Infectious arthritis in children can be caused by bacteria, viruses, fungi, or mycoplasma. Pyogenic arthritis is characterized by a purulent inflammatory response, usually caused by bacterial infection. Reactive (inflammatory) arthritis is inflammation of one or more joints that can result from a response to infection elsewhere in the body or from a systemic inflammatory or autoimmune disorder.

**INFECTIONOUS ARTHRITIS**

**Pyogenic (Bacterial) Arthritis**

**Epidemiology**

The incidence of pyogenic arthritis is less than that of transient synovitis and varies substantially (from 1/100,000 to 37/100,000 children) depending on the population studied. Although pyogenic arthritis occurs in all age groups, the peak incidence of disease is in children under 3 years of age. A history of trauma temporally related to the onset of arthritis caused by *Staphylococcus aureus* is common. Upper respiratory tract infection frequently precedes pyogenic arthritis caused by *Haemophilus influenzae type b* (Hib) and *Kingella kingae*. Gastroenteritis and aphthous stomatitis also can precede arthritis with *K. kingae*.

Although most children have no underlying disorder, risk factors for pyogenic arthritis include immunodeficiency, hemoglobinopathy, diabetes, intravenous drug abuse, and rheumatoid arthritis.

**Pathophysiology**

Most cases of pyogenic arthritis in childhood follow hematogenous spread of organisms to the vascular synovium of the joint space. Animal models of Hib bacterial arthritis illustrate possible mechanisms of articular damage. Bacterial endotoxin within the joint space stimulates release of tumor necrosis factor and interleukin-1. These cytokines stimulate production of proteinases by synovial cells and chondrocytes, enhancing leukocyte migration. Neutrophil elastases augment destruction of cartilage matrix within the joint.

Bacteria also can spread to joints from contiguous osteomyelitis. The presence of transphysseal blood vessels in the child younger than 18 months facilitates spread of infection from the metaphysis across the growth plate to the epiphysis and adjacent joint space. In addition, the joint capsule of the hip and shoulder overlies the bony metaphysis of the femur and humerus, allowing direct extension of bone infection into these joint spaces. Primary pyogenic arthritis rarely extends into the bone to cause a secondary osteomyelitis.

Joints also can be infected from penetrating wounds, intra-articular injections of medications, arthroscopy, and prosthetic joint surgery.

**Etiology**

Age is the most important predictor of etiology of pyogenic arthritis. *S. aureus*, enteric gram-negative organisms, and group B streptococcus (GBS) are the most frequent causes of pyogenic arthritis among neonates. *S. aureus* (methicillin-susceptible (MSSA) and community-associated methicillin-resistant (CA-MRSA)), *Kingella kingae*, *Streptococcus pyogenes*, and *Streptococcus pneumoniae* cause pyogenic arthritis in children younger than 5 years of age. In one series, *K. kingae* was the most common cause of pyogenic arthritis in children younger than 36 months. *K. kingae* is being reported with increasing frequency as a cause of pyogenic arthritis in the United States. Approximatively one third of bone and joint infections caused by *S. pneumoniae* are caused by strains with decreased susceptibility to penicillin. Although *S. pneumoniae* caused approximately 6% of cases of pyogenic arthritis prior to universal conjugate vaccination, cases of invasive disease due to vaccine serotypes now have been reduced dramatically. *S. aureus* and *S. pyogenes* are the most common causes of pyogenic arthritis in children older than 5 years.

CA-MRSA osteoarticular infections are now common, and are more aggressive than MSSA infections involving multiple bones and joints and sometimes are associated with venous thrombosis and pulmonary disease. *S. aureus* isolates (either MRSA or MSSA) possessing Panton-Valentine leukocidin appear to cause particularly severe infections.

Other organisms reported to cause pyogenic arthritis in children include *K. kingae*, *Neisseria meningitidis*, *Salmonella* spp., *β*-hemolytic streptococci other than serogroups A or B, and rarely, anaerobic bacteria. Joint infections caused by *Pseudomonas aeruginosa* and *Candida* spp. are reported in intravenous drug abusers. *Brucella* spp. infection should be considered if a history of travel to endemic areas, contact with livestock, or consumption of unpasteurized dairy products is elicited. Arthritis related to *Bartonella henselae* infection has been reported.

**Clinical Manifestations**

Fever, malaise, poor appetite, and irritability are heralding systemic symptoms. Pain in the affected joint usually occurs early in the course of the illness. As infection progresses, the joint becomes swollen and the overlying skin red. Limp or refusal to walk occurs with infection of a lower extremity. If the affected joint is in the upper extremity, “pseudoparalysis” or refusal to use the affected joint is seen; manipulation causes pain. The infected joint is swollen, red, warm, and tender on palpation. Range of joint motion is decreased.

The joints of the lower extremities, especially the knees, are the most common sites of pyogenic arthritis (Table 79-1). More than
90% of cases of pyogenic arthritis are monoarticular. However, multiple joints can be involved, particularly with infections caused by Neisseria gonorrhoeae, N. meningitidis, and Salmonella spp.

The diagnosis of pyogenic arthritis of the hip can be difficult because often there is no obvious joint swelling, and signs and symptoms are nonspecific, especially in infants and young children. Infants with pyogenic arthritis of the hip are irritable when the hip is moved (e.g., during diaper changes); soft-tissue swelling around the hip joint occasionally is noted and can extend to involve the entire leg. The affected hip often is held in a flexed, externally rotated and abducted position. Older children with pyogenic arthritis of the hip limp or refuse to walk and complain of pain, which sometimes is referred to the knee. Range of motion of the hip joint is decreased markedly.

**Diagnosis**

The erythrocyte sedimentation rate (ESR) is more than 20 mm/hour (mean, 44 to 65 mm/hour) in most patients with pyogenic arthritis. Similarly, the level of C-reactive protein (CRP) often is increased (mean, 8.5 mg/dL). A normal CRP is a good negative predictor for pyogenic arthritis. In one study, the probability that the patient did not have pyogenic arthritis was 87% if the CRP was <1.0 mg/dL. Excellent sensitivity for diagnosis of osteoarticular infections is obtained by utilizing both ESR and CRP.

Analysis of joint fluid is helpful in differentiating bacterial and other causes of arthritis (Table 79-2). Joint fluid in bacterial arthritis typically has a cloudy appearance. A leukocyte count >50,000 cells/mm³, with a predominance of neutrophils, is strongly suggestive of bacterial infection, even if culture of the joint fluid is negative. However, synovial fluid white blood cell (WBC) counts of less than 50,000/mm³ can occur in bacterial arthritis, particularly in cases of infection caused by K. kingae. WBC counts >50,000/mm³ with neutrophil predominance can occur in children with juvenile rheumatoid arthritis or Lyme disease. Synovial fluid glucose and protein levels do not differentiate reliably among most infectious and inflammatory processes and, therefore, have limited value.

Blood culture should be obtained and synovial fluid sent for Gram stain, culture, and WBC count. Isolation of K. kingae is enhanced when synovial fluid is inoculated directly into fluid blood culture medium. Use of 16S ribosomal DNA polymerase chain reaction (PCR) increased the identification of K. kingae in one series of children with osteoarticular infections.

In the adolescent, specimens also should be obtained from the cervix or urethra, throat, skin lesions, and rectum for isolation of N. gonorrhoeae.

When appropriate cultures are obtained, the bacterial cause is confirmed in 60% to 70% of cases of pyogenic arthritis. Blood cultures are positive in 40% to 70% of cases and joint fluid culture is positive in 50% to 60%.

**Imaging Studies**

Children with suspected pyogenic arthritis should have plain radiographic studies to exclude osteomyelitis or other osseous abnormalities. Soft-tissue swelling and widening of the joint can be observed in children with pyogenic arthritis. Erosion of subchondral bone may be evident 2 to 4 weeks after onset of infection.

Swelling of the hip capsule and lateral displacement or obliteration of the gluteal fat planes are early radiographic findings in pyogenic arthritis of the hip. With continued swelling of the hip capsule, the femoral head is displaced upward and outward, and lateral subluxation can occur. Concomitant osteomyelitis of the femur may be present. These findings are particularly common in infants, although in this age group, radiographic findings are difficult to interpret because of minimal ossification of the proximal femur. Plain radiograph sometimes is normal in children with proven pyogenic arthritis of the hip.

Ultrasoundography (US) should be performed in suspected pyogenic arthritis of the hip. If fluid is present in the joint, a diagnostic aspiration should be performed under US guidance. False-negative US results are reported in children later diagnosed with pyogenic arthritis; these are the result of either inadequate imaging or imaging performed very early (<24 hours) after onset of symptoms.

Although technetium phosphate radionuclide scan generally is not used in the diagnosis of pyogenic arthritis, a scan can be valuable in evaluating involvement of deep joints, such as the hip or sacroiliac joint. A characteristic finding is increased activity in the early (blood pool) phase and increased bony uptake on both sides of the joint (which would be uncharacteristic in osteomyelitis). Similarly, computed tomography (CT) may be helpful in the diagnosis of arthritis in areas of complex anatomy, such as the shoulder, hip, and sacroiliac joint.

Magnetic resonance imaging (MRI) is highly sensitive for the early detection of inflamed/infectected joints. Abnormal MRI findings in pyogenic arthritis include periarticular high-intensity signal and periarticular abscesses in some cases. MRI can delineate abnormalities of adjacent bone, soft tissue, and the extent of cartilage destruction. Compared with patients with transient synovitis, those with pyogenic arthritis are more likely to have MRI findings of high intensity in the bone marrow and decreased signal in the femoral epiphysis on fat-suppressed gadolinium-enhanced T₁-weighted images.

**Treatment**

Children with pyogenic arthritis should be managed in conjunction with an orthopedic surgeon experienced in treating children. Goals of therapy include decompression, sterilization of the joint space, and removal of inflammatory debris.

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**Table 79-1. Frequency of Joint Involvement in 1050 Children with Pyogenic Arthritis**

<table>
<thead>
<tr>
<th>Site</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee</td>
<td>467</td>
<td>41</td>
</tr>
<tr>
<td>Hip</td>
<td>287</td>
<td>25</td>
</tr>
<tr>
<td>Ankle</td>
<td>143</td>
<td>13</td>
</tr>
<tr>
<td>Elbow</td>
<td>116</td>
<td>10</td>
</tr>
<tr>
<td>Shoulder</td>
<td>53</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>70</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>1136</td>
<td>100</td>
</tr>
</tbody>
</table>

*Includes sacroiliac joint, joints of hands and feet, sternoclavicular joint.

*Some children had more than one joint affected.

Data from references 3, 4, 6, 8, 96, 98.

**Table 79-2. Characteristic Synovial Fluid Findings**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>WBC/mm³ (Typical)</th>
<th>WBC/mm³ (Range)</th>
<th>% PMNs (Typical)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;150</td>
<td>–</td>
<td>&lt;25</td>
</tr>
<tr>
<td>Bacterial arthritis</td>
<td>&gt;50,000</td>
<td>2000–300,000</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Tuberculous arthritis</td>
<td>10,000–20,000</td>
<td>40–136,000</td>
<td>&gt;50 (10–99)</td>
</tr>
<tr>
<td>Lyme arthritis</td>
<td>40,000–80,000</td>
<td>180–140,000</td>
<td>&gt;75</td>
</tr>
<tr>
<td>Candidal arthritis</td>
<td>–</td>
<td>7500–150,000</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Viral arthritis</td>
<td>15,000</td>
<td>3000–50,000</td>
<td>&lt;50 (variable)</td>
</tr>
<tr>
<td>Reiter syndrome</td>
<td>15,000</td>
<td>10,000–22,000</td>
<td>&gt;70 (37–98)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>–</td>
<td>2000–50,000</td>
<td>&gt;70</td>
</tr>
<tr>
<td>Rheumatic fever</td>
<td>25,000</td>
<td>2000–50,000</td>
<td>&gt;70</td>
</tr>
</tbody>
</table>

PMNs, polymorphonuclear cells; WBC, white blood cells.

Data from references 59, 61, 62, 148, 152, 180.
All children with pyogenic arthritis of the hip require prompt surgical drainage and irrigation of the joint space.\textsuperscript{24,25,26} Delay in drainage increases the likelihood of permanent damage because increased intra-articular pressure can compromise blood supply, resulting in avascular necrosis of the femoral head; muscle spasms also can occur, predisposing the patient to dislocation. Open surgical drainage of joints other than the hip usually is not required. However, aspiration must be performed promptly to decompress the joint and obtain synovial fluid for analysis. Repeated aspirations often are necessary when fluid reaccumulates. Concurrent osteomyelitis can be associated with the need for repeated debridements of the joint.\textsuperscript{27} Debridement by arthroscopy has been undertaken in some cases of pyogenic arthritis of the knee and hip.\textsuperscript{28,29}

The initial choice of antibiotics is based on age, clinical history, and physical examination. Adequate penetration into the joint is essential. Penicillin, ampicillin, nafcillin, methicillin, dicloxacillin, some first- and third-generation cephalosporins, clindamycin, vancomycin, and aminoglycosides attain acceptable concentrations in joints after intravenous or intramuscular administration. Agents that are well absorbed from the gastrointestinal tract attain adequate joint space concentrations after oral administration.\textsuperscript{28–45} Because antibiotics achieve high synovial fluid-to-serum ratios, there is no role for intra-articular instillation of antibiotics, which can produce chemical irritation and inflammation.

Parenteral administered therapy is used initially (Table 79-3). Antistaphylococcal therapy should be given for a child of any age. Infants younger than 3 months of age should be treated with antibiotics active against \textit{S. aureus}, gram-negative enteric organisms, and GBS. Children 3 months to 5 years of age should receive empiric therapy for \textit{S. aureus}, \textit{K. kingae}, \textit{S. pneumoniae}, and \textit{S. pyogenes}. Although Hib infection is uncommon in immunized children, other serotypes of \textit{Haemophilus} occasionally cause pyogenic arthritis.\textsuperscript{84} Children older than 5 years are treated for the most likely pathogens, \textit{S. aureus} or \textit{streptococci}. Empiric therapy for \textit{N. gonorrhoeae} is indicated for the sexually active adolescent.\textsuperscript{85}

Empiric therapy with vancomycin or clindamycin is indicated where CA-MRSA isolates exceed 10\%.\textsuperscript{86} Resistance to clindamycin may preclude its use as empiric therapy in many communities. Most \textit{S. pyogenes} and \textit{S. pneumoniae} isolates are susceptible to vancomycin and clindamycin, though susceptibility testing should be performed for both organisms. Neither of these drugs is effective in treating infection caused by \textit{K. kingae}. Most \(\beta\)-lactam antibiotics, including ampicillin, ampicillin-sulbactam and second- and third-generation cephalosporins, have activity against \textit{K. kingae}.\textsuperscript{26}

### TABLE 79-3. Empiric Antibiotic Therapy for Pyogenic Arthritis in Children

<table>
<thead>
<tr>
<th>Age</th>
<th>Likely Pathogen</th>
<th>Antibiotic</th>
<th>Dosage</th>
<th>Doses/day</th>
</tr>
</thead>
</table>
| Neonate (doses are for infants >2000 g and >7 days old with normal serum creatinine) | Staphylococcus aureus\textsuperscript{a}  
Group B streptococcus  
Gram-negative bacilli | Nafcillin or Vancomycin or Clindamycin \textsuperscript{b} plus Cefotaxime or Gentamicin | 100 or 30 or 20–30 or 100–150 or 5–7.5 mg/kg per day | 4 or 2 or 3 or 3 or 3 |
| Child, ≤5 years           | S. aureus\textsuperscript{a}  
Haemophilus influenzae\textsuperscript{b}  
Kingella kingae\textsuperscript{c}  
Streptococcus pyogenes  
Streptococcus pneumoniae | Nafcillin or Vancomycin or Clindamycin \textsuperscript{d} plus Cefotaxime or Cefuroxime or Ampicillin-sulbactam | 150 or 45–60 or 30–40 or 300–1000 Unasyn | 4 or 3 or 3 or 3 |
| Child, >5 years           | S. aureus\textsuperscript{a}  
Streptococcus pyogenes | Nafcillin or Vancomycin or Clindamycin \textsuperscript{d} | 150 or 45–60 or 30–40 mg/kg per day | 4 or 3 or 3 |
| Adolescent (sexually active) | Neisseria gonorrhoeae (consider) | Ceftriaxone \textsuperscript{e} | 50 mg/kg per day | 1 |

\textsuperscript{a}If more than 10% of community-acquired isolates are methicillin-resistant Staphylococcus aureus, consider empiric therapy with either vancomycin or clindamycin until culture and susceptibility results are available. If infection is confirmed to be caused by MRSA, see Clinical Practice Guidelines by the Infectious Diseases Society of America for treatment of MRSA infections in adults and children for specific dosing recommendations.\textsuperscript{85a}

\textsuperscript{b}Children who have been completely immunized are less likely to have Haemophilus influenzae type b infection.

\textsuperscript{c}If empiric therapy with vancomycin or clindamycin is used, consider adding a second- or third-generation cephalosporin for Kingella kingae coverage in patients <36 months of age.\textsuperscript{85a}

\textsuperscript{d}Maximum oral dose of clindamycin is 1.8 g/day; adult dose is 600 mg/dose PO/IV given every 8 hours.

\textsuperscript{e}The dose is for the drug Unasyn (300 mg Unasyn = 200 mg ampicillin plus 100 mg sulbactam). Sulbactam dose in an adult should not exceed 4 g. Unasyn is not approved for infant <1 year of age, or for this indication.

\textsuperscript{f}The dose of ceftriaxone for children ≥45 kg is 1 g/day, given in a single dose.
Nafcillin, oxacillin, or a first-generation cephalosporin remain the drugs of choice if MSSA is isolated. Choices of antibiotics for MRSA infections in children are limited. Vancomycin is effective, but no absorbable oral formulation exists. If MRSA is susceptible to clindamycin (including no inducible resistance), clindamycin is an excellent choice as an oral agent. Linezolid and daptomycin have been used in some patients with serious MRSA infection, although data regarding daptomycin use in children is limited. Linezolid has excellent oral bioavailability, however thrombocytopenia, anemia, and leukopenia can occur after 2 or 3 weeks; and lactic acidosis has been reported. Longer-term use is associated with peripheral and optic neuropathy. Linezolid is a weak reversible monoamine oxidase inhibitor and serotonin syndrome has occurred in children who also are receiving a serotonin-receptor inhibitor. The Infectious Diseases Society of America has published guidelines for the management of MRSA infections.

Specific therapy based on culture results and susceptibility testing is continued parenterally until the child is afebrile; joint pain, swelling, and erythema have decreased; and joint mobility has increased. In addition, markers of acute phase response should decrease. Because CRP normalizes more quickly than ESR (which typically is elevated for up to 2 weeks), CRP is used to monitor early response to therapy. Open drainage of any joint (with lysis and irrigation of loculated collections) should be undertaken when aspirations yield samples that are persistently positive on culture.

Orally administered antibiotic therapy can be substituted for parenteral treatment after adequate control of infection and inflammation has been achieved, if an oral antibiotic with appropriate coverage is available and if adherence and careful monitoring can be ensured. Use of clinical practice guidelines has been successful in decreasing the number of days parenteral antibiotics are given and duration of hospitalization, without increasing complications or sequelae.

For children in whom oral therapy is not feasible, outpatient parenteral antibiotic therapy administered through a tunneled central venous catheter or a peripherally inserted central catheter has been successful. Catheter-related mechanical and infectious complications may occur with prolonged intravenous administration of antibiotics and the risk versus benefit of prolonged central venous access should be considered carefully.

Duration of antimicrobial therapy remains a subject of considerable debate. Duration generally is determined by the specific pathogen, clinical and laboratory response, and whether adjacent osteomyelitis is present. Joint infections caused by S. aureus and gram-negative enteric organisms generally are treated for at least 3 to 4 weeks; a longer course of therapy may be necessary for pyogenic arthritis of the hip. Arthritis caused by H. influenzae, S. pneumoniae, S. pyogenes, and K. kingae is treated for 2 to 3 weeks, depending on clinical response. Therapy for less than 2 weeks in children in Finland with culture-positive arthritis was successful in most cases. Notably, none of the children in this study had MRSA infection and several children with hip infections required longer courses of treatment. A larger, controlled, prospective study is necessary to more adequately evaluate the adequacy of short-course antibiotic therapy.

### Prognosis

Sequelae of pyogenic arthritis in children include abnormalities of bone growth, limitation of joint mobility, unstable articulation, and chronic dislocation of the joint. Joint dysfunction may not become apparent for months to years after infection. An estimated 10% to 25% of children with pyogenic arthritis have residual dysfunction.

A number of risk factors for development of sequelae have been identified and include: (1) age younger than 6 months; (2) infection of the adjacent bone, which is evident in 10% to 16% of children with pyogenic arthritis and increases the likelihood of sequelae to approximately 50%; (3) infection of the hip or shoulder; (4) a delay of ≥4 days before decompression and antibiotic therapy; and (5) prolonged time to sterilization of synovial fluid. Staphylococcal and gram-negative bacillary infections carry a high risk of sequelae, whereas meningococcal and gonococcal infections carry a low risk.

### SPECIAL SITUATIONS AND PATHOGENS

#### Neonatal Arthritis

Risk factors for pyogenic arthritis in the neonate include umbilical vessel catheterization, presence of a central venous catheter, femoral vessel blood sampling, and possibly fetal breech presentation. Pyogenic arthritis often is a complication of osteomyelitis, and the onset may be insidious (see Chapter 94, Bacterial Infections in the Neonate). The hip and knee are the most frequently involved joints. S. aureus, N. gonorrhoeae, and Candida spp. frequently cause polyarticular infection.

If infection is contracted in the hospital, MRSA and MSSA, enteric gram-negative organisms, and Candida spp. are common. GBS, S. aureus, and N. gonorrhoeae are the pathogens most commonly isolated from neonates who develop joint infections after hospital discharge.

#### Gonococcal Arthritis

Arthritis caused by N. gonorrhoeae must be considered in sexually active adolescents. The incidence of disseminated gonococcal infection in individuals with urethritis or cervicitis is approximately 1%. Disseminated gonococcal infection is characterized by mild fever, polyarthralgia, rash, tenosynovitis, and supplicative arthritis, and is more common in girls, often during menstruation. Suppurative arthritis most often involves the knee. The hand, wrist, ankle, elbow, and foot are involved less often, and infection of the shoulder or hip is uncommon. Skin lesions occur in approximately 40% of patients. Lesions typically are few in number, and represent vasculitis. Lesions occur most frequently on extremities or over affected joints, are papular with a hemorrhagic component, and evolve into vesiculopustular lesions on an erythematous base. Other skin lesions, including bullae and purpura, have been described.

Culture of joint fluid is positive in only 25% to 35% of cases. Cultures of blood, cervix, urethra, rectum, vagina, skin lesions, or throat specimens may be positive when joint fluid is negative. Cultures obtained from normally sterile sites should be inoculated onto chocolate agar. Cultures from nonsterile sites should be inoculated immediately onto Thayer–Martin agar and incubated in carbon dioxide. N. gonorrhoeae also can be detected by PCR or other DNA amplification tests on first-voided urine specimens and urethral and cervicovaginal swab samples.

Because of the increasing prevalence of penicillin-resistant N. gonorrhoeae, 7 days of treatment with a parenterally administered third-generation cephalosporin, such as ceftriaxone or cefotaxime, is recommended. Marked improvement in fever and joint pain usually occurs 1 to 2 days after beginning therapy. Sequelae are rare.

#### Polyarthritis, Fever, and Rash

Bacterial causes of the clinical syndrome of fever, polyarthritis, and rash include infection with N. meningitidis and N. gonorrhoeae, rat

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**TABLE 79-4. Dosage of Antibiotics Commonly Used in Oral Treatment of Pyogenic Arthritis**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage (mg/kg per day)</th>
<th>Doses/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dicloxacillin</td>
<td>75–100</td>
<td>4</td>
</tr>
<tr>
<td>Cefalexin</td>
<td>100–150</td>
<td>4</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>30–40</td>
<td>3–4</td>
</tr>
</tbody>
</table>

*Dosages can be modified depending on results of serum bactericidal levels. In general, the oral dose of β-lactam antibiotics used for osteoarticular infections is two to three times the usual dose.*
bite fever (Streptobacillus moniliformis or Spirillum minus), bacterial endocarditis, and rheumatic fever.112 multiple viruses also are considered (see below). Noninfectious causes include Kawasaki disease, serum sickness, erythema multiforme, and other autoimmune and autoimmune diseases.

Lyme Arthritis
Lyme disease is caused by the tickborne spirochete Borrelia burgdorferi.113 Arthralgia occurs early in the course of infection and is recurrent in 18% of individuals. Approximately one half of patients with Lyme disease have arthritis,114 with typical onset 1 to 2 months after erythema migrans with sudden onset of monoarticular or oligoarticular joint pain. Joints involved, in descending order of frequency, include the knee, shoulder, elbow, temporomandibular joint, ankle, and wrist. Involvement of the hip or small joints is unusual.54 Patients characteristically are not ill, although about one half have fever. Affected joints are warm and swollen, have large effusions but motion typically is not severely limited. The peripheral white blood cell count often is normal, but the ESR and CRP usually are modestly elevated.115 Synovial fluid leukocyte counts range from 180 to 140,000/mm³; polymorphonuclear cells predominate.52 B. burgdorferi DNA has been detected by PCR of synovial fluid of patients with Lyme arthritis.116 Patients with Lyme arthritis are more likely to have MRI findings of myositis, lymphadenopathy, and lack of subcutaneous edema compared with children with pyogenic arthritis (P < 0.01).117 Lyme arthritis is treated with amoxicillin or doxycycline, depending on age (see Chapter 185, Borrelia burgdorferi (Lyme Disease)). Duration of therapy usually is 4 weeks. Children with multiple recurrences or persistent arthritis sometimes require intravenous or intramuscular ceftriaxone or intravenous penicillin.52 If untreated, recurrences of arthritis are common. Recurrences usually are separated by months to years. Frequency and duration of attacks decrease over time. Chronic synovitis develops in approximately 11% of untreated individuals.

Viral Arthritis
Arthritis as a result of viral infection can occur by direct viral invasion of the synovium or through immune complex deposition (Box 79-1). The viruses most commonly associated with the development of arthritis include rubella, parovirus B19, certain arboviruses, and hepatitis B.

Rubella virus. Arthritis following rubella infection is uncommon in childhood but is reported in 30% of women and 15% of men. Arthritis usually develops 1 to 2 days after onset of rash, although it has preceded the rash in a few cases. Symmetrical involvement of small joints of the hands is most common. Wrists and knees are sometimes affected. Analysis of joint fluid shows a predominance of mononuclear cells. Rubella virus has been isolated from synovial fluid. Symptoms resolve after several days, and long-term sequelae do not occur. Arthralgia and arthritis occur in approximately 25% of postpubertal females who receive live attenuated rubella vaccine. Joint symptoms begin 7 to 21 days after vaccination and usually are mild and self-limited.120,121

Parvovirus. Symptoms of arthritis or arthralgia were reported in 80% of adults and 8% of children during an outbreak of erythema infectiosum,122 and arthritis can occur in the absence of rash. Infection often is symmetric and polyarticular, and the joints of the hands, wrists, and knees are involved most commonly. Children are more likely to have symmetric involvement of a few joints. Levels of total hemolytic complement are low in some individuals with parovirus B19 arthritis, suggesting an immune complex-mediated pathogenesis. Arthritis associated with parovirus B19 infection usually is self-limited; resolution of symptoms occurs within 1 to 2 months.

Hepatitis viruses. Arthralgia can occur as a prodromal symptom of infection with hepatitis A or B viruses, but arthritis occurs only with hepatitis B infection.123,124 Joint symptoms precede the onset of icterus by 1 or 2 weeks. Multiple small joints of the hands usually are involved. In addition, sometimes symmetric involvement of knees, elbows, ankles, and shoulders is seen. An urticarial or maculopapular rash, usually involving the lower extremities, appears simultaneously with the joint findings in 30% to 40% of patients with arthritis. Hepatitis C viral infection has been associated with development of polyarthralgia and polyarthritis in a few patients.125

Arboviruses. Several arboviruses in the family Togaviridae, genus alphavirus, found in Australia, Africa, Asia, and South America cause systemic illness in which arthritis is a predominant manifestation. All are transmitted by bites of mosquitoes or ticks. Epidemic polyarthritis caused by Ross River virus occurs most frequently in Australia.126 Clinical manifestations include fever, papular, petechial or morbilliform skin rash, adenopathy, and polyarthritis. Small joints of the hands and feet are affected most commonly. Most patients recover spontaneously within 2 weeks. Barmah Forest virus, also endemic to Australia, causes fever, polyarthralgia, and rash.127

Chikungunya virus infection is endemic in Africa, India, and Southeast Asia and imported cases occur worldwide.128 Illness is biphasic, heralded by abrupt onset of fever, nausea, vomiting, and intense pain in one or more joints. The first phase of illness lasts 1 to 6 days, the patient becomes afebrile for 3 days, and then fever recurs. The second phase of illness is characterized by pharyngitis, rash, lymphadenopathy, and persistent arthritis. Children sometimes have febrile seizures and severe hemorrhagic manifestations.

Chikungunya virus (East Africa), Sindbis virus (Africa, Australia, Asia, Europe, and the Middle East), and Mayaro virus (Central and South America) infections cause febrile illnesses that are characterized by rash, adenopathy, arthralgia, and arthritis. Other viruses. Other viruses less commonly associated with arthralgia or arthritis include Epstein–Barr virus,129 enteroviruses (echovirus and coxsackie B),130 mumps virus,131 varicella-zoster virus,132–134 cytomegalovirus, and herpes simplex virus.136 Persistent or intermittent arthralgia involving the knee or shoulder has been reported in 35% to 45% of adults with human immunodeficiency virus infection135,136 but in only 15% of children with this infection.139

Mycoplasma Species
Mycoplasma pneumoniae, M. hominis, M. salivarium, and Ureaplasma urealyticum have been identified in joint fluid of patients with arthritis.140–143 Most patients are immunocompromised or have

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**Box 79-1. Viruses that Cause Arthritis**

<table>
<thead>
<tr>
<th>Togaviridae</th>
<th>Retroviridae</th>
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<tbody>
<tr>
<td>Rubella virus</td>
<td>Human immunodeficiency virus (type 1)</td>
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<tr>
<td>Ross River virus</td>
<td>Human T-lymphotropic virus (type 1)</td>
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<tr>
<td>Chikungunya virus</td>
<td>Herpes simplex virus 1</td>
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<td>O’nyong-nyong virus</td>
<td>Varicella-zoster virus</td>
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<td>Mayaro virus</td>
<td>Cytomegalovirus</td>
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<td>Sindbis virus</td>
<td>Epstein–Barr virus</td>
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<td>Barmah Forest virus</td>
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<td>Parvoviridae</td>
<td>Flaviviridae</td>
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<td>Parovirus B19</td>
<td>Hepatitis C virus</td>
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<tr>
<td>Paramyxoviridae</td>
<td>Hepadnaviridae</td>
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<td>Mumps virus</td>
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<td>Picornaviridae</td>
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<td>Echovirus</td>
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<td>Coxsackie B virus</td>
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suffered trauma to the joint. Characteristically, onset is insidious, with minimal systemic signs and a mildly affected, boggy joint with relative preservation of movement.

**Mycobacterium Species**

Skeletal tuberculosis occurs in 1% to 6% of all cases of tuberculosis. Isolated tuberculosis of the joint is uncommon.146 Articular infection can represent reactivated or primary infection. The knees and hips are affected most commonly, but infection of other joints can occur. Chronic swelling or pain of the affected joint without systemic symptoms is common. The skin test for tuberculosis (STS) is expected to be positive.147 Synovial fluid WBC count typically ranges between 10,000 and 20,000 cells/mm³, and neutrophils predominate. Synovial fluid cultures are positive in 79% of cases; synovial biopsy is diagnostic in more than 90%.148 MRI shows joint effusion with high-intensity signal on T₁-weighted images, and post contrast enhancement on T₁-weighted images. Hypointense internal debris, synovial thickening, and cartilage destruction also may be noted.149

Nontuberculous mycobacteria can cause osteoarticular infections in immunocompromised hosts.150,151

**Fungi**

Fungal arthritis is unusual in healthy children, except in areas endemic for specific fungi. Chronic monoarticular arthritis is typical of most fungal joint infections. The diagnosis of arthritis usually requires microscopic evaluation of synovial biopsy specimens and culture of synovial tissue and fluid. **Candida species.** Arthritis caused by *Candida* spp. occurs by hematogenous spread or, rarely, by direct inoculation of the organism into the joint space.152 Risk factors in neonates include prematurity, use of broad-spectrum antibiotics, intravenous alimentation, and presence of an intravascular catheter.153,154 Risk factors in older children include immunosuppression and intravenous drug use. Clinical manifestations vary. Children with disseminated disease have an acute onset of fever, systemic illness, and joint symptoms. In other cases, systemic symptoms are mild or absent. Joint symptoms may persist for months to years before a diagnosis is established. Neonates often have polyarticular involvement, but monoarticular infection is typical in older children. The knee is most frequently affected. Arthritis caused by *Candida* spp. in intravenous drug users often occurs in fibrocartilaginous joints, such as the sacroiliac joint, costochondral joints, and intervertebral disks.155

Synovial fluid WBC counts range from 7500 to 150,000 WBCs/μL, with neutrophil predominance. Diagnosis of fungal arthritis is confirmed by culture of synovial fluid or tissue. Culture of blood, urine, or cerebrospinal fluid may be positive in cases of systemic disease and especially in neonates.152

Amphotericin B or liposomal amphotericin B followed by prolonged (at least 6 weeks) treatment with fluconazole has been successful.154,155 An echinocandin antifungal may be used as an alternative therapy.144 *Candida* spp. should be tested for susceptibility to fluconazole if this drug is considered. Adequate debridement of the joint is necessary for successful therapy. **Sporothrix schenckii** is a dimorphic fungus found worldwide in soil and decayed plant material. Individuals at risk for infection include those whose occupations place them in frequent contact with plant debris and moist soil. Infection in children is rare. S. schenckii causes both cutaneous and extracutaneous infection. Osteoarticular sporotrichosis is the most common manifestation of extracutaneous infection.156 Joints most frequently involved include the knee, ankle, wrist, and elbows. Itraconazole is the treatment of choice, with amphotericin B recommended as alternative therapy.157 **Aspergillus species.** Aspergillus infection of the joint is uncommon and usually occurs secondary to extension of infection from adjacent bone. Children at risk include those with chronic granulomatous disease, chronic neutropenia, underlying cancer, and prolonged immunosuppression.158

**Coccidioides immitis** is found in soil in the southwestern U.S. and northern Mexico. Infection usually is asymptomatic or associated with localized pulmonary disease. Extrapulmonary manifestations include cutaneous lesions, lymphadenopathy, central nervous system infection, and osteoarticular infection. Joint involvement usually is unilateral and often adjacent to sites of osteomyelitis.159 **Cryptococcus neoformans** is found in soil contaminated by bird droppings. Infection typically involves the lungs, skin, or the central nervous system. Although bone lesions are found in 5% to 10% of cases, joint involvement is rare and usually secondary to infection in adjacent bone.160 **Histoplasma capsulatum** is endemic to the central and southeastern U.S., where large quantities of fungus are found in soil contaminated by bat or bird droppings. Infection usually is asymptomatic. Symptomatic infection is characterized by fever, chills, headache, cough, and chest pain. Approximately 10% of symptomatic patients have arthritis or severe arthralgia accompanied by erythema nodosum. Arthritis and arthralgia can be prolonged. Antifungal therapy is not always indicated in the immunocompetent host (see Chapter 250, *Histoplasma capsulatum* (Histoplasmosis)).161,162 Nonsteroidal anti-inflammatory drugs are recommended for relief of joint pain.163

**Blastomyces dermatitidis** is found commonly in warm moist soil containing decayed vegetation east of the Mississippi River. Blastomycosis typically involves the lungs, skin, and genitourinary system. Skeletal disease occurs in 10% to 15% of cases.164 Arthritis usually results from extension of osteomyelitis from adjacent bone and usually is monoarticular but can be oligoarticular.144 Fungi are identifiable on a wet preparation of synovial fluid.165 Itraconazole or other imidazoles have been used to treat blastomycoses.166

Other fungal organisms, such as *Scedosporium* spp., are rare causes of arthritis.167

**REACTIVE ARTHRITIS**

Reactive arthritis is defined as inflammation in one or more joints related to an infection at a site distant from the joint.168 Infections of the gastrointestinal, genitourinary, and respiratory tract are associated with reactive arthritis and an increasing number of pathogens are implicated169–172 Children are less likely than adults to develop reactive arthritis after enteric infection. Organisms most commonly associated with reactive arthritis are listed in **Box 79–2**.168–170,172,173,175,176 Immune-complex associated arthritis occurs in 2% to 16% of cases of meningococcal disease.177

A genetic susceptibility exists for development of reactive arthritis due to distant infection; individuals who are HLA-B27 antigen-positive have an increased incidence of disease.178

Reiter syndrome consists of arthritis, urethritis, and bilateral conjunctivitis. In children, symptoms usually follow a diarrheal illness.179 In adults, Reiter syndrome also can follow an episode of

**Box 79-2. Bacteria Associated with Reactive Arthritis**

**GASTROINTESTINAL PATHOGENS**

| Shigella spp. |
| Salmonella spp. |
| Yersinia enterocolitica |
| Campylobacter spp. |
| Clostridium difficile |

**SEXUALLY TRANSMITTED PATHOGEN**

| Chlamydia trachomatis |

**PYOGENIC AND REACTIVE ARTHRITIS-CAUSING ORGANISMS**

| Streptococcus pyogenes |
| Neisseria gonorrhoeae |
| Neisseria meningitidis |
nongonococcal urethritis. Although Reiter syndrome and reactive arthritis are sometimes used interchangeably, reactive arthritis is diagnosed in many children who do not have the triad of symptoms.

Reactive arthritis usually is polyarticular and involves the large joints of the lower extremities. Small joints, wrists, and elbows are involved less frequently. Sacroiliitis is more common among adults than children. Urethritis, if present, manifests with dysuria and pyuria. Mucous membrane ulcers (in the mouth, rectum, or vagina or on the glans penis) sometimes are present. Abnormalities of the eye include keratitis, uveitis, and corneal ulcerations.

WBC count and ESR usually are elevated. Synovial fluid WBC count is less than 50,000 cells/mm$^3$, with a predominance of neutrophils. ESR ranges from 20 to $>100$ mm/hour. Responsible pathogens are sometimes identified in stool or urethral specimens.

Nonsteroidal anti-inflammatory agents are useful in controlling symptoms. Antibiotic treatment of the predisposing bacterial organism may be appropriate when cultures are positive at the time of onset of joint symptoms. In children, joint symptoms persist for 1 to 12 months and recurrences are rare. The long-term prognosis of the disease is unknown.

Some bacteria cause both direct infection of the joint and reactive arthritis. For example, *S. pyogenes* causes infective pyogenic arthritis and also is associated with postinfectious reactive arthritis and rheumatic fever. Poststreptococcal reactive arthritis typically occurs 3 to 14 days after streptococcal infection, and is differentiated from the arthritis of acute rheumatic fever in that arthritis generally is symmetric, can involve both large and small joints, and is nonmigratory.

Similarly, *N. meningitidis*, *N. gonorrhoeae*, and *Salmonella* spp. sometimes are isolated from synovial fluid but, in other cases, infection at another site is associated with reactive arthritis. In addition to being a response to a pathogen, reactive arthritis can occur in association with a more generalized autoinflammatory or immunologic disorder, such as Crohn disease, ulcerative colitis, rheumatoid and rheumatic disorders, Kawasaki disease, hereditary autoinflammatory disorders, serum sickness, or Henoch–Schönlein purpura.
REFERENCES


Clinical Syndromes and Cardinal Features of Infectious Diseases: Approach to Diagnosis and Initial Management

Bone and Joint Infections


