no consensus about the benefit of anticoagulation in the management of vein thrombosis in BD.

In patients without major organ involvement, colchicine significantly improves oral and genital ulcers, skin features, and disease activity. In pediatric patients with vascular involvement with venous thrombosis, steroids and azathioprine have been used, whereas those with pulmonary arterial or cardiac involvement are initially treated with cyclophosphamide; follow-up of at least 18 mo demonstrated that those treated are free of vascular relapses. Patients treated with anti-TNF drugs have had persistent responses in 90%, 89%, 100%, and 91% of patients with resistant mucocutaneous, ocular, gastrointestinal, and central nervous system involvement, respectively.

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 improves the outcome of BD.

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Chapter 162

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, with potential for systemic manifestations. It is rare in children and predominantly affects middle-age women with classic symptoms of dry eyes (**keratoconjunctivitis sicca**) and dry mouth (**xerostomia**).

EPIDEMIOLOGY

Sjögren syndrome typically manifests at 35-45 yr of age, with 90% of cases among women, but it is underrecognized in children as symptoms often start in childhood. The mean age at diagnosis in children is 9-10 yr; 75% are girls. 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, scleroderma, or mixed connective tissue disease, and 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 162-1). Recurrent parotid gland enlargement and parotitis are the most common manifestations in children (>70%), whereas sicca syndrome (dry mouth, painful mucosa, sensitivity to spicy foods, halitosis, widespread dental caries) predominate in 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 involvement (5%).

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, and antibodies to Ro [SSA] and SSB [La]) and articular manifestations are significantly more frequent in adults. Frequencies of the finding of antinuclear antibodies and SSA and SSB antibodies in children are reported to be 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 central nervous system (optic neuritis, transverse myelitis, meningoencephalitis).

Table 162-1 Proposed Criteria for Pediatric Sjögren Syndrome

I. CLINICAL SYMPTOMS
   1. Oral: recurrent parotitis or enlargement of parotid gland, dry mouth (xerostomia)
   2. Ocular: dry eyes (xerophthalmia) recurrent conjunctivitis without obvious allergic or infectious etiology, keratoconjunctivitis sicca
   3. Other mucosal: recurrent vaginitis
   4. Systemic: fever, non-inflammatory arthralgias, hypokalemic paralysis, abdominal pain

II. IMMUNOLOGIC ABNORMALITIES: presence of at least 1 of the following antibodies: anti-SSA, anti-SSB, high titer antinuclear antibody, rheumatoid factor

III. OTHER ABNORMALITIES OR INVESTIGATIONS
   1. Biochemical: elevated serum amylase
   2. Hematologic: leukopenia, high sedimentation rate
   3. Immunologic: polyclonal hyperimmunoglobulinemia
   4. Renal: renal tubular acidosis
   5. Histologic proof of lymphocytic infiltration of salivary glands or other organs (i.e., liver)
   6. Objective documentation of ocular dryness (Bengal red staining or Schirmer test)
   7. Positive findings of parotid gland scintigraphy

IV. Exclusion of all other autoimmune diseases

Diagnosis requires ≥4 criteria.
From Bartunkova J. Primary Sjögren syndrome in children and adolescents: proposal for diagnostic criteria, Clin Exp Rheumatol *17:381–386, 1999.*

Non–exocrine disease manifestations of Sjögren syndrome may be related to inflammatory vascular disease (in skin, muscle and joints, serosal surfaces, and peripheral and central nervous systems), noninflammatory vascular disease (Raynaud phenomenon), mediator-induced disease (hematologic cytopenias, fatigue, and 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 this disorder. 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 detection of SSA and SSB antibodies. Anti–β-fodrin autoantibodies, directed against an apoptotic cleavage product of α-fodrin, are a useful diagnostic marker for juvenile Sjögren syndrome. The **Schirmer test** detects abnormal tear production (≤5 mm of wetting of filter paper strip in 5 min) and **Rose-Bengal staining** detects damaged ocular epithelial conjunctival and corneal cells. Imaging studies, including MRI, technetium ^{99m}Tc scintigraphy, and sialography, are useful in the diagnostic evaluation for Sjögren syndrome (Fig. 162-1).

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, it is seen in the younger children (3-6 yr of age), 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. In these conditions,



Figure 162-1 T2-weighted MRI of child with Sjögren syndrome showing parotitis *(arrows)*.

sicca complex, rash, arthralgia, and antinuclear antibodies 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 functional disorders 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 the neonatal lupus syndrome (see Chapter 158.1).

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Chapter 163

Hereditary Periodic Fever Syndromes and Other Systemic Autoinflammatory Diseases

Amanda K. Ombrello and Daniel L. Kastner

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. They are subsumed among a larger group of disorders, the systemic autoinflammatory diseases, that were first recognized for their seemingly unprovoked episodes of inflammation, without the high-titer autoantibodies or antigen-specific T cells commonly seen in autoimmune diseases such as systemic lupus erythematosus or rheumatoid arthritis. Whereas the autoimmune diseases are disorders of the adaptive immune system, with its lymphocyte effector cells and receptors that somatically rearrange and mutate, the autoinflammatory diseases largely represent disorders of the phylogenetically more primitive innate immune system, mediated by myeloid effector cells and germline-encoded receptors. The autoinflammatory diseases can cause an intense acute phase response with elevation of the erythrocyte sedimentation rate, C-reactive protein, and serum amyloid A, in some cases leading to amyloid A (AA) amyloidosis (see Chapter 164).

The hereditary periodic fever syndromes include 2 illnesses with an autosomal recessive mode of inheritance, familial Mediterranean fever (FMF; MIM249100) and the hyperimmunoglobulinemia D with periodic fever syndrome (HIDS; MIM260920). Hereditary periodic fever syndromes with an autosomal dominant mode of inheritance include the tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS; MIM191190) and a spectrum of disorders known as the cryopyrin-associated periodic syndromes (CAPSs), or cryopyrinopathies. From mildest to most severe, CAPS includes the 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, or CINCA) (Table 163-1).

There are a number of other mendelian autoinflammatory diseases that present in childhood and are not considered hereditary periodic fever syndromes. 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 (also known as early-onset sarcoidosis; MIM186580), chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE; MIM256040), autoinflammation with phospholipase $C\gamma_2$-associated antibody deficiency and immune dysregulation (APLAID; MIM614878), and deficiency of adenosine deaminase-2 (DADA2) (Table 163-2). Other disorders include congenital sideroblastic anemia with B-cell immunodeficiency, periodic fevers and developmental delay (SIFD) due to biallelic mutations of the *TRNT1* gene as well as disease produced by mutations in the phospholipase *C*γ_2 gene (cold-induced urticaria, granulomatous rash, bronchiolitis, enterocolitis, eye inflammation) or by mutations in the cat-eye syndrome chromosome region, candidate 1 (*CECR1*) causing fever, stroke, rash, and vasculitis. An interferonopathy due to upregulation of *TMEM173* that encodes STING (stimulation of

Table 163-1 Differential Diagnosis of Familial Autoinflammatory Syndromes

		Mevalonate Kinase Deficiency (MKD)			Cryopyrin-Associated Periodic Syndrome (CAPS)			
	FAMILIAL MEDITERRANEAN FEVER (FMF)	HYPERIMMUNOGLOBULIN D SYNDROME (HIDS)	MEVALONIC ACIDURIA	TUMOR NECROSIS FACTOR RECEPTOR–ASSOCIATED PERIODIC SYNDROME (TRAPS)	FAMILIAL COLD AUTOINFLAMMATORY SYNDROME (FCAS)	MUCKLE-WELLS SYNDROME (MWS)	CHRONIC INFANTILE NEUROLOGIC CUTANEOUS AND ARTICULAR SYNDROME (CINCA)	DEFICIENCY OF IL-1 RECEPTOR ANTAGONIST (DIRA)
Mode of Inheritance	Autosomal recessive	Autosomal recessive	Autosomal recessive	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal recessive
Age at Onset (yr)	<20	<1	<1	<20	<1	<20	<1	Birth, <4 wk
Duration of attack (days)*	<2	4-6	4-5	>14	<2	1-2	?	Continuous
Cutaneous Involvement	Erysipelas-like erythema	Maculopapular rash	Morbilliform rash	Migratory rash, overlying area of myalgia	Cold-induced urticaria-like lesions	Urticaria-like rash	Urticaria-like lesions	Generalized pustulosis
Musculoskeletal Involvement	Monoarthritis common	Arthralgia, occasional oligoarthritis	Arthralgia common	Severe myalgia common; occasional frank monoarthritis	Arthralgia common; occasional mild myalgia	Lancing limb pain, arthralgia common; arthritis can occur	Epiphyseal bone formation	Sterile pustulous osteomyelitis
Abdominal Involvement	Sterile peritonitis common	Splenomegaly, severe pain common	Splenomegaly, pain may occur	Severe pain common	None	May occur	Hepatosplenomegaly	
Eye Involvement	Uncommon	Uncommon	Uncommon	Conjunctivitis and periorbital edema common	Conjunctivitis	Conjunctivitis; sometimes optic nerve elevation	Papilledema with possible loss of vision, uveitis	
Distinguishing Clinical Symptoms	Erysipelas-like erythema	Prominent cervical lymphadenopathy	Dysmorphic features, neurologic symptoms	Migratory nature of myalgia and rash, periorbital edema	Cold-induced urticaria-like lesions	Sensorineural hearing loss	Chronic aseptic meningitis, sensorineural hearing loss, arthropathy	
Gene Involved	*MEFV*	*MVK*	*MVK*	*TNFRSF1A*	*CIAS1 = NLRP3*	*CIAS1 = NLRP3*	*CIAS1 = NRLP3*	*IL-1RN*
Protein Involved	Pyrin (marenostrin)	Mevalonate kinase	Mevalonate kinase	Type 1 tumor necrosis factor receptor	Cryopyrin	Cryopyrin	Cryopyrin	IL-1RA

Note: For details on Blau syndrome, DIRA, and pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome, see text.

*Duration may vary; this is a typical duration.

Modified from Hull KM, Shoham N, Chae JJ, et al: The expanding spectrum of systemic autoinflammatory disorders and their rheumatic manifestations, Curr Opin Rheumatol *15:61–69, 2003.*

Table 163-2 Clinical Grouping of Autoinflammatory Diseases by Fever and Skin Manifestations

1. Nonspecific maculopapular rashes with recurrent episodic fever and abdominal pain (the classic "periodic fever syndromes")
   Recurrent fever attacks of short duration (typically <7 days)
   - FMF: familial Mediterranean fever
   - HIDS: mevalonate kinase deficiency/hyperimmunoglobulinemia D with periodic fever syndrome

   Recurrent fever attacks of longer duration (typically >7 days)
   - TRAPS: TNF receptor-associated periodic fever syndrome
2. Neutrophilic urticaria (the cryopyrinopathies)
   Recurrent fever attacks of short duration (typically <24 hr)
   - CAPS/FCAS: familial cold autoinflammatory syndrome
   - CAPS/MWS: Muckle-Wells syndrome

   Continuous low-grade fever
   - CAPS/NOMID: neonatal onset multisystem inflammatory disease (NOMID)/chronic infantile neurologic cutaneous and articular syndrome (CINCA)
3. Granulomatous skin lesions and minimal or low-grade fever attacks
   - Blau syndrome/early-onset sarcoidosis (pediatric granulomatous arthritis)
4. Pustular skin rashes and episodic 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

   With inflammatory bowel disease
   - Early-onset inflammatory bowel disease

   Without other organ involvement
   - DITRA: deficiency of interleukin-36-receptor antagonist
   - CAMPS: CARD14-mediated psoriasis
5. Atypical neutrophilic dermatosis with histiocytic-like infiltrate
   - PRAAS: proteasome associated autoinflammatory syndromes
6. Syndromes with autoinflammation and immunodeficiency
   - PLAID: PLCγ_2-associated antibody deficiency and immune dysregulation
   - APLAID: autoinflammation and PLCγ_2-associated antibody deficiency and immune dysregulation
   - HOIL-1 deficiency

From Almeida de Jesus A, Goldbach-Mansky R: Monogenic autoinflammatory diseases: concept and clinical manifestations. Clin Immunol *147:155-174, 2013, Table 1.*

interferon genes) produces infantile onset of neutrophilic rash, increased acute-phase reactants, fever, interstitial lung disease, paratracheal adenopathy, and facial nodules.

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) (Table 163-3). Other genetically complex disorders that are sometimes considered autoinflammatory are covered elsewhere in this volume: systemic-onset juvenile idiopathic arthritis (see Chapter 155), Behçet disease (see Chapter 161), and Crohn disease (see Chapter 336). Distinguishing one disorder from the others may be difficult; Tables 163-4 and 163-5 and Figures 163-1 and 163-2 can be helpful to this end.

FAMILIAL MEDITERRANEAN FEVER

FMF is a recessively inherited autoinflammatory disease usually characterized by recurrent 1-3 day self-limited episodes of fever, serositis, mono- or pauciarticular arthritis, or an erysipeloid rash, sometimes complicated by AA amyloidosis.

Etiology

FMF is caused by mutations in *MEFV*, a 10 exon gene located on the short arm of chromosome 16 encoding a 781 amino acid protein denoted pyrin (from the Greek for fever). Pyrin is expressed in granulocytes, monocytes, and dendritic cells, and in peritoneal, synovial, and dermal fibroblasts. The N-terminal ~90 amino acids of pyrin are the prototype for a motif (the PYRIN domain) that mediates protein-protein interactions and is found in more than 20 different human proteins that regulate inflammation and apoptosis. 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.

Many of the FMF-associated mutations in pyrin are found at the C-terminal B30.2 domain of pyrin, encoded by exon 10 of *MEFV.* More than 50 such FMF mutations are listed in an online database (http://fmf.igh.cnrs.fr/ISSAID/infevers/), nearly all of which are missense substitutions. Homozygosity for the M694V mutation 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 to be either a mild mutation or a functional polymorphism in the pyrin protein. The combined frequencies of FMF mutations among several Mediterranean populations are extraordinarily high (up to 1:3), suggesting the possibility of a heterozygote advantage. It is also noteworthy that there is a small percentage of patients of typical ethnicity and the clinical findings of FMF who have no demonstrable *MEFV* mutations, suggesting the possibility of a second FMF locus.

Epidemiology

FMF occurs primarily among ethnic groups of Mediterranean ancestry, most commonly Jews, Turks, Armenians, Arabs, and Italians. Owing to a higher frequency of the M694V mutation, FMF is more severe and more readily recognized in the Sephardic (North African) than the Ashkenazi (East European) Jewish population. Nevertheless, due to demographics, most Jewish FMF patients in the US are of Ashkenazi ancestry. With the advent of genetic testing, mutation-positive FMF has been documented worldwide, although at lower frequency than in the Mediterranean basin and Middle East. Most patients present with symptoms in childhood, with 90% of patients presenting prior to the age of 20 yr.

Pathogenesis

It appears that FMF mutations lead to a gain-of-function and IL-1β–dependent inflammation, with a gene-dosage effect. These results may explain why many heterozygous carriers of FMF mutations have biochemical evidence of inflammation, why as many as 30% of symptomatic FMF patients have only 1 demonstrable *MEFV* mutation, and why IL-1 inhibitors have a therapeutic effect in FMF.

Table 163-3 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 (a.k.a. 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; 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; M-CSF, macrophage–colony-stimulating factor; MIP-1α, macrophage inflammatory protein-1α; PAP, phosphatidate phosphatase; PPP, palmer-plantar pustulosis; PSTPIP2, proline-serine-threonine phosphatase interacting protein; RANKL, receptor activator of nuclear factor-κB ligand; RANTES, regulated upon activation, normal T-cell expressed and secreted; SH3BP2, SH3 binding protein 2; TGF, transforming growth factor; TNF-α, tumor necrosis factor α.

From Ferguson PJ, Laxer RM: Autoinflammatory bone disorders. In Cassidy JT, Petty RE, Laxer RM, et al, editors: Textbook of pediatric rheumatology, *ed 6, Philadelphia, 2010, Saunders, Table 44-2.*

Clinical Manifestations

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 can be generalized or localized to 1 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. 163-3). 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 1-2 flares/year.

Diagnosis

The diagnosis of FMF can often be made clinically, paying special attention to the duration and recurrence of episodes, documentation of fever, the characteristic serositis, synovitis, or erysipeloid rash, responsiveness to daily colchicine prophylaxis, and the absence of other causative factors. The differential diagnosis includes other hereditary periodic fever syndromes, and, depending on the specific circumstances, may include PFAPA, systemic-onset juvenile idiopathic arthritis (Still disease), cyclic hematopoiesis, gynecologic disorders (when abdominal pain predominates), porphyria, hereditary angioedema, septic arthritis, and the crystalline arthritides.

Genetic testing can be used as adjunctive evidence in ambiguous cases, and in circumstances in which the clinician has little experience with FMF or related conditions. Although FMF is often regarded as a recessively inherited disorder, with the attendant expectation that patients will have 2 mutations in *trans*, it should be noted that in some series as many as 30–50% of patients with typical FMF, responsive to colchicine, have only a single demonstrable mutation, and a small percentage have no identifiable *MEFV* mutation. The interpretation of genetic testing may be further complicated by the presence of complex alleles in which 2 mutations may be found in *cis* (usually an exon 10 mutation with E148Q in exon 2).

Treatment

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 complaints. Some patients develop lactose intolerance while taking colchicine. Gastrointestinal 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/day), reflecting the fact that children metabolize the drug more rapidly than adults. It is not always possible to find a tolerated dose of colchicine at which all

Table 163-4 Clues That May Assist in the Diagnosis of Autoinflammatory Syndromes

AGE OF ONSET	
At birth	NOMID, DIRA, FCAS
Infancy and 1st yr 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
Can occur in blacks (West Africa 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 h	FCAS, FMF
1–3 d	FMF, MWS, DITRA (fever)
3–7 d	HIDS, PFAPA
>7 d	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

DIRA, deficiency of the IL-1 receptor antagonist; DITRA, deficiency of the IL-36 receptor antagonist (generalized pustular psoriasis); FCAS, familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; HIDS, hyperimmunoglobulinemia D 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.

*For intraarticular steroids.

From Hashkes PJ, Toker O: Autoinflammatory syndromes. Pediatr Clin North Am *59:447–470, 2012, Table 2.*

Table 163-5 Differential Diagnosis of Periodic Fever

1 Hereditary (see Table 163-1)
2 Nonhereditary
- a Infectious
  - i Hidden infectious focus (e.g., aortoenteric fistula, Caroli disease)
  - ii Recurrent reinfection (e.g., chronic meningococcemia, host defense defect)
  - iii Specific infection (e.g., Whipple disease, malaria)
- b Noninfectious inflammatory disorder, e.g.:
  - i Adult-onset Still disease
  - ii Juvenile chronic rheumatoid arthritis
  - iii Periodic fever, aphthous stomatitis, pharyngitis, and adenitis
  - iv Schnitzler syndrome
  - v Behçet syndrome
  - vi Crohn disease
  - vii Sarcoidosis
  - viii Extrinsic alveolitis
  - ix Humidifier lung, polymer fume fever
- c Neoplastic
  - i Lymphoma (e.g., Hodgkin disease, angioimmunoblastic lymphoma)
  - ii Solid tumor (e.g., pheochromocytoma, myxoma, colon carcinoma)
- d Vascular (e.g., recurrent pulmonary embolism)
- e Hypothalamic
- f Psychogenic periodic fever
- g Factitious or fraudulent

From Simon A, van der Meer JWM, Drenth JPH: Familial autoinflammatory syndromes. In Firestein GS, Budd RC, Gabriel SE, et al, editors: Kelley's textbook of rheumatology, *ed 9, Philadelphia, 2012, Saunders, Table 97-2.*

symptoms are suppressed, but approximately 90% of patients have a marked improvement in disease-related symptoms. Colchicine is generally continued during pregnancy and lactation.

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, a randomized placebo-controlled trial demonstrated the safety and effectiveness of rilonacept, an IL-1 inhibitor, in FMF, and there are case reports of the effectiveness of anakinra, a recombinant IL-1 receptor antagonist.

Complications and Prognosis

Amyloidosis is the most serious complication of FMF, and in its absence FMF patients may live a normal life span. 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, most commonly in the kidneys, gastrointestinal 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. There are a small number of case reports, mostly from the Middle East, in which 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 M694V *MEFV* mutation, polymorphisms of the *serum AA* gene (encoding AA), noncompliance with colchicine treatment, male gender, and a positive family history of AA amyloid. For reasons that are unclear, 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 there are documented cases in which 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 yr.

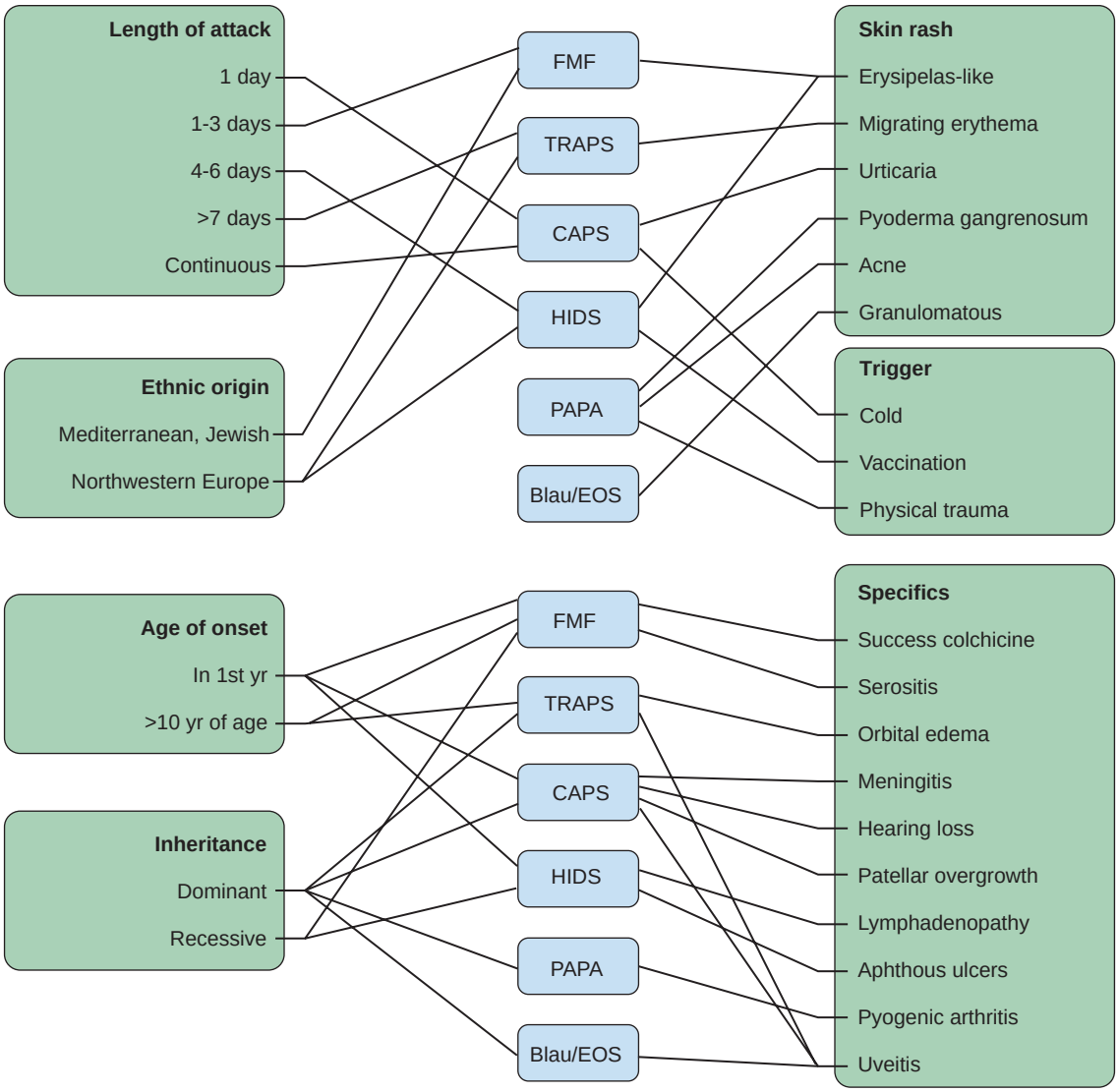


Figure 163-1 Differential diagnosis of the familial autoinflammatory syndromes. First exclude other, more common causes of fever and inflammation in the patient. When a familial autoinflammatory syndrome seems likely, check the clinical characteristics found in the patient on the *right* and *left* of the diagram, and assign 1 point to each syndrome that is linked to these characteristics by a line (1 characteristic could lead to or point to more than 1 syndrome). The final combined score assigns a rank for the likelihood of the disorders in this patient and offers help in deciding on the correct subsequent diagnostic tests. This algorithm is not evidence based but is solely derived from expert opinion. CAPS, cryopyrin-associated periodic syndrome; EOS, early-onset sarcoidosis; FMF, familial Mediterranean fever; HIDS, hyper-IgD syndrome; PAPA, pyogenic sterile arthritis, pyoderma gangrenosum, and acne; 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, editors:* Kelley's textbook of rheumatology, *ed 9, Philadelphia, 2012, Saunders, Fig. 97-2.)*

HYPERIMMUNOGLOBULINEMIA D WITH PERIODIC FEVER SYNDROME

HIDS, also known as **mevalonate kinase deficiency**, was initially described in a cohort of Dutch patients and occurs primarily in patients of Northern European descent. HIDS is recessively inherited and caused by mutations of *MVK*, a gene located on the long arm of chromosome 12 that encodes mevalonate kinase (MK). HIDS-associated mutations are distributed throughout the MK protein, but the 2 most common mutations 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).

MK 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 mutations have markedly reduced, but not absent, MK enzymatic activity. HIDS patients usually have low-normal serum cholesterol levels, but the deficiency of isoprenoids may cause increased IL-1β production by aberrant activation of the small guanosine triphosphatase Rac1. Temperature elevation may further exacerbate this process by more complete inhibition of MK activity, leading to a possible positive feedback loop. Complete genetic deficiency of MK results in a more severe phenotype known as mevalonic aciduria (see Chapter 85).

The clinical features of HIDS generally appear within the 1st 6 mo of life. Febrile attacks last between 3 and 7 days with abdominal pain that is often accompanied by diarrhea, nausea, and vomiting. Other clinical manifestations include cervical lymphadenopathy, diffuse macular rash, aphthous ulcers, headaches, and occasional splenomegaly (Figs. 163-4 to 163-6). Arthritis/arthralgia can be present in an oligoarticular or polyarticular pattern. Inflammatory 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. Patients with mevalonic

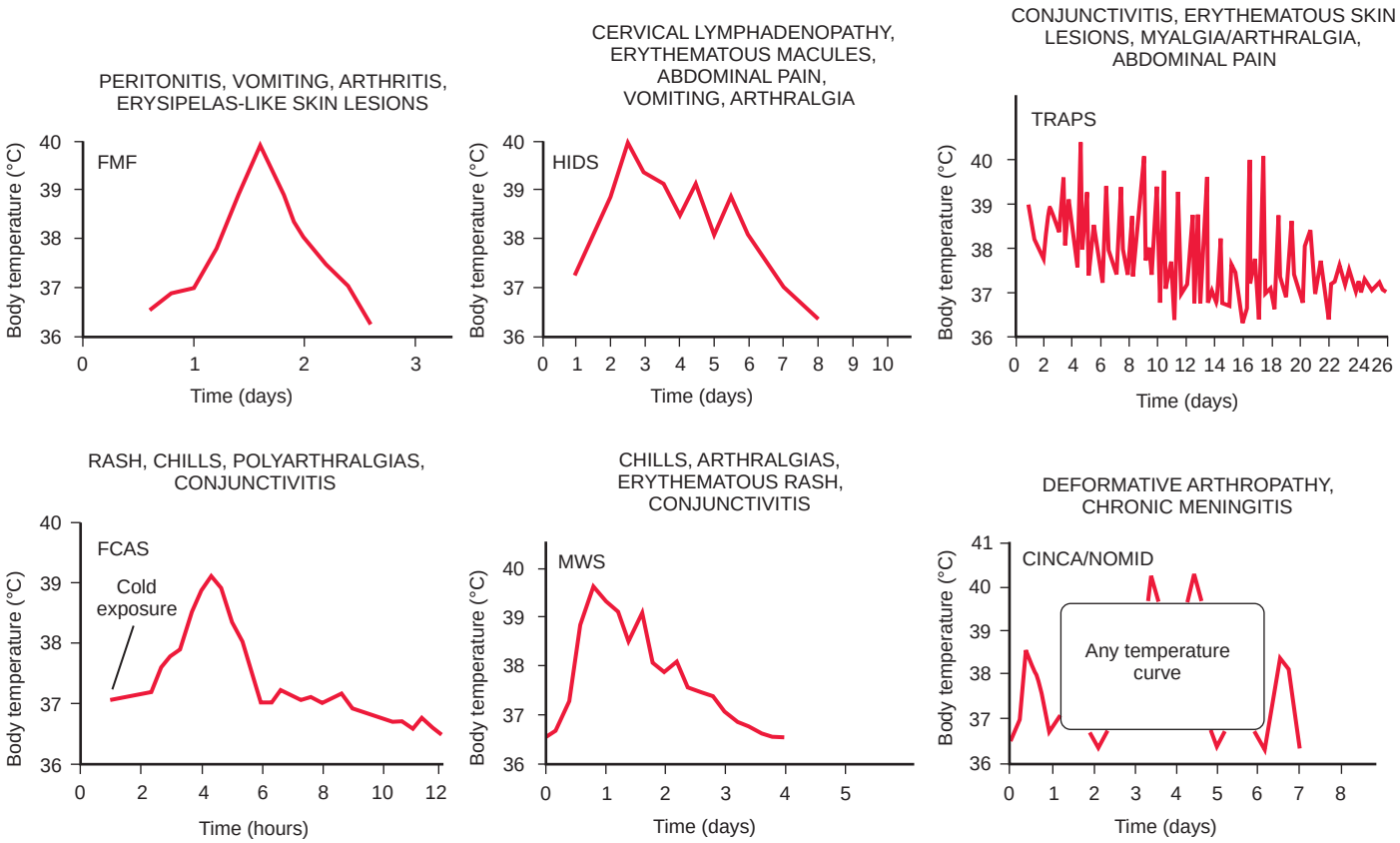


Figure 163-2 Characteristic patterns of body temperature during inflammatory attacks in the familial autoinflammatory syndromes. Interindividual variability for each syndrome is considerable, and even for the individual patient, the fever pattern may vary greatly from episode to episode. Note the different 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, editors:* Kelley's textbook of rheumatology, *ed 9, Philadelphia, 2012, Saunders, Fig. 97-1.)*



Figure 163-3 Characteristic erysipeloid erythema associated with familial Mediterranean fever. This rash appears during a flare and overlies the ankle or dorsum of the foot.



Figure 163-4 Polymorphic rash on the hands, arms, and legs of a patient with hyperimmunoglobulinemia D 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 *48:2646, 2003.)*

aciduria present with severe mental retardation, ataxia, myopathy, cataracts, and failure to thrive (see Chapter 85).

The diagnosis of HIDS may be confirmed either by the presence of 2 mutations in *MVK* (approximately 10% of patients with seemingly typical disease have only a single identifiable mutation) and/or elevated levels of mevalonate in the urine during acute attacks. The eponymous elevation in serum IgD levels is not universally present, especially in young children, and is thought to be an epiphenomenon. Conversely, serum IgD levels may be increased in other autoinflammatory diseases as well as some chronic infections. During attacks, leukocytosis and increased serum levels of acute-phase reactants and proinflammatory cytokines are commonly present.

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. Standards for the treatment of HIDS are evolving. Very few



Figure 163-5 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, editors:* Kelley's textbook of rheumatology, *ed 9, Philadelphia, 2012, Saunders, Fig. 97-7.)*



Figure 163-6 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, editors:* Kelley's textbook of rheumatology, *ed 9, Philadelphia, 2012, Saunders, Fig. 97-8.)*

patients respond to colchicine; milder disease may respond to nonsteroidal antiinflammatory drugs. Corticosteroids are of limited utility. Small trials of both etanercept and either intermittent or daily anakinra in HIDS are promising.

THE TUMOR NECROSIS FACTOR RECEPTOR-ASSOCIATED PERIODIC SYNDROME

Like FMF and HIDS, TRAPS is characterized by recurrent fevers and localized inflammation, but it is inherited in an autosomal dominant fashion and has a number of distinguishing clinical and immunologic features. TRAPS 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 mutations in *TNFRSF1A* were discovered not only in the original Irish family, but in families from a number of other ethnic backgrounds. *TNFRSF1A* is located on the short arm of chromosome 12, and encodes the 55 kDa receptor (denoted p55, TNFR1, or CD120a) for TNF that is widely expressed on a number of cell types. A second 75 kDa receptor largely restricted to leukocytes is encoded on chromosome 1.

TRAPS was originally defined as an autoinflammatory disorder resulting from *TNFRSF1A* mutations, and thus genetic testing is required to make the diagnosis. To date, more than 90 disease-associated *TNFRSF1A* mutations are listed on the online *Infevers* database, as well as a smaller number of variants of unknown significance. Nearly all of the TRAPS-associated mutations in 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 mutations 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, resulting in the release of proinflammatory cytokines such as IL-1β and TNF-α. The substitution of glutamine for arginine at residue 92 (R92Q) and the substitution of leucine for proline at residue 46 (P46L) are seen in greater than 1% of the white and African-American populations, respectively. These variants do not lead to the same biochemical or signaling abnormalities seen with more-severe TRAPS mutations, and, like E148Q in FMF, there is debate as to whether they are mild mutations or functional polymorphisms.

Patients with TRAPS typically present within the 1st decade of life. Flares can occur with variable frequency but the duration is often substantially longer when compared to FMF or HIDS flares. The febrile episodes of TRAPS last at least 3 days and can persist for weeks at a time. As in FMF, there may be pleural and/or 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. There are a number of rashes that 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 as well as a serpiginous rash (Fig. 163-7). Approximately 10-15% of patients with TRAPS may develop AA amyloidosis; the presence of cysteine mutations and a positive family history are risk factors for this complication. If amyloidosis does not develop, TRAPS patients have a normal life expectancy.

Colchicine is generally not effective in TRAPS. For relatively mild disease, nonsteroidal anti-inflammatory agents 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. Because some patients with TRAPS exhibit a defect in activation-induced TNF receptor shedding, and have diminished levels of immune modulatory soluble TNFR in the blood, etanercept, the soluble p75 TNFR:Fc fusion protein has been studied in this disorder. 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 monoclonal antibodies has sometimes led to a paradoxical worsening of disease. Experience with both anakinra, a recombinant IL-1 receptor antagonist, and canakinumab, a monoclonal anti–IL-1β antibody, has been favorable in TRAPS patients.



Figure 163-7 Cutaneous manifestations of tumor necrosis factor receptor-associated periodic syndrome. **A,** Right flank of a patient with the T50M mutation. **B,** Serpiginous rash involving the face, neck, torso, and upper extremities of a child with the C30S mutation. **C,** Erythematous, macular patches with crusting on the flexor surface of the right arm of a patient with the T50M mutation. *(From Hull KM, Drewe, Aksentijevich I, et al: The TNF receptor-associated periodic syndrome [TRAPS]: emerging concepts of an autoinflammatory syndrome,* Medicine (Baltimore) *81:349–368, 2002.)*

CRYOPYRIN-ASSOCIATED PERIODIC FEVER SYNDROMES

CAPS represents a spectrum of clinical disorders, including FCAS, MWS, and NOMID/CINCA. Although 3 separate clinical diagnoses have been defined, it should be emphasized that the cryopyrinopathies are really a continuum, and that patients may present with overlap syndromes that do not fit neatly into a single diagnosis. This spectrum of illness is caused by mutations in *NLRP3* (formerly known as *CIAS1*), located on the long arm of chromosome 1, which encodes a protein variously denoted cryopyrin or NLRP3. More than 100 disease-associated *NLRP3* mutations 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. Patients with cryopyrinopathies have gain-of-function mutations in *NLRP3* that result in constitutive or easily-triggered activation of the NLRP3 inflammasome.

The cryopyrinopathies are characterized by recurrent fevers and an urticaria-like rash that develops early in infancy (Fig. 163-8). 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 hr 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 hr. AA amyloidosis rarely occurs in FCAS.

In contrast to FCAS, the febrile episodes of MWS are not cold-induced, but are characterized by the same urticarial rash seen in FCAS (Fig. 163-9). Many MWS patients also develop progressive sensorineural hearing loss, and, untreated, approximately 30% of MWS patients develop AA amyloidosis. NOMID patients present in the neonatal



Figure 163-8 Urticarial 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 interleukin-1 receptor antagonist (DIRA). *(From Jesus AA, Goldbach-Mansky R: IL-1 blockade in autoinflammatory syndromes.* Annu Rev Med *65:223–244, 2014, Fig. 2.)*

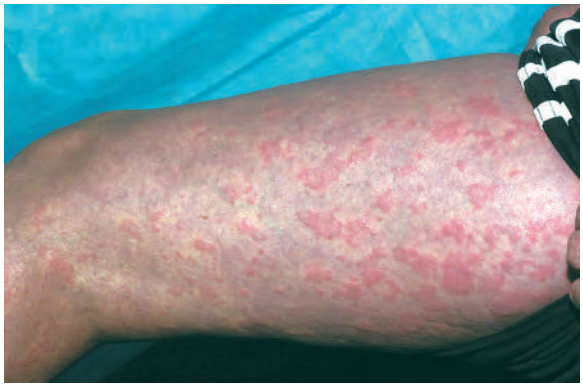


Figure 163-9 Urticarial skin rash in a patient with Muckle-Wells syndrome. *(Courtesy Dr. D. L. Kastner, National Institutes of Health, Bethesda, Maryland; from Simon A, van der Meer JWM, Drenth JPH: Familial autoinflammatory syndromes. In Firestein GS, Budd RC, Gabriel SE, et al, editors:* Kelley's textbook of rheumatology, *ed 9, Philadelphia, 2012, Saunders, Fig. 97-14.)*



Figure 163-10 A 3 yr old girl with neonatal-onset multisystem inflammatory disease (NOMID)/chronic infantile neurologic cutaneous and articular (CINCA) disease. Note the markedly deformed hands, rash, frontal bossing, and large head. *(From Padeh S: Periodic fever syndromes,* Pediatr Clin North Am *52:577–560, 2005.)*

period with a diffuse, urticarial rash, daily fevers, and dysmorphic features. Significant joint deformities, particularly of the knees, may develop because of bony overgrowth of the epiphyses of the long bones (Figs. 163-10 and 163-11). 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. 163-12). Because of the severe disabilities associated with untreated NOMID, this disorder appeared to be sporadic before *NLRP3* mutations were identified in these patients.



Figure 163-11 Metaphyseal bone overgrowth. 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 interleukin-1 receptor antagonist (DIRA). *(From Jesus AA, Goldbach-Mansky R: IL-1 blockade in autoinflammatory syndromes.* Annu Rev Med *65:223–244, 2014, Fig. 2.)*

Targeted therapy with anakinra, a recombinant IL-1 receptor antagonist, has been life-changing for NOMID patients, not only controlling fever and rash, but also preventing end-organ damage. Anakinra was FDA-approved for NOMID. Rilonacept, a soluble IL-1 receptor decoy, and canakinumab, a long-acting, fully humanized IgG_1 anti–IL-1β monoclonal antibody, are effective in both FCAS and MWS, and are FDA-approved for both conditions. Aggressive IL-1 blockade has resulted in attenuation of amyloidosis in the cryopyrinopathies.

OTHER MENDELIAN AUTOINFLAMMATORY DISEASES

The Syndrome of Pyogenic Arthritis with Pyoderma Gangrenosum and Acne

PAPA syndrome is a rare autosomal dominant disorder caused by mutations in *PSTPIP1*, a gene located on chromosome 15 that encodes the cytoskeletal proline serine threonine phosphatase-interacting (PSTPIP) protein. The PSTPIP1 protein interacts with a number of immunologically important molecules, including CD2, the Wiskott-Aldrich syndrome protein (WASP), and pyrin. PAPA-associated PSTPIP1 mutations markedly increase its affinity to pyrin and cause increased IL-1β production.

Clinical manifestations of PAPA syndrome include recurrent episodes of sterile, pyogenic arthritis that leads to erosions and joint destruction, and appears to develop spontaneously or after minor trauma. The onset of arthritis is often in early childhood. Cutaneous manifestations tend to develop in adolescence, at which time patients are prone to developing severe cystic acne. Additionally, PAPA patients commonly develop ulcerating pyoderma gangrenosum lesions (Fig. 163-13), and some develop pathergy reactions.

The treatment of PAPA syndrome may involve the use of corticosteroids, IL-1 antagonists, and TNF inhibitors, sometimes in combination. The joint manifestations of PAPA appear to respond to IL-1

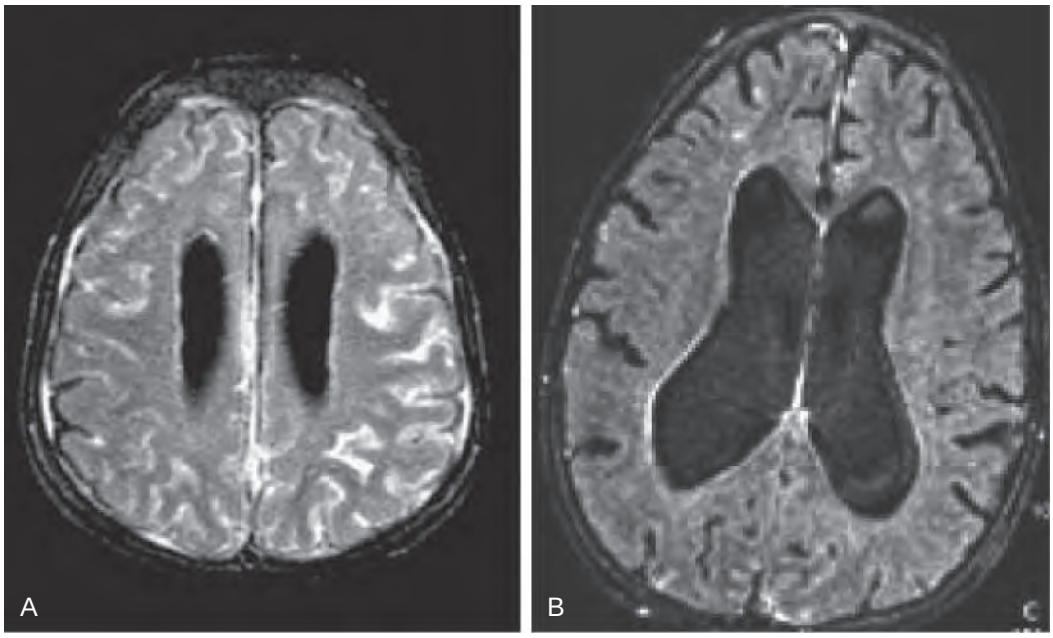


Figure 163-12 **A,** Leptomeningeal enhancement; **B,** hydrocephalus and cerebral atrophy. Inflammatory clinical manifestations and organ damage in the IL-1–mediated diseases; in neonatal-onset multisystem inflammatory disease (NOMID), which is the severe form of cryopyrin-associated periodic syndromes (CAPS); and deficiency of interleukin-1 receptor antagonist (DIRA). *(From Jesus AA, Goldbach-Mansky R: IL-1 blockade in autoinflammatory syndromes.* Annu Rev Med *65:223–244, 2014, Fig. 2.)*



Figure 163-13 Pyoderma gangrenosum lesions in a patient with PAPA syndrome and the A230T mutation in *PSTPIP1.* Note the diffuse scarring indicative of prior lesions on his upper back.

blockade, whereas the cutaneous manifestations seem to respond more favorably to TNF 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 the Interleukin-1 Receptor Antagonist

DIRA is an autosomal recessive autoinflammatory disease that is distinct from the cryopyrinopathies. DIRA is characterized by systemic inflammation and a neutrophilic pustulosis, sterile multifocal osteomyelitis, widening of the anterior ends of the ribs, periostitis, osteopenia, and usually a neonatal onset (Figs. 163-14 and 163-15). Although fever is not a prominent clinical feature, patients do have markedly elevated acute-phase reactants. DIRA is caused by loss-of-function mutations in *IL1RN*, encoding the IL-1 receptor antagonist. The treatment of choice is anakinra, a recombinant form of the protein these patients lack.

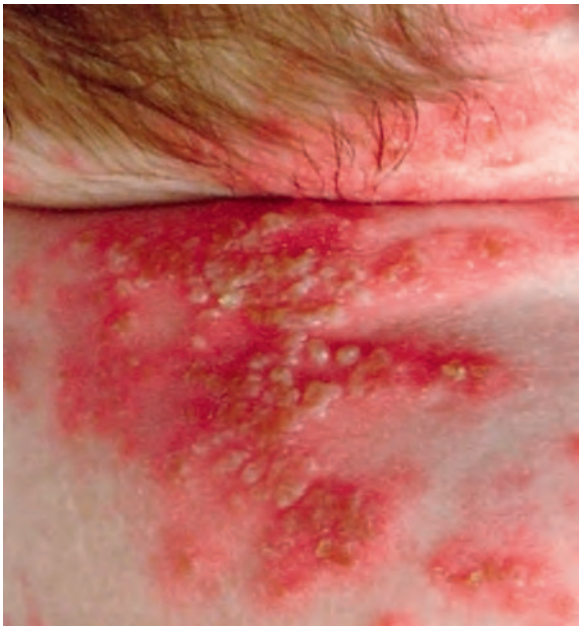


Figure 163-14 **Pustular rash.** Inflammatory clinical manifestations and organ damage in the IL-1–mediated diseases; in neonatal-onset multisystem inflammatory disease (NOMID), which is the severe form of cryopyrin-associated periodic syndromes (CAPS); and deficiency of interleukin-1 receptor antagonist (DIRA). *(From Jesus AA, Goldbach-Mansky R: IL-1 blockade in autoinflammatory syndromes.* Annu Rev Med *65:223–244, 2014, Fig. 2.)*

Blau Syndrome

Blau syndrome is a rare autosomal dominant disorder that manifests as early-onset 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 mutations in *CARD15/*

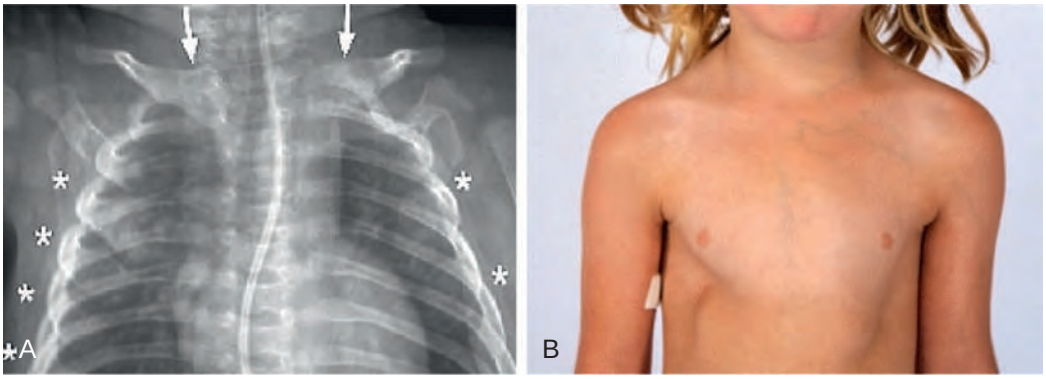


Figure 163-15 A, Widening of multiple ribs (*) and clavicles *(arrows)* in DIRA osteomyelitis; **B,** chest deformity. Inflammatory clinical manifestations and organ damage in the IL-1-mediated diseases; in neonatal-onset multisystem inflammatory disease (NOMID), which is the severe form of cryopyrin-associated periodic syndromes (CAPS); and deficiency of interleukin-1 receptor antagonist (DIRA). *(From Jesus AA, Goldbach-Mansky R: IL-1 blockade in autoinflammatory syndromes.* Annu Rev Med *65:223–244, 2014, Fig. 2.)*

NOD2 on chromosome 16. The protein encoded by this gene, variously denoted caspase recruitment domain protein 15 or nucleotide-binding oligomerization domain 2 protein, is an intracellular sensor of bacterial products in dendritic cells, myelomonocytic cells, and Paneth cells. Mutations in the NACHT oligomerization domain of this protein cause Blau syndrome/early-onset sarcoidosis, while variants primarily in the leucine-rich repeat domain of this protein are associated with susceptibility to Crohn disease. Corticosteroids have been the mainstay of therapy for Blau syndrome. There are a number of case reports of the beneficial effects of TNF inhibitors, in Blau syndrome.

Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature

CANDLE is an autosomal recessive disease resulting from mutations in *PSMB8.* This gene encodes the β5i subunit of the immunoproteasome, a macromolecular complex that degrades proteins in immune cells for presentation on major histocompatibility complex class I molecules. Disease-associated mutations result in a loss of function. Patients present in the 1st yr of life with recurrent fevers, violaceous swollen eyelids, purpuric skin lesions with a mixed mononuclear and neutrophilic infiltrate, arthralgia, delayed physical development, and anemia. Acute-phase reactants are also elevated in these patients and, over time, they develop progressive lipodystrophy. On gene expression profiling, CANDLE patients have a robust interferon signature. There is no established treatment for CANDLE, although the interferon pathway may represent a therapeutic target. Two other disorders, **Nakajo-Nishimura syndrome** and the **syndrome of joint contractures, muscular atrophy, microcytic anemia, and panniculitis-induced lipodystrophy**, are clinically similar to CANDLE and are also caused by mutations in *PSMB8.*

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 mild immunodeficiency. It is caused by gain-of-function mutations in *PLCG2,* leading to increased signaling through the phospholipase Cγ$_2$ pathway in immune cells. To date there is no established therapy for APLAID.

Deficiency of Adenosine Deaminase 2

DADA2 is an autoinflammatory disorder caused by loss-of-function mutations in *CECR1*, encoding adenosine deaminase 2, characterized by recurrent fevers and a spectrum of vascular manifestations that includes livedo racemosa, early-onset ischemic lacunar strokes, and polyarteritis nodosa. Patients may also present with hepatosplenomegaly and a mild immunodeficiency. ADA2 is a protein produced primarily by monocytes and macrophages, which appear to act as a growth factor both for endothelial cells and for the antiinflammatory M2 subset of macrophages. Patients experience a vicious circle of vasculopathy and inflammation. Although there is no established therapy, there is anecdotal evidence supporting the use of etanercept.

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 the ages of 2 and 5 yr with recurring episodes of fever, malaise, exudative-appearing tonsillitis with negative throat cultures, cervical lymphadenopathy, oral aphthae, and, less commonly, headache, abdominal pain, and arthralgia. The episodes last 4-6 days, regardless of antipyretic or antibiotic treatment, and often occur with clock-like regularity on 3-6 wk 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. The majority of 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 given at doses of 20-40 mg/kg/day is effective at preventing recurrences in approximately one-third of cases. Complete resolution has also been reported after tonsillectomy in some but not all patients. A pilot study of anakinra (1 mg/kg subcutaneously) given for 1-2 days at the onset of symptoms showed promising results.

Chronic Recurrent Multifocal Osteomyelitis

CRMO is a form of inflammatory bone disease most commonly seen in children (see Table 163-3). Histologically and radiologically, CRMO is virtually indistinguishable from infectious osteomyelitis. Patients typically present with bone pain and may also have fever, soft-tissue swelling, and elevated acute-phase reactants. Cultures are sterile. The etiology of sporadic CRMO is unknown. Rarely CRMO can occur with congenital dyserythropoietic anemia (Majeed syndrome), caused by mutations in *LPIN2.* CRMO has also been seen in association with inflammatory bowel disease and inflammatory skin disease such as palmoplantar pustulosis. There is evidence for reduced production of the antiinflammatory cytokine IL-10 in CRMO. Initial therapy includes nonsteroidal antiinflammatory medications. Second-line treatments include corticosteroids, TNF inhibitors, and bisphosphonates.

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Chapter 164
Amyloidosis

Karyl S. Barron and Amanda Ombrello

Amyloidosis comprises a group of diseases characterized by extracellular deposition of insoluble, fibrous amyloid proteins in various body tissues.

ETIOLOGY

Amyloidosis is a disease caused by protein misfolding. These misfolded proteins infiltrate, aggregate, and form insoluble fibrils that can affect the normal function of a number of vital organs.

In the amyloidosis nomenclature, there is a distinction made between amyloidosis that develops from mutations in the *amyloid fibril protein itself* versus amyloidosis associated with genetic mutation in nonamyloid proteins. The former are referred to as hereditary amyloidoses; examples include mutations in the genes for transthyretin and apolipoprotein A, both of which are uncommon in children. This is in contrast to amyloid A (AA) amyloidosis, which develops in patients with chronic inflammatory states. It is estimated that, worldwide, approximately 45% of all amyloid cases are AA amyloidosis. In the past, chronic infectious diseases such as tuberculosis, malaria, leprosy, and chronic osteomyelitis accounted for most cases of AA amyloidosis. With effective treatment for these infections, other causes of AA have become more common. A number of chronic inflammatory rheumatic diseases such as rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), 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 granulomatous diseases such as sarcoidosis, cystic fibrosis, Crohn disease, malignancies such as mesothelioma and Hodgkin diseases, intravenous drug abuse, and other infections, such as bronchiectasis and HIV. Approximately 6% of AA amyloidosis cases have no identified disease association. AL amyloidosis (formally known as idiopathic amyloidosis or myeloma-associated amyloidosis) is extremely rare in children, occurring in middle-aged or older individuals.

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, because many individuals with long-standing inflammatory disease do not demonstrate tissue amyloid deposition, while some children with relatively recent onset of disease may develop amyloid. In developed countries, prior to the initiation of therapy with disease-modifying anti-rheumatic drugs (DMARDs) and biologic agents, RA was the most common inflammatory disease associated with AA amyloidosis. Patients who had a long history of poorly controlled severe disease with extraarticular manifestations were the most at risk for developing amyloidosis and the median time from first symptoms of their rheumatic condition to the diagnosis of amyloidosis was 212 mo. The full effect of DMARD and biologic therapy in RA-associated amyloidosis has yet to be fully appreciated, but studies are showing a sustained decline in the number of new cases.

JIA is another rheumatic disease that is associated with the development of AA amyloidosis with the highest prevalence in patients with systemic JIA followed by those with polyarticular disease (see Chapter 155). In the pre-DMARD and biologic era, the prevalence of AA amyloidosis in JIA patients ranged from 1-10%. Higher prevalence was seen in Northern European patients, especially Polish patients who had a prevalence of 10.6%; lower prevalence was observed in North America. The reasons for this discrepancy are not completely understood although it is speculated that selection bias, genetic background, and tendency toward more early aggressive therapy in North Americans may have played a role.

The **hereditary autoinflammatory diseases** define a group of illnesses that are 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 (see Chapter 163). Whereas autoimmune diseases such as systemic lupus erythematosus and RA result from a derangement in the adaptive immune system, the autoinflammatory syndromes are a result of malfunctions in the innate immune system. The inflammatory attacks are mediated by cells of the innate immune system (neutrophils and macrophages). Although seemingly unprovoked, these attacks are often initiated by stress, immunization, or trauma, suggesting that gene–environment interactions play an important role in pathogenesis. Although there is some variability among the autoinflammatory diseases, common findings include fevers, cutaneous rashes, arthritis, serositis, and ocular involvement. The inflammatory attacks are accompanied by intense acute phase responses (erythrocyte sedimentation rate and C-reactive protein) and high levels of serum amyloid A (SAA). Amyloidosis AA is associated with some but not all the 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 Sephardi Jewish populations. FMF is an autosomal recessive disease that results from mutations in the *MEFV* gene, which encodes the pyrin/marenostrin protein. *MEFV* mutations affecting the M680 and M694 amino acid residues are associated with early onset of FMF, severe disease, and an increased risk of AA amyloidosis. Patients residing in Armenia, Turkey, and Arabian countries have an increased risk of developing AA amyloidosis compared to patients with the same mutations of *MEFV* living in North America.

Tumor necrosis factor receptor associated periodic syndrome (TRAPS) is associated with mutations in the *TNFRSF1A* gene, which encode the 55 kDa tumor necrosis factor (TNF) receptor protein (TNFR1). It is estimated that 14-25% of patients with TRAPS develop AA amyloidosis. Patients with mutations in *TNFRSF1A* that affect cysteine residues have the highest risk of developing AA amyloidosis. It is thought that these cysteine residues participate in assembly of disulfide bonds important for TNFR1 folding and disruption of these bonds affects protein folding.

Mutations in the *NLRP3* gene (also known as *CIAS1*, **cold-induced autoinflammatory syndrome 1)** cause 3 clinically distinct diseases: familial cold autoinflammatory syndrome, Muckle-Wells syndrome (MWS), and neonatal onset multisystem inflammatory disease (NOMID) that is also known as chronic infantile neurologic cutaneous and articular (CINCA) syndrome. Mutations in *NLRP3* are inherited in an autosomal dominant fashion or as *de novo* mutations in patients with the most severe disease. Familial cold autoinflammatory syndrome is generally 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. Historically 20% of patients died before reaching adulthood but with current therapies, many are living longer lives. There have been NOMID patients who develop AA amyloidosis as they get older, although cases are not as frequent as those with MWS, possibly due to a shortened life span in these patients.

Hyper IgD syndrome (HIDS) is another autoinflammatory disease that presents in early childhood with chills, high fevers, abdominal pain, lymphadenopathy, and occasional rash. HIDS is an autosomal recessive disease that involves loss of function mutations in the *MVK* gene that encodes the mevalonate kinase enzyme. Inflammatory markers, including SAA, are high during attacks and may remain elevated in the intercurrent period. AA amyloidosis is rare in HIDS but has been reported.

Although seen less frequently than in the hereditary periodic fever syndromes, the risk of AA amyloidosis has been well established in patients with Crohn disease. It is estimated that AA amyloidosis occurs in approximately 1% of patients in the United States and up to 3% in Northern European patients. Conversely, AA amyloidosis presenting

in patients with ulcerative colitis is extremely rare, with estimated prevalence of 0.07%. The patients have a long-standing history of aggressive, poorly controlled disease; however there are reports of amyloidosis in patients with well-controlled inflammatory markers.

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 SAA. SAA is produced in the liver 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.

Under normal circumstances SAA is secreted by the liver and 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 a flaw resulting in incomplete degradation and accumulation of intermediate SAA products. In these patients, SAA is transferred to the lysosome where the c-terminal portion of the SAA protein is cleaved, allowing the remaining protein to fold into a β-pleated sheet configuration. Deposited amyloid contains only 66-76 amino acids compared to the 104 in secreted SAA. These cleaved fragments polymerize and form fibrils that are deposited in the extracellular space and bind proteoglycans and other proteins such as serum amyloid P. These fibrils then become resistant to proteolysis and deposit in organ tissues.

CLINICAL MANIFESTATIONS

Although organ involvement may vary, AA amyloidosis most commonly 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 controlled or if diagnosis is delayed. Median survival after diagnosis has been reported to be 133 mo; patients with higher SAA levels had significantly higher risk of death than those with lower SAA levels. Gastrointestinal involvement is seen in approximately 20% of patients and usually manifests as chronic diarrhea, gastrointestinal bleeding, abdominal pain, and malabsorption, whereas testes are frequently involved (87%). Relatively uncommon findings associated with AA amyloidosis include anemia, amyloid goiter, hepatomegaly, splenomegaly, adrenal involvement, and pulmonary involvement. Tissues, such as the heart, tongue, and skin, are rarely involved.

DIAGNOSIS

The diagnosis of amyloidosis is established by biopsy demonstrating amyloid fibril proteins in affected tissues. The tissues most commonly tested 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. Amyloid can also be recognized with routine hematoxylin and eosin staining and electron microscopy.

LABORATORY FINDINGS

Patients with AA amyloidosis usually show elevated acute-phase reactants and high levels of immunoglobulins. Specific laboratory testing is possible only for AL amyloidosis, and most patients with this form of amyloidosis show increased plasma cells in the bone marrow and serum or urine monoclonal immunoglobulin (Ig) or free light chain. A biopsy showing amyloid deposition along with a monoclonal serum protein distinguishes AL amyloidosis from monoclonal gammopathy of uncertain significance, which is common in older adults.

TREATMENT

There is no established therapy to AA amyloidosis and, thus, the primary means of treatment of AA amyloidosis is aggressive management of the underlying inflammatory or infectious disease, which decreases levels of SAA protein. As newer therapies have been developed to treat the underlying condition, there is emerging evidence 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. Children with FMF who are homozygous for the M694V mutation in the *MEFV* gene are at greater risk for development of amyloidosis and should be monitored closely.

Unlike AA amyloidosis associated with FMF, AA amyloidosis associated with other autoinflammatory diseases (including TRAPS, cryopyrin-associated periodic syndrome, and HIDS) and chronic rheumatic diseases (JIA, RA, and ankylosing spondylitis) do not respond to colchicine. Although AA amyloidosis associated with JIA may respond to chlorambucil, this drug is associated with chromosome breakage and a risk of subsequent malignancy.

Increasing use of biologic medicines against proinflammatory cytokines to treat RA, JIA, spondyloarthropathies, and the hereditary autoinflammatory diseases seems to impact risk factors for the development of AA amyloidosis. The class of medications referred to as the anti–TNF-α drugs have been paramount in the management of RA and other autoimmune disease. In both autoimmune and autoinflammatory conditions with accompanying AA amyloidosis, 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, thus careful screening should be performed before instituting therapy. Additionally, the development of various antibodies, autoantibodies, and autoimmune disease has been noted in patients taking anti-TNF agents. Extreme caution should be used in prescribing anti-TNF agents to patients with a history of heart failure or demyelinating disease, as use can cause exacerbations in their underlying cardiac and neurologic diseases.

The IL-1 pathway is the target of multiple biologic medications used in autoimmune and autoinflammatory diseases. The 3 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). 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 associated 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. Eprodisate disodium is currently in international trial in patients with AA amyloidosis–associated nephropathy. By binding the amyloidogenic precursor proteins, eprodisate disodium attempts to prevent the deposition of amyloid in organ, hence preserving renal function.

COMPLICATIONS AND PROGNOSIS

End-stage renal failure is the underlying cause of death in 40-60% of patients with amyloidosis, with a median survival time from diagnosis of 2-10 yr. 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 (of 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 165

Sarcoidosis

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Sarcoidosis is a rare multisystem granulomatous disease of unknown etiology. The name is derived from a Greek word meaning "flesh-like condition," in reference to the characteristic skin lesions. There appear to be 2 age-dependent distinct 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 yr 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 1 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 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. Missense mutations in the *CARD15/NOD2* gene on chromosome 16 have been found in affected family members and appear to be associated with development of sarcoidosis. The 2 most common amino acid substitutions are R334W (arginine to glutamine) and R334Q (arginine to tryptophan). Similar genetic mutations also 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 163).

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 yr. The most common age of reported childhood cases is 13-15 yr. Annual incidence is about 11 per 100,000 in adult white Americans and is 3 times higher in African-Americans. There is no clear sex predominance in childhood sarcoidosis. Within the United States, the majority of childhood sarcoidosis cases are reported in the Southeastern and South Central states.

An international registry and Spanish cohort of Blau syndrome and EOS reported the mean age of disease onset as 30 mo and 36 mo, respectively. All but 3 of these young patients presented before 5 yr of age. There does not appear to be a sex preference in either condition.

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 not known. 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-α (TNF-α) and other proinflammatory mediators. The CD4+ T lymphocytes differentiate into type 1 helper T cells and release interleukin (IL)-2 and interferon-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 to 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 (Fig. 165-1) on chest radiograph is the most common finding, but parenchymal infiltrates and miliary nodules may also be seen (Fig. 165-2). Patients with lung involvement are commonly 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. 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



Figure 165-1 Chest radiograph demonstrating a stage I disease with enlarged mediastinal and hilar lymph nodes. *(From Iannuzzi M: Sarcoidosis. In Goldman L, Schafer AI, editors,* Goldman's Cecil medicine, *ed 24, Philadelphia, 2012, Saunders, Fig. 95-1, p. 582.)*



Figure 165-2 Chest radiograph of a 10 yr old girl with sarcoidosis showing widely disseminated peribronchial infiltrates, multiple small nodular densities, hyperaeration of the lungs, and hilar lymphadenopathy.



Figure 165-3 Sarcoidosis nodules on the face. *(From Shah BR, Laude TA:* Atlas of pediatric clinical diagnosis, *Philadelphia, 2000, Saunders.)*

on the face, neck, upper back, and extremities are the most common skin finding (Fig. 165-3). 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. Central nervous system (CNS) involvement is rare in early childhood but may manifest as seizures, cranial nerve involvement, intracranial mass lesions, and hypothalamic dysfunction. Kidney disease also occurs infrequently in children but typically manifests as renal insufficiency, proteinuria, transient pyuria, or microscopic hematuria as a result of either early monocellular infiltration or granuloma formation in kidney tissue. Only a small fraction of children have hypercalcemia or hypercalciuria, which is therefore an infrequent cause of kidney disease. Sarcoid granulomas can also infiltrate the heart and lead to cardiac arrhythmias and, rarely, sudden death. Other 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. Pulmonary disease and lymphadenopathy are less common. The arthritis is polyarticular and symmetric, with large boggy effusions. Large and small joints are involved; tenosynovitis is an associated finding. Joints are stiff and moderately tender. The rash may wax and wane and is diffuse (mostly truncal), erythematous or tan, macular–papular, and often desquamates at times being confused with eczema or ichthyosis vulgaris. Tender subcutaneous nodules resembling erythema nodosum may be seen on the legs. Noncaseating granulomas are demonstrated with biopsy of the skin or joint synovium.

Granulomatous iridocyclitis and posterior uveitis may progress to panuveitis, which has a high risk for vision loss. Iris nodules, photophobia, erythema, cataracts, or glaucoma may be present or develop over time.

Patients with NOD2 mutations in particular display this more restricted phenotype but may also have visceral disease, whereas those without a NOD2 mutation often show extended manifestations, including fever, hepatosplenomegaly, lymphadenopathy, and lung, kidney, and CNS involvement.

Infantile onset panniculitis with uveitis and systemic granulomatosis is an uncommon manifestation of sarcoidosis. Sarcoidosis has also been reported in adults treated with type 1 interferons for hepatitis or multiple sclerosis.

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 erythrocyte sedimentation rate and C-reactive protein value. 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 more than 50% of children with sarcoidosis. In addition, ACE values may be difficult to interpret because reference values for serum ACE are age dependent. Fluorodeoxyglucose F18 positron emission tomography can help identify nonpulmonary sites for a diagnostic biopsy.

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 should include chest radiography, pulmonary function testing with measurement of diffusion capacity, hepatic enzyme measurements, and renal function assessment. Ophthalmologic slit-lamp examination is essential, as ocular findings are frequent 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.

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. Immunodeficiencies that may manifest with granulomatous lesions include common variable immunodeficiency, selective immunoglobulin A 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 juvenile idiopathic arthritis. Evaluation for endocrine disorders is needed in the setting of hypercalcemia or hypercalciuria.

TREATMENT

Treatment should be based on disease severity as well as 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 wk until manifestations improve. Corticosteroid dosage is then gradually decreased over 6-12 mo 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 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).

With regard to treatment of EOS, there are also few case reports on the successful use of thalidomide and infliximab. Findings of elevated IL-1 levels and response to human IL-1 receptor antagonist (anakinra) in EOS, however, have been inconsistent.

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, though a significant number have morbid sequelae, mainly involving the lungs and eyes. Children with EOS 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 childhood 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 mo as recommended in children with juvenile idiopathic arthritis.

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Chapter 166

Kawasaki Disease

Mary Beth F. Son and Jane W. Newburger

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 vasculitis with a predilection for the coronary arteries. Approximately 20-25% of untreated children develop coronary artery abnormalities (CAA) including aneurysms, whereas <5% of children treated with intravenous gammaglobulin (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, but certain epidemiologic and clinical features support an infectious origin. These features include the young age group affected, epidemics with wave-like 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 younger than 3 mo, likely the result of maternal antibodies, and the rarity of cases in adults, likely the result of prior exposures with subsequent immunity. However, there are features that are not consistent with an infectious origin. For example, 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 a comprehensive search.

A genetic role in the pathogenesis of KD seems likely, 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. Furthermore, linkage studies and genome-wide association studies have identified significant associations between polymorphisms in the *ITPKC* gene, a T-cell regulator, with increased susceptibility to KD and to more-severe disease. Polymorphisms in a high-affinity receptor for immunoglobulin G (*FCGR2A)* have also been identified as significant variants in KD patients.

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 boys. Utilizing the Kids Inpatient Database to study trends in KD hospitalizations in 2006, Holman et al reported that more than 75% of all KD-associated hospitalizations in patients <18 yr were recorded in children <5 yr, with a mean age of 3 yr. Children of Asian and Pacific Islander descent had the highest hospitalization rate of 30.3/100,000 children, compared with 17.5/100,000 black, non-Hispanic children, 15.7/100,000 Hispanic children, and 12/100,000 white, non-Hispanic children. The hospitalization rate for KD in 2006 was 20.8/100,000 in children <5 yr of age, which was consistent with the prior 10 yr of hospitalization rates in the United States. In other countries, such as the United Kingdom, Korea, and Japan, the rate of KD seems to be increasing.

In Japan, nationwide surveys have been administered every 2 yr to monitor trends in KD incidence. In 2010, the highest recorded rate thus far of 239.6 per 100,000 children ages 0-4 yr was described, with the highest rate in very young children ages 6-11 mo. Infants <6 mo and children >5 yr were at the highest risk for CAA in the latest Japanese 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, male gender,

persistent fever, poor response to IVIG, and laboratory abnormalities including neutrophilia, thrombocytopenia, transaminitis, hyponatremia, hypoalbuminemia, elevated levels of N-terminal-probrain natriuretic protein and elevated C-reactive protein levels. Asian and Pacific Islander race and Hispanic ethnicity are also risk factors for CAA. Three specific risk scores have been constructed by Japanese researchers; of these, the Kobayashi score is the most widely used and has high sensitivity and specificity. Unfortunately, application of these risk scores in non-Japanese populations does not appear to accurately identify all children at risk for IVIG resistance and CAA.

PATHOLOGY

KD is a vasculitis that predominantly affects the medium-size arteries. The coronary arteries are the most commonly involved, although other arteries, such as the popliteal and brachial arteries, can also develop dilation. A 3-phase process to the arteriopathy of KD has been described. The 1st phase is a neutrophilic necrotizing arteritis occurring in the 1st 2 wk 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 cause progressive stenosis. Thrombi may form in the lumen and obstruct blood flow.

CLINICAL MANIFESTATIONS

Fever is characteristically high (≥38.3°C [101°F]), unremitting, and unresponsive to antibiotics. The duration of fever without treatment is generally 1-2 wk, but may persist for 3-4 wk. In addition to fever, the **5 principal clinical criteria** of KD are: bilateral **nonexudative** conjunctival injection with limbal sparing; erythema of the oral and pharyngeal mucosa with strawberry tongue and red, cracked lips; edema and erythema of the hands and feet; rash of various forms (maculopapular, erythema multiforme, or scarlatiniform); and nonsuppurative cervical lymphadenopathy, usually unilateral, with node size >1.5 cm (Table 166-1; Figs. 166-1 to 166-4). Perineal desquamation is common in the acute phase. Periungual desquamation of the fingers and toes begins 2-3 wk after the onset of illness and may progress to involve the entire hand and foot (Fig. 166-5).

Symptoms other than the clinical criteria are common in the 10 days prior to 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 symptoms (vomiting, diarrhea, or abdominal pain) occur in more than 60% of patients, and at least 1 respiratory symptom (rhinorrhea or cough) occurs in 35%. Other clinical findings include significant irritability that is especially prominent in infants and likely a consequence of aseptic meningitis, mild hepatitis, hydrops of the gallbladder, urethritis and meatitis with sterile pyuria, and arthritis. Arthritis may occur early in the illness or may develop in the 2nd or 3rd wk. Small or large joints may be affected, and the arthralgias

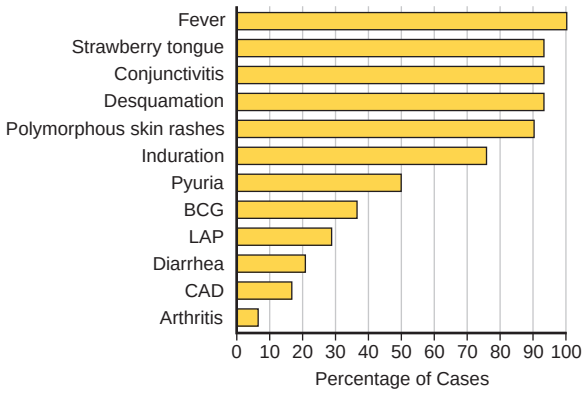


Figure 166-1 Clinical symptoms and signs of Kawasaki disease. A summary of the clinical features from 110 cases of Kawasaki disease seen in Kaohsiung, Taiwan. LAP, lymphadenopathy in head and neck area; BCG, reactivation of bacille Calmette-Guérin inoculation site; CAD, coronary artery dilation, defined 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 *24:998–1004, 2005.)*

Table 166-1 Clinical and Laboratory Features of Kawasaki Disease

EPIDEMIOLOGIC CASE DEFINITION (CLASSIC CLINICAL CRITERIA)*
Fever persisting at least 5 days†
Presence of at least 4 principal features:
Changes in extremities:
Acute: Erythema of palms, soles; edema of hands, feet
Subacute: Periungual peeling of fingers, toes in weeks 2 and 3
Polymorphous exanthem
Bilateral bulbar conjunctival injection without exudate
Changes in lips and oral cavity: erythema, lip cracking, strawberry tongue, diffuse injection of oral and pharyngeal mucosa
Cervical lymphadenopathy (>1.5 cm diameter), usually unilateral
Exclusion of other diseases with similar findings‡
OTHER CLINICAL AND LABORATORY FINDINGS
Cardiovascular findings:
Congestive heart failure, myocarditis, pericarditis, valvular regurgitation
Coronary artery abnormalities
Aneurysms of medium-size noncoronary arteries
Raynaud phenomenon
Peripheral gangrene
Musculoskeletal system:
Arthritis, arthralgias
Gastrointestinal tract:
Diarrhea, vomiting, abdominal pain
Hepatic dysfunction
Hydrops of gallbladder
Central nervous system:
Extreme irritability
Aseptic meningitis
Sensorineural hearing loss
Genitourinary system:
Urethritis/meatitis
Other findings:
Erythema, induration at bacille Calmette-Guérin inoculation site
Anterior uveitis (mild)
Desquamating rash in groin
LABORATORY FINDINGS IN ACUTE KAWASAKI DISEASE
Leukocytosis with neutrophilia and immature forms
Elevated erythrocyte sedimentation rate
Elevated C-reactive protein
Anemia
Abnormal plasma lipids
Hypoalbuminemia
Hyponatremia
Thrombocytosis after week 1§
Sterile pyuria
Elevated serum transaminases
Elevated serum gamma glutamyl transpeptidase
Pleocytosis of cerebrospinal fluid
Leukocytosis in synovial fluid

*Patients with fever at least 5 days and <4 principal criteria can be diagnosed with Kawasaki disease when coronary artery abnormalities are detected by 2-dimensional echocardiography or angiography.

†In the presence of ≥4 principal criteria, Kawasaki disease diagnosis can be made on day 4 of illness. Experienced clinicians who have treated many patients with Kawasaki disease may establish diagnosis before day 4.

‡See differential diagnosis (Table 166-2).

§Some infants present with thrombocytopenia and disseminated intravascular coagulation.

From Newburger JW, Takahashi M, Gerber MA, et al: Diagnosis, treatment, and long-term management of Kawasaki disease, Pediatrics *114:1708–1733, 2004.*



Figure 166-2 Strawberry tongue in mucocutaneous lymph node syndrome (Kawasaki disease). *(Courtesy of Tomisaku Kawasaki, MD. From Hurwitz S:* Clinical pediatric dermatology, *ed 2, Philadelphia, 1993, Saunders.)*

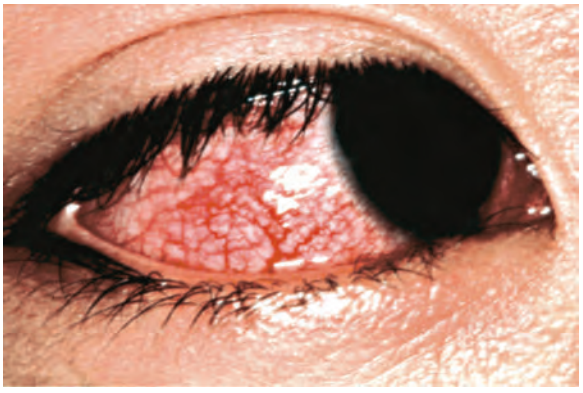


Figure 166-3 Congestion of bulbar conjunctiva in a patient with mucocutaneous lymph node syndrome (Kawasaki disease). *(Courtesy of Tomisaku Kawasaki, MD. From Hurwitz S:* Clinical pediatric dermatology, *ed 2, Philadelphia, 1993, Saunders.)*



Figure 166-4 Indurative edema of the hands in mucocutaneous lymph node syndrome (Kawasaki disease). *(Courtesy of Tomisaku Kawasaki, MD. From Hurwitz S:* Clinical pediatric dermatology, *ed 2, Philadelphia, 1993, Saunders.)*



Figure 166-5 Desquamation of the fingers in a patient with mucocutaneous lymph node syndrome (Kawasaki disease). *(Courtesy of Tomisaku Kawasaki, MD. From Hurwitz S:* Clinical pediatric dermatology, *ed 2, Philadelphia, 1993, Saunders.)*

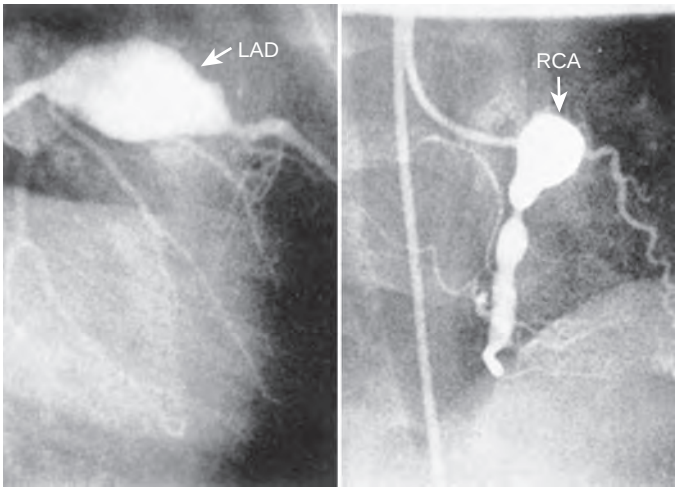


Figure 166-6 Coronary angiogram demonstrating giant aneurysm of the left anterior descending coronary artery (LAD) with obstruction and giant aneurysm of the right coronary artery (RCA) with an area of severe narrowing in 6 yr old boy. *(From Newburger JW, Takahashi M, Gerber MA, et al: Diagnosis, treatment, and long-term management of Kawasaki disease,* Pediatrics *114:1708–1733, 2004.)*

may persist for several weeks. Clinical features that are less consistent with KD include exudative conjunctivitis, exudative pharyngitis, generalized lymphadenopathy, discrete oral lesions, and bullous, pustular, or vesicular rashes.

Cardiac involvement is the most important manifestation of KD. Myocarditis occurs in most patients with acute KD and manifests as tachycardia disproportionate to fever, along with diminished left ventricular systolic function. Occasionally, patients with KD present in cardiogenic shock (KD shock syndrome), with markedly diminished left ventricular function. 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. CAA develop in up to 25% of untreated patients in the 2nd to 3rd wk of illness. Giant coronary artery aneurysms (classic definition of >8 mm internal diameter) pose the greatest risk for rupture, thrombosis or stenosis, and myocardial infarction (Fig. 166-6). Axillary, popliteal, iliac, or other arteries may also become dilated, which manifest as a localized pulsating mass.

Occasionally KD initially presents with only fever and lymphadenopathy (node-first KD). This presentation may be confused with

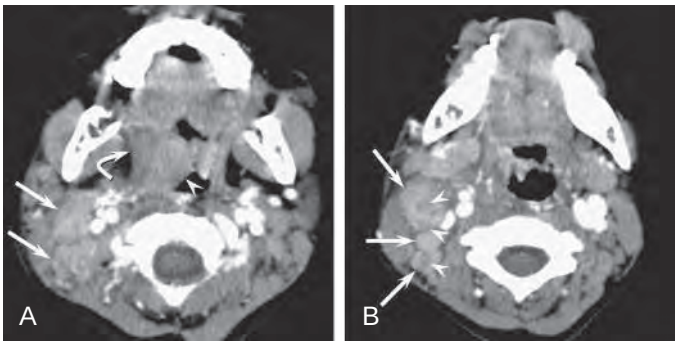


Figure 166-7 Kawasaki disease in a 3 yr old boy. **A,** Contrast-enhanced CT shows right-sided cervical lymphadenopathy *(arrows)*, peritonsillar hypodense area *(curved arrow)*, and swelling of right palatine tonsil *(arrowhead)*. **B,** Contrast-enhanced CT shows right-sided cervical lymphadenopathy 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 *36(1):138–142, 2012, Fig. 1, p. 139.)*

Table 166-2 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
• Meningococcemia
RHEUMATOLOGIC DISEASE
• Systemic-onset juvenile idiopathic arthritis
• Behçet disease
OTHER
• Toxic shock syndromes
• Staphylococcal scalded skin syndrome
• Drug hypersensitivity reactions
• Stevens-Johnson syndrome

bacterial or viral cervical lymphadenopathy/lymphadenitis and may delay the diagnosis of KD. Persistence of high fever, unresponsive to antibiotics and the eventual development of other signs of KD result in the diagnosis. Children with node-first KD tend to be older (4 vs. 2 yr) and have more days of fever and higher C-reactive protein levels. In addition to cervical adenopathy, many had retropharyngeal and peritonsillar inflammation on CT scans (Fig. 166-7).

KD can be divided into 3 clinical phases. The **acute febrile phase** is characterized by fever and the other acute signs of illness and usually lasts 1-2 wk. The **subacute phase** is associated with desquamation, thrombocytosis, the development of CAA, the highest risk of sudden death in patients in whom aneurysms have developed, and generally lasts about 3 wk. The **convalescent phase** begins when all clinical signs of illness have disappeared and continues until the erythrocyte sedimentation rate (ESR) returns to normal, typically about 6-8 wk 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 1st wk of illness and rapidly increases by the 2nd to 3rd wk of illness, sometimes exceeding 1,000,000/mm^3. An elevated ESR and/or C-reactive protein 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.

Two-dimensional echocardiography is the most useful test to monitor for development of CAA and should be performed by a pediatric cardiologist. Although frank aneurysms are rarely detected early in the illness, lack of normal tapering of the vessels is typical. Moreover, coronary artery dimensions, adjusted for body surface area, may be increased in the 1st 5 wk after presentation. Body surface area–adjusted coronary artery dimensions on baseline echocardiography in the 1st 10 days of illness appear to be good predictors of involvement during early follow-up. However, children with non-KD febrile illnesses also have mildly increased *z* scores as compared to nonfebrile controls, but not to the same degree as patients with KD. Aneurysms have been defined with use of absolute dimensions by the Japanese Ministry of Health and are classified as small (<5 mm internal diameter), medium (5-8 mm internal diameter), or giant (>8 mm internal diameter). Some experts believe that a *z*-score–based system for classification of aneurysm size may be more discriminating given the range in sizes of patients with KD. Under such a system, a *z* score ≥10 is considered giant and hence defines the threshold at which anticoagulation should be initiated.

Echocardiography should be performed at diagnosis and again after 2-3 wk of illness. If the results are normal, a repeat study should be performed 6-8 wk 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 without coronary abnormalities at any time during the illness, performance of echocardiography and a lipid profile is recommended 1 year later. After this time, periodic evaluation for preventive cardiology counseling is warranted, and some experts recommend cardiologic follow-up every 5 yr. For patients with coronary abnormalities, the type of testing and the frequency of cardiology follow-up visits are tailored to the patients' coronary status.

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 4 days and at least 4 of 5 of the other principal characteristics of the illness (see Table 166-1). In **atypical or incomplete KD,** patients have persistent fever but fewer than 4 of the 5 characteristics. In these patients, laboratory and echocardiographic data can assist in the diagnosis (Fig. 166-8). Incomplete cases are most frequent in infants, who, unfortunately, 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 institution of treatment is essential to prevent potentially devastating coronary artery disease.

DIFFERENTIAL DIAGNOSIS

Adenovirus, measles, and scarlet fever lead the list of common childhood infections that mimic KD (Table 166-2). 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 hr 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, as well as leukopenia. Cervical lymphadenitis can

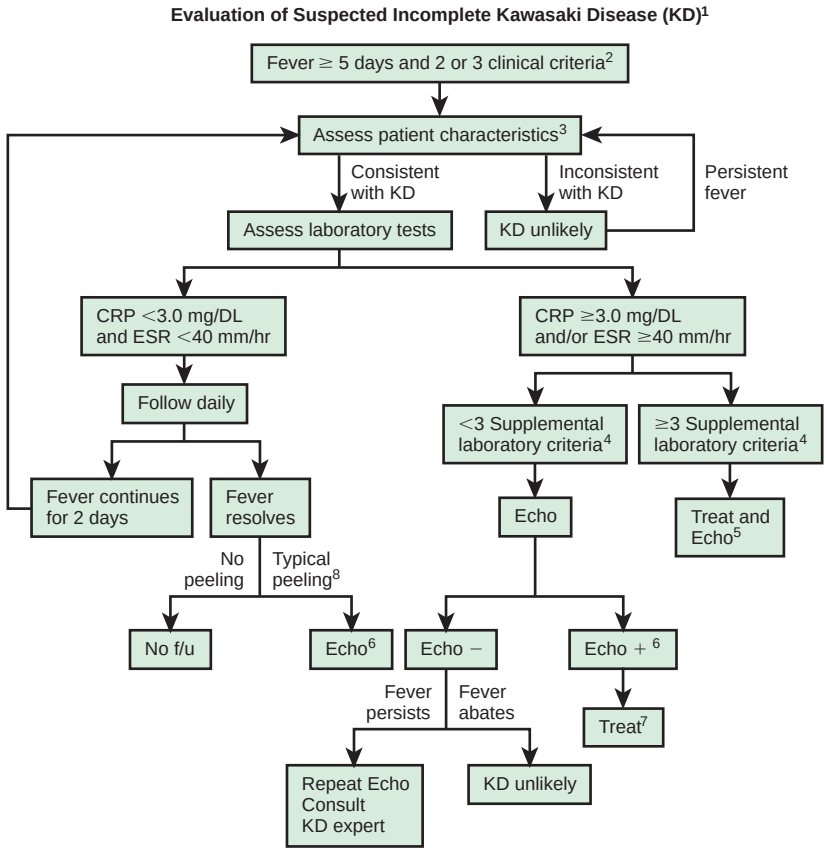


Figure 166-8 Algorithm for evaluation of suspected incomplete Kawasaki disease (KD). (1) In the absence of a gold standard for diagnosis, this algorithm cannot be evidence based, but rather represents the informed opinion of the expert committee. Consultation with an expert should be sought anytime assistance is needed. (2) Infants ≤6 mo old on day ≥7 of fever or later without other explanation should undergo laboratory testing and, if evidence of systemic inflammation is found, given an echocardiogram (Echo), even if they have no clinical criteria. (3) Patient characteristics suggesting KD are listed in Table 166-1. Characteristics suggesting disease other than KD include exudative conjunctivitis, exudative pharyngitis, discrete intraoral lesions, bullous or vesicular rash, and generalized adenopathy. Consider alternative diagnoses (see Table 166-2). (4) Supplemental laboratory criteria include albumin ≤3.0 g/dL, anemia for age, elevation of alanine aminotransferase, platelet count after 7 days ≥450,000/mm^3, white blood cell count ≥15,000/mm^3, and urine white blood cell count ≥10/high-power field. (5) Can treat before performing echocardiogram. (6) Echocardiogram findings are considered positive (Echo+) for purposes of this algorithm if any of 3 conditions are met: *z* score of left anterior descending coronary artery (LAD) or right coronary artery (RCA) ≥2.5; coronary arteries meet Japanese Ministry of Health criteria for aneurysms; ≥3 other suggestive features exist, including perivascular brightness, lack of tapering, decreased left ventricle (LV) function, mitral regurgitation, pericardial effusion, or *z* scores in LAD or RCA of 2-2.5. (7) If echocardiogram findings are positive, treatment should be given to children within 10 days of fever onset and to those beyond day 10 with clinical and laboratory signs (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR]) of ongoing inflammation. (8) Typical peeling begins under nail beds of fingers and then toes. Echo–, negative echocardiogram findings; f/u, follow-up. *(From Newburger JW, Takahashi M, Gerber MA, et al: Diagnosis, treatment, and long-term management of Kawasaki disease,* Pediatrics *114:1708–1733, 2004.)*

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, centripedal rash, and petechiae on the palms and soles. Leptospirosis can also be an illness of considerable severity. Risk factors include exposure to water contaminated 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.

Children with KD and pronounced myocarditis may demonstrate hypotension with a clinical picture similar to that of toxic shock syndrome. Features of toxic shock syndrome that are not commonly seen in KD include renal insufficiency, coagulopathy, pancytopenia, and myositis. Drug hypersensitivity reactions, including Stevens-Johnson syndrome, share some characteristics with KD. Drug reaction features such as the presence of periorbital edema, oral ulcerations, and a normal or minimally elevated ESR are not seen in KD. Systemic-onset juvenile idiopathic arthritis is also characterized by fever and rash, but physical findings include diffuse lymphadenopathy and hepatosplenomegaly. Arthritis is required to develop at some point in the disease course to make the diagnosis, but may not be present in the 1st few wk of illness. Laboratory findings may include coagulopathy, elevated fibrin degradation product values, and hyperferritinemia. Interestingly, there are reports of children with systemic-onset juvenile idiopathic arthritis who have echocardiographic evidence of abnormal coronary arteries. Coronary aneurysms have also been reported in Behçet disease, primary cytomegalovirus infection, and meningococcemia.

TREATMENT

Patients with acute KD should be treated with 2 g/kg of IVIG and high-dose aspirin (80-100 mg/kg/day divided q6h) within 10 days of disease onset and ideally as soon as possible after diagnosis (Table 166-3). The

Table 166-3 Treatment of Kawasaki Disease

ACUTE STAGE
• Intravenous immunoglobulin 2 g/kg over 10-12 hr *and* • Aspirin 80-100 mg/kg/day divided every 6 hr orally until patient is afebrile for at least 48 hr
CONVALESCENT STAGE
• Aspirin 3-5 mg/kg once daily orally until 6-8 wk after illness onset if normal coronary findings throughout course
LONG-TERM THERAPY FOR PATIENTS WITH CORONARY ABNORMALITIES
• Aspirin 3-5 mg/kg once daily orally • Clopidogrel 1 mg/kg/day (maximum: 75 mg/day) • Most experts add warfarin or low-molecular-weight heparin for those patients at particularly high risk of thrombosis
ACUTE CORONARY THROMBOSIS
• Prompt fibrinolytic therapy with tissue plasminogen activator or other thrombolytic agent under supervision of a pediatric cardiologist

mechanism of action of IVIG in KD is unknown, but treatment results in defervescence and resolution of clinical signs of illness in approximately 85% of patients. The prevalence of coronary disease, 20-25% in children treated with aspirin alone, is <5% in those treated with IVIG and aspirin within the 1st 10 days of illness. Strong consideration should be given to treating patients with persistent fever and/or signs of systemic inflammation who are diagnosed after the 10th day of fever. The dose of aspirin is usually decreased from antiinflammatory to antithrombotic doses (3-5 mg/kg/day as a single dose) after the patient has been afebrile for 48 hr, although some experts prescribe high-dose aspirin until the 14th day of illness. Aspirin is continued for its antithrombotic effect until 6-8 wk 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 and may require anticoagulation, depending on the degree of coronary dilation (see later).

Corticosteroids have been trialed 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 utilizing the Kobayashi score to identify high-risk children demonstrated improved coronary outcomes with a regimen of prednisolone (2 mg/kg) plus IVIG as primary therapy. Despite these promising results, administration of corticosteroids, as primary therapy to all children with KD awaits the development of a risk score that identifies high-risk children in a multiracial population.

IVIG-resistant KD occurs in approximately 15% of patients and is defined by persistent or recrudescent fever 36 hr after completion of the initial IVIG infusion. Patients with IVIG resistance are at increased risk for CAA. Typically, another dose of IVIG at 2 g/kg is administered to patients with IVIG resistance. Corticosteroids in varying doses and via different routes have also been used as secondary or "rescue" therapy when fever persists after the first IVIG. However, the lack of clear data regarding the most effective way to administer corticosteroids as rescue therapy has led to significant practice variation across centers. Tumor necrosis factor inhibitors, including infliximab and etanercept, have also been given for the treatment of IVIG-resistant disease. To date, there is no evidence of improved coronary outcomes with the use of these medications.

COMPLICATIONS

The patient with KD who has had a small solitary aneurysm should continue aspirin indefinitely. Patients with larger or numerous aneurysms may require the addition of other antiplatelet agents or anticoagulation; such decisions should be made in consultation with a pediatric cardiologist. Acute thrombosis may occasionally occur in an aneurysmal or stenotic coronary artery; thrombolytic therapy may be lifesaving in this circumstance.

Long-term follow-up of patients with coronary artery aneurysms should include periodic echocardiography with stress testing and possibly angiography if large aneurysms are present. Catheter intervention with percutaneous transluminal coronary rotational ablation, directional coronary atherectomy, and stent implantation have been used for the management of coronary stenosis due to KD, with some patients requiring coronary artery bypass grafting.

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 wk after varicella vaccination. As IVIG may interfere with the immune response to live virus vaccines as a result of specific antiviral antibody, the measles-mumps-rubella and varicella vaccinations should generally be deferred until 11 mo after IVIG administration. Non-live vaccinations do not need to be delayed.

PROGNOSIS

The vast majority of patients with KD return to normal health, as timely treatment reduces the risk of coronary aneurysms to less than 5%. Acute KD recurs in 1-3% of cases. The prognosis for patients with coronary abnormalities depends on the severity of coronary disease; therefore, recommendations for follow-up and management are stratified according to coronary artery status. Published fatality rates are very low, generally <1.0%. Overall, 50% of coronary artery aneurysms regress to normal lumen diameter by 1-2 yr 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 functional behavior of the vessel wall. Giant aneurysms are less likely to regress to normal lumen diameter and are most likely to lead to thrombosis or stenosis. Coronary artery bypass grafting may be required if myocardial perfusion is significantly impaired; 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 in which 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-year survival rate approached 90%.

Whether children who have had KD and normal echocardiography findings throughout their course are at higher risk for the development of atherosclerotic heart disease in adulthood remains unclear, as 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 American Heart Association recommends treatment thresholds for risk factors for atherosclerotic heart disease that are lower than those for the normal population.

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Chapter 167

Vasculitis Syndromes

Stacy P. Ardoin and Edward Fels

Childhood vasculitis encompasses a broad spectrum of diseases that share in common 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; others may occur in the setting of preexisting autoimmune disease. 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). Additionally, some forms of small vessel vasculitis are characterized by the presence of antineutrophil cytoplasmic antibodies (ANCAs) (Table 167-1), 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 utilized to classify vasculitis (Tables 167-2 to 167-4).

Childhood vasculitis varies from a relatively benign and self-limited disease such as Henoch-Schönlein purpura to catastrophic disease with end-organ damage as can be 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 occlusion or glomerulonephritis, can be more subtle. 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.

Bibliography is available at Expert Consult.

Table 167-2 Classification of Childhood Vasculitis

I. Predominantly Large Vessel Vasculitis
- Takayasu arteritis

II. Predominantly Medium Vessel Vasculitis
- Childhood polyarteritis nodosa
- Cutaneous polyarteritis nodosa
- Kawasaki disease

III. Predominantly Small Vessel Vasculitis
A. Granulomatous:
- Granulomatosis with polyangiitis (Wegener granulomatosis)*
- Eosinophilic granulomatosis with polyangiitis (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 disease
- Isolated vasculitis of the central nervous system
- Cogan syndrome
- Unclassified

*Associated with antineutrophil cytoplasmic antibody.

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 *69:798-806; 2010.*

Table 167-1 Common Disease Associations with Antibodies to Neutrophil Cytoplasmic Antigens

ANTIGEN	ANCA PATTERN	DISEASE ASSOCIATION	FREQUENCY (%)
PR3	cANCA	Wegener granulomatosis Churg-Strauss	30 to 90 25 to 50
MPO	pANCA	Microscopic polyarteritis Ulcerative colitis Sclerosing cholangitis Crohn disease	25 to 75 40 to 80 65 to 85 10 to 40
BPI	ANCA	Cystic fibrosis	80 to 90
Actin	pANCA	Autoimmune hepatitis type 1	70 to 75

ANCA, Antibodies directed at neutrophil cytoplasmic antigen; BPI, Bactericidal permeability increasing protein. cANCA, cytoplasmic ANCA; pANCA, perinuclear ANCA.

From Cabral D, Benseler S: Granulomatous vasculitis, microscopic polyangiitis and primary angiitis of the central nervous system. In Cassidy JT, Petty RE, Laxer RM, Lindsley CB, editors, Textbook of pediatric rheumatology, *ed 6, Philadelphia, 2011, Elsevier/Saunders, Table 34-3, p. 526.*

Table 167-3 Features That Suggest a Vasculitic Syndrome

CLINICAL FEATURES
Fever, weight loss, fatigue of unknown origin
Skin lesions (palpable purpura, vasculitic urticaria, livedo reticularis, nodules, ulcers)
Neurologic lesions (headache, mononeuritis multiplex, focal central nervous system lesions)
Arthralgia or arthritis, myalgia, or myositis
Serositis
Hypertension
Pulmonary infiltrates or hemorrhage
LABORATORY FEATURES
Increased erythrocytes sedimentation rate or C-reactive protein level
Leukocytosis, anemia
Eosinophilia
Antineutrophil cytoplasmic antibodies
Elevated factor VIII–related antigen (von Willebrand factor)
Cryoglobulins
Circulating immune complexes
Hematuria, proteinuria, elevated serum creatinine

From Cassidy JT, Petty RE: Textbook of pediatric rheumatology, *ed 5, Philadelphia, 2005, Elsevier/Saunders.*

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Table 167-4 Clinical and Pathologic Characteristics of Some 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	Common	Arterioles and venules, often small arteries and veins	Leukocytoclasis; mixed cells, eosinophils, immunoglobulin A deposits in affected vessels
Hypersensitivity angitis	Rare	Arterioles and venules	Leukocytoclastic or lymphocytic, varying eosinophils, occasionally granulomatous; widespread lesions at same stage of evolution
GRANULOMATOUS VASCULITIS			
Granulomatosis with polyangiitis	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, *ed 5, Philadelphia, 2005, Elsevier/Saunders.*

167.1 Henoch-Schönlein Purpura

Stacy P. Ardoin and Edward Fels

Henoch-Schönlein purpura (HSP) is the most common vasculitis of childhood and is characterized by leukocytoclastic vasculitis and immunoglobulin (Ig) A deposition in the small vessels in the skin, joints, gastrointestinal tract, and kidney.

EPIDEMIOLOGY

HSP occurs worldwide and affects all ethnic groups but is more common in white and Asian populations. The incidence of HSP is estimated at 14-20/100,000 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 the ages of 3 and 10 yr. HSP is distinctly less common in adults, in whom severe and chronic complications are often encountered. 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 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. 167-1), 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) or on pressure points (buttocks) (see Figs. 167-1 and 167-2). The skin lesions often evolve in groups, typically lasting 3-10 days, and may recur up to 4 mo after initial presentation. Subcutaneous edema localized to the dorsa of 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 the lower extremities, and does not lead to deformities. The arthritis usually resolves within 2 wk but can recur.

Gastrointestinal manifestations of HSP occur in up to 80% of children with HSP and include abdominal pain, vomiting, diarrhea, paralytic ileus and melena; intussusception, mesenteric ischemia, intestinal perforation are uncommon. Endoscopic evaluation is usually not needed but may identify purpura of the intestinal tract.

Renal involvement occurs in up to 50% of children with HSP, manifesting as microscopic hematuria, proteinuria, hypertension, frank nephritis, nephrotic syndrome, and acute or chronic renal failure. Progression to end-stage renal disease is uncommon in children (1-2%) (see Chapter 515).

Neurologic manifestations of HSP, caused by hypertension or central nervous system (CNS) vasculitis, may also occur. They include intracerebral hemorrhage, seizures, headaches, and behavior changes. Other less-common potential manifestations of HSP are orchitis, carditis, inflammatory eye disease, testicular torsion, and pulmonary hemorrhage.

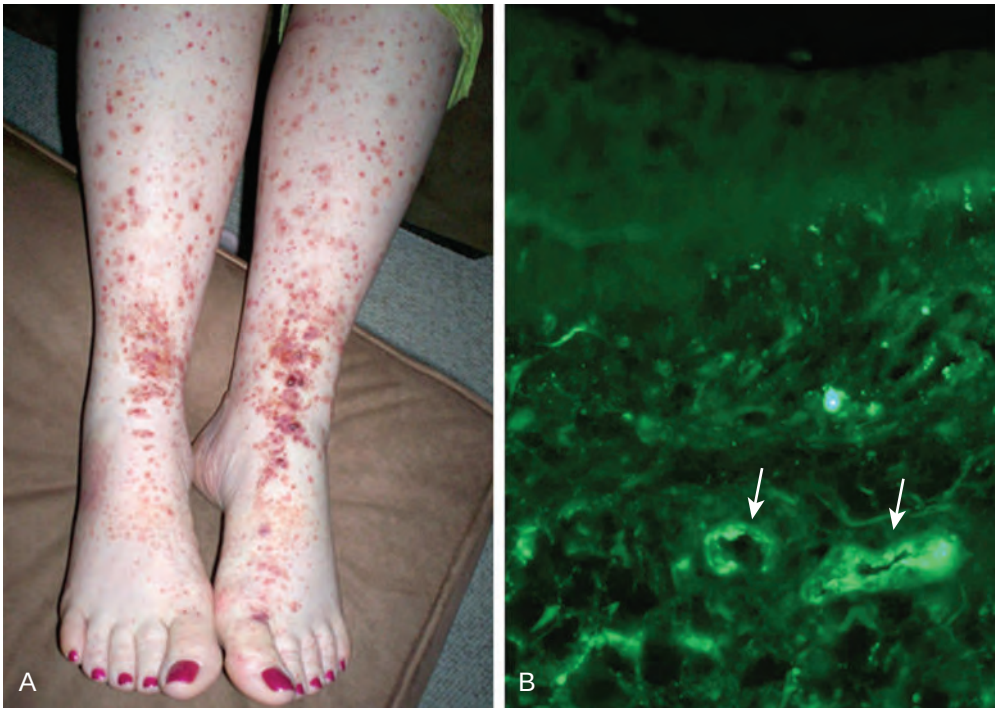


Figure 167-1 **A,** Typical palpable purpura in the lower extremities of a girl with Henoch-Schönlein purpura. **B,** Skin biopsy of lesion from the same patient, showing direct immunofluorescence of immunoglobulin A within the walls of dermal capillaries.



Figure 167-2 Henoch-Schönlein purpura. *(From Korting GW:* Hautkrankheiten bei Kindern und Jungendlichen, *ed 3, Stuttgart, 1982, FK Schattaur Verlag.)*

DIAGNOSIS

The diagnosis of HSP is a clinical one and is 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 167-5 summarizes the classification criteria for HSP. The differential diagnosis for HSP depends on specific organ involvement but usually includes other small vessel vasculitides, infections, acute post streptococcal glomerulonephritis, hemolytic-uremic syndrome, coagulopathies, and other acute intraabdominal processes.

Acute hemorrhagic edema (AHE), an isolated cutaneous leukocytoclastic vasculitis that affects infants <2 yr 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. 167-3). 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, the nature of the lesions, absence of other organ involvement, and a biopsy may help distinguish AHE from HSP.

Papular-purpuric gloves-and-socks syndrome is most commonly caused by parvovirus B19 and initially manifests with symmetric edema and erythema over the hands and feet. These well-demarcated lesions end at the ankle and wrist and evolve into purpuric papules. Fever, oral lesions, and leukopenia are inconsistent findings. Complications include mononeuritis multiplex. Adolescents are more often affected than young children. In contrast to erythremia infectiosum, patients with papular-purpuric gloves-and-socks syndrome are usually infectious at the time of appearance of the rash.

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



Figure 167-3 Typical lesions of acute hemorrhagic edema on the arm of an infant. *(From Eichenfield LF, Frieden IJ, Esterly NB:* Textbook of neonatal dermatology, *Philadelphia, 2001, WB Saunders.)*

Table 167-5 Classification Criteria for Henoch-Schönlein Purpura*

AMERICAN COLLEGE OF RHEUMATOLOGY CLASSIFICATION CRITERIA†
Two of the following criteria must be present:
• Palpable purpura
• Age at onset ≤20 yr
• Bowel angina (postprandial abdominal pain, bloody diarrhea)
• Biopsy demonstrating intramural granulocytes in small arterioles and/or venules
EUROPEAN LEAGUE AGAINST RHEUMATISM/PEDIATRIC RHEUMATOLOGY EUROPEAN SOCIETY CRITERIA‡
Palpable purpura (in absence of coagulopathy or thrombocytopenia) and 1 or more of the following criteria must be present:
• Abdominal pain (acute, diffuse, colicky pain)
• Arthritis or arthralgia
• Biopsy of affected tissue demonstrating predominant immunoglobulin A deposition
• Renal involvement (proteinuria >3 grams/24 hr), hematuria or red cell casts

*Classification criteria are developed for use in research and not validated for clinical diagnosis.

†Developed for use in adult and pediatric populations. Adapted from Mills JA, Michel BA, Bloch DA, et al: The American College of Rheumatology 1990 criteria for classification of Henoch-Schönlein purpura, *Arthritis Rheum* 33:1114–1121, 1990.

‡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 *69:798–806; 2010.*

(CRP). The platelet count is normal in HSP. Occult blood is frequently found in stool specimens. Serum albumin levels may be low due to renal or intestinal protein loss. Autoantibody testing 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 gastrointestinal 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 IgA deposition in affected tissues.

TREATMENT

Treatment for mild and self-limited HSP is supportive, with an emphasis on assuring adequate hydration, nutrition, and analgesia. Steroids are most often used to treat significant gastrointestinal involvement or other life-threatening manifestations. Prednisone (1 mg/kg/day for 1-2 wk, followed by taper) reduces abdominal and joint pain but does not alter overall prognosis nor prevent renal disease. Rapid tapering of corticosteroids may lead to a flare of HSP symptoms. Although few data are available to demonstrate efficacy, intravenous immune globulin and plasma exchange are sometimes used in the setting of severe disease. In some cases, chronic HSP renal disease is managed with a variety of immunosuppressants, including azathioprine, cyclophosphamide, cyclosporine, and mycophenolate mofetil. End-stage renal disease develops in up to 8% of children with HSP nephritis.

COMPLICATIONS

Acutely, serious gastrointestinal involvement such as 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 mo after diagnosis but rarely does so if the initial urinalyses findings are normal. It is recommended that children with HSP undergo serial monitoring of blood pressure and urinalyses for several months after diagnosis to monitor for the 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 wk. From 15-60% of children with HSP experience 1 or more recurrences, typically within 4-6 mo of diagnosis. With each relapse, symptoms are usually milder than at presentation. Children with a more-severe initial course are at higher risk for relapse. The long-term prognosis usually depends upon the severity and duration of gastrointestinal or renal involvement. Chronic renal disease develops in 1-2% of children with HSP, and approximately 8% of those with HSP nephritis go on to have end-stage renal disease. The risk of HSP recurrence and graft loss following renal transplantation is estimated at 7.5% after 10 yr.

Bibliography is available at Expert Consult.

167.2 Takayasu Arteritis

Stacy P. Ardoin and Edward Fels

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 Asians. Age of onset is typically between 10 and 40 yr. Most children are diagnosed as adolescents, on average at 13 yr of age. Up to 20% of individuals with TA are diagnosed prior to age 19 yr. 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

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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 vas 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 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-α (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 "pre-pulseless" 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 pulses, asymmetric blood pressures, 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, while infradiaphragmatic (mid-aortic syndrome) disease may produce hypertension, abdominal bruits, and pain. Most patients have involvement in both areas.

DIAGNOSIS

Specific pediatric criteria for TA have been proposed (Table 167-6). 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 exceedingly rare in childhood. Noninflammatory conditions that can cause large vessel compromise include fibromuscular dysplasia, Marfan syndrome, and Ehlers-Danlos syndrome.

Table 167-6 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)

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* 69:798–806; 2010.

LABORATORY FINDINGS

The laboratory findings in TA are nonspecific, and there is no specific diagnostic laboratory test. ESR and CRP value are typically elevated, and other nonspecific markers of chronic inflammation may include leukocytosis, thrombocytosis, anemia of chronic inflammation, and hypergammaglobulinemia. Autoantibodies 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 167-4 shows a conventional arteriogram in a child with TA. Although not yet thoroughly validated in TA, magnetic resonance angiography and CT angiography 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 may detect vessel wall inflammation but has not been studied extensively. Ultrasound with duplex color-flow Doppler imaging also identifies vessel wall thickening and assesses arterial flow. Echocardiography is recommended to assess for aortic valvular 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) 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, tocilizumab or anti–TNF-α therapy may be beneficial in select patients. 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 following angioplasty and stent placement. Aortic valve replacement may be required if significant aortic insufficiency develops.

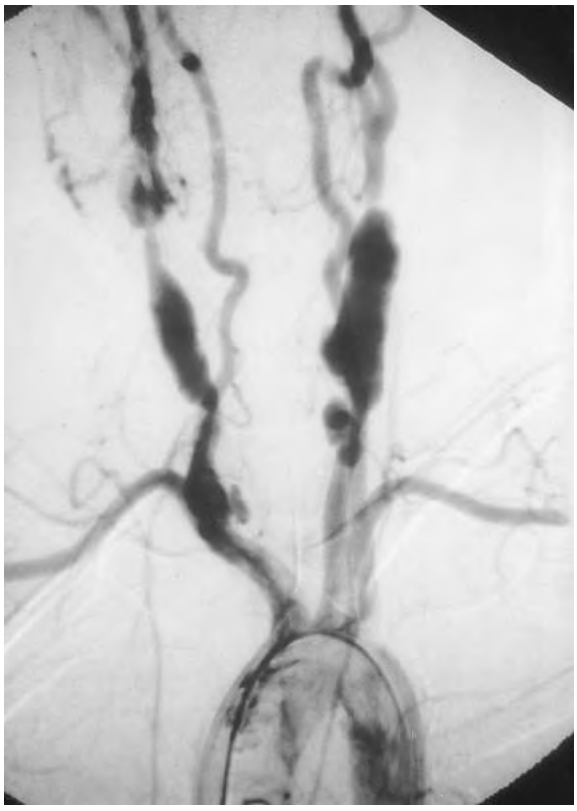


Figure 167-4 Conventional angiogram in a child with Takayasu arteritis showing massive bilateral carotid dilation, stenosis, and poststenotic dilation.

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 yr and 87% at 10 yr. 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 outcome in TA.

Bibliography is available at Expert Consult.

167.3 Polyarteritis Nodosa and Cutaneous Polyarteritis Nodosa

Stacy P. Ardoin and Edward Fels

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. Boys and girls are equally affected, and the mean age at presentation is 9 yr. The cause is unknown, but the development of PAN following 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. As in Henoch-Schönlein purpura, there is a possible association between PAN and familial Mediterranean fever.

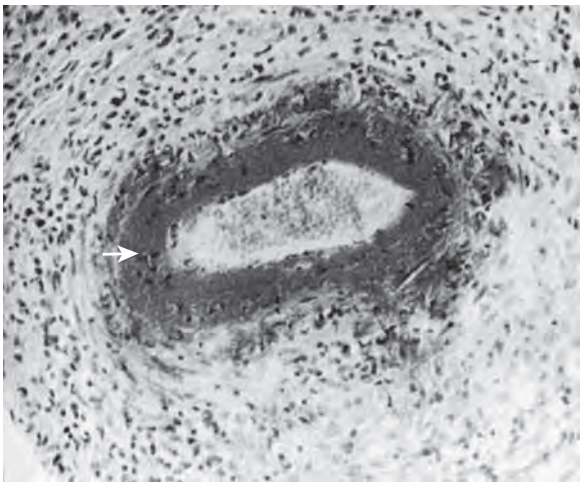


Figure 167-5 Biopsy specimen from a medium-size muscular artery that exhibits marked fibrinoid necrosis of the vessel wall *(arrow). (From Cassidy JT, Petty RE: Polyarteritis and related vasculitides. In* Textbook of pediatric rheumatology, *ed 5, Philadelphia, 2005, Elsevier/Saunders.)*

PATHOLOGY

Biopsies show necrotizing vasculitis with granulocytes and monocytes infiltrating the walls of small and medium-size arteries (Fig. 167-5). 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. There is no clear genetic association with PAN, and 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. Familial disease in Georgian Jewish patients has been reported to be due to mutations in the *CECR1* gene, which encodes adenosine deaminase 2.

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. 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 167-7). Biopsy of cutaneous lesions

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Table 167-7	Proposed Classification Criteria for Pediatric-Onset Polyarteritis Nodosa*
Histopathology	Necrotizing vasculitis in medium or small arteries
Angiographic abnormalities	Angiography showing aneurysm, stenosis, or occlusion of a medium or small size artery not from a 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 all 5 criteria provides 89.6% sensitivity and 99.6% specificity for the diagnosis of childhood onset polyarteritis nodosa.

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* 69:798–806; 2010.

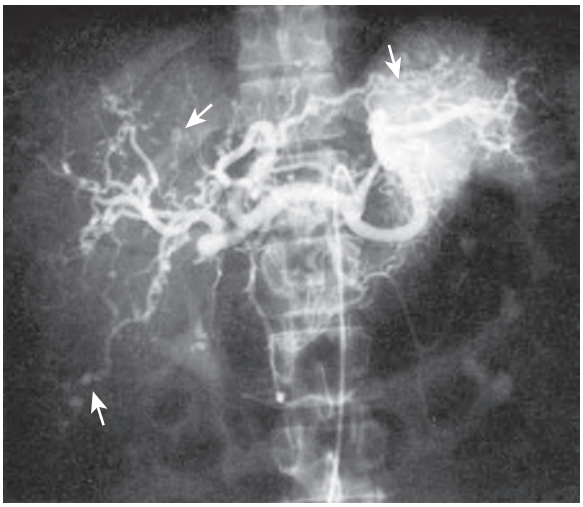


Figure 167-6 Celiac angiography in an 18 yr old boy showing aneurysms in multiple vessels. *(From Cassidy JT, Petty RE: Polyarteritis and related vasculitides. In* Textbook of pediatric rheumatology, *ed 5, Philadelphia, 2005, Elsevier/Saunders.)*

shows small or medium vessel vasculitis (see Fig. 167-5). 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. 167-6). Magnetic resonance angiography and CT angiography, less-invasive imaging alternatives, are gaining acceptance, but may not be as effective in identifying small vessel disease or in younger children.

DIFFERENTIAL DIAGNOSIS

Early skin lesions may resemble those of HSP, although the finding of nodular lesions and 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 systemic lupus erythematosus, 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.

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.

TREATMENT

Oral (1-2 mg/kg/day) and intravenous pulse (30 mg/kg/day) prednisone is the mainstay of therapy. Oral or intravenous cyclophosphamide are 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 358). Most cases of cutaneous PAN can be treated with less-intense therapy such as corticosteroids alone, nonsteroidal antiinflammatory agents, and methotrexate. Azathioprine, mycophenolate mofetil, intravenous immunoglobulin, thalidomide, cyclosporine, and anti-TNF have all been reported as successful in treatment of refractory cutaneous or systemic PAN, although clinical trials are lacking. If an infectious trigger for PAN is identified, antibiotic prophylaxis can be considered.

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 gastrointestinal 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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167.4 Antineutrophilic Cytoplasmic Antibody–Associated Vasculitis

Stacy P. Ardoin and Edward Fels

The ANCA-associated vasculitides are characterized by small vessel involvement, circulating ANCAs, and pauci-immune complex deposition in affected tissues. ANCA-associated vasculitis is categorized into 3 distinct forms: **granulomatosis with polyangiitis (GPA; formerly**

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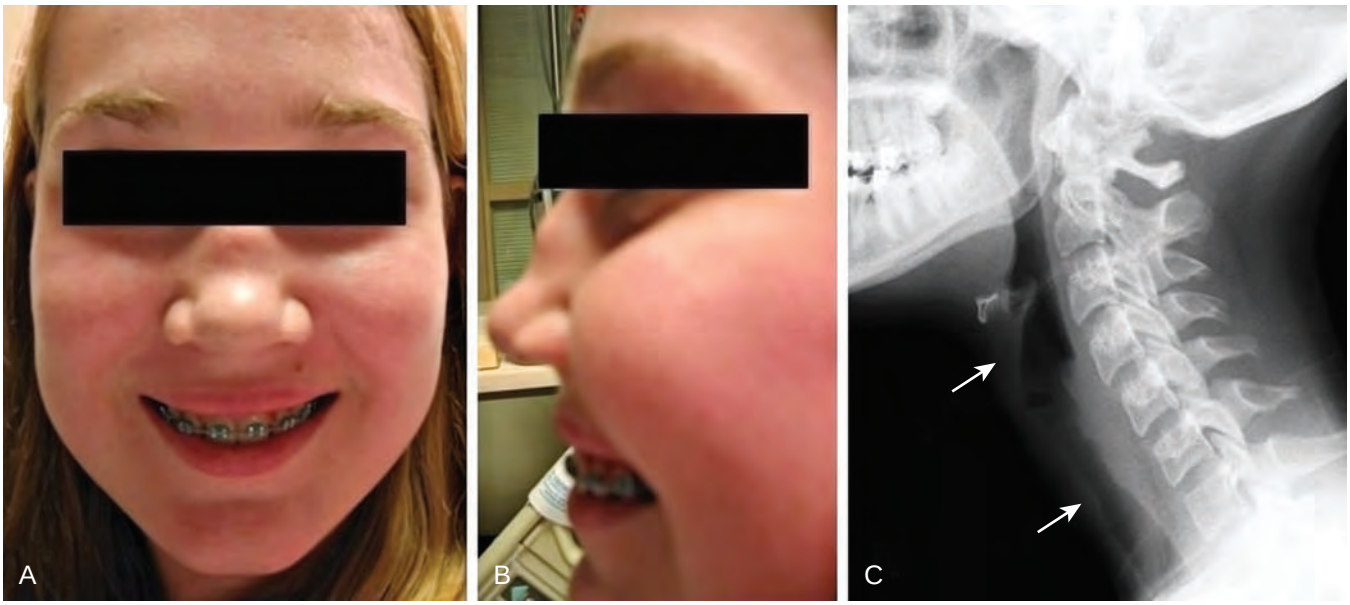


Figure 167-7 **A** and **B,** Anterior and lateral views of saddle nose deformity in an adolescent girl with Wegener granulomatosis. **C,** Segment of subglottic posterior tracheal irregularity (between *arrows*) on lateral neck radiograph in the same patient.

Wegener granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis, formerly called **Churg-Strauss syndrome (CSS)** (see Table 167-1).

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. Although most cases of GPA occur in adults, the disease also occurs in children with a mean age at diagnosis of 14 yr. There is a female predominance of 3-4:1, and pediatric GPA is most prevalent in whites.

MPA is a small vessel necrotizing vasculitis with clinical features similar to those of GPA. **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 systemic lupus erythematosus. Although granulomatous inflammation is common in GPA and CSS, it is typically not present in MPA. Biopsies showing perivascular eosinophilic infiltrates distinguish CSS syndrome from both MPA and GPA (see Table 167-7).

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

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 (see Fig. 167-5). Inflammation-induced damage to the nasal cartilage can produce a saddle nose deformity (Fig. 167-7). 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: respiratory tract, 84%; kidneys, 88%; joints, 44%; eyes, 60%; skin, 48%; sinuses, 56%; and nervous system, 12%. Table 167-8 outlines 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, arthralgias may be dominant. MPA predominantly affects the kidney and lungs; other organ systems include skin, CNS, muscle, heart, and eyes. **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, and difficult to treat asthma. Eosinophilia with pulmonary infiltrates may precede a vasculitic phase. Other organ involvement includes skin, cardiac, peripheral nerves, gastrointestinal 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. 167-8). The diagnosis is confirmed by the presence of anti-PR3–specific ANCAs (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 but have 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 approximately 70% of cases of **CSS**, and MPO-ANCAs are more common than PR3-ANCAs. The presence of chronic asthma and peripheral eosinophilia suggests the diagnosis of CSS.

Table 167-8 EULAR/PReS Classification Criteria for Pediatric-Onset Granulomatosis with Polyangiitis*

Histopathology showing granulomatous inflammation
Upper airway involvement
Laryngeal, tracheal or bronchial involvement
ANCA positivity
Renal involvement
Proteinuria, hematuria, red blood cell casts, necrotizing pauci-immune glomerulonephritis

*Diagnosis requires 3 of 6 criteria.
Adapted from: Ozen S, Pistorio A, Iusan SM, et al: EULAR/PRINTO/PRES criteria for Henoch-Schonlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: final classification criteria. Ann Rheum Dis *69:798–806; 2010.*

DIFFERENTIAL DIAGNOSIS

ANCAs are absent in other granulomatous diseases, such as sarcoidosis and tuberculosis. Goodpasture disease 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. Systemic lupus erythematous and HSP can manifest as pulmonary hemorrhage and nephritis.

LABORATORY FINDINGS

Elevated ESR and CRP values, leukocytosis, and thrombocytosis 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 2 distinct immunofluorescence patterns: perinuclear and cytoplasmic. In addition, ANCAs can also be defined by their specificity for PR3 or MPO antigen. GPA is strongly associated with cytoplasmic ANCAs/anti-PR3 antibodies (see Tables 167-1 and 167-9).

TREATMENT

When the lower respiratory tract or kidneys are significantly involved, initial induction therapy usually consists of corticosteroids (2 mg/kg/day oral or 30 mg/kg/day × 3 days given intravenously) in conjunction with daily oral cyclophosphamide (2 mg/kg/day). Rituximab is an option for induction therapy in ANCA positive vasculitides although

Table 167-9 Differential Diagnostic Features of Small Vessel Vasculitis

FEATURE	HENOCH-SCHÖNLEIN PURPURA	GRANULOMATOSIS WITH POLYANGIITIS	CHURG-STRAUSS SYNDROME	MICROSCOPIC POLYANGIITIS
Signs and symptoms of small vessel vasculitis*	+	+	+	+
Immunoglobulin A–dominant immune deposits	+	–	–	–
Circulating antineutrophil cytoplasmic antibodies	–	+ (PR3)	+ (MPO > PR3)	+ (MPO)
Necrotizing vasculitis	–	+	+	+
Granulomatous inflammation	–	+	+	–
Asthma and eosinophilia	–	–	+	–

MPO, myeloperoxidase-reactive antibodies; PR3, proteinase 3–reactive antibodies; +, presence; –, absent.
*Signs and symptoms of small vessel vasculitis include purpura, other rash, arthralgias, arthritis, and constitutional symptoms.
Adapted from Jeannett JC, Falk RJ: Small-vessel vasculitis, N Engl J Med *337:1512–1523, 1997.*

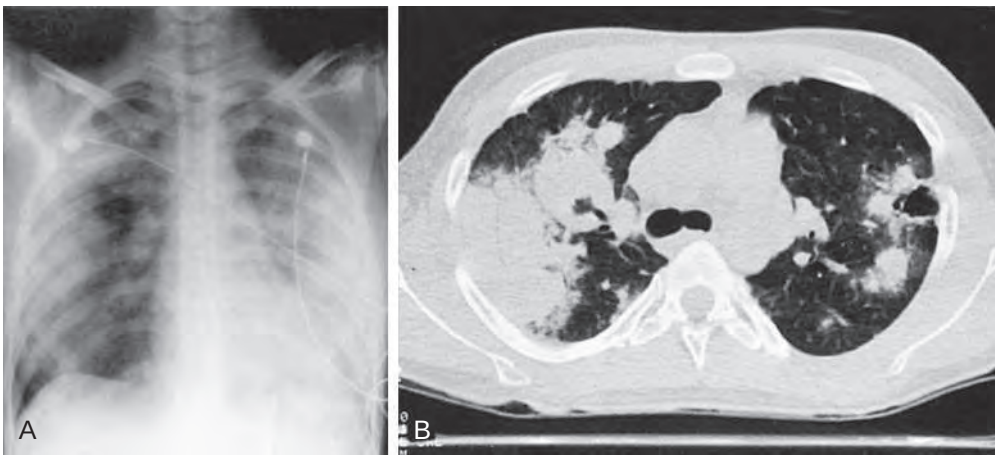


Figure 167-8 Radiographs of lower respiratory tract disease in granulomatosis with polyangiitis. **A,** A chest radiograph of a 14 yr old girl with Wegener granulomatosis and pulmonary hemorrhage. Extensive bilateral, fluffy infiltrates are visualized. **B,** CT scan of the chest in a 17 yr old boy with Wegener granulomatosis. 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, *ed 3, Philadelphia, 1995, WB Saunders;* ***B,*** *From Kuhn JP, Slovis TL, Haller JO:* Caffey's pediatric diagnostic imaging, *ed 10, vol 1, Philadelphia, 2004, Mosby.)*

has been studied primarily in adults. Patients are transitioned to a less toxic maintenance medication (usually methotrexate, azathioprine, or mycophenolate mofetil) within 3-6 mo once remission is achieved. Trimethoprim-sulfamethoxazole (one 180 mg/800 mg tablet 3 days/wk) is often prescribed both for prophylaxis against *Pneumocystis jiroveci* 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/wk) may be first-line treatment.

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 due to subglottic stenosis. Chronic lung disease secondary to granulomatous inflammation, cavitary lesions, and scarring can predispose to infectious complications. Chronic glomerulonephritis may progress to end-stage renal disease 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 multiple organ involvement, renal involvement, and subglottic stenosis.

Bibliography is available at Expert Consult.

167.5 Other Vasculitis Syndromes

Stacy P. Ardoin and Edward Fels

In addition to the more common vasculitides discussed earlier in this chapter, other vasculitic conditions can occur in childhood, the most common of which is Kawasaki disease (see Chapter 166). **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). **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, gastrointestinal symptoms, arthritis, and glomerulonephritis. **Cryoglobulinemic vasculitis** can complicate mixed essential cryoglobulinemia and is a small vessel vasculitis affecting skin, joints, kidneys, and lungs.

Primary angiitis of the CNS represents vasculitis confined to the CNS and requires exclusion of other systemic vasculitides. Large vessel disease (angiography positive) 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 plus behavioral disorders are seen in 30-40%. Small vessel (angiography negative, biopsy positive) involvement more often demonstrates language problems and diffuse deficits such as cognitive, memory, behavior, and concentration problems as well as focal seizures.

Benign angiitis of the CNS, also known as transient CNS angiopathy, represents a self-limited variant. **Cogan syndrome** is rare in children; its potential clinical manifestations include constitutional symptoms, inflammatory eye disease, vestibuloauditory dysfunction, arthritis, and aortitis.

Identification of these vasculitis syndromes requires a comprehensive history and physical exam. Table 167-10 outlines other diagnostic considerations. Although treatment is tailored to disease severity, treatment generally includes prednisone (up to 2 mg/kg/day) plus steroid-sparing immunosuppressive medications if necessary. For hypersensitivity vasculitis, withdrawal of the triggering medication or toxin is indicated if possible.

Table 167-10 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 the CNS	Conventional, CT, or MR angiographic evidence of CNS vasculitis Consideration of dura or brain biopsy
Benign angiitis of the CNS	Conventional, CT, or MR angiographic evidence of CNS vasculitis
Cogan syndrome	Ophthalmology and audiology evaluations Conventional, CT, or MR angiographic evidence of CNS or aortic vasculitis

CNS, central nervous system; CT, computed tomography; MR, magnetic resonance.

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Chapter 168

Musculoskeletal Pain Syndromes

Kelly K. Anthony and Laura E. Schanberg

Musculoskeletal pain is a frequent complaint of children presenting to general pediatricians and is the most common presenting problem of children referred to pediatric rheumatology clinics. Prevalence estimates of persistent musculoskeletal pain in community samples range from roughly 10-30%. Although diseases such as juvenile idiopathic arthritis and systemic lupus erythematosus may manifest as persistent musculoskeletal pain, the majority of musculoskeletal pain complaints in children turn out to be benign in nature and attributable to trauma, overuse, and normal skeletal growth variations. There is a subset of children in whom chronic pain complaints develop in the absence of physical and laboratory abnormalities. Children with idiopathic musculoskeletal pain syndromes, also typically develop marked subjective distress and functional impairment. Therefore, the treatment of children with musculoskeletal pain syndromes optimally includes both pharmacologic and nonpharmacologic interventions.

CLINICAL MANIFESTATIONS

Chronic musculoskeletal pain syndromes involve pain complaints of at least 3 mo in duration in the absence of objective abnormalities on physical examination and laboratory screening. Additionally, children and adolescents with musculoskeletal pain syndromes often complain

of persistent pain despite previous treatment with nonsteroidal antiinflammatory drugs and analgesic agents. The location varies, with pain complaints either localized to a single extremity or more diffuse and involving multiple extremities. It is not uncommon for the pain to start in a single area of the body before intensifying and radiating to other areas over time. The prevalence of musculoskeletal pain syndromes increases with age and is higher in females, thus rendering adolescent girls at highest risk.

The somatic complaints of children and adolescents with musculoskeletal pain syndromes are commonly accompanied by psychological distress, sleep difficulties, and functional impairment across home, school, and peer domains. Psychological distress may include symptoms of anxiety and depression, such as frequent crying spells, fatigue, sleep disturbance, feelings of worthlessness, poor concentration, and frequent worry. Indeed, a substantial number of children with musculoskeletal pain syndromes display the full range of psychological symptoms warranting an additional diagnosis of a comorbid mood or anxiety disorder (e.g., major depressive episode, generalized anxiety disorder). **Sleep disturbance** in children with musculoskeletal pain syndromes may include difficulty falling asleep, multiple night awakenings, disrupted sleep-wake cycles with increased daytime sleeping, nonrestorative sleep, and fatigue.

For children and adolescents with musculoskeletal pain syndromes, the constellation of pain, psychological 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, as well as changes in gait and posture, as children avoid contact with or use of the body area affected by pain. Peer relationships may also be disrupted due to decreased opportunities for social interaction due to pain. As such, children and adolescents with musculoskeletal pain syndromes often report loneliness and social isolation characterized by having few friends and lack of participation in extracurricular activities.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of a musculoskeletal pain syndrome is typically one of exclusion when careful, repeated physical examinations and laboratory testing do not reveal an etiology. At initial presentation, children with pain complaints require a thorough clinical history and a complete physical examination to look for an obvious etiology (e.g., sprains, strains, or fractures), characteristics of the pain (localized or diffuse), and evidence of systemic involvement. A comprehensive history can be particularly useful in providing clues to the possibility of underlying illness or systemic disease. The presence of current or recent fever can be indicative of an inflammatory or neoplastic process if the pain is also accompanied by worsening symptoms over time or weight loss.

Subsequent, repeated physical examinations of children with musculoskeletal pain complaints may reveal eventual development and manifestations of rheumatic or other diseases. The need for additional testing should be individualized, depending on the specific symptoms and physical findings. Laboratory screening and/or radiographs should be pursued if there is suspicion of certain underlying disease processes. Possible indicators of a serious, as opposed to a benign, cause of musculoskeletal pain include pain present at rest and relieved by activity, objective joint swelling on physical examination, stiffness or limited range of motion in joints, bony tenderness, muscle weakness, poor growth and/or weight loss, and constitutional symptoms (e.g., fever, malaise) (Table 168-1). In the case of laboratory screenings, a complete blood count and erythrocyte sedimentation rate are likely to be abnormal in children whose pain is secondary to a bone or joint infection, systemic lupus erythematosus, or a malignancy. Bone tumors, fractures, and other focal pathology resulting from infection, malignancy, or trauma can often be indentified through imaging studies, including plain film x-rays, MRI, and technetium-99m bone scans.

The presence of persistent pain, accompanied by psychological distress, sleep disturbance, and/or functional impairment, in the absence of objective laboratory or physical examination abnormalities, suggest the diagnosis of a musculoskeletal pain syndrome. All pediatric musculoskeletal pain syndromes share this general constellation of symptoms at presentation. Several more specific pain syndromes routinely seen by pediatric practitioners can be differentiated by anatomic region and associated symptoms. Pediatric musculoskeletal pain syndromes are listed in Table 168-2 and includes growing pains (see Chapter 168.1), fibromyalgia (see Chapter 168.3), complex regional pain syndrome (see Chapter 168.4), localized pain syndromes, low back pain, and chronic sports-related pain syndromes (e.g., Osgood-Schlatter disease).

TREATMENT

The primary goal of treatment for pediatric musculoskeletal pain syndromes is to improve function rather than relieve pain, and these two desirable outcomes may not occur simultaneously. Indeed, it is common for children with musculoskeletal pain syndromes to continue complaining of pain even as they resume normal function (e.g., increased school attendance and participation in extracurricular activities). For all children and adolescents with pediatric musculoskeletal pain syndromes, regular school attendance is crucial, as this is a hallmark of normal functioning in this age group. The dual nature of treatment, targeting both function and pain, needs to be clearly

Table 168-1 Potential Indicators of Benign Versus Serious Causes of Musculoskeletal Pain

CLINICAL FINDING	BENIGN CAUSE OF MUSCULOSKELETAL PAIN	SERIOUS CAUSE OF MUSCULOSKELETAL PAIN
Effects of rest versus activity on pain	Relieved by rest and worsened by activity	Relieved by activity and present at rest
Time of day pain occurs	End of the day and nights	Morning*
Objective joint swelling	No	Yes
Joint characteristics	Hypermobile/normal	Stiffness, limited range of motion
Bony tenderness	No	Yes
Muscle strength	Normal	Muscle weakness
Growth	Normal growth pattern or weight gain	Poor growth and/or weight loss
Constitutional symptoms (e.g., fever, malaise)	Fatigue without other constitutional symptoms	Yes
Lab findings	Normal CBC, ESR, CRP	Abnormal CBC, raised ESR and CRP
Radiographic findings	Normal	Effusion, osteopenia, radiolucent metaphyseal lines, joint space loss, bony destruction

CBC, complete blood count; CRP, C-reactive protein level; ESR, erythrocyte sedimentation rate.
*Cancer pain is often severe and worst at night.
Adapted from Malleson PN, Beauchamp RD: Diagnosing musculoskeletal pain in children. CMAJ *165:183–188, 2001.*

Table 168-2 Common Musculoskeletal Pain Syndromes in Children by Anatomic Region

ANATOMICAL 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 Juvenile fibromyalgia Generalized pain syndrome	

Adapted from Anthony KK, Schanberg LE. Box 1 in assessment and management of pain syndromes and arthritis pain in children and adolescents. Rheum Dis Clin North Am *33:625–660, 2007.*

explained to children and their families to better outline the goals by which treatment success will be measured. Indeed, children and families need to be supported in disengaging from the sole pursuit of pain relief and embracing broader treatment goals of improved functioning.

Recommended treatment modalities typically 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 tricyclic antidepressants (amitriptyline 10-50 mg orally 30 min before bedtime) are indicated for treatment of sleep disturbance; selective serotonin reuptake inhibitors (sertraline 10-20 mg daily) may prove useful in treating symptoms of depression and anxiety if present. Referral for psychological evaluation is warranted if these symptoms do not resolve with initial treatment efforts or if suicidal ideation is present. Cognitive-behavioral and/or other psychotherapeutic interventions are typically 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; additional targets of therapy include sleep hygiene and activity scheduling, all with the goal of restoring normal sleep patterns and activities of daily living. Parent education and involvement in the psychological intervention is 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 child pain, and maladaptive models for pain coping in the family.

COMPLICATIONS AND PROGNOSIS

Musculoskeletal pain syndromes can negatively affect child development and future role functioning. Worsening pain and the associated symptoms of depression and anxiety can lead to substantial school absences, peer isolation, and developmental delays later in adolescence and early adulthood. Specifically, adolescents with 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 musculoskeletal pain syndromes experience this degree of impairment and the likelihood of positive health outcomes is increased with multidisciplinary treatment.

168.1 Growing Pains

Kelly K. Anthony and Laura E. Schanberg

More appropriately termed **benign nocturnal pains of childhood** growing pains affect 10-20% of children, with a peak age incidence between 4 and 12 yr. Pain does not occur during periods of rapid growth or at growth sites. The most common cause of recurrent musculoskeletal pain in children, growing pains are intermittent and bilateral, predominantly affecting the anterior thigh, shin, and calf but not joints. Occasionally there may be bilateral upper extremity pain associated with leg pain; isolated upper extremity pain does not occur. Children most commonly describe cramping or aching that occurs in the late afternoon or evening. Pain may wake the child from sleep and may last a few minutes to hours, but resolves quickly with massage or analgesics; pain is never present the following morning (Table 168-3). Pain often follows a day with exercise or other physical activities. Physical findings are normal, and gait is not impaired. Growing pains are generally considered a benign, time-limited condition; there is evidence suggesting that growing pains represent a pain amplification syndrome. Indeed, growing pains persist in a significant percentage of children, with some children developing other pain syndromes such as abdominal pain and headaches. Growing pains are more likely to persist in children with a parent who has a history of a pain syndrome and in children who have lower pain thresholds. Treatment should also focus on reassurance, education, and healthy sleep hygiene. Massage

Table 168-3 Definition of "Growing Pains"

	INCLUSIONS	EXCLUSIONS
Nature of pain	Intermittent; some pain-free days and nights, deep aching, cramping	Persistent; increasing intensity, pain during the day
Unilateral or bilateral	Bilateral	Unilateral
Location of pain	Anterior thigh, calf, posterior knee—in muscles	Articular, back, or groin pain
Onset of pain	Late afternoon or evening	Pain still present next morning
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, C-reactive protein, abnormal complete blood count, radiography, bone scan or MRI

From Evans AM, Scutter SD: Prevalence of "growing pains" in young children, J Pediatr 145:255–258, 2004.

during the episode is very effective, and nonsteroidal antiinflammatory drugs agents may be useful for frequent episodes.

Restless leg syndrome, seen more commonly among adults, is a sensorimotor disturbance that may be confused with growing pains (see Chapter 19). Restless leg syndrome is a difficult to control urge to move the leg that is exacerbated during rest and at night and is relieved by movement.

168.2 Small Fiber Polyneuropathy

Kelly K. Anthony and Laura E. Schanberg

Many patients with juvenile onset widespread pain syndromes, as well as patients with pediatric fibromyalgia (see Chapter 168.3), complex regional pain syndrome type I (see Chapter 168.4), and erythromelalgia 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. Fibromyalgia (see Chapter 168.3) includes chronic widespread pain defined as ≥3 mo duration of axial pain that is often bilateral and also affects the upper and lower extremities. In addition, many patients have associated chronic cardiovascular (dizziness, postural orthostasis syndrome) symptoms, as well as chronic abdominal pain and ileus, headaches, fatigue and erythromelalgia, suggestive of dysautonomia.

There are no typical findings on physical exam or standard laboratory tests. The diagnosis of small fiber polyneuropathy requires distal leg skin immunolabeled biopsy to identify epidermal nociceptive fibers and autonomic function testing to examine cardiovagal, adrenergic, and sudomotor small fiber function.

Treatment of patients with small fiber polyneuropathy and isolated juvenile-onset widespread pain syndrome, or those subsets of patients with small fiber polyneuropathy and fibromyalgia, complex regional pain syndrome, or erythromelalgia is evolving and has included prednisone or intravenous immunoglobulin.

Bibliography is available at Expert Consult.

168.3 Fibromyalgia

Kelly K. Anthony and Laura E. Schanberg

Juvenile primary fibromyalgia syndrome (JPFS) is a common pediatric musculoskeletal pain syndrome. Approximately 25-40% of children with chronic pain syndromes can be diagnosed with JPFS. Although specific diagnostic criteria for JPFS have not been determined, children and adolescents with JPFS have diffuse, multifocal, waxing and waning, and at times migratory musculoskeletal pain in at least 3 areas of the body that persists for at least 3 mo in the absence of an underlying condition. Results of laboratory tests are normal, and physical examination reveals at least 5 well-defined tender points (Fig. 168-1). Children and adolescents with JPFS also present with many associated symptoms, including nonrestorative sleep, fatigue, paresthesias, chronic anxiety or tension, chronic headaches, subjective soft-tissue swelling, and pain modulated by physical activity, weather, and anxiety or stress. There is considerable overlap among symptoms associated with JPFS and complaints associated with other **functional disorders** (e.g., irritable bowel disease, migraines, temporomandibular joint disorder, premenstrual syndrome, mood and anxiety disorders, and chronic fatigue syndrome), raising speculation that these disorders may be part of a larger spectrum of related syndromes.

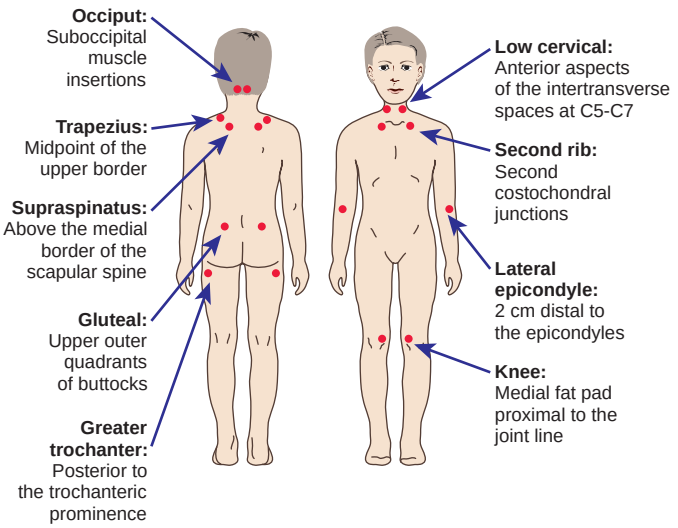


Figure 168-1 Fibromyalgia tender points.

Although the precise cause of JPFS is unknown, there is an emerging understanding that the development and maintenance of JPFS are related both to biologic and psychological factors. JPFS is an abnormality of central pain processing characterized by disordered sleep physiology, enhanced pain perception with abnormal levels of substance P in cerebrospinal fluid, disordered mood, and dysregulation of hypothalamic–pituitary–adrenal and other neuroendocrine axes resulting in lower tender-point pain thresholds and increased pain sensitivity. Children and adolescents with fibromyalgia often find themselves in a vicious cycle of pain, whereby symptoms build upon one another and contribute to the onset and maintenance of new symptoms (Fig. 168-2).

JPFS has a chronic course that can detrimentally affect child health and development. Adolescents with JPFS who do not receive

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Figure 168-2 Vicious cycle promoting juvenile primary fibromyalgia syndrome symptom maintenance. *(Adapted from Anthony KK, Schanberg LE. Juvenile primary fibromyalgia syndrome.* Curr Rheumatol Rep *3:167–171, 2001, Fig. 1.)*

treatment or are inadequately treated may withdraw from school and the social milieu, complicating their transition to adulthood. Treatment of JPFS generally follows consensus statements of the American Pain Society. The major goals are to restore function and alleviate pain, as well as improve comorbid mood and sleep disorders. Treatment strategies include parent/child education, pharmacologic interventions, exercise-based interventions, and psychological interventions. Graduated aerobic exercise is the recommended exercise-based intervention, whereas psychological interventions should include training in pain coping skills, stress management skills, emotional support, and sleep hygiene. Cognitive-behavioral interventions are particularly effective in reducing symptoms of depression in children and adolescents with JPFS and also help to reduce functional disability. Drug therapies, although largely unsuccessful in isolation, may include tricyclic antidepressants (amitriptyline 10-50 mg orally 30 min before bedtime), selective serotonin reuptake inhibitors (sertraline 10-20 mg daily), and anticonvulsants. Pregabalin and duloxetine hydrochloride are approved by the FDA for treatment of fibromyalgia in adults (18 yr of age and older), but neither has been studied in children. Muscle relaxants are generally not used in children because they affect school performance.

Evolving evidence suggests that up to 50% of patients with fibromyalgia may have a small fiber polyneuropathy (see Chapter 168.2).

Bibliography is available at Expert Consult.

168.4 Complex Regional Pain Syndrome

Kelly K. Anthony and Laura E. Schanberg

Complex regional pain syndrome (CRPS) is characterized by ongoing burning limb pain that is subsequent to an injury, immobilization, or another noxious event affecting the extremity. CRPS1, formerly called reflex sympathetic dystrophy, has no evidence of nerve injury, whereas CRPS2, formerly called causalgia, follows a prior nerve injury. Key associated features are pain disproportionate to the inciting event, persisting **allodynia** (a heightened pain response to normally non-noxious stimuli), **hyperalgesia** (exaggerated pain reactivity to noxious stimuli), swelling of distal extremities, and indicators of **autonomic dysfunction** (i.e., cyanosis, mottling, and hyperhidrosis) (Table 168-4).

The diagnosis requires the following: an initiating noxious event or immobilization; continued pain, allodynia, and hyperalgesia out of proportion to the inciting event; evidence of edema, skin blood flow

Table 168-4 Diagnostic Criteria for Complex Regional Pain Syndrome*

NEUROPATHIC DESCRIPTORS	AUTONOMIC DYSFUNCTION
Burning	Cyanosis
Dysesthesia	Mottling
Paresthesia	Hyperhidrosis
Allodynia	Coolness (≥3°)
Cold hyperalgesia	Edema

*A diagnosis of CRPS requires regional pain, sensory symptoms, plus 2 neuropathic pain descriptors and 2 physical signs of autonomic dysfunction.
Data from Wilder RT, Berde CB, Wolohan, M, et al. Reflex sympathetic dystrophy in children: clinical characteristics and follow-up of seventy patients. J Bone Joint Surg Am *74: 910–919, 1992.*

abnormalities, or sudomotor activity; and exclusion of other disorders. Associated features include atrophy of hair or nails; altered hair growth; loss of joint mobility; weakness, tremor, dystonia; and sympathetically maintained pain.

Although the majority of pediatric patients with CRPS present with a history of minor trauma or repeated stress injury (e.g., caused by competitive sports), a sizeable proportion are unable to identify a precipitating event. Usual age of onset is between 8 and 16 yr, and girls outnumber boys 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 commonly affected. The incidence of CRPS in children is unknown, largely because it is often undiagnosed or diagnosed late, with the diagnosis frequently delayed by nearly a year. Left untreated, CRPS can have severe consequences for children including bone demineralization, muscle wasting, and joint contractures.

An evidence-based approach to the treatment of CRPS continues to suggest a multistage treatment approach. Aggressive physical therapy should be initiated as soon as the diagnosis is made and cognitive-behavioral interventions (CBT) added as needed. Physical therapy (PT) is recommended 3-4 times per week, and children may need analgesic premedication at the onset, particularly prior to 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. Sympathetic and epidural nerve blocks should be attempted only under the auspices of a pediatric pain specialist. The intent of both pharmacologic and adjunctive treatments for CRPS is to provide sufficient pain relief to allow the child to participate in aggressive physical rehabilitation. If CRPS is identified and treated early, the majority of children and adolescents with the disease can be treated successfully with low-dose amitriptyline (10-50 mg orally 30 min prior to bedtime), aggressive PT, and CBT interventions. Opioids and anticonvulsants such as gabapentin can also be helpful. Notably, multiple studies have shown noninvasive treatments, particularly PT and CBT, are at least as efficacious as nerve blocks in helping children with CRPS achieve resolution of their symptoms.

There is growing evidence that some patients with CRPS I have a small fiber polyneuropathy (see Chapter 168.2).

Bibliography is available at Expert Consult.

168.5 Erythromelalgia

Laura E. Schanberg

Children with **erythromelalgia** experience episodes of intense pain, erythema, and heat in their hands and feet (Fig. 168-3). Less commonly involved are the face, ears, or knees. Symptoms may be triggered by exercise and exposure to heat, lasting for hours and occasionally for days. It is more common in girls and in the teenage years and diagnosis is often delayed for years. Although most cases are sporadic, an

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Figure 168-3 Typical redness and edema of the foot in 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 *19:49-52, 2009, Fig. 1A, p. 50.)*

autosomal dominant hereditary form results from mutations of the SCN9A gene on chromosome 2q31-32, causing a painful channelopathy. Secondary erythromelalgia is associated with an array of disorders, including myeloproliferative diseases, peripheral neuropathy, frostbite, hypertension, and rheumatic disease. Treatment includes avoidance of heat exposure as well as other precipitating situations and the utilization of cooling techniques that do not cause tissue damage during attacks. Nonsteroidal antiinflammatories, narcotics, anesthetic agents (lidocaine patch), anticonvulsants (oxcarbazepine, carbamazepine, gabapentin), and antidepressants, as well as biofeedback and hypnosis may be useful in helping manage pain. Drugs acting on the vascular system (aspirin, sodium nitroprusside, magnesium, misoprostol) may also be somewhat effective. However, a reliably efficacious treatment is not available, resulting in substantial negative impact on physical and mental health.

There is growing evidence that some patients with erythromelalgia have a small fiber polyneuropathy (see Chapter 168.2).

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Chapter 169

Miscellaneous Conditions Associated with Arthritis

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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 due to inflammation near the auditory and vestibular nerves. Children may initially relate episodes of intense erythema over the outer ears. Other dermatologic manifestations such as erythema nodosum, maculopapular rash and purpura may be seen. 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 169-1). 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 commonly in the adult population, RP may coexist with other inflammatory diseases, such as systemic lupus erythematosus, Sjögren syndrome, and Henoch-Schönlein purpura. The differential diagnosis includes antineutrophilic cytoplasmic antibody–associated vasculitis (granulomatosis with polyangiitis) (see Chapter 167.4) and Cogan syndrome, which is characterized by auditory nerve inflammation and keratitis but not chondritis. Many children respond to nonsteroidal antiinflammatory drugs, but some require corticosteroids or other immunosuppressive agents (azathioprine, methotrexate, hydroxychloroquine, colchicine, cyclophosphamide, cyclosporine, and anti–tumor necrosis factor agents), as reported in small series and case reports.

Table 169-1 Empiric Diagnostic Criteria for Relapsing Polychondritis*

MAJOR CRITERIA
Proven inflammatory episodes involving auricular cartilage
Proven inflammatory episodes involving nasal cartilage
Proven inflammatory episodes involving laryngotracheal cartilage
MINOR CRITERIA
Ocular inflammation (conjunctivitis, keratitis, episcleritis, uveitis)
Hearing loss
Vestibular dysfunction
Seronegative inflammatory arthritis

*The diagnosis is established by the presence of 2 major criteria or of 1 major and 2 minor criteria. Histologic examination of affected cartilage is not required.

From Michet CJ Jr, McKenna CH, Luthra HS, et al: Relapsing polychondritis: survival and predictive role of early disease manifestations, Ann Intern Med *104:74–78, 1986.*

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. Different stages of development are usually seen at once. **PLEVA fulminans** or **febrile ulceronecrotic Mucha-Habermann disease** is the severe, life-threatening form of PLEVA. Large coalescing ulceronecrotic lesions are seen, and are accompanied by high fever and an elevated erythrocyte sedimentation rate. Systemic manifestations can include interstitial pneumonitis, abdominal pain, malabsorption, arthritis, and neurologic manifestations. There is a male predominance and it occurs more frequently in childhood. The diagnosis is confirmed by biopsy of skin lesions that reveal perivascular and intramural lymphocytic inflammation affecting capillaries and venules in the upper dermis that may lead to keratinocyte necrosis. 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–tumor necrosis factor agents have 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

Table 169-2 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 (100.4°F)
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 (3 of 4): 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 2 major criteria plus 2 of the 4 minor criteria.

From Cohen PR: Sweet's syndrome—a comprehensive review of an acute febrile neutrophilic dermatosis, Orphanet J Rare Dis *2:34, 2007.*

face, extremities, and trunk. Skin biopsy reveals neutrophilic perivascular infiltration in the upper dermis. Female predominance is seen in the adult population, whereas in children, gender distribution is equal. Established criteria are useful for diagnosis (Table 169-2). Children can also have arthritis, sterile osteomyelitis, myositis, and other extracutaneous manifestations. The syndrome may be idiopathic or secondary to malignancy (particularly acute myelogenous leukemia), drugs (granulocyte colony-stimulating factor), or rheumatic diseases (Behçet disease, antiphospholipid antibody syndrome, systemic lupus erythematosus). The condition usually responds to treatment with corticosteroids.

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 children with chronic pulmonary disease (cystic fibrosis), congenital heart disease, gastrointestinal disease (malabsorption syndromes, biliary atresia, inflammatory bowel disease), and malignancies (nasopharyngeal sarcoma, osteosarcoma, Hodgkin disease). HOA may precede diagnosis of cardiopulmonary disease or malignancy. The pathogenesis of HOA is unknown; symptoms often improve if the underlying condition is treated successfully. HOA-related pain can be disabling, and 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.

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 commonly 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 diagnosis difficult. Ultrasound or magnetic resonance imaging can be useful in identifying the foreign body. Removal of the foreign body via 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 either 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 where 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.

Bibliography is available at Expert Consult.

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