

THE JOURNAL OF BONE & JOINT SURGERY

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J Bone Joint Surg Am. 2004;86:2305-2318.

This information is current as of February 9, 2010

Letters to The Editor are available at
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Publisher Information

The Journal of Bone and Joint Surgery
20 Pickering Street, Needham, MA 02492-3157
www.jbjs.org

CURRENT CONCEPTS REVIEW

OSTEOMYELITIS IN LONG BONES

BY LUCA LAZZARINI, MD, JON T. MADER, MD, AND JASON H. CALHOUN, MD

- Osteomyelitis in long bones remains challenging and expensive to treat, despite advances in antibiotics and new operative techniques.
- Plain radiographs still provide the best screening for acute and chronic osteomyelitis. Other imaging techniques may be used to determine diagnosis and aid in treatment decisions.
- The decision to use oral or parenteral antibiotics should be based on results regarding microorganism sensitivity, patient compliance, infectious disease consultation, and the surgeon's experience. A suppressive antibiotic regimen should be directed by the results of cultures.
- Standard operative treatment is not feasible for all patients because of the functional impairment caused by the disease, the reconstructive operations, and the metabolic consequences of an aggressive therapy regimen.
- Operative treatment includes débridement, obliteration of dead space, restoration of blood supply, adequate soft-tissue coverage, stabilization, and reconstruction.

Osteomyelitis is defined as infection in bone. The root words *osteon* (bone) and *myelo* (marrow) are combined with *itis* (inflammation) to define the clinical state in which bone is infected with microorganisms. Osteomyelitis in long bones includes infections that differ from one another with regard to duration, etiology, pathogenesis, extent of bone involvement, and type of patient (which can be an infant, child, adult, or compromised or uncompromised host). In the past thirty years, the pathogenesis of this disease has almost been clarified, and many factors that account for the persistence of infection have been identified. A number of antimicrobial agents, with different spectrums of activity against pathogens and different pharmacokinetics and pharmacodynamics, have been used to treat osteomyelitis. New operative methods, including the use of muscle flaps, the Ilizarov technique, and antibiotic-loaded beads, have been applied to the field of bone infection. Despite many advances, osteomyelitis remains difficult to treat, and the cure rates are still unsatisfactory.

Classification

Although several systems for classification of osteomyelitis have been described by different authors, the two most widely used in the medical literature and in clinical practice are those presented by Waldvogel et al.¹ and Cierny et al.² In the former, osteomyelitis is described as either acute or chronic, according to the duration of the disease. Osteomyelitis is also classified according to the source of the infection: it is defined as hematogenous when it originates from a bacteremia and as contiguous focus when it originates from an infection in nearby

tissue^{3,4}. A third category in this classification is osteomyelitis in the presence of vascular insufficiency. A category not considered by Waldvogel et al., but which is increasingly relevant, is infection originating from direct penetration of microorganisms into the bone, as may happen following penetrating injuries or surgery. Because of the wide variability in the etiology of osteomyelitis, a classification based on the pathogenesis of the disease, such as that of Waldvogel et al., is of little value in clinical practice.

The other commonly used classification was described by Cierny et al.² This system, known as the Cierny-Mader classification, includes four anatomic stages. Stage-1, or medullary, osteomyelitis is confined to the medullary cavity of the bone. Hematogenous osteomyelitis and infections in the presence of an intramedullary rod are examples of this stage. Stage-2, or superficial, osteomyelitis involves only the cortical bone and usually originates from a direct inoculation or a contiguous focus infection. Stage-3, or localized, osteomyelitis usually involves both cortical and medullary bone. However, in this stage, the bone is still stable because the infectious process does not involve the entire diameter of the bone. Stage-4, or diffuse, osteomyelitis involves the entire thickness of the bone, with loss of stability, as in an infected nonunion. With this system, a patient with osteomyelitis is classified as an A, B, or C host. An A host has no systemic or local compromising factors, a B host is affected by one or more compromising factors, and a C host is so severely compromised that the radical treatment necessary would have an unacceptable risk-benefit ratio (Table I). Although the C-host definition is to some ex-

TABLE I Cierny-Mader Staging System

Description	
Anatomic type	
Stage 1	Medullary osteomyelitis
Stage 2	Superficial osteomyelitis
Stage 3	Localized osteomyelitis
Stage 4	Diffuse osteomyelitis
Physiologic class	
A host	Normal
B host	
Bs	Systemic compromise
Bl	Local compromise
Bls	Systemic and local compromise
C host	Treatment worse than the disease

tent subjective, this classification seems to be of value in clinical practice and has been used in several clinical studies of both antibiotic and operative treatment.

Etiology

In hematogenous osteomyelitis, a single pathogenic organism is almost always recovered from the bone. In infants, *Staphylococcus aureus*, *Streptococcus agalactiae*, and *Escherichia coli* are most frequently isolated from blood or bone. However, in children over one year of age, *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Haemophilus influenzae* are most commonly isolated⁵. The incidence of *Haemophilus influenzae* infection decreases after the age of four years. Also, the overall incidence of *Haemophilus influenzae* as a cause of osteomyelitis is decreasing because of the new *Haemophilus influenzae* vaccine now being given to children^{6,7}. In adults, *Staphylococcus aureus* is the most common organism isolated⁴.

Multiple organisms are usually isolated from bone infected as a result of direct inoculation or contiguous focus infection. *Staphylococcus aureus* remains the most commonly isolated pathogen. However, gram-negative bacilli and anaerobic organisms are also frequently isolated.

Skeletal tuberculosis is the result of hematogenous spread of *Mycobacterium tuberculosis* early in the course of a primary infection. Rarely, skeletal tuberculosis is a contiguous infection from an adjacent caseating lymph node. Atypical mycobacteria, including *Mycobacterium marianum*, *Mycobacterium avium-intracellulare*, *Mycobacterium fortuitum*, and *Mycobacterium gordonae*, have been associated with osteoarticular infections. Bone infections may also be caused by a variety of fungal organisms, including those causing coccidioidomycosis, blastomycosis, cryptococcosis, and sporotrichosis⁸.

Epidemiology

The epidemiology of osteomyelitis has several broad trends. The incidence of hematogenous osteomyelitis seems to be decreasing. In one study, in Glasgow, Scotland, of 275 cases of acute hematogenous osteomyelitis in children under thirteen

years of age, the authors reported a decrease in incidence from eighty-seven to forty-two per 10,000 per year over the twenty-year period of the investigation⁷. The number of cases of osteomyelitis involving long bones decreased while the rate of osteomyelitis at all other sites remained the same. The prevalence of *Staphylococcus aureus* infections also decreased, from 55% to 31%, over the twenty-year time period⁷. In contrast to hematogenous osteomyelitis, the incidence of osteomyelitis due to direct inoculation or contiguous focus infection is increasing⁹. This is probably due to motor-vehicle accidents and the increasing use of orthopaedic fixation devices and total joint implants. Males have a higher rate of contiguous focus osteomyelitis than do females⁹. Finally, osteomyelitis occurs with a higher frequency in immunocompromised patients⁹.

Pathogenesis

Source of Infection

As noted above, osteomyelitis can be caused by hematogenous spread, direct inoculation of microorganisms into bone, or a contiguous focus of infection. Hematogenous osteomyelitis usually involves the metaphysis of long bones in children or the vertebral bodies in adults. The most common causes of direct-inoculation osteomyelitis are penetrating injuries and surgical contamination. Contiguous focus osteomyelitis commonly occurs in patients with severe vascular disease.

Host Factors

Host factors are primarily involved in the containment of the infection once it has been introduced adjacent to or into the bone. On occasion, host factors may predispose individuals to the development of osteomyelitis. Host deficiencies that lead to bacteremia favor the development of hematogenous osteomyelitis. Host deficiencies that are involved in the direct inoculation of organisms and/or contiguous spread of infection from an adjacent area of soft-tissue infection are primarily involved in the lack of containment of the initial infection. Three patient groups with an unusual susceptibility to acute skeletal infections are those with sickle cell anemia, chronic granulomatous disease, and diabetes mellitus^{10,11}. Many systemic and local factors influence the ability of the host to elicit an effective response to infection and treatment (Table II).

Pathology

Acute Osteomyelitis

Acute osteomyelitis presents as a suppurative, or pus-producing, infection accompanied by edema, vascular congestion, and small-vessel thrombosis. In early acute disease, the vascular supply to the bone is decreased by infection extending into the surrounding soft tissue. When both the medullary and the periosteal blood supplies are compromised, large areas of dead bone (sequestra) may be formed¹². However, if treated promptly and aggressively with antibiotics and possibly with surgery, acute osteomyelitis can be arrested before dead bone, the hallmark of chronic disease, develops. Once the infection is established, fibrous tissue and chronic inflammatory cells form around the granulation tissue and dead bone. After the

infection is contained, there is a decrease in the vascular supply to it; therefore, an effective inflammatory response cannot be produced. The coexistence of infected, nonviable tissues and an ineffective host response leads to the chronicity of this disease. Acute osteomyelitis, if ineffectively treated, can lead to chronic disease as seen clinically and histologically¹³.

Necrosis of bone tissue is an important feature of osteomyelitis. Dead bone is resorbed by the action of enzymes produced by the granulation tissue developing at its surface. Resorption takes place earliest and most rapidly at the junction of living and necrotic bone. If the area of dead bone is small, it is entirely destroyed, leaving a cavity behind. The necrotic cancellous bone in localized osteomyelitis, even though it is extensive, is usually resorbed. Some of the dead cortical bone is detached gradually from the living bone to form a sequestrum. The organic elements in the dead bone are largely disrupted by the action of proteolytic enzymes produced by host defense cells, mainly the macrophages or polymorphonuclear leukocytes. Because of lost blood supply, dead bone appears whiter than living bone. While cancellous bone is reabsorbed rapidly and may be completely sequestered or destroyed within two to three weeks, necrotic cortical bone may require two weeks to six months for separation. After complete separation (a process termed *sequestration*), the dead bone is slowly eroded and resorbed¹⁴. The surviving bone in the field usually becomes osteoporotic during the active period of infection. This is the result of both the inflammatory reaction and disuse atrophy. New bone formation is another characteristic pathologic feature of osteomyelitis, but it is usually found in subacute and chronic osteomyelitis¹³.

Chronic Osteomyelitis

Pathologic features of chronic osteomyelitis are the presence of necrotic bone, the formation of new bone, and the exudation of polymorphonuclear leukocytes joined by large numbers of lymphocytes, histiocytes, and occasionally plasma cells. New bone forms from the surviving fragments of periosteum and endosteum in the region of the infection.

It forms an encasing sheath of live bone, known as an *involucrum*, surrounding the dead bone under the periosteum. The involucrum is irregular and is often perforated by openings through which pus may track into the surrounding soft tissues and eventually drain to the skin surfaces, forming a chronic sinus. The involucrum may gradually increase in density and thickness to form part or all of a new diaphysis. New bone increases in amount and density for weeks or months, according to the size of the bone and the extent and duration of the infection. Endosteal new bone may proliferate and obstruct the medullary canal. After host defense or operative removal of the sequestrum, the remaining cavity may fill with new bone, especially in children. However, in adults, the cavity may persist or the space may be filled with fibrous tissue, which may connect with the skin surface by means of a sinus tract¹³.

Findings from Experimental Studies

The inflammatory response to osteomyelitis has been the object of investigation. Prostaglandin-E production has been shown to be five to thirtyfold higher in infected bone than in normal bone¹⁵. In studies of an animal model of osteomyelitis, the production of large amounts of prostaglandin was postulated to be responsible for bone resorption and sequestrum formation, and experimental treatment of rabbit osteomyelitis with sodium salicylate was shown to prevent bone resorption and sequestration^{16,17}. Experimental treatment of osteomyelitis in rats with ibuprofen has been shown to reduce prostaglandin production in infected bone and concurrently reduce gross bone abnormalities and radiographic changes, without any change in the bacterial counts^{18,19}. According to the research on bone resorption due to metastatic cancer, it seems more likely that bone resorption is mediated by several cytokines and growth factors, including tumor necrosis factor and transforming growth factors alpha and beta, rather than by prostaglandins²⁰. It is possible, therefore, that many instances of prostaglandin-induced bone resorption may have been due to other factors that stimulate prostaglandin production in bone²⁰.

Effective phagocytosis has been shown to be an important factor in host defense in patients with osteomyelitis. Use of recombinant granulocyte-macrophage colony-stimulating factor, a growth factor with anti-inflammatory and pro-phagocytic properties, combined with standard antibiotic treatment was more effective than antibiotics alone in the treatment of experimental acute osteomyelitis in rats²¹. In a rabbit study, intramedullary oxygen tensions in infected bone were lower than those in normal bone; oxygen tensions of <30 mm Hg impair normal phagocytic function²². In the same model, hyperbaric oxygen therapy was demonstrated to significantly ($p < 0.001$) reduce colony-forming units compared with nontreated controls and antibiotic-treated controls²³.

Some bacterial factors have been recognized to be important in the pathogenesis of osteomyelitis. Since the pathogen must colonize the target tissue in order to initiate infection, adequate receptors are required to adhere to the bone, to the

TABLE II Systemic or Local Factors That Affect Immune Surveillance, Metabolism, and Local Vascularity

Systemic (Bs)	Local (Bl)
Malnutrition	Chronic lymphedema
Renal, hepatic failure	Venous stasis
Diabetes mellitus	Major vessel compromise
Chronic hypoxia	Arteritis
Immune disease	Extensive scarring
Malignancy	Radiation fibrosis
Extremes of age	Small vessel disease
Immunosuppression or immune deficiency	Neuropathy
Asplenia	
HIV/AIDS	
Ethanol and/or tobacco abuse	

extracellular matrix, and to implanted medical devices. Staphylococci have a large variety of adhesive proteins and glycoproteins that mediate binding with bone components^{24,25}. An important factor in the pathogenesis of osteomyelitis is the formation of a glycocalyx surrounding the infecting organisms. This glycocalyx protects the organisms from the action of phagocytes and prevents access by most antimicrobials. Evidence indicates that a surface negative charge of devitalized bone or a metal implant promotes organism adherence and subsequent glycocalyx formation²⁶.

Another way in which bacteria elude host defenses and produce bone infections is by gaining access to the interior of the cell. This was demonstrated with staphylococci in human osteoblasts and osteocytes in an *in vivo* model²⁷. More recently, an *in vitro* study showed that dead or dying osteoblasts are capable of releasing viable *Staphylococcus aureus* that is still able to reinfect human osteoblasts in culture²⁸. These findings are of interest because they may contribute to the understanding of the persistence and flare-ups of osteomyelitis.

Clinical Manifestations

Signs and Symptoms

Children with hematogenous osteomyelitis may present with acute signs of infection including fever, irritability, lethargy, and local signs of inflammation. However, in a study of eighty-six children, 50% of them presented with vague symptoms, including pain in the involved limb of one to three months' duration and minimal, if any, temperature elevation²⁹. Children with hematogenous osteomyelitis usually have noninfected soft tissue enveloping the infected bone and are capable of mounting an effective response to the infection. The joint is usually spared from infection unless the metaphysis is intracapsular, as is found in the proximal part of the radius, humerus, or femur^{29,30}.

Adults with primary or recurrent hematogenous osteomyelitis usually present with vague symptoms consisting of nonspecific pain and low-grade fever of one to three months' duration. However, acute clinical presentations with fever, chills, swelling, and erythema over the involved bone or bones are occasionally seen. The source of bacteremia may be a trivial skin infection or a more serious infection such as acute or subacute bacterial endocarditis. Hematogenous osteomyelitis that involves either long bones or vertebrae is an important complication of injection drug abuse³¹.

Patients with contiguous focus osteomyelitis often present with localized bone and joint pain, erythema, swelling, and drainage around the area of trauma, surgery, or wound infection. Signs of bacteremia such as fever, chills, and night sweats may be present in the acute phase of osteomyelitis but are not seen in the chronic phase.

Both hematogenous and contiguous focus osteomyelitis can progress to a chronic condition. Local bone loss, sequestrum formation, and bone sclerosis are common. Persistent drainage and/or sinus tracts are often found adjacent to the area of infection. The patient usually presents with chronic pain and drainage. If fever is present, it is low grade. The

erythrocyte sedimentation rate is usually elevated, reflecting chronic inflammation, but the blood leukocyte count is usually normal. Chronic disease is usually either nonprogressive or slowly progressive. If a sinus tract becomes obstructed, the patient may present with a localized abscess and/or an acute soft-tissue infection.

Laboratory Studies

The leukocyte count may be elevated in cases of acute osteomyelitis, but it is often normal in chronic cases. The erythrocyte sedimentation rate is usually elevated in both acute and chronic osteomyelitis, and it decreases after successful treatment. The erythrocyte sedimentation rate usually rises immediately after operative débridement. An erythrocyte sedimentation rate that returns to normal during the course of therapy is a favorable prognostic sign³²⁻³⁶. However, the interpretation of a persistently elevated erythrocyte sedimentation rate as an isolated finding after treatment should be carefully scrutinized, especially when it is found in a compromised host, in whom the erythrocyte sedimentation rate may be altered for reasons other than osteomyelitis. Finally, the erythrocyte sedimentation rate is not sensitive enough to rule out acute or chronic osteomyelitis.

The C-reactive protein level is another inflammatory index that rises in acute and chronic osteomyelitis and decreases faster than the erythrocyte sedimentation rate in successfully treated patients. In a study of children with acute osteomyelitis, the C-reactive protein level was found to decrease markedly after three days of antibiotic treatment in the patients with favorable outcomes, whereas higher values were observed in those with complications³⁵. Even though the C-reactive protein level is probably a more sensitive parameter than the erythrocyte sedimentation rate, its normality cannot be used to confidently exclude the diagnosis of osteomyelitis³⁴. The leukocyte count, erythrocyte sedimentation rate, and C-reactive protein level should be monitored at the time of admission and during treatment and follow-up in all patients with osteomyelitis. In patients with acute hematogenous osteomyelitis, these parameters should be measured on a weekly basis. However, to our knowledge, there is no information in the literature regarding the frequency of testing for patients with chronic osteomyelitis. In our practice, we perform the studies every two weeks during antibiotic treatment and at the end of treatment.

A number of different laboratory tests should be requested for patients with osteomyelitis to monitor drug toxicity (serum creatinine level and liver function tests), nutritional status (serum albumin level and total iron-binding capacity), and comorbidities (e.g., blood glucose levels for patients with diabetes).

Microbiology

The diagnosis and determination of the etiology of osteomyelitis in the long bones depend on the isolation of the pathogen or pathogens in cultures of specimens from the bone lesion, blood, or joint fluid. In patients with Cierny-Mader

TABLE III Antibiotics Used in the Oral Treatment of Osteomyelitis

Drug	Spectrum	Dosage in Adults	Side Effects and Toxicity
Clindamycin	Staphylococci, anaerobic bacteria	300 mg four times a day	Antibiotic-associated diarrhea, pseudomembranous colitis
Rifampin	Staphylococci	600 mg once a day	Hepatotoxicity
Ciprofloxacin	Enterobacteriaceae, <i>Pseudomonas aeruginosa</i>	750 mg twice a day	Hepatotoxicity, tendon damage
Levofloxacin	Streptococci, staphylococci, Enterobacteriaceae	750 mg once a day	Hepatotoxicity, tendon damage
Gatifloxacin	Streptococci, staphylococci, Enterobacteriaceae	400 mg once a day	Hepatotoxicity, tendon damage
Cotrimoxazole	Streptococci, staphylococci, Enterobacteriaceae	160 mg trimethoprim/800 mg sulfamethoxazole twice a day	Rash, Stevens-Johnson syndrome, hepatotoxicity
Linezolid	Gram-positive cocci, including methicillin-resistant <i>Staphylococcus aureus</i>	600 mg twice a day	Bone marrow toxicity: anemia, thrombocytopenia

Stage-1, or hematogenous, osteomyelitis, positive cultures of blood or joint fluid can often obviate the need for a bone biopsy when there is radiographic evidence of osteomyelitis. With the exception of hematogenous osteomyelitis, for which positive blood or joint fluid cultures may suffice, antibiotic treatment of osteomyelitis should be based on sensitivity studies in meticulously performed cultures of bone taken at the time of débridement or deep bone biopsies^{37,38}. If possible, culture specimens should be obtained before antibiotics are initiated. However, empirically selected antibiotics are often started before culture specimens are obtained. In this case, the empiric regimen should be discontinued for three days before the collection of samples for cultures³⁸. Cultures of specimens from the sinus tract are not reliable for predicting which organisms will be isolated from infected bone^{39,40}. However, a positive correlation has been found between the growth of *Staphylococcus aureus* on culture of specimens from the sinus tract and such growth on bone culture.

Conventional microbiological techniques are usually used for the diagnosis of osteomyelitis. However, some authors have established that the use of improved techniques for processing purulent materials may yield a higher percentage of isolated strains⁴¹. A lysis-centrifugation technique has been described to improve the sensitivity of cultures of osteomyelitis samples⁴². Removed hardware requires mild ultrasonication to provide optimal bacterial removal⁴³. Polymerase chain reaction, a well-known technique of gene amplification, has been used in the diagnosis of bone infection due to unusual or difficult pathogens, such as *Mycoplasma pneumoniae*⁴⁴, *Brucella* species⁴⁵, *Bartonella henselae*⁴⁶, and both tuberculous and nontuberculous *Mycobacterium* species⁴⁷. Polymerase chain reaction has detected *Mycobacterium tuberculosis* in formaldehyde solution-fixed, paraffin-embedded tissue samples from patients with Pott disease⁴⁸.

Radiographic Findings

In hematogenous osteomyelitis, radiographic changes usually

reflect the destructive process but lag at least two weeks behind the process of infection. The earliest changes are swelling of the soft tissue, periosteal thickening and/or elevation, and focal osteopenia. At least 50% to 75% of the bone matrix must be destroyed before radiographs show lytic changes⁴⁹. The more diagnostic lytic changes are delayed and are associated with subacute and chronic osteomyelitis. Radiographic evidence of improvement may lag behind clinical recovery, even when the patient is receiving appropriate antimicrobial therapy⁴⁹. In contiguous focus osteomyelitis, the radiographic changes are subtle; often are associated with other, nonspecific radiographic findings; and require careful clinical correlation to achieve diagnostic relevance.

Computed axial tomography may play a role in the diagnosis of osteomyelitis. Increased bone-marrow density occurs early in the course of the infection, and intramedullary gas has been reported in patients with hematogenous osteomyelitis^{50,51}. A computed tomography scan can also help to identify areas of necrotic bone and to demonstrate the involvement of the surrounding soft tissues. One disadvantage of this study is the scatter phenomenon, which occurs when metal is present in or near the area of bone infection and results in a substantial loss of image resolution.

Magnetic resonance imaging has been recognized as a useful modality for diagnosing the presence and scope of musculoskeletal infection⁵¹⁻⁵³. The resolution of magnetic resonance imaging makes it useful for differentiating between bone and soft-tissue infection, which is often a problem with radionuclide studies⁵⁴. Unlike radionuclide studies, magnetic resonance imaging is not useful for whole-body examinations. Also, a metallic implant in the region of interest may produce focal artifacts, thereby decreasing image quality⁵⁵. Initial screening with magnetic resonance imaging usually consists of a T1-weighted and a T2-weighted spin-echo pulse sequence. In a T1-weighted study, edema is dark and fat is bright. In a T2-weighted study, the reverse is true. The typical appearance of acute osteomyelitis is a localized area of abnor-

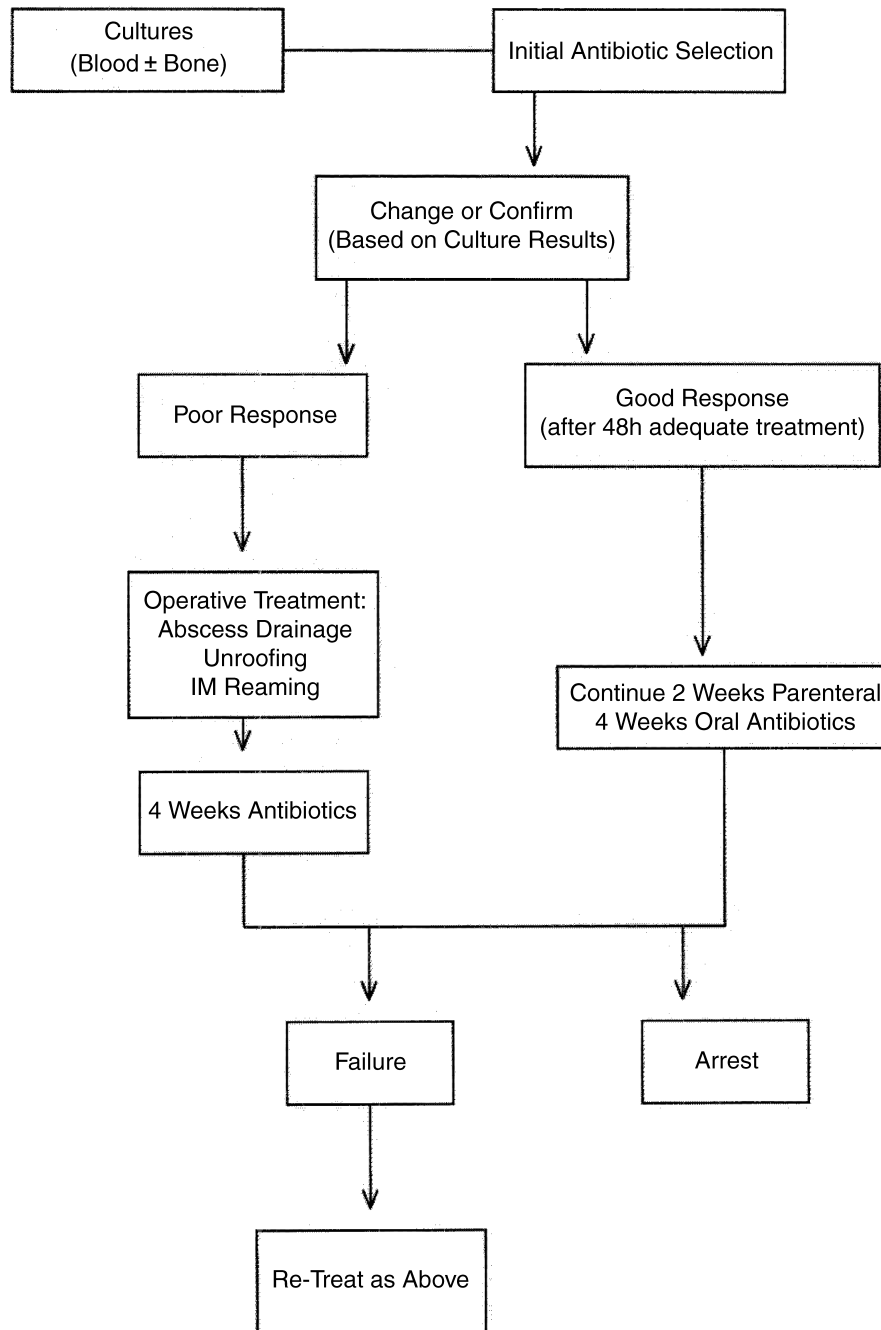


Fig. 1

Treatment algorithm of Cierny-Mader Stage-1, or hematogenous, long-bone osteomyelitis.

mal marrow with decreased signal intensity on T1-weighted images and increased signal intensity on T2-weighted images. On occasion, there may be decreased signal intensity on T2-weighted images⁵⁵. Posttraumatic or surgical scarring of the marrow is seen as a region of decreased signal intensity on T1-weighted images with no change on T2-weighted images. Sinus tracts are seen as areas of high signal intensity extending from the marrow and bone through the soft tissues and through the skin on T2-weighted images. Cellulitis is seen as diffuse areas of

intermediate signal on T1-weighted images of the soft tissues, with increased signal seen on T2-weighted images of the same area. Magnetic resonance imaging has very high sensitivity and specificity for the diagnosis of osteomyelitis⁵¹.

Radionuclide scans may be performed when the diagnosis of osteomyelitis is ambiguous or to help gauge the extent of bone and soft-tissue inflammation. In general, it is not necessary to perform these scans for the diagnosis of long-bone osteomyelitis. The actual mechanism of bone-labeling with

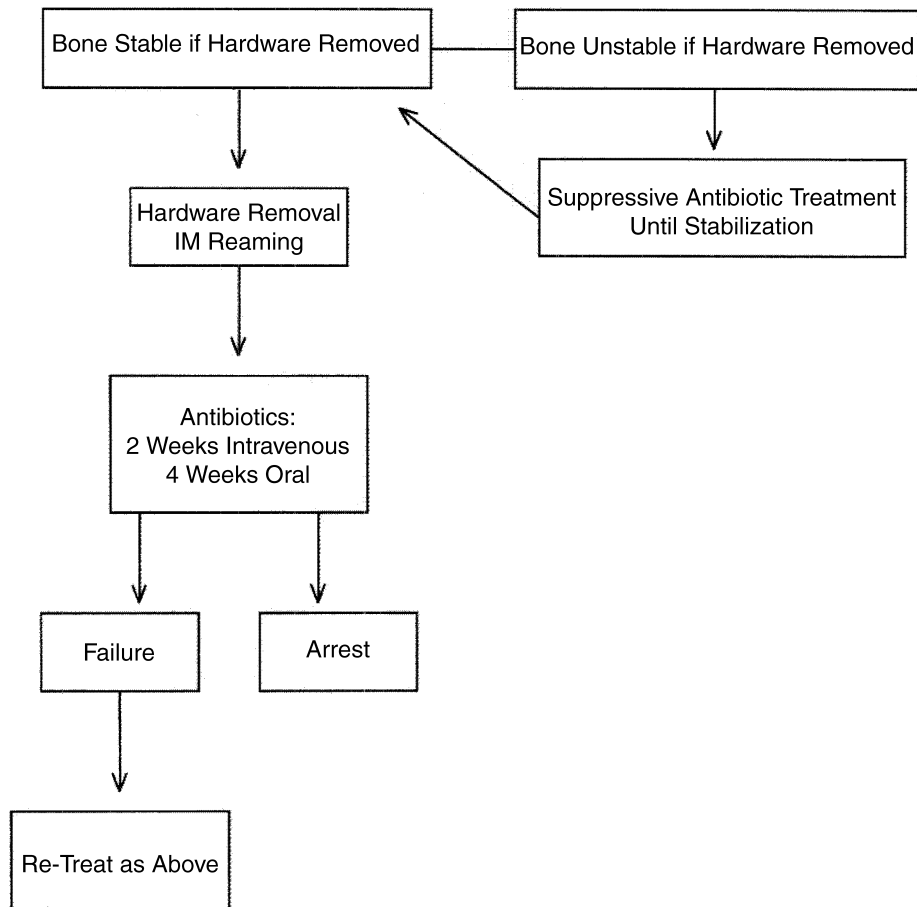


Fig. 2

Treatment algorithm of Cierny-Mader Stage-1 long-bone osteomyelitis associated with infection at the site of hardware.

radiopharmaceuticals is still unclear. The 99m -technetium polyphosphate scan demonstrates increased isotope accumulation in areas of increased blood flow and reactive new bone formation⁵⁶. In biopsy-confirmed cases of hematogenous osteomyelitis, such a scan is usually positive as early as forty-eight hours following the initiation of the bone infection⁵⁷. However, a technetium- 99m scan may be negative for a patient with documented osteomyelitis because of a decrease in blood flow to the infected area⁵⁸.

A second class of radiopharmaceuticals used for the evaluation of osteomyelitis includes gallium citrate. Gallium attaches to transferrin, which leaks from the bloodstream into areas of inflammation. The gallium scan also shows increased isotope uptake in areas of concentrated polymorphonuclear leukocytes and macrophages and in malignant tumors⁵⁹. Since the gallium citrate scan does not show bone detail well, it is often difficult to distinguish between bone and soft-tissue inflammation; a comparison with a technetium- 99m scan can help to resolve this question⁶⁰. Gallium citrate is also found to accumulate in areas of infected and noninfected nonunions⁵⁹. Because gallium accumulates in areas of inflammation, it has a high sensitivity and a low specificity for the diagnosis of osteomyelitis⁵⁹.

An indium-labeled leukocyte scan is another useful tool for the diagnosis of acute and chronic osteomyelitis. Indium-labeled leukocyte scans are positive in up to 80% of patients with acute osteomyelitis; however, sensitivity is lower for patients with chronic vertebral osteomyelitis⁶¹.

Even though we found no guidelines for the clinical use of radiographic studies in the literature, we recommend that plain radiographs be made whenever acute or chronic osteomyelitis is suspected because they are simple, economical, and usually effective. Magnetic resonance imaging should be requested if the diagnosis is doubtful. If magnetic resonance imaging is not feasible because of the presence of hardware, bone scintigraphy (ideally, leukocyte scans for acute osteomyelitis and technetium scans for chronic osteomyelitis) should be performed. Computed tomography scans can be used to help establish a surgical plan both for acute and for chronic osteomyelitis.

Treatment

Appropriate therapy for osteomyelitis includes adequate drainage, thorough débridement, obliteration of dead space, wound protection, and specific antimicrobial coverage. If the patient is a compromised host, an effort is made to correct or reduce the

host defect or defects. In particular, attention should be paid to good nutrition, to a smoking cessation program, and to control of specific diseases such as diabetes. Thus, an attempt is made to improve the nutritional, medical, and vascular status of the patient and to provide optimal treatment of any underlying disease. Ideally, the standard of care involves a team approach including infectious disease specialists, plastic surgeons, and other consulting physicians as appropriate.

Antibiotic Treatment

Many aspects of the antibiotic treatment of osteomyelitis have not been completely investigated. The traditional duration of treatment in most stages of osteomyelitis (Cierny-Mader Stages 1, 3, and 4) is four to six weeks. The rationale for this duration is based on the results of animal studies⁶² and the observation that revascularization of bone after débridement takes about four weeks. Longer courses of intravenous or oral antibiotics (six months or more) have been attempted by some authors⁶³⁻⁶⁵, but the outcomes of those trials do not suggest any improvement in comparison with those following six weeks of therapy. Failures occur in all clinical trials, whatever the duration of treatment, mostly as a result of emergence of resistant strains or inadequate surgical débridement.

Outpatient therapy with an intravenous access catheter, such as a peripherally inserted central catheter, a Hickman catheter, or a Groshong catheter, has been proven to reduce treatment cost and to improve the patient's quality of life⁶⁶⁻⁶⁹.

The drugs of proven efficacy in the oral treatment of osteomyelitis are clindamycin, rifampin, cotrimoxazole, and fluoroquinolones (Table III). Clindamycin, a lincosamide antibiotic active against most gram-positive bacteria, has an excellent bioavailability and is currently given orally after initial intravenous treatment of one to two weeks in duration^{70,71}. Linezolid, a novel oral and intravenous antibiotic active against methicillin-resistant staphylococci, has proven effec-

tive for treating serious infections, including osteomyelitis⁷². Oral therapy with quinolones for gram-negative organisms is currently being used in adult patients with osteomyelitis⁷³⁻⁷⁵. The second-generation quinolones (ciprofloxacin and ofloxacin) have poor activity against *Streptococcus* species, *Enterococcus* species, and anaerobic bacteria⁷⁶. The third-generation quinolones (levofloxacin and gatifloxacin) have excellent activity against *Streptococcus* species but minimal coverage of anaerobic bacteria⁷⁷. The fourth-generation quinolone trovafloxacin has excellent coverage of *Streptococcus* species and anaerobic organisms^{77,78}. Trovafloxacin is approved only for inpatient treatment and must be used with caution because, in rare cases, it can lead to serious liver toxicity. None of the quinolones have reliable coverage of *Enterococcus* species. The currently available quinolones exhibit variable coverage of *Staphylococcus aureus* and *Staphylococcus epidermidis*, and resistance to the second and third-generation quinolones is increasing⁷⁹. Coverage of methicillin-sensitive *Staphylococcus aureus* should be obtained with another oral antibiotic such as clindamycin or ampicillin-sulbactam. Before changing to a non-quinolone oral regimen, we usually treat the patient with two weeks of parenteral antibiotic therapy. The patient must be compliant with the treatment regimen and have close outpatient follow-up. Because of their excellent oral absorption, quinolones can be given orally as soon as the patient is able to take them. High doses of the quinolone class of antibiotics have been reported to damage articular cartilage in young animals⁸⁰, a finding that has generated some concern regarding the long-term use of these agents in infants and children. Therefore, in most circumstances, pediatric patients should not be given the quinolone class of antibiotics.

The decision to use oral rather than parenteral antibiotics should be based on results regarding microorganism sensitivity, patient compliance, infectious disease consultation, and the surgeon's experience.

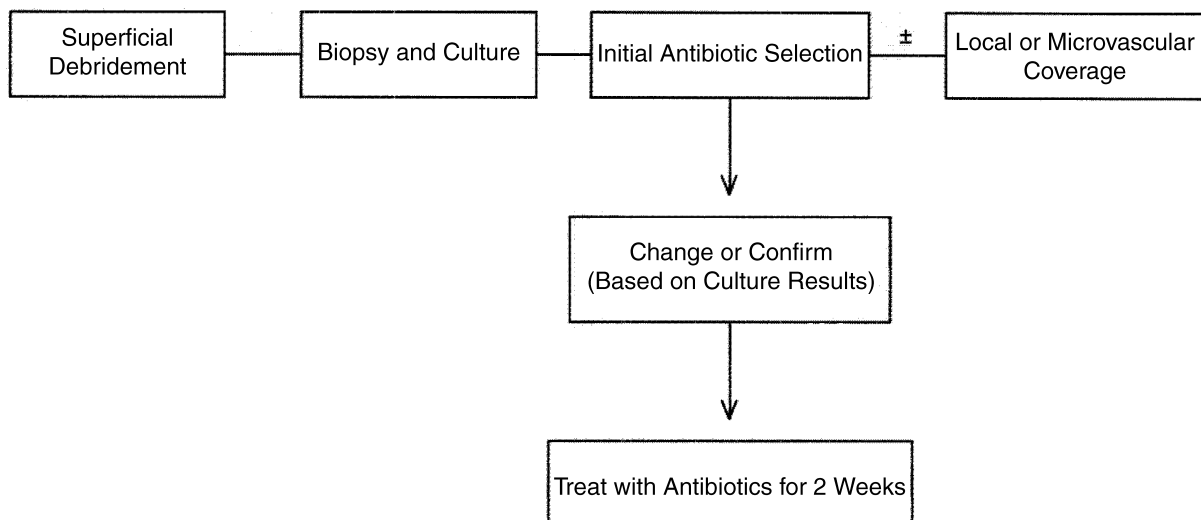


Fig. 3

Treatment algorithm of Cierny-Mader Stage-2 long-bone osteomyelitis.

A combination of parenteral and oral antibiotics has been used in some situations. Oral rifampin is currently used as a combination drug in both parenteral and oral regimens for *Staphylococcus aureus* infections. It should not be used alone because of the rapid emergence of resistant strains^{81,82}.

Even though the serum bactericidal activity has been associated with a favorable outcome in the treatment of hematogenous osteomyelitis in general, it is not necessary to follow serum bactericidal levels⁸³ because most treatment failures are probably due to a lack of adequate surgical débridement rather than inadequate antibiotic efficacy⁸⁴. It may be necessary to follow serum levels in patients with relatively resistant organisms or to gauge the efficacy of oral antibiotic therapy.

Ideally, the treatment of osteomyelitis should be based on the results of bone cultures. After culture specimens are obtained by means of a bone biopsy or during débridement, a parenteral antimicrobial regimen is begun to cover the clinically suspected pathogens. Once the organism is identified, the treatment may be modified according to the sensitivity of the isolated microorganisms (Table III). However, when the patient is acutely ill, antibiotic treatment should not be delayed in order to wait for bone débridement.

Antibiotic Treatment by Stage

Stage-1 osteomyelitis (Fig. 1) in children can usually be treated with antibiotics alone^{70,71} because the bones of children are very vascular and have an effective response to infection.

Stage-1 osteomyelitis in adults (Fig. 2) is more refractory to therapy and is usually treated with antibiotics and operative intervention. The patient is treated with appropriate parenteral antimicrobial therapy for four weeks, dated from the initiation of the therapy or from the last major operative débridement. If the initial medical management fails and the patient is clinically compromised by a recurrent infection, bone and/or soft-tissue débridement is necessary in conjunction with another four-week course of antibiotics.

Oral antibiotic therapy can be used to treat Stage-1 osteomyelitis in children. However, in most studies in the literature, the children initially received one to two weeks of parenteral antibiotic therapy prior to changing to an oral regimen^{70,71}. In Stage-2 osteomyelitis (Fig. 3), shorter courses of antibiotics are usually needed. In a study in which a two-week course of antibiotics was given following débridement of the cortex and soft-tissue coverage, the osteomyelitis was arrested in close to 100% of A hosts and 79% of B hosts⁸⁵.

We treat patients with Stage-3 or 4 osteomyelitis (Fig. 4) with antimicrobial therapy for four to six weeks, dated from the last major débridement. Without adequate débridement, the failure rate is high regardless of the duration of therapy. Even when all necrotic tissue has been adequately débrided, the remaining bed of tissue must be considered contaminated with the responsible pathogen or pathogens. Therefore, it is important to treat the patient with antibiotics for at least four weeks¹. The arrest rate is about 98% in A hosts and 80% (for Stage 4) to 92% (for Stage 3) in B hosts⁸⁵.

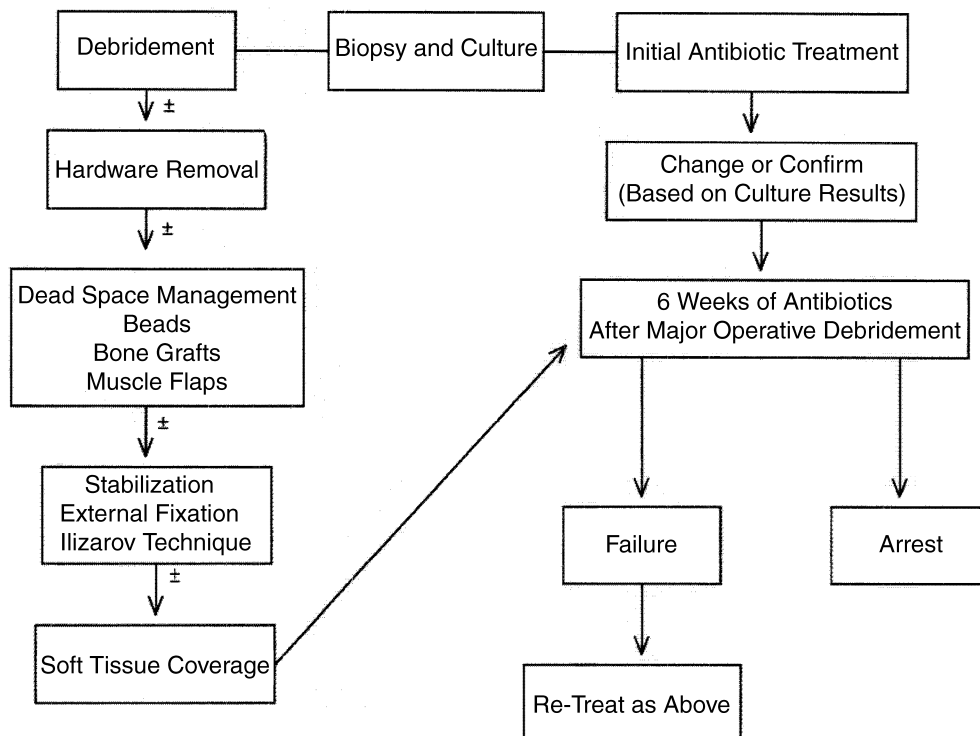


Fig. 4

Treatment algorithm of Cierny-Mader Stages-3 and 4 long-bone osteomyelitis.

Suppressive Antibiotic Therapy

When operative treatment of osteomyelitis is not feasible, suppressive antibiotic therapy, usually administered orally, is usually given to control the disease and to prevent flare-ups. Ideal drugs for suppression must possess good bioavailability, have low toxicity, and be able to penetrate bone adequately. The suppressive regimen should be directed by the results of cultures. The causative microorganism must be susceptible to the antibiotic or antibiotics used for suppression. Suppressive therapy for infections around orthopaedic implants has been studied extensively. Rifampin (in combination with other antibiotics), fusidic acid, ofloxacin, and cotrimoxazole have been administered, for six to nine months, to patients with infections around implants^{41,86-88}. After discontinuation of treatment, there was no recurrence of the infection during the follow-up period in twenty-six (67%) of thirty-nine patients treated with cotrimoxazole⁴¹, in eleven (55%) of twenty treated with fusidic acid and rifampin, and in eleven (50%) of twenty-two treated with rifampicin and ofloxacin⁸⁷. Failures were thought to be due to persistence of the infection or to resistance to the antibiotic. The efficacy of suppressive therapy is probably due to a prolonged action against bacteria replicating at a slow rate, or it may be due to its action against suspended bacterial cells liberated from the glycocalyx^{89,90}. The efficacy of suppressive treatment of long-bone osteomyelitis without an implant in place has not been determined.

Suppressive therapy is traditionally administered for six months. If the infection recurs after discontinuation of the therapy, a new, lifelong suppressive regimen is begun.

Operative Treatment

Operative management of osteomyelitis can be very challenging. The principles of treating any infection are equally applicable to the treatment of infection in bone. These principles include adequate drainage, extensive débridement of all necrotic tissue, obliteration of dead spaces, adequate soft-tissue coverage, and restoration of an effective blood supply^{84,85}.

Operative treatment of a compromised host is even more challenging. The functional impairment caused by the disease, reconstructive operations, and metabolic consequences of aggressive therapy influence the selection of patients for treatment. At times, the procedures required to arrest or palliate the disease are of such magnitude they can lead to the loss of function, limb, or the life of the compromised host. Therefore, standard operative treatment of osteomyelitis is not feasible in all cases, and some patients, particularly severely compromised hosts, are candidates for more radical treatment (e.g., amputation) or for nonoperative treatment (e.g., antibiotic suppression).

Bone Débridement

The goal of débridement is to leave healthy, viable tissue. Débridement of bone is done until punctate bleeding is noted, giving rise to the term *the paprika sign*⁸⁴. However, even when all necrotic tissue has been adequately débrided, the remaining bed of tissue must still be considered contaminated. Re-

cently, the importance of the extent of operative débridement has been reinvestigated in both normal and compromised hosts⁹¹. B hosts treated with marginal resection (i.e., with a clearance margin of <5 mm) had a higher rate of recurrence than did normal hosts. According to the authors of that study, the extent of resection therefore appears to be much more important in B hosts, whereas a marginal resection may be acceptable in normal hosts.

Reconstruction of Bone Defects and Management of Dead Space

Adequate débridement may leave a large bone defect, termed a *dead space*. This space is a problem because it is poorly vascularized, which is a predisposing condition for the persistence of infection. Appropriate management of any dead space created by débridement is mandatory to arrest the disease and to maintain the integrity of the skeletal part. The goal of dead-space management is to replace dead bone and scar tissue with durable vascularized tissue^{84,92}. A free vascularized bone graft has been used successfully to fill dead space^{93,94}. These grafts are usually obtained from the fibula or ilium. Local tissue flaps or free flaps can also be used to fill dead space⁹⁵⁻⁹⁹. An alternative technique is to place cancellous bone grafts beneath local or transferred tissues where structural augmentation is necessary. Careful preoperative planning is critical to the conservation of the patient's limited cancellous bone reserves. Open cancellous grafts without soft-tissue coverage are useful when a free tissue transfer is not an option and local tissue flaps are inadequate¹⁰⁰.

Antibiotic-impregnated acrylic beads may be used to sterilize and temporarily maintain a dead space. The beads are usually removed within two to four weeks and are replaced with a cancellous bone graft^{92,101-106}. The antibiotics that are most commonly used in beads are vancomycin, tobramycin, and gentamicin. The rate of arrest of osteomyelitis has ranged from 55% in a study of fifty-four patients¹⁰⁷ to 96% in a study of forty-six patients⁴⁶. Since most beads act as a biomaterial surface to which bacteria preferentially adhere, infection associated with bead use has been described¹⁰⁸. To avoid such a problem, biodegradable antibiotic-impregnated beads have been employed recently and have shown favorable antibiotic-release kinetics¹⁰⁹. Antibiotic-impregnated cancellous bone grafts were recently used in a clinical trial of forty-six patients, and the osteomyelitis was arrested in 95% of them¹¹⁰. Antibiotics (clindamycin and amikacin) have also been delivered directly into dead spaces with an implantable pump, and very high local and low systemic levels of antibiotics have been achieved^{111,112}.

An additional option that may aid healing of soft-tissue wounds is the vacuum-assisted closure system, a device that applies localized negative pressure over the surface of wounds and aids in the removal of fluids. In one case study of children, this system helped to increase the rate of granulation tissue formation and healing of extensive soft-tissue injury¹¹³. Herscovici et al. also demonstrated its usefulness as an adjunct therapy for high-energy soft-tissue injuries, in a nonrandomized study of twenty-one patients who had sustained trauma;

the authors reported that 57% of the patients did not require additional treatment or a split-thickness skin graft after approximately twenty days of negative-pressure treatment¹¹⁴. The potential applications of vacuum-assisted closure systems are promising; however, to our knowledge, no large, controlled clinical trials have been completed to determine their efficacy and risks in patients with established osteomyelitis. The authors of one case study reported the development of an anaerobic wound infection, apparently potentiated by topical negative pressure¹¹⁵.

Bone Stabilization

If skeletal instability is present at the site of an infection, measures must be taken to achieve stability with plates, screws, rods, and/or an external fixator. External fixation is preferred over internal fixation because of the tendency of the sites of medullary rods to become secondarily infected and to spread the extent of the infection. Ilizarov external fixation allows reconstruction of segmental defects and difficult infected nonunions¹¹⁶. This method is based on the technique of distraction osteogenesis whereby an osteotomy created in the metaphyseal region of the bone is gradually distracted to fill in the defect. The Ilizarov technique is used for difficult cases of osteomyelitis when stabilization and bone-lengthening are necessary. The method may also be used to compress nonunions and to correct malunions. The technique is labor-intensive and requires an extended period of treatment with the device, averaging 8.5 months¹¹⁷. In addition, the sites of the wires or pins usually become infected and the device is painful. In studies in which this technique was used, osteomyelitis arrest rates have ranged between 75% in a series of twenty-eight patients¹¹⁸ and 100% in a series of thirteen patients¹¹⁹.

Soft-Tissue Coverage

Adequate soft-tissue coverage of the bone is necessary to arrest osteomyelitis. Small soft-tissue defects may be covered with a split-thickness skin graft. In the presence of a large soft-tissue defect or an inadequate soft-tissue envelope, local muscle flaps and free vascularized muscle flaps may be placed in one or two stages. Local muscle flaps and free vascularized muscle transfers improve the local biological environment by bringing in a blood supply important for host defense mechanisms, antibiotic delivery, and osseous and soft-tissue healing.

Local and microvascular muscle flaps as well as microvascular flaps alone have been used in combination with antibiotics and operative débridement^{97,120,121}. The rate of arrest of the osteomyelitis ranged from 90% in a study of thirty-

three patients¹²⁰ to 100% in a study of eighteen patients¹²⁰.

Finally, healing by so-called secondary intention should be discouraged, since the scar tissue that fills the defect may later become avascular. Complete wound closure should be obtained whenever possible.

Overview

Despite all of the advances in antibiotic and operative treatment, osteomyelitis remains difficult to treat, with considerable morbidity and health-care costs. Bacteria reach the bone through the bloodstream, from a contiguous focus of infection, as a result of penetrating trauma, or from operative intervention. Bone necrosis occurs early, leading to a chronic process and limiting the possibility of eradicating the pathogens. The presence of poorly vascularized tissues, the adherence of bacteria to bone structures and implants, and a slow bacterial replication rate all contribute to the persistence of the infection. Appropriate treatment of osteomyelitis involves adequate antimicrobial therapy and operative débridement of all necrotic bone and soft tissues. Antibiotic treatment must be determined on the basis of the results of cultures and the identification of sensitivities to antibiotics. Treatment often involves a combination of antibiotics. Operative treatment should include débridement, obliteration of dead space, adequate soft-tissue coverage, restoration of blood supply, and stabilization. A close interaction between various specialists (orthopaedic surgeons, plastic and vascular surgeons, and infectious disease specialists) is important to improve the management of this disease.

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The authors did not receive grants or outside funding in support of their research or preparation of this manuscript. They did not receive payments or other benefits or a commitment or agreement to provide such benefits from a commercial entity. No commercial entity paid or directed, or agreed to pay or direct, any benefits to any research fund, foundation, educational institution, or other charitable or nonprofit organization with which the authors are affiliated or associated.

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