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Osteomyelitis Osteomyelitis, an infection of bone, can be caused by various microorganisms that arrive at bone through different routes. Spon taneous hematogenous osteomyelitis may occur in otherwise healthy individuals, whereas local microbial spread mainly affects either indi viduals who have underlying disease (e.g., vascular insufficiency) or patients who have compromised skin or other tissue barriers, with con sequent exposure of bone. The latter situation typically follows surgery involving bone, such as sternotomy or orthopedic repair. The manifestations of osteomyelitis are different in children and adults. In children, circulating microorganisms seed mainly long bones, whereas in adults, the vertebral column is the most commonly affected site. Management of osteomyelitis differs greatly depending on whether an implant is involved. The most important aim of the management of either type of osteomyelitis is to prevent progression to chronic osteomyelitis by rapid diagnosis and prompt treatment. Therefore, unambiguous case definitions are required. Device-related bone and joint infection necessitates a multidisciplinary approach requiring antibiotic therapy and, in many cases, surgical removal of the device. For most types of osteomyelitis, the optimal duration and route of anti biotic treatment have not been established in clinical trials. Therefore, the recommendations for therapy in this chapter reflect mainly expert opinions. CLASSIFICATION There is no generally accepted, comprehensive system for classification of osteomyelitis, primarily because of the multifaceted presentation of this infection. Different specialists are confronted with different facets of bone disease. Most often, however, general practitioners or

internists are the first to encounter patients with the initial signs and symptoms of osteomyelitis. These primary care physicians should be able to recognize this disease in any of its forms. Osteomyelitis cases can be classified by various criteria, including pathogenesis, duration of infection, location of infection, and presence or absence of foreign material. The widely used Cierny-Mader staging system is useful mainly for trauma surgeons. It classifies osteomyelitis according to anatomic site, comorbidity, and radiographic findings, with stratifica tion of long-bone osteomyelitis to optimize surgical management; this system encompasses both systemic and local factors affecting immune status, metabolism, and local vascularity.

Any of three mechanisms can underlie osteomyelitis: (1) hematog enous spread; (2) spread from a contiguous site following surgery; and (3) secondary infection in the setting of vascular insufficiency or con comitant neuropathy. Hematogenous osteomyelitis in adults typically involves the vertebral column. In only about half of patients a primary focus can be detected. The most common primary foci of infection are the urinary tract, skin/soft tissue, intravascular catheterization sites, and the endocardium. Spread from a contiguous source follows either bone trauma or surgical intervention. Wound infection leading to osteomyelitis typically occurs after cardiovascular intervention involv ing the sternum, orthopedic repair after open fracture, or prosthetic joint insertion. Osteomyelitis secondary to vascular insufficiency or peripheral neuropathy most often follows chronic, progressively deep skin and soft tissue infection of the foot. The most common underlying condition is diabetes. In diabetes that is poorly controlled, the diabetic foot syndrome is caused by skin, soft tissue, and bone ischemia com bined with motor, sensory, and autonomic neuropathy. CHAPTER 136 Classification of osteomyelitis according to the duration of infec tion, although ill defined, is useful because the management of acute and chronic osteomyelitis differs. However, not a defined duration of infection, but the presence or absence of bone necrosis (sequesters) is crucial. Acute osteomyelitis without bone necrosis can generally be treated with antibiotics alone. In contrast, for chronic osteomyelitis antibiotic treatment should be combined with debridement surgery. Acute hematogenous or contiguous osteomyelitis evolves over a short period—i.e., a few days or weeks. In contrast, subacute or chronic osteomyelitis lasts for weeks or months before treatment is started. Typical examples of a subacute course are vertebral osteomyelitis due to tuberculosis or brucellosis and delayed implant-associated infections caused mainly by low-virulence microorganisms (coagulase-negative staphylococci, Cutibacterium acnes). A special form of osteomyelitis is Brodie’s abscess, mainly occurring in young males. Chronic osteomy elitis develops when insufficient therapy leads to persistence or recur rence, most often after sternal, mandibular, or foot infection. Osteomyelitis Classification by location distinguishes among cases in the long bones, the vertebral column, and the periarticular bones. Long bones are generally involved after hematogenous seeding in children or contiguous spread following trauma or surgery. The risk of vertebral osteomyelitis in adults increases with age. Periarticular osteomyelitis, which complicates septic arthritis that has not been adequately treated, is especially common in periprosthetic joint infection. Osteomyelitis involving a foreign device requires surgical manage ment for cure. Even acute implant-associated infection calls for pro longed antimicrobial therapy. Therefore, identification of this type of disease is of practical importance. VERTEBRAL OSTEOMYELITIS ■ ■PATHOGENESIS Vertebral osteomyelitis, also referred to as disk-space infection, septic diskitis, spondylodiskitis, or spinal osteomyelitis, is the most common manifestation of hematogenous bone infection in adults. This designa tion reflects a pathogenic process leading to involvement of the adja cent vertebrae and the corresponding intervertebral disk. In adults, the disk is avascular. Microorganisms invade via the segmental

arterial cir culation in adjacent endplates and then spread into the disk. Alterna tive routes of infection are retrograde seeding through the prevertebral venous plexus and direct inoculation during spinal surgery, epidural

infiltration, or trauma. In the setting of implant surgery, microorgan isms are inoculated either during the procedure or, if wound healing is impaired, in the early postoperative period.

■ ■EPIDEMIOLOGY Vertebral osteomyelitis occurs more often in male than in female patients (ratio, 1.5:1). Between 1995 and 2008, the incidence rate increased from 2.2 to 5.8 cases/100,000 person-years. There is a clear age-dependent increase. Men age ≥70 years have a sixfold higher inci dence rate than those <70 years. The observed increase in reported cases over time may reflect improvements in diagnosis resulting from the broad availability of MRI technology. In addition, the fraction of cases of vertebral osteomyelitis acquired in association with health care is increasing as a consequence of comorbidity and the rising number of invasive interventions. ■ ■MICROBIOLOGY Vertebral osteomyelitis is typically classified as pyogenic or nonpyo genic. However, this distinction is arbitrary: in “nonpyogenic” cases (tuberculous, brucellar), macroscopic pus formation (caseous necrosis, abscess) is quite common. A more accurate scheme is to classify cases as acute or subacute/chronic. Whereas the microbiologic spectrum of acute cases is similar in different parts of the world, the spectrum of subacute/chronic cases varies according to the geographic region. The great majority of cases are monomicrobial in etiology. Of episodes of acute vertebral osteomyelitis, 40–50% are caused by Staphylococcus aureus, 12% by streptococci, and 20% by gram-negative bacilli—mainly Escherichia coli (9%) and Pseudomonas aeruginosa (6%). Subacute vertebral osteomyelitis is typically caused by Mycobacterium tubercu losis or Brucella species in regions where these microorganisms are endemic. Osteomyelitis due to viridans streptococci also has a subacute presentation; these infections most often occur as secondary foci in patients with endocarditis. In vertebral osteomyelitis due to Candida species, the diagnosis is often delayed by several weeks; this etiology should be suspected in IV drug users who do not use sterile parapher nalia. In implant-associated spinal osteomyelitis, coagulase-negative staphylococci and C. acnes—which, in the absence of an implant, are generally considered contaminants—typically cause low-grade (chronic) infections. As an exception, coagulase-negative staphylococci can cause native spinal osteomyelitis in cases of prolonged bacteremia (e.g., in patients with infected pacemaker electrodes or implanted vas cular catheters that are not promptly removed). PART 5 Infectious Diseases ■ ■CLINICAL MANIFESTATIONS The signs and symptoms of vertebral osteomyelitis are nonspecific. Only about half of patients develop fever >38°C (>100.4°F), perhaps because patients frequently use analgesic drugs. Back pain is the lead ing initial symptom (>85% of cases). The location of the pain corre sponds to the site of infection: the cervical spine in ~10% of cases, the thoracic spine in 30%, and the lumbar spine in 60%. One exception is involvement at the thoracic level in two-thirds of cases of tuberculous osteomyelitis and at the lumbar level in only one-third. This difference is due to direct mycobacterial spread via pleural or mediastinal lymph nodes in pulmonary tuberculosis. Neurologic deficits, such as radiculopathy, weakness, or sensory loss, are observed in about one-third of cases of vertebral osteomyelitis. Neurologic signs and symptoms are caused mostly by spinal epidural abscess. This complication starts with severe localized back pain and progresses to radicular pain, reflex changes, sensory abnormalities, motor weakness, bowel and bladder dysfunction, and paralysis. A primary focus should always be sought but is found in only half of cases. Overall, endocarditis is identified in ~10% of patients. In osteo myelitis caused by viridans streptococci, endocarditis is the

source in about half of patients. Implant-associated spinal osteomyelitis can present as either early- or late-onset infection. Early-onset infection is diagnosed within 30 days after implant placement. S. aureus is the most common patho gen. Wound healing impairment and fever are the leading findings. Late-onset infection is diagnosed beyond 30 days after surgery, with

low-virulence organisms such as coagulase-negative staphylococci or C. acnes as typical infecting agents. Fever is rare. One-quarter of patients have a sinus tract. Because of the delayed course and the lack of classic signs of infection, rapid diagnosis requires a high degree of suspicion. ■ ■DIAGNOSIS Leukocytosis and neutrophilia have low levels of diagnostic sensitivity (only 65% and 40%, respectively). In contrast, an increased erythrocyte sedimentation rate or C-reactive protein (CRP) level has been reported in 98% and 100% of cases, respectively; thus, these tests are helpful in excluding vertebral osteomyelitis. The fraction of blood cultures that yield positive results depends heavily on whether the patient has been pretreated with antibiotics; across studies, the range is 30–78%. In view of this low rate of positive blood culture after antibiotic treatment, such therapy should be withheld until microbial growth is proven unless the patient has sepsis syndrome. In patients with negative blood cultures, CT-guided or open biopsy is needed. Whether a CT-guided biopsy with a negative result is repeated or followed by open biopsy depends on the experience of personnel at the specific center. Bone samples should be cultured for aerobic, anaerobic, and fungal agents, with a portion of the sample sent for histopathologic study. In cases with a subacute/chronic presentation, a suggestive history, or a granuloma detected during histopathologic analysis, mycobacteria and brucellae also should be sought. When blood and tissue cultures are negative despite suggestive histopathology, nonculture techniques (eubacterial or multiplex polymerase chain reaction analysis, metagenomics) of biopsy specimens or aspirated pus should be considered. These tech niques allow detection of unusual pathogens such as Helicobacter spp. or Tropheryma whipplei. Given that signs and symptoms of osteomyelitis are nonspecific, the clinical differential diagnosis of febrile back pain is broad, includ ing pyelonephritis, pancreatitis, and viral syndromes. In addition, multiple noninfectious pathologies of the vertebral column, such as osteoporotic fracture, seronegative spondylitis (ankylosing spondylitis, psoriasis, reactive arthritis, enteropathic arthritis), and spinal stenosis must be considered. Imaging procedures are the most important tools not only for the diagnosis of vertebral osteomyelitis but also for the detection of pyo genic complications and alternative conditions (e.g., bone metastases or osteoporotic fractures). Plain radiography is a reasonable first step in evaluating patients without neurologic symptoms and may reveal an alternative diagnosis. Because of its low sensitivity, plain radiography generally is not helpful in acute osteomyelitis, but it can be useful in subacute or chronic cases. The gold standard is MRI, which should be performed expeditiously in patients with neurologic impairment in order to rule out a herniated disk or to detect pyogenic complications in a timely manner (Fig. 136-1, left). Even if the pathologic findings on MRI suggest vertebral osteomyelitis, alternative diagnoses should be considered, especially when blood cultures are negative. The most common alternative diagnosis is erosive osteochondrosis. Septic bone necrosis, gouty spondylodiskitis, and erosive diskovertebral lesions (Andersson lesions) in ankylosing spondylitis may likewise mimic ver tebral osteomyelitis. CT is less sensitive than MRI but may be helpful in guiding a percutaneous biopsy. Positron emission tomography (PET) with 18F-fluorodeoxyglucose, which has a high degree of diagnostic accuracy, is an alternative imaging procedure when MRI is contra indicated (Fig. 136-1, right). 18F-fluorodeoxyglucose PET should be considered for patients with implants and patients in whom several foci are suspected. TREATMENT Vertebral Osteomyelitis The aims of therapy for vertebral osteomyelitis are (1) elimination of the

pathogen(s), (2) protection from further bone loss, (3) relief of back pain, (4) prevention of complications, and (5) stabilization, if needed.

A FIGURE 136-1 Left: MRI from a 53-year-old man suffering from prosthetic aortic valve endocarditis (Aggregatibacter actinomycetemcomitans). In addition, he experienced lumbar pain for 7 weeks. MRI sagittal sequence shows on T1 fat-saturated post-gadolinium image enhancement in the intervertebral disk space (ventral arrow) and a small epidural abscess (dorsal arrow). Right: PET/CT from the same patient 4 weeks earlier. PET/CT fusion shows fluorodeoxyglucose uptake at L5 ventral (small arrow) and dorsal of S1 (large arrow: epidural abscess). (Figures courtesy of Damien Toia, MD, Kantonsspital Baselland; with permission.) Table 136-1 summarizes suggested antimicrobial regimens for infections attributable to the most common etiologic agents. For optimal antimicrobial therapy, identification of the infecting agent is required. Therefore, in patients without sepsis syndrome, antibiotics should not be administered until the pathogen is identified in a blood culture, a bone biopsy, or an aspirated pus collection. Traditionally, bone infections are at least initially treated by the IV route. However, the preference for the IV route is not evidence based. There are no good arguments for the assumption that IV therapy is superior to oral administration if the following requirements are met: (1) opti mal antibiotic spectrum, (2) excellent bioavailability of the oral drug, (3) clinical studies confirming efficacy of the oral drug, (4) normal intestinal function, and (5) no vomiting. Indeed, in a controlled trial in patients with bone and joint infections, including vertebral osteomyelitis, oral antibiotic therapy was noninferior to intravenous therapy when used during the first 6 weeks. Nevertheless, a short initial course of parenteral therapy with a β-lactam antibiotic may lower the risk of emergence of fluoroquinolone resistance, especially if P. aeruginosa infection is treated with ciprofloxacin or staphylo coccal infection with the combination of a fluoroquinolone plus rifampin. These suggestions are based on observational studies and expert opinion. A randomized, controlled trial showed that 6 weeks of antibiotic treatment is not inferior to a 12-week course in patients with pyogenic vertebral osteomyelitis. The cure rate was 90.9% in both groups 1 year after therapy. Thus, prolonged antibiotic therapy is required only for patients with undrained abscesses and for patients with spinal implants. Treatment efficacy should be regularly monitored through inquiries about signs and symptoms (fever, pain) and assessment for signs of inflammation (elevated CRP concentra tions). Follow-up MRI is appropriate only for patients with pyogenic complications since the correlation between clinical healing and improvement on MRI is very poor. Surgical treatment generally is not needed in acute hematog enous vertebral osteomyelitis. However, it is always necessary in implant-associated spinal infection. Early infections (those occur ring up to 30 days after internal stabilization) can be cured with debridement, implant retention, and a 3-month course of antibi otics (Table 136-2). In contrast, in late infection with a duration

B CHAPTER 136 of >30 days, implant removal and a 6-week course of antibiotics (Table 136-1) are required for complete elimination of the infection. If implants cannot be removed, oral suppressive long-term treat ment should follow the initial course of IV antibiotics. The optimal duration of suppressive therapy is unknown. However, if antibiotic therapy is discontinued after, for example, 1 year, close clinical and laboratory (CRP) follow-up is needed. Osteomyelitis ■ ■COMPLICATIONS Complications should be suspected when there is persistent pain, a persistently increased CRP level, and new-onset or persistent neuro logic impairment. In cases of persistent pain with or without signs of inflammation, paravertebral, epidural, or psoas abscesses must be sought. Epidural abscesses occur in 15–20% of cases. This complica tion is more common in the cervical

column (30%) than in the lumbar spine (12%). Risk factors for severe neurologic deficit were epidural abscess, cervical and/or thoracic involvement, and S. aureus vertebral osteomyelitis. Persistent pain despite normalization of CRP values indicates mechanical complications such as severe osteonecrosis or spinal instability. These patients require a consult with an experienced orthopedic surgeon. ■ ■GLOBAL CONSIDERATIONS The incidence rate of acute vertebral osteomyelitis is similar in dif ferent regions of the world. In contrast, subacute/chronic vertebral osteomyelitis predominates in defined regions. Cases attributable to brucellosis predominate in endemic areas such as the Middle East, Africa, Central and South America, and the Indian subcontinent. Tuberculosis is an especially frequent cause in Africa and Asia (India, Indonesia, China), where more than two-thirds of the global tubercu losis burden is reported. Thus, specific diagnostic tests are needed in patients either living in or having traveled to these regions. OSTEOMYELITIS IN LONG BONES ■ ■PATHOGENESIS Osteomyelitis in long bones is a consequence of hematogenous seed ing, exogenous contamination during trauma (open fracture), or

TABLE 136-1 Antibiotic Therapy for Osteomyelitis in Adults without Implantsa MICROORGANISM ANTIMICROBIAL AGENT (DOSE,b ROUTE) Staphylococcus spp. Methicillin-susceptible Nafcillin or oxacillinc (2 g IV q6h) followed by Rifampin (300–450 mg PO q12h) plus levofloxacin (750 mg PO q24h or 500 mg PO q12h) Methicillin-resistant Vancomycind (15 mg/kg IV q12h) or daptomycin (8–10 mg/kg IV q24h) followed by Rifampin (300–450 mg PO q12h) plus Levofloxacin (750 mg PO q24h or 500 mg PO q12h) or TMP-SMXe (1 double-strength tablet PO q8h)

or fusidic acid (500 mg PO q8h) Streptococcus spp. Penicillin Gc (5 million units IV q6h) or ceftriaxone (2 g IV q24h) Enterobacteriaceae Quinolone-susceptible Quinolone-resistantf Ciprofloxacin (750 mg PO q24h) Imipenem (500 mg IV q6h) or meropenem (1–2g IV q8h) Pseudomonas aeruginosa Cefepime or ceftazidime (2 g IV q8h) plus an aminoglycosideg or Piperacillin-tazobactam (4.5 g IV q8h) plus an aminoglycosideg for 2–4 weeks followed by PART 5 Infectious Diseases Ciprofloxacinh (750 mg PO q12h) Anaerobes Clindamycin (600 mg IV q6–8h) for 2–4 weeks followed by Clindamycini (300 mg PO q6h) aUnless otherwise indicated, the total duration of antimicrobial treatment is generally 6 weeks. bAll dosages are for adults with normal renal function. cWhen the patient has delayed-type penicillin hypersensitivity, cefuroxime (1.5 g IV q6–8h) can be administered. When the patient has immediate-type penicillin hypersensitivity, the penicillin should be replaced by vancomycin (1 g IV q12h). dTarget vancomycin trough level: 15–20 μg/mL. eTrimethoprim-sulfamethoxazole. A double-strength tablet contains 160 mg of trimethoprim and 800 mg of sulfamethoxazole. fIncluding isolates producing extended-spectrum β-lactamase. gThe need for addition of an aminoglycoside has not yet been proven. However, this addition may decrease the risk of emergence of resistance to the β-lactam. hThe rationale for starting ciprofloxacin treatment only after pretreatment with a β-lactam is the increased risk of emergence of quinolone resistance in the presence of a heavy bacterial load. iAlternatively, penicillin G (5 million units IV q6h) or ceftriaxone (2 g IV q24h) can be used against gram-positive anaerobes (e.g., Cutibacterium acnes), and metronidazole (500 mg IV/PO q8h) can be used against gram-negative anaerobes (e.g., Bacteroides spp.). Source: From W Zimmerli: Vertebral osteomyelitis. N Engl J Med 362:1022, 2010. Copyright © 2010 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. perioperative contamination during surgery involving bone. Hematog enous infection in long bones typically occurs in children. In adults, the leading pathogenic source is exogenous fracture-related infection, mainly associated with internal fixation devices. For classification, the presence of a sequestrum and the status of the

surrounding soft tissue are crucial for the decision as to whether a surgical intervention is required. Chronic osteomyelitis can be reactivated after a symptomfree interval of >70 years. Such recurrences are most common among elderly patients who developed S. aureus osteomyelitis in the preanti biotic era. ■ ■EPIDEMIOLOGY In adults, most cases of long-bone osteomyelitis are posttraumatic or postsurgical; less frequently, late recurrence arises from hematog enous infections during childhood. For postoperative or postsurgical osteomyelitis, the term “facture-related infection” was generated. The risk of infection depends on the type of fracture. After closed fracture, implant-associated infection occurs in fewer than 1% of patients. In contrast, after open fracture, the risk of osteomyelitis ranges from ~2%

up to 30%, with the precise figure depending on the degree of tissue damage during trauma and the time between injury and admission to a specialized center. ■ ■MICROBIOLOGY The spectrum of microorganisms causing hematogenous long-bone osteomyelitis does not differ from that in vertebral osteomyelitis. S. aureus is most commonly isolated in each type of osteomyelitis. In rare cases, mycobacteria or fungal agents such as Cryptococcus species, Sporothrix schenckii, Blastomyces dermatitidis, or Coccidioides species are found in patients who live or have traveled in endemic regions. Impaired cellular immunity (e.g., in HIV infection or after transplantation) predisposes to these etiologies. Coagulase-negative staphylococci are the second most common etiologic agents (after S. aureus) in implant-associated osteomyelitis. After open fracture, contiguous long-bone osteomyelitis is typically caused by gram-negative bacilli or a polymicrobial mixture of organisms. ■ ■CLINICAL MANIFESTATIONS The leading symptoms in adults with primary or recurrent hematog enous long-bone osteomyelitis are pain and low-grade fever. Infection occasionally manifests as clinical sepsis and local signs of inflamma tion (erythema and swelling). After internal fixation, osteomyelitis can be classified as early (acute; <3 weeks), delayed (3–10 weeks), or late (chronic) infection. Early/acute long-bone osteomyelitis manifests as signs of surgical site infection, such as erythema and impaired wound healing. Acute implant-associated infection may also follow hematog enous seeding at any time after implantation of a device. Typical symp toms are new-onset pain and signs of sepsis. Delayed or late (chronic) infections are usually caused by low-virulence microorganisms or occur after ineffective treatment of early-onset infection. Patients may present with persisting pain, subtle local signs of inflammation, intermittent discharge of pus, or fluctuating erythema over the scar (Fig. 136-2). A special form of subacute osteomyelitis is Brodie’s abscess, which is characterized by pain (98%) and swelling (53%), mainly in the tibia or the femur. Fever and inflammatory markers are typical. The median delay from symptoms to diagnosis is 3 months. Thus, a young patient with unclear localized pain in the tibia or femur should be worked-up with an imaging modality (plain x-ray, MRI, or CT). ■ ■DIAGNOSIS The diagnostic workup for acute hematogenous long-bone osteomy elitis is similar to that for vertebral osteomyelitis. Bone remodeling and thus marker uptake are increased for at least 1 year after surgery. Therefore, the three-phase bone scan is not useful during this interval. However, in late recurrences it allows rapid diagnosis at low cost. If the results are positive, CT is required to estimate the extent of inflamed tissue and detect bone necrosis (sequesters). Implant-associated infec tion should be suspected if CRP values do not return to the normal range or rise after an initial decrease. Clinical and laboratory suspicion should prompt surgical exploration and sampling. In osteomyelitis of >1 year’s duration, single-photon emission CT plus conventional CT (SPECT/CT) is a good option, either with 99mTc methylene diphosphonate (99mTc-MDP)–labeled leukocytes or with labeled monoclonal antibodies to granulocytes. Surgical debridement is needed for diagnostic (biopsy culture, histology) and therapeutic reasons. TREATMENT Osteomyelitis in Long Bones

Treatment for acute hematogenous infection in long bones is iden tical to that for acute vertebral osteomyelitis (Table 136-1). The suggested duration of antibiotic therapy is 4–6 weeks. In patients with good soft tissue condition and no sequestra or implants, generally no surgical intervention is required. According to a controlled trial, oral treatment can be given, provided that a regi men with excellent oral biocompatibility is available. An initial IV course can be as short as a few days, if the microorganism and

TABLE 136-2 Antibiotic Therapy for Osteomyelitis Associated with Orthopedic Devices MICROORGANISM ANTIMICROBIAL AGENTa (DOSE, ROUTE) Staphylococcus spp. Recommendation for initial treatment phase (2 weeks with implant) Methicillin-susceptible Rifampin (450 mg PO/IV q12hb) plus Nafcillin or oxacillinc (2 g IV q6h) Methicillin-resistant Rifampin (450 mg PO/IV q12hb) plus Vancomycin (15 mg/kg IV q12h) or daptomycin (8–10 mg/kg IV q24h) Staphylococcus spp. Recommendation after completion of initial treatment phase Rifampin (450 mg PO q12hb) plus Levofloxacin (750 mg PO q24h or 500 mg PO q12h) or ciprofloxacin (750 mg PO q12h) or fusidic acid (500 mg PO q8h) or TMP-SMXd (1 double-strength tablet PO q8h) or minocycline (100 mg PO q12h) or linezolid (600 mg PO q12h) or clindamycin (1200–1350 mg/d PO in 3 or 4 divided doses) Streptococcus spp.e Penicillin Gc (18–24 million units/d IV in 6 divided doses) or ceftriaxone (2 g IV q24h) for 4 weeks followed by Amoxicillin (750–1000 mg PO q6–8h) or clindamycin (1200–1350 mg/d PO in 3 or 4 divided doses) Enterococcus spp.f Penicillin-susceptible Penicillin Gc (24 million units/d IV in 6 divided doses) or ampicillin or amoxicilling (2 g IV q4–6h) Penicillin-resistant Vancomycin (15 mg/kg IV q12h) or daptomycin (6–10 mg/kg IV q24h) or linezolid (600 mg IV/PO q12h) Enterobacteriaceae A β-lactam selected in light of in vitro susceptibility profile for 2 weeksh followed by Ciprofloxacin (750 mg PO q12h) Enterobacter spp.i and nonfermentersj (e.g., Pseudomonas aeruginosa) Cefepime or ceftazidime (2 g IV q8h) or meropenem (1–2 g IV q8hk) for 2–4 weeks followed by Ciprofloxacin (750 mg PO q12h) Cutibacterium spp. Penicillin Gc (18–24 million units/d IV in 6 divided doses) or clindamycin (600–900 mg IV q8h) for 2–4 weeks followed by Amoxicillin (750–1000 mg PO q6–8h) or clindamycin (1200–1350 mg/d PO in 3 or 4 divided doses) Gram-negative anaerobes

(e.g., Bacteroides spp.) Metronidazole (500 mg IV/PO q8h) Mixed bacteria (without

methicillin-resistant staphylococci) Ampicillin-sulbactam (3 g IV q6h) or amoxicillin-clavulanatel (2.2 g IV q6h) or piperacillin-tazobactam (4.5 g IV q8h)

or imipenem (500 mg IV q6h) or meropenem (1–2 g IV q8hk) for 2–4 weeks followed by Individualized oral regimens chosen in light of antimicrobial susceptibility aAntimicrobial agents should be chosen in light of the isolate’s in vitro susceptibility, the patient’s drug allergies and intolerances, potential drug interactions, and contraindications to specific drugs. All dosages recommended are for adults with normal renal and hepatic function. See text for total durations of antibiotic treatment. bOther dosages and intervals of administration with equivalent success rates have been reported. cWhen the patient has delayed-type penicillin hypersensitivity, cefazolin (2 g IV q8h) can be administered. When the patient has immediate-type penicillin hypersensitivity, the penicillin should be replaced by vancomycin (1 g IV q12h). dTrimethoprim-sulfamethoxazole. A double-strength tablet contains 160 mg of trimethoprim and 800 mg of sulfamethoxazole. eDetermination of the minimal inhibitory concentration (MIC) of penicillin is advisable. fCombination therapy with an aminoglycoside is optional since its superiority to monotherapy for

prosthetic joint infection is unproved. When using combination therapy, monitor for signs of aminoglycoside ototoxicity and nephrotoxicity; the latter is potentiated by other nephrotoxic agents (e.g., vancomycin). gFor patients with hypersensitivity to penicillin, see treatment options for penicillin-resistant enterococci. hCiprofloxacin (PO or IV) can be administered to patients with hypersensitivity to β-lactams. iCeftriaxone and ceftazidime should not be administered for treatment targeting Enterobacter species, even strains that test susceptible in the laboratory, but can be used against nonfermenters. Strains producing extended-spectrum β-lactamases should not be treated with any cephalosporin, including cefepime. Enterobacter infections can also be treated with ertapenem (1 g IV q24h); however, ertapenem is not effective against Pseudomonas spp. and other nonfermenters. jAddition of an aminoglycoside is optional. Use of two active drugs can be considered in light of the patient's clinical condition. kThe recommended dosage is in line with the guidelines of the Infectious Diseases Society of America. In Europe, 2 g IV q8h is suggested for P. aeruginosa infections. lNot available as an IV formulation in the United States. Source: Modified from W Zimmerli et al: N Engl J Med 351:1645, 2004. Massachusetts Medical Society. its antibiotic susceptibility is known. In recurrences of chronic osteomyelitis as well as in each type of exogenous osteomyelitis (acute, chronic, with or without an implant), a combination of surgical debridement, obliteration of dead space, and long-term antibiotic therapy is required. The length of therapy depends on the completeness of the surgical intervention (removal of seques tra, implants, and necrotic tissue). The therapeutic aims in patients whose infections are associ ated with internal fixation devices are consolidation of the fracture and prevention of chronic osteomyelitis. Stable implants can be maintained except in patients with uncontrolled sepsis. In a sys tematic review reporting the outcome of 276 patients, the success rate with retention of the implant was 86–100% in early, 82–89% in delayed, and only 67% in late fracture-related infection. Appropri ate antimicrobial therapies are listed in Table 136-2. The cure rate

 for early staphylococcal implant-associated infections treated with a fluoroquinolone plus rifampin is >90%. Rifampin is efficacious against staphylococcal biofilms of ≤3 weeks' duration. Similarly, fluoroquinolones are active against biofilms formed by gram-negative bacilli. In these cases, a short initial course of IV therapy with a β-lactam antibiotic is suggested to minimize the risk of emergence of resistance to the oral drugs. The total duration of treatment is 3 months, and the device can be retained even after antibiotics have been discontinued. In contrast, in cases caused by rifampin-

resistant staphylococci or fluoroquinolone-resistant gram-negative bacilli, all hardware should be removed after consolidation of the fracture and before discontinuation of antibiotics. These patients are treated with an oral antibiotic (suppressive therapy) as long as the hardware is retained.

FIGURE 136-2 A 42-year-old man who had sustained a malleolar fracture 6 weeks previously had persistent pain and slight inflammation after orthopedic repair. His infection was treated with oral antibiotics without debridement surgery. This insufficient management of an implant-associated Staphylococcus aureus infection was complicated by a sinus tract. ■ ■COMPLICATIONS The main complication of long-bone osteomyelitis is the persistence of infection with progression to chronic osteomyelitis. This risk is especially high after internal fixation of an open fracture and among patients with implant-associated osteomyelitis that is treated without surgical debridement. In longstanding osteomyelitis, recurrent sinus tracts result in severe damage to skin and soft tissue

(Fig. 136-2). Patients who have chronic open wounds need a therapeutic approach combining orthopedic repair and plastic reconstructive surgery. PART 5 Infectious Diseases ■ ■GLOBAL CONSIDERATIONS In North American and Western European countries, tuberculous osteomyelitis is extremely rare, occurring mainly in very old people, HIV-infected patients, and immigrants from endemic countries. In contrast, in countries where the prevalence of tuberculosis is high (India, Indonesia, China), tuberculous osteomyelitis must routinely be considered. PERIPROSTHETIC JOINT INFECTION ■ ■PATHOGENESIS Implanted foreign material is highly susceptible to local infection due to local immunodeficiency around the device. Infection occurs by either the exogenous or the hematogenous route. More rarely, con tiguous spread from adjacent sites of osteomyelitis or deep soft-tissue infection may cause periprosthetic joint infection (PJI). The fact that foreign devices are covered with host proteins such as fibronectin favors the adherence of staphylococci and the formation of a biofilm that resists phagocytosis. ■ ■EPIDEMIOLOGY The risk of infection manifesting during the first 2 postoperative years varies according to the joint. It is lowest after hip and knee arthroplasty (0.3–1.5%) and highest after ankle and elbow replacement (4–10%). The risk of hematogenous PJI is highest in the early postoperative period. However, hematogenous seeding occurs throughout life, and most cases therefore develop >2 years after implantation. The rate of risk for secondary PJI during S. aureus bacteremia is 30–40%. ■ ■MICROBIOLOGY About 50–70% of cases of PJI are caused by staphylococci (S. aureus and coagulase-negative staphylococci), 6–10% by streptococci, 4–10% by gram-negative bacilli, and the rest by various other microorganisms. In patients with hematogenous PJI, the fraction of streptococci and

FIGURE 136-3 Acute postoperative periprosthetic joint infection of the left hip caused by group B streptococci in a 68-year-old woman. gram-negative bacilli is higher and the fraction of coagulase-negative staphylococci is much lower. All microorganisms can cause PJI, includ ing fungi and mycobacteria. C. acnes causes up to one-third of episodes of periprosthetic shoulder infection. ■ ■CLASSIFICATION AND CLINICAL MANIFESTATIONS PJI is traditionally classified as early (<3 months after implantation), delayed (3–24 months after surgery), or late (>2 years after implanta tion). For therapeutic decision-making (see below), it is more useful to classify PJI as (1) acute hematogenous PJI with <3 weeks of symptoms, (2) early postinterventional PJI manifesting within 1 month after sur gery, or (3) chronic PJI with symptom duration of >3 weeks. Acute exogenous PJI typically presents with local signs of infection (Fig. 136-3). In contrast, acute hematogenous PJI is most often caused by S. aureus and is characterized by new-onset pain. Local inflamma tory signs are rare in hip PJI but frequent in knee PJI. Fever is rare after the initial phase of bacteremia. Key findings in chronic PJI are joint effusion, local pain, implant loosening, and occasionally a sinus tract. Chronic PJI is most commonly caused by low-virulence microorgan isms such as coagulase-negative staphylococci or C. acnes. These infec tions are characterized by nonspecific symptoms, such as chronic pain caused by low-grade inflammation or early loosening. ■ ■DIAGNOSIS Blood tests such as the measurement of CRP (elevated levels, ≥10 mg/L) and erythrocyte sedimentation rate (elevated rates, ≥30 mm/h) are sensitive (91–97%) but not specific (70–78%). Synovial fluid cell counts are ~90% sensitive and specific, with threshold values of 1700 leukocytes/μL in periprosthetic knee infection and 4200 leukocytes/ μL in periprosthetic hip infection. A biomarker, α-defensin, can be tested in synovial fluid; this biomarker is highly specific and therefore useful in confirming PJI. However, this test is expensive and its sensi tivity is limited; therefore, it should not be used for screening. During debridement surgery, at least three but optimally six tissue samples should be obtained for culture and histopathology. If implant mate rial (modular parts, screws, or the prosthesis) is removed, sonication of this material followed by culture and/or use of molecular

methods to examine the sonicate fluid allows the detection of microorganisms in biofilms. The three-phase bone scan is very sensitive for detecting PJI but is not specific. As mentioned above, this test does not differentiate bone remodeling from infection and therefore is not useful during at least the first year after implantation. CT and MRI detect soft tissue infec tion, prosthetic loosening, and bone erosion, but imaging artifacts caused by metal implants limit their use. 18F-fluorodeoxyglucose PET (18F-FD-PET) is an alternative method with good sensitivity but low specificity for the detection of PJI. Therefore, 18F-FDG-PET/CT is use ful only in excluding but not confirming PJI.

TREATMENT Periprosthetic Joint Infection The outcome following treatment of PJI is better when managed using a multidisciplinary approach involving an experienced ortho pedic surgeon, an infectious disease specialist, a plastic reconstruc tive surgeon, and a microbiologist. Therefore, most patients are referred to a specialized center. In general, the goal of treatment is cure—i.e., a pain-free functional joint with complete eradication of the infecting pathogen(s). However, for patients with severe comor bidity, lifelong suppressive antimicrobial therapy may be preferred. As a rule, antimicrobial therapy without surgical intervention is not curative but merely suppressive. There are four curative surgi cal options: debridement and implant retention, one-stage implant exchange, two-stage implant exchange, and implant removal with out replacement. The least invasive treatment option should be selected for each patient without compromising the cure rate. The choice can be guided following a treatment algorithm. However, the different surgical options have not been tested in a randomized controlled trial. Implant retention offers a good chance of infectionfree survival (>80%) only if the following conditions are fulfilled: (1) acute infection, (2) stable implant, (3) pathogen susceptible to a biofilm-active antimicrobial agent (see below), and (4) skin and soft tissue in good condition. Table 136-2 summarizes pathogen-specific antimicrobial therapy for PJI. Initial IV therapy is followed by long-term oral antibiotics. Efficacious treatment is best defined in staphylococcal implantassociated infections. Rifampin exhibits excellent activity against biofilms composed of susceptible staphylococci. Because of the risk of rapid emergence of resistance, rifampin must always be com bined with another effective antibiotic. If gram-negative infections are treated with implant retention, fluoroquinolones should be used because of their activity against gram-negative biofilms. ■ ■PREVENTION OF HEMATOGENOUS INFECTION As mentioned above, hematogenous seeding may occur throughout life. This risk is highest during S. aureus bacteremia from a distant focus. Therefore, documented bacterial infections should be promptly treated in patients with prosthetic joints. However, according to a prospective case-control study, the risk of prosthetic hip or knee infec tion is not increased following dental procedures. Therefore, antibiotic prophylaxis is not needed during dental work. ■ ■GLOBAL CONSIDERATIONS Rifampin and fluoroquinolones are still the only antimicrobial agents with good activity against staphylococcal and gram-negative biofilms, respectively. Thus, in countries with high rates of rifampin resistance in staphylococci and/or high rates of fluoroquinolone resistance in gramnegative bacilli, debridement with implant retention generally does not yield a good cure rate. STERNAL OSTEOMYELITIS ■ ■PATHOGENESIS Sternal osteomyelitis occurs primarily after sternal surgery (with the entry of exogenous organisms) and more rarely by hematogenous seeding or contiguous extension from adjacent sites of sternocostal arthritis. Exogenous sternal osteomyelitis after open sternal surgery is also called deep sternal-wound infection. Exogenous infection may fol low minor sternal trauma, sternal fracture, and manubriosternal septic arthritis. Tuberculous sternal osteomyelitis typically manifests during hematogenous seeding in children or as reactivated infection in adults. Reactivation is sometimes preceded by blunt trauma. In rare cases, tuberculous

sternal osteomyelitis is caused by continuous infection from an infected internal mammary lymph node. ■ ■EPIDEMIOLOGY The incidence of poststernotomy wound infection varies from 0.5% to 2%, but figures are even higher among patients with risk factors such

as diabetes, obesity, chronic renal failure, emergency surgery, use of bilateral internal mammary artery grafts, and re-exploration for bleed ing. Rapid diagnosis and correct management of superficial sternal wound infection prevent its progression to sternal osteomyelitis. Pri mary (hematogenous) sternal osteomyelitis accounts for only 0.3% of all cases of osteomyelitis. Risk factors are IV drug use, HIV infection, radiotherapy, blunt trauma, cardiopulmonary resuscitation, alcohol abuse, liver cirrhosis, and hemoglobinopathy.

■ ■MICROBIOLOGY Poststernotomy osteomyelitis is generally caused by S. aureus (10–20% of cases), coagulase-negative staphylococci (40–60%), gram-negative bacilli (5-15%), or C. acnes (2–10%). The spectrum of microorganisms greatly varies in different populations (as represented in different pub lications); this is perhaps due to local epidemiologic conditions, such as antimicrobial stewardship and the incidence of chronic infections. Polymicrobial cases are rare in acute infection and indicate exogenous superinfection during therapy. Hematogenous sternal osteomyelitis is caused most commonly by S. aureus. Other microorganisms play a role in special populations—e.g., P. aeruginosa in IV drug users, Salmonella species in individuals with sickle cell anemia, and M. tuberculosis in patients from endemic areas who have previously had tuberculosis. ■ ■CLINICAL MANIFESTATIONS Exogenous sternal osteomyelitis manifests as fever, increased local pain, erythema, wound discharge, and sternal instability (Fig. 136-4). Contiguous mediastinitis is a feared complication, occurring in ~10–30% of patients with sternal osteomyelitis. Hematogenous sternal osteomyelitis is characterized by sternal pain, swelling, and erythema. In addition, most patients have systemic signs and symptoms of sepsis. CHAPTER 136 The differential diagnosis of hematogenous sternal osteomyelitis includes immunologic processes typically presenting as systemic or multifocal inflammation of the sternum or of the sternoclavicular or sternocostal joints (e.g., SAPHO [synovitis, acne, pustulosis, hyperos tosis, osteitis], vasculitis, chronic multifocal relapsing osteomyelitis). Osteomyelitis ■ ■DIAGNOSIS In primary sternal osteomyelitis, the diagnostic workup does not differ from that in other types of hematogenous osteomyelitis (see above). When a patient has grown up in regions where tuberculosis is endemic, a specific workup for mycobacterial infection should be performed, especially if osteomyelitis had its onset after a blunt sternal trauma. In secondary sternal osteomyelitis, leukocyte counts may be normal, but the CRP level is >100 mg/L in most cases. Tissue sampling for microbiologic studies is crucial. In osteomyelitis associated with ster nal wires, low-virulence microorganisms, such as coagulase-negative staphylococci, play an important role. In order to differentiate between colonization and infection, samples from at least three deep biopsies should be subjected to microbiologic examination. Superficial swab cultures are not diagnostic and may be misleading. No studies have FIGURE 136-4 Sternal osteomyelitis caused by Staphylococcus epidermidis 5 weeks after sternotomy for aortocoronary bypass in a 72-year-old man.

compared the value of the various imaging modalities in suspected pri mary sternal osteomyelitis. However, MRI is the current gold standard for detection of each type of osteomyelitis.

TREATMENT Sternal Osteomyelitis In cases of deep sternal-wound infection, a combined approach using both surgery and antibiotic treatment is required. Antimi crobial therapy should be started

immediately after samples have been obtained for microbiologic analyses in order to control clini cal sepsis. To protect a newly inserted heart valve, initial treatment should be directed against staphylococci, with consideration of the local susceptibility pattern. In centers with a high prevalence of methicillin-resistant S. aureus, vancomycin or daptomycin should be added to a broad-spectrum β-lactam drug. As soon as cultures of blood and/or deep wound biopsies have confirmed the pathogen's identity and susceptibility pattern, treatment should be optimized and narrowed accordingly. Tables 136-1 and 136-2 show appropri ate therapeutic choices for the most frequently identified microor ganisms causing sternal osteomyelitis in the absence and presence, respectively, of an implanted device. In a recent observational study of patients with staphylococcal deep sternal-wound infection, the use of a rifampin-containing regimen was predictive of success. The optimal duration of antibiotic therapy has not been established. In acute sternal osteomyelitis without hardware, a 6-week course is the rule. In patients with remaining sternal wires, treatment duration is generally prolonged to 3 months (Table 136-2). Like other types of tuberculous bone infection, tuberculous sternal osteomyelitis is treated for 6–12 months. PART 5 Infectious Diseases Primary sternal osteomyelitis can generally be treated without surgery. In contrast, in secondary sternal osteomyelitis, debride ment is always required. This procedure should be performed by a team of experienced surgeons, since mediastinitis, bone infection, and skin and soft tissue damage may need to be treated during the same intervention. ■ ■PROGNOSIS Primary sternal osteomyelitis poses a minimal mortality risk. In con trast, the mortality rates from secondary sternal osteomyelitis during the first year after diagnosis are 6–20%. ■ ■GLOBAL CONSIDERATIONS In endemic areas, microorganisms such as M. tuberculosis, Salmonella species, and Brucella species should be considered during sampling for microbiologic diagnosis. FOOT OSTEOMYELITIS ■ ■PATHOGENESIS Osteomyelitis of the foot is a feared complication in patients with diabetic foot ulcers. It also usually occurs in patients with peripheral arterial insufficiency, or peripheral neuropathy and after foot surgery. These entities are often linked to each other, especially in diabetic patients with late complications. However, foot osteomyelitis is also seen in patients with isolated peripheral neuropathy and can manifest as implant-associated osteomyelitis in patients without comorbidity due to a deep wound infection after foot surgery (hallux valgus surgery, arthrodesis, total ankle arthroplasty). Foot osteomyelitis is acquired almost exclusively by the exogenous route. It is a complication of deep pressure ulcers and of impaired wound healing after surgery. ■ ■EPIDEMIOLOGY About 34% of people with diabetes develop a foot ulcer during their lifetime. Among patients with foot ulcer, the annual incidence of pro gression to foot osteomyelitis is 5%. The condition starts with skin and soft tissue lesions and progresses to osteomyelitis, especially in patients with risk factors. Diabetic foot osteomyelitis increases the risk of

FIGURE 136-5 Neuropathic joint disease (Charcot foot) complicated by chronic foot osteomyelitis in a 78-year-old woman with diabetes mellitus complicated by severe neuropathy. amputation. With adequate management of the early stage of diabetic foot infections, the rate of amputation can be lowered. ■ ■RISK FACTORS Risk factors for diabetic foot infection are (1) peripheral motor, sensory, and autonomic neuropathy; (2) neuro-osteoarthropathic deformities (Charcot foot; Fig. 136-5); (3) arterial insufficiency; (4) uncontrolled hyperglycemia; (5) disabilities such as reduced vision; and (6) maladaptive behavior. ■ ■MICROBIOLOGY The correlation between cultures from bone biopsy and those from wound swabs or even deep soft-tissue punctures is poor. In a study of 31 patients with simultaneous sampling, the correlation between needle biopsy and bone biopsy cultures was only 24%. The correlation is better when S. aureus is isolated (40–50%) than when anaerobes (20–35%), gram-negative bacilli (20–30%), or coagulase-negative staphylococci (0–20%)

are identified. When only bone-biopsy samples are considered, the leading pathogens are S. aureus (25–40%), anaer obes (5–20%), and various gram-negative bacilli (18–40%). The precise distribution depends on whether the patient has already been treated with antibiotics. Anaerobes are especially prevalent in chronic wounds. Pretreatment typically selects for P. aeruginosa, methicillin-resistant S. aureus, or enterococci. ■ ■DIAGNOSIS In many cases, foot osteomyelitis can be diagnosed clinically, without imaging procedures. Most clinicians rely on the “probe-to-bone” test, which has a positive predictive value of ~90% in populations with a high pretest probability. Thus, in a patient with diabetes who is hospitalized for a chronic deep foot ulcer, the diagnosis of foot osteomyelitis is highly probable if bone can be directly touched with a metal instrument. In a patient with a lower pretest probability, MRI should be performed because of its high sensitivity (80–100%) and specificity (80–90%). Plain x-rays have typical features character izing diabetic foot osteomyelitis. However, their sensitivity is only 30–90% and the specificity varies between 50% and 90%; thus, it is mainly useful for follow-up of patients with confirmed diabetic foot osteomyelitis. TREATMENT Foot Osteomyelitis As mentioned above, correlation between cultures of bone and those of wound swabs or wound punctures is poor. Antibiotic treatment should be based on bone culture. If no bone biopsy is

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