Systemic Antimicrobial Therapy in Osteomyelitis

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ABSTRACT

Appropriately designed antibiotic regimens are critical to the management of all stages of osteomyelitis, although goals of therapy may vary in different stages of infection. The most important consideration for antibiotic selection is spectrum of action. Route of administration by intravenous or oral route is less important than drug levels that are achievable at the site of infection. Outpatient parenteral therapy and use of oral agents has simplified delivery of long-term treatment regimens. There are few high-quality studies that compare specific treatment regimens or durations of therapy, and recommendations for drugs and duration of antibiotic therapy are based on expert opinion, case series, and extrapolations from animal models. Intravenous β-lactams are the treatment of choice for methicillin-susceptible *Staphylococcus aureus*, but there are also oral options available. Vancomycin has been the treatment of choice for methicillin-resistant *Staphylococcus aureus* osteomyelitis, but there are several newer parenteral and oral agents for treatment of methicillin-resistant *Staphylococcus aureus* including linezolid and daptomycin. Rifampin combined with other staphylococcal agents may increase cure rates, especially for device-associated infections. Oral fluoroquinolones and parenteral β-lactam agents can be used for treatment of gram-negative osteomyelitis, but increasing resistance has complicated management of these infections.

KEYWORDS: Osteomyelitis, *Staphylococcus aureus* osteomyelitis, methicillin-resistant *Staphylococcus aureus*, outpatient parenteral antibiotic therapy, fluoroquinolones

Effective antimicrobial therapy is an essential component of most curative treatment regimens for osteomyelitis. In stage 1 osteomyelitis, such as acute medullary osteomyelitis of the long bones or vertebrae, appropriately targeted antimicrobial therapy alone without other therapeutic measures may be adequate to achieve eradication of infecting organisms and cure of infection.[1,2] However, successful management of higher stage acute and chronic osteomyelitis generally requires a combination of targeted antimicrobial therapy to eradicate infecting microorganisms and surgical interventions for debridement of necrotic and devitalized tissue, drainage of abscesses, and removal of infected hardware and other prosthetic material.

GENERAL PRINCIPLES OF ANTIMICROBIAL THERAPY RELEVANT TO BONE INFECTION

Defining the Goals of Antimicrobial Therapy

Choosing optimal antimicrobial agents depends on the overall goals of the treatment regimen. When the goal is cure of infection or achieving a long-term remission, antibiotic therapy should be optimized with regard to

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choice of specific agent(s), route of administration, dosing frequency, and duration of therapy. Treatment options may be different when the goal is suppression of a noneradicable infection. Infection may be noneradicable because of site and extent of the infection, host factors that limit treatment options, or presence of a highly antimicrobial-resistant pathogen. This discussion will focus primarily on curative antimicrobial regimens.

Spectrum of Activity of Antimicrobial Agent

The single most important parameter in selecting an antimicrobial agent for treatment of bone infection is its spectrum of activity—is the drug active against the targeted pathogen? Standard susceptibility tests provide in vitro data to assess a particular "drug-bug" combination, and generally lack of susceptibility in vitro correlates with clinical failure. However, susceptibility as determined by minimal inhibitory concentration (MIC) or disk diffusion testing does not necessarily predict clinical success. Susceptibility interpretations are based on achievable serum levels, and these may differ significantly from levels achievable in bone in surrounding tissue. In healthy bone specimens removed at surgery, levels of cefazolin and other cephalosporins may range from 10 to 20% of serum levels,[1] and levels may be even lower in diseased tissues with poor vascular perfusion. Drugs also differ in ability to penetrate biofilms or function in the specific pH and oxidative microenvironment where infection occurs. Infecting organisms, especially those in more chronic infections, may also be slowly replicating or in near-stationary growth phase and thus less responsive to many classes of antimicrobial agents. Much information regarding activity of different agents has been extrapolated from well-established animal models, but there remains a paucity of published clinical experience in humans with many of the newer antimicrobial agents and even some of the older drugs.[3–5] The mechanism of activity of an antimicrobial agent and whether it is bactericidal (lethal) or bacteriostatic (inhibitory) in vitro is not as important for successful treatment of osteomyelitis as it is for other difficult-to-eradicate infections such as bacterial endocarditis. However, the pharmacodynamic properties (i.e., the relationship between drug concentration and activity against the target organism over time) of an antibiotic and the relative ease of selection of antimicrobial-resistant mutants for different agents are theoretical parameters that may be important in antibiotic selection.[6]

Route of Administration

The goal of administering antimicrobial therapy is to optimize antimicrobial activity at the site of infection. Generally, this also correlates with achievable serum levels of drug, though there are some exceptions where volume of distribution of a drug is large and drug concentrations in tissues may exceed achievable serum levels. The route of administration is much less important than whether desired blood and tissue levels can be achieved, thus drugs with good to excellent oral bioavailability such as fluoroquinolones and linezolid can be given orally or enterally in patients with functional gastrointestinal tracts.[7,8] Several studies have demonstrated equivalence of appropriately chosen oral agents compared with parenteral therapy.[8,9] For the patient, oral therapy has advantages of simplicity and convenience, especially for prolonged treatment regimens, and avoids the risks of intravenous catheters and the generally higher costs associated with long-term parenteral therapy. For some agents with both oral and parenteral formulations, especially penicillins and cephalosporins, parenteral therapy provides much higher serum levels, or may be better tolerated than the high oral doses necessary to achieve target serum levels. Many important antimicrobials, including broad-spectrum cephalosporins, vancomycin, aminoglycosides, and carbapenems, can only be delivered intravenously. Agents with parenteral and oral bioequivalence are listed in Table 1. A major evolution in health care has been improvement in delivery of long-term parenteral antimicrobial therapy.[10] The availability of long-term intravenous access options such as peripherally inserted central catheters has simplified the process of antibiotic delivery. The proliferation of outpatient infusion services now permits patients to receive appropriately monitored treatment at home or at infusion centers rather than in acute- or intermediate-care hospitals. Insurance and social issues may still be barriers to arranging outpatient intravenous therapy. Therapy of bone and joint infection is the second most common indication for outpatient intravenous antimicrobial therapy.[10] In addition to the primary considerations of spectrum of action and toxicity for choosing antimicrobial agents, other factors such as drug costs and convenience of the treatment regimen (e.g., dosing frequency, need for laboratory monitoring) must be considered.

Lessons from Animal Models of Antimicrobial Therapy in Osteomyelitis

Much of the current approach to osteomyelitis is based on animal infection models. The most widely employed are variations of the rabbit *Staphylococcus aureus* model developed by Norden and colleagues in the late 1960s.[11] More recently developed sheep, goat, and dog large-animal models permit manipulation of surgical parameters as well as evaluation of antimicrobial therapy.[12,13] Animal models have contributed to understanding of revascularization and bone remodeling that occur after infection and debridement and have demonstrated

Table 1 Antimicrobials Most Commonly Used for Treatment of Osteomyelitis, Route of Administration, and Dose

Antimicrobials for Which Oral Dosing Is Bioequivalent to Parenteral Dosing

Drug	Class	Usual Intravenous Dose	Usual Oral Dose
Ciprofloxacin	Fluoroquinolone	400 mg q 12 h	750 mg q 12 h
Levofloxacin	Fluoroquinolone	500–750 mg q 24 h	500–750 mg q 24 h
Moxifloxacin	Fluoroquinolone	400 mg q 24 h	400 mg q 24 h
Clindamycin	Lincomycin	600–900 mg q 8 h	300–450 mg q 6 h
Linezolid	Oxazolidinone	600 mg q 12 h	600 mg q 12 h
Trimethoprim-sulfamethoxazole	Sulfa	5–10 mg/kg q 24 h trimethoprim divided q 8–12 h; 1 DS tablet = 160 mg	
Minocycline	Tetracycline	100 mg q 12 h	100 mg q 12 h
Metronidazole	Nitroimidazole	500 mg q 8 h	500 mg q 8 h
Rifampin	Rifamycin	600 mg q 24 h or 300 mg q 12 h	600 mg q 24 h or 300 mg q 12 h
Fluconazole	Azole antifungal	400 mg q 24 h	400 mg q 24 h

Antibiotics for Which Oral Therapy Is *Not* Usually Equivalent to Parenteral Dosing

Parenteral Agent	Class	Usual Intravenous Dose	Oral Alternatives
Penicillin G	Penicillin	3–4 million units q 4–6 h	Penicillin,* amoxicillin
Nafcillin	Penicillin	1–2 g q 4–6 h	Dicloxacillin, cloxacillin*
Ampicillin	Penicillin	2 g q 4–6 h	Ampicillin, amoxicillin
Ampicillin-sulbactam	β-Lactamase inhibitor	1.5–3 g q 6 h	Amoxicillin–clavulanic acid
Cefazolin	First-generation cephalosporin	2 g q 8 h	Cephalexin, cefadroxil*

Antibiotics Only Available in Parenteral Form for Systemic Therapy

Class	Agent	Usual Dose	Class	Agent	Usual Dose
Broad-spectrum cephalosporin*	Ceftriaxone	1–2 g q 24 h	Glycopeptide	Vancomycin	1 g q 12 h
	Cefepime	1–2 g q 8–12 h		Teicoplanin	400 mg q 24 h†
	Ceftazidime	2 g q 8 h	Lipopeptide	Daptomycin	6 mg/kg q 24 h
Monobactam	Aztreonam	2 g q 8 h	Glycylcycline	Tigecycline	50 mg q 12 h
Carbapenem	Imipenem	500 mg q 6 h	Aminoglycoside*	Gentamicin	5 mg/kg q 24 h
	Meropenem	1–2 g q 8 h		Tobramycin	5 mg/kg q 24 h
	Ertapenem	1 g q 24 h		Amikacin	15 mg/kg q 24 h
β-Lactamase inhibitors	Ampicillin-sulbactam	1.5–3 g q 6 h	Streptogramin	Quinupristin-dalfopristin	7.5 mg/kg q 8 h
	Piperacillin-tazobactam	4.5 g q 6 h	Colistin	Polymyxin	2.5–5 mg kg^{-1} day^{-1}‡

*Other agents also used.
†Not available in the United States.
‡Depends on formulation: colistin or colistin methane sulfone; divided q 8–12 h.
q, every.

effectiveness of agents such as clindamycin and rifampin-containing combinations in *S. aureus* infections.[11,12] However, some drugs are toxic in animal models, and for others there is poor correlation between animal data and clinical experience. For example, vancomycin fared poorly in the rabbit models but has been used successfully in many human infections.[12]

Review of Human Trials of Antibiotics in the Treatment of Osteomyelitis

Despite the frequency with which clinicians see patients with this diagnosis, there are relatively few well-done studies addressing the optimal antimicrobial therapy for osteomyelitis.[3,4] There are currently no published evidence-based guidelines that comprehensively address the antibiotic management of osteomyelitis. Limited recommendations do exist for osteomyelitis associated with diabetic foot infections and are being developed for osteomyelitis associated with prosthetic joints.[14] Most published recommendations regarding specific drugs and routes of administration are based on expert opinion.[1,5]

The initial studies defining durations of therapy of 4 to 6 weeks for most forms of osteomyelitis were performed in the 1970s and 1980s.[1,3,4] Treatment courses were extrapolated from animal models assessing bone revascularization and healing after debridement, and clinical practices have not significantly changed since that time. There have been more than 100 published clinical trials of antimicrobial therapy of acute and chronic osteomyelitis in the past 40 years, though the majority have been noncomparative trials of individual agents and have included only small numbers of patients.[3,4] A recent review by Lazzarini et al critically evaluated all adequately documented trials of six or more patients published from 1968 through 2000, including 93 studies of nearly 2500 patients.[3] Their major conclusions from these studies were limited: outcomes for acute were better than those for chronic osteomyelitis, and oral therapy could be equivalent to parenteral therapy. Most studies employed 6 weeks of therapy, and the few studies of prolonged courses of up to 6 months did not clearly show improved outcomes. A meta-analysis by Stengel et al of randomized trials of osteomyelitis antibiotic therapy found similar limitations with the published data.[4] Better studies are clearly needed.

Information comparing effectiveness and toxicity of antibiotic regimens for osteomyelitis can also be obtained from retrospective reviews. Several large studies have analyzed clinical experience from registries of patients receiving outpatient intravenous therapy.[10,15] However, defining optimal treatment from both clinical trials and retrospective reviews remains limited by the fact that they describe heterogeneous groups of patients with different stages of acute and chronic infections and varied extent of surgical intervention.

Consensus recommendations for duration of curative antimicrobial therapy for most patients with osteomyelitis who have received "stage-appropriate" surgical interventions remain a minimum of 4 to 6 weeks.[1,5] Patients with more extensive infections and limited surgery may require more prolonged treatment; those with Cierney type 2 disease and adequate surgery may only require 2 weeks of treatment. In practice, clinicians often adopt a "goal-directed" approach to treatment duration, using clinical assessment and normalization of inflammatory markers (C-reactive protein and/or sedimentation rates) to define duration of therapy. Inflammatory markers have been proved useful in managing acute hematogenous pediatric osteomyelitis and in one recent study correlated with success of therapy in pyogenic vertebral osteomyelitis, but their role in determining duration of therapy in adults has not been thoroughly evaluated.[16,17]

ANTIBIOTIC TREATMENT RECOMMENDATIONS FOR SPECIFIC MICROBIAL PATHOGENS

S. aureus and Methicillin-Resistant *S. aureus*

Staphylococcus aureus remains the predominant pathogen isolated in all forms and stages of osteomyelitis. Strains are increasingly methicillin-resistant due to the continued increase in hospital-associated methicillin-resistant *Staphylococcus aureus* (MRSA) and the recent emergence of community-associated MRSA, which have become a major cause of aggressive bone and joint infections in children and adults.[18,19] Options for treatment of *S. aureus* infections are listed in Table 2.

Beta-lactam antimicrobials remain the drugs of choice for nonallergic patients with methicillin-susceptible *Staphylococcus aureus* (MSSA) infections.[1] Less than 5% of *S. aureus* is still susceptible to penicillin; for such strains, intravenous penicillin G is used at doses of 3 to 4 million units every 4 to 6 hours. For other MSSA, the penicillinase-resistant penicillin drugs (oxacillin, nafcillin, flucloxacin) given intravenously have traditionally been considered the drugs of choice.[1] The first-generation cephalosporin cefazolin allows more convenient every-8-hour dosing and may have a better safety profile with lower rates of neutropenia and hypersensitivity and has been found equivalent to nafcillin or oxacillin in a retrospective study.[10] Dosing for bone infection is 2 g every 8 hours in adults with normal renal function. Broad spectrum third- and fourth-generation cephalosporins have also been used for MSSA infections, due to their more convenient dosing schedules, though this must be weighed against the impact of their broader spectrum of action and suppression of normal host bacterial flora and impact on resistance. Ceftriaxone is particularly attractive due to its once-daily dosing

Table 2 Treatment Options for *S. aureus* and MRSA Osteomyelitis

			Evidence for Effectiveness					
Antimicrobial Agent	**Route**	**Active for MRSA?**	**Animal Studies**	**Case Report**	**Case Series**	**Clinical Trial***	**RCT†**	**Comments**
Nafcillin	IV	No	X	X	X	X	X	MSSA drug of choice
Cefazolin	IV	No	X	X	X	X	X	MSSA drug of choice
Ceftriaxone	IV	No	X	X	X	X	X	Probably comparable with nafcillin
Vancomycin	IV	Yes	X	X	X	X	X	MRSA drug of choice
Teicoplanin‡	IV	Yes	X	X	X	X	X	Similar to vancomycin
Linezolid	Oral, IV	Yes	X	X	X	X		? Comparable with vancomycin
Fluoroquinolone§	Oral, IV	Some¶	X	X	X	X	X	? Need for combination Rx especially for MRSA
Daptomycin	IV	Yes	X	X	X			Limited data
Clindamycin	Oral, IV	Some¶	X	X	X	X	X	? Comparable with nafcillin
Trimethoprim-sulfamethoxazole	Oral, IV	Most strains	X	X	X	X	X	Data mostly for device infections
Minocycline	Oral	Most strains		X	X	X		Limited data
Tigecycline	IV	Yes	X	X				Insufficient data
Quinupristin-dalfopristin	IV	Most strains	X	X	X			Limited data
Fusidic acid‡	Oral	Most strains	X	X	X	X		Use in combination therapy only
Rifampin	Oral, IV	Yes	X	X	X	X	X	Use in combination therapy only

*Therapeutic trial or prospective case series.
†Randomized clinical trial.
‡Not available in the United States.
§Includes ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin, gemifloxacin though potency versus *S. aureus* may vary.
¶Usually only community-associated MRSA strains still susceptible.
IV, intravenous.

schedule, although the MICs of ceftriaxone against MSSA are generally higher than those of cefazolin, raising concern for potential treatment failure. Two retrospective studies showed no difference in relapse rates for ceftriaxone or cefazolin therapy in patients with *S. aureus* osteomyelitis.[10,20] Serum levels of parenteral β-lactams exceed the MIC of susceptible MSSA throughout most of the dosing interval. Such levels cannot reliably be achieved with oral regimens, due to their more limited oral bioavailability. Bone levels, typically 10 to 20% of serum levels, are even less likely to remain above the MIC. Thus, parenteral therapy is almost always preferred for curative β-lactam regimens.[1] One exception to this is acute pediatric osteomyelitis, where oral "step-down" therapy with β-lactam agents has been successfully used after an initial 1- to 2-week course of parenteral therapy.[21,22] There is less data supporting use of oral β-lactam therapy in adults.

Although considered inferior to parenteral β-lactam therapy, there are several parenteral and oral options for treating MSSA osteomyelitis in patients allergic to penicillins and cephalosporins. Despite poor results in animal models,[23] intravenous vancomycin has been used successfully for treating both MSSA and MRSA infections. Similar results have been achieved with teicoplanin, another glycopeptide not available the United States. Use of vancomycin for treatment of osteomyelitis has increased dramatically with the emergence of MRSA, which now comprises the majority of *S. aureus* infections seen in hospitals throughout all regions of the United States.[24] Glycopeptides should not routinely be used for nonallergic patients with MSSA. Retrospective studies have demonstrated higher relapse rates after vancomycin compared with those after a β-lactam for non-MRSA bone infections,[10] and vancomycin is inferior to a β-lactam for other serious infections including endocarditis.[25] One consequence of increasing vancomycin use is emergence of strains with decreased vancomycin susceptibility including strains resistant (MIC $>$ 8 μg/mL) and intermediately resistant (MIC 4 to 8 μg/mL) to vancomycin.[24,26] Infections caused by these strains will fail vancomycin therapy; fortunately, these remain quite rare.[24,26] Much more common are *S. aureus* strains that are vancomycin "heteroresistant" and contain a subpopulation of more resistant cells, as well as S. *aureus* strains with vancomycin MICs of 2 μg/mL. Both of these phenotypes are associated with higher rates of vancomycin failure.[24,26] Optimal vancomycin dosing and acceptable targets for serum trough levels are also controversial. Serum trough levels higher than the traditional targets of 5 to 10 μg/mL (e.g., 15 μg/mL or even higher) may be necessary to achieve bone levels consistently above the MIC for strains with vancomycin MICs of 2 μg/mL.[27] However, such higher

troughs may also be associated with increased nephrotoxicity without clear evidence of increased efficacy.[27]

Clindamycin has excellent bone penetration and oral bioavailability and performed as well as β-lactam monotherapy in the rabbit osteomyelitis model and has been used successfully for *S. aureus* osteomyelitis in both children and adults.[9,28,29] Initial dosing is 600 mg intravenously every 6 to 8 hours for 1 to 2 weeks followed by oral dosing of 300 to 450 mg every 6 hours. *S. aureus* isolates that are clindamycin-susceptible but erythromycin-resistant should be tested for inducible clindamycin resistance using the "D-test." Strains with inducible clindamycin resistance (D-test positive) may develop resistance to clindamycin on treatment, resulting in clinical failure.[30] Trimethoprim-sulfamethoxazole is another agent with excellent oral bioavailability that has been used to treat MSSA and MRSA bone infections, though most of the published experience is with courses of longer than 6 weeks and in device-associated infections.[31] Trimethoprim-sulfamethoxazole is bactericidal against most *S. aureus* strains. There are no trials comparing trimethoprim-sulfamethoxazole with vancomycin or other agents for MRSA bone infection, though older studies suggest that trimethoprim-sulfamethoxazole is equivalent to vancomycin for nonbacteremic skin and soft tissue infections.[32] Optimal dosing should be weight based: 5 to 10 mg/kg of trimethoprim/day divided into 2 or 3 doses in individuals with normal renal function. Another oral agent not available in the United States is fusidic acid, which most commonly is combined with oral rifampin to prevent emergence of resistance.[33]

The fluoroquinolones are another drug class used for MSSA and MRSA infections. Most published data are for ciprofloxacin and ofloxacin, though there is clinical experience with newer agents as well.[3,4,34] Fluoroquinolones have excellent oral bioavailability and demonstrate good bone penetration in vitro and effectiveness in animal models.[34] Fluoroquinolones have inhibited fracture healing in an experimental model, but this observation has not been verified in humans.[1] Fluoroquinolones have also been associated with human joint and tendon problems.[35] A major concern with fluoroquinolones is emergence of resistance on therapy. Staphylococci have a relatively low genetic barrier to selection of resistant mutants, especially in high inoculum infections.[36] Third- and fourth-generation agents including levofloxacin, moxifloxacin, and gemifloxacin are more active against gram-positive pathogens than are the second-generation agents ciprofloxacin and ofloxacin and have a higher barrier to emergence of resistance.[36] One strategy to enhance fluoroquinolone regimens for staphylococci and to prevent resistance has been to combine them with rifampin.[37] Unfortunately, most hospital-acquired MRSA isolates are fluoroquinolone-resistant, and community-associated MRSA isolates are increasingly resistant as well.

Many *S. aureus* and MRSA strains remain susceptible to tetracyclines.[38] Of the orally available agents, minocycline has the greatest staphylococcal activity and the least rate of resistance and also has excellent bioavailability. Minocycline is extensively used as an oral option for community-acquired MRSA soft tissue infections. A recent review of clinical experience with tetracyclines for MRSA infections found few published reports of osteomyelitis treated with minocycline.[38] Several newer agents with good in vitro and in vivo activity against MRSA have recently been introduced. These include linezolid, daptomycin, and tigecycline. The optimal use of these agents and their role in treatment of acute and chronic osteomyelitis and comparative activity to intravenous vancomycin are still being evaluated. The best studied of these is linezolid, a bacteriostatic, protein synthesis inhibitor of the novel oxazolidinone class. Linezolid is active against *S. aureus* including nearly all MRSA strains, though resistance can very infrequently develop on therapy. Linezolid has nearly 100% oral bioavailability and demonstrates good bone penetration, with bone levels in healthy adults undergoing hip replacement surgery of 50% of serum levels.[39] Linezolid has demonstrated success rates comparable with or superior to those of vancomycin in clinical trials of skin and soft tissue infections and comparable with those of ampicillin-sulbactam for diabetic foot infections. Published experience with linezolid for osteomyelitis was recently reviewed by Falagas and colleagues, including case reports, analysis of data from the linezolid compassionate-use program, and several small prospective case series[7,40–42] Successful outcomes or cure were reported in 55 to 100% of published cases.[41] Toxicities of linezolid after more than 2 weeks include anemia and thrombocytopenia, thus hematologic parameters must be monitored, although in one small trial, rates were similar for vancomycin and linezolid therapy.[42] Other serious toxicities reported with prolonged linezolid therapy include lactic acidosis syndromes, optic neuritis, and peripheral neuropathy[7,41] In one study, 80% of 66 patients with chronic *S. aureus* osteomyelitis were cured after prolonged courses of linezolid (mean 13 weeks), but treatment-limiting toxicities occurred in one third of patients.[7] Thus, linezolid is not an ideal agent for very prolonged treatment courses or chronic suppressive therapy.

Daptomycin is a novel, parenteral cyclic lipopeptide with a unique bactericidal mechanism of action against gram-positive pathogens.[43] Daptomycin was noninferior to vancomycin for treatment of skin and soft tissue infections and for *S. aureus* and MRSA bacteremia. The approved dose for *S. aureus* bacteremia is 6 mg/kg every 24 hours. There is limited data on human daptomycin bone levels. Clinical experience with 67 osteomyelitis patients from a registry of patients receiving daptomycin was recently published.[44] Sixty-three percent were cured and 19% improved in this

heterogeneous group of patients, most of whom had MRSA infections. Predominant toxicity is to skeletal muscle, and creatine phosphokinase should be monitored.

Tigecycline, a novel parenteral glycylcycline agent that is a synthetic derivative of minocycline, has excellent in vitro and in vivo activity against gram-positive pathogens including *S. aureus* and MRSA and was effective in animal models of chronic MRSA osteomyelitis, but published human experience in osteomyelitis is limited.[45] As noted above, rifampin has been extensively used for staphylococcal osteomyelitis in combination with a variety of other agents including fluoroquinolones, vancomycin, minocycline, trimethoprim-sulfamethoxazole, and fusidic acid. Rifampin has excellent oral bioavailability and tissue penetration and activity in biofilms. Rifampin has potent intrinsic antistaphylococcal activity and is not used alone due to rapid emergence of resistance. Combination therapy protects against development of rifampin resistance and in some instances may prevent development of resistance to the companion agent. Rifampin resistance may still emerge when rifampin is used for infections with a high inoculum of bacteria and inadequate surgical drainage. Animal osteomyelitis models have shown potent activity of rifampin plus vancomycin combinations.[23] Clinical studies have suggested benefits of addition of rifampin to fluoroquinolone regimens for treatment of *S. aureus* and MRSA bone and joint infections, especially device-associated infections and chronic osteomyelitis.[1,3,4,23,46]

Coagulase-Negative Staphylococci

Although less virulent than *S. aureus* and rarely a problem in acute hematogenous osteomyelitis, the coagulase-negative staphylococci (CNS) have become important pathogens in posttraumatic and prosthetic device–associated and implant-associated infections. Treatment of methicillin-susceptible CNS is similar to treatment of MSSA, but the majority of CNS strains are methicillin-resistant. Susceptibilities to fluoroquinolones, clindamycin, trimethoprim-sulfamethoxazole, and tetracyclines are more variable, and low-level vancomycin resistance is occasionally seen. Methicillin-resistant CNS osteomyelitis is usually treated with intravenous vancomycin. Daptomycin and linezolid have also been used, but published experience is limited.

Streptococcal Osteomyelitis

Most streptococcal osteomyelitis is due the β-hemolytic streptococci, especially *Streptococcus agalactiae* (group B) and *Streptococcus pyogenes* (group A). These organisms remain highly susceptible to penicillins and cephalosporins, and intravenous penicillin at doses of 12 to 24 million units/day remains the drug of choice, though other intravenous penicillins, cephalosporins, and carbapenems are also effective.[1,2] Intravenous cefazolin and intravenous ceftriaxone are probably equivalent to penicillin and allow more convenient dosing. For penicillin-allergic patients, clindamycin may be used, though resistance to this agent is increasing. Vancomycin remains an option for those resistant to or intolerant of other choices.[1] *Streptococcus pneumoniae* and the viridans group streptococci are occasional causes of hematogenous osteomyelitis, and susceptibility patterns are more variable than for the β-hemolytic streptococci. For isolates resistant to penicillin and cephalosporins, treatment decisions should be based on in vitro susceptibility data. Nearly all remain susceptible to vancomycin and linezolid.

Enterococci and Vancomycin-Resistant Enterococci

Enterococcal osteomyelitis formerly was a complication of enterococcal bacteremia and endocarditis,[47] but enterococci and vancomycin-resistant enterococci (VRE) are increasingly important in chronic osteomyelitis underlying diabetic and ischemic ulcers and in device-associated infections. Enterococci are intrinsically resistant to many antibiotics including cephalosporins and clindamycin. Most enterococcal infections are caused by *Enterococcus faecalis*. These are usually susceptible to ampicillin, although this drug is only bacteriostatic, and intravenous ampicillin is the drug of choice. *Enterococcus faecium* now cause an increasing proportion of enterococcal infections. *Enterococcus faecium* are usually ampicillin and carbapenem resistant and are increasingly vancomycin resistant as well.[48] For ampicillin-resistant but vancomycin-susceptible strains, vancomycin can be used. Most reported experience for treatment of ampicillin-resistant VRE osteomyelitis has been with linezolid.[41] Other agents used include chloramphenicol, tetracyclines, daptomycin, and quinupristin-dalfopristin. Tigecycline is also active against VRE. Linezolid resistance develops more frequently in enterococci than in staphylococci. Combination therapy with aminoglycosides and cell wall agents for enterococcal osteomyelitis is associated with significant nephrotoxicity.[49]

Gram-Negative Osteomyelitis

Treatment of gram-negative osteomyelitis depends on the infecting organism and in vitro susceptibility data. Parenteral options include broad-spectrum penicillins and cephalosporins, aztreonam, carbapenems, and aminoglycosides. Oral options for treatment of gram-negative infections are more limited than for gram-positive infections and include fluoroquinolones and trimethoprim-sulfamethoxazole. Oral fluoroquinolones have

been shown to be equivalent to parenteral agents for the treatment of acute and chronic osteomyelitis due to susceptible gram-negative organisms, including *Pseudomonas aeruginosa*.[3,4,34] Unfortunately, resistance to fluoroquinolones has increased dramatically among common gram-negative organisms including *Escherichia coli, Klebsiella*, and *Pseudomonas*, limiting treatment choices for these infections.

For osteomyelitis due to fluoroquinolone-susceptible Enterobacteriaceae including *Escherichia coli*, *Klebsiella, Enterobacter,* and others, fluoroquinolones remain the drugs of choice.[1] The most gram-negative active agent is ciprofloxacin. Levofloxacin has equivalent activity against most organisms other than *Pseudomonas,* but none of the available newer drugs are active against ciprofloxacin-resistant strains. Oral dosing is appropriate in most situations. Fluoroquinolones are not currently approved in the United States for use in children, though pediatric use has increased for treatment of resistant infections.[50] Parenteral options for Enterobacteriaceae are based on susceptibility results and include cephalosporins, carbapenems (imipenem, meropenem, and ertapenem), and the β-lactamase inhibitor agents (ampicillin-sulbactam, ticarcillin–clavulanic acid, and piperacillin-tazobactam). Aztreonam is an option for patients highly allergic to penicillins and cephalosporins. Aminoglycosides remain active against most gram-negative pathogens, but use should be restricted to infections that cannot be treated with less toxic alternatives, and drug levels as well as renal function must be monitored closely. High-dose, extended-interval aminoglycoside regimens are preferred for patients with normal renal function.

Options for *P. aeruginosa* infections are generally more limited than for other gram-negative organisms, and treatment is further compromised by emergence of resistance. Although combination therapy with a β-lactam or ciprofloxacin and an aminoglycoside is generally recommended for *P. aeruginosa* bacteremia and pneumonia, the relative benefits of combination therapy for osteomyelitis remains uncertain when compared with increased toxicity of these regimens.[51] The need for addition of an aminoglycoside may also depend on the choice of primary therapeutic agent and the extent of surgical intervention. Local delivery of aminoglycosides could potentially eliminate the need for systemic aminoglycosides. Pseudomonas-active agents include piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, imipenem and meropenem, and the aminoglycosides. Oral options include only fluoroquinolones. Relapse rates for *Pseudomonas* osteomyelitis, regardless of the regimens used, may be up to 3 times higher than those for staphylococcal osteomyelitis.[10]

Other multidrug-resistant gram-negative organisms that have recently emerged as nosocomial pathogens and occasional causes of osteomyelitis are multiresistant *Acinetobacter* and carbapenem-resistant *Klebsiella*. Some strains are resistant to all routinely used antibiotics. Colistin, an older parenteral polymyxin E agent, has been used for treatment of resistant *Acinetobacter*, *Klebsiella,* and *Pseudomonas* bone infections.[52] Tigecycline can also be used for some *Acinetobacter* and *Klebsiella* infections but is not active against *Pseudomonas*.

Anaerobic Infections

Agents generally active against most anaerobes include clindamycin, the second-generation cephalosporins cefoxitin and cefotetan, β-lactamase inhibitor drugs, and the carbapenems. Metronidazole is also highly active against gram-negative anaerobes and clostridial species though not against some of the oral anaerobic streptococci. Both clindamycin and metronidazole have excellent oral bioavailability. Among the newer fourth-generation fluoroquinolones, moxifloxacin also has good anaerobic activity.

Polymicrobial Infections

Most osteomyelitis in diabetic foot infections and ischemic ulcers is polymicrobial and includes mixtures of aerobic and anaerobic organisms.[1,14] Microbiologic specimens may identify the most abundant pathogens but may miss other important organisms, and not all isolated organisms are equally virulent. The need to treat an organism in a mixed culture depends in part on its relative virulence and the extent of surgery. Initial empiric regimens may need to include several drugs with activity against different classes of pathogens.[14] Use of broad-spectrum agents such as ampicillin-sulbactam, piperacillin-tazobactam, or a carbapenem will provide empiric activity against most potential aerobic and anaerobic pathogens, but even these broad-spectrum agents may be inadequate, especially if MRSA is a concern. Good microbiologic data are critical to developing a long-term antibiotic treatment plan for osteomyelitis.

Osteomyelitis Due to Unusual and Atypical Organisms

Bone and joint tuberculosis is a common presentation of extrapulmonary tuberculosis, comprising 11% of cases of extrapulmonary disease in the United States. Treatment regimens for tuberculous osteomyelitis are similar to those for pulmonary disease and include initiation of isoniazid, rifampin, ethambutol, and pyrazinamide, with revision of therapy based on susceptibilities. Regimens consist of two or more drugs continued for at least 6 to 9 months.[53] Atypical mycobacterial organisms most commonly causing bone infection include *Mycobacterium marinum*, *Mycobacterium kansasii*, *Mycobacterium avium*

complex, and the rapid-growing mycobacteria. Treatment options will depend on the specific pathogen identified and host immune status.[54] Another chronic granulomatous disease that is rare in the United States but is a common cause of osteoarticular disease worldwide is brucellosis. The most common chronic bone manifestation is spondylitis, which can be particularly difficult to treat. Agents active for brucellosis include doxycycline, aminoglycosides, fluoroquinolones, rifampin, and trimethoprim-sulfamethoxazole, and these are most commonly used in two- or three-drug combinations.[55] Treatment for spondylitis is for a minimum of 3 months.

Actinomycosis is a rare but important cause of osteomyelitis, especially osteomyelitis of the mandible but also from extension of thoracic or abdominal disease. *Actinomyces* are anaerobes that are highly susceptible to penicillins, clindamycin, tetracyclines, and erythromycins. Treatment is prolonged, typically 6 to 12 months.[56] Most commonly, intravenous penicillin is given for the first few weeks, followed by prolonged oral therapy with amoxicillin, a tetracycline, or clindamycin.

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