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Arthritis in Children and Adolescents

Janice John, DO, MS,
MPH,* Latha Chandran,
MD, MPH*

Objectives   After reading this article, readers should be able to:

1. Identify the common causes of arthritis in children.
2. Develop a broad differential diagnosis for arthritis in the pediatric population.
3. Distinguish toxic synovitis from septic arthritis.
4. Recognize and manage a patient with septic arthritis.
5. Discuss the diagnostic and treatment approaches to reactive arthritis, acute rheumatic fever, Lyme arthritis, toxic synovitis, and juvenile idiopathic arthritis.

Introduction

Arthritis is simply defined as inflammation of a joint. Arthritis may affect one or more joints and often is accompanied by swelling, redness, tenderness, warmth, and pain with movement. The pathophysiology of this inflammatory process varies depending on the underlying cause of arthritis. Monoarthritis is inflammation limited to one joint. In the context of juvenile idiopathic arthritis (JIA), oligoarthritis is defined as arthritis involving fewer than five joints, whereas polyarthritis is arthritis of five or more joints. Although there is a broad differential diagnosis, a thorough history and physical examination should provide sufficient information to direct the evaluation and management of the patient with arthritis. An overview of pediatric arthritis as well as a discussion of the most common causes, evaluation, and treatment is offered in this article.

History and Physical Examination

It is important to differentiate arthralgia from arthritis. Arthralgia is the presence of joint pain without objective signs of inflammation (warmth, erythema, tenderness, and swelling) on physical examination. Several rheumatologic diseases, such as systemic lupus erythematosus, may present with arthralgia early in the course; it is also important to consider viral as well as other causes of arthralgia.

Children who have arthritis may present with pain, limited range of motion, limp, and refusal to use or move the affected joint. Presence of fever, rash, and other constitutional symptoms may suggest an infectious or autoimmune cause. It is important to discern whether the arthritis is migratory and to ascertain the specific joints and number of joints affected. A complete history, including the history of present illness, recent illness, or injury, associated symptoms, prior similar episodes, and prior signs and symptoms, must be elicited. In addition, immunization status and family history of autoimmune disorders must be obtained.

Because the causes of arthritis are varied, patients may present with a multitude of other organ system findings suggestive of the underlying cause. Therefore, a comprehensive physical examination is necessary. A toxic or ill appearance may suggest a serious disorder such as pyogenic arthritis. Signs of concurrent upper respiratory infection such as rhinorrhea or pharyngitis may be present in patients who have toxic synovitis. In sexually active patients, reactive arthritis and gonococcal arthritis may occur; hence, a thorough genital and pelvic examination is necessary to evaluate for

Abbreviations

ANA:	antinuclear antibody
ARF:	acute rheumatic fever
CRP:	C-reactive protein
ESR:	erythrocyte sedimentation rate
FDA:	Food and Drug Administration
GAS:	group A *Streptococcus*
HLA:	human leukocyte antigen
Ig:	immune globulin
JIA:	juvenile idiopathic arthritis
MRI:	magnetic resonance imaging
NSAIDs:	nonsteroidal anti-inflammatory drugs
RF:	rheumatoid factor
SCFE:	slipped capital femoral epiphysis

*Department of Pediatrics, Stony Brook University School of Medicine, Stony Brook, NY.

Table 1. **Common Conditions Causing Arthritis and Associated Additional Physical Findings**

Underlying condition	Physical examination findings associated with the arthritis
Disseminated gonorrhea	Fever, new heart murmur (in endocarditis), tenosynovitis, urethral discharge, cervicitis, genital lesions, oral or other lesions, meningismus, impaired mental status, and a maculopapular, pustular, necrotic, vesicular rash
Juvenile idiopathic arthritis	Fever, uveitis, pericardial rub, lung fields dull to percussion, decreased pulmonary aeration, hepatomegaly, splenomegaly, salmon patch (evanescent, maculopapular, linear rash prominent when febrile)
Late Lyme disease	Fever, Bell palsy, other cranial nerve palsies, mild meningismus
Reactive arthritis	Fever, conjunctivitis, uveitis, episcleritis, keratitis, corneal ulcerations, axial spine tenderness, enthesitis (especially of the plantar aponeurosis and Achilles tendon), dactylitis, urethritis, cervicitis, salpingitis, vulvovaginitis, small shallow penile ulcers (balanitis circinata), pustules that coalesce into psoriatic–like plaques (keratoderma blennorrhagica)
Rheumatic fever	Fever, ill appearance, pericardial rub, new heart murmur, erythema marginatum, subcutaneous nodules (wrist, elbow, knees), choreiform movements
Septic arthritis	Ill appearance, fever, refusal to bear weight, pseudoparalysis
Systemic lupus *erythematosus*	Fever, pallor, pericardial rub, lung fields dull to percussion, decreased aeration, ulcerations, malar rash, discoid rash, other rashes, psychosis
Toxic synovitis	Low grade fever, rhinorrhea, pharyngitis

urethritis or cervicitis. The presence of a rash or a typical lesion may be suggestive of a specific disorder. Table 1 lists several disease processes that present with arthritis and their additional physical findings that may be helpful in narrowing the broad differential diagnoses.

On physical examination, the joints must be evaluated for crepitus, warmth, tenderness, swelling, joint effusion, erythema, contractures, or decreased range of motion. The patient's preferred position at rest must be observed. The joints should be tested for passive and active range of motion. Examination of the contralateral joints is important for comparison purposes. The patient's gait should be observed carefully.

Differential Diagnosis of Arthritis/Limping

Commonly encountered causes of arthritis in children include septic arthritis, reactive arthritis, acute rheumatic fever (ARF), Lyme arthritis, toxic synovitis, and JIA. Arthritis may occur in patients afflicted with inflammatory bowel disease, systemic lupus erythematosus, Henoch-Schönlein purpura, Kawasaki disease, sarcoidosis, and other autoimmune and connective tissue disorders. Patients who have arthritis affecting the lower extremities often present with a limp. In a limping child, orthopedic processes such as trauma, slipped capital femoral epiphysis (SCFE), Legg-Calvé-Perthes disease, enthesitis (inflammation of the enthesis, the point at which ligaments, tendons, and fascia attach to bone), and overuse injuries such as Osgood-Schlatter disease must be considered. Leukemia, lymphoma, bone and other soft tissue masses, neuroblastoma, hemarthrosis and sickle cell crisis may present with limping as well. Other infectious causes such as osteomyelitis or a psoas muscle abscess also must be considered in a febrile limping child. Because the differential diagnosis for arthritis is extensive, this article will focus on a few common conditions that affect children and adolescents.

Septic Arthritis

Septic arthritis, also known as pyogenic arthritis, occurs when there is bacterial invasion of the synovium and joint space followed by an inflammatory process. In the pediatric population, the incidence of septic arthritis peaks between 2 and 3 years of age and has a male predominance (2:1). Except in the neonatal population, *Staphylococcus aureus* is the most common pathogen implicated in pediatric septic arthritis. The most common pathogens that cause septic arthritis in neonates are group B *Streptococcus*, *Staphyloccus aureus*, and gram-negative bacilli. Other common pathogens causing pyogenic arthritis in childhood include *Streptococcus pyogenes* and *S pneumoniae*. *Kingella kingae* is isolated in young children who have a recent history of upper respiratory infection. Because of widespread immunization in the United States, *Haemophilus influenzae* is no longer a frequent pathogen causing septic arthritis. However, the incidence of community acquired methicillin-resistant *Staphylococcus aureus* in cases of musculoskeletal infec-

Table 2. Pathogens and Antimicrobials in Septic Arthritis Based on Age Group/Risk Factors

Population/Pattern	Organism(s)	Empiric Treatment
Neonate	Group B *Streptococcus, Staphylococcus aureus (MSSA, MRSA), Escherichia coli*, and other enteric gram–negative organisms	Nafcillin or oxacillin OR Vancomycin or clindamycin PLUS Cefotaxime or gentamicin
If premature or exposed to broad spectrum antibiotics, intravenous alimentation, intravascular catheter	*Candida albicans*	Amphotericin B ± Fluconazole
Children younger than 5 y	*S. aureus (MSSA, MRSA), Kingella kingae, Streptococcus pyogenes, Streptococcus pneumoniae, Haemophilus influenza type b (rare if immunized)*	Nafcillin or oxacillin OR Vancomycin or clindamycin if MRSA suspected PLUS third–generation cephalosporin
Children older than 5 y	*S. aureus* and *S. pyogenes*	Nafcillin or oxacillin OR Vancomycin or clindamycin if MRSA suspected
History of intravenous drug use	*Pseudomonas aeruginosa* *Candida spp.*	Antipseudomonal cephalosporin ± aminoglycoside Amphotericin B ± fluconazole
Preceding upper respiratory infection	*Haemophilus influenzae type b (rare if immunized), Kingella kingae*	Nafcillin or oxacillin PLUS third generation cephalosporin
Sickle cell anemia	*Salmonella spp.*	Cefotaxime or ceftriaxone
History of sexual activity	*Neisseria gonorrhoeae*	Ceftriaxone
Contact with livestock Ingestion of unpasteurized dairy products or travel to endemic area	*Brucella spp.*	Doxycycline or TMP-SMZ PLUS gentamicin PLUS Rifampin

Antibiotic choices, dosing, and duration of therapy should be confirmed because each clinical situation is unique and practice standards may change with time. MRSA=methicillin-resistant *Staphylococcus aureus*; MSSA=methicillin-sensitive *Staphylococcus aureus*; TMP-SMZ=trimethoprim-sulfamethoxazole.

tion, including septic arthritis, has been increasing. Other pathogens to consider when more than one joint is involved include *Neisseria gonorrhoeae, N meningitidis,* and *Salmonella* species. Table 2 details some common causes of pyogenic arthritis in specific populations and presents treatment options.

Because the synovial membrane is vascular in nature, hematogenous seeding of bacteria is the most common mechanism of infection in septic arthritis. Alternatively, septic arthritis may result from the spread of an adjacent osteomyelitis or other infection. The hip and shoulder are particularly vulnerable to contiguous spread. Besides hematogenous and contiguous spread, it is important to consider trauma, instrumentation, and intra-articular injections as potential precursors to arthritis.

Patients present often with localized symptoms such as pain, swelling, limp, and refusal to ambulate or to move the affected area (pseudoparalysis). Generalized symptoms such as fever, malaise, fussiness, and decreased appetite are other common manifestations of septic arthritis. The joints of the lower extremities (hips, knees, and ankles) are affected in the vast majority of cases, with the knee being the most commonly affected joint. (1)(2) The patient often is febrile with signs of inflammation and limited range of motion of the affected joint. Patients position the affected limb to optimize intracapsular volume and minimize pain. Therefore, it is important to note the patient's position at rest. Individuals who have septic arthritis of the knee tend to keep the affected knee moderately flexed. Those with septic arthritis of the hip keep the hips flexed, externally rotated, and abducted. (2)

Table 3. **Characteristics of Pyogenic Arthritis, Toxic Synovitis, and Lyme Arthritis**

Feature	Pyogenic Arthritis	Toxic Synovitis	Lyme Arthritis
Clinical			
General Appearance	Generally ill appearing	Generally well appearing	Generally well appearing
Fever	Usually present	Low-grade or absent	Low-grade or absent
Limp	Yes, if affecting lower extremity	Often	Possible
Range of Motion	Markedly decreased	Slightly decreased, limited by pain	Decreased, depending on extent of effusion
Laboratory			
Serum WBC count	Elevated with left shift	Usually normal	Usually normal
ESR	Elevated (usually >40 mm/h)	Normal to mildly elevated (<40 mm/h)	Elevated
CRP	Greater than 1 mg/dL (modest to significant increase)	Less than 1 mg/dL	Greater than 1 mg/dL (modest increase)
Synovial Fluid Results			
Color	Yellow, white, gray	Yellow	Xanthochromic, white
WBC (WBC/mm^3)	>50,000	5,000–15,000	~25,000 (wide range reported)
Culture	Positive 50%–80% of the time	Negative	Negative
Imaging			
Plain radiograph	Early soft tissue swelling, subchondral bony changes (2–4 wk later), obliteration or lateral displacement of the gluteal fat planes and capsular swelling	Usually normal	Usually normal, soft tissue swelling
Ultrasonography	Joint effusion always present	Joint effusion may be present but small	Joint effusion often present
MRI	Abnormalities of soft tissue, bone, and cartilage damage. Low signal on T1 weighted and a high signal on T2 weighted	Normal or thickening of the articular surface	Often normal, limited data

CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; MRI=magnetic resonance imaging; WBC=white blood cell.

Laboratory Testing

Arthrocentesis is mandatory for any patient in whom septic arthritis is considered strongly. Arthrocentesis can serve both diagnostic and therapeutic purposes. Laboratory tests most useful in diagnosing pyogenic arthritis are culture, Gram stain, and white blood cell counts of the synovial fluid (Table 3). Synovial fluid cultures are positive in 70% to 80% of cases; (3) however, a negative culture does not exclude the diagnosis of pyogenic arthritis. A complete blood count may indicate leukocytosis with a left shift. A blood culture may be positive in approximately one third of septic arthritis cases. Elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) concentration also are supportive of this diagnosis. If *N. gonorrhoeae* is suspected in sexually active patients, pelvic, urethral, throat, skin, and rectal cultures should be obtained.

Imaging

Plain radiographs in patients who have septic arthritis may reveal widened joint spaces or bulging of the soft tissues. Soft tissue swelling may be identified in radiographs as early as 48 hours into the infection. Plain radiographs also may reveal subchondral bony changes after 2 weeks of onset of the illness. (4) It is important to bear in mind that a normal plain radiograph does not rule out a pyogenic joint. Ultrasonography is a fast and non-invasive test that is useful in identifying and quantifying the joint effusion, as well as aiding in needle aspiration of the joint. In contrast to plain radiographs, magnetic resonance imaging (MRI) with gadolinium contrast is more sensitive for early detection of a septic joint. Because MRI gives reliable soft tissue and bone contrast, this modality is effective in identifying cartilaginous involvement. MRI may reveal abnormalities in surround-

ing soft tissue and bone and delineate the extent of cartilaginous damage. A low signal on T1 weighted studies and a high signal on T2 weighted studies are indicative of active inflammatory or infectious processes. (4) Making the diagnosis of septic arthritis requires a high degree of suspicion while evaluating the constellation of symptoms, physical findings, and laboratory and imaging results.

Septic Arthritis in Neonates and Infants

Clinically, septic arthritis is more challenging to diagnose in neonates, infants, and young children. Because neonates and infants have less mature inflammatory and immune responses, they may present with only vague symptoms. There may be no obvious joint involvement or fever. Pseudoparalysis is observed often. The hip is the most common joint affected in the neonatal population. (2) Infants have a higher rate of coexisting osteomyelitis and septic arthritis because the spread of infection from the metaphysis to the joint space is enhanced by the unique transphyseal vasculature in this age group. (4) Unique risk factors predisposing patients in this age group to the development of septic arthritis include a history of urinary infection, prematurity, and umbilical catheterization. (4) Young infants may not show an elevation in inflammatory markers such as white blood cells, ESR, and CRP. Due to the decreased overall muscle tone in neonates, widening of the hip space may lead to upward displacement or lateral subluxation of the femoral head being evident on plain radiograph. (4)

Treatment

Ideally, empiric antimicrobial therapy should be initiated promptly after joint aspiration is completed and cultures are obtained. However, antibiotic therapy should not be delayed while waiting for arthrocentesis. Immediate aspiration of the synovial fluid is essential to decompress the intracapsular space, remove infected fluid, and provide specimens for Gram stain, cell count, and culture. Although some patients respond well to needle aspiration and antibiotics, specific joints such as the hips and shoulder require open drainage. Many cases necessitate repeat needle aspiration, arthroscopic drainage, or even arthrotomy.

Age, risk factors, and Gram stain (when positive) should direct initial antibiotic choice. Ultimately, positive synovial fluid or other culture and sensitivity results (as from blood, cerebrospinal fluid, cervix, and urethra) should dictate antibiotic selection. Antibiotics generally are administered for 2 to 6 weeks, depending on the organism and clinical resolution of signs and symptoms.

However, it is important that parenteral antibiotic therapy be administered at least for the first week. A downward trend in ESR and CRP concentrations is reassuring evidence of the effectiveness of ongoing therapy in reducing inflammation. When patients are not improving clinically, additional or alternate antibiotic regimens should be considered. Especially in community acquired methicillin-resistant *Staphylococcus aureus* infection, input from infectious disease specialists must be obtained to tailor therapy specifically to the results of local antibiotic susceptibility testing. Ultimately, the management of a pediatric patient who has septic arthritis is accomplished best by using a multidisciplinary approach with input from the orthopedic surgeon and the infectious disease specialist.

Complications and Pitfalls

Pyogenic arthritis affecting the hip is particularly challenging to diagnose because frequently there is no apparent joint swelling. However, it is critical to make a timely diagnosis of septic arthritis, especially of the hip, because pressure on the precarious vascular supply to the femoral head makes it susceptible to long-term sequelae such as avascular necrosis, limb length disparities, pseudarthrosis (false joint), joint dislocations, and other bony or joint deformities. (4) Risk factors for long-term complications include age younger than 6 months, concomitant osteomyelitis, involvement of high risk joints such as the hip or shoulder, and delay in appropriate initial management (decompression and initiation of antibiotics) by 4 days or longer. (1)

Reactive Arthritis

Reactive arthritis is a type of arthritis associated with an infection at a distant site, distinct from that of the affected joints. Reactive arthritis is more common in the adult population than in children. However, it is an important entity to consider, particularly in adolescence. There is a 3:1 male predominance. Male patients and those who are human leukocyte antigen-B27 (HLA-B27) positive tend to have more severe disease. The pathogenesis of reactive arthritis is understood poorly. Although commonly associated with sexually transmitted pathogens such as *Chlamydia trachomatis* and *N gonorrhoeae,* reactive arthritis can be associated with other genitourinary, gastrointestinal, and upper respiratory pathogens. The most common pathogen associated with reactive arthritis in the United States is *Chlamydia trachomatis.* Gastrointestinal infections caused by *Shigella* species, *Salmonella* species, *Yersinia* species, or *Campylobacter* species potentially can lead to

Table 4. Treatment Approach to Common Causes of Pediatric Arthritis

Disease Process	General Treatment Approach
Septic arthritis	• Arthrocentesis/drainage • Obtain cultures • Immediate administration of antibiotics
Reactive arthritis	• Supportive care: NSAIDs, cold packs, rest • Antibiotics and treatment of sexual partners when indicated • Chronic reactive arthritis: possible DMARDS
Rheumatic fever	• Penicillin • Anti-inflammatory drugs • Cardiac medications if indicated • Medications to control chorea if needed • Rest • Antibiotic prophylaxis
Lyme arthritis	• First line: doxycycline or amoxicillin • Second line: ceftriaxone
Toxic synovitis	• Supportive care: rest, NSAIDs
Juvenile idiopathic arthritis	• NSAIDs • Local and systemic steroids (selective cases) • DMARDs • Biologics

DMARD=disease-modifying antirheumatic drug; NSAID=nonsteroidal anti-inflamatory drug.

reactive arthritis. Among respiratory pathogens, *S pyogenes* has been known to cause reactive arthritis. *N meningitidis* can be associated with reactive arthritis as well.

Clinically, patients who have reactive arthritis present with monoarthritis or oligoarthritis, frequently accompanied by other musculoskeletal inflammatory changes, as well as ophthalmologic, dermatologic, and genitourinary changes. One well-known presentation of reactive arthritis (previously known as Reiter syndrome) is the triad of arthritis, urethritis, and bilateral mucopurulent conjunctivitis. Other manifestations include pain, enthesitis, dactylitis, urinary symptoms, urethral discharge, cervicitis, uveitis, photophobia, and skin findings. In the presence of HLA-B27, reactive arthritis typically presents with calcaneal and plantar pain and

tenderness. Systemic symptoms that can accompany reactive arthritis include arthralgia, fever, weight loss, and malaise. Reactive arthritis is asymmetric and often involves large joints such as the knee, hip, ankle, and sacroiliac joint. The joints of the lower extremity are implicated more often than those of the upper extremities. Symptoms start from a few days to 6 weeks after infection.

According to one study, reactive arthritis should be diagnosed clinically based on two major criteria: 1) the presence of mono or oligoarthritis of the lower extremities, and 2) exclusion of other causes of arthritis, such as septic arthritis, Lyme arthritis, ARF, and trauma. (5) If both criteria have been met in a patient who has a history of preceding *Chlamydia* infection, the diagnosis of reactive arthritis is highly probable (up to 90%). If both criteria have been met, and the patient has a positive stool culture, the diagnosis of reactive arthritis is highly probable also (up to 70%). (5) Because reactive arthritis can be triggered by a multitude of pathogens, there is no single gold standard diagnostic test. However, this diagnosis is supported by an elevated ESR and CRP concentration or positive urine, cervical, or urethral culture for *C. trachomatis.* Synovial fluid tests can be helpful in excluding other disease processes. HLA-B27 positivity is supportive of the diagnosis of reactive arthritis in a patient who has a consistent history and physical findings. Antinuclear antibody (ANA) and rheumatoid factor (RF) should be considered in a patient who has a history or physical finding consistent with an autoimmune process. Imaging studies often are normal, but should be obtained particularly if other disorders such as pyogenic arthritis or osteomyelitis are considered.

Treatment is primarily supportive and involves giving nonsteroidal anti-inflammatory drugs (NSAIDs), local cold treatment, and avoidance of overuse of the affected joints. A positive genitourinary culture requires treatment of the patient and sexual partners with appropriate antibiotics. The beneficial effects of treatment of gastrointestinal infections accompanying reactive arthritis are unclear. Certain musculoskeletal manifestations can be treated with local corticosteroid injections. Symptoms of reactive arthritis may last weeks to months. If the arthritis fails to resolve in 6 months, it is categorized as chronic reactive arthritis. This outcome occurs in approximately 4% to 19% of patients for whom a rheumatology referral is warranted. In this subset, diseases modifying antirheumatic drugs may be used to manage the patient's symptoms. (5)

Acute Rheumatic Fever

ARF is an inflammatory process involving many organ systems precipitated by preceding group A *Streptococcus* (GAS) pharyngitis. In the United States, the incidence of ARF has declined in the past several decades; however, focal outbreaks occur periodically. ARF is diagnosed clinically using the well-established Jones criteria. The major Jones criteria are polyarthritis, carditis, subcutaneous nodules, chorea, and erythema marginatum. Erythema marginatum is a rash that involves the extremities and trunk in a serpiginous fashion with central clearing and salmon-colored margins. The minor criteria are fever, arthralgia, prolonged P-R interval on electrocardiogram, and elevated acute phase reactants. Confirmation of an antecedent GAS infection plus two major criteria or one major and two minor criteria must be fulfilled to make the diagnosis of ARF. Prior GAS infection can be confirmed by positive throat culture, positive rapid streptococcal antigen test, and elevated titers of anti- streptolysin O or other streptococcal antibodies. The arthritis of ARF is a nondeforming migratory polyarthritis usually involving large joints such as the knees, wrists, elbows, or ankles. Most experts recommend a single dose of intramuscular benzathine penicillin G or 10 days of oral penicillin to eliminate any remaining GAS infection regardless of throat culture results. The other mainstays of treatment are anti-inflammatory drugs, restriction of activity, and antibiotic prophylaxis. Antibiotic prophylaxis is critical in the prevention of future streptococcal infections, which potentially may worsen the cardiac disease. The arthritis in ARF tends to be exquisitely responsive to aspirin. In patients afflicted with carditis, cardiology consultation is helpful in determining the role of diuretics (in those who have secondary heart failure) and for the follow-up of potential long-term cardiac sequelae.

Lyme Arthritis

Lyme arthritis is the most common late manifestation of Lyme disease, a tick-borne disease caused by *Borrelia burgdorferi*. Although early Lyme disease tends to occur more in the late spring or early summer, late disease has no true seasonality. The *Borrelia* organisms residing within the digestive tract of the *Ixodes* ticks migrate to the salivary glands after the tick bites and attaches to the victim's skin. Approximately 48 hours post bite, the organisms are transmitted to the bloodstream of the victim. Seeding the synovium hematogenously, the *Borrelia* induces mononuclear cell infiltration and stimulates complement, cytokines, neutrophils, and immune complexes to accumulate within the joint space, leading to inflammation and pain. In contrast to septic arthritis, *B burgdorferi* does not produce proteases that are responsible for rapid joint destruction. (6)

A history of a rash consistent with erythema migrans is supportive but not required for the diagnosis of Lyme arthritis. In about 30% of patients given a diagnosis of Lyme disease, this rash is not identified. (3) Patients may experience migratory arthralgias, myalgias, or fatigue early in the course. Occasionally, patients who have Lyme arthritis have fever or other systemic symptoms. Lyme arthritis usually presents as an asymmetric mono or oligoarticular arthritis. Typically, a single knee joint is affected. However, other joints, such as the shoulder, ankle, elbow, temporomandibular joint, and wrist, are affected commonly. Unlike a patient who has pyogenic arthritis in which pain is severe and constant, the pain of Lyme arthritis waxes and wanes and is of lesser severity. In fact, this joint involvement tends to resemble the symptoms experienced by children who have oligoarticular juvenile arthritis and was misdiagnosed historically as JIA before the epidemiologic and basic science research that elucidated the etiology of Lyme disease. Physical examination reveals a mild to moderately inflamed joint with an effusion. Range of motion is not decreased significantly.

Lyme arthritis occasionally is confused with trauma because it may present with remarkable joint effusion and no fever. Confirmation of *B burgdorferi* infection requires a two-step process. The first step involves a sensitive enzyme immunoassay for serum antibodies. The second step is a confirmatory result on a Western immunoblot for specific bands of antibodies in the immune globulin G (IgG) or IgM classes, depending on the stage of the disease. Synovial fluid testing may reveal a white blood cell count around 21,000 to 24,000 cells/microliter (6) (can vary significantly), with a neutrophil predominance. ESR rates usually are about 20 to 30 mm/hour. Soft tissue changes and joint effusions are noted on imaging studies. However, imaging generally is not helpful.

If treated adequately, early Lyme disease does not progress to arthritis or other manifestations of late disease. Once arthritis develops, generally 28 days of appropriate oral antibiotic therapy is required. Treatment options include doxycycline (for children older than 8 y) 4 mg/kg per day divided in two doses (maximum 100 mg/dose) or amoxicillin 50 mg/kg per day divided in three doses (maximum 500 mg/dose). Cefuroxime 30 mg/kg per day divided in two doses (maximum 500 mg/dose) is the second line treatment. The vast majority of patients respond to a single course of oral

antibiotics. If the patient experiences minimal improvement of symptoms, a second course of oral antibiotics is recommended. In those who exhibit minimal or no response despite an additional 4 weeks of oral antibiotics, parenteral antibiotic therapy for 1 month (usually employing ceftriaxone) is warranted. (6) Adjunctive use of NSAID therapy can be helpful in controlling symptoms of some patients who have Lyme arthritis. If Lyme arthritis is accompanied by neurologic symptoms, disease should be treated as per the management of the neurologic disease. Although the prognosis for those who have Lyme arthritis is good, a small subset of patients has symptoms lasting months to years after given a diagnosis of Lyme disease. Immunogenetic factors have been implicated in the variation of the clinical course of Lyme disease.

Other Infectious Etiologies

Nonbacterial pathogens implicated in arthritis include viruses and fungi. Viral pathogens commonly implicated include rubella, parvovirus B19, arboviruses, and hepatitis B. Other viral pathogens less commonly associated with arthritis are coxsackie, Epstein-Barr, herpes simplex, varicella-zoster, and mumps virus. *Mycobacterium* species, *Candida* species, and other fungi are rare but are potential pathogens that may cause arthritis in children and should be considered, particularly if any risk factors exist.

Toxic Synovitis and Hip Pain

Toxic synovitis, also called acute transient synovitis, is a relatively common cause of sudden onset of hip pain and limping and is frequently considered in the differential diagnosis of septic arthritis of the hip. Hip pain can be due to a variety of disease processes depending on the age and sex. SCFE, Legg-Calvé-Perthes disease, and osteoid-osteoma all can result in significant hip pain. In SCFE, disruption of the proximal femoral growth plate results in varying degrees of displacement of the femoral head. This entity typically presents in the obese peri-pubertal patient, with boys being affected almost twice as often as girls. Legg-Calvé-Perthes disease is an osteonecrosis of the capital femoral epiphysis. This disorder occurs in younger children but with an impressive male predominance (4:1 male-to-female ratio). Often affecting the upper femur, osteoid osteoma may present with hip pain. The pain associated with this benign tumor is localized to the lesion, is worse at night, and often improves with oral salicylates. Osteoid osteoma affects individuals of all ages but occurs most frequently in the second and third decades after birth.

Toxic synovitis is a relatively benign entity that is characterized by inflammation of the synovium, most frequently of the hip joint. Often there is a joint effusion as well. Toxic synovitis commonly affects children 3 to 10 years of age. The male-to-female ratio is about 2:1. The exact pathophysiology of this process is uncertain. However, most children who have toxic synovitis have had a prodrome of upper respiratory or gastrointestinal symptoms or have a concurrent infectious process. This process often presents as an acute onset of hip, thigh, or knee pain or limp. Patients often are not ill appearing and are afebrile, although low-grade fevers may be present. The patient may be uncooperative because of pain when eliciting range of motion of the knee or hip, making the range of motion appear more limited than it actually is. Often there is decreased internal rotation and adduction of the affected hip.

Distinguishing transient synovitis from septic arthritis is critical because clinical presentations may overlap. Often patients who have toxic synovitis are not as irritable or ill appearing, may have bouts of improved pain (in contrast to the constant pain of septic arthritis), and although they may limp, often can bear weight. In one pediatric study, four independent multivariate predictors were found to be useful in distinguishing septic arthritis from toxic synovitis. (7) These variables are a history of fever, inability to bear weight, ESR over 40 mm/hour, and white blood cell count higher than $12,000/mm^3$. Presence of all four variables had a 99.6% predictive probability of septic arthritis. In toxic synovitis, the white count often is normal, with normal to mildly elevated ESR and CRP. Another study revealed a CRP concentration <1.0 mg/dL as an excellent negative predictor for septic arthritis. (8) If clinical presentation and blood tests are reassuring (afebrile, full range of motion in the joint, and low risk ESR, CRP, and white blood cell count), the patient may be watched without further testing. If the clinical picture is not reassuring, a synovial fluid aspirate is required to rule out septic arthritis.

The synovial fluid in toxic synovitis often is yellow and clear or slightly turbid, has a normal to slightly elevated white blood cell count, and usually is small in volume in contrast to septic arthritis. Table 3 compares the clinical features and diagnostic test results of septic arthritis, toxic synovitis, and Lyme arthritis. Synovial fluid testing is by far the most reliable way to distinguish toxic synovitis from septic arthritis, and one should never be reluctant to proceed with hip aspiration if there is any question as to the presence of a septic process. Radiographs may reveal capsular distension, widening of the joint space, and distortion of soft tissue planes. Ultrasonography

and plain radiography may not help differentiate toxic synovitis from septic arthritis because children who have toxic synovitis often have joint effusions. However, MRI may be helpful. MRI usually is normal or may show thickening of the articular surface or joint effusion in toxic synovitis.

The usual treatment for toxic synovitis is anti-inflammatory medication and limitation of activity. Most commonly, symptoms resolve within days; occasionally, it may take up to 2 weeks from the onset of symptoms for the patient to return to baseline. Overall, this condition is self-limited; however, a small percentage experience recurrences. The risk of future development of Legg-Calvé-Perthes disease in those who have a history of toxic synovitis may be slightly higher than in the general population.

Juvenile Idiopathic Arthritis

Previously known as juvenile rheumatoid arthritis, JIA is a term used to label a wide spectrum of arthritides that occur before the age of 16 years, last longer than 6 weeks, and do not fulfill the diagnostic criteria of other known entities. JIA is the most common pediatric rheumatic disease; however, it is a diagnosis of exclusion. Although the pathophysiology is not fully elucidated, evidence suggests an autoimmune process. Both genetic and environmental components have been implicated. For many years, T lymphocytes have been thought to be central to the pathogenesis of JIA. New research reveals that innate immunity, specifically neutrophils, may play additional important roles in this disease process.

The International League of Associations for Rheumatology has classified this heterogeneous group of arthritides into seven subgroups. These groups are oligoarthritis (~40% of cases), RF positive polyarthritis (~5%), RF negative polyarthritis (~20%), systemic arthritis (~10% of cases), enthesitis related arthritis (~5%), psoriatic arthritis (~5%), and undifferentiated arthritis (~15%). Children afflicted with oligoarthritis have arthritis limited to four or fewer joints within the first 6 months of onset of the disease. Iridocyclitis, inflammation of the iris and ciliary body, occurs in about one third of patients who have oligoarthritis and potentially can lead to loss of vision. Typically, patients have asymptomatic iridocyclitis; therefore, regular screening for this condition should be part of their routine care. There is a strong female predominance in those who have oligoarthritis who present at less than 6 years old (early onset). Individuals who have oligoarthritis have a positive ANA about 70% of the time, normal complete blood count results, and normal to mildly elevated acute phase reactants.

RF positive and negative polyarthritis involve a minimum of five joints being affected during the first 6 months after onset. RF positive polyarthritis requires two positive IgM RFs documented at least 3 months apart. Typically, these patients have an insidious onset of inflammation in the small joints of the hands and feet. Both RF positive and negative polyarthritis have a female predominance. A slight elevation in ESR is likely for both groups.

Systemic arthritis is the most serious of the JIA subtypes. This variation classically presents with fever, rash, and arthritis. Frequently evaluated for infectious diseases, these children typically have quotidian spiking high fevers ($\geq39°C$) that defervesce quickly. A salmon-colored migratory rash, typically accentuated by showering, often accompanies this fever. Fever must persist for at least 2 weeks to meet the diagnostic criteria. Fever and rash can precede arthritis by several weeks, making the diagnosis difficult. Contrary to a septic child, children who have systemic arthritis usually are well appearing between their febrile episodes. Although initially the arthritis involves only a few joints, chronic polyarthritis eventually ensues in most cases. Lymphadenopathy, hepatosplenomegaly, and serositis also are potential manifestations of systemic onset JIA. Boys and girls are affected equally. Leukocytosis, anemia, thrombocytosis, and elevated ESR and CRP are supportive laboratory findings. However, these test results, along with the nonspecific initial presentation, may make it challenging to differentiate early systemic arthritis from infectious and malignant causes. Patients who have systemic arthritis are at risk for developing macrophage activation syndrome, which presents with an acute onset of persistent fever, hepatosplenomegaly, neurologic changes, hematologic symptoms, and pancytopenia. This fatal complication requires early diagnosis and aggressive immediate treatment.

Enthesitis-related and psoriatic arthritis have more elaborate criteria than what is mentioned here. However, simply stated, enthesitis-related arthritis is a form of JIA in which patients present with both arthritis and enthesitis; this subtype is most common in boys older than 6 years. Psoriatic arthritis is characterized by the presence of arthritis with psoriasis. Those affected by this subtype of JIA may have chronic and erosive disease, making early aggressive therapy necessary. Patients who have psoriatic arthritis often are ANA positive. Finally, undifferentiated JIA captures those patients who do not meet the criteria of the other subtypes.

An interdisciplinary approach addressing physical and occupational therapy, psychosocial support, and pharmacologic treatments must be utilized for optimum management of JIA. (9) NSAIDs serve as the initial treatment for patients who have JIA. Triamcinolone hexacetonide intra-articular injections may be used in addition to or instead of NSAIDs in patients who have a limited number of affected joints. Rheumatologists may use systemic corticosteroids in specific situations (eg, acute flares); however, corticosteroids are not considered the treatment of choice for long-term management. Methotrexate is used as a second-line agent to treat persistent and active arthritis.

Etanercept and adalimumab are the only anti-tumor necrosis factor agents approved by the Food and Drug Administration (FDA) for use in children over 4 years of age with JIA. (10) Abatacept, an interleukin 6 blocker, is the first of a new class of biologic agents approved for severe polyarticular JIA in children older than 6 years of age. (10) Recent clinical trials suggest other biologics may be effective as well and are used currently by rheumatologists in the treatment of JIA. Other drugs may be beneficial, depending on the JIA subtype and individual patient. Long-term prognosis has been affected favorably by the advances in pharmacologic therapy and better utilization of multidisciplinary teams.

Suggested Reading

Gutierrez K. Bone and joint infections in children. *Pediatr Clin North Am.* 2005;52:779–794, vi

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

Marques AR. Lyme disease: a review. *Curr Allergy Asthma Rep.* 2010;10:13–20

McCarthy JJ, Noonan KJ. Toxic synovitis. *Skeletal Radiol.* 2008; 37:963–965

References

1. Gutierrez KM. Infectious and inflammatory arthritis. In: Long SS, Pickering LK, Prober CG, eds. *Principles and Practice of Pediatric Infectious Diseases, 3rd ed.* Philadelphia: Churchill Livingstone/Elsevier; 2009:484–492

2. Frank G, Mahoney HM, Eppes SC. Musculoskeletal infections in children. *Pediatr Clin North Am.* 2005;52:1083–1106, ix

3. Frank G, Eppes SC. Bone, joint, and soft tissue infections. In: Zaoutis LB, Chiang WV, eds. *Comprehensive Pediatric Hospital Medicine.* Philadelphia: Mosby; 2007

4. Offiah AC. Acute osteomyelitis, septic arthritis and discitis: differences between neonates and older children. *Eur J Radiol.* 2006;60:221–232

5. Sieper J, Rudwaleit M, Braun J, van der Heijde D. Diagnosing reactive arthritis: role of clinical setting in the value of serologic and microbiologic assays. *Arthritis Rheum.* 2002;46:319–327

6. Puius YA, Kalish RA. Lyme arthritis: pathogenesis, clinical presentation, and management. *Infect Dis Clin North Am.* 2008;22: 289–300, vi–vii

7. Kocher MS, Zurakowski D, Kasser JR. Differentiating between septic arthritis and transient synovitis of the hip in children: an evidence-based clinical prediction algorithm. *J Bone Joint Surg Am.* 1999;81:1662–1670

8. Levine MJ, McGuire KJ, McGowan KL, Flynn JM. Assessment of the test characteristics of C-reactive protein for septic arthritis in children. *J Pediatr Orthop.* 2003;23:373–377

9. Ravelli A, Martini A. Juvenile idiopathic arthritis. *The Lancet.* 2007;369:767–778

10. Breda L, Del Torto M, De Sanctis S, Chiarelli F. Biologics in children's autoimmune disorders: efficacy and safety. *Eur J Pediatr.* 2011;170:157

Summary

- Arthritis can be a manifestation of multiple disease processes. Therefore, the clinician must consider a broad differential diagnosis, keeping a high degree of suspicion for diseases that may have serious consequences. Although this article reviews more common disease processes that present with arthritis, it is imperative to think outside of the scope of infectious and musculoskeletal entities and consider autoimmune, oncologic, and other processes as well.
- The diagnostician should use a complete history and physical examination to determine further evaluation. In most cases, the diagnosis can be confirmed by the constellation of supporting historic features, examination findings, and laboratory or imaging results.
- Appropriate diagnosis and management of pediatric arthritis can facilitate prompt recovery and prevent debilitating consequences. Table 4 offers a brief summary for treatment management.
- Strong research evidence suggests that delay in decompression of infected joints, especially the hips and shoulders, and delayed initiation of antibiotics are poor prognostic factors.
- Moderate research evidence indicates that the presence of fever, inability to bear weight, ESR >40 mm/hour, and a white blood cell count >12×106 is highly suggestive of pyogenic arthritis.
- Some evidence exists regarding safety and efficacy of the use of biologic agents in treating children who have JIA.
- Based on expert opinion, an interdisciplinary approach to the treatment of JIA results in improved quality of life.

PIR Quiz

Quiz also available online at: http://pedsinreview.aappublications.org.

NOTE: Beginning in January 2012, learners will only be able to take *Pediatrics in Review* quizzes and claim credit online. No paper answer form will be printed in the journal.

6. Among the following, the clinical characteristic that arthritis and arthralgia have in common is

   A. erythema
   B. pain
   C. swelling
   D. tenderness
   E. warmth

7. The most common mechanism of infection in septic arthritis is

   A. contiguous spread
   B. hematogenous seeding
   C. instrumentation
   D. intra-articular injections
   E. trauma

8. A 16-year-old-boy has had signs of arthritis in his left ankle for almost 2 weeks. He denies any trauma to the joint. His antistreptolysin O and Lyme titers are negative. Aspiration of the joint reveals clear fluid. He also complains of crusting of his eyelids in the morning. Among the following, the additional test you are most likely to order is a

   A. blood culture
   B. sputum culture
   C. stool for ova and parasites
   D. urethral culture
   E. urinalysis

9. Among the following, the preferred treatment of arthritis associated with acute rheumatic fever is

   A. acetaminophen
   B. ibuprofen
   C. naproxen
   D. salicylate
   E. steroid

10. Which of the following findings commonly occurs in both septic arthritis and toxic synovitis

   A. effusion of a hip joint
   B. marked elevation of erythrocyte sedimentation rate
   C. high fever
   D. inability to bear weight
   E. white blood cell count higher than 12,000/mm^3

Parent Resources From the AAP at HealthyChildren.org

The reader is likely to find material to share with parents that is relevant to this article by visiting this link: http://www.healthychildren.org/English/health-issues/conditions/orthopedic/pages/Arthritis.aspx.

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