Osteomyelitis is inflammation of bone. Bacteria are the usual etiologic agents, but fungal osteomyelitis occurs occasionally. Osteomyelitis in children primarily has hematogenous origin, occurring less commonly as a result of trauma, surgery, or infected contiguous soft tissue. Osteomyelitis due to vascular insufficiency is rare in children.

ACUTE HEMATOMGENOUS OSTEOMYELITIS

Pathogenesis

Acute hematogenous osteomyelitis (AHO) is primarily a disease of young children, presumably because of the rich vascular supply of their rapidly growing bones.\(^1\) Infection begins at the point of entry into the circulatory system and spreads to the bone via the nutrient artery. The organism extravasates into the metaphysis, the metaphyseal region being preferential because of rich blood supply. The metaphyseal region is largely avascular, permitting rapid spread. The metaphysis has a lower degree of phagocytic cells, allowing greater invasion and proliferation by the bacteria. The metaphysis has a lower degree of phagocytic cells, allowing greater invasion and proliferation by the bacteria. The metaphysis is permeable to the bone through the nutrient artery and then travels to the metaphyseal vessels, and lack of phagocytic cells lining the capillaries.\(^2\) Bacteria proliferate, spread through vascular tunnels, and are anchored to areas of exposed cartilaginous matrix. Large colonies of bacteria surround by glycocalyx obstruct capillary lumens, impairing phagocytosis and antibiotic penetration.\(^3\)

Age-related differences in the anatomy of the bone and its blood supply influence the clinical manifestations of osteomyelitis.\(^2\) Transphyseal vessels are present in most children younger than 18 months, providing a vascular connection between the metaphysis and the epiphysis.\(^4\) As a result, in infants, infection originating in the metaphysis can spread to the epiphysis and joint space. The risk of ischemic damage to the growth plate is greater in the young infant with osteomyelitis.\(^5\) Before puberty, the periosteum is not firmly anchored to underlying bone. Infection in the metaphysis of a bone can spread to perforate the bony cortex, causing subperiosteal elevation and extension into surrounding soft tissue. Bony destruction can spread to the diaphysis. By age of 2 years, the cartilaginous growth plate usually prevents extension of infection to the epiphysis and into the joint space. When the metaphysis of the proximal femur or humerus is involved, however, infection can extend into the hip or shoulder joint at any age, because at these sites, the metaphysis is intracapsular.

Histologic features of acute osteomyelitis include localized suppuration and abscess formation, with subsequent infarction and necrosis of bone. Segments of bone that lose blood supply and become separated from viable bone are called sequestra. An involucrum is a layer of living bone surrounding dead bone.\(^6\) A Brodie abscess is a subacute, well-demarcated focal infection, usually in the metaphysis but sometimes in the diaphysis of bone.

Epidemiology

Approximately half of all cases of AHO occur in the first 5 years of life.\(^7\) Boys are affected twice as frequently as girls, except in the first year of life.\(^8\) One-third of patients have minor trauma to the affected extremity before infection, but the specific importance of this history is unclear, because virtually all young children experience frequent mild trauma.\(^9\)

The relative risk of developing osteomyelitis appears to be higher in some populations. In one study, Polynesian and Maori children were more likely to develop complicated osteomyelitis with *Staphylococcus aureus* than other children in the same New Zealand community.\(^10\) It is unclear whether genetic or socioeconom or environmental factors accounted for this difference.

Microbiology

*S. aureus* is the most common cause of AHO.\(^11,14,19–21\) *Kingella kingae*, *Streptococcus pneumoniae*,\(^15,16\) and *S. pyogenes*\(^17\) are the organisms isolated in most other cases of AHO in children. *K. kingae* and *S. pneumoniae* infections are most common in children less than 3 years of age. *S. pneumoniae* accounts for a relatively small proportion of infections, especially in the context of widespread immunization with the pneumococcal conjugate vaccine.\(^22,23\) *K. kingae* can be associated with small outbreaks of bone and joint infections in childcare centers.\(^20,26\) Coagulase-negative staphylococci (CoNS) (almost exclusively as a complication of medical intervention), enteric gram-negative bacilli, and anaerobic bacteria are uncommon causes of AHO. *Bartonella henselae* can cause granulomatous infection of bone.\(^7,27–29\) *Actinomyces* spp. cause facial and cervical osteomyelitis.\(^30\) Infection with *Serratia* spp. and *Aspergillus* spp. should be considered in children with chronic granulomatous disease.\(^31\) Before widespread use of *Haemophilus influenzae* type b (Hib) conjugate vaccines, 10% to 15% of cases of osteomyelitis in children younger than 3 years were caused by this organism.\(^15,32\) Invasive disease is rare in immunized children.\(^12\)

Figure 78-1. Gross specimen showing osteomyelitis of the proximal humerus in a 6-week-old infant. Note metaphyseal location and bony destruction (arrows). (Courtesy of S.S. Long.)
Community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) AHO has been increasing dramatically. Some CA-MRSA isolates causing osteoarticular infection carry the genes for Panton–Valentine leukocidin (PVL), a virulence factor or marker for complicated infections.\(^{3,7,38}\)

**Clinical Characteristics and Differential Diagnosis**

Most patients with AHO have symptoms for <2 weeks before they are brought to medical attention, although a small proportion have low-grade fever and intermittent bone pain for several weeks.\(^{13,17}\) The most common manifestations are fever, pain at the site of infection, and reluctance to use an affected extremity.\(^{18,39}\) Less common complaints are anorexia, malaise, and vomiting. Physical findings consist of focal swelling, tenderness, warmth, and erythema (usually over the metaphysis of a long bone). Rarely, a draining fistulous tract develops over the affected bone.\(^{17}\) Tenderness out of proportion to soft-tissue findings suggests osteomyelitis rather than soft-tissue infection or cellulitis. Exaggerated immobility of the joint and lack of point tenderness over the metaphysis suggest pyogenic arthritis. Other causes of bone pain are fracture, bone infarction secondary to hemoglobinopathy, leukemia, vitamin deficiency, and bony neoplasms such as metastatic neuroblastoma and Ewing sarcoma.

Osteomyelitis most frequently occurs in the long bones (Figure 78-2), although in some series, 10% to 25% of cases involve short or nontubular bones, including the pelvis, clavicle, calcaneus, skull, ribs, and scapula.\(^{17,18,40}\) Multiple bones are involved in about 5% of cases.

Compared with methicillin-sensitive *S. aureus* (CA-MSSA), patients with CA-MRSA infections have more protracted courses of fever, as well as hospitalization, multiple foci of infection, pyomyositis, and subperiosteal and intraosseous abscesses.\(^{36,38,41,42}\) A recent retrospective study demonstrated that four independent predictive factors (temperature 38°C, hematocrit <34%, WBC count >12,000 cells/mm⁴ and C-reactive protein level >1.3 mg/dL) were useful in differentiating MRSA from MSSA osteomyelitis. Prospective validation of this scoring system is pending.\(^{33}\) Patients with PVL-positive CA-MRSA are at increased risk for deep-vein thrombosis or septic emboli to the lungs.\(^{35,39-41}\) Compared with infection due to PVL-negative organisms, infection with PVL-positive *S. aureus* also appears more likely to result in chronic osteomyelitis.\(^{23}\)

**Laboratory Diagnosis**

Bacteriologic diagnosis can be confirmed in 50% to 80% of cases of AHO; the yield is highest when multiple specimens, including blood, bone, and joint fluid, are sampled.\(^{5,11,13,17,18,39}\) Cultures obtained by imaging-guided bone biopsy are more likely to be positive if larger volumes (>2 mL) of purulent material are aspirated.\(^{43}\) Diagnosis of *K. kingae* infection is enhanced with intraoperative inoculation of culture material directly into liquid media or onto agar plates or when polymerase chain reaction (PCR) analysis is performed.\(^{20,21,44}\) Cultures should be held for at least 7 to 10 days.

The erythrocyte sedimentation rate (ESR) is elevated in up to 90% of cases of osteomyelitis, and the C-reactive protein (CRP) level in 95%.\(^{17,18,39,40}\) The mean ESR is 40 to 60 mm/h, but levels >100 mm/h can occur. ESR generally peaks 3 to 5 days after initiation of therapy and returns to normal in approximately 3 weeks. CRP levels peak by the second day (mean, 8.3 mg/dL) and return to normal (<2.0 mg/dL) after approximately 1 week of therapy.\(^{45}\) Patients infected with PVL-positive versus PVL-negative *S. aureus* are more likely to have positive blood cultures and higher ESR and CRP levels at presentation.\(^{46}\) Higher levels of CRP at diagnosis may predict greater risk of sequelae.\(^{46,47}\) The peripheral white blood cell count can be elevated or normal; thrombocytosis can be noted, especially if symptoms have been present for more than 1 week.

**Radiologic Diagnosis**

**Plain Radiographs**

Radiographic abnormalities in osteomyelitis reflect inflammation, destruction, and new formation of bone.\(^{34,44}\) The earliest abnormalities, seen within the first 3 days of onset of symptoms, are deep soft-tissue swelling and loss of the normally visible tissue planes around the affected bone. Osteopenia or osteolytic lesions from destruction of bone usually are not visible until approximately 50% of bone has been demineralized. Lytic lesions, periosteal new bone formation appear approximately 10 to 20 days after onset of symptoms. Sclerosis of bone is seen when infection has been present for longer than a month. If deep soft-tissue swelling is noted on plain radiograph in a patient with a short history of symptoms and with point tenderness over the affected metaphysis, no further imaging studies are necessary to support the diagnosis of osteomyelitis.

**Radionuclide Scanning**

Radionuclide scans are useful in the early diagnosis of osteomyelitis, even when plain radiographs are normal. Technetium-labeled methylene diphosphonate isotope is most frequently used because its uptake by infected bone is enhanced when osteoblastic activity is increased.

The reported sensitivity of technetium-99 bone scanning is between 80% and 100% (Table 78-1).\(^{35,36}\) (Figures 78-3 and 78-4). The bone scan can be normal in 5% to 20% of children with osteomyelitis in the first few days of illness.\(^{52,54-56}\) Bone scan is less expensive than MRI, and sedation usually is not required. Bone scan is particularly useful when multifocal bone involvement is suspected.\(^{57}\) A variety of disorders, including malignancy, deep soft-tissue infection, cellulitis, pyogenic arthritis, trauma, fracture, and bone...
Osteomyelitis

Figure 78-3. Typical technetium-99 bone scan findings of acute osteomyelitis in a 4-year-old girl who had a 2-day history of fever, ankle pain, and swelling, and refusal to bear weight. Plain radiograph was unremarkable. Triple-phase anterior images of bone scan show increased tracer activity in the region of the right ankle in the angiographic (immediate) phase (A), increased tracer activity in the soft tissues in the region of the ankle in the blood pool (15-minute) phase (B), and localization of tracer in the distal tibial metaphysis (arrow) without periarticular distribution in the delayed (2.5-hour) phase (C). Diagnosis was confirmed at surgery with finding of subperiosteal pus; Streptococcus pyogenes was isolated. (Courtesy of E. Geller and S.S. Long, St. Christopher’s Hospital for Children, Philadelphia, PA.)

Figure 78-4. Plain film and technetium-99 bone scan of acute osteomyelitis and pyogenic arthritis in a 7-month-old boy who had a 3-day history of high fever, fussiness and redness, and swelling of the lateral right leg from the thigh to the lower leg, with limitation of motion of the knee. Aspiration of the knee revealed 169,000 white blood cells/mm² and gram-positive cocci. Plain film shows obscuration of right lateral subcutaneous fat–muscle plane, from the thigh to the lower leg (A). Triple-phase bone scan shows increased tracer activity in the region of the right knee in the angiographic phase (B) and in the periarticular soft tissues in the blood pool phase (C), as well as localization of tracer in the distal femur (arrow) but not in the proximal tibia in the delayed phase (D). Diagnosis of osteomyelitis of the femur was confirmed at surgery. Methicillin-susceptible Staphylococcus aureus was isolated from blood, joint and bone specimens. (Courtesy of E. Geller and S.S. Long, St. Christopher’s Hospital for Children, Philadelphia, PA.)

TABLE 78-1. Technetium Bone Scans for Osteomyelitis in Children

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Patient Age</th>
<th>Sensitivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuson et al.</td>
<td>1994</td>
<td>6 months–13 years</td>
<td>92</td>
</tr>
<tr>
<td>Hamdan et al.</td>
<td>1987</td>
<td>6 months–14 years</td>
<td>89</td>
</tr>
<tr>
<td>Howie et al.</td>
<td>1983</td>
<td>6 weeks–13 years</td>
<td>89</td>
</tr>
<tr>
<td>Sullivan et al.</td>
<td>1980</td>
<td>3 weeks–13 years</td>
<td>81†</td>
</tr>
<tr>
<td>Bressler et al.</td>
<td>1984</td>
<td>&lt;6 weeks</td>
<td>100</td>
</tr>
</tbody>
</table>

*Superscript numbers indicate references.
†The 2 patients younger than 6 weeks of age had normal scans.

In some cases of osteomyelitis, bone scans show areas of decreased technetium uptake (“cold scans”), probably reflecting compromised vascular supply to the bone from ischemia or thrombosis; such findings make differentiation of osteomyelitis from infarction associated with sickle-cell disease difficult. Patients with osteomyelitis and decreased uptake on bone scan may have more complicated infection, frequently with thrombosis and ischemic necrosis.

Infarction, can result in positive scan results. Metaphyseal site of maximal uptake and lack of uptake in bone on both sides of a joint support the diagnosis of AHO, rather than pyogenic arthritis. Diaphyseal uptake suggests tumor, trauma, or infarction.
Nuclear scanning using gallium-67 citrate or indium-111-labeled leukocytes is positive in diseases characterized by increased bone turnover and, thus, have limited specificity for osteomyelitis. Indium scanning, which reflects migration of white blood cells into areas of inflammation, can be useful in the diagnosis of osteomyelitis associated with trauma, surgery, chronic ulcers, or prosthetic devices, but is limited by poor localization of infection (i.e., bone versus soft tissue), decreased sensitivity in diagnosing infection in the central skeleton, and relatively high radiation exposure. Simultaneous performance of a technetium bone scan sometimes increases specificity.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is a sensitive bone-imaging test. Its reported sensitivity for detection of osteomyelitis ranges from 92% to 100%. Normal red and fatty portions of the bone marrow have a characteristic appearance on MRI. Fatty marrow produces a bright signal on T1-weighted images. Changes in marrow caused by infection and inflammation produce an area of low signal intensity within the bright fatty marrow. Areas of low signal intensity in infected marrow seen on a T1-weighted image change to bright signal intensity on a T2-weighted image. These changes are not specific for osteomyelitis and can be seen with malignancy, fracture, and bone infarction.

MRI can detect signal alterations in soft tissue and is particularly useful in differentiating cellulitis from osteomyelitis. MRI also may differentiate acute from chronic osteomyelitis.

Gadolinium-enhanced MRI can be particularly useful in the diagnosis of osteomyelitis in cases in which bone and soft-tissue edema are seen on unenhanced images. MRI has been used to identify bone marrow infection in cases of *Bartonella henselae* infection, particularly when plain films and computed tomography (CT) of the affected bones appear normal.

**TREATMENT**

Antibiotic Choice

Considerations in choosing a specific antimicrobial regimen include the age of the child, underlying medical conditions, suspected pathogens and their susceptibility pattern, antibiotic pharmacodynamics, and the safety and efficacy of the antibiotic.

Most β-lactam antibiotics achieve therapeutic concentrations in bone. Clindamycin has particularly good bone penetration, attaining a high bone-to-serum ratio. Vancomycin has excellent penetration into the bones of experimental animals. Aminoglycoside agents theoretically have poor bactericidal activity in bone because of local tissue hypoxia and acidosis. Although ciprofloxacin penetrates well into bone, fluoroquinolones are not recommended routinely for use in young children.

Most cases of AHO in any age group are caused by *S. aureus*. Empiric therapy should include coverage for this organism. Parenterally administered nafcillin, clindamycin, or a first-generation cephalosporin historically have been the usual choices for empiric therapy; however, the increase in CA-MRSA infections has made the choice of initial antibiotic therapy challenging. Direct sampling of bone for culture is increasingly important. Clindamycin remains a good choice for empiric therapy in communities where resistance (both constitutive and inducible) occurs in fewer than 10% of *S. aureus* isolates. In communities where CA-MRSA resistance to clindamycin and methicillin is greater than 10% to 15%, vancomycin is the drug of choice for empiric therapy. Clindamycin and vancomycin are active against most isolates of *S. pyogenes* and *S. pneumoniae*. Neither offers coverage for K. kingae infection, which is susceptible to most β-lactam antibiotics. Ampicillin-sulbactam should be considered in addition to clindamycin or vancomycin, especially in young children.

Empiric therapy for young children who have not been immunized against *Haemophilus influenzae* type b should include a third-generation cephalosporin in addition to antistaphylococcal coverage. A second-generation cephalosporin such as cefuroxime alone is a reasonable alternative if suspicion for MRSA is low. However, with the dramatic reduction of cases of Hib disease in the United States, it is reasonable to use only an antistaphylococcal-antistreptococcal antibiotic in the fully immunized and immunocompetent child.

Neonates with osteomyelitis should be treated with antibiotics active against *S. aureus*, group B streptococcus (GBS), and gram-negative enteric organisms. Suggested initial empiric parenteral antibiotic therapy for neonates and children with AHO is outlined in Table 78-2.

Antibiotic therapy should be modified according to results of culture and susceptibility testing. Nafcillin, oxacillin, a first-generation cephalosporin, or clindamycin (if susceptible) are the drugs of choice for infections caused by MSSA. Clindamycin is a good definitive choice for susceptible MRSA and MSSA but should not be used if inducible resistance is detected because of reports of treatment failure under this circumstance.

There are few antibiotic choices for clindamycin-resistant CA-MRSA infection in children. Recently published guidelines by the Infectious Disease Society of America (IDSA) recommend vancomycin plus/minus rifampin for the treatment of MRSA osteomyelitis in children. Linezolid is suggested as an alternative choice. Limited data support efficacy of linezolid. In one group of pediatric patients, linezolid was as effective as vancomycin in treating infections caused by MRSA, although efficacy in treating bone or joint infections was not specifically evaluated. Linezolid has excellent oral bioavailability and offers an alternative to prolonged intravenous therapy. However, it is expensive and many children object to the taste of the oral suspension. Long-term use has been associated with neutropenia, thrombocytopenia, and elevated serum transaminase levels. There are rare reports of lactic acidosis and optic neuropathy associated with linezolid therapy.

Most CA-MRSA isolates are susceptible to trimethoprim-sulfamethoxazole, tetracyclines, and rifampin. Clinical experience with these drugs for osteoarticular infections is limited. Rifampin should not be used as a single agent because of rapid development of resistance. Although daptomycin and tigecycline have activity against MRSA, neither is approved for use in children. The IDSA guidelines suggest that daptomycin may be used in children in selected circumstances. If no organism is isolated, and the symptoms are resolving, initial empiric therapy should be continued. Most cases of culture-negative osteomyelitis respond to therapy with antistaphylococcal antibiotics.

Management of children with osteomyelitis should include concurrent care by an orthopedic surgeon. Indications for surgery include desirability of specific pathogen diagnosis; prolonged fever, erythema, pain, and swelling; persistent bacteremia despite adequate antibiotic therapy; soft-tissue or periosteal abscess; formation of a sinus tract; and presence of necrotic, nonviable bone.

**Duration of Therapy**

Duration of antibiotic therapy depends on the cause and extent of infection as well as the clinical course. The usual duration ranges from 3 to 6 weeks and should be individualized on the basis of severity of illness and clinical response. Historical evidence suggests that <3 weeks of treatment is associated with higher rates of relapse or recurrence than longer duration of therapy. Plain radiographs obtained at the end of therapy may be useful as a marker of maximal anticipated destruction, a baseline for further studies, and a guide to possible complications.

Peripherally inserted or tunneled central venous catheter (PICC/CVC) often is placed to continue intravenous antibiotics at home. Use of PICC or CVC for >2 weeks in children with osteomyelitis can be associated with an increase in catheter-related complications, including catheter malfunction, thrombosis and catheter-associated bloodstream infections.
TABLE 78-2. Antibiotic Selection for Initial Treatment of Osteomyelitis

<table>
<thead>
<tr>
<th>Patient Age</th>
<th>Likely Pathogen</th>
<th>Antibiotic Selection</th>
<th>Dosage</th>
<th>Doses/Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3 years</td>
<td>Staphylococcus aureus</td>
<td>Nafcillin or Clindamycin&lt;sup&gt;c&lt;/sup&gt; or Vancomycin</td>
<td>150 mg/kg per day</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30–40 mg/kg per day</td>
<td>3–4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>45–60 mg/kg per day</td>
<td>3–4</td>
<td></td>
</tr>
<tr>
<td>&lt;3 years</td>
<td>S. aureus</td>
<td>Nafcillin or Clindamycin&lt;sup&gt;c&lt;/sup&gt; or Vancomycin or Cefotaxime or Ceftriaxone or Cefuroxime or Ampicillin-sulbactam</td>
<td>150 mg/kg per day</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30–40 mg/kg per day</td>
<td>3–4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>45–60 mg/kg per day</td>
<td>3–4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Haemophilus influenzae type b&lt;sup&gt;a&lt;/sup&gt; Kingella kingae&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Nafcillin or Clindamycin&lt;sup&gt;c&lt;/sup&gt; or Vancomycin plus Cefotaxime or Ceftriaxone or Cefuroxime or Ampicillin-sulbactam</td>
<td>100–150 mg/kg per day</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 mg/kg per day</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>75–150 mg/kg per day</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Neonate</td>
<td>S. aureus</td>
<td>Nafcillin or Vancomycin plus Gentamicin&lt;sup&gt;OR&lt;/sup&gt; Nafcillin or Vancomycin plus Gentamicin</td>
<td>100 mg/kg per day</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Group B streptococcus Enteric gram-negative bacteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 mg/kg per day</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5–7.5 mg/kg per day</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 mg/kg per day</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 mg/kg per day</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>150 mg/kg per day</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> If patient is fully immunized against Haemophilus influenzae type b, consider using only antistaphylococcal coverage.

<sup>b</sup> If patient is treated with either clindamycin or vancomycin, consider adding an ampicillin or cephalosporin agent for Kingella kingae.

<sup>c</sup> Clindamycin 40 mg/kg/day recommended for treatment of susceptible MRSA osteomyelitis.

Sequential parenteral–oral antibiotic regimens can be successful. Early transition to oral therapy was not associated with a higher risk of treatment failure in a recent study. The change to oral antibiotics is generally made when fever, pain, and signs of local inflammation have resolved and laboratory values, especially CRP, are normalizing. The willingness of the child to take oral medication and the likelihood of adherence to the regimen also must be assessed. The oral antibiotic should have the same spectrum of coverage as the parenteral drug. If a β-lactam agent is used, dosage required is generally two to three times the usual oral dose (Table 78-3).

TABLE 78-3. Dosage of Antibiotics Commonly Used in the Oral Phase of Treatment of Osteomyelitis<sup>a</sup>

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage</th>
<th>Doses/Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dicloxacillin</td>
<td>75–100</td>
<td>4</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>100–150</td>
<td>4</td>
</tr>
<tr>
<td>Clindamycin&lt;sup&gt;b&lt;/sup&gt;</td>
<td>30–40</td>
<td>3–4</td>
</tr>
</tbody>
</table>

<sup>a</sup> In general, the dose of β-lactam antibiotics used for osteomyelitis is 2–3 times the usual dose.

<sup>b</sup> Clindamycin 40 mg/kg/day is recommended for treatment of susceptible MRSA osteomyelitis.

Once the change to oral therapy is made, the child should be monitored to ensure continued clinical improvement. The CRP level is expected to return to normal 7 to 10 days after initiation of appropriate therapy, and the ESR normalizes within 3 to 4 weeks.

SPECIAL CLINICAL SITUATIONS

Neonatal Osteomyelitis

Osteomyelitis is uncommon in the neonatal period. The incidence is estimated to be approximately 1 to 3 cases for every 1000 intensive-care nursery admissions. Associated risk factors include prematurity, low birthweight, preceding infection, bacteremia, exchange transfusion, and the presence of an intravenous or umbilical catheter. Osteomyelitis of the skull secondary to contiguous spread of infection has occurred as a complication of fetal scalp electrode monitoring and in association with infected cephalohematoma. Osteomyelitis of the calcaneus has complicated heel lancet puncture.

The diagnosis of osteomyelitis in neonates often is delayed because of nonspecific symptoms. Signs and symptoms include fever, irritability, swelling or decreased movement of a limb (pseudoparalysis), erythema, and tenderness over the affected bone. Preterm infants are more likely than term infants to manifest symptoms of septicemia.
Approximately 20% to 50% of neonates with osteomyelitis have infection of multiple bones, and about 75% have suppurrative arthritis of contiguous joints (Figure 78-5). S. aureus (including CA-MRSA), GBS, and enteric gram-negative bacilli are the most common causes (Table 78-4); fungi, Ureaplasma urealyticum, CoNS, Neisseria gonorrhoeae, and anaerobic bacteria are unusual causes.

Infants with GBS bone infection usually have had an uncomplicated neonatal course and have infection of a single bone. There is a predilection for involvement of long bones on the right, particularly the right proximal humerus, which may be related to trauma during vaginal delivery. Misdiagnosis of bone infection as trauma in these mildly ill infants is common. Since the release of the 1996 consensus guidelines for prevention of GBS disease, the incidence of early-onset perinatal GBS disease but not late-onset disease has declined in the U.S.

The white blood cell count commonly is normal; ESR and CRP often are elevated. In most infants, an osteolytic lesion is visible on plain radiograph 10 to 12 days after onset of symptoms (frequently the time of diagnosis). Radionuclide bone scans can be positive but sometimes are less sensitive than plain radiographs. Neonatal osteomyelitis can lead to permanent joint abnormalities or disturbance in skeletal growth secondary to damage to the cartilaginous growth plate, including arthritis, decreased range of motion, limb length discrepancy, and gait abnormalities. The reported incidence of permanent sequelae varies from 6% to 50%.

### TABLE 78-4. Frequency of Organisms Causing Neonatal Osteomyelitis (n = 128)

<table>
<thead>
<tr>
<th>Single Organism</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>60.6</td>
</tr>
<tr>
<td>β-Hemolytic streptococcus</td>
<td></td>
</tr>
<tr>
<td>Group B</td>
<td>16.5</td>
</tr>
<tr>
<td>Group A</td>
<td>3.1</td>
</tr>
<tr>
<td>Enteric gram-negative bacilli</td>
<td>8.7</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>2.4</td>
</tr>
<tr>
<td>Nonhemolytic streptococcus</td>
<td>2.4</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>0.8</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>0.8</td>
</tr>
<tr>
<td>Multiple organisms</td>
<td>4.7</td>
</tr>
</tbody>
</table>

**Ventral Osteomyelitis**

Vertebral osteomyelitis accounts for approximately 1% to 3% of cases of osteomyelitis in children. Boys are affected twice as frequently as girls. Infection usually occurs as a result of hematogenous seeding of the vertebral bodies by arterial or venous vessels. Osteomyelitis also can result from extension of soft-tissue infection or as a complication of a surgical procedure.

Clinical manifestations can be indolent and nonspecific, leading to delayed diagnosis. Young infants can have nonspecific signs of sepsis. Symptoms in older children include back, chest, abdominal, or leg pain as well as loss of normal curvatures. Rarely, children manifest dysphagia secondary to a paravertebral or retropharyngeal abscess or acute spinal cord paresis/paralysis due to paraspinal compression. Fever is common, and tenderness over the involved vertebrae is expected. Neurologic deficits are found in 15% to 20% of cases.

S. aureus is isolated in most cases. In one review, Salmonella spp. caused 12% of cases of childhood vertebral osteomyelitis. Gram-negative bacilli such as Escherichia coli cause vertebral osteomyelitis in adults, particularly those with a history of recent urinary tract infection or instrumentation. Vertebral osteomyelitis in intravenous drug users is commonly caused by Pseudomonas aeruginosa and less commonly by S. aureus, Stenotrophomonas spp., Klebsiella spp., Enterobacter spp., or Candida spp. Tuberculosis and brucellosis should be considered if symptoms and radiographs suggest chronic infection.

Characteristic findings on plain radiograph consist of narrowing of the involved disk space, lucency of the adjacent vertebral bodies, and, eventually, reactive sclerosis of the bone with fusion of vertebral bodies. Vertebral osteomyelitis is differentiated from diskitis radiographically by the minimal vertebral endplate involvement associated with diskitis (see Chapter 80, Diskitis). MRI is reported to be highly sensitive (96%) and specific (92%) for diagnosis of vertebral osteomyelitis.

Blood culture results are positive in only about 30% of acute cases. When blood culture results are negative, strong consideration should be given to obtaining a biopsy specimen from the vertebral body for culture and histologic examination.

Children with uncomplicated vertebral osteomyelitis and no evidence of abscess formation should be treated with at least 4 weeks of antibiotic administered parenterally. Surgical decompression or debridement or both are indicated in the presence of spinal epidural abscess, signs of spinal cord compression, or extensive bony destruction.

Complications of vertebral osteomyelitis include neurologic deficits secondary to epidural abscess, paravertebral abscess, and infected aneurysms of the aorta.

**Pelvic Osteomyelitis**

Approximately 6% to 9% of all cases of hematogenous osteomyelitis involve the bones of the pelvis. The ilium and ischium are most commonly involved; infection of the sacrum, acetabulum, or pubic symphysis is rare. Risk factors (not always present) include a history of pelvic trauma, intravenous drug use, and genitourinary procedures.

Most patients with pelvic osteomyelitis have fever, gait abnormalities, and pain that is often localized to the hip, groin, or buttock. Pain with hip movement and point tenderness over the affected bone often is observed. Clinical features can mimic those of pyogenic arthritis of the hip; however, in pelvic osteomyelitis there is more likely to be near-normal range of motion of the hip, absence of referred pain to the knee, specific point tenderness over the affected bone (or pain on rocking of the pelvic girdle), and abnormal rectal findings. Responsible pathogens are similar to those that cause osteomyelitis of long bones.
Plain radiographs of the pelvis often are normal. Technetium scanning, MRI, or CT can suggest the correct diagnosis and may be useful for differentiating osteomyelitis from bacterial infection of the muscles of the pelvic girdle. MRI has the advantage of identifying abscesses associated with pelvic osteomyelitis and is the imaging technique of choice.144

Patients should be treated for at least 4 weeks with antibiotics parenterally.137-140,143 Surgical drainage or debridement should be considered in cases of extraneous abscess formation or in patients whose symptoms do not respond to intravenous antibiotic therapy.

Children with Sickle Hemoglobinopathies

Children with sickle-cell disease have increased susceptibility to bacterial infections, including osteomyelitis.145 The suspected pathogenesis is primary microscopic infarction in the intestinal mucosa and bone, resulting in bacteremia and focal bone infection. Splenic hypofunction, impaired opsonization, impaired macrophage function, and microembolism as well as tissue infarction are likely contributing factors in osteomyelitis.146-148 Manifestations of osteomyelitis are difficult to differentiate from those of acute vaso-occlusive crisis. Fever, bone pain, and leukocytosis are common to both conditions. Temperature >39°C, toxic appearance, and an absolute band count >500 cells/mm² are more consistent with infection; however, there is considerable clinical and laboratory overlap.148

Plain radiograph, technetium scanning, and MRI cannot differentiate infarction from infection.132,135 Therefore, if fever and bone pain have not improved after supportive care has been given for vaso-occlusive crisis, needle aspiration of the affected area of bone for Gram stain and culture should be performed.

A prolonged course of parenteral antibiotic therapy (6 to 8 weeks) may be necessary for treatment of osteomyelitis in patients with sickle hemoglobinopathy. Oral therapy can be substituted for parenteral treatment once a pathogen has been confirmed and there is clinical improvement; therapy may need to be very protracted. Relapses especially when due to Salmonella are not infrequent.134,135

**OSTEOMYELITIS DUE TO UNUSUAL ORGANISMS**

**Fungal Osteomyelitis**

Fungal osteomyelitis is unusual in healthy children, occurring occasionally in neonates, immunocompromised patients, and intravenous drug users.131,135-137 Osteomyelitis caused by Candida spp. is reported in intravenous drug users and in prematurely born neonates.131,135-138 Aspergillus spp. cause osteomyelitis in children with chronic granulomatous disease, often resulting from contiguous spread of pulmonary infection.139 Blastomyces dermatitidis, Coccidioides immitis, Histoplasma capsulatum, and Cryptococcus neoformans cause osteomyelitis in indigenous geographic regions and in immunosuppressed hosts.140-145

**Tuberculous Osteomyelitis**

Skeletal lesions occur in approximately 1% of children with tuberculosis.130,134 Bones and joints are infected through hematogenous or lymphatic dissemination of Mycobacterium tuberculosis. Infection can smolder for years before clinical signs are apparent. The most commonly involved bones are the vertebrae (tuberculous spondylitis), femur, long bones around knees and ankles, and small bones of the hands and feet.135 Other sites less frequently infected are the ribs, mandible, sternum, clavicle, and other long bones. Multifocal osteomyelitis is reported in 10% to 15% of cases.136,137

Clinical signs and symptoms of skeletal tuberculosis include low-grade fever, weight loss, pain, and soft-tissue swelling at the site of infection. Vertebral involvement begins in the anterior vertebral body, eventually causing disk space collapse and anterior wedging of vertebral bodies, and sometimes gibbus deformity. The lower thoracic spine is the usual site of involvement (Pott disease), followed by the lumbar spine.

The Mantoux tuberculin skin reaction is usually positive. The role of interferon-γ release assays in the diagnosis of Pott disease is currently being evaluated. Plain radiographic findings include periarticular osteopenia, lytic lesions in the body of the vertebra, joint space narrowing, and soft-tissue swelling.142 The chest radiograph often is normal. CT is useful for the evaluation of bone destruction, adjacent soft-tissue abscess formation, and calcification, and in guiding percutaneous biopsy.139,140 MRI is helpful in determining extent of bone and soft-tissue disease.141 Biopsy specimens should be obtained in an attempt to demonstrate the organism with stains and culture.

Antituberculous therapy includes 2 months of therapy with four drugs, followed by 7 to 10 months of isoniazid and rifampin (for susceptible organisms) daily or twice weekly (see Chapter 134, Mycobacterium tuberculosis).132 Surgical intervention is indicated in cases of spinal instability and neurologic impairment secondary to paravertebral abscess formation and for drainage of soft-tissue abscesses. Nontuberculous Mycobacterium spp. infrequently cause osteomyelitis in immunocompromised individuals.

**Anaerobic Bacterial Osteomyelitis**

Anaerobic bacteria are associated with chronic and nonhematogenously acquired osteomyelitis.134-137 Risk factors include surgery, trauma, diabetes mellitus, human bites, chronic otitis media or sinusitis, dental infection, fibrous dysplasia of bone, presence of a prosthesis, and decubitus ulcers (Figure 78-6). Children are more likely than adults to experience anaerobic osteomyelitis of the skull and facial bones.137 Osteomyelitis of ribs follows contiguous spread from aspiration lung infection; Actinomyces spp. are the primary pathogens. Soft-tissue swelling or abscess can be the presenting abnormality. Similarly, Actinomyces spp. can cause osteomyelitis of the maxilla or mandible, frequently without dental pathology.

Infection usually is polymicrobial; gram-positive cocci, Bacteroides spp., Prevotella spp., and Fusobacterium spp. are the most common anaerobes, and S. aureus is the most commonly associated aerobic isolate.137 Therapy consists of treatment of underlying conditions, surgical debridement of necrotic bone, and appropriate antibiotic therapy. Examples of effective antibiotics are clindamycin, metronidazole, imipenem, and amoxicillin-clavulanate.

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**BOX 78-1. Bacterial Causes of Osteomyelitis in Children with Sickle-Cell Disease**

**COMMON**

- Salmonella spp.
- Staphylococcus aureus

**LESS COMMON**

- Escherichia coli
- Haemophilus influenzae type b
- Shigella spp.
- Streptococcus pneumoniae

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Many anaerobic isolates are susceptible to penicillin. The choice of antibiotic depends on the specific organisms isolated and their potential for β-lactamase production. Therapy is protracted, frequently exceeding 1 year of oral penicillin or amoxicillin plus probenecid for actinomycosis.

NONHEMATOGENOUS OSTEOMYELITIS

Contiguous Infection

Factors associated with the development of nonhematogenous osteomyelitis include open fractures requiring surgical reduction,176,177 implanted orthopedic devices, decubitus ulcers,178,179 and neuropathic ulcers.176,177 Facial osteomyelitis usually is secondary to untreated mastoiditis, sinusitis, or periodontal abscesses.176,177 Osteomyelitis can occur after local soft-tissue infection or direct inoculation of bone from human and animal bites.180,181 Puncture wounds can lead to osteomyelitis of the foot (e.g., stepping on a nail or toothpick180) or the patella (e.g., kneeling on a needle).

Indolent presentation is common among children with nonhematogenous osteomyelitis. Fever is present in less than half of patients.177 Persistent drainage or ulceration of the soft tissue over the affected bone is typical. Plain radiograph shows bony destruction. Peripheral white blood cell count often is normal, and ESR and CRP can be normal.

Nonhematogenous osteomyelitis often is caused by S. aureus, although coinfection with gram-negative and anaerobic organisms occurs.174 Examination of specimens from an associated sinus tract is unreliable in defining the etiology of osteomyelitis.184 Biopsy with culture of the affected bone is the best method of determining appropriate antibiotic therapy. Therapy should be prolonged if infection is chronic, sometimes with parenteral therapy followed by oral therapy for a total of 4 to 6 months.

The rate of recurrence in nonhematogenous osteomyelitis is as high as 40%, even with prolonged courses of antibiotic therapy.185 Aggressive surgical debridement or other interventions are required in addition to antibiotic therapy. Implanted devices commonly must be removed for cure. Debridement followed by muscle flap procedure to re-establish the blood supply in decubitus ulcer-associated osteomyelitis frequently is beneficial.185

Figure 78-6. Actinomycosis of the mandible in a 9-year-old girl with history of painless expansion of the jaw over several months. Reconstructed spiral computed tomography shows expansion of bone with complex lytic and sclerotic mass (arrow). Surgical biopsy confirmed Actinomyces osteomyelitis and fibrous dysplasia of bone. (Courtesy of L. Kablan and M. Pasternack, Massachusetts General Hospital; and S.S. Long, St. Christopher’s Hospital for Children, Philadelphia, PA.)

PUNCTURE WOUND OSTEochondritis of the Foot

Bacterial osteochondritis is a complication of puncture wounds of the foot, occurring in approximately 1.5% of such injuries.182,186-184 Symptoms of osteochondritis, which appear several days to weeks after the initial injury, include increasing tenderness, erythema, and swelling at the site of the puncture.

Infection usually is caused by Pseudomonas aeruginosa,189 often as a result of inoculation from the colonized moist soles of tennis shoes.190 S. aureus is the usual pathogen if symptoms began within 3 to 5 days of injury. Obtaining specimens from bone for microbiologic diagnosis is desirable.

Empiric antibiotic therapy should include coverage for P. aeruginosa and S. aureus. Ticarcillin-clavulanate, piperacillin-tazobactam, ceftazidime or cefepime, with or without an aminoglycoside, would be appropriate empiric therapy if MRSA is not likely. With appropriate surgical debridement, short-duration (7 to 10 days) parenteral antibiotic therapy has been effective for P. aeruginosa,189,191 as has 3 to 4 weeks of antibiotic therapy without debridement.190 Treatment with oral ciprofloxacin in conjunction with surgical debridement also is successful192 (see Chapter 292, Antimicrobial Agents).

CHRONIC RECURRENT MULTIFOCAL OSTEOMYELITIS

Chronic recurrent multifocal osteomyelitis (CRMO) is an inflammatory disease of children and young adults characterized by recurring episodes of low-grade fever, swelling, and pain over affected bones and by radiologic abnormalities suggestive of osteomyelitis.193,194 Females are more frequently affected than males.195 The median age of onset of illness is 10 years. CRMO sometimes is associated with palmoplantar pustulosis,196 psoriasis, arthritis, sacroiliitis, inflammatory bowel disease,197 and Sweet syndrome.

Radiographic abnormalities occur most commonly in the metaphysis of long bones and are characterized by radiolucent bone lesions with reactive sclerosis and soft-tissue swelling.195,198,199 The sternal end of the clavicle, the vertebral bodies, and the smaller bones of the hands and feet often are involved. Radiographic changes are similar to those seen in acute osteomyelitis, but multiple, often symmetrical lesions are present in CRMO. Bone scanning and MRI are useful in determining the extent and evolution of disease.190-200 An infectious cause of CRMO has not been determined.

The course of CRMO consists of prolonged bone pain with remissions and relapses over several years; the mean duration of disease is 6 years.200 In a long-term follow-up study of 23 patients with CRMO, 26% had active disease at a median of 13 years after diagnosis.197 Although the clinical outcome in most patients is good, approximately 20% of patients have a prolonged and severe course. Young age at onset and multiple sites of involvement predict less favorable outcome.201 Treatment with a variety of antibiotics has no apparent effect on the course or outcome. Some experts have advocated the use of corticosteroids or nonsteroidal anti-inflammatory agents for relief of symptoms.193,198 Other therapies utilized in small numbers of patients have included colchicine, INF-γ, IFN-α, and infliximab.192,203,204

Because multifocal bone lesions in childhood can occur with neuroblastoma, histiocytosis X, leukemia, and staphylococcal osteomyelitis, histologic examination and culture of bone specimens should be performed. Histologic findings in CRMO are nonspecific and chronic inflammatory changes; in the chronic phase of the disease, granulomatous changes can be seen.205

CHRONIC OSTEOMYELITIS

Chronic osteomyelitis develops in fewer than 5% of cases of AHO.12,206 It more often follows nonhematogenous osteomyelitis.183
Surgical debridement of necrotic bone is primary management. Alternative therapeutic approaches include the use of antibiotic-impregnated polymethyl methacrylate beads, local antibiotic delivery via implantable pumps, and suction vacuum devices or bone grafts, skin grafts, and muscle flaps to eliminate dead space and improve vascularity.

Chronic osteomyelitis is characterized by alternating periods of quiescence and recurrent pain, swelling, and sinus tract drainage, persisting for years despite prolonged antibiotic therapy. Infections are often polymicrobial, and the original metaphyseal infection, with skeletal growth, moves to become a lytic lesion in the diaphysis.
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