

Antimicrobial Treatment of Chronic Osteomyelitis

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Chronic osteomyelitis has been a difficult problem for patients and the treating physicians. Appropriate antibiotic therapy is necessary to arrest osteomyelitis along with adequate surgical therapy. Factors involved in choosing the appropriate antibiotic(s) include infection type, infecting organism, sensitivity results, host factors, and antibiotic characteristics. Initially, antibiotics are chosen on the basis of the organisms that are suspected to be causing the infection. Once the infecting organism(s) is isolated and sensitivities are established, the initial antibiotic(s) may be modified. In selecting specific antibiotics for the treatment of osteomyelitis, the type of infection, current hospital sensitivity resistance patterns, and the risk of adverse reactions must be strongly appraised. Antibiotic classes used in the treatment of osteomyelitis include penicillins, β -lactamase inhibitors, cephalosporins, other β -lactams (aztreonam and imipenem), vancomycin, clindamycin, rifampin, aminoglycosides, fluoroquinolones, trimethoprim-sulfamethoxazole, metronidazole, and new investigational agents including teicoplanin, quinupristin/dalfopristin, and oxazolidinones. Traditional treatments have used operative procedures followed by 4 to 6 weeks of

parenteral antibiotics. Adjunctive therapy for treating chronic osteomyelitis may be achieved by using beads, spacers, or coated implants to deliver local antibiotic therapy and/or by using hyperbaric oxygen therapy (once per day for 90-120 minutes at two to three atmospheres at 100% oxygen).

Based on etiologic considerations, bone infections traditionally have been classified as either hematogenous osteomyelitis, osteomyelitis secondary to a contiguous focus of infection, or chronic osteomyelitis.⁹⁸ Contiguous focus osteomyelitis has been subdivided further into osteomyelitis in patients having normal vascularity and those having generalized vascular insufficiency. All etiologic classes of osteomyelitis may progress to a chronic disease process.

Appropriate antibiotic therapy is necessary to arrest osteomyelitis along with adequate surgical therapy. Factors involved in choosing the appropriate antibiotic(s) include infection type, infecting organism, sensitivity results, host factors, and antibiotic characteristics. Initially, antibiotics are chosen on the basis of the organisms that are suspected to be causing the infection. Later, when an infecting organism is isolated and sensitivities are established, the initial antibiotic(s) may be modified.

In hematogenous osteomyelitis one organism usually is responsible for the infec-

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tion with *Staphylococcus aureus* being the most common isolate. In contrast to hematogenous osteomyelitis, more than one pathogen usually is isolated in contiguous focus osteomyelitis and chronic osteomyelitis. In contiguous focus osteomyelitis, *Staphylococcus aureus* is the most commonly isolated pathogen, but aerobic Gram negative rods and anaerobic organisms often are found.

BACTERIAL ANTIBIOTIC RESISTANCE

Beta-lactamase production primarily is mediated by plasmids. This enzyme is responsible for the resistance approximately 90% of *Staphylococcus aureus* isolates to penicillin. Of the penicillins, the penicillinase resistant semisynthetic penicillins have become the antistaphylococcal drugs of choice because of their stability in the presence of *Staphylococcus aureus* β -lactamase.

Intrinsic resistance is chromosomally mediated and heterogeneous. This type of resistance is present in only a small percentage of a given *Staphylococcus aureus* inoculum. Methicillin resistant *Staphylococcus aureus* and *Staphylococcus epidermidis* are the significant examples of intrinsic resistance. These isolates are resistant to the semisynthetic penicillins and to the cephalosporins. The expression of this intrinsically resistant subpopulation can be enhanced by altering several cultural conditions such as the use of agar containing high salt concentrations and incubation at 30° C.⁷⁷ Methicillin resistant *Staphylococcus aureus* and methicillin resistant *Staphylococcus epidermidis* are isolated frequently in large tertiary care hospitals and nursing homes.⁸⁵

Tolerance of organisms to antibiotics is understood poorly. It is an *in vitro* phenomenon characterized by resistance to the lethal action of a normally bactericidal drug. There is a marked discrepancy between the mean inhibitory concentration and mean bactericidal concentration of the bactericidal antibiotic to

the organism. A functional definition of tolerance is a mean bactericidal concentration that is 32-fold or greater than the mean inhibitory concentration.⁷⁶ The clinical significance of tolerance is still controversial. One study suggested that seriously ill patients who are treated with an antimicrobial to which the infecting organism was tolerant did less well than patients treated with bactericidal therapy.⁵³ The existence of tolerance is another reason to perform mean inhibitory concentration and mean bactericidal concentration testing on all pathogens isolated from infected bone.

Chronic osteomyelitis or infected joints with replacements are treated for 4 to 6 weeks or more.^{1,6,29,36,38,41,45} These lengthy antibiotic regimens become even more problematic when the patient is infected with methicillin resistant *Staphylococcus aureus*, vancomycin resistant enterococcus, or other multiresistant bacterial species. In particular, because some methicillin resistant *Staphylococcus aureus* strains are resistant to all current antibiotics except vancomycin, these infections must be resolved with parenteral vancomycin treatment with its associated clinical toxicity.^{55,56} Also, it has been shown in the laboratory that the vancomycin resistance gene cluster found in *Enterococcus faecalis* can be transferred to *Staphylococcus aureus* via conjugation and can express high level resistance.⁵³ Vancomycin resistance also has been seen in serial passaged *Staphylococcus aureus* laboratory isolates and has been found in the clinical setting in Japan, New Jersey, and Oregon. Therefore, vancomycin, the last chance antimicrobial for many strains of methicillin resistant *Staphylococcus aureus*, soon may become ineffective because of the development of resistant strains.

SENSITIVITY TESTING

Once the organism(s) is isolated, the specific antibacterial activity of various antibiotics can be determined by appropriate sensitivity techniques. The disk diffusion method is the

most commonly used method for susceptibility testing. The diameter of a zone of inhibition around an antimicrobial impregnated paper disk relates approximately linearly to the antibiotic's \log_2 mean inhibitory concentration. Inhibition diameters are interpreted as signifying susceptibility, intermediate susceptibility, or resistance to each antimicrobial agent tested according to published criteria.⁵⁴ Standard procedures must be followed for these criteria to retain their validity. The interpretive criteria only apply to organisms that grow rapidly. The disk diffusion method is simple to perform and relatively inexpensive. However, the method provides only semi-quantitative or qualitative data about the susceptibility of a given organism to a given antibiotic. Nonetheless, if the test is done carefully, it provides information that is clinically useful. Quantitative data are provided by methods that incorporate serial dilution of antibiotics in agar containing or broth culture media. Quantitative sensitivity testing by macro or microdilution techniques is a prerequisite for the determination of the least concentration of the antibiotic required to inhibit (mean inhibitory concentration) and kill (mean bactericidal concentration) the isolated organisms.¹⁴ Clinical prejudice demands selection of an antibiotic or antibiotic combination having a low mean inhibitory concentration and mean bactericidal concentration activity relative to its expected serum concentration. Quantitative testing is useful for selecting antibiotics for difficult aerobic infections and/or where therapy will be prolonged. Selection of the best antibiotic or antibiotic combination is crucial in these situations. It is reasonable to use quantitative testing to determine the best antibiotic therapy for osteomyelitis, septic joint infections, and prosthetic joint infections. Quantitative testing of anaerobic organisms is not yet standardized.

BACTERICIDAL LEVELS

Peak and trough serum bacteriostatic and bactericidal levels described by Schlichter

and MacLean⁸² often are used to assess the bacteriostatic and bactericidal capabilities of the treatment antibiotic(s). Initially, patient serum samples are obtained after dosing to obtain the peak and trough serum levels. The serum samples then are diluted serially and the dilution fractions are tested against an inoculum of the infecting bacterial species. Using this method, one can obtain an estimation of the antibiotic dose necessary to obtain adequate serum inhibitory and bactericidal antibiotic levels. These results are expressed as minimal inhibitory dilutions and minimum serum bactericidal dilutions. The interpretation criteria and significance of the data vary for different laboratories and a standard uniform system for minimal inhibitory dilutions and minimum serum bactericidal dilutions studies currently is needed.^{68,71,90} Most investigators strive for a peak minimum serum bactericidal dilution of 1:8 or greater (eightfold or higher dilution of patient's serum still is capable of having a bactericidal effect on the infecting bacterial species or strain).⁷⁴ In patients with osteomyelitis, serum bactericidal concentrations have been used to verify the likelihood of treatment success, especially when second choice antibiotics are necessary for treatment in patients with drug allergies.³⁴ Minimum serum bactericidal dilutions also have been used to ensure the adequacy of oral antibiotic therapy.⁹⁴ In a typical patient with osteomyelitis where optimal antibiotics are selected by mean inhibitory concentration testing, the likelihood of success is governed by the adequacy of debridement surgery rather than by the adequacy of serumcidal levels.

ANTIBIOTIC CHARACTERISTICS

In selecting specific antibiotics for the treatment of osteomyelitis, the type of infection, current hospital sensitivity and resistance patterns, and the risk of adverse reactions must be appraised strongly. No one antibiotic or antibiotic combination can be expected to be effective in all clinical settings.

Antibiotic factors that may lead to the decreased activity of antibiotics include pH, the presence of purulent material, and decreased blood flow.⁵⁶ It has been shown that the aminoglycosides such as gentamicin, tobramycin, amikacin, and netilmicin are less active under anaerobic, acidic, and hypercapnic conditions. Although agents may diffuse into infected tissue, the conditions present in the area may reduce significantly the ability of these antibiotics to eradicate sensitive organisms.^{71,96}

There are also organism factors that must be considered in the treatment of osteomyelitis. The most common organism involved in osteomyelitis is *Staphylococcus aureus*, which has three recognized types of staphylococcal resistance: β -lactamase production, intrinsic resistance, and tolerance.⁷⁹

ANTIBIOTICS

The initial choice of antibiotics for Gram positive, Gram negative, and anaerobic organisms are shown in Tables 1, 2, and 3. The initial antibiotic regimen is modified, if necessary, by the culture and sensitivity results.

Penicillins

The penicillin class of antibiotics frequently is used for the treatment of osteomyelitis. The penicillins can be divided into general groups on the basis of their antibacterial activity. Overlap exists among the groups, but the differences within a group are usually of a pharmacologic nature, although one compound within a group may be more active than another. The major penicillin groups of interest to an orthopaedic surgeon are natural penicillins, aminopenicillins, penicillinase resistant penicillins, antipseudomonal penicillins, and extended spectrum penicillins.

Penicillin G is the major natural penicillin. Penicillin G has a half life of 30 to 60 minutes, but it can be combined with procaine or benzathine to make a repository penicillin. This antimicrobial negatively interacts with erythromycin and tetracyclines to reduce an-

timicrobial effectiveness. Penicillin is the drug of choice for the treatment of *Streptococcus pyogenes* and *Streptococcus agalactiae*. However, *Streptococcus pneumoniae* continues to become more resistant to penicillin. Currently, *Streptococcus pneumoniae* has an intermediate resistance of 28% and a high level resistance of 16% to penicillin. In addition, penicillin has a good anaerobic spectrum of activity except for the *Bacteroides fragilis* group. Penicillin G is a drug of choice for the treatment of *Clostridia perfringens*.

The parenteral penicillinase resistant penicillins include methicillin, nafcillin, and the isoxazolyl penicillins (including cloxacillin, dicloxacillin, flucoxacillin, and oxacillin). These drugs are resistant to staphylococcal β -lactamase, and are used when methicillin sensitive *Staphylococcus aureus* is present or suspected. The semisynthetic penicillins are also active against *Streptococcus pyogenes* and *Streptococcus pneumoniae*, but they have no activity against *Enterococcus* species or Gram negative bacilli. The most active parenteral semisynthetic penicillins are nafcillin and oxacillin. Nafcillin and oxacillin may cause interstitial nephritis, leukopenia, and reversible hepatic dysfunction.^{29,66} Methicillin is associated with the greatest potential for producing interstitial nephritis.¹⁰⁴ Cloxacillin and dicloxacillin are the oral semisynthetic penicillins of choice.

The major aminopenicillins include ampicillin and amoxicillin. Ampicillin may be given parenterally or orally, whereas amoxicillin is only an oral agent. The antibacterial activity of the aminopenicillins is similar. They are not stable to β -lactamase, and are less active than penicillin G against *Streptococcus pyogenes* and *Streptococcus agalactiae*. They are the antibiotics of choice for the treatment of *Enterococcus* species (*Enterococcus faecalis*, *Enterococcus faecium*).⁵⁵ The aminopenicillins are also active against many highly susceptible Gram negative rods, such as *Escherichia coli* and *Proteus mirabilis*.

TABLE 1. Gram Positive Organisms: Initial Choice of Antibiotics for Therapy (Adult Doses)

Organism	First Choice Antibiotics	Alternative Antibiotics
Methicillin sensitive	Nafcillin 2 g every 6 hours or Clindamycin 900 mg every 8 hours	Cefazolin Vancomycin
Staphylococcus aureus or Coagulase negative	Nafcillin 2 g every 6 hours or Clindamycin 900 mg every 8 hours	Cefazolin Vancomycin
Methicillin Resistant	Vancomycin 1 g every 12 hours	SXT* or Minocycline ± Rifampin
Staphylococcus aureus or Coagulase negative	Vancomycin 1 g every 12 hours or Clindamycin 900 mg every 8 hours**	SXT* or Minocycline ± Rifampin
Staphylococcus species		
Group A streptococcus	Penicillin G 2 mU every 4 hours	Clindamycin, Cefazolin, Vancomycin
Streptococcus pyogenes		
Group B streptococcus	Penicillin G 2 mU every 4 hours	Clindamycin, Cefazolin, Vancomycin
Streptococcus agalactiae		
Penicillin Sensitive		
Streptococcus pneumoniae	Penicillin G 2 mU every 4 hours	Erythromycin, Clindamycin
Intermediate Penicillin Resistance		
Streptococcus pneumoniae	Cefotaxime 1 g every 6 hours	Erythromycin, Clindamycin
Penicillin Resistant		
Streptococcus pneumoniae	Vancomycin 1 g every 12 hours L-Ofloxacin 500 mg daily	Sparfloxacin
Enterococcus species	Ampicillin 1 g every 6 hours† Vancomycin 1 g every 12 hours	Ampicillin-Sulbactam

*Sulfamethoxazole-Trimethoprim

**Dose every 8 hours if sensitive to Clindamycin

†In a serious Enterococcus species infection ampicillin ± Sulbactam plus an aminoglycoside is used

Ticarcillin is an antipseudomonal penicillin. Ticarcillin has a β -lactam ring and is susceptible to β -lactamase of Gram positive and Gram negative organisms. Ticarcillin has a Gram negative spectrum of activity similar to ampicillin, but is more active than ampicillin against *Pseudomonas* species, *Enterobacter* species, *Serratia* species, and certain strains of the *Bacteroides fragilis* group. Ticarcillin has poor activity against *Klebsiella* species.⁵⁷ Side effects include sodium loading and bleeding problems because of platelet dysfunction.⁵⁹

The extended spectrum penicillins include mezlocillin and piperacillin. These penicillins have an antibacterial spectrum similar to ticarcillin. In vitro, these antibiotics are active against *Enterococcus* species, *Streptococcus* species and they inhibit the majority of *Klebsiella* species. They

are also more active than ticarcillin against *Haemophilus influenza* and the *Bacteroides fragilis* group.^{19,67} These drugs act in synergy with the aminoglycosides against *Pseudomonas aeruginosa* and most of the *Enterobacteriaceae*. They have the same side effects as ticarcillin, except they cause less sodium loading and bleeding dysfunction.

β -lactamase Inhibitors

Clavulanic acid, sulbactam, and tazobactam are potent inhibitors of β -lactamase produced by Gram positive and Gram negative organisms.⁵⁸ Beta-lactamase of Gram positive species are exoenzymes. Clavulanic acid, sulbactam, and tazobactam have been shown to inhibit β -lactamase for numerous clinically important Gram positive organisms including *Staphylococcus aureus* and *Staphylococcus epidermidis*.⁷⁰ Beta-lacta-

TABLE 2. Gram Negative Organisms: Initial Choice of Antibiotics for Therapy (Adult Doses)

Organism	Antibiotics of First Choice	Alternative Antibiotics
Acinetobacter species	Ceftazidime 1 g every 8 hours	Gentamicin, Imipenem
Enterobacter species	Cefotaxime 1 g every 8 hours; Mezlocillin; Ceftazidime	L-Ofloxacin, Gentamicin
Escherichia coli	Ampicillin 1 g every 6 hours; Gentamicin; SXT*	Cefazolin, L-Ofloxacin
Haemophilus influenza	Cefotaxime 1 g every 8 hours; Ampicillin-sulbactam; SXT*	Ampicillin,** L-Ofloxacin
Klebsiella species	Cefazolin 2 g every 8 hours; Cefotaxime	L-Ofloxacin, Gentamicin
Proteus mirabilis	Ampicillin 1 g every 6 hours; Gentamicin	L-Ofloxacin, Cefazolin
Proteus vulgaris	Cefotaxime 2 g every 8 hours	Mezlocillin, L-Ofloxacin, or Gentamicin
Proteus rettgeri or Morganella morganii		
Neisseria gonorrhoea	Ceftriaxone 125 mg	Doxycycline, L-Ofloxacin, Ampicillin†
Providencia species	Cefotaxime 2 g intravenously every 8 hours Gentamicin 1.67 mg/kg every 8 hours	SXT* Tobramycin Ticarcillin Clavulanic Acid
Pseudomonas aeruginosa	Ceftazidime‡ 2 g every 8 hours or Ciprofloxacin‡ 400 mg every 12 hours Piperacillin‡ 3 g every 6 hours	Ticarcillin Clavulanic Acid Tobramycin, Imipenem
Serratia marcescens	Cefotaxime 2 g every 8 hours	Ofloxacin, Gentamicin

*Sulfamethoxazole-Trimethoprim

**Nonβ-lactamase producing strain of Haemophilus influenzae

†Nonpenicillinase producing strain of Neisseria gonorrhoea

‡In a serious infection should be used with an aminoglycoside—Gentamicin or Tobramycin 5 mg/kg per day every 8 hours

mase of Gram negative and most anaerobic organisms is situated in the periplasmic space and is chromosome and plasmid induced.⁷³ Clavulanic acid, sulbactam, and tazobactam will inhibit β-lactamase of many Gram negative organisms including most Escherichia coli, Klebsiella species, and Bac-

teroides species. Currently, clavulanic acid is commercially available with amoxicillin (Augmentin® Smithkline Beecham, Philadelphia, PA), and ticarcillin (Timentin®, Smithkline Beecham). Sulbactam is available with ampicillin (Unasyn®, Pfizer Inc, New York, NY). Tazobactam is combined

TABLE 3. Anaerobic Organisms: Initial Choice of Antibiotics for Therapy (Adult Doses)

Organism	Antibiotic of First Choice	Alternative Antibiotics
Bacteroides fragilis group	Clindamycin 900 mg every 8 hours Metronidazole 500 mg every 8 hours	Ampicillin-sulbactam, Ticarcillin-clavulanic acid
Prevotella species	Clindamycin 900 mg every 8 hours	Ampicillin-sulbactam, Cefotetan
Peptostreptococcus species	Metronidazole 500 mg every 8 hours Penicillin G 2 mU every 4 hours	Ticarcillin-clavulanic acid Clindamycin, Metronidazole Cefotetan
Clostridium species	Clindamycin 900 mg every 8 hours	Metronidazole, Penicillin

with piperacillin (Zosyn®, Wyeth-Ayerst Laboratories, Philadelphia, PA). The β -lactam inhibitors enhance the Gram positive coverage and to a lesser extent the Gram negative spectrum of these antibiotics.

Cephalosporins

The cephalosporins have been divided into first, second, third, and fourth generation agents. The first generation cephalosporins include cephalothin, cephapirin, cephadrine, and cefazolin, and are active against *Staphylococcus aureus*, *Staphylococcus epidermidis*, and streptococcus species. They have limited Gram negative activity, but are active against *Escherichia coli*, *Klebsiella* species, and *Proteus mirabilis*. The first generation cephalosporins are safe antibiotics, but occasionally are associated with the production of allergic reactions, drug eruptions, phlebitis, and diarrhea. Cefazolin is the first generation cephalosporin most widely used by the orthopaedic community for the treatment of staphylococcal infections, including osteomyelitis. Large amounts of β -lactamase produced by *Staphylococcus aureus* (10^9 organisms per gram tissue) will inactivate cefazolin.¹⁷ However, high numbers of *Staphylococcus aureus* are not the norm in staphylococcal osteomyelitis where 10^5 or less organisms per gram of bone usually are found. Cefazolin has a longer half life and higher serum concentration than the other first generation cephalosporins.³⁶ The remainder of the first generation cephalosporins is comparable. They are all more stable to β -lactamase than they are to cefazolin.

There are many second generation cephalosporins, but the major ones include cefamandole, cefoxitin, cefotetan, cefuroxime, ceforanide, and cefonicid. The second generation cephalosporins have somewhat increased activity against Gram negative organisms as compared with the first generation, but are less active than the third generation agents. Cefoxitin and cefotetan are more active than the other first or second generation cephalosporins against the anaer-

obes, especially the *Bacteroides fragilis* group.³⁵

The major third generation cephalosporins include: cefotaxime, ceftriaxone, ceftizoxime, cefoperazone, and ceftazidime. The third generation cephalosporins are generally less active than the first generation cephalosporins against Gram positive organisms, but are more active against the enterobacteriaceae.⁹⁵ Cefotaxime, ceftriaxone, and ceftizoxime and are third generation cephalosporins with similar antibacterial activity. They are highly resistant to β -lactamase, and have activity against Gram positive organisms with the exception of the *Enterococcus* species. They have good activity against most Gram negative organisms except for *Pseudomonas aeruginosa*. Cefotaxime, ceftizoxime, and ceftriaxone have half lives of 1.1, 1.7, and 8 hours, respectively.

Ceftazidime is similar in activity to cefotaxime, ceftizoxime, and ceftriaxone against the Enterobacteriaceae, but it has superior activity against *Pseudomonas aeruginosa*. It inhibits approximately 91% of the *Pseudomonas aeruginosa* strains found in the University of Texas Medical Branch Hospitals. However, this percentage may differ in other hospitals. Ceftazidime is the cephalosporin of choice for the treatment of sensitive *Pseudomonas aeruginosa*.⁶⁰ For serious *Pseudomonas aeruginosa* infections ceftazidime should be combined with an aminoglycoside or quinolone.⁸⁴ Ceftazidime is half as active against Gram positive organisms as is cefotaxime, ceftizoxime, and ceftriaxone.

The fourth generation cephalosporins are represented by cefepime. Cefepime has excellent activity against aerobic Gram positive organisms including methicillin sensitive *Staphylococcus aureus* and Gram negative organisms including *Pseudomonas aeruginosa*. In vitro data suggest increased activity of cefepime against multiresistant Enterobacter species. Similar to other cephalosporins, cefepime has no activity against *Enterococcus* species.

Other β -lactam Antibiotics

Aztreonam is a monocyclic β -lactam antibiotic, which is active against most Enterobacteriaceae and *Pseudomonas aeruginosa*.⁹³ Aztreonam has no appreciable antibacterial activity against aerobic Gram positive or anaerobic bacteria. The drug must be given parenterally. No major adverse reactions have been reported. It also offers low liability of cross sensitivity in patients allergic to penicillin or cephalosporin.

Imipenem is an antimicrobial agent belonging to the β -lactam class of antibiotics. Biochemically they are carbapenems. Imipenem has excellent in vitro activity against aerobic Gram positive organisms including *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcal* species, and *Enterococcus* species. Imipenem has excellent Gram negative activity including the Enterobacteriaceae and *Pseudomonas aeruginosa*. Imipenem also inhibits most anaerobic species, including the *Bacteroides fragilis* group.⁶¹ Side effects include seizure activity. Resistance to *Pseudomonas aeruginosa* may develop during therapy and fungal superinfection may occur.

Vancomycin

Vancomycin has excellent activity against *Staphylococcus aureus*, *Staphylococcus epidermidis*, and the *Enterococcus* species. It is the antibiotic of choice in individuals who are unable to tolerate either the penicillins or the cephalosporins.²³ Vancomycin is also the antibiotic of choice for the treatment of methicillin resistant *Staphylococcus aureus*⁸⁹ and *Staphylococcus epidermidis*.¹ Recent reports of vancomycin resistant *Enterococcus* species dictate increased vigilance and caution.^{52,88} Vancomycin may be associated with nephrotoxicity or ototoxicity, especially when given concurrently with an aminoglycoside.⁸⁵ When used as monotherapy, the end organ toxicity of vancomycin is minimal. A red man syndrome often is observed when vancomycin is administered in less than 1 hour.

Clindamycin

Clindamycin is one of the most active antibiotics against clinically significant anaerobic bacteria, particularly the *Bacteroides fragilis* group. However, clindamycin is ineffective against 10% to 20% of clostridial species other than *perfringens*.⁹² In addition to its anaerobic activity, clindamycin is also effective against *Staphylococcus aureus*, *Staphylococcus epidermidis*, and the *Streptococcus* species. The half life of clindamycin is 2.4 hours, clindamycin is ideally given every 8 hours. Clindamycin has good penetration into most tissues including bone,^{65,91} and it penetrates well into abscesses. Clindamycin is relatively nontoxic, but may cause diarrhea and pseudomembranous colitis in a small percentage of patients.³⁸

Rifampin

Rifampin exhibits bactericidal activity against various Gram positive and negative organisms. Rifampin is the most active anti-staphylococcal agent known.⁷⁸ However, rifampin has less activity than the aminoglycosides against most Gram negative bacteria. When rifampin is used alone for the treatment of bacterial infections, a rifampin resistant subpopulation rapidly develops.¹⁶ Expression of rifampin resistance can be lessened by the addition of a second effective antibiotic. Rifampin in combination with a semisynthetic penicillin has been used to treat methicillin sensitive *Staphylococcus* species osteomyelitis. Trimethoprim and sulfamethoxazole or minocycline plus rifampin have been used to treat methicillin resistant *Staphylococcus* species osteomyelitis. In a multicenter study, Norden et al⁶⁴ has shown that the combination of rifampin and nafcillin was slightly superior to nafcillin alone. However, the results of the study only reached a 0.2 statistical significance. Side effects of rifampin include red discoloration of body fluids, gastrointestinal complaints, hepatitis, and possibly mild immunosuppression. Rifampin induces liver enzyme activity

resulting in the inactivation of numerous drugs, including verapamil, corticosteroids, quinidine, cyclosporin, oral anticoagulants, estrogens, and oral contraceptives. Drug regimens for patients must be monitored carefully with adjustments of drug doses when indicated.

Aminoglycosides

The aminoglycosides include gentamicin, tobramycin, amikacin, and netilmicin. The aminoglycosides are the standard to which other antibiotics are measured for the treatment of aerobic Gram negative infections. The aminoglycosides generally have poor activity against Gram positive organisms. Initially, they may be used for the treatment of *Staphylococcus aureus*, but resistance to the aminoglycoside may develop rapidly.^{62,101} They have no effect against the *Streptococcus* species or anaerobes. The aminoglycosides have excellent activity against the Enterobacteriaceae and *Pseudomonas aeruginosa*. The aminoglycosides may be inactivated by enzymatic modification. Amikacin has fewer available sites than the other aminoglycosides for enzymatic inactivation. Consequently, the percentage of strains susceptible to amikacin is greater than for tobramycin, gentamicin, or netilmicin.⁸⁰ There is no evidence to support amikacin having greater or lesser activity than the other aminoglycosides. Toxicity of the aminoglycosides includes nephrotoxicity and ototoxicity.

Fluoroquinolones

The fluoroquinolones currently are being used to treat adult patients with orthopaedic infections including osteomyelitis. The quinolones are divided into four generations. The first generation quinolone, nalidixic acid, is not used to treat orthopaedic infections.

The second generation quinolones include ciprofloxacin and ofloxacin. Ciprofloxacin and ofloxacin provide adequate serum, tissue, and urine concentrations. Ciprofloxacin

and ofloxacin have efficacy against most Gram negative organisms. Most streptococcal strains and anaerobic organisms are resistant to ciprofloxacin and ofloxacin. Reports of resistance in some *Staphylococcus aureus* and *Staphylococcus epidermidis* strains dictate caution.^{3,39,81} Ciprofloxacin is particularly advantageous in the treatment of Gram negative bone infections, which traditionally require prolonged parenteral antibiotic therapy.⁴⁵ Ciprofloxacin is the more active quinolone against *Pseudomonas aeruginosa*.

The third generation includes levofloxacin and sparfloxacin. L-ofloxacin and sparfloxacin provide higher serum levels than either ciprofloxacin or ofloxacin. These agents have excellent activity against *Streptococcus* species including penicillin intermediate and resistant *Streptococcus pneumoniae*. These agents are also active against atypical respiratory pathogens (*Mycobacterium pneumoniae*, *Legionella* species, and *Chlamydia pneumoniae*). These agents have efficacy against most Gram negative organisms. The fourth generation (trovafloxacin, grepafloxacin) quinolones have similar aerobic Gram positive and Gram negative coverage as the third generation quinolones. Unlike the third generation quinolones, the fourth generation quinolones have excellent anaerobic organism coverage.^{15,97} These agents have efficacy against most Gram negative organisms.

Although second, third, and fourth generation quinolones are formulated for parenteral administration, the oral mode of these quinolones provides excellent serum concentrations. Oral administration of these quinolones results in decreased length of hospitalization and reduced treatment costs. In most cases, the patient is begun on the parenteral quinolone and switched to oral quinolone therapy unless the patient has a contraindication to oral antibiotic therapy. The switch to oral therapy usually occurs at 1 to 2 days into therapy. Patients who have not completed puberty should not be given antimicrobial therapy with the quinolone class of antibiotics because of bone growth

problems found in young beagle dogs. Toxicity to the quinolones is low. Gastrointestinal disturbances (nausea, vomiting, and dyspepsia) are the more commonly found side effects (2%–5%). Central nervous system reaction (1%–2%) may occur in the form of headache, dizziness, tiredness, or insomnia. Moderate to severe phototoxicity may be manifested by some of the quinolones (lomefloxacin, sparfloxacin). Sparfloxacin causes prolongation of the Q-T interval. Rarely, Achilles tendon rupture may occur as a result of quinolone therapy.

None of the quinolones have reliable *Enterococcus* species coverage. The current quinolones have variable *Staphylococcus aureus* and *Staphylococcus epidermidis* coverage, and resistance to the second generation quinolones is increasing.³

Trimethoprim-sulfamethoxazole

Trimethoprim-sulfamethoxazole is an antimetabolite composed of a fixed combination of a trimethoprim and sulfonamide. In vitro these agents are more active together than either agent is alone.⁶ Aerobic Gram negative bacteria including *Escherichia coli*, *Proteus mirabilis*, *Haemophilus influenzae*, and *Stenotrophomonas maltophilia* are consistently susceptible. In addition, *Klebsiella pneumoniae*, *Enterobacter* species, *Serratia marcescens*, indolepositive proteus, and non-aeruginosa *Pseudomonas* are also frequently susceptible. The principle targets of trimethoprim-sulfamethoxazole are aerobic Gram negative organisms, but some Gram positive bacteria such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes* are often susceptible.¹⁰² In some hospitals, the combination of trimethoprim-sulfamethoxazole and rifampin may be effective for the oral treatment of methicillin resistant *Staphylococcus aureus* and *Staphylococcus epidermidis*.¹⁰⁰ Trimethoprim-sulfamethoxazole may be given either parenterally or orally. The combination is useful as suppressive therapy for osteomyelitis. Side effects include gastroin-

testinal disturbances, serum sicknesslike syndrome, hemolytic anemia, and hypersensitivity reactions. Trimethoprim-sulfamethoxazole should not be administered during the last month of pregnancy.

Metronidazole

Metronidazole is a useful and inexpensive antibiotic for the treatment of anaerobic organisms. This antibiotic is a reducing compound that leads to the formation of toxic O₂ radicals. Toxic O₂ radicals are lethal for strict anaerobic organisms because they lack the protective enzymes superoxide dismutase and catalase. Metronidazole is active against all anaerobic organisms except for actinomycetes and microaerophilic streptococci.⁷⁵ The drug is well absorbed and penetrates into tissues and abscesses. Side effects are rare, but include metallic taste, seizures, cerebellar dysfunction, disulfiram reaction with alcohol, and pseudomembranous colitis.

Investigational Agents

Several new antimicrobial agents are currently in clinical trials. They offer much needed alternatives to currently available antimicrobials, particularly in the treatment of infections caused by multiresistant Gram positive bacteria such as vancomycin resistant *Enterococcus* species and methicillin resistant *Staphylococcus aureus*.

Teicoplanin is a glycopeptide antibiotic related to vancomycin but possessing several properties that make it clinically useful. Teicoplanin has a prolonged elimination half life of approximately 60 hours allowing one per day administration. The antimicrobial spectrum of teicoplanin includes *Staphylococcal* species and *Streptococcus* species including some methicillin resistant *Staphylococcus aureus* and vancomycin resistant *Enterococcus* species Type B organisms. Teicoplanin toxicity profile is similar to vancomycin including reports of ototoxicity. Teicoplanin may be given by intramuscular or intravenous route.^{2,69}

Quinupristin and dalfopristin (Synercid® Rhône-Poulenc Rorer Inc, Collegeville, PA), is a fixed combination of two streptogramins in a ration of 30:70 recently approved for use in the United States by the Food and Drug Administration. It possesses *in vitro* inhibitory and bactericidal activity against most Gram positive organisms including vancomycin resistant *Enterococcus faecium*.²⁰ Quinupristin/dalfopristin may have a role in the treatment of methicillin resistant *Staphylococcus aureus*, Group D enterococcus, and possible coagulase negative *Staphylococcus* species infections in patients who cannot receive vancomycin therapy. Adverse reactions seem to be mild and include self limited local reactions such as itching, pain and burning, vomiting, and diarrhea. Additional clinical experience is needed to define the role of this antibiotic in clinical practice.^{8,20}

New synthetic classes of antimicrobials, the oxazolidinones, currently are undergoing clinical trials. The analogs linezolid and eperzolid are representatives of this new class. These agents have bacteriostatic activity against numerous important organisms including methicillin resistant *Staphylococcus aureus*, penicillin resistant *Streptococcus pneumoniae*, and vancomycin resistant *Enterococcus* species.¹³ They seem to have efficacy when administered either orally or parenterally. Tongue discoloration and a folliculitis type rash are the commonly reported adverse effects.

LENGTH OF THERAPY

Osteomyelitis traditionally is treated with 4 to 6 weeks of parenteral antibiotics after definitive debridement surgery. However, this time frame has no documented superiority over other time intervals. Because of failure rates of 20% in clinical studies, some authors advocate treatment with 6 to 8 weeks of intravenous therapy followed by a course of 3 months or longer of oral therapy.^{40,98} In this era of resistance development, long duration antibiotic therapies must be scrutinized care-

fully. There is no evidence that prolonged parenteral antibiotics will penetrate necrotic bone. Surgical debridement is necessary to ensure the physician that he or she is treating living vascularized bone. It takes approximately 4 to 6 weeks for debrided bone to be protected by revascularized tissue.⁹⁸ Because patient treatment failures are caused mostly by inadequate surgical debridement rather than the duration of antimicrobials, some clinicians advocate administering intravenous antimicrobials for as little as 2 weeks followed by 4 weeks of oral therapy. In cases of relapse, redebridement is advocated. This treatment method is based on the assumption that if 4 to 6 weeks of antibiotics fail to cure the disease, then longer treatment courses are unlikely to be curative unless the dead devitalized bone is removed.⁹⁸

TREATMENT MODALITIES

Parenteral Versus Oral

Osteomyelitis is a difficult problem for patients and the treating physicians. Flareups of infection require multiple admissions, surgeries leading to pain, and lengthy antibiotic therapy with the associated administration problems and toxicities. The ultimate goal in management of osteomyelitis is to eradicate and prevent recurrence of infection.

Four to 6 weeks of parenteral antibiotic administration after the last major debridement has become the standard length of antibiotic therapy. In the past, patients were hospitalized for the entire duration of antimicrobial treatment. Now home health and outpatient services use heparin locks, peripheral inserted central catheter lines, and implantable catheters, which allow parenteral antibiotic treatment outside the hospital setting. Although outpatient antibiotic therapy has decreased costs, 4 to 6 weeks of outpatient intravenous therapy is still expensive for the patient and healthcare systems.^{11,25,32,48} An antibiotic treatment regimen that begins with parenteral therapy and ends with the self administration of oral an-

tibiotic therapy would reduce significantly the cost of antibiotic administration.

There is little difference in effectiveness between the intravenous and oral administration of an antibiotic as long as both routes provide adequate serum and bone concentrations. Oral antibiotic therapy has been used for treatment of childhood osteomyelitis. It is recommended that the patient initially receives 1 to 2 weeks of parenteral antibiotic therapy before changing to an oral regimen.^{5,33,37,94} The patient must be compliant and have close outpatient followup. In the child, serumcidal levels usually are used to monitor absorption and activity of the orally administered antibiotic.

Currently 4 to 6 weeks of intravenous antibiotics and close followup is recommended for adult patients with osteomyelitis.^{48,63} Comparable therapeutic experience with intravenous antibiotics followed by oral antibiotics and oral antibiotic therapy alone is not well described in adults. In a small series of patients, oral ciprofloxacin and ofloxacin have been shown to be safe and effective as parenteral antibiotics in the treatment of chronic osteomyelitis caused by susceptible organisms.^{22,45}

Shirtliff et al⁸⁷ retrospectively compared the clinical efficacy of 4 weeks of intravenous antibiotics versus 2 weeks of intravenous antibiotics followed by 4 weeks of appropriate oral antibiotics. The patients were followed up at least 12 months after treatment for outcome determination. Osteomyelitis was arrested in 16 of 19 patients in the group treated with 4 weeks of intravenous antibiotic therapy, resulting in an arrest rate of 84.3%. Osteomyelitis was arrested in 17 of 19 in the group treated with 2 weeks of antibiotics followed by 4 weeks of oral antibiotics, resulting in an arrest rate of 89.5%. The data were analyzed and the difference was not statistically significant ($p > 0.05$, χ^2 analysis). Treatment results for 4 weeks of intravenous antibiotics versus 2 weeks of intravenous antibiotics followed by 4 weeks of oral antibiotics in the treatment of

long bone osteomyelitis are not significantly different in this study. This study was limited because of the small sizes of the groups and the variables between the groups.

The major treatment variable between orally prescribed and intravenous antibiotics is patient compliance. Every treating physician must judge whether the patient will be compliant and will be able to independently complete the prescribed oral regimen. If the patient is not compliant, oral antibiotic therapy can be monitored in a direct observation oral dosing program. Increased reliance on oral antibiotic therapy for osteomyelitis will lead to a reduction of intravenous catheter associated infections.

Because osteomyelitis is a surgical disease, complete surgical debridement and not a particular antibiotic regimen is the most important factor for a successful outcome.^{48,98} Osteomyelitis is characterized by its ability to recur after long periods of quiescence and long term followup is required for these patients. Various authors have proposed the use of parenteral antibiotics for periods ranging from 14 days to 6 weeks followed by a variable course of oral antibiotics for the treatment of osteomyelitis.^{9,11,22,45,48,63,87} Antibiotics work best when used in conjunction with adequate debridement, foreign body and dead bone removal, abscess drainage, and dead space obliteration.

Local Therapy Through Antibiotic Beads

In patients with osteomyelitis implant materials impregnated with antibiotics have been used to manage dead space created by debridement surgery. Beads are placed in local defects and spacers are used after the infected total joint prosthesis is removed. Antibiotic beads provide high local concentrations of an antimicrobial agent(s) to the infected dead space. Thus, a high local concentration of antibiotic can be attained without exposing the patient to systemic toxic antibiotic levels, which could result in toxic side effects.

Polymethylmethacrylate is an implant material that has been used successfully with numerous antibiotics, including vancomycin, clindamycin, tobramycin, and gentamicin. However, various problems have been associated with polymethylmethacrylate use. First, antibiotic impregnated polymethylmethacrylate requires a second surgery for its removal. Second, the implant produces local immune compromise by impairing natural killer, lymphocytic, and phagocytic cell activity. Polymethylmethacrylate implants also have been linked to decreasing the amount of superoxide, a mediator of bacterial killing within phagocytic cell phagosome and reducing the amount of lymphocyte blastogenesis.⁷ Normal phagocytic processes are devoted to the removal of the implant foreign material and polymethylmethacrylate particles use energy and resources of the immune system that normally would be used to fight infection. Third, polymethylmethacrylate beads usually provide local bactericidal levels of antibiotics for only 2 to 4 weeks. Once the level of antibiotics eluting from the implant has waned, there is an increased propensity for the overgrowth of antibiotic resistant organisms that were not eliminated by the original high concentration of antimicrobials. Finally, the antibiotics in the polymethylmethacrylate material often leech from the outer cortex of implant, leaving behind a central core of unused antibiotics. Once the antibiotics have leached from the implant cortex, the polymethylmethacrylate material provides a perfect substrate for additional bacterial colonization. Once colonized, many bacteria are able to synthesize a slime layer, termed the glycocalyx. This layer prevents the inward diffusion of numerous antimicrobials, allowing bacterial escape from the bactericidal and bacteriostatic effects of antimicrobial therapy. Also, the glycocalyx displays host antigenic properties, thereby allowing the bacteria to evade detection by the immune system of the host.

New implant materials may be able to reduce or eliminate many of the problems as-

sociated with the clinical standard of polymethylmethacrylate bead therapy for dead space management. Several studies have been performed that use alternative materials for implantation. Zhang et al¹⁰⁵ showed that, in vitro, gentamicin containing high molecular weight biodegradable poly (D,L-lactide) cylinders provided a small initial burst followed by a gradual and sustained release of gentamicin. Although this group did not test the eluted antibiotic against known osteomyelitic organisms, the detected gentamicin concentrations were sufficiently above minimum bactericidal concentrations for these pathogens. In another related in vitro model, Shinto et al⁸⁶ described the ability of gentamicin impregnated Ca hydroxyapatite biodegradable beads to deliver five times the minimum inhibitory concentrations for *Staphylococcus* species for at least 12 weeks. Although in vivo models are lacking, there has been some research in this area. Garvin et al²¹ showed that polyglycolic beads loaded with gentamicin resulted in the effective treatment of tibial *Staphylococcus aureus* osteomyelitis in a canine model. In another study, Calhoun and Mader⁷ showed the efficacy of a biodegradable antibiotic implant composed of polylactic acid and poly(DL-lactide): co-glycolide combined with vancomycin. In the localized rabbit tibial *Staphylococcus aureus* osteomyelitis model, antibiotic impregnated, biodegradable implant treatment resulted in a significant reduction in infection when compared with treatment with systemic vancomycin. However, this study did not compare the efficacy of infection reduction with polymethylmethacrylate beads.

Cripps et al¹⁰ showed vancomycin impregnated hydroxyapatite implant material had approximately equal efficacy in clearing *Staphylococcus aureus* osteomyelitis when compared with vancomycin polymethylmethacrylate beads in rabbits. Hydroxyapatite material impregnated with antibiotics may be better than polymethylmethacrylate beads and intravenous antibiotics in various

ways. First, this material could provide bactericidal concentrations of antibiotics for the prolonged period necessary to treat completely the particular orthopaedic infection. Second, because the hydroxyapatite material is resorbed, there is no need for bead removal such as in the case of polymethylmethacrylate antibiotic impregnated beads. Third, variable resorbability from weeks to months may allow many types of infections to be treated. Fourth, the polymethylmethacrylate and polylactic acid material does not provide for a Ca source necessary for new bone formation in the repair process after infection. Finally, because the hydroxyapatite material is replaced slowly by new bone formation, the soft tissue or bone defect may fill slowly with tissue eliminating additional need for reconstruction.

BONE CONCENTRATIONS

Studies quantifying the bone concentrations of the semisynthetic penicillins, first generation cephalosporins, clindamycin, levofloxacin, and vancomycin have been performed.^{10,41,42,65,91} There still are unresolved methodologic problems. The results of bone concentrations studies are provided in μg per gram and serum concentrations are in μg per mL. Most investigators use an elution technique to recover antibiotic from bone, and optimal extraction procedures that recover antibiotic completely from bone still have to be standardized for each antibiotic. Current methodology does not allow for the reliable distinction between cancellous or cortical bone antibiotic concentrations. Despite these problems an estimate of mean bone concentrations can be determined and evaluated. Vancomycin, clindamycin, nafcillin, cefazolin, and tobramycin bone concentrations have been determined using an identical elution technique. The reference curves were performed in bone powder suspensions. Simultaneous bone and serum concentrations were determined using antibiotic doses that provided optimal serum concentrations for

each antibiotic. Clindamycin was found to have the greatest bone to serum ratio followed by vancomycin, nafcillin, tobramycin, and cefazolin (Table 4). The significance of antibiotic bone concentrations is unclear, but clindamycin had the best results of any single antibiotic therapy (nafcillin, oxacillin, cephalothin, cefamandole, moxalactam, vancomycin, rifampin, trimethoprim, gentamicin) in eradicating experimental *Staphylococcus aureus* osteomyelitis.⁴¹

HYPERBARIC OXYGEN THERAPY

The results of several open clinical trials have shown that adjunctive hyperbaric O_2 therapy may be useful in the treatment of chronic osteomyelitis.⁴³ Morrey et al⁵¹ reported on 40 patients with chronic osteomyelitis who met all of the following criteria: the infection had persisted longer than 1 month; at least one surgical debridement had been performed; at least 2 weeks of parenteral antibiotics had been administered; and all had been followed up for at least 1 year after treatment. All patients had chronic refractory osteomyelitis with a recurrence of this infection despite previous aggressive antibiotics and surgical treatment. After hyperbaric O_2 therapy, appropriate surgery, and treatment with antibiotics, 34 patients (85%) remained clinically free of disease, and six experienced recurrences of their osteomyelitis. Using the same criteria, Davis et al¹² evaluated 38 patients who were treated with adjunctive hyperbaric O_2 . Of these 38 patients, 34 remained free of clinical signs of osteomyelitis. Although the results of these clinical trials are encouraging, the adjunctive role of hyperbaric O_2 in the treatment of osteomyelitis is difficult to assess because of patient, surgical, organism, bone, and antibiotic variables.

Animal studies performed in an experimental *Staphylococcus aureus* osteomyelitis model have shown that hyperbaric O_2 administered under standard treatment conditions was as effective as cephalothin in eradicating

TABLE 4. Infected Bone Concentrations After Antibiotic Administration in Experimental Staphylococcus aureus Osteomyelitis

Antibiotic (dose)	Infected Serum $\mu\text{g/mL}$	Bone $\mu\text{g/g}$	Percentage
Clindamycin (70 mg/kg)	12.1 \pm 0.6	11.9 \pm 1.9	98.3
Vancomycin (30 mg/kg)	36.4 \pm 4.6	05.3 \pm 0.8	14.5
Nafcillin (40 mg/kg)	21.8 \pm 4.6	02.1 \pm 0.3	9.6
Moxalactam (40 mg/kg)	65.2 \pm 5.2	06.2 \pm 0.7	9.5
Tobramycin (5 mg/kg)	14.3 \pm 1.3	01.3 \pm 0.1	9.1
Cefazolin (15 mg/kg)	67.2 \pm 2.6	04.1 \pm 0.7	6.1
Cefazolin (5 mg/kg)	45.6 \pm 3.2	02.6 \pm 0.2	5.7
Cephalothin (40 mg/kg)	34.8 \pm 2.8	01.3 \pm 0.2	3.7

Staphylococcus aureus from infected bone.⁴⁶ Osteomyelitic bone in this experimental model has decreased blood flow and greatly decreased partial pressure of O₂. Hyperbaric O₂ was found to restore intramedullary O₂ tensions to physiologic or suprphysiologic tensions, but did not acutely increase blood flow in osteomyelitic bone. Because in vitro hyperoxia does not directly affect this strain of Staphylococcus aureus, hyperbaric O₂ was effective in Staphylococcus aureus osteomyelitis because it increased intramedullary O₂ to tensions at which phagocytic killing may proceed more efficiently.⁴⁴

Whereas superoxide dismutase and catalase are among the enzymatic mechanisms used by aerobic bacteria to degrade toxic O₂ radicals,²⁶ anaerobic and many microaerophilic organisms lack these enzymes.⁵⁰ Therefore, anaerobic organisms are rendered sensitive to O₂ radicals developed intracellularly and extracellularly during hyperbaric O₂ therapy. As a result, increased O₂ tension is directly lethal to fastidious anaerobic organisms and to some microaerophilic organisms, but not aerobes.⁴ In addition, several clinical reports support the adjunctive role of hyperbaric O₂ therapy in the treatment of nonclostridial anaerobic infections.^{47,83,94} The role of hyperbaric O₂ therapy in the treatment of infection secondary to Clostridial species is well validated.²⁸ Also, in vivo studies have shown hyperbaric O₂ to have an indirect

killing mechanism on Clostridium perfringens mediated through the polymorphonuclear leukocytes. Thus, hyperbaric O₂ provides the necessary substrate (O₂) for the killing of aerobic and probably anaerobic organisms by the polymorphonuclear leukocyte.

The effects of hyperbaric O₂ on antibiotic efficacy were shown in a Pseudomonas aeruginosa osteomyelitis model, in which hyperbaric O₂ potentiated the aminoglycoside tobramycin.^{42,72,66} Other aminoglycosides and antibiotics including vancomycin, the quinolone class of antibiotics, nitrofurantoin, and certain sulfonamides are far less active in hypoxic environments. Such conditions are found readily in ischemic tissues and in normal bone. Therefore, hyperbaric O₂ therapy also may be beneficial by augmenting the effects of these antibiotics.

Wound healing is a dynamic process that requires an adequate O₂ tension to proceed.^{30,31} In the ischemic or infected wound, hyperbaric O₂ provides O₂ to promote collagen production, angiogenesis, and ultimately wound healing.

Hyperbaric O₂ therapy often is used as adjunctive therapy in the treatment of posttraumatic osteomyelitis and chronic refractory osteomyelitis. Posttraumatic osteomyelitis often requires significant bone healing because trauma and the infective process can result in significant bony destruction. Besides the beneficial effects of direct inhibition of anaerobes, upregulation of polymorphonuclear in-

tracellular killing, augmenting antibiotic activity, and maintaining muscle and skin flaps, hyperbaric O₂ therapy can promote accelerated bone repair. The optimum hyperbaric O₂ treatment regimens are one to two treatments per day for 60 to 120 minutes at two to three atmospheres of pressure with 100% O₂. Oxygenation below this level (such as occurs in infected bone) will result in slow bone healing because of inhibition of fibroblast, osteoclast, osteoblast, and macrophage activity.¹⁰³ When O₂ levels are raised beyond optimum levels for a sustained period, fibroblast activity is highly upregulated, resulting in a thick collagenous deposition.⁴⁹ Many *in vitro* studies have reported an upregulated osteoclast activity caused by long exposures to O₂ radicals including hydrogen peroxide associated with hyperoxygen growth conditions.^{18,24,27} The end result of sustained hyperoxygenation is the development of a repair process that is rich in collagen and structurally weak. Therefore, maximal bone healing may be achieved when hyperbaric O₂ treatment is provided within the optimal range of treatments for 90 to 120 minutes at two to three atmospheres of pressure with 100% O₂ once daily.

Acknowledgments

The authors thank Michael Cripps, BS, Donna Milner Mader, BA, and Maureen D. Shirtliff, RN, for manuscript research and preparation.

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