Chapter 141: Bone and Joint Infections

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KEY CONCEPTS

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1. The most common cause of osteomyelitis (particularly that acquired by hematogenous spread) and infectious arthritis is *Staphylococcus aureus* (*S. aureus*).
2. Culture and susceptibility information are essential as a guide for antimicrobial treatment of osteomyelitis and infectious arthritis.
3. Joint aspiration and examination of synovial fluid are extremely important to evaluate the possibility of infectious arthritis.
4. The most important treatment modality of acute osteomyelitis is the administration of appropriate antibiotics in adequate doses for a sufficient length of time.
5. Antibiotics generally are given in high doses so that adequate antimicrobial concentrations are reached within the infected bone and joints.
6. Oral antimicrobial therapies can be used for osteomyelitis to follow a parenteral regimen in children who have a good clinical response to IV antibiotics and in adults without diabetes mellitus or peripheral vascular disease when the organism is susceptible to the oral antimicrobial, a suitable oral agent is available, and adherence is ensured.
7. The standard duration of antimicrobial treatment for acute osteomyelitis is 4 to 6 weeks.
8. The three most important therapeutic approaches to the management of infectious arthritis are appropriate antibiotics, joint drainage, and joint rest.
9. Monitoring of antibiotic therapy is important and typically involves noting clinical signs of inflammation, periodic white blood cell (WBC) counts, C-reactive protein, and erythrocyte sedimentation rate (ESR) determinations.

BEYOND THE BOOK

BEYOND THE BOOK

Activity #1 The long-acting lipoglycopeptide antibiotics, dalbavancin and oritavancin, are potentially useful treatments for bone and joint infections because of their infrequent dosing and gram-positive spectrum of activity. Conduct a literature search to identify one primary research report published on these agents in the last 2 years. If the manuscript provides data on the safety or effectiveness of these drugs in treating deep-seated infection for longer than 2 weeks, reflect on the advantages and disadvantages for this type of treatment strategy.

Activity #2 The OVIVA trial, as discussed in the chapter, was a practice changing study for many clinicians and has significantly motivated the process of shifting more treatment courses for bone and joint infections away from IV agents, which require OPAT, toward appropriate oral regimens. However, the results of this trial aren't applicable to all clinical situations that arise. Review the OVIVA study methods, results, and conclusions (https://www.nejm.org/doi/full/10.1056/NEJMoa1710926) and make a list of the clinical situations and oral regimens for which these study results may apply. This will help you advocate for the use of oral therapy in the most appropriate circumstances.

INTRODUCTION

Bone and joint infections are comprised of two disease processes known, respectively, as *osteomyelitis* and *septic* or *infectious arthritis*. They are unique and separate infectious entities with different signs and symptoms and infecting organisms. Prosthetic joint infections, resulting from the advancement of modern technology, are distinct and blend attributes of each disease. Despite therapy, these infections all cause significant morbidity from residual damage with chronic or recurring infections. Emphasis on initiating antibiotic therapy, targeted to the most likely pathogens, as soon as possible is important in reducing long-term complications.

EPIDEMIOLOGY

Osteomyelitis

1 Osteomyelitis has historically been an uncommon disease. One classic publication reported that 247 patients had osteomyelitis in a prominent American teaching hospital during a 4-year period.[1] In Spain there were more than 500 cases of osteoarticular infections per year over the course of a decade.[2] Over that time, the incidence increased from 11.4 to 24.4 cases per 100,000 person-years.[3] Acute osteomyelitis has an annual incidence of 0.4 per 1,000 children. Osteomyelitis cases have been rising in adults due to an aging population having more cases of diabetic foot infections and prosthetic joint replacements. Osteomyelitis can be caused by contiguous spread, including postoperative contamination, direct puncture from trauma, or associated with adjacent soft tissue infections, which is the most common source. *Hematogenous osteomyelitis* comprises 19% of infections, and osteomyelitis occurring in patients with significant peripheral vascular disease comprises 34% of infections.

The bacteriology of hematogenous osteomyelitis is unique, in that one pathogen, *S. aureus*, is responsible for more than 80% of these infections. Streptococci and *Escherichia coli* (*E. coli*) make up the remainder in most of the population. One exception is in children 3 months to 4 years of age. With the advent of molecular diagnostics, *Kingella kingae* (*K. kingae*), an organism that is part of the oral microbiota, has been identified as a common cause of preschool osteoarticular infections.[4] After children reach the age of 4 years, *S. aureus* again accounts for nearly 80% of infections. *Haemophilus influenzae* type b used to be an important pathogen but has been almost completely eliminated with the use of the conjugate vaccine. Osteomyelitis in neonates can result from organisms transferred from the mother at birth such as Group B Streptococcus, and *E. coli*, but is most commonly from infection with *S. aureus*.

Vertebral osteomyelitis occurs through hematogenous spread and has several unique features, being most common in adults over 50 years of age and often misdiagnosed initially. It typically presents with recalcitrant back pain unresponsive to usual symptomatic therapies, elevated inflammatory markers, and sometimes fever.[5] The lumbar and thoracic regions are the locations of most infections. Infections are most likely to develop in the vascular areas near the subchondral plate region of the vertebral body. These infections are typically monomicrobial and are caused principally by staphylococci.[5] Gram-negative organisms, most commonly the Enterobacterales, *E. coli* and *Klebsiella pneumoniae,* that originate within the urinary tract or intra-abdominal cavity are more common in older patients.[7] *Mycobacterium tuberculosis* and fungi also are known to cause infections in the spine, albeit rarely. Skin and respiratory tract infections are other sources of infection known to lead to vertebral infections.

Contiguous-spread disease has several important differences compared with hematogenous osteomyelitis. Although *S. aureus* is still the most common organism isolated, polymicrobial infections occur more often than with hematogenous osteomyelitis. *Streptococcus spp., Staphylococcus epidermidis*, *E. coli*, *Pseudomonas aeruginosa* (*P. aeruginosa*), and anaerobes can also be isolated.

Patients with diabetes mellitus frequently have infections that involve the foot. Cases extending to the bone may result in mixed infection, including with gram-negative bacilli. Puncture injuries to the foot, causing osteochondritis, are another reason for gram-negative infection, sometimes caused by *P. aeruginosa*. *S. aureus* remains a significant pathogen in these patients due to its prevalence on the skin. When anaerobes are grown from cultures, they usually are found in association with other organisms, including aerobic bacteria. *Bacteroides fragilis* comprises the majority of anaerobic isolates. Predisposing factors in patients who have anaerobic osteomyelitis include vascular disease, peripheral neuropathy, trauma, bites, or contiguous infections such as abscess.

Infectious Arthritis

Infectious or septic arthritis is an inflammatory reaction within the joint space. Septic arthritis is one of the most common causes of new cases of arthritis. The incidence of proven or likely septic arthritis is 4 to 10 cases per 100,000 patient-years. The incidence of septic arthritis increases 10-fold among patients that have rheumatoid arthritis.[8]

Although relatively infrequent, neonates can have infectious arthritis because of a broad range of organisms similar to osteomyelitis, with *S. aureus*, Group B *Streptococcus*, and *E. coli* being most common. *K. kingae* is now considered predominant in those 6 months to 4 years old, while *S. aureus* is the most common pathogen in children 4 years of age and older.[9] Pneumococcal arthritis is decreasing in incidence as a result of conjugate pneumococcal vaccine administration to infants.[10] If the child has not been fully vaccinated or is immunocompromised, *S. pneumoniae* or *H. influenzae* type b may be a cause.

Some organisms, such as *S. aureus* and *Neisseria gonorrhoeae*, are especially likely to infect a joint during bacteremia. Gonococcal arthritis is a common manifestation of disseminated gonococcal infection, occasionally with associated osteomyelitis.[11] Gonococcal arthritis is now uncommon in North America and Europe, although it remains an important concern in developing countries.

Within the adult population, *S. aureus* is responsible for the majority of arthritis cases.[12] Streptococcal infections are the second most common, followed by gram-negative organisms. Among the latter, *E. coli* is the most common; however, *P. aeruginosa* can be seen in special situations such as in people who inject drugs (PWID) or nosocomial infections.

Although rare, infectious arthritis can be caused by fungi, mycobacteria, or viruses such as varicella-zoster, rubella, or parvovirus.[13] Penetrating injury of the joint can result in an infection due to *Pasteurella* or *Capnocytophaga* from dog or cat bites, *Eikanella* in human bites, or *Pantoea* when the injury is induced by a thorn.

ETIOLOGY

Osteomyelitis

The most common method of classifying osteomyelitis is based on the mode of acquisition of the bone infection. Disease that results from spread through the bloodstream is termed hematogenous osteomyelitis, while that reaching the bone from an adjoining soft tissue infection is termed *contiguous osteomyelitis*. Patients with peripheral vascular disease are at risk for the development of contiguous osteomyelitis, and they present unique management features so are sometimes classified separately. Osteomyelitis that results from direct inoculation, such as from trauma, puncture wounds, or surgery, generally is also classified as inoculation osteomyelitis.

Osteomyelitis also can be classified based on the duration of the disease. Acute osteomyelitis describes infections of recent onset, with symptoms usually present about one week, whereas chronic infections are those of a longer duration. Some authors describe chronic infections as those with symptoms for more than one month before therapy, while other authors define chronic infections as any relapse of an initial infection. Hematogenous osteomyelitis almost always involves one bone, whereas contiguous osteomyelitis can present in multiple bones, especially when vascular insufficiency is an underlying risk factor.

Infectious Arthritis

Most infecting organisms produce an infection in a single joint, termed *monoarticular infection*; however, infections also can involve two or more joints, especially when associated with bacteremia. As with osteomyelitis, joint infections also can be classified according to the mechanisms by which the infecting organism reaches the joint. Infectious arthritis can result by spread from an adjacent bone infection, direct contamination of the joint space through trauma or surgery, or hematogenous dissemination. Hematogenous spread of the disease comprises the majority of infections; spread from osteomyelitis and direct inoculation are much less frequent. Septic arthritis is most prevalent in children and the elderly. Approximately, one-third of people with septic arthritis are children younger than 2 years of age.[8]

Unlike children, adults often have significant systemic diseases that predispose them to septic arthritis, such as diabetes mellitus, immunosuppressive states (eg, cancer or liver disease), or preexisting joint disease, particularly rheumatoid arthritis. Additional risk factors associated with adult septic arthritis (more than one factor may be present) are systemic corticosteroid use, arthrocentesis, distant infection, or trauma. PWID and individuals with intravascular infections such as endocarditis also are prone to develop septic arthritis.

PATHOPHYSIOLOGY

Osteomyelitis

Hematogenous Osteomyelitis

Hematogenous osteomyelitis is typically a disease of the growing bone in children, but occurs primarily in vertebrae of adults. Table 141-1 summarizes the primary characteristics of osteomyelitis.

TABLE 141-1

Types of Osteomyelitis, Age Distribution, Common Sites, and Risk Factors

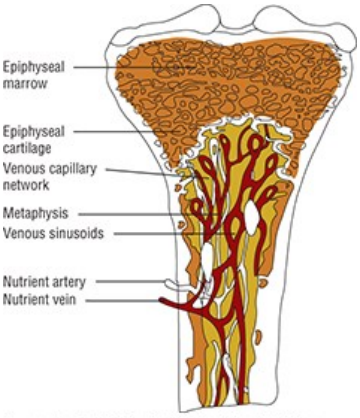
Type of Osteomyelitis	Typical Age (years)	Site(s) Involved	Risk Factors
Hematogenous	<1	Long bones and joints	Prematurity, umbilical or other central venous catheter or venous cut-down, respiratory distress syndrome, and perinatal asphyxia
	1-20	Long bones (femur, tibia, and humerus)	Infection (pharyngitis, cellulitis, and respiratory infections), trauma, and sickle cell disease
	Older than 50	Vertebrae	Diabetes mellitus, blunt trauma to spine, and urinary tract infection
Contiguous	Older than 50	Femur, tibia, and mandible	Hip fractures and open fractures, soft tissue infections or abscesses
Direct Inoculation	<18	Feet and hands	Puncture injury to extremity or other trauma
Vascular insufficiency	Older than 50	Feet and toes	Diabetes mellitus, peripheral vascular disease, and pressure sores

Unique features of the anatomy and vascular supply of long bones appear to predispose them to become infected.[14] Bacteria are seeded within the metaphysis (Fig. 141-1) as the nutrient arteries of the long bones divide within the medullary canal of the bone into small arterioles. These end in hairpin turns near the growth plate and flow into veins, of much wider diameter, that drain the medullary cavity.[1] The infection is initiated within the

bend of arterioles where there is considerable slowing of blood flow in the hairpin capillary loops. This sludging of blood flow allows bacteria present within the bloodstream to settle and initiate an inflammatory response. They have access to the bone by gaps in the endothelium and the absence of a basement membrane. In addition to these structural features, phagocytosis is less active within the metaphysis. After the bacteria settle in the bone, avascular necrosis can occur from occlusion of the nutrient vessels and release of bacterial enzymes. Once the infection is initiated, exudate begins to form within the bone marrow and the fluid accumulates under increased pressure. The age of the patient largely determines the next stage in the pathophysiology.

FIGURE 141-1

Cross-section of normal bone.



Neonatal infections commonly involve multiple bones. The vascular supply of long bones in neonates has unique anatomic characteristics that affect their clinical presentation. Bridging blood vessels go across the epiphyseal plate from the metaphysis into the epiphysis, thus enabling an infection that started within the metaphyseal area to spread easily to involve the epiphyses and then break into the joint. Therefore, in infants, not only can the infection spread under the periosteum or break through the periosteum and the shaft as in older children, but the infection also can spread directly through the bridging blood vessels to involve the joint.

In children older than 12 to 18 months, hematogenous osteomyelitis typically involves a single bone and has a predilection for involvement of the long bones, such as the femur, tibia, humerus, and fibula. The infection that started in the metaphysis of a long bone is prevented from spreading into the epiphysis and the adjacent joint space because of the epiphyseal growth plate which acts as a physical barrier; however, the exudate often dissects from the medulla through the soft cortex to the subperiosteal space as the periosteum in these children is loosely attached to the underlying cortex. The periosteum is thick and not easily ruptured; thus, the subperiosteal space retains the pus, sometimes forming a subperiosteal abscess. If there is significant damage to the periosteum, the pus can decompress into a soft tissue abscess. The cortex obtains most of its blood supply from the periosteum and a subperiosteal abscess can impair the blood flow to the outer portion of the cortical bone resulting in a devitalized piece of dead bone termed a *sequestrum*. The elevated periosteum remains viable because its blood supply, derived from the overlying muscle, is unaffected. The raised periosteum will continue to produce bone; however, this new bone is now separated from the cortex because the periosteum has been raised from the infection. This new bone that is deposited under the periosteum is termed *involucrum*. In addition to these anatomic and functional features, there is some evidence that trauma is associated with developing an infection in specific bones. Children who develop hematogenous osteomyelitis may report some type of trauma before the onset of their symptoms, and animal data indicate that traumatized bone is more likely to become infected than normal bone.

In adults, the periosteum is tightly bound to the cortex which is thick. These anatomic features generally cause the infections to remain intramedullary. As expected, subperiosteal abscess formation is less common in this population. The infection can spread to subperiosteal structures through the Haversian and Volkmann canals.

Osteomyelitis of the vertebrae is also acquired hematogenously and this occurs most frequently in patients older than 50 years of age.[5] Vertebral disease in younger adults and children usually involves the disk space and the two vertebral facets adjoining it because of the nature of the vascular supply of the vertebrae at that age. This syndrome is known as diskitis.

Direct Inoculation Osteomyelitis

This category of osteomyelitis includes infections caused by direct entrance of organisms from a source outside the body. Penetrating wounds (eg, trauma), open fractures, and various invasive orthopedic procedures can result in direct inoculation of organisms into the bone. More than 80% of cases of postoperative osteomyelitis are known to occur following open reduction of fractures. Specifically, these infections occur most commonly after internal fixation of a hip, femoral, or tibial shaft fracture. Inoculation osteomyelitis can also occur as a result of penetrating foreign bodies, most commonly nail puncture injuries to the foot.

Contiguous Spread Osteomyelitis

Osteomyelitis secondary to spread from an adjacent soft tissue infection is called *contiguous osteomyelitis*. It can result from pressure ulcers (typically from laying in the decubitus position) or from adjacent soft tissue infections that most often involves the distal extremities (eg, diabetic foot infection). Less commonly, infection can spread from infected teeth to involve the mandible, or occur secondary to sinus infections by spreading through the mucosal lining of the sinuses into the vascular system surrounding the bone.

Contiguous-spread osteomyelitis occurs most commonly in patients older than age 50, likely because predisposing factors, such as diabetes mellitus, vascular diseases, or hip fractures, exist more often in this age group.

Patients with osteomyelitis in association with severe vascular insufficiency are extremely difficult to manage.[15] Frequently, patients with vascular disease develop osteomyelitis in their toes or even their fingers, and there is typically an adjacent area of infection, such as cellulitis or dermal ulcers. Importantly, infections in these patients can be polymicrobial, usually including *Staphylococcus* and *Streptococcus*, or a combination of those and Enterobacterales. Enterococci and anaerobic organisms also can be involved, but not as often.

Chronic Osteomyelitis

Chronic osteomyelitis is more likely to occur if large segments of bone become avascular and necrotic. It is common in inadequately managed foot infections of patients with diabetes. This results in a piece of devitalized bone to which antimicrobial delivery is impaired. As a result, the infection is prone to exacerbations and may lead to weakening of that bone or to the formation of draining sinuses to the skin.

Infectious Arthritis

Infectious arthritis usually is acquired by hematogenous spread. The synovial tissue is highly vascular and does not have a basement membrane, so organisms in the blood can easily reach the synovial fluid. Table 141-2 summarizes the characteristics of acute infectious arthritis.

TABLE 141-2

Characteristics of Acute Infectious Arthritis

Feature	Finding
Peak incidence	Children younger than 16 years Adults older than 50 years
Clinical findings	Fever of 38-40°C (100.4-104°F) in children; painful swollen joint in the absence of trauma Physical examination: Effusion, restriction of joint motion, tenderness, redness, and warmth of joint
Most commonly affected joints	Knee, hip, ankle, elbow, wrist, and shoulder
Laboratory findings Erythrocyte sedimentation rate White blood cell count Left shift Blood culture	 Elevated in 90% of cases Elevated in 30%-60% of cases Seen in two-thirds of patients Positive in 40% of cases
Needle aspiration of joint	Gram-stain diagnostic in 30%-50% of cases. Synovial fluid cultures are positive in 60%-80% of cases. Synovial fluid yields an elevated white blood cell count with a high percentage of neutrophils. Synovial fluid glucose decreased relative to serum glucose. Lactic acid levels elevated in nongonococcal infectious arthritis, but not in gonococcal infectious arthritis

Preexisting abnormal joint architecture, joint trauma, and surgery are risk factors because chronic inflammation or trauma makes the joint more susceptible to infection. Individuals with rheumatoid arthritis can be prone to bacterial infection because of an inherent phagocytic defect, as well as concomitant corticosteroid therapy, biologic response modifier, or other immunosuppressants. Patients infected with disseminated or untreated *N. gonorrhoeae* are at risk of gonococcal arthritis.

In addition to hematogenous spread, organisms can gain access to the joint from a deep-penetrating wound injury, intra-articular steroid injections, arthroscopy, prosthetic joint surgery, or spread to the joint from a contiguous focus of osteomyelitis. After bacteria gain access to the joint, the organisms begin to multiply and produce a purulent exudate within the joint. If this joint effusion is present beyond 7 days, chronic and sometimes irreversible damage can occur to the bone and joint as a result of proteolytic enzymes and pressure necrosis. Purulent effusions can promote cartilage destruction by increasing leukocyte enzyme activity. In conjunction with the development of the effusion, almost all patients will develop a hot, swollen, and painful joint.

CLINICAL PRESENTATION

Osteomyelitis

The clinical presentation of acute hematogenous osteomyelitis is summarized in Table 141-3. Although neonatal hematogenous osteomyelitis can spread rapidly to involve the joint, often there are few associated systemic symptoms.[14] A joint effusion is present in 60% to 70% of neonatal infections. Decreased limb motion or edema over the affected area may be the only signs from which to suspect the diagnosis. While it is sometimes acute in onset, the disease is often insidious in children.

Vertebral osteomyelitis produces nonspecific symptoms, such as constant back pain, fever or night sweats, and weight loss.[5] The pain typically is present at rest and increases in severity with movement. Serious neurologic complications can occur if the infection extends and compresses the spinal cord.

The presentation of osteomyelitis after surgery or trauma depends on the precipitating cause. If the infection follows surgery or bone trauma, the symptoms usually are noted within 1 month. The most frequent symptom is pain in the area of infection. Less commonly, patients also can develop a fever and elevated WBC count.

With contiguous-spread osteomyelitis there is often an area of localized tenderness, warmth, edema, and erythema over the infected site. Patients with significant vascular insufficiency usually have less pronounced local symptoms, such as pain, swelling, and redness. Less commonly, they also can have fever and elevated WBC count.

Infectious Arthritis

Patients with nongonococcal bacterial arthritis almost always present with a fever, and 50% of patients have an elevated WBC count (see Table 141-2). Nongonococcal bacterial arthritis is almost always monoarticular. The knee is the most commonly involved joint, but infections also can occur in the shoulder, wrist, hip, ankle, interphalangeal joints, and elbow joints. Sometimes, the initial focus of infection that acted as the portal of entry can be identified. Common routes for bacterial entrance include infections of the respiratory tract, skin, and urinary tract or which led to subsequent bacteremia; often no specific source can be identified. Blood cultures are important in these patients because they can be positive in 50% of patients.

The most frequent initial sign of disseminated gonococcal infections is the triad of dermatitis, tenosynovitis (inflammation and swelling of a tendon), and migratory polyarthralgia or polyarthritis. Women are more prone to develop disseminated gonococcal infections than men by a ratio of 4:1. The second and third trimesters of pregnancy and the time of menses appear to be the times of greatest risk for developing gonococcal bacteremia, hypothesized to be associated with mucosal vascularity. Common joints involved include the knee, wrist, elbow, and ankle. Presentation varies slightly depending on whether or not the woman is pregnant. In nonpregnant women, duration of symptoms are longer, presence of joint effusion is more likely, and white blood cells are more often present within the synovial fluid.[16]

Another type of infectious arthritis occurs following prosthetic joint surgery. The most common symptom is pain. Local signs of inflammation and fever are common in acute infections but chronic infections present in a more subtle fashion, typically with pain alone and often loosening of the prosthesis. With these infections, the C-reactive protein (CRP) typically is elevated, although a leukocytosis often is absent. Infections from intra-operative contamination usually become apparent within 1 year of surgery. Those that present early (<3 months) are usually *S. aureus,* but occasionally gram-negative, anaerobic, or polymicrobial infections are also seen. Less virulent skin organisms such as *S. epidermidis, Enterococcus*, or the anaerobic gram-positive bacillus, *Cutibacterium* (formerly *Propionibacterium*) *acnes* present later, often 3 to 12 months from surgery. After 1 year, hematogenous spread becomes a risk factor for *S. aureus* infection again.

Radiologic and Laboratory Tests

Osteomyelitis

2 The evaluation of a patient who may have osteomyelitis has several unusual aspects. Radiographs of the involved area should be obtained to rule out other processes such as a fracture. Bone changes characteristic of osteomyelitis appear late and are not typically seen until at least 10 to 14 days after the onset of the infection, as more than 50% of the bone matrix must be decalcified before the lesions can be detected radiologically. Magnetic resonance imaging (MRI) is the most sensitive and commonly used diagnostic imaging modality in those without metal hardware. It offers the advantage of better anatomic definition, especially of abscesses or joint effusions, compared to plain radiograph or traditional computed topography (CT) scan. Radionuclide bone scanning (with technetium or gallium) CT or positron emission tomography (PET) scanning can be useful in identifying the focus of osteomyelitis in patients unable to have an MRI.[17]

Despite the seriousness of osteomyelitis, often there are few laboratory abnormalities. The erythrocyte sedimentation rate (ESR), CRP, and WBC count may be the only laboratory abnormalities. The degree of abnormality of these laboratory findings does not correlate with the disease outcome; however, these inflammatory markers are useful for monitoring therapy. CRP is generally the more sensitive marker of response to therapy and often increases and decreases before the ESR.

When a clinical assessment of osteomyelitis is suspected, it is important to establish a bacteriologic diagnosis by culture of the infected bone and blood. Accurate culture information is especially important as a guide for treatment of osteomyelitis in this era of increasing antimicrobial resistance. Bone aspiration or bone biopsy is valuable in determining an accurate bacteriologic diagnosis. In addition, they help determine whether or not there is an abscess present. If an abscess is identified, it must be drained and the pus cultured with a Gram stain performed. Aspirates of subperiosteal pus or metaphyseal fluid yield a pathogen in 70% of cases. Cultures should be done for both aerobic and anaerobic bacteria. A Gram-stain result from the aspirate can be useful in initiating appropriate empirical antibiotic therapy.

If a specimen is obtained from a previously undrained or unopened wound abscess, the true etiologic pathogen usually can be identified. In chronic osteomyelitis, however, identification can be more difficult. Open wounds and draining sinuses frequently are contaminated with colonizing organisms and thus provide inaccurate culture information. They cannot be relied on to reflect the true etiologic pathogen unless consecutive deep sinus tract cultures reveal the same pathogens.[15] Cultures of loculated pus aspirates in the area of orthopedic devices removed from infected bone can be trusted, however, to identify the true etiologic organism. The preferable time to obtain culture material in a patient with a chronic draining sinus is at the time of open surgical debridement.

In addition to performing cultures from the involved bone, it also is important to obtain cultures from any site believed to be the primary source of a bacteremia. Approximately 50% of patients with hematogenous osteomyelitis will have positive blood cultures and may obviate the need for bone aspiration in these patients.

Infectious Arthritis

3 Radiographs of infected joints often reveal distension of the joint capsule with soft tissue swelling in the adjacent space. MRI can be helpful in identifying an infected joint, especially the shoulder and hip. In patients who have developed an infected prosthetic joint, loosening of the prosthesis can be seen radiographically.

When evaluating the possibility of a patient having infectious arthritis, immediate joint aspiration with analysis of the synovial fluid is extremely important. The presence of purulent fluid usually indicates the presence of a septic joint, although other inflammatory arthritic conditions such as rheumatoid arthritis or gout can also demonstrate purulence. The synovial fluid WBC count and percentage of neutrophils found are important factors in defining an infectious etiology. The specific values best predictive of infection are variable based on multiple factors, including whether a native or prosthetic joint is being sampled, and exist along a continuum of sensitivity and specificity, as illustrated in Table 141-4. As with osteomyelitis, most patients will have an elevated CRP concentration and ESR. However, serum WBC, ESR, and CRP may not be useful acutely in septic arthritis.[18] Approximately half of patients with an infected native joint have a low synovial glucose level, usually less than 40 mg/dL (2.2 mmol/L). Both blood and joint fluid should be cultured aerobically and anaerobically in a patient suspected of having an infected joint. These cultures or Gram stains of joint fluid demonstrate bacteria in > 50% of patients with septic arthritis; however, such results are positive in only 25% of patients with gonococcal arthritis. Pharyngeal, rectal, cervical, or urethral smears and cultures, as well as cultures of cutaneous lesions, should be performed if a disseminated gonococcal infection is considered. Nucleic acid–based assays should also be used for the diagnosis of genital gonococcal infection.

TABLE 141-3

Clinical Presentation of Hematogenous Osteomyelitis

Signs and symptoms Significant tenderness of the affected area, pain, swelling, fever, chills, decreased motion, and malaise
Laboratory tests Elevated erythrocyte sedimentation rate, C-reactive protein, and white blood cell count 50% of patients will have positive blood cultures
Diagnostic studies Bone changes observed on radiographs 10-14 days after the onset of infection. Magnetic resonance imaging and technetium scans positive as early as 1 day after the onset of infection

TABLE 141-4

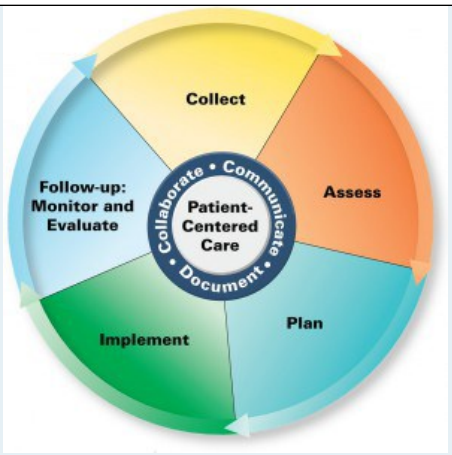
Synovial Fluid Analysis Associated with Infectious Arthritis

Native Joint Fluid	
WBC >50,000 cells/μL (50×10^9/L) >90% (0.90) neutrophil count	Sensitivity 62%, Specificity 92%, Sensitivity 73%, Specificity 79%.
Prosthetic Joint Fluid	
Knee	
Acute (<6 weeks from arthroplasty) WBC >8100 cells/μL (8.1×10^9/L) *Chronic (>6 months from arthroplasty)*WBC >1700 cells/μL (1.7×10^9/L) OR >65% (0.65) neutrophil count	Sensitivity 86%, Specificity 89%, Sensitivity ≈95%, Specificity ≈90%.
Hip	
WBC >4200 cells/μL (4.2×10^9/L)	Sensitivity 84%, Specificity 93%.

Data from References 60-63.

PATIENT CARE PROCESS

Patient Care Process for Bone and Joint Infections



Collect

- Patient characteristics (eg, age, sex, pregnancy status)
- Patient medical history
- Social history (eg, ethanol or injection drug use) and living conditions
- Current medications and recent antibiotic use
- Objective data
  - Culture of bone, synovial fluid, or deep tissue (not superficial)
  - Labs including white blood cells (WBC), serum creatinine (SCr), and C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR)
  - Imaging for infection

Assess

- Risk factors for bone and joint infections (Table 141-1)
- Markers of infection (Tables 141-2 and 141-3)
- Culture results and antimicrobial susceptibilities
- Ability/willingness to adhere to treatment regimen, including self-administration of outpatient parenteral therapy or travel to infusion center
- Ability/willingness to pay for treatment options (eg, home health, infusion center visits, and/or prescriptions from pharmacy)
- Ability/willingness to obtain laboratory monitoring tests (eg, WBC, SCr, serum drug concentrations)
- Emotional status (eg, presence of anxiety, depression)

Plan*

- Drug therapy regimen including specific antibiotic dose, route, frequency, and duration (see Table 141-6)
- Monitoring parameters including efficacy (eg, WBC, CRP or ESR, pain, limb swelling) and safety (eg, complete blood count, SCr, diarrhea); frequency and timing of follow-up (Table 141-7)
- Patient education (eg, purpose of treatment, invasive procedures, drug-specific information, medication administration/injection technique)

- Self-monitoring for resolution of symptoms, occurrence of adverse effects, when to seek emergency medical attention
- Referrals to other providers when appropriate (eg, infectious diseases specialist, orthopedic surgeon, vascular surgeon, endocrine/diabetes specialist)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up (2-4 weeks)

Follow-up: Monitor and Evaluate

- Resolution of symptoms (eg, pain, limb/joint swelling, instability)
- Presence of adverse effects (eg, cytopenias, diarrhea, hypersensitivity reactions)
- Patient adherence to treatment plan using multiple sources of information
- Reevaluate again at the end of therapy

****Collaborate with patient, caregivers, and other healthcare professionals.***

TREATMENT

Desired Outcome

Osteomyelitis

The goals of treatment are resolution of the infection and prevention of long-term sequelae. The ultimate outcome of osteomyelitis depends on the acute or chronic nature of the disease and how rapidly appropriate therapy including surgical drainage where appropriate is initiated. Patients with acute osteomyelitis have the best prognosis. Cure rates exceeding 80% can be expected for patients with acute osteomyelitis who have surgery when indicated and receive appropriate antibiotics for 4 to 6 weeks. When the growth plate is involved in children, discrepancies in the growth of bones or angular bone deformities can result. The infection is almost never fatal.

In contrast, patients with chronic osteomyelitis have a much poorer prognosis. Dead bone and other necrotic material from the infection act as a bacterial reservoir and make the infection very difficult to eliminate. Adequate surgical debridement to remove all the dead bone and necrotic material, combined with prolonged administration of antibiotics, provides the best chance to obtain a cure. The inability to remove all the dead bone can allow residual infection and require suppressive antibiotics to control the infection. Amputation, declines in quality of life, and recurrent infection are not uncommon with chronic osteomyelitis.

Infectious Arthritis

While many patients who develop infectious arthritis recover with no long-term sequelae, 50% are left with decreased joint function or mobility. Gonococcal arthritis usually resolves rapidly with antibiotics and has fewer sequelae. Individuals at greatest risk for long-term sequelae are those who have symptoms present for more than 7 days before starting therapy and those with infections occurring within the hip joint and infections caused by gram-negative organisms. Common long-term residual effects following infectious arthritis are limited joint motion and persistent pain.

During the initial phase of the infection, weight bearing such as walking on the joint should be avoided. Passive range-of-motion exercises should be initiated when the pain begins to subside to maintain joint mobility. Approximately one-third of patients with bacterial arthritis have a poor joint outcome, such as severe functional deterioration. Poor joint outcomes are associated with older patients, those with preexisting joint disease, and

patients with an infected joint containing synthetic material.

General Approach to Treatment

Osteomyelitis

Following completion of the steps needed to determine the infecting organism, the most important treatment modality of acute osteomyelitis is the administration of appropriate antibiotics in adequate doses for a sufficient length of time. It is important to stress that early antibiotic therapy can mitigate the need for surgery, subsequent sepsis, chronic infection, disruption of longitudinal bone growth, and angular deformity of the bone. A long delay in treatment can allow bone necrosis to occur and make eradication of the infection much more difficult. In these patients with chronic osteomyelitis, exacerbations of the infection can result if all necrotic tissue or infected indwelling hardware are not removed surgically and all microorganisms eliminated. Chronic suppressive antimicrobial therapy and adjunctive treatment with hyperbaric oxygen or antibiotic-impregnated implants during surgery also have been used.

If a patient with hematogenous osteomyelitis does not respond by having a decrease in fever, local swelling, redness, and pain following the initiation of adequate antibiotic therapy, the patient should undergo surgical debridement of the infected area. It is important to emphasize the priority of starting antibiotics immediately after the cultures have been obtained for best microbiological yield and outcomes.[19]

Infectious Arthritis

Patients with infectious arthritis are typically admitted to the hospital to obtain synovial fluid and blood cultures and initiate antimicrobial therapy. An attempt to decrease bacterial burden in the joint space is made by performing either open or arthroscopic debridement. Empiric antibiotics are started as soon as culture specimens are collected. As with osteomyelitis, early initiation of antibiotic therapy is important to avoid complications such as avascular necrosis, limb-length discrepancy, and pathologic fractures. Staphylococci and streptococci are the most common organisms found in septic arthritis, accounting for approximately 70% to 85% of all cases, so treatment should be directed accordingly.[20,21]

In patients with prosthetic joint devices, orthopedic surgeons must work alongside infectious disease practitioners to determine the best course of action.[22] The gold standard treatment method includes resection of the implant, placement of a temporary antibiotic-impregnated cement spacer, and delayed component reimplantation. Retention of the implant may be necessary in patients who will receive irrigation and debridement in addition to antibiotic therapy, or antibiotic therapy alone in patients unable to tolerate surgical procedures.[23]

Pharmacologic Therapy

Osteomyelitis

Antibiotic Selection

A critical component in the management of osteomyelitis is the selection of appropriate antibiotics. Empiric therapy must be selected on the basis of the most likely infecting organism while the results of culture and susceptibility data are pending. Once culture and susceptibility results are obtained, the antimicrobial therapy should be tailored. Table 141-5 summarizes empiric therapy recommendations.

TABLE 141-5

Empiric Treatment of Osteomyelitis

Patient Subtype	Likely Infecting Organism	Antibiotic[a]	Recommendation Grades[b]
Newborn	*Staphylococcus aureus*, Group B *Streptococcus, Escherichia coli*	Cefazolin 50-150 mg/kg/day IV	B-3
Children 3 years of age or younger	1. If vaccinated for *Haemophilus influenzae* type b: *K. kingae, S. aureus* or streptococci 2. If not vaccinated against *H. influenzae* type b (*or Streptococcus pneumoniae)*	1. Cefazolin 100-150 mg/kg/day IV 2. Cefuroxime 150 mg/kg/day IV Alternatives are ceftriaxone 75 mg/kg/day IV or amoxicillin-clavulanate 40-45 mg/kg/day orally	B-3 B-3
Children 4 years of age and older	*S. aureus*	Vancomycin 60 mg/kg/day IV, clindamycin 40 mg/kg/day, or cefazolin 100-150 mg/kg/day IV	A-3
Adults	*S. aureus*	Vancomycin 15 mg/kg every 12 hours or cefazolin 2 g IV every 8 hours	A-3
Persons who inject drugs	*S. aureus, Pseudomonas*	Vancomycin 15 mg/kg every 12 hours plus ciprofloxacin 750 mg orally twice daily, ceftazidime or cefepime 2 g IV every 8 hours	B-3
Postoperative or posttrauma patients	Gram-positive and gram-negative organisms	Vancomycin 15 mg/kg IV every 12 hours plus ceftazidime or cefepime 2 g IV every 8 hours	B-3
Patients with vascular insufficiency	Gram-positive and gram-negative organisms	Vancomycin 15 mg/kg IV every 12 hours plus ceftriaxone 2 g every 24 hours	B-3
	If anaerobes suspected (e.g. necrosis)	Add metronidazole 500 mg every 8 hours or clindamycin 900 mg IV every 8 hours or substitute ertapenem for ceftriaxone	C-3

IV, intravenous.

[a]Dosage should be adjusted for some agents in patients with renal and/or hepatic dysfunction.

[b]Strength of recommendations: A, B, C = good, moderate, and poor evidence to support recommendation, respectively. Quality of evidence: 1 = Evidence from more than one properly randomized, controlled studies or multiple time series; or dramatic results from uncontrolled experiments. 2 = Evidence from more than one well-designed clinical trial with randomization, from cohort or case-controlled analytic studies. 3 = Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert communities.

With *Staphylococcus* being the most common bacteria in osteomyelitis, resistance patterns must be considered when deciding on an empiric agent. For communities showing low evidence of resistant strains of *S. aureus*, oxacillin or nafcillin has historically been the drug of choice, although cefazolin is now being used more often to treat susceptible strains due to ease of dosing, lower cost, and fewer adverse effects compared to anti-staphylococcal penicillins.[22-24] Clindamycin can be used in less severe cases, in patients with severe beta-lactam allergies or where methicillin-resistant

Staphylococcus aureus (MRSA) rates are unknown.[25,26] Clindamycin is used more commonly in children because MRSA is more likely to be community-acquired and susceptible to clindamycin in this population. If 10% or more of *S. aureus* isolates are methicillin resistant in the surrounding community, then an agent active against MRSA should be selected empirically. Vancomycin is the treatment of choice in this scenario and in adults since they often have risk factors for hospital-associated MRSA.[25,26] Daptomycin is an effective alternate in patients where mitigation of the adverse effects associated with vancomycin or a more convenient dosing strategy are prioritized.[27]

In the setting of vertebral osteomyelitis, empiric therapy should be initiated in conjunction with culture if the patient is hemodynamically unstable, septic, or experiencing neurologic compromise; otherwise, it is recommended empiric therapy be held while awaiting culture results.[5] Vancomycin in combination with a fluoroquinolone or third/fourth-generation cephalosporin such as ceftriaxone is a reasonable empiric regimen.

Antibiotic Bone Concentration

5 Antibiotics used in the management of acute osteomyelitis generally are given in high doses (adjusted for weight, renal function, hepatic function, or both) so that adequate antimicrobial concentrations are reached within the infected bone and joint.[23,28] Table 141-6 summarizes antibiotic doses that have been successful in the treatment of osteomyelitis.

TABLE 141-6

Antimicrobial Agents and Typical Doses for the Treatment of Bone and Joint Infections

Antimicrobial	Dose[a]	Comments
Amoxicillin	Adult: 1 g orally every 8 hours Children: 80-90 mg/kg/day divided every 12 hours	500-875 mg orally twice daily to 500 mg three times daily may be used for chronic suppression in adults
Amoxicillin/Clavulanate	Adult: 2,000/125 mg orally every 12 hours Children: 80-90 mg/kg/day of amoxicillin divided every 12 hours	875/125 mg orally twice daily or 500/125 mg three times daily may be used for step-down therapy or chronic suppression
Ampicillin	Adult: 2 g IV every 4 hours[21] Children: 150-200 mg/kg/day in four equal doses (max 8-12 g daily) VO: 12 g IV every 24 hours, continuous, or in six divided doses	May add IV aminoglycoside or ceftriaxone when treating *Enterococcus* spp. Continue adjunct therapy for 4-6 weeks in patients with infective endocarditis
Ampicillin/Sulbactam	Adult: 3 g IV every 6	3-g dose equals 2-g ampicillin and 1-g sulbactam

	hours	
Anti-staphylococcal penicillins (nafcillin, oxacillin, dicloxacillin)	Adult: Nafcillin or oxacillin 2 g IV every 4 hours Children: ≤200 mg/kg/day in four equal doses (max dose 8-12 g daily) VO: Nafcillin or oxacillin 2 g IV every 4 hours or continuous infusion	Adverse effects and cost are higher than cefazolin Dicloxacillin 500 mg three or four times daily may be used for suppression in adults
Aztreonam	Adult: 2 g IV every 8 hours	Use for patients with severe penicillin allergy and quinolone-resistant strains
Cefepime	Adult: 2 g IV every 8-12 hours	For Enterobacterales, 2 g IV every 12 hours
Cefotetan	Adult: 2 g IV every 12 hours	
Ceftazidime	Adult: 2 g IV every 8 hours	
Ceftriaxone	Adult: 2 g IV every 24 hours Children: 80-100 mg/kg/dose every 12-24 hours	
Ciprofloxacin	Adult: 400 IV every 8-12 hours or 500-750 mg orally every 12 hours	Should not be used as monotherapy for *Staphylococcus* infection, but may be combined with rifampin. Higher dose for *Pseudomonas.*
Clindamycin	Adult: 600 mg IV every 6 hours or 300-600 mg orally every 6 hours Children: 40 mg/kg/day in four equal doses (max dose 3 g daily)	Recommended as second line for sensitive staphylococcal infection. 300 mg twice daily or three times daily may be used for suppression in adults.

	VO: 600-900 mg IV every 8 hours, or 300-450 mg orally four times daily	
Daptomycin	Adult: 6-8 mg/kg IV every 24 hours	
Doxycycline	Adult: 100 mg orally twice daily	Can be used in addition to rifampin for Brucella infection
Ertapenem	Adult: 1 g IV every 24 hours Children: 15 mg/kg every 12 hours	
First-generation cephalosporin (Cefazolin, Cephalexin)	Adult: Cefazolin 2 g IV every 8 hours Children: 100-150 mg/kg/day in 3 equal doses (max dose 6 g daily)	Cephalexin 500 mg orally every 6 hours or 1 g orally every 8 hours for step-down treatment.[21] Cephalexin 500 mg twice or three times daily may be used for suppression
Imipenem/cilastatin	Adult: 500 mg IV every 6 hours	Can add IV aminoglycoside empirically for treatment of *P. aeruginosa*
Levofloxacin	Adult: 500-750 mg IV once daily or 750 mg orally once daily	Add rifampin for treatment of *S. aureus*
Linezolid	Adult: 600 mg IV or orally every 12 hours Children: 30 mg/kg/day in three equal doses (max dose 1.2 g for no more than 28 days)	Long-term use can lead to cytopenias
Meropenem	Adult: 1 g IV every 8 hours	
Metronidazole	Adult: 500 mg orally or IV every 8	Drug of choice for *Bacteroides* species and other susceptible anaerobes

	hours	
Minocycline	Adult: 200 mg orally initially, then 100 mg orally twice daily	
Moxifloxacin	Adult: 400 mg orally once daily	For streptococci, Enterobacterales, and other susceptible gram-negative organisms. Not recommended for staphylococcal infection unless combined with rifampin.
Penicillin G	Adult: 3-4 million units IV every 4 hours or 20 million units IV continuous every 24 hours	For *Enterococcus*, add 4-6 weeks of aminoglycoside therapy in patients with infective endocarditis
Piperacillin/Tazobactam	Adult: 4.5 g IV every 6-8 hours	Every 6 hours or extended infusion (over 4 hours) for *P. aeruginosa*
Rifampin	Adult: 300 mg orally twice daily Children: 10 mg/kg/day orally divided twice daily	Only to be used in combination with another antimicrobial
Trimethoprim–Sulfamethoxazole	Adult: 1-2 double-strength tablets orally twice daily or 1 double-strength tablet orally three times a day	Second-line agent for Enterobacterales and other susceptible aerobic gram-negative organisms.
Vancomycin	Adult: 15 mg/kg IV every 12 hours Children: 60 mg/kg/day in four equal doses	Adjust based on patient and pharmacokinetic parameters. Target trough of 15 mcg per milliliter (mg/L; 10.4 µmol/L) or area under the concentration-curve of 400-600. Consider loading dose for MRSA. For *Enterococcus*, add 4-6 weeks of aminoglycoside therapy in patients with infective endocarditis. If bacteria is known, use only if resistant to beta-lactams or patient is allergic to first-line options

IV, intravenous; MRSA, methicillin resistant *Staphylococcus aureus*; VO, vertebral osteomyelitis.

[a]Dosage should be adjusted for some agents in patients with renal and/or hepatic dysfunction.

Oral Antibiotic Therapy

6 Criteria for the use of oral outpatient antibiotic therapy for osteomyelitis include all of the following:

- Confirmed osteomyelitis
- Initial positive clinical response to parenteral antibiotics
- A suitable oral agent is available
- Adherence is ensured

Suitable candidates are children with good clinical response to intravenous therapy and adults without diabetes mellitus or peripheral vascular disease.

The use of oral antibiotics is well studied in children.[29-31] Typically, injectable antibiotics are used initially and then switched to oral antibiotics when the patient is afebrile and there is a decrease in the signs of inflammation.[19] If pus is obtained on the initial needle aspirate, or if a reduction in fever, local swelling, and tenderness does not occur despite adequate rest, immobilization, and intensive antibiotic therapy, patients undergo surgical drainage. The patients enrolled in oral antibiotic trials generally had disease of recent onset, identification of a specific infecting organism, enforced adherence, and surgery as indicated. In patients who meet these criteria, oral antibiotics appear to offer a great advantage in the treatment of osteomyelitis. Patients not meeting these criteria may have a higher risk of developing chronic osteomyelitis if oral therapy is inappropriate or not strictly adhered to. In adults, oral antibiotics are used more conservatively due to more limited blood flow to the bones, but evidence is emerging that oral therapy can be effective for adult osteomyelitis and septic arthritis.[32-34] Ciprofloxacin and levofloxacin are well-studied oral primary therapy due to their high bioavailability and great distribution into bone.[35] Fluoroquinolones (with the exception of delafloxacin) are not reliably effective against staphylococci on their own as resistance develops rapidly and should not be used alone empirically. They have successfully been combined with rifampin when isolates are susceptible to both classes of drugs.[36] Rifampin is particularly useful for treating infections with biofilms that have a propensity to grow on smooth surfaces such as bone, and especially prosthetic devices.[37] However, rifampin has a multitude of drug interactions, and caution should be used when adding to a regimen.

Duration of Antibiotic Therapy

7 Following debridement, bone takes 3 to 4 weeks to revascularize, which becomes the basis of treatment duration. The specific duration of antibiotic therapy needed in the management of osteomyelitis and septic arthritis has traditionally been 4 to 6 weeks and 3 to 4 weeks, respectively.[38] For adults, those durations of treatment are still recommended but newer studies in children have explored shorter durations along with more liberal transitions to oral antibiotics. For children with *septic arthritis*, a course as short as 10 days is sufficient as long as the CRP level normalizes.[39] French guidelines recommend treatment for a minimum of 3 weeks in children with osteomyelitis as failure rates approaching 20% have been observed with antibiotics administered for less than that.[40] This is based on studies showing that improvement in the patient's clinical signs and symptoms in addition to normalization of the CRP level or ESR is an important parameter for predicting efficacy.[41,42] Treatment failures may be due to the presence of residual bacteria in necrotic bone or infected hardware (wires, plates, screws, and rods) that could not be removed.[35] If signs or symptoms are still present at the end of therapy, treatment should be extended. For adults, guidelines from the Infectious Diseases Society of America (IDSA) recommend therapy for 8 weeks in adults with osteomyelitis from MRSA,[43] particularly in patients with vertebral osteomyelitis at high risk of relapse such as those with end-stage renal disease or undrained paravertebral/psoas abscesses.[44] In some cases of chronic osteomyelitis, lifelong suppressive therapy might be the most appropriate option, particularly when prosthetic devices remain.[45] The goal in chronic suppressive therapy is to avoid readmissions from exacerbation of established infection; however, the use of this approach must be balanced with the risk for development of antimicrobial resistance and toxicity over extended periods.[46] Often specific dosing regimens of oral therapies are utilized in this situation (see Table 141-6).[46]

Duration of antibiotic administration for vertebral osteomyelitis can vary depending on the infecting organism, extent of bone destruction, or presence of abscesses. The IDSA guidelines recommend a minimum of 6 weeks of either parenteral therapy or highly bioavailable oral therapy.[3] This is necessary because of the outcomes in older patients with degenerative bone disease that have reduced blood flow to the site of infection and are most at risk of the disease. With gram-negative bacteria a longer duration (8 weeks or greater) is associated with less rates of recurrence compared to

shorter durations (4-6 weeks).[7] One prospective trial compared 6 and 12 weeks of treatment for patients with pyogenic vertebral osteomyelitis (most commonly *S. aureus*) and found the longer duration to be no better.[47] However, patients with prosthetic joint infections have benefited from 12 weeks of antibiotic therapy.[48] For patients with retained hardware following prosthetic joint infection, 3 to 6 months of therapy is often necessary.[45] Many questions remain on the optimal duration for bone infections in adults and whether it is safe to use shorter courses.[35]

Special Populations

Osteomyelitis in PWID has unique features. More than 50% of such infections involve the vertebral column and up to 20% of infections are located in either the sternoarticular or pelvic girdle. Infections are much less frequent within the extremities. They also have an unusual spectrum of organisms. Although *Staphylococcus* and *Streptococcus* are sometimes cultured, with MRSA being more common than in the general population, gram-negative bacteria are responsible for many infections. In one outbreak *P. aeruginosa*, either singly or in combination with other organisms, was cultured in 78% of all such infections. *Klebsiella, Enterobacter*, and *Serratia* species also can be less commonly identified. Spinal infections are caused predominately by *S. aureus.*[49]

Patients with sickle cell anemia and related hemoglobinopathies also represent a unique population, in that two-thirds of bone infections in these patients are caused by *Salmonella* species, while the rest are usually caused by staphylococci and other gram-negative organisms.[50] Bowel infarctions from sickle cell disease can facilitate the entry of salmonellae from the colon into the bloodstream with resultant hematogenous spread to the bone. Osteomyelitis in patients with sickle cell disease may occur in any bone, but it most commonly involves the medullary cavity of long or tubular bones. Because of the difficulty in separating bone pain during a sickle cell crisis from that of an infection, osteomyelitis can be relatively advanced in these patients by the time the diagnosis is made.

Infectious Arthritis

Antibiotic Selection

8 The three most important treatments for infectious arthritis are appropriate antibiotics, joint drainage, and joint rest. Smears of the synovial fluid can be useful to select appropriate antibiotic therapy initially.[8] If bacteria are not observed on the Gram stain in a patient who has a purulent joint effusion, antibiotics still should be initiated because of the low sensitivity of the Gram stain. A delay in initiating antibiotics significantly increases the likelihood for long-term complications. The specific antibiotic selected depends on the most likely infecting organism, but it should typically target *Staphylococcus* spp. (eg, vancomycin, daptomycin, or clindamycin). When staphylococci infect prosthetic hardware that cannot be removed, rifampin is recommended to be added to the therapy for its effects on biofilm, but drug–drug interactions should always be evaluated with use of this agent.[45]

Antibiotic Joint Space Concentration

The antibiotics selected usually are administered parenterally to achieve sufficient concentrations within the synovial fluid, and thus intra-articular antibiotic injections are unnecessary.

In prosthetic joint infections, antimicrobial cement spacers are often used to aid in delivery of the antimicrobial to the site of infection. The most common antimicrobials used include vancomycin and aminoglycosides (tobramycin or gentamicin).[51] However, the doses of each agent are widely variable and it is uncertain whether the placement of antimicrobial cement spacers adds outcome benefit to systemic therapy.[51,52] The idea that antimicrobial cement spacers provide only beneficial local exposure of the antimicrobial agent without systemic consequences has been questioned.[53] The incidence of acute kidney injury in patients receiving treatment with antimicrobial cement spacers was 4.8%, with the incidence ranging from 2% to 17% based on the definition of acute kidney injury used.[54]

Similar to osteomyelitis, once the infection is confirmed and initial response to parenteral therapy is achieved, culture susceptibilities have resulted, and adherence is ensured, then selected oral antibiotics can be used for the treatment of infectious arthritis.

Home Antibiotic Therapy

Because the management of bone and joint infections frequently requires prolonged parenteral antibiotics, administration of intravenous treatment

in the home or a clinic is commonly performed. This is called outpatient parenteral antimicrobial therapy (OPAT).[55] Although acute osteomyelitis is one of the more common infectious diseases that can be treated with long-term intravenous antibiotics outside the hospital, not all patients are acceptable candidates for home administration. Patients must be screened to include those who are receiving a stable treatment, are interested and motivated in participating, who have good venous access, often have support from family members or caregivers, and safe and stable housing including refrigerated drug storage capability. Certain exclusion criteria also must be considered. Patients are not eligible if their eyesight or dexterity prevent them from attaching the admixture to their catheter when they do not have a caregiver that can help them daily. Although many providers are leery about allowing patients to receive parenteral antibiotics at home if they have any recent history of intravenous drug use, this bias is inappropriate in the setting of a structured therapy program for opioid use disorder which can lead to better outcomes for both disease states.[56] In addition to meeting these initial screening criteria, patients complete training before hospital discharge. Understanding of aseptic technique, proper catheter care, and correct administration techniques must be documented. Complications in patients receiving outpatient courses of parenteral antibiotics are fairly common (18%), and often lead to readmission when they occur.[57,58] Patients without adequate insurance or the support at home necessary to administer intravenous antibiotics may choose to come to an infusion center for each treatment. Others may need to be admitted to a skilled nursing facility for the duration of their therapy. A midline or central intravenous catheter is often required for long-term venous access. This is most commonly accomplished with a peripherally inserted central catheter (PICC).

The specific antibiotic regimen characteristics must also be considered when evaluating a patient for home antibiotics. After susceptibility of the microbiologic culture, the number of required daily antimicrobial doses is important. Most skilled nursing facilities are only able to accommodate infusions once each day. The stability of the antibiotic at room temperature is relevant when considering a continuous infusion (that can ideally be exchanged once daily), and shelf life can determine the required frequency of deliveries. Aminoglycosides and vancomycin have unique requirements for monitoring of the regimen, such as more frequent serum creatinine and drug-level monitoring. Although an organism can be susceptible to several antimicrobial agents, the use of the most practically simple regimen may often take precedence in OPAT over antimicrobial stewardship principles of selecting the most narrow spectrum agent.[58]

Individualized Therapy

Individualized therapy is important in the treatment of osteomyelitis and infectious arthritis. Patient quality of life may be significantly diminished in the short term from an inconvenient treatment regimen, but the long-term sequelae of inadequately treated infection can be much worse, such as impaired joint motion-draining sinus tracts, or even amputation, if it is required. Patient demographics, infection characteristics (eg, infecting organism and its susceptibility patterns), treatment cost, and quality-of-life issues all play a major role in evaluating individualized treatment alternatives (oral therapy or OPAT) rather than requiring patients to remain hospitalized to receive 4 to 6 weeks of intravenous antibiotics. Although serious adverse reactions are uncommon, in one study 85.7% of children receiving vancomycin had some form of adverse drug events and 42.9% of patients required the drug be discontinued.[59] Monitoring is important to ensure that personalized therapy is effective to both cure the infection and minimize the risk for complications.

EVALUATION OF THERAPEUTIC OUTCOMES

Monitoring of the Pharmaceutical Care Plan

9 Patients with bone and joint infections must be monitored closely. Table 141-7 summarizes a pharmaceutical care monitoring protocol. An assessment of a therapy's success or failure is based on the patient's clinical findings and laboratory values. The clinical signs of inflammation, such as swelling, tenderness, pain, redness, and fever, should resolve relatively quickly with appropriate therapy. Initially, the clinical signs are assessed daily until improvement and then periodically thereafter. Elevations in the CRP or ESR may not return to normal until after several weeks of therapy. The WBC count usually is obtained once (or twice) per week until it returns to the normal range and then is monitored for myelosuppression along with other blood cells. If by the end of the 4- to 6-week antibiotic course the clinical findings of osteomyelitis are no longer present and the CRP and ESR are within normal limits, the patient can be considered a clinical cure. Patients can relapse, however, after initially appearing to be cured. No relapse for 1 year generally is considered a complete cure.

TABLE 141-7

Monitoring Protocol

Parameter	Frequency	Notes
Culture and susceptibility	At initiation of treatment	No need to repeat unless clinical failure or original was not from a deep culture site (surgical sample)
Basic or complete metabolic laboratory panel	Weekly	Monitoring for electrolyte abnormalities and renal function
C-reactive protein or erythrocyte sedimentation rate	At initiation and completion of treatment	Although some providers will obtain weekly, this is often unnecessary as levels may not normalize until several weeks of therapy are complete
Therapeutic drug monitoring	Weekly	Agents such as vancomycin, aminoglycosides, and some antifungal therapies require ongoing monitoring for efficacy, toxicity, or both
Clinical signs of inflammation (redness, pain, swelling, tenderness, and fever)	Daily during initiation of therapy	
Adherence of outpatient therapy	Reinforce before starting therapy and with each healthcare visit	Adherence is critical if treatment is to be successful
Complete blood count	Weekly	White blood cell count is monitored for normalization to indicate efficacy. Certain antimicrobial agents may cause blood dyscrasias when used for long-term therapy (eg, linezolid, trimethoprim–sulfamethoxazole, as well as vancomycin and beta-lactams to a lesser extent)

If a patient fails to resolve the clinical signs and symptoms of inflammation after appropriate empirical antibiotics, suspicion for an abscess should be raised. Additional imaging and surgical debridement may be needed, particularly in situations where there was retained hardware or incompletely resected infection. In addition, the patient might have a resistant or an atypical infecting organism that may require a modification of the antibiotic therapy. It is especially important to identify the infecting organism and its susceptibility pattern. Follow-up cultures at subsequent debridements can be useful to assess the antibiotic therapy in patients with unresolved infection.

Despite apparently adequate surgery and antibiotics, some patients can fail therapy and have relapses in their infection. This scenario is more common in those having chronic osteomyelitis, especially with peripheral vascular disease. These patients can require long-term oral suppressive antimicrobial therapy to keep the infection under control.

ABBREVIATIONS

CRP	C-reactive protein
CT	computed tomography
ESR	erythrocyte sedimentation rate
IDSA	Infectious Diseases Society of America
MRI	magnetic resonance imaging
MRSA	methicillin-resistant *Staphylococcus aureus*
OPAT	outpatient parenteral antimicrobial therapy
PET	positron emission tomography
PICC	peripherally inserted central catheter
PWID	person who injects drugs
WBC	white blood cell
VO	vertebral osteomyelitis

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SELF-ASSESSMENT QUESTIONS

1. What type of osteomyelitis occurs most commonly in children?
   A. Chronic
   B. Contiguous
   C. Direct inoculation
   D. Hematogenous
2. Infectious arthritis most commonly involves how many joints?
   A. 1
   B. 2
   C. 3
   D. 4
3. Which of these bacteria is most likely to cause a joint infection in a patient who had a prosthetic knee replacement 7 months ago?
   A. *S. aureus*
   B. *S. epidermidis*
   C. *N. gonorrheae*
   D. *K. kingae*
4. In a child known to have osteomyelitis from methicillin-susceptible *S. aureus,* what is the standard duration of antimicrobial therapy if they have responded adequately?
   A. 1 week
   B. 3 weeks
   C. 6 weeks
   D. 12 weeks
5. What is the most common organism causing hematogenous osteomyelitis?
   A. *Group B Streptococcus*
   B. *Haemophilus influenzae*

C. *Pseudomonas aeruginosa*

D. *Staphylococcus aureus*

6. Compared to other types of bone infections, which of these most accurately describes the pathogens that cause osteomyelitis in a patient with diabetic foot infection?

A. Anaerobic

B. Gram negative

C. Gram positive

D. Multiple organisms

7. What is the most common organism causing adult bacterial arthritis?

A. *E. coli*

B. *P. aeruginosa*

C. *S. aureus*

D. *S. pyogenes*

8. What would be the most useful long-term monitoring strategy for a patient with osteomyelitis?

A. C-reactive protein daily

B. White blood count daily

C. Erythrocyte sedimentation rate every 6 months

D. C-reactive protein at the beginning and end of therapy

9. When used alone, oral ciprofloxacin for osteomyelitis would be most likely to fail with which infecting organism?

A. *Serratia marcescens*

B. *S. aureus*

C. *Enterobacter cloacae*

D. *E. coli*

10. Which antimicrobial regimen would be most appropriate for empiric treatment of hematogenous osteomyelitis in a 7-year-old boy?

A. Ampicillin

B. Cefuroxime

C. Doxycycline

D. Clindamycin

11. Which antimicrobial regimen would be most appropriate for empiric treatment of hematogenous osteomyelitis in an IV drug abuser?

A. Levofloxacin

B. Vancomycin and ceftazidime

C. Nafcillin and cefepime

D. Clindamycin

12. Which of these antimicrobial agents is most commonly used in cement spacers following prosthetic joint infection?

A. Ampicillin

B. Ceftriaxone

C. Ciprofloxacin

D. Tobramycin

13. Which antimicrobial is most likely to cause thrombocytopenia if used for a prolonged time period?

A. Ampicillin

B. Ceftriaxone

C. Linezolid

D. Metronidazole

14. What location is most common for contiguous osteomyelitis to occur in adults?

A. Foot

B. Humerus

C. Mandible

D. Vertebrae

15. What duration of therapy is most appropriate for a patient with vertebral osteomyelitis caused by MRSA?

A. 2 weeks

B. 4 weeks

C. 8 weeks

D. 16 weeks

SELF-ASSESSMENT QUESTION-ANSWERS

1. **D.** Hematogenous osteomyelitis occurs most often in children. The source of infection likely comes from minor breaks in the skin or normal oral bacteria that enter into the bloodstream. Due to good blood flow to growing bones infection is usually curable and does not progress to chronic stage (A) Contiguous osteomyelitis (B) often comes from adjacent soft tissue infection which is more common in patients with diabetes. Direct inoculation (C) can result from surgery or trauma such as a motor vehicle accident that are rare overall.

2. **A.** Infectious (septic) arthritis most commonly inflicts only one joint. The exception is when hematogenous infection seeds multiple joints. This would be more common in patients with a continuous source such as infective endocarditis where the body is unable to eliminate the bacteria because of limited immune activity on heart valves where bacteria are attached in a protective biofilm-forming vegetation.

3. **B.** *Staphyloccocus epidermidis* is the most likely bacteria to cause prosthetic joint infection 6 to 12 months after surgery. Although it is not normally considered a pathogen because of being a nonvirulent skin commensal, it can contaminate prosthetic devices during surgery and cause an indolent infection. It is often not detected until many months after surgery and can sometimes present with signs such as joint loosening, which is not as indicative of infection. That is why it is very important to collect multiple cultures when exploring the joint to diagnosis infection. A single culture with *S. epidermidis* is difficult to assess as infection without more traditional symptoms. White blood cells in the synovial fluid or detected in tissue during surgery are the best way to determine if it is a potential causative organism. It is an organism that has a strong propensity to form biofilm on prosthetic surfaces and it can be very difficult to eradicate. *S. aureus* also has the ability to attach to foreign surfaces but is very aggressive and presents weeks to a few months after surgery if it is introduced into the wound during the operation. It causes more traditional signs of infection such as redness, pain, and swelling. Even a single colony of *S. aureus* detected is enough to warrant treatment. After 12 months, *S. aureus* can also infect the new joint following skin abrasions, even those that are not detected by the patient. *Neisseria gonorrheae* can cause septic arthritis in those that are young and sexually active but it is not a pathogen of concern following prosthetic joint infection. *K. kingae* is common in young children from 6 months to about 3 years old, but it is not seen in prosthetic joint infection.

4. **B.** Children have more vascular bones that means antibiotics and white blood cells can reach the site of infection better. Healing is typically much more rapid than in adults and relapse rates lower. Therefore, 3 to 4 weeks is the usual duration of therapy in children compared to 6 to 8 in older patients, especially when the pathogen is known and empiric antibiotic therapy was effective. Many European countries have a low rate of MRSA and guidelines recommend 3 weeks of therapy. The United States has higher MRSA rates and some practitioners might be hesitant to use short courses but children can also develop adverse effects of antibiotics prescribed for long periods. Although septic arthritis has been treated with 10 days of therapy, 1 week is too short for any bone or joint infection. Twelve weeks on the other hand is unnecessarily long in a typical patient.

5. **D.** *S. aureus* is the most common pathogen causing hematogenous osteomyelitis. It is an aggressive pathogen that has a tendency to spread from other areas of the body and seed locations such as the bones that are difficult for the immune system to eradicate. Group B *Streptococcus* can occur in neonates following birth to a mother that is positive for the organism, particularly when perinatal antibacterial prophylaxis was not properly administered. *Haemophilus influenzae* (B) still causes respiratory infection but type B that was responsible for invasive disease has been nearly eradicated from developed countries through the use of conjugate vaccine. *P. aeruginosa* (C) is rare but can be seen in patients who use unclean needles or tap water for injecting drugs or those with open fractures occurring outdoors, especially following contact with water.

6. **D.** Although gram-positive pathogens are still the most likely cause of osteomyelitis in patients with diabetes, the chance of having mixed infection of the foot is enhanced due to proximity with multiple organisms inside shoes and dirt. Also, the poor vasculature of many patients with diabetes means lack of oxygen that impairs wound healing and increases risk of anaerobic infection.

7. **C.** As with osteomyelitis, *S. aureus* is the most common organism to cause bacterial septic arthritis in adults. Gram negatives such as *E. coli* and *P. aeruginosa* are rare while *Streptococcus pyogenes* is more typical of neonates.

8. **D.** C-reactive protein is an acute inflammatory marker that can be used to help assess response to therapy in patients with bone infections. Some clinicians follow it weekly with other labs such as WBC and Scr. Most important is to compare the initial C-reactive protein value with the value at the expected end of therapy. This is the basis for when to choose a shorter length of therapy in children and helps reassure prescribers that therapy is adequate in adults. (A) Checking daily is not needed. (B) White blood cell count is often assessed daily for the initial part of infection to watch for resolution of leukocytosis but it typically normalizes in a few days, making prolonged daily checks unnecessary. Continued monitoring is more useful to assess for cytotoxic effects from the antibacterials and this can be accomplished with weekly monitoring.(C) Erythrocyte sedimentation rate is another nonspecific inflammatory marker like CRP, but it usually takes longer to increase and decrease. Sometimes it never becomes positive if infection is detected early. When positive, monitoring is often done with CRP but an argument could be made that only one or the other needs to be checked. Waiting 6 months, however, is not likely to be useful.

9. **B.** Ciprofloxacin should not be used alone for *S. aureus*. This is because fluoroquinolones have a propensity for a single-stage mutation that leads to not only resistance of the class but also beta-lactams, converting *S. aureus* into MRSA (perhaps with the exception of delafloxacin, which is still new but is reported to be much more stable to resistance). Fluoroquinolones have quite a bit of data for the treatment of *S. aureus* in combination with rifampin, another class of antibiotic that should not be used alone for therapy. *Serratia marcescens* and *Enterobacter cloacae* are good choices to treat with fluoroquinolones because both can possess an inducible beta-lactamase called ampC that makes cure with other traditional agents, such as ceftriaxone, more difficult. Although resistance in *E. coli* (and *P. aeruginosa*) has increased to 25% to 30% in most areas of the United States, fluoroquinolones are still effective choice for susceptible gram-negative bone infections.

10. **D.** Due to high rates of MRSA (>30% in most parts of the United States), clindamycin is the only treatment from the list that can be recommended empirically. Vancomycin would be an alternative. In parts of Europe, MSSA is much more common and cefuroxime could be chosen, although nafcillin, cefazolin, or other equivalents (oxacillin, flucloxacillin) would more likely be used. Cefuroxime would also be effective against *K. kingae* which is more common in younger preschool children. Clindamycin is a well-studied treatment in pediatrics and popular because most community-acquired MRSA remains susceptible. Ampicillin is a drug of choice for *Enterococcus faecalis* and could be used for streptococcal infection, but is not recommended empirically for osteomyelitis. Doxycycline is considered an effective treatment for *S. aureus* but not recommended in children due to potential staining of bones and teeth.

11. **B.** IV drug abuser have a higher rate of MRSA infection than the general population and have a propensity for infection with gram-negative infections, especially *P. aeruginosa*. Therefore, combination therapy is commonly employed to provide empiric treatment for both. Vancomycin is effective for MRSA while ceftazidime retains good activity against *P. aeruginosa*. None of the other choices are reliable against both pathogens. Once the infective organisms have been identified it is always advisable to de-escalate therapy to a more narrow, targeted spectrum of activity.

12. **D.** Tobramycin is often used in bone cement because aminoglycosides have attractive concentration-dependent pharmacodynamics that can be enhanced with high doses at the site of surgery. Despite this theoretical benefit, little data exist on their actual contribution to improvement in clinical care and there remains a documented risk of systemic absorption resulting in toxicity such as acute kidney injury. Beta-lactams have time-dependent effects and are occasionally used locally, while fluoroquinolones are very rarely used in cement.

13. **C.** Linezolid has a propensity to cause thrombocytopenia when used for more than 1 to 2 weeks. That is why linezolid is typically not chosen to treat bone or even joint infections despite it having excellent activity against MRSA and adequate concentrations present in bone. While beta-lactams such as ampicillin and ceftriaxone can also cause cytopenias and cell counts should be monitored on therapy, the adverse event is much less common. Metronidazole can be associated with dysgeusia and peripheral neuropathies, especially during prolonged use, but most experts do not exclude it as a treatment for anaerobic osteomyelitis.

14. **A.** Contiguous osteomyelitis occurs from adjacent soft tissue infection. This is much more likely to occur in the foot due to the propensity of wounds in that area of the body to track all the way to the bone. This is common in patients with diabetes who have neuropathy and do not initially recognize the seriousness of their injury and subsequent foot infection. The mandible is another area of the body prone to contiguous osteomyelitis, but the occurrence of dental infection is much less in general. The humerus is unlikely to become infected except by direct inoculation from trauma or potentially hematogenous spread. The source of vertebral osteomyelitis is almost always from hematogenous infection but can be associated with adjacent diskitis or epidural abscess.

15. **C.** Eight weeks is the recommended treatment duration for MRSA vertebral osteomyelitis because it is considered an infection at high risk of relapse. By default, vertebral osteomyelitis occurs in adults who have less robust blood supply to their bones, and bacteria have a propensity to find degenerated areas in the spine to develop infection. This and the less than ideal pharmacologic agents used to treat MRSA infection lead patients to require a longer course of therapy than might be necessary for children and even other types of osteomyelitis in adults. Two and 4 weeks are too short, while 16 weeks is not likely to improve outcomes but puts patients at increased risk of adverse drug events.