Antimicrobial Options in the Treatment of Adult Staphylococcal Bone and Joint Infections in an Era of Drug Shortages

Allison L. Mruk, PharmD; Kenneth E. Record, PharmD, BCPS

Abstract: Staphylococcus aureus is the most pathogenic bacterium and the most common cause of osteomyelitis, affecting 50% to 70% of cases. Many antistaphylococcal agents with varying activity against methicillin-susceptible S aureus and methicillin-resistant S aureus are available in the US market. This article reviews the most common antistaphylococcal agents used in the treatment of bone and joint infections in adult patients and focuses on the antimicrobial agent’s mechanism of action, US Food and Drug Administration–approved indications, place in therapy, monitoring parameters, and common side effects.

In an era where drug shortages are increasing, reliance on alternative treatment regimens are becoming more commonplace. Staphylococcus is a gram-positive bacterium that can cause severe disease in orthopedic patients. Staphylococci have been implicated in osteomyelitis, septic arthritis, and device-related osteoarticular infections. Staphylococcus aureus is the most pathogenic bacterium and most common cause of osteomyelitis, affecting 50% to 70% of cases, whereas coagulase-negative Staphylococcus is more prevalent in prosthetic joint infections.1,2 Successful treatment of bone and joint infections is predicated on 3 principles:

- Surgical debridement and drainage
- Antimicrobial agents with an appropriate spectrum of activity against the offending bacterium
- Longer durations of therapy, necessitating particular attention to dosing adjustments and side-effect profiles (Table)

This article focuses on the antistaphylococcal agents used to treat methicillin-susceptible S aureus (MSSA) and methicillin-resistant S aureus (MRSA). Emphasis is placed on the antimicrobial agents’ mechanism of action, US Food and Drug Administration (FDA)–approved indications, place in therapy, monitoring parameters, and common side effects.

Staphylococcal Resistance

Most Staphylococcus isolates produce beta-lactamase enzymes.3 Beta-lactam antimicrobials (eg, penicillins and cephalosporins) contain a lactam ring that, when hydrolyzed by beta-lactamases, results in the loss of microbiological activity. Methicillin and first-generation cephalosporins were developed to overcome this resistance mechanism.

Methicillin resistance in most MRSA isolates can be traced to the mecA gene, which produces an alternative penicillin-binding protein (PBP-2a). Beta-lactams have low affinity for the PBP-2a binding site, resulting in ineffective microbial activity. The mecA gene is located on a plasmid and is readily transferred to susceptible bacteria.4 In the United States, more than half of S aureus isolates cultured from hospitalized patients are resistant to methicillin (MRSA).5

Vancomycin (a glycopeptide) resistance, although rare, has been identified.5 Vancomycin-intermediate S aureus occurs when the bacteria synthesizes extra peptidoglycan residues. These residues trap vancomycin and prevent it from reaching its binding site.5 Vancomycin-resistant S aureus isolates have also been identified. The mechanism of resistance is derived from the transfer of a plasma-mediated gene (vanA) from enterococcal species to S aureus. This results in an alteration of the
# Table

## Antistaphylococcal Agent Profiles

<table>
<thead>
<tr>
<th>Drug</th>
<th>MSSA</th>
<th>MRSA</th>
<th>Killing Type</th>
<th>Dosing Adjustments</th>
<th>Strength of Evidence</th>
<th>FDA-approved Orthopedic Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-lactam: penicillins⁶⁻⁸</td>
<td></td>
<td></td>
<td>Time</td>
<td>None</td>
<td>&quot; ** &quot;</td>
<td>Osteomyelitis</td>
</tr>
<tr>
<td>Naflcin</td>
<td></td>
<td></td>
<td>Time</td>
<td>None</td>
<td>&quot; ** &quot;</td>
<td>Bone and joint infections</td>
</tr>
<tr>
<td>Beta-lactam: cephalosporins⁶⁻⁷⁻⁹⁻¹⁰</td>
<td></td>
<td></td>
<td>Time</td>
<td>Renal</td>
<td>&quot; ** &quot;</td>
<td>Bone and joint infections; surgical prophylaxis</td>
</tr>
<tr>
<td>First generation: cefazolin</td>
<td></td>
<td></td>
<td>Time</td>
<td>Renal</td>
<td>&quot; ** &quot;</td>
<td>Bone and joint infections</td>
</tr>
<tr>
<td>Third generation: ceftriaxone</td>
<td></td>
<td></td>
<td>Time</td>
<td>None</td>
<td>&quot; ** &quot;</td>
<td>None</td>
</tr>
<tr>
<td>Fifth generation: ceftaroline</td>
<td></td>
<td></td>
<td>Time</td>
<td>Renal</td>
<td>Limited data</td>
<td>None</td>
</tr>
<tr>
<td>Beta-lactam: carbapenems⁶⁻¹¹</td>
<td></td>
<td></td>
<td>Time</td>
<td>Renal</td>
<td>Limited data</td>
<td>Bone and joint infections</td>
</tr>
<tr>
<td>Imipenem/cilastatin</td>
<td></td>
<td></td>
<td>Time</td>
<td>Renal</td>
<td>Limited data</td>
<td>Bone and joint infections</td>
</tr>
<tr>
<td>Licosamides⁶⁻¹²⁻¹⁴</td>
<td></td>
<td></td>
<td>Time</td>
<td>Renal</td>
<td>Limited data</td>
<td>Bone and joint infections</td>
</tr>
<tr>
<td>Clindamycin</td>
<td></td>
<td></td>
<td>Concentration</td>
<td>Renal</td>
<td>&quot; ** &quot;</td>
<td>Unlabeled: antibiotic prophylaxis for surgical procedures</td>
</tr>
<tr>
<td>Quinolones⁶⁻¹⁵⁻¹⁶</td>
<td></td>
<td></td>
<td>Time</td>
<td>Renal</td>
<td>&quot; ** &quot;</td>
<td>Bone and joint infections</td>
</tr>
<tr>
<td>Ciprofloxacin⁶⁻¹⁰</td>
<td></td>
<td></td>
<td>Concentration</td>
<td>Renal</td>
<td>&quot; ** &quot;</td>
<td>Bone and joint infections</td>
</tr>
<tr>
<td>Rifamycins¹⁷²⁻¹⁸⁻¹⁹</td>
<td></td>
<td></td>
<td>Concentration</td>
<td>Hepatic</td>
<td>&quot; ** &quot;</td>
<td>Unlabeled: used in combination to treat staphylococcal infections</td>
</tr>
<tr>
<td>Glycopeptides⁶⁻⁷</td>
<td></td>
<td></td>
<td>Time</td>
<td>Renal</td>
<td>&quot; ** &quot;</td>
<td>Serious or severe MRSA infections</td>
</tr>
<tr>
<td>Vancomycin</td>
<td></td>
<td></td>
<td>Time</td>
<td>Renal</td>
<td>&quot; ** &quot;</td>
<td>Serious or severe MRSA infections</td>
</tr>
<tr>
<td>Lipopeptides⁶⁻¹⁰⁻¹¹</td>
<td></td>
<td></td>
<td>Concentration</td>
<td>Renal</td>
<td>&quot; ** &quot;</td>
<td>Unlabeled: severe MRSA infections</td>
</tr>
<tr>
<td>Daptomycin</td>
<td></td>
<td></td>
<td>Concentration</td>
<td>Renal</td>
<td>&quot; ** &quot;</td>
<td>Unlabeled: severe MRSA infections</td>
</tr>
<tr>
<td>Oxazolidinones⁶⁻¹⁴</td>
<td></td>
<td></td>
<td>Time</td>
<td>None</td>
<td>&quot; ** &quot;</td>
<td>None</td>
</tr>
<tr>
<td>Linezolid</td>
<td></td>
<td></td>
<td>Time</td>
<td>None</td>
<td>&quot; ** &quot;</td>
<td>None</td>
</tr>
<tr>
<td>Sulfonamides⁶⁻¹⁰⁻¹¹⁻¹²⁻¹³⁻¹⁴⁻¹⁵⁻¹⁶⁻¹⁷⁻¹⁸⁻¹⁹⁻²⁰⁻²¹</td>
<td></td>
<td></td>
<td>Concentration</td>
<td>Renal</td>
<td>&quot; ** &quot;</td>
<td>Unlabeled: alternative treatment to MRSA infections</td>
</tr>
<tr>
<td>Miscellaneous agents⁶⁻¹⁰⁻¹¹⁻¹³⁻¹⁴⁻¹⁵⁻¹⁶⁻¹⁷⁻¹⁸⁻¹⁹⁻²⁰⁻²¹</td>
<td></td>
<td></td>
<td>Time</td>
<td>Renal</td>
<td>&quot; ** &quot;</td>
<td>None</td>
</tr>
</tbody>
</table>

Abbreviations: FDA, Food and Drug Administration; MRSA, methicillin-resistant Staphylococcus aureus; MSSA, methicillin-susceptible Staphylococcus aureus.

¹Time- or concentration-dependent killing.
²Evidence based on the availability of 5 categories of data: animal studies, case reports, case series, prospective clinical trial or series, and randomized clinical trial. Each star represents the number of categories where data are available for each antimicrobial agent.
³Activity if erythromycin resistance methylase gene absent.
⁴In community-acquired MRSA infections only.
⁵Use in combination to increase Staphylococcus aureus activity and decrease development of resistance.
⁶Use in combination only.
peptidoglycan layer, causing low affinity of vancomycin to its binding site.5

PHARMACODYNAMICS: ANTIMICROBIAL KILLING CHARACTERISTICS

Antimicrobial agents fall into 2 types of characteristic killing patterns: time and concentration dependent. Time-dependent killing requires that drug concentrations remain above the minimum inhibitory concentration of the individual bacterium over the dosing interval.6 Time-dependent agents are typically dosed more frequently or administered by extended or continuous infusion.

Concentration-dependent killing is characterized by the ratio of drug concentration to minimum inhibitory concentration. As this ratio increases, bacterial killing also increases.6 In addition, concentration-dependent killing agents exhibit a postantibiotic effect.6 When the concentration of the antimicrobial agent falls below the minimum inhibitory concentration, the bacterium does not recover and reenters a log growth pattern. The duration of the postantibiotic effect is approximately 2 to 6 hours and is species- and drug-dependent. This allows higher doses of antimicrobial agents to be administered at longer intervals.6

ANTISTAPHYLOCCAL AGENTS PRIMARILY DIRECTED AGAINST MSSA Penicillins

Penicillins interfere with bacterial cell wall synthesis by binding to PBPs. This disrupts the integrity of the bacterial cell wall, leading to cell death.7 These antimicrobial agents exhibit time-dependent killing, and their spectrum of activity against staphylococcal species is variable. Antistaphylococcal penicillins, such as nafcillin and methicillin, were developed to provide stability against beta-lactamase enzyme degradation. Nafcillin is considered the drug of choice and is approved for the treatment of MSSA osteomyelitis. However, nafcillin is not active against MRSA. Common side effects of the antistaphylococcal penicillins include hypersensitivity reactions, gastrointestinal symptoms, interstitial nephritis, and myoclonic seizures with high doses.8 Hematologic toxicity, such as neutropenia, is rare.8

Cephalosporins

Cephalosporins have a similar mechanism of action as penicillins. They are more stable to beta-lactamase-producing staphylococci.7 Cephalosporins are divided into 5 generations, and each possesses time-dependent killing. The first-generation cephalosporins, such as cephalaxin and cefazolin, have good activity against MSSA and no activity against MRSA. Cefazolin, a parenteral cephalosporin, is the preferred antimicrobial agent used for surgical prophylaxis in patients undergoing orthopedic procedures to decrease infection rates and as an alternative treatment option for bone and joint infections.22,24 As we move through the second and third generations, the spectrum of activity expands to include beta-lactamase-producing gram-negative bacteria and anaerobes at the expense of staphylococcal activity. With once-daily dosing, a third-generation cephalosporin, ceftriaxone, has sufficient evidence to suggest that its efficacy is comparable with nafcillin. The fifth-generation cephalosporin, ceftaroline, is active against MSSA and is the first cephalosporin with MRSA activity.9

In 2010, ceftaroline was approved by the FDA for the treatment of acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia.9 Studies demonstrating that ceftaroline may be a promising therapeutic option for the treatment of MRSA osteomyelitis are currently underway.25 Common side effects of cephalosporin use include hypersensitivity reactions and gastrointestinal symptoms.10 Cross reactivity between the penicillins and cephalosporins is approximately ≤3%.26

Carbapenems

Carbapenems possess the broadest spectrum of activity of all beta-lactams; however, they lack MRSA activity. Imipenem/cilastatin is the only carbapenem with FDA approval for bone and joint infections caused by MSSA. To reduce the selection for resistant bacteria, carbapenems are not commonly used as first-line therapy. Common side effects of carbapenem use include hypersensitivity reactions, gastrointestinal symptoms, and seizures. Seizures are more commonly associated with imipenem/cilastatin compared with other carbapenems.11

Clindamycin

Clindamycin is an anti-staphylococcal agent that inhibits protein synthesis through ribosomal translocation. It demonstrates activity against MSSA and community-acquired MRSA (but not hospital-acquired MRSA). It is available in both intravenous and oral formulations. Clindamycin has good penetration into many tissues, including the bone and synovial fluid.1,18,27 Clindamycin is recommended as an alternative agent for antimicrobial prophylaxis when a patient has a beta-lactam allergy.24 Although not approved by the FDA for treatment of bone and joint infections, some experts suggest that clindamycin may be considered as an alternative agent to nafcillin or cefazolin.2

When interpreting susceptibilities, S aureus becomes resistant to clindamycin via the erythromycin resistance methylase (erm) gene. The microbiology laboratory may report clindamycin as susceptible to S aureus, and it is important to determine whether an additional test was performed to detect the erm gene. A positive test suggests that the erm gene is present and will result in clindamycin resistance and likely treatment failure.12 It has been shown that approximately 68% of MSSA and 12.3% of MRSA isolates
possess the erm gene. The most common side effect of clindamycin is gastrointestinal symptoms, specifically diarrhea. Of note, clindamycin was the first drug identified to cause *Clostridium difficile* diarrhea and colitis; however, this risk traverses all antimicrobial agents.

**Fluoroquinolones**

As antistaphylococcal agents, fluoroquinolones inhibit bacterial topoisomerases II and IV, leading to DNA breakage and bacterium death. They exhibit concentration-dependent killing and a significant postantibiotic effect. Ciprofloxacin is the only fluoroquinolone approved by the FDA for bone and joint infections and contains the most data on bone penetration compared with other fluoroquinolones. Ciprofloxacin has been used in combination with rifampin for synergy to prevent the development of resistance in prosthetic implant-related staphylococcal infections. Other fluoroquinolones, such as levofloxacin, ofloxacin, moxifloxacin, and gemifloxacin, have varying activity against MSSA and MRSA and may be useful alternative agents. Combination therapy should be used due to reports of increased resistance of *S. aureus* to the fluoroquinolones, which has limited their use as monotherapy.

A study involving 17 US hospitals demonstrated a strong correlation between prior fluoroquinolone use and the prevalence of MRSA. Common side effects of fluoroquinolones include rashes, gastrointestinal symptoms, photosensitivity, and headaches. Also, fluoroquinolones have the potential to cause QT prolongation and tendonitis with tendon rupture. Rifampin

As an unlabeled FDA indication, rifampin can be used as adjunctive therapy for the treatment of staphylococcal infections. To prevent the development of resistance, rifampin should never be used as monotherapy. Typically, it is used to treat staphylococcal osteomyelitis with orthopedic hardware-related infections. Rifampin exhibits activity against bacteria that adhere to prosthetic material in addition to penetrating biofilms. Rifampin also has many side effects, including anaphylaxis, thrombocytopenia, leukopenia, granulocytopenia, gastrointestinal symptoms, and discoloration of bodily fluids to a red-brown color.

**Antistaphylococcal Agents Primarily Directed Against MRSA Vancomycin**

Vancomycin is widely considered the drug of choice for MRSA infections. It is a glycopeptide antimicrobial agent that inhibits peptidoglycan cross linking, which impairs cell wall synthesis. Its activity is primarily directed at gram-positive bacteria and exhibits time-dependent killing. Vancomycin is an option for antimicrobial prophylaxis in orthopedic surgeries if a patient has a beta-lactam allergy or a MRSA infection; however, its use is discouraged for prophylaxis.

For treatment, vancomycin has poor bone penetration and, therefore, has been shown to achieve low cure rates in osteomyelitis compared with beta-lactams. Systemic infections should be treated with intravenous therapy only because oral vancomycin is minimally absorbed from the gastrointestinal tract.

Vancomycin dosing should be individualized, and serum concentrations should be monitored throughout therapy, especially in those with unstable renal function. The recommended vancomycin trough concentration should range between 15 and 20 mg/L in bone and joint infections. The most common side effect of vancomycin is an infusion-related reaction (red-man syndrome) that can usually be overcome by increasing the infusion duration. Ototoxicity and nephrotoxicity are sometimes problematic when vancomycin is combined with aminoglycosides and may be of concern when higher doses are used in bone and joint infections.

**Daptomycin**

Daptomycin activity is primarily targeted at gram-positive bacteria. Daptomycin is a lipopeptide only suitable for intravenous administration that disturbs the bacterial membrane potential via calcium-dependent binding. It exhibits concentration-dependent killing and has a postantibiotic effect against *S. aureus*. It is FDA approved for complicated skin and skin structure infections but not for bone and joint infections or osteomyelitis. However, case reports and series of patients treated with daptomycin have shown cure rates of approximately 65% to 75%, and it has been shown to be an efficacious antimicrobial agent for the treatment of osteomyelitis caused by gram-positive bacteria. Commonly, daptomycin is used as salvage
therapy after vancomycin failure in bone and joint infections.\textsuperscript{37} The most important side effects associated with daptomycin use are musculoskeletal toxicities manifested by myalgias and myopathies, which are correlated with drug frequency and not total dose.\textsuperscript{35} Other side effects that may affect patient adherence to drug therapy include peripheral neuropathies and gastrointestinal symptoms.

**Linezolid**

Linezolid is an oxazolidinone antimicrobial agent, available intravenously and orally, that binds to the 23S ribosomal RNA of 50S subunit, preventing ribosomal protein synthesis.\textsuperscript{14} It exhibits activity against staphylococci (MSSA and MRSA) and has 100\% oral bioavailability. Although not FDA approved for bone and joint infections, it may be an alternative oral therapy to intravenous antimicrobial therapy in osteomyelitis.\textsuperscript{38} Currently, no cross resistance is found to other antimicrobial agents, and linezolid resistance is rare.\textsuperscript{39}

In March 2007, the FDA released safety concerns demonstrated in an open-laboratory, randomized trial showing that patients with cather-related bloodstream infections caused by both gram-positive and gram-negative pathogens, gram-negative pathogens alone, or those without an infection when they were enrolled had an increased risk of mortality. No mortality difference was seen in patients with only gram-positive infections treated with linezolid.\textsuperscript{20}

The most important side effect of linezolid is thrombocytopenia, which typically occurs approximately 14 days into therapy.\textsuperscript{1} In addition, linezolid has monoamine oxidase inhibitor activity, which can interact with serotonergic psychiatric drugs, such as selective serotonin reuptake inhibitors, increasing the risk of serotonin syndrome.\textsuperscript{14}

**Sulfamethoxazole/Trimethoprim**

Sulfamethoxazole/trimethoprim inhibits folate synthesis.\textsuperscript{15,19} In combination, it exhibits better activity against MSSA and MRSA compared with sulfonamide alone.\textsuperscript{15} It has been shown to be effective against MSSA bone and joint infections.\textsuperscript{18} It is not FDA approved for the treatment of orthopedic infections; however, it is mentioned here due to its use as long-term oral suppressive therapy in which debridement or device removal is not advised.\textsuperscript{18} Prior to initiation, patients should be screened for G6PD deficiency to minimize the risk of hemolytic anemia. Other side effects include gastrointestinal symptoms, hyperkalemia, headache, thrombocytopenia, and hypersensitivity reactions (including Stevens-Johnson syndrome).\textsuperscript{20}

**Tigecycline**

Tigecycline is an intravenous glycyclline that binds to the 30S ribosomal subunit, inhibiting bacterial protein synthesis. As a derivative of minocycline, tigecycline exhibits time-dependent killing against MSSA and MRSA.\textsuperscript{14,19} Tigecycline does not have an FDA indication for MRSA bone and joint infections. This antimicrobial agent reaches high concentrations in the tissues but not in the serum. Case reports have demonstrated tigecycline use in osteomyelitis; however, insufficient data exist to determine its place in therapy.\textsuperscript{41} The most common side effects of tigecycline are nausea and occasional vomiting.\textsuperscript{14}

**Quinupristin/Dalfopristin**

Quinupristin/dalfopristin is a combination of 2 streptogramin antibiotics that inhibit protein synthesis and exhibit time-dependent killing against MSSA and MRSA.\textsuperscript{2,18} As an intravenous drug, limited data are available regarding its use in bone and joint infections.\textsuperscript{41} Common toxicities include infusion-related effects, arthralgias, and myalgias.\textsuperscript{14,19} 

**REFERENCES**

2. Que Y, Moreillon P. Staphylococcus aureus (in-

---

**The Bottom Line**

- There is an increased prevalence of MRSA infections in hospitalized patients.
- Surgical debridement and drainage is the mainstay for the treatment of bone and joint infections.
- The best predictor of a successful outcome is selection of an antimicrobial regimen that is effective against the offending bacterium.
- Longer durations of therapy are required for adequate treatment of MRSA bone and joint infections; therefore, particular attention to the antimicrobial agent’s spectrum of activity, dosing adjustments, and side effects is necessary.


