# ANTIBIOTIC THERAPY FOR MUSCULOSKELETAL INFECTIONS

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*An Instructional Course Lecture, American Academy of Orthopaedic Surgeons*

Antibiotics are grouped into categories on the basis of their mechanisms of action. These categories include cell-wall active antibiotics, ribosomal active antibiotics, RNA active antibiotics, DNA active antibiotics, antimetabolites, and the reducing compounds.

## Cell-Wall Active Antibiotics

The cell-wall active antibiotics include penicillins, β-lactamase inhibitors, cephalosporins, other β-lactam antibiotics, and vancomycin. β-lactamase inhibitors are combined with the penicillins to enhance the antibiotic activity against β-lactamase-producing organisms.

### *Penicillins*

The penicillin class of antibiotics is frequently used for the treatment of musculoskeletal infections. The penicillins can be divided into general groups on the basis of their antibacterial activity. The major penicillin groups of interest to an orthopaedic surgeon are natural penicillins, aminopenicillins, penicillinase-resistant penicillins, antipseudomonal penicillins (carboxypenicillins), and extended spectrum penicillins (ureidopenicillins). There is overlap among these groups; the differences are usually pharmacological in nature.

The major side effects of all of the penicillins are hypersensitivity reactions that range in severity from a rash to anaphylaxis[1]. Immediate hypersensitivity reactions have been reported to occur in 0.0004% to 0.15% of patients[2]. Of those patients, urticaria occurs in 1% to 5% and a rash occurs in 2% to 9%. Hemolytic anemia and central nervous system toxicities can also occur with penicillin administration. Serum sickness rarely occurs with penicillins. Additionally, exfoliative dermatitis and erythema multiforme are rare forms of allergic reactions to penicillin.

Penicillin G is the major natural penicillin. Although penicillin G has a half-life of thirty to sixty minutes, it can be combined with procaine or benzathine to produce a repository penicillin. Penicillin is the drug of choice for the treatment of *Streptococcus pyogenes, Streptococcus agalactiae,* and *Clostridium perfringens.* In addition, penicillin has a good anaerobic spectrum of activity except for the *Bacteroides fragilis* group. *Streptococcus pneumoniae* continues to become more resistant to penicillin. Currently, *Streptococcus pneumoniae* has an intermediate resistance to penicillin in 15% of cases and a high-level resistance to penicillin in 15%.

The major side effects of the natural penicillins are immediate hypersensitivity reactions, including anaphylaxis, bronchospasm, and hives, as well as delayed reactions, including skin rashes[3]. Other potential side effects are renal failure, Coombs-positive hemolytic anemia, and seizure activity, which usually occurs with aqueous penicillin doses of $>20 \times 10^6$ U/day.

The parenteral penicillinase-resistant penicillins are methicillin, nafcillin, and the isoxazolyl penicillins (including oxacillin, cloxacillin, dicloxacillin, and flucloxacillin). The most active parenteral semisynthetic penicillins are nafcillin 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*. However, they have no activity against Enterococcus species or gram-negative bacilli.

Methicillin is associated with the greatest potential for producing interstitial nephritis[4]. Nafcillin and oxacillin may cause interstitial nephritis, leukopenia, and reversible hepatic dysfunction[5,6]. Cloxacillin and dicloxacillin are the oral semisynthetic penicillins of choice in the United States, and they have fewer side effects than the parenteral semisynthetic penicillins.

The major aminopenicillins in-

clude ampicillin and amoxicillin. Ampicillin may be given parenterally or orally, whereas amoxicillin may be given only orally. The antibacterial activities of the aminopenicillins are similar. They are the antibiotics of choice for the treatment of sensitive Enterococcus species *(Enterococcus faecalis* and *Enterococcus faecium)*[7]. The aminopenicillins are also active against many highly susceptible gram-negative rods, such as *Escherichia coli* and *Proteus mirabilis*. They are not stable to β-lactamase and are less active than penicillin G against *Streptococcus pyogenes* and *Streptococcus agalactiae*. While the aminopenicillins may cause skin rashes, an idiosyncratic rubelliform rash occurs in 99% of patients who have mononucleosis and are given the aminopenicillins.

Ticarcillin (carboxypenicillin) is an antipseudomonal penicillin. Ticarcillin has a β-lactam ring and is susceptible to β-lactamase of both 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[8]. The side effects of this class of penicillins include sodium-loading and bleeding problems secondary to platelet dysfunction[9].

The extended spectrum penicillins (ureidopenicillins) include mezlocillin and piperacillin. They have an antibacterial spectrum similar to that of ticarcillin. *In vitro,* these antibiotics are active against Enterococcus species and Streptococcus species, and they inhibit the majority of Klebsiella species. They are also more active than ticarcillin against *Haemophilus influenzae* and the *Bacteroides fragilis* group[10,11]. 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.

Penicillins as a group have a number of drug interactions. However, these interactions are generally uncommon. The carboxypenicillins and ureidopenicillins inactivate the aminoglycosides[12,13]. This drug interaction is seen in patients who have underlying renal dysfunction[14,15]. Probenecid inhibits tubular secretion of the penicillins and increases the drug half-life of these agents[16].

### *β-lactamase Inhibitors*

β-lactamase of gram-positive species is an exoenzyme. Clavulanic acid, sulbactam, and tazobactam are potent inhibitors of β-lactamase produced by gram-positive and gram-negative organisms[17]. Clavulanic acid, sulbactam, and tazobactam have been shown to inhibit β-lactamase for a number of clinically important gram-positive organisms, including *Staphylococcus aureus* and *Staphylococcus epidermidis*[18]. β-lactamase of both gram-negative and most anaerobic organisms is situated in the periplasmic space and is chromosome and plasmid-induced[19]. Clavulanic acid, sulbactam, and tazobactam inhibit β-lactamase of many gram-negative organisms, including *Escherichia coli,* and most Klebsiella and Bacteroides species. Currently, clavulanic acid is commercially available with amoxicillin (Augmentin; SmithKline Beecham Pharmaceuticals, Philadelphia, Pennsylvania) and ticarcillin (Timentin; SmithKline Beecham Pharmaceuticals). Sulbactam is available with ampicillin (Unasyn; Pfizer, New York, NY). Tazobactam is combined with piperacillin (Zosyn; Lederle, Pearl River, New York). The β-lactam inhibitors enhance the gram-positive coverage and, to a lesser extent, the gram-negative spectrum of these antibiotics. The side effects are the same as those of the penicillin class of antibiotics.

### *Cephalosporins*

The cephalosporins have been divided into first, second, third, and fourth-generation agents. The first-generation cephalosporins include cephalothin, cephapirin, cephradine, 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 are occasionally associated with allergic reactions, drug eruptions, phlebitis, and diarrhea. Cefazolin is the first-generation cephalosporin used by the orthopaedic community for the treatment of staphylococcal infections, including osteomyelitis. The large amounts of β-lactamase produced by *Staphylococcus aureus* ($10^9$ organisms per gram of tissue) inactivate cefazolin[20]. However, high numbers of *Staphylococcus aureus* are not the norm in staphylococcal osteomyelitis; $\leq 10^5$ organisms per gram of bone are usually found. Cefazolin has a longer half-life and higher serum concentration than the other first-generation cephalosporins[21]. The remainder of the first-generation cephalosporins are comparable. They are all more stable to β-lactamase than cefazolin is.

There are many second-generation cephalosporins, but the major parenteral ones are cefamandole, cefoxitin, cefotetan, and cefuroxime. The major oral cephalosporins are cefuroxime, cefprozil, and loracarbef. The second-generation cephalosporins are somewhat more active against gram-negative organisms than are the first-generation agents, but they are less active than the third-generation agents. Cefoxitin and cefotetan are more active against the anaerobes, especially the *Bacteroides fragilis* group, than are the first-generation or the other second-generation cephalosporins[22]. The second-generation cephalosporins have the same toxicity potential as the first-generation cephalosporins with the exception of those that have a methylthiotetrazole side chain.

The major third-generation cephalosporins are cefotaxime, ceftriaxone, ceftizoxime, cefoperazone, and ceftazidime. Compared with the first-generation cephalosporins, the third-generation cephalosporins are generally less active against gram-positive organisms but are more active against the Enterobacteriaceae[23]. Cefotaxime, ceftriaxone, and ceftizoxime are

third-generation cephalosporins with similar antibacterial activity. They are highly resistant to β-lactamase, and they 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 8.0 hours, respectively.

Ceftazidime is similar to cefotaxime, ceftizoxime, and ceftriaxone with regard to activity against the Enterobacteriaceae, but it has superior activity against *Pseudomonas aeruginosa*[24]. For serious *Pseudomonas aeruginosa* infections, it should be combined with an aminoglycoside[25]. The activity of ceftazidime against gram-positive organisms is half that of 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 have suggested increased activity of cefepime against multiresistant Enterobacter species. Like other cephalosporins, cefepime has no activity against Enterococcus species.

In general, the cephalosporins have a low prevalence of adverse reactions. A cross-reactivity occurs in 3% to 7% of patients with an allergy to penicillin. This may be a true cross-reactivity (allergy) or those patients may be more allergic. The allergic reactions to the cephalosporins include a type-I immediate hypersensitivity reaction, including bronchospasm, hives, and skin rashes, occurring three to five days after the initiation of therapy. Fever, lymphadenopathy, eosinophilia, and serum-sickness reactions may also occur. The cephalosporins cause a Coombs-positive anemia in approximately 3% of patients. Neutropenia occurs in approximately 1% of patients, usually after three weeks of the therapy. Liver function abnormalities, with elevation of liver enzyme levels, occur in 1% to 7% of patients. Antibiotic-associated colitis is associated with cephalosporin administration as well.

Some second and third-generation cephalosporins, including cefotetan and cefamandole (second generation) as well as moxalactam and cefoperazone (third generation), have the methylthiotetrazole side chain. Antibiotics with the methylthiotetrazole side chain can cause a disulfiram reaction when a patient drinks alcohol[26-30], and they are also associated with hypoprothrombinemia[31-35]. The cephalosporins have very few reported drug-drug and drug-food interactions.

### *Other β-lactam Antibiotics*

Aztreonam is a monocyclic β-lactam antibiotic, which is active against most Enterobacteriaceae and *Pseudomonas aeruginosa*[36]. 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 with this antibiotic[37,38]. Minor reactions to aztreonam include nausea, vomiting, and diarrhea. On occasion, the drug may cause elevated levels of liver transaminases. Aztreonam has a low probability of cross-reactivity (allergy) in patients allergic to penicillin or cephalosporin.

Imipenem is an antimicrobial agent belonging to the β-lactam class of antibiotics. Biochemically, it is a carbapenem. Imipenem also has excellent *in vitro* activity against aerobic gram-positive organisms, including *Staphylococcus aureus, Staphylococcus epidermidis,* and Streptococcal species. Imipenem also has excellent activity against gram-negative organisms, including the Enterobacteriaceae and *Pseudomonas aeruginosa*. In addition, imipenem inhibits most anaerobic species, including the *Bacteroides fragilis* group[39]. Some patients have nausea, vomiting, and diarrhea with imipenem therapy. Penicillin cross-reactivity occurs with imipenem. *Grand mal* seizures occur in 1% to 4% of patients receiving this antibiotic. The prevalence of seizures is increased in patients with renal dysfunction[40,41] and/or a history of seizure activity. Finally, resistance to *Pseudomonas aeruginosa* and fungal superinfection may develop during therapy.

### *Vancomycin*

Vancomycin has excellent activity against *Staphylococcus aureus, Staphylococcus epidermidis,* and Enterococcus species. It is the antibiotic of choice for individuals who are unable to tolerate either the penicillins or the cephalosporins[42]. Vancomycin is also the antibiotic of choice for the treatment of methicillin-resistant *Staphylococcus aureus*[43] and coagulase-negative Staphylococcus species[44]. Recent reports on vancomycin-resistant Enterococcus species have dictated increased vigilance and caution[45,46].

When used as monotherapy, the end organ toxicity of vancomycin is minimal. The "red man syndrome"[47,48] may be observed with vancomycin therapy. This syndrome includes flushing of the head, neck, and upper torso and is often associated with hypotension. It occurs in 5% to 13% of patients, especially when the infusion is given over less than one hour. Allergic reactions rarely occur with vancomycin therapy. Vancomycin may be associated with nephrotoxicity[49-52] or ototoxicity, especially when given concurrently with an aminoglycoside. Vancomycin may also cause neutropenia[53,54] and thrombocytopenia[55,56].

## Ribosomal Active Antibiotics

The ribosomal active antibiotics include clindamycin, macrolides, quinupristin/dalfopristin, tetracyclines, oxazolidinones, and aminoglycosides.

### *Clindamycin*

Clindamycin is one of the antibiotics most active against clinically important anaerobic bacteria, particularly the *Bacteroides fragilis* group. However, clindamycin is ineffective against clostridial species, other than *Clostridium perfringens,* in 10% to 20% of cases[57]. In addition to its anaerobic activity, clindamycin is also effective against *Staphylococcus aureus,* coagulase-negative Staphylococcus species,

and the Streptococcus species. Clindamycin has a half-life of 2.4 hours and is ideally given every eight hours. Clindamycin demonstrates good penetration into most tissues, including bone[58,59], and penetrates well into abscesses.

Clindamycin is relatively nontoxic but causes diarrhea and pseudomembranous colitis in approximately 8% of patients[60]. In 10% of patients who have antibiotic-associated diarrhea, pseudomembranous colitis develops secondary to toxins produced by the overgrowth of *Clostridium difficile*. Hypersensitivity reactions, including rashes, urticaria, and erythema multiforme, may occur with clindamycin administration. Clindamycin drug interactions are rare, but clindamycin may potentiate the action of neuromuscular blocking agents[61-63].

***Macrolides***

Erythromycin is the prototype of the macrolide class of antibiotics[64]. These agents work at the ribosomal level and are bacteriostatic. Erythromycin has *in vitro* activity against Streptococcus species*, Listeria monocytogenes, Moraxella catarrhalis, Mycoplasma pneumoniae, Legionella pneumophila,* and *Chlamydia pneumoniae*. The new macrolides (clarithromycin and azithromycin) can inhibit *Mycoplasma pneumoniae,* Legionella species, and *Chlamydia pneumoniae* at lower concentrations. They are also more active against *Haemophilus influenzae, Mycobacterium avium-intracellulare,* and other atypical mycobacteria. The new macrolides are active against the agent of Lyme disease, *Borrelia burgdorferi*. Because of its high intracellular concentration, azithromycin is more active against *Chlamydia trachomatis* and *Toxoplasma gondii* and clarithromycin is very active against *Helicobacter pylori*. The macrolides are indicated for the treatment of upper and lower respiratory tract infections and skin structure infections. The new macrolides are the agents of choice for *Mycobacterium avium-intracellulare* infections.

The macrolides are generally considered to be very safe drugs. They cause gastrointestinal reactions, including nausea, vomiting, and abdominal cramps, in approximately 20% of patients. These problems are less frequent with newer erythromycins such as azithromycin and clarithromycin. The macrolides have a number of drug interactions. They stimulate hepatic microsomal activity with cytochrome P-450 complexes. This stimulation causes increased levels of theophylline, warfarin, cyclosporin, carbamazepine, and cisapride. Azithromycin has the least drug-interaction potential of the macrolides.

***Quinupristin/Dalfopristin***

Quinupristin/dalfopristin (Synercid; Aventis, Parsippany, New Jersey) is a fixed combination of two streptogramins in a ratio of 30:70. This antibiotic produces *in vitro* inhibitory and bactericidal activity against most gram-positive organisms, including vancomycin-resistant *Enterococcus faecium*[65]. Quinupristin/dalfopristin also has a role in the treatment of methicillin-resistant *Staphylococcus aureus* and coagulase-negative Staphylococcus species infections in patients who cannot tolerate vancomycin therapy. Adverse reactions[66] to quinupristin/dalfopristin appear to be mild and include self-limited local reactions such as itching, pain, and burning as well as vomiting and diarrhea[67]. Major side effects are phlebitis, especially in the smaller veins. The antibiotic should be given through a central line. In a recent study[68], the drug caused severe myalgia in approximately 15% to 20% of thirty-two patients who received it.

***Tetracyclines***

The tetracyclines are divided into three groups: the short-acting compounds (chlortetracycline, oxytetracycline, and tetracycline), an intermediate group (demeclocycline), and the more recently developed longer-acting group (doxycycline and minocycline). The tetracyclines are primarily bacteriostatic. They are useful drugs for the treatment of relatively uncommon diseases, including brucellosis and granuloma inguinale. Tetracyclines are also active against mycoplasma, rickettsia, and Lyme disease *(Borrelia burgdorferi)*. In addition, they also are useful in the treatment of chlamydial diseases, including lymphogranuloma venereum, psittacosis, and trachoma. Minocycline is the most active drug of the tetracycline class against *Staphylococcus aureus*. Minocycline is often used in combination with rifampin for the oral treatment of methicillin-resistant *Staphylococcus aureus* and coagulase-negative Staphylococcus species.

The tetracyclines have excellent tissue distribution probably because of their high lipid solubility. Minocycline is the most lipid-soluble tetracycline. The high lipid solubility and diffusion make it useful for the treatment of metabolically inactive organisms. Tetracyclines accumulate in bone.

The tetracyclines have major side effects, including anorexia, nausea, vomiting, and diarrhea. Tetracyclines also cause hepatotoxicity, especially in pregnant women. They should not be given to children less than twelve years of age, as they cause gray-brown-yellowish discoloration of teeth and may impair bone growth in this age-group. Tetracyclines are catabolic and aggravate preexisting renal failure. They have a propensity to cause major photosensitivity reactions. Other side effects include esophageal ulcers and hypersensitivity reactions. Minocycline causes vestibular toxicity in some patients.

Tetracycline antibiotics have a number of drug interactions. Divalent metals, including calcium, magnesium, and aluminum (antacids)[69-71], when given concurrently, lead to decreased absorption of the tetracyclines. A number of drugs increase hepatic metabolism of the tetracyclines, which causes a decreased half-life of this class of antibiotics.

***Oxazolidinones***

The oxazolidinones[72,73] are a new synthetic class of antimicrobials. These agents have bacteriostatic activity against a number of important organisms,

including methicillin-resistant *Staphylococcus aureus,* penicillin-resistant *Streptococcus pneumoniae,* and vancomycin-resistant Enterococcus species[74]. They have efficacy when administered either parenterally or orally. Side effects include tongue discoloration, a folliculitis type of rash, nausea, vomiting, and diarrhea.

### *Aminoglycosides*

The aminoglycosides, which include gentamicin, tobramycin, amikacin, and netilmicin, are the standard against 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 may develop rapidly[75,76]. They have no effect against the Streptococcus species or anaerobes, but they 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 that susceptible to tobramycin, gentamicin, or netilmicin[77]. There is no evidence that establishes whether amikacin has greater or lesser activity than the other aminoglycosides.

The aminoglycosides can cause nephrotoxicity and ototoxicity. Ototoxicity reactions include hearing loss, tinnitus, ear fullness, and vestibular problems such as nausea, vomiting, vertigo, nystagmus, and difficulty with gait. Other aminoglycoside toxicities include neuromuscular blockade and hypersensitivity reactions.

The aminoglycosides have some drug interactions. There is increased nephrotoxicity and ototoxicity when cyclosporin, vancomycin, amphotericin B, ethacrynic acid, neuromuscular blocking agents, nonsteroidal anti-inflammatory drugs, or radiographic contrast agents are given concurrently with the aminoglycosides.

## RNA Active Antibiotics (Rifampin)

Rifampin exhibits bactericidal activity against a wide variety of gram-positive and gram-negative organisms. Rifampin is the most active antistaphylococcal agent known[78]. However, it is less active against most gram-negative bacteria than are the aminoglycosides. When rifampin is used alone for the treatment of bacterial infections, a rifampin-resistant subpopulation rapidly develops[79]. 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 osteomyelitis caused by methicillin-sensitive Staphylococcus species. Trimethoprim-sulfamethoxazole or minocycline and rifampin have been used to treat osteomyelitis caused by methicillin-resistant Staphylococcus species.

Side effects of rifampin include orange-red discoloration of body fluids, gastrointestinal symptoms, hepatitis, and possibly mild immunosuppression. There are a number of rifampin drug interactions[80-82]. The co-administration of rifampin with INH (isoniazid) leads to a higher rate of hepatotoxicity[83]. Co-administration of rifampin with ketoconazole[84] can result in a failure of either drug. Food interferes with the absorption of rifampin, and this antibiotic must be taken on an empty stomach. Rifampin induces hepatic microsomal enzymes and can decrease the level of certain drugs (Table I). Patients taking these medications must be carefully monitored, and their drug doses must be adjusted when indicated.

**TABLE I Drugs Affected by Rifampin***

| |
|---|
| Acetaminophen |
| Benzodiazepines |
| Clofibrate |
| Cyclosporine |
| Digoxin |
| Hydantoins |
| Quinidine |
| Theophyllines |
| Oral anticoagulants |
| Beta-blockers |
| Oral contraceptives |
| Digitoxin |
| Enalapril |
| Methadone |
| Sulfones |
| Tocainide |
| Barbiturates |
| Chloramphenicol |
| Corticosteroids |
| Disopyramide |
| Estrogens |
| Mexiletine |
| Sulfonylureas |
| Verapamil |

*Rifampin induces hepatic microsomal enzymes and can decrease the effect of these drugs.

## DNA Active Antibiotics (Fluoroquinolones)

There are four generations of quinolones. The first generation, nalidixic acid, is used to treat urinary tract infections. The second, third, and fourth-generation quinolones may be used to treat musculoskeletal infections, including osteomyelitis[85].

The second-generation quinolones include ciprofloxacin and ofloxacin, which provide adequate serum, tissue, and urine concentrations and have efficacy against most gram-negative organisms. Most streptococcal strains and anaerobic organisms are resistant to ciprofloxacin and ofloxacin. Reports of resistance by some *Staphylococcus aureus* and *Staphylococcus epidermidis* strains dictate caution. Ciprofloxacin is advantageous in the treatment of gram-negative bone infections, which previously required prolonged parenteral antibiotic therapy[85].

The third-generation quinolones include levofloxacin and sparfloxacin, which provide higher serum levels than do either ciprofloxacin or ofloxacin.

These agents have excellent activity against Streptococcus species, including penicillin-intermediate strains and resistant *Streptococcus pneumoniae*. They are also active against atypical respiratory pathogens *(Mycoplasma pneumoniae,* Legionella species, and *Chlamydia pneumoniae).* They have efficacy against most gram-negative organisms as well.

The fourth-generation (trovafloxacin) quinolones have aerobic gram-positive and gram-negative organism coverage similar to that of the third-generation quinolones, but, unlike the third-generation quinolones, the fourth-generation quinolones have excellent anaerobic organism coverage[86,87]. In a small number of patients, trovafloxacin has been associated with serious liver injury leading to liver transplant and/or death. While this problem has been reported with both short and long-term therapy, treatment for more than two weeks is associated with an increased risk of liver injury. Currently, trovafloxacin may be used only for serious life or limb-threatening infections in a hospital or nursing-care facility.

None of the quinolones have reliable Enterococcus species coverage[88]. The current quinolones have variable *Staphylococcus aureus* and *Staphylococcus epidermidis* coverage, and resistance to the second and third-generation quinolones is increasing[89].

Although second, third, and fourth-generation quinolones are formulated for parenteral administration, oral administration provides excellent serum concentrations and is associated with a decreased duration of hospitalization and reduced treatment costs. In most cases, treatment with quinolone is begun parenterally and, after one to two days, is switched to oral therapy unless that is contraindicated.

Patients who have not completed puberty should not be treated with the quinolone class of antibiotics because altered bone growth has been found in studies on young beagles[90].

Overall, the toxicity of the quinolones is low[91]. Gastrointestinal disturbances consisting of nausea, vomiting, and/or dyspepsia occur in 2% to 5% of patients. Central nervous system reactions, including headache, dizziness, tiredness, and insomnia, occur in 1% to 2% of patients. The quinolones may cause hypersensitivity reactions, including skin rashes. Moderate-to-severe phototoxicity may be caused by some of the quinolones, especially lomefloxacin and sparfloxacin. The quinolones may also cause tendinitis and a predisposition to rupture of the Achilles tendon, and, rarely, this class of antibiotic may cause acute interstitial nephritis. While all quinolones cause mild toxicity, individual quinolones have the propensity for certain side effects. Sparfloxacin, for example, causes prolongation of the Q-T interval (Table II). The quinolones also have multiple drug-drug interactions[92]. Antacids, including sucralfate, iron, zinc, and calcium, decrease the absorption and the efficacy of most quinolones. Certain quinolones have specific drug-drug interactions (Table III).

## Antimetabolites

The antimetabolites include the sulfonamides and trimethoprim-sulfamethoxazole.

### *Trimethoprim-Sulfamethoxazole*

Trimethoprim-sulfamethoxazole is a fixed combination of a trimethoprim and sulfonamide. *In vitro,* these agents are more active together than either agent is alone[93]. 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,* indole-positive Proteus, and nonaeruginosa Pseudomonas are frequently susceptible. The principal 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[94]. 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*[95]. Trimethoprim-sulfamethoxazole may be given either parenterally or orally. The combination is useful as suppressive therapy for osteomyelitis.

All of the sulfonamides, including trimethoprim-sulfamethoxazole, have multiple side effects, including gastrointestinal disturbances. Other side effects include blood dyscrasias such as acute hemolytic anemia, glucose-6-phosphate dehydrogenase deficiency problems, agranulocytosis, aplastic anemia, and thrombocytopenia. Hypersen-

**TABLE II Toxicity by Specific Quinolone**

| Toxicity | Specific Quinolone |
|---|---|
| Phototoxicity | Enoxacin, lomefloxacin, sparfloxacin |
| Central nervous system toxicities, insomnia | Ofloxacin |
| Seizures | Lomefloxacin |
| Prolonged Q-T interval | Sparfloxacin |
| Increased bilirubin | Trovafloxacin |
| Dizziness | Trovafloxacin |
| Persistent hypoglycemia with glyburide | Ciprofloxacin |

**TABLE III Quinolone: Drug Interactions**

| Drug | Quinolone | Effect |
|---|---|---|
| Antacids (sucralfate, iron, zinc, and calcium) | All | Decreased absorption and efficacy |
| Theophylline | Enoxacin, ciprofloxacin | Theophylline toxicity |
| Caffeine | Enoxacin | Nervousness, insomnia |
| Warfarin | Enoxacin, ciprofloxacin, ofloxacin | Increased prothrombin time |
| Cyclosporine | Ciprofloxacin | Transient increased levels of cyclosporine |
| Phenytoin | Ciprofloxacin | Increased or decreased phenytoin levels |

sitivity reactions include erythema multiforme, urticaria, and erythema nodosum. The sulfonamides may cause a focal or diffuse hepatitis and neurologic symptoms consisting of headache, confusion, and peripheral neuropathy. A serum-sickness-like syndrome can occur with the sulfonamides, and a drug fever occurs in 3% of patients taking these drugs. The sulfonamides have also been reported to cause nephrotoxicity and pruritus without a rash. Trimethoprim-sulfamethoxazole should not be administered during the last month of pregnancy.

The sulfonamides have a number of drug interactions, which include increased anticoagulation effects of warfarin[96,97] and increased levels of phenytoin[98]. They also potentiate the hypoglycemic effects of the sulfonylurea compounds[99-102]. Finally, the sulfonamides potentiate the bone-marrow suppression by methotrexate[103].

## Reducing Compounds (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 oxygen radicals. Toxic oxygen radicals are lethal for strict anaerobic organisms, since they lack the protective enzymes superoxide dismutase and catalase. Metronidazole is active against all anaerobic organisms except for actinomycetes and microaerophilic streptococci[104]. The drug is absorbed well and penetrates into tissues and abscesses.

Side effects are rare but can include metallic taste, seizures, cerebellar dysfunction, disulfiram reaction with alcohol, and pseudomembranous colitis. Metronidazole may also have gastrointestinal side effects, including anorexia, nausea, vomiting, diarrhea, abdominal pain, and pancreatitis.

## Clinical Usage

In selecting specific antibiotics for the treatment of musculoskeletal infections, the type of infection, hospital sensitivity patterns, and risk of adverse reactions must be appraised. Once the infecting organism or organisms are isolated and the sensitivities are established, the initial antibiotic regimen should be modified, if indicated. The initial choices of antibiotics for gram-positive, gram-negative, and anaerobic organisms are shown in Tables IV, V, and VI. The initial antibiotic regimen is modified, if necessary, on the basis of culture and sensitivity results.

### *Sensitivity Testing*

Once the organism or organisms are isolated, the specific antibacterial activity of a variety of antibiotics can be determined by appropriate sensitivity techniques. The disk diffusion method is commonly used for susceptibility testing for fastidious and slow-growing organisms. 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[105]. Quantitative data are provided by methods that incorporate serial dilution of antibiotics in agar-containing or broth culture media.

Quantitative sensitivity testing by macrodilution or microdilution techniques is a prerequisite for the determination of the lowest concentration of the antibiotic required to inhibit (mean inhibitory concentration) and kill (mean bactericidal concentration) the isolated organism or organisms[106]. Clinical prejudice demands selection of an antibiotic or antibiotic combination with a low mean inhibitory concentration-to-mean bactericidal concentration ratio relative to its expected serum concentration. Most clinical laboratories report only mean inhibitory concentrations.

### *Serum-cidal Concentrations*

Peak and trough serum bacteriostatic and bactericidal levels, as described by Schlicter and MacLean[107], are often employed to assess the bacteriostatic and bactericidal capabilities of the treatment antibiotic or antibiotics. Initially, serum samples are obtained from the

patient after administration of a dose of the antibiotic in order to obtain the peak and trough serum levels. The serum samples are then serially diluted, and the dilution fractions are tested against an inoculum of the infecting bacterial species. With use of this method, one can estimate the antibiotic dose necessary to obtain adequate serum inhibitory and bactericidal antibiotic levels. These results are expressed as minimum inhibitory dilutions and minimum serum bactericidal dilutions. The interpretation criteria and importance of the data vary among different laboratories[108-110]. Most investigators strive for a peak minimum serum bactericidal dilution of ≥1:8 (that is, an eightfold or higher dilution of a patient's serum has a bactericidal effect on the infecting bacterial species or strain)[111]. In children with osteomyelitis, minimum serum bactericidal dilutions have been utilized to ensure the adequacy of oral antibiotic therapy[112]. In a typical patient with osteomyelitis for whom optimal antibiotics are selected by mean inhibitory concentration testing, the likelihood of success is governed by the adequacy of débridement rather than by the adequacy of serum bactericidal levels.

### *Antibiotics in Pregnancy*

All antibiotics must be used with caution in pregnancy[113]. Antibiotics that have the best safety record include penicillins, cephalosporins, and erythromycin. Other antibiotics can cause problems; the aminoglycosides, for instance, can cause deafness. The sulfonamides, when given in the third trimester, displace bilirubin from albumin leading to kernicterus. The tetracyclines alter bone growth in the baby and can

**TABLE IV Gram-Positive Organisms: Initial Choice of Antibiotics for Therapy (Adult Doses)**

| Organism | First Choice of Antibiotics | Alternative Antibiotics |
|---|---|---|
| **Methicillin-sensitive** | | |
| *Staphylococcus aureus* | Nafcillin (2 g every 4 h) or clindamycin (900 mg every 8 h) | Cefazolin or vancomycin |
| Coagulase-negative Staphylococcus species | Nafcillin (2 g every 6 h) or clindamycin (900 mg every 8 h) | Cefazolin or vancomycin |
| **Methicillin-resistant** | | |
| *Staphylococcus aureus* | Vancomycin (1 g every 12 h) or linezolid (600 mg every 12 h) | Trimethoprim-sulfamethoxazole or minocycline with or without rifampin |
| Coagulase-negative Staphylococcus species | Vancomycin (1 g every 12 h) or linezolid (600 mg every 12 h) | Trimethoprim-sulfamethoxazole or minocycline with or without rifampin, clindamycin* |
| Group-A Streptococcus or *Streptococcus pyogenes* | Penicillin G ($2 \times 10^6$ U every 4 h) or ampicillin (2 g every 6 h) | Clindamycin, cephalosporine or vancomycin |
| Group-B streptococcus or *Streptococcus agalactiae* | Penicillin G ($2 \times 10^6$ U every 4 h) or ampicillin (2 g every 6 h) | Clindamycin, cephalosporine or vancomycin |
| **Sensitive** | | |
| Streptococcus pneumoniae | Penicillin G ($2 \times 10^6$ U every 4 h) | Clindamycin or erythromycin |
| **Intermediate** | | |
| Streptococcus pneumoniae | Cefotaxime (1 g every 8 h) | Clindamycin or erythromycin |
| **Resistant** | | |
| Streptococcus pneumoniae | Vancomycin (1 g every 12 h) or levofloxacin (500 mg daily) | Quinupristin/dalfopristin or linezolid |
| **Sensitive** | | |
| Enterococcus species | Ampicillin (1 g every 6 h)† or vancomycin (1 g every 12 h) | Ampicillin-sulbactam linezolid |
| **Resistant** | | |
| Enterococcus faecium | Quinupristin/dalfopristin (7.5 mg/kg every 8 h) or linezolid (600 mg every 12 h) | Chloramphenicol and rifampin |

*If organism is sensitive to clindamycin. †Ampicillin and an aminoglycoside are used for a serious Enterococcus species infection.

cause pancreatitis and liver dysfunction in the mother. Metronidazole is carcinogenic in rats. The quinolones alter cartilage growth in juvenile animals. Rifampin, trimethoprim, and clarithromycin are either teratogenic in rodents or cause adverse outcomes in nonhuman primates.

*Antibiotics in Nursing Mothers*

Many antibiotics, such as sulfonamides, quinolones, and chloramphenicol, appear in breast milk when administered to lactating women and can have adverse effects on infants. It is prudent for the mother to discontinue breast-feeding temporarily during antibiotic therapy, while maintaining milk flow by means of a breast pump. If there is any question concerning a specific antibiotic, specific references or specialists should be consulted[114].

## Duration of Therapy

The duration of antibiotic therapy varies according to the type of musculoskeletal infection (cellulitis, erysipelas, septic arthritis, or osteomyelitis in a long bone or a diabetic foot).

*Cellulitis and Erysipelas*

Among the musculoskeletal infections, cellulitis and erysipelas need the shortest duration of antibiotic therapy (ten to fourteen days)[115]. Parenteral therapy can be changed to oral therapy when the patient is clinically stable. Erysipelas has a higher relapse rate, and a longer course of parenteral therapy is usually recommended for this specific soft-tissue infection.

*Septic Arthritis*

Septic arthritis is treated with parenteral antibiotic therapy, usually for two

**TABLE V Gram-Negative Organisms: Initial Choice of Antibiotics for Therapy (Adult Doses)**

| Organism | First Choice of Antibiotics | Alternative Antibiotics |
|---|---|---|
| Acinetobacter species | Ceftazidime (1 g every 8 h) and levofloxacin (500 mg daily) or imipenem (500 mg every 6 h) | Ampicillin-sulbactam |
| Enterobacter species | Cefotaxime (1 g every 6 h) or imipenem (500 mg every 6 h) | Levofloxacin, mezlocillin, or ticarcillin-clavulanate |
| *Escherichia coli* | Ampicillin-sulbactam (3 g every 6 h) | Cefazolin, levofloxacin, gentamicin, or trimethoprim-sulfamethoxazole |
| *Haemophilus influenzae* | Cefotaxime (1 g every 8 h) or ampicillin-sulbactam (3 g every 6 h) | Levofloxacin, trimethoprim-sulfamethoxazole, ampicillin*, or azithromycin |
| Klebsiella species | Cefotaxime (1 g every 6 h) or levofloxacin (500 mg daily) | Ampicillin-sulbactam or gentamicin |
| *Proteus mirabilis* | Ampicillin (1 g every 6 h) or levofloxacin (500 mg daily) | Cefazolin, trimethoprim-sulfamethoxazole or gentamicin |
| *Proteus vulgaris, Proteus rettgeri,* or *Morganella morganii* | Cefotaxime (2 g every 8 h) or imipenem (500 mg every 6 h) or levofloxacin (500 mg daily) | Mezlocillin, gentamicin, or ticarcillin-clavulanate |
| *Neisseria gonorrhoeae* | Ceftriaxone (one intramuscular injection of 125 mg) and azithromycin (one dose of 1 g orally) | Levofloxacin and azithromycin |
| Providencia species | Cefotaxime (2 g given intravenously every 8 h) or levofloxacin (500 mg daily) | Trimethoprim-sulfamethoxazole, amikacin, or imipenem |
| *Pseudomonas aeruginosa* | Cefepime† (2 g every 12 h) or piperacillin† (3 g every 6 h) or imipenem (500 mg every 6 h) | Ticarcillin-clavulanate, tobramycin, amikacin, or ciprofloxacin‡ |
| *Serratia marcescens* | Cefotaxime (2 g every 6 h) | Levofloxacin, gentamicin, or imipenem |

*Should be used for non-β-lactamase-producing strains of *Haemophilus influenzae*. †For a serious infection, cefepime or piperacillin should be used with an aminoglycoside—gentamicin or tobramycin (5 mg/kg/day). ‡Increasing resistance to the quinolones, including ciprofloxacin.

**TABLE VI Anaerobic Organisms: Initial Choice of Antibiotics for Therapy (Adult Doses)**

| Organism | First Choice of Antibiotic | Alternative Antibiotics |
|---|---|---|
| *Bacteroides fragilis* group | Clindamycin (900 mg every 8 h) or metronidazole (500 mg every 8 h) | Ampicillin-sulbactam, ticarcillin-clavulanic acid |
| Prevotella species | Clindamycin (900 mg every 8 h) or metronidazole (500 mg every 8 h) | Ampicillin-sulbactam, cefotetan |
| Peptostreptococcus species | Penicillin G ($2 \times 10^6$ U every 4 h) or clindamycin (900 mg every 8 h) | Clindamycin, metronidazole |
| Clostridium species | Clindamycin (900 mg every 8 h) or penicillin G ($2 \times 10^6$ U every 4 h) | Ampicillin-sulbactam, metronidazole |

to three weeks after aspiration or arthroscopic or open débridement[116,117]. A two-week course can be given when the septic arthritis is caused by organisms that are very susceptible to antibiotic therapy, including *Haemophilus influenzae,* Streptococcus species, and *Neisseria gonorrhoeae*. For the more resistant organisms, including *Staphylococcus aureus* and gram-negative bacilli, three weeks of parenteral antibiotic therapy is usually given.

***Osteomyelitis***

Osteomyelitis is traditionally treated with parenteral antibiotic therapy, usually for four to eight weeks after the last major débridement. Many open-label studies but few randomized studies have justified the current duration of osteomyelitis treatment. The best data on this subject come from animal models. With use of an experimental *Staphylococcus aureus* osteomyelitis model, Norden and Dickens treated groups of animals with cephaloridine for two, four, or six weeks[118]. The longer that the animals were treated with cephaloridine, the better the treatment results. The animal model used in that study is not amenable to surgery; antibiotics alone must eradicate the infection. Parenteral antibiotic therapy has been investigated in eight randomized studies[119-125]. The arrest rates associated with four to eight weeks of parenteral antibiotic therapy in those studies ranged from 50% to 100%. The optimal duration of antibiotic therapy has not been clearly determined.

Streamlining from parenteral to oral therapy may be an effective alternative strategy for the treatment of osteomyelitis. In a historical control study by Swiontkowski et al.[126], ninety-three patients were managed with five to seven days of parenteral therapy followed by six weeks of oral therapy. Treatment was successful in 91% (seventy-nine) of the eighty-seven who were able to be followed. In a randomized study of the treatment of long-bone osteomyelitis, Shirtliff et al.[127] compared four weeks of parenteral antibiotic therapy with two weeks of parenteral therapy followed by four weeks of oral antibiotic therapy. The arrest rate was 84.3% in the group that received parenteral antibiotic therapy and 89.5% in the group managed with parenteral antibiotic therapy followed by oral antibiotic therapy.

The current recommendation for the duration of antibiotic therapy in the treatment of long-bone osteomyelitis is four to six weeks. Children are given two weeks of parenteral therapy followed by four weeks of oral therapy. The traditional treatment for adults is four to six weeks of parenteral therapy. However, many centers use two weeks of parenteral therapy followed by four to six weeks of oral therapy.

***Osteomyelitis in the Diabetic Foot***

The duration of antibiotic treatment of osteomyelitis in the diabetic foot is usually based on the type of surgical therapy[128]. When surgical therapy is not possible or is unacceptable, the patient can be treated with long-term oral antibiotic suppressive therapy. When osteomyelitis is in a bone that is amenable to débridement, the infection may be debrided and four to six weeks of antibiotic therapy should be administered after surgery. When the patient is managed with ablative therapy and the entire bone containing the osteomyelitis is removed, antibiotics are given for two weeks in order to treat any residual soft-tissue infection. When the infected bone is transected, the patient is given four to six weeks of culture-directed antibiotic therapy. Finally, when amputation is performed remote to the site of infection, the patient is treated with a short course of antibiotic therapy, which is usually less than three days. Occasionally, a diabetic patient with osteomyelitis of the foot is treated with long-term oral antibiotic therapy for eradication of the infection. This is possible only for the treatment of osteitis (involvement of the outer cortex of the bone). Eradication of full-thickness osteomyelitis with long-term antibiotic therapy probably is not possible.

NOTE: The authors thank Kristi Overgaard, Melinda Stevens, Donna Milner Mader, JD, and the late Stephen C. Bergquist, MS, for their assistance in the research and preparation of this manuscript.

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

Printed with permission of the American Academy of Orthopaedic Surgeons. This article, as well as other lectures presented at the Academy's Annual Meeting, will be available in March 2002 in *Instructional Course Lectures,* Volume 51. The complete volume can be ordered online at www.aaos.org, or by calling 800-626-6726 (8 A.M.-5 P.M., Central time).

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