These are interesting times in the treatment of infections caused by *Staphylococcus aureus*, with shifting epidemiology of antibiotic resistance; changing prevalence of clinical syndromes (probably reflecting changes in virulence of circulating strains); and the recent availability of a variety of new agents with activity against multidrug-resistant gram-positive cocci. In the wake of the well-documented explosion in methicillin resistance in *S aureus*, one can confidently predict more limited use for currently approved β-lactam drugs for the treatment of *S aureus* infections, although several investigational β-lactams have clinically useful activity against methicillin-resistant *S aureus* (MRSA). Despite initial reports showing general susceptibility to non-β-lactam drugs (with the exception of erythromycin), it has become increasingly apparent that at least some community-associated MRSA (CA-MRSA) have become multidrug resistant and this trend is almost certain to continue as these clones cause more infections and are exposed to more courses of various non-β-lactam drugs.1

After 40 years of vancomycin use for treatment of MRSA infections and for methicillin-susceptible *S aureus* (MSSA) in β-lactam–allergic patients, there is gathering evidence hinting at reduced efficacy of that drug. Clearly, there are isolated reports of vancomycin-resistant *S aureus* (VRSA) and vancomycin-intermediate *S aureus* (VISA), but some experts have begun to debate the efficacy of vancomycin even against isolates that test susceptible to vancomycin using the updated Clinical and Laboratory Standards Institute (CLSI) breakpoint for susceptibility of 2 µg/mL.2–4

The magnitude of this evidence has perhaps been amplified by the efforts of pharmaceutical companies to position newer Food and Drug Administration (FDA)–approved and premarket branded agents. However, it is impossible to ignore reports of rising vancomycin minimum inhibitory concentrations (MICs), despite the fact that this has not been a universal finding,5,6 and the effect that higher vancomycin MICs within the susceptible range seem to have on treatment outcomes in some retrospective

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**KEYWORDS**

- *Staphylococcus aureus*
- β-Lactam drugs
- Methicillin-resistant *S aureus*
- Vancomycin-intermediate *S aureus*
One prospective observational study, not to mention the observations of increased vancomycin toxicity at currently used higher trough concentrations. The abundance of riches in new drugs for the multidrug-resistant gram-positive space is timely, and these agents show great potential, but as yet have incompletely tested durability and comparative efficacy. This article reviews the advantages and disadvantages of the variety of antistaphylococcal agents by providing basic information including mechanism of action; mechanisms of resistance; clinical use (including dosing for and data supporting common indications); drug toxicities; and major drug interactions.

β-LACTAMS

The family of β-lactam antibiotics is a large and diverse group of drugs that have variable degrees of activity against \textit{S. aureus}. A detailed review of these agents is encyclopedic and beyond the scope of this article, but can be found in various standard texts. Thus, we will limit our consideration to agents that are currently available in the United States, focusing on common themes, common usage of these drugs for staphylococcal infection, and notable exceptions. β-lactams act by binding to so-called “penicillin-binding proteins,” which are proteins involved in cell-wall synthesis. These drugs are typically bactericidal against susceptible staphylococci in a time-dependent manner. Resistance to β-lactam drugs in \textit{S. aureus} is mediated by two major mechanisms. The first is a highly prevalent narrow-spectrum β-lactamase that confers resistance to penicillins exclusive of the penicillinase-resistant penicillins dicloxacillin, oxacillin, and nafcillin. Most cephalosporins and the carbapenems are not greatly hydrolyzed by this enzyme, and β-lactamase inhibitors can protect otherwise vulnerable penicillins. The other major mechanism of resistance is the presence of the penicillin-binding protein PBP2a, mediated by the \textit{mecA} gene that confers resistance to all currently FDA-approved β-lactams creating the MRSA phenotype.

The adverse drug reactions caused by β-lactams include a number of class effects that occur to varying degrees after exposure to these agents and several effects that are particularly prominent with specific agents. The former can include various hypersensitivity reactions ranging from urticaria to allergic interstitial nephritis to anaphylaxis; rash; drug fever; serum sickness; gastrointestinal toxicity (particularly, although not exclusively, with oral formulations); hematologic toxicity; and seizures (relatively rare). Most β-lactams have relatively limited drug interactions, eg, most increase the anticoagulant effects of warfarin; whereas others (antistaphylococcal penicillins) actually reduce this effect and so interactions should always be reviewed for specific agents.

Penicillins

Most \textit{S. aureus} isolates produce a narrow-spectrum β-lactamase that inactivates penicillins (other than nafcillin, oxacillin, and dicloxacillin). The current prevalence of β-lactamase–producing \textit{S. aureus} is difficult to assess because the substrate drugs are not typically tested in large surveys; however, 72.5% of 690 community-acquired lower respiratory tract isolates of \textit{S. aureus} from Europe and the United States from 1992 to 1993 produced β-lactamase. This is much greater susceptibility than is seen in the authors’ center currently, where 99% of all \textit{S. aureus} isolates tested were resistant to penicillin. Against the relatively rare penicillin-susceptible \textit{S. aureus}, penicillin (or ampicillin or amoxicillin) may be used for treatment of infections. Because most MSSA isolates are resistant to penicillin (and ampicillin, amoxicillin, piperaclillin, and ticarcillin), the penicillinase-resistant penicillins, nafcillin, oxacillin, and dicloxacillin are
typically used and are the mainstay of treatment. The MICs of these drugs for penicillinase-positive and -negative MSSA are typically 0.25 to 0.4 μg/mL.11 Oxacillin and nafcillin are the most frequently used parenteral drugs in this group, and dicloxacillin is the major oral formulation. Nafcillin and oxacillin are typically dosed at 1 to 2 g every 4–6 hours depending on the severity of the infection. Dicloxacillin is given at 250 or 500 mg four times a day.11,13 These drugs are primarily metabolized by the liver, so dose adjustments are not made for reduced renal function. Because of their hepatic metabolism, these drugs may interact with other medications metabolized by the liver (eg, the known interaction between warfarin and nafcillin or dicloxacillin that may result in larger warfarin doses to maintain a desirable international normalized ratio).16,18 In addition to the standard penicillin class adverse drug reactions, these drugs may cause elevations of liver enzymes, perhaps oxacillin to a greater extent than nafcillin,19 and it is prudent to follow liver enzymes in patients on high doses of these agents. Also, these drugs may cause other significant reactions including neutropenia, allergic interstitial nephritis, hypokalemia, and tissue necrosis from extravasation.11,13,20 These drugs are the drugs of choice for treating serious infections caused by MSSA, and as such are recommended in guidelines for treatment for endocarditis, community-acquired pneumonia, and meningitis caused by MSSA,21–23 in addition to their standard use in the treatment of skin and soft tissue infections (SSTI) and osteomyelitis. Because of their status as standard-of-care treatment, these agents are often used as the control arm in clinical trials of newer drugs; their relative efficacy against those agents is discussed further in later sections.24–30

**β-Lactam–β-Lactamase Inhibitor Combinations**

The β-lactam–β-lactamase inhibitor combinations (amoxicillin-clavulanate, only available in oral formulation in the United States; ticarcillin-clavulanate [IV]; ampicillin-sulbactam [IV]; and piperacillin-tazobactam [IV]) all have good activity against MSSA, but not MRSA, and are active against anaerobes and gram-negative bacilli to varying degrees, making them appropriate choices for the treatment of polymicrobial infections including MSSA, such as complicated SSTI.12 For example, in a randomized, double-blinded trial, outcomes of treatment of limb-threatening diabetic foot infections were similar with ampicillin-sulbactam and imipenem-cilastatin.31

**Cephalosporins**

Cephalosporins are among the most frequently prescribed antibiotic medications and have a long record of efficacy and relative safety. They possess the typical β-lactam class adverse drug reactions. Cephalosporins are generally grouped into so-called “generations” based on antimicrobial spectrum of activity.10 The first-generation drugs include the parenteral agent cefazolin (typically dosed at 1 g every 8 hours, but as much as 1.5 g every 6 hours can be used) and the oral drug cephalixin (typically dosed at 500 mg four times a day).10,13 These drugs have good activity against MSSA (MIC that inhibits 90% of isolates tested [MIC$_{90}$] of 2–4 μg/mL) and Streptococcus pyogenes, but only limited activity against gram-negative bacilli. Some second-generation drugs, such as cefuroxime, maintain good antistaphylococcal activity (MIC$_{90}$ of 2 μg/mL) with somewhat greater gram-negative activity. The MICs of the cephemycins, however, such as cefetetan and cefoxitin (also grouped in the second generation), versus MSSA are higher (MIC$_{90}$ of 8–16 μg/mL). The third-generation drugs have even broader gram-negative spectrum and several are active against MSSA. The notable exceptions (ie, drugs lacking clinically useful activity against MSSA) include the antipseudomonal cephalosporin ceftazidime and the oral third-generation drugs cefixime and ceftibuten. The more recently developed fourth-generation drug
Cefepime has very broad gram-negative activity and maintains clinically useful activity against MSSA with MIC\(_{90}\) of 4.\(^{10}\)

The first-generation cephalosporins are drugs of choice for the treatment of MSSA infections in patients who are unable to tolerate antistaphylococcal penicillins. In the absence of a severe penicillin allergy, such as anaphylaxis (because of concerns for cross-reactivity), they are favored over use of vancomycin in this setting.

**Carbapenems**

Carbapenems are broad-spectrum β-lactam antibiotics with activity against anaerobes, gram-negative bacteria, and gram-positive bacteria, including MSSA. As a class, currently approved carbapenems lack clinically useful activity against MRSA. In the United States, carbapenems available for clinical use include imipenem, meropenem, ertapenem, and doripenem. Side effects associated with this class are essentially similar between these agents and are similar to those seen among other β-lactams, with the exception that seizures seem to be more associated with imipenem than the other carbapenems.\(^{12}\) In vitro data reveal that imipenem and doripenem have slightly greater activity against MSSA than either meropenem or ertapenem, as assessed by the MIC\(_{90}\).\(^{32}\) As a class they have been shown to be effective against *S. aureus* in numerous clinical studies.\(^{33–39}\)

Imipenem has the broadest spectrum of FDA approval for the treatment of *S. aureus* infections, including lower respiratory tract, urinary tract, intra-abdominal, gynecologic, orthopedic, and SSTI, in addition to endocarditis, bacterial septicemia caused by penicillinase-producing MSSA, and polymicrobial infections that include non–penicillinase-producing *S. aureus* (ie, penicillin-susceptible).\(^{40}\) Meropenem is approved by the FDA for the treatment of complicated SSTI caused by *S. aureus* (MSSA).\(^{41}\) Ertapenem has been approved for the treatment of MSSA-related complicated SSTI, including diabetic foot infections (excluding osteomyelitis).\(^{42}\) Although doripenem demonstrates in vitro against MSSA and has been approved by the FDA for the treatment of complicated intra-abdominal infections and complicated urinary tract infections, it has not been specifically approved for the treatment of *S. aureus* infections.\(^{43}\)

Given their broad-spectrum of activity, the carbapenems may be most appropriate in settings that require broad, empiric therapy that includes MSSA coverage or when treating a polymicrobial infection that includes MSSA. If culture data subsequently reveal a monomicrobial MSSA infection, narrowing the antibiotic spectrum may be prudent to prevent the selection of antibiotic-resistant bacteria.

**Monobactams**

The monobactam drug aztreonam is a parenteral agent with activity against aerobic gram-negative bacilli, but lacks clinically relevant activity against *S. aureus*.\(^{12}\)

**VANCOMYCIN**

Vancomycin is a glycopeptide antibiotic derived from the actinomycete *Streptomyces orientalis* and was first approved by the FDA for clinical use in 1958.\(^{44}\) It is not absorbed from the gastrointestinal tract in clinically relevant concentrations, and so it must be used as a parenteral agent for systemic infections. For adult patients with normal renal function, vancomycin is typically dosed at 30 mg/kg in divided doses, typically 1 g every 12 hours or 500 mg every 6 hours, but must be adjusted for reduced renal function. Although the pharmacokinetics of the drug are fairly predictable for many patients and despite the evidence that serum concentrations are not well-correlated to clinical outcomes, the testing of trough levels is advisable for patients.
receiving concurrent treatment with a nephrotoxic drug; those with rapidly changing renal function; patients undergoing hemodialysis or continuous venovenous hemofiltration; and patients who are morbidly obese, have severe burns, or have an infection where maintaining adequate therapeutic levels might be particularly critical, such as endocarditis, osteomyelitis, pneumonia, or meningitis. There is also some evidence from in vitro studies that exposure to subtherapeutic concentrations may tend to select for reduced susceptibility to vancomycin.\textsuperscript{45,46} Testing of peak serum vancomycin concentrations is rarely required, but may be reasonable for patients receiving unusually high doses (>2–3 g/d) or being maintained with high trough concentrations (>25 \(\mu\)g/mL) of vancomycin. It is generally viewed as a slowly bactericidal drug against \textit{S aureus} with time-dependent killing and acts by binding to the terminus of the peptidoglycan precursor, the building block for the bacterial cell wall.\textsuperscript{47,48} In most large series, most \textit{S aureus} isolates are inhibited by 1 \(\mu\)g/mL of vancomycin (roughly 94\% in almost 30,000 \textit{S aureus} isolates from the SENTRY database).\textsuperscript{5} In vitro resistance to vancomycin in clinical isolates of staphylococci was unknown until 1996 when the first of what is currently referred to as VISA (MIC of vancomycin 4–8 \(\mu\)g/mL) was reported from a pediatric patient in Japan.\textsuperscript{49} The mechanism of this resistance seems to be the development of a thickened abnormal cell wall that essentially traps vancomycin by providing an excess of target molecules.\textsuperscript{50,51} Isolates with this mechanism remain uncommon,\textsuperscript{5,52} but because of the limitations in current antimicrobial susceptibility testing methods and perhaps geographic differences, the prevalence of isolates with heterogeneous reduced susceptibility to vancomycin (hVISA) is much less certain and possibly significantly higher.\textsuperscript{53,54} This is concerning because the current understanding is that under selective pressure from vancomycin, a series of sequential mutations are selected for as an organism transitions from full susceptibility to hVISA to VISA.\textsuperscript{51} More recently, there have been isolated reports of fully VRSA (MIC of vancomycin \(\geq 16 \mu\)g/mL) from the United States, but these remain quite rare.\textsuperscript{55} The mechanism in these cases seems to be the transfer of the vancomycin resistance gene cluster from vancomycin-resistant enterococci into \textit{S aureus}.\textsuperscript{56}

The toxicities associated with vancomycin are well known, but may have been overestimated historically because of impurities of early preparations of the drug.\textsuperscript{44} Phlebitis is a relatively common adverse reaction, and a variety of hypersensitivity reactions including rash may occur in a small number of patients. These must be distinguished from the “red-man syndrome” and hypotension, which have typically been associated with rapid infusion of the drug and do not represent true drug allergies.\textsuperscript{57} These infusion-related events can often be avoided by using a slower vancomycin infusion. The frequency of these events may be higher in uninfected patients receiving vancomycin (eg, receiving vancomycin for surgical prophylaxis) than in infected patients.\textsuperscript{58,59} Nephrotoxicity is often attributed to vancomycin, but is relatively uncommon in clinical use unless the drug is used at high trough levels (eg, \(>15 \mu\)g/mL) or combined with other nephrotoxic agents, such as aminoglycosides.\textsuperscript{9,60} This synergistic nephrotoxicity is also vancomycin’s most significant drug interaction.\textsuperscript{9,60} Ototoxicity, historically associated with vancomycin, is actually uncommon.\textsuperscript{44}

Vancomycin remains the standard treatment for serious MRSA infections and serious MSSA infections in patients with \(\beta\)-lactam allergies. Its label notes the effectiveness of vancomycin in the treatment of staphylococcal endocarditis and other indications including septicemia, bone infections, lower respiratory tract infections, and skin and skin structure infections.\textsuperscript{61} For treatment of \textit{S aureus} endocarditis, vancomycin has been noted to produce a relatively slow clinical response. In a study of vancomycin (with and without rifampin) treatment of \textit{S aureus} endocarditis predominated by right-sided endocarditis cases, the median duration of fever and bacteremia
were 7 and 9 days, respectively. The efficacy of vancomycin (when combined with an aminoglycoside) was not statistically inferior to daptomycin in a recent clinical trial of S aureus bacteremia and endocarditis. In the current version of the American Heart Association endocarditis treatment guidelines (endorsed by the Infectious Diseases Society of America), vancomycin remains the recommended treatment for native (6 weeks) and prosthetic valve endocarditis (PVE; at least 6 weeks) caused by MRSA and for MSSA infections in patients with anaphylactic reactions to β-lactams.

For the native-valve endocarditis, the potential benefit (likely nominal) of 3 to 5 days of an aminoglycoside must be balanced with the risk of synergistic nephrotoxicity, whereas for PVE vancomycin is typically combined with 2 weeks of treatment with an aminoglycoside and a full 6 weeks or more of rifampin. Whereas the American Heart Association guideline suggests trough vancomycin concentration of 10 to 15 μg/mL and a peak concentration of 30 to 40 μg/mL, some expert opinion suggests higher trough concentrations (15–20 μg/mL) and less attention to peak concentrations unless the daily dose of vancomycin exceeds 2 g. A nonrandomized study of patients with MSSA bacteremia requiring hemodialysis found that the group treated with vancomycin (typically using a loading dose of vancomycin of 15 mg/kg followed by 500 mg after each dialysis session with a resulting median serum concentration of 14 μg/mL) failed treatment more often (31% versus 13%) than those treated with cefazolin (dosed at 2–3 g after each session of hemodialysis). In vitro, it has been reported that β-lactams kill more rapidly than vancomycin. The study by Stryjewski and colleagues adds further support to a bit of staphylococcal treatment dogma: the concept that because of superior efficacy MSSA infections should be treated with β-lactams, not vancomycin, whenever possible. Additional clinical evidence in this regard was found in a retrospective study of S aureus bacteremias compiled by Chang and colleagues that found that receipt of vancomycin (versus nafcillin) was associated with a higher rate of persistent bacteremia and relapse.

For the treatment of staphylococcal pneumonia, often hospital-acquired MRSA and often ventilator-associated, vancomycin remains one of the drugs of choice, as noted in the American Thoracic Society and the Infectious Diseases Society of America guidelines for the management of adults with hospital-acquired, ventilator-associated, and health care–associated pneumonia. Those guidelines suggest a trough concentration of vancomycin of 15 to 20 μg/mL for the treatment of hospital-acquired pneumonia and ventilator-associated pneumonia based on poor outcomes of treatment of S aureus pneumonias and pharmacokinetic modeling. Vancomycin achieves lower epithelial-lining fluid concentrations than linezolid and there has been considerable discussion of the results of a post hoc subset analysis of patients with MRSA from two clinical trials that suggested linezolid was superior to vancomycin for the treatment of hospital-acquired pneumonia. Although biologically plausible, this purported superiority has yet to be demonstrated in a prospective fashion (see the section on linezolid for additional details). Vancomycin remains the standard of care for treatment of SSTI (caused by MSSA in patients with severe hypersensitivity to β-lactams and for MRSA) requiring parenteral therapy and has often been used as the standard treatment arm for many clinical trials testing new drugs for the treatment of complicated SSTI. Cure rates in clinical trials including more than 5000 patients with MRSA infections ranged from 69% to 90%, as summarized by Stryjewski and Chambers, and in no blinded study did the new agent show statistically superior efficacy to vancomycin. Vancomycin is often recommended as a standard treatment for osteomyelitis caused by MRSA or MSSA in β-lactam–intolerant patients, but there are only limited clinical data to...
support this common practice. Vancomycin is recommended for treatment of cases of *S. aureus* meningitis (MRSA or in the presence of β-lactam allergy), but achieves relatively low concentrations in the central nervous system (better for inflamed than noninflamed meninges) prompting some recommendations for using higher than standard dosing (30–45 mg/kg) and consideration of the addition of rifampin for methicillin-resistant staphylococcal meningitis, particularly in the setting of a cerebrospinal fluid shunt infection.

Vancomycin remains a drug of choice for the treatment of serious MRSA infections or MSSA infections in patients with severe β-lactam allergy. It is a slowly bactericidal drug and has been shown to produce a similarly slow response in the treatment of some staphylococcal infections. Because of poor penetration into epithelial lining fluid, vancomycin may ultimately be supplanted by successor drugs for the treatment of MRSA pneumonia, but conclusive clinical trials are still pending. Concerns have arisen regarding possible deterioration in efficacy in recent years, but most clinical trials have not demonstrated superiority of newer agents.

**Daptomycin**

Daptomycin is a cyclic lipopeptide antibiotic derived from *Streptomyces roseosporus*. It achieves bactericidal activity against gram-positive bacteria by inserting into cell membranes and causing membrane depolarization. It has an MIC₉₀ of 0.5 μg/mL for both MSSA and MRSA. Daptomycin has been approved in the United States for use in the treatment of adults with complicated SSTI caused by gram-positive pathogens including *S. aureus* (methicillin susceptible and resistant) at a dose of 4 mg/kg intravenously once daily by and *S. aureus* bacteremia and right-sided endocarditis at a dose of 6 mg/kg once daily by the intravenous route. Dosing should be adjusted for renal function. In addition, there are no currently established dosing regimens for populations under the age of 18.

Daptomycin has been compared with β-lactam and vancomycin in several clinical studies. For the treatment of complicated SSTI, pooled data from two prospective, randomized, controlled trials comparing daptomycin with either vancomycin or a penicillinase-resistant penicillin revealed that among 761 microbiologically evaluable patients cure rates for daptomycin were equivalent to the comparator drugs for both MSSA (85.9% and 87%, respectively) and MRSA infections (75% and 69.4%, respectively).

Another prospective, randomized, controlled study evaluated the treatment of *S. aureus* bacteremia (including right-sided endocarditis) with daptomycin versus the combination of low-dose gentamicin plus either vancomycin or an antistaphylococcal penicillin. The modified intention-to-treat analysis consisted of 120 patients in the daptomycin-treated arm and 115 patients in the comparator arm. In this analysis, daptomycin was noninferior to the comparator regimen at the 6-week posttreatment test-of-cure assessment, with a successful outcome achieved in 44.2% of patients in the daptomycin versus 41.7% in the comparator group. Success in the MITT group was defined as those patients with documented clinical improvement who did not suffer treatment-limiting adverse events; did not receive additional, potentially active non-study antibiotics; did not prematurely discontinue the study medication; and had documented negative posttreatment blood cultures. When considering only those patients that failed therapy because of lack of clinical efficacy of the treatment, success rates were 70% (daptomycin recipients) and 68.7% (comparator recipients). MRSA accounted for about 38% of isolates in both arms of the study, and whereas time to clearance of bacteremia was greater for MRSA infections (8–9 days) versus MSSA...
infections (3–4 days), the times to clearance did not differ between daptomycin and the comparator agents. Adverse events that occurred significantly more often in the daptomycin-treated patients included creatinine kinase elevation and bacteremia, whereas peripheral neuropathy, arthralgias, nausea, bronchospasms, and renal insufficiency were significantly less common in the daptomycin-treated patients when compared with patients receiving either vancomycin or an antistaphylococcal penicillin plus gentamicin.28

A post-hoc analysis of the bacteremia study was conducted to assess the efficacy of daptomycin for the treatment of osteoarticular infections (septic arthritis or osteomyelitis) Thirty-two cases of osteoarticular infections were identified among the enrolled patients with complicated S aureus bacteremia (21 receiving daptomycin, 7 receiving antistaphylococcal penicillin, 4 receiving vancomycin). At the posttreatment follow-up visit, a clinically successful outcome was achieved in 67% and 55% of patients in the daptomycin and comparator groups, respectively. The authors acknowledged, however, that the small numbers of patients with osteoarticular infections limited their ability to assess for significant differences between the two treatment groups.29

Following the exclusion of patients who received any other effective antibiotic therapy before study enrollment, pooled data from two clinical trials comparing daptomycin (dosed at 4 mg/kg/d) with ceftriaxone (given 2 g/d) for the treatment of community-acquired pneumonia revealed that daptomycin was associated with significantly worse overall clinical outcome compared with ceftriaxone.79 Furthermore, eradication rates of S aureus were lower for patients receiving daptomycin (69.2%) compared with ceftriaxone (90.5%) and this difference approached statistical significance. The lack of efficacy of daptomycin for the treatment of bronchoalveolar pneumonia has been attributed to surfactant-mediated inhibition of daptomycin.80

Of note, early studies investigating the emergence of daptomycin resistance indicated a spontaneous mutation frequency of less than 10−10 for S aureus.81 Subsequently, there have been reports of clinical failures of daptomycin therapy for the treatment of S aureus infections with the associated emergence of daptomycin nonsusceptible S aureus.82,83 In the previously mentioned study evaluating the efficacy of daptomycin for the treatment of S aureus bacteremia, daptomycin nonsusceptible S aureus isolates emerged in 6 of the 19 patients who had microbiologic failure while receiving daptomycin therapy.28 The authors noted that most cases of microbiologic failure occurred in settings of inadequate surgical debridement of deep-seated infections. In addition to these findings, other investigators have shown a positive in vitro correlation between reduced daptomycin susceptibility and vancomycin-intermediate susceptibility among S aureus that is independent of prior daptomycin exposure.84,85

Pharmacy acquisition costs should never be the sole determinant of antibiotic selection and must be balanced by considerations of efficacy, toxicity, drug interactions, drug allergies, and so forth. It is notable, however, that the average weighted price of a 500-mg vial of daptomycin, the daily dose at the 6 mg/kg dose for a 83-kg patient, is $232.09 versus the daily cost of $34.24 for 2 g (about 24 mg/kg) of vancomycin.86

Daptomycin is a bactericidal agent with potent in vitro activity against S aureus (MSSA and MRSA) and has been shown to be noninferior to β-lactams and vancomycin in clinical trials of SSTI and bacteremia. Clinicians should be aware of the lack of efficacy in treating bronchoalveolar pneumonia. Development of daptomycin nonsusceptible S aureus during treatment, although rare, has been documented, particularly in the setting of deep-seated S aureus infections that require surgical
debridement in addition to antibiotic therapy. Finally, given that cross-resistance to daptomycin has been noted in VISA, clinicians should confirm daptomycin susceptibility before switching to this agent in patients failing vancomycin therapy for S. aureus infections.

LINEZOLID

Approved in 2000, linezolid was the second of the newer generation of agents (following quinupristin-dalfopristin in 1998) with antimicrobial activity against resistant gram-positive pathogens, and the first new drug in 50 years with an FDA-approved indication for treatment of infections caused by MRSA. Linezolid is an oxazolidinone and the only approved agent in this class. Although there are and have been a number of oxazolidinones in development, to date none have progressed to late-stage clinical trials. These drugs act by binding to the bacterial ribosome, inhibiting protein synthesis. They are generally considered bacteriostatic against staphylococci using the standing definition of a 3-log kill in 24 hours. Initially, it was thought that cross-resistance to linezolid was not conferred by mechanisms of resistance against agents acting on the ribosome; however, the more recently described typically plasmid-mediated ribosomal methyltransferase encoded by *cfr* does confer cross-resistance to linezolid, chloramphenicol, lincosamides, streptogramin A, and pleuromutins. Despite 8 years of rapidly escalating use of linezolid, resistance to this drug among staphylococci remains distinctly uncommon, with a recent survey of United States isolates showing nonsusceptibility (MIC > 4) in fewer than 0.1% of *S. aureus* isolates and 1.6% of coagulate-negative staphylococci, and only 0.5% of coagulate-negative staphylococci and no *S. aureus* isolates in a recent survey of non–United States isolates. There have been a number of reports of linezolid resistance in *S. aureus* and coagulate-negative staphylococci at individual centers, and some evidence of clonal clusters of linezolid-resistant coagulate-negative staphylococci isolates, so susceptibility should never be assumed.

A major advantage of linezolid is that it has excellent, nearly 100% absorption from the gastrointestinal tract. It also has an IV formulation. It can be dosed twice daily because of a half-life of approximately 5 hours without regard for renal function, but because it is a dialyzable drug (about one third of the drug is removed by a standard high-flux hemodialysis session), it should be dosed after hemodialysis. Standard dosing is 600 mg every 12 hours (IV and by mouth). A 400-mg dose was approved for uncomplicated skin infections, but it has not been manufactured in the United States. Pediatric dosing is 10 mg/kg every 8 hours for children up to 11 years of age, and adult dosing for children 12 years of age and older. Its major drug interaction liabilities relate the linezolid’s activity as a monoamine oxidase inhibitor, and the propensity to potentiate serotonergic and adrenergic drugs (rarely resulting in the serotonin syndrome and a pressor response, respectively). Because of the potential for a pressor response, foods containing large quantities of tyramine (>100 mg during a meal) should be avoided, although this is probably only rarely clinically relevant. The most common side effects of linezolid in clinical trials were diarrhea, headache, and nausea in descending frequency. A prominent toxicity of this drug is on the bone marrow, primarily but not exclusively manifested by thrombocytopenia occurring after 2 weeks of treatment, prompting the recommendation to check complete blood counts weekly in patients receiving linezolid. Other serious but uncommon toxicities, mostly occurring after prolonged use, include optic neuritis, peripheral neuropathy, and lactic acidosis.
Current FDA-approved indications for linezolid include complicated skin and skin structure infections caused by *S. aureus* including MRSA, but only including MSSA for uncomplicated skin infections, and hospital-acquired pneumonia caused by *S. aureus* including MRSA, but only including MSSA for community-acquired pneumonia.

The only published randomized double-blind trial of linezolid for complicated SSTI excluded MRSA infections. In that study, wherein patients could receive aztreonam for gram-negative activity if necessary, linezolid intravenous or oral showed statistically equivalent efficacy to intravenous oxacillin and oral dicloxacillin with clinical cure rates in the intent-to-treat population of 69.8% versus 64.9%, respectively (*P* = .141; 95% confidence interval [CI], 1.58–85.8). A company-sponsored open-label study comparing the efficacy of linezolid intravenous or oral with vancomycin intravenous for the treatment of suspected or proved MRSA-complicated SSTI did show superior efficacy for the linezolid arm, but only in the subset of patients found to have MRSA.

Linezolid plus aztreonam was equivalent to vancomycin plus aztreonam in two double-blind studies of hospital-acquired pneumonia (the second study being a continuation of the first), including cases caused by MRSA. A post hoc subset analysis of patients from the two trials suggested superior efficacy for linezolid versus vancomycin for MRSA hospital-acquired pneumonia. Because of the distinct advantage of attainment of excellent epithelial-lining fluid concentrations achieved by linezolid (essentially 100% of serum levels), it is plausible that linezolid is the more active drug for this indication versus vancomycin (which achieves only about a 1:6 ratio of epithelial-lining fluid/serum), but this has yet to be demonstrated in a prospective, double-blinded fashion. A Letter to the Editor written by authors at the FDA in response to the report by Wunderink and colleagues raised substantial questions about the conclusions drawn by authors of the aforementioned study. A company-sponsored phase IV clinical trial is currently enrolling to test this hypothesis in a more definitive fashion and has an estimated completion date of March 2012.

Current FDA-approved indications for linezolid do not explicitly include *S. aureus* or coagulase-negative staphylococcal bacteremia; however, pooled data from randomized clinical trials suggest linezolid is noninferior to vancomycin for patients with secondary *S. aureus* bacteremia. Somewhat perplexing results came from a large study of catheter-related bloodstream infections treated with linezolid versus vancomycin with potential switch to oxacillin-dicloxacillin and use of aztreonam or an aminoglycoside antibiotic for known or suspected gram-negative infection at the discretion of the investigators. Linezolid was reported to be noninferior, but there was excess mortality in linezolid-treated patients with blood cultures that grew gram-negative organisms or were sterile, prompting a warning to be issued by FDA regarding lack of FDA approval for use of linezolid to treat catheter-related bloodstream infections and a reminder to providers that the drug lacks gram-negative activity. Case reports have described the use of linezolid to treat infective endocarditis, as summarized by Falagas and colleagues, but this indication has not been studied in a clinical trial. Because of its activity as an inhibitor of protein synthesis, an effect that is shared by clindamycin, linezolid may be a useful agent in staphylococcal toxin-mediated diseases, including toxic shock syndrome and necrotizing pneumonia.

Pediatric use of linezolid has been studied directly in pharmacokinetic studies, and in a few randomized clinical trials. The largest pediatric clinical study was a randomized, open label, multicenter study of hospitalized subjects from birth to 12 years of age comparing linezolid with vancomycin in the treatment of nosocomial pneumonia, complicated skin and skin structure infections, catheter-associated bacteremia, bacteremia of unknown source or other systemic infections caused predominantly by *S. aureus* and coagulase-negative staphylococci. The two drugs showed comparable
efficacy and linezolid had fewer adverse drug reactions (19% versus 34%; $P < .001$). There was a randomized, blinded, multicenter study of hospitalized subjects from 5 to 17 years of age that demonstrated equivalence of linezolid to cefadroxil in the treatment of uncomplicated skin and skin structure infections. The package insert includes pediatric use for nosocomial pneumonia, community-acquired pneumonia, and complicated skin and skin structure infections for pediatric patients from birth to 11 years of age, and uncomplicated skin and skin structure infections in patients from 5 to 17 years of age.

No discussion of the clinical use of linezolid is complete without consideration of the cost of the drug. At the current (September 2008) average wholesale price per day of $173.80 for the oral form and $222.70 for the IV formulation, linezolid is approximately 5.1- and 6.5-fold more expensive than vancomycin (respectively) by pharmacy cost. Despite the substantially higher pharmacy costs, a number of studies have concluded that use of linezolid could be cost-effective. For example, one analysis showed a shorter hospital length of stay in clinically evaluable patients with SSTI treated with linezolid median 8 days (95% CI, 6–13; $P = .0025$), mean of 15.4 days (SE 1.9; $P = .0025$) versus vancomycin (median 16 days [95% CI, 13–19]; mean of 20.3 days [SE 1.7]).

Linezolid is a very useful but expensive antistaphylococcal agent. It remains active against most $S$ aureus isolates. Because of its excellent bioavailability, the option of oral treatment is very appealing and can reduce hospital length of stay. In clinical trials published to date and in a meta-analysis, when only blinded clinical trials are considered, linezolid has not been demonstrated to be superior to comparators.

TRIMETHOPRIM-SULFAMETHAXAZOLE

Both trimethoprim and sulfonamides inhibit enzymes in the bacterial folate biosynthesis pathway. Combining the trimethoprim with a sulfonamide achieves bactericidal activity and reduces the emergence of bacterial resistance. Trimethoprim-sulfamethaxazole (TMP-SMX) is available in oral and IV formulations. Because of its renal elimination dosing must be adjusted for renal function. Among the side effects associated with TMP-SMX are gastrointestinal upset; dermatologic reactions (ranging from rash to Stevens-Johnson syndrome); cytopenias; and hepatic and renal dysfunction. In a recent study, sulfonamides (along with clindamycin and moxifloxacin) was one of the drugs associated with the highest frequency of estimated emergency department visits (per prescription visit) for antibiotic-associated adverse drug reactions, and had the highest frequency of moderate-to-severe allergic reactions. Folate antagonists, such as TMP-SMX, are not recommended for use during pregnancy. Although antibacterial drugs in general may affect the anticoagulant effects of warfarin, TMP-SMX seems to be a particularly problematic agent in this regard and relatively frequently causes supratherapeutic international normalized ratios.

In terms of antistaphylococcal activity, in vitro studies have shown that the combination of TMP-SMX is synergistic and bactericidal against MSSA and MRSA, and demonstrates significantly greater activity than either of the drugs alone in an MRSA mouse intraperitoneal infection model. Despite these in vitro data, a review summarizing the existing literature on the use of TMP-SMX for the treatment of $S$ aureus infections reported a cumulative failure rate of 50% among 221 patients treated between 1972 and 2005. It is important to note, however, that the studies included in this review varied greatly in their designs (prospective versus retrospective, different routes of drug administration, and whether the efficacy of TMP-SMX was being compared with that of another antibiotic). In addition, the studies included multiple types of infection (bacteremia, right-sided...
endocarditis, SSTI, bone and joint infections, meningitis, bronchiectasis, and peritoneal dialysis catheter infection). Because of these differences, it is difficult accurately to assess the efficacy of TMP-SMX for the treatment of *S aureus* from these aggregate data. Some of the individual studies included in this review, however, provide some insights into the potential role of TMP-SMX in the treatment of *S aureus* infections.

A small prospective, randomized clinical trial compared TMP-SMX (160 mg/800 mg orally twice a day) with doxycycline (100 mg orally twice a day) for 7 days for the treatment of SSTI following incision and drainage of the wound. Most infections were caused by CA-MRSA (68%) and intention-to-treat analysis failed to demonstrate a significant difference between the two treatment arms at the 10- to 14-day follow-up (11 of 14 patients cured in TMP-SMX arm versus 19 of 20 cured in doxycycline arm). Szumowski and colleagues conducted a retrospective analysis of 200 cases of SSTI caused by MRSA presenting to a community health clinic. The authors found that improved clinical outcomes coincided with the increased use of TMP-SMX as the empiric antibiotic of choice for these patients. This statistically significant difference persisted even after controlling for the use of wound incision and drainage. Taken together, these data suggest TMP-SMX is a viable oral option for the treatment of SSTI caused by *S aureus* infections, especially when resistance rates to other antistaphylococcal agents in the community are high. This is reflected in the Infectious Diseases Society of America’s treatment guidelines for SSTI, in which TMP-SMX is one of the options for disease caused by either MSSA or MRSA for both adult and pediatric patients. For adults the recommended dosing is one to two double-strength TMP-SMX tablets (160 mg of trimethoprim in each double-strength tablet) twice daily and in pediatric patients the dose is 8 to 12 mg/kg (based on trimethoprim component) in two to four daily divided doses depending on route of administration.

In a randomized, controlled trial comparing the efficacy of intravenous TMP-SMX (320 mg/1600 mg IV every 12 hours) with vancomycin (1 g IV every 12 hours) for the treatment of *S aureus* infections among parenteral drug users (including SSTI, bone and joint infections, right-sided endocarditis, and suppurative thrombophlebitis), Markowitz and colleagues evaluated 101 (43 in the TMP-SMX arm, 58 in the vancomycin arm). Among the study population, nearly two thirds were bacteremic and nearly half of the infections were caused by MRSA. Overall, there were no statistically significant differences between the two arms in terms of duration of positive *S aureus* cultures, duration of fever, or hospital stay. The cure rate in the TMP-SMX arm (86%) was significantly lower, however, compared with the vancomycin arm (98% cure rate). Interestingly, in subgroup analysis, the difference in cure rates between the two arms of the study occurred because of reduced efficacy of TMP-SMX against MSSA infections (cure rates of 73% versus 97% for vancomycin). All patients with MRSA infection were cured in both arms.

Other investigators have looked at the use of TMP-SMX in the treatment of MRSA osteomyelitis. In this noncomparative study, four (67%) of six patients treated with oral TMP-SMX for a minimum of 8 weeks had a positive clinical response.

In an era of increasing community-associated MRSA SSTI, TMP-SMX may be an attractive therapeutic option, contingent on local susceptibility patterns. Susceptibility to this drug seems to be largely preserved, even in otherwise multidrug-resistant CA-MRSA. The studies by Markowitz and colleagues and Yeldandi and colleagues suggest that in more complicated or invasive staphylococcal infections, TMP-SMX could be considered a treatment alternative if other first-line antistaphylococcal antibiotics fail, are not tolerated, or are otherwise contraindicated. Also, TMP-SMX may be an oral “step-down” treatment option for certain complicated *S aureus* infections (eg, osteomyelitis) following initial clinical improvement with a course of appropriate IV antibiotic therapy.
TETRACYCLINES AND GLYCYCLOCLINES

The tetracyclines are bacteriostatic agents that act by binding to the bacterial ribosome to inhibit protein synthesis. Doxycycline and minocycline have greater staphylococcal activity than tetracycline, and tigecycline is the most active agent of this group against MRSA. The tetracyclines (tetracycline, doxycycline, and minocycline) are highly bioavailable and can be administered either orally or parenterally; however, the IV formulation of minocycline is not currently available in the United States. Tigecycline is only available as a parenteral drug. Side effects are varied and include photosensitivity; lupus-like reactions (seen with minocycline); gastrointestinal symptoms (notably tigecycline); hepatotoxicity; vestibular toxicity (seen with minocycline); and pseudotumor cerebrii. They are also contraindicated in children less than 8 years old and pregnant women because of the accumulation in developing bone and teeth.129–131

Doxycycline and Minocycline

In a review of the literature regarding the use of long-acting tetracyclines (doxycycline and minocycline) for the treatment of *S aureus* infections, Ruhe and colleagues132 found that among nine separate studies, published between 1971 and 1990, a total of 85 patients with *S aureus* infections were treated with the long-acting tetracyclines (either as monotherapy or in conjunction with rifampin). The overall cure rate in this population was 85%. SSTI represented the most common treatment indication (53 [62%] of 85 patients). There were too few patients with other treatment indications (pneumonia, osteomyelitis, septic thrombophlebitis, urinary tract infection, endocarditis, and liver abscess) to determine adequately the efficacy of using tetracyclines for infections other than SSTI. These same authors also retrospectively reviewed patients treated at their institution between 1999 and 2004 with either doxycycline or minocycline for culture-proved complicated SSTI (exclusive of folliculitis or other simple skin infection), urinary tract infections, and invasive infections caused by MRSA. Of 24 patients meeting their study criteria, 18 received monotherapy, whereas five patients were treated also with rifampin (four) or TMP-SMX (one). Similar to their literature review findings, 16 patients (67%) had SSTI (cure rates were 91% for individuals treated with doxycycline and 100% for those receiving minocycline) and the overall cure rate for the entire group of 24 patients treated at their institution was 83%.132 In a larger retrospective cohort study, Ruhe and Menon133 also evaluated the role of the long-acting tetracyclines for the treatment of CA-MRSA SSTI in patients at their institution between 1999 and 2007. Among 90 cases of MRSA SSTIs treated with doxycycline (97% of cases) or minocycline (3% of cases), the overall cure rate was 96%. Important caveats to this study include the facts that 95% of MRSA isolates identified at the authors’ institution during the study period were susceptible to tetracyclines, and most patients (69%) treated with tetracyclines for SSTI underwent surgical drainage of a purulent focus of infection at the time of diagnosis. Finally, in a small prospective study comparing the efficacy of incision and drainage plus either doxycycline or TMP-SMX for the treatment of SSTI, among 34 enrolled patients (27 of whom had *S aureus* infection) the cure rate was at least 95% among the 20 patients receiving doxycycline and adequate surgical wound management (one patient with MRSA was lost to follow-up and could not be assessed).126

Based on these studies, and contingent on local susceptibility patterns and appropriate surgical drainage, doxycycline and minocycline seem to be effective for the treatment of SSTI caused by *S aureus*. Although there are case series and reviews describing the use of the tetracycline-class in the treatment of other types of
staphylococcal infections, including pneumonia, osteomyelitis, prosthetic joint infections, and endocarditis, in the absence of more detailed investigations it is difficult to recommend this class of antibiotic as first-line therapy in these settings.

**Tigecycline**

Tigecycline is a glycyclycline, a modification of the minocycline molecule that was designed to circumvent known mechanisms of resistance to the tetracycline class of antibiotics, including ribosomal modification and efflux pump mediated resistance. The drug has an extremely broad spectrum of activity, and the MIC of tigecycline for nearly 600 *S aureus* clinical isolates (including both MSSA and MRSA), collected from four phase 3 clinical trials, was low and ranged between 0.06 and 1 μg/mL with an MIC$_{90}$ of 0.25 μg/mL. Also of note, the tigecycline MIC was less than or equal to 0.5 μg/mL for 11 minocycline-resistant *S aureus* isolates. The pharmacokinetics of tigecycline are notable in that the drug has a very large volume of distribution and the maximum serum concentration using the FDA-approved 50-mg dose was a fairly modest 0.62 μg/mL after multiple 50-mg doses.

Tigecycline has been approved by the FDA for the treatment of adults with complex skin and soft tissue structure infections and complex intra-abdominal infections. In a pooled analysis of two studies comparing the efficacy of tigecycline in the treatment of complicated SSTI with that of the combination of vancomycin and aztreonam, the microbiologic cure rates were equivalent for infection caused by both MSSA (approximately 90% in both arms) and MRSA (approximately 75% in both arms). Although there are case series reports describing the use of tigecycline in the treatment of other invasive staphylococcal infections, clinicians must exercise care and give consideration to the modest serum concentration achievable with standard dosing schedules of tigecycline before extrapolating the use of this agent for the treatment of *S aureus* infections that are beyond its currently approved treatment indications.

**AMINOGLYCOSIDES**

Aminoglycosides are bactericidal agents that disrupt protein synthesis by binding to the bacterial ribosome. Class-specific side effects include nephrotoxicity and ototoxicity. In the treatment of staphylococcal infections, aminoglycosides function as a component of multidrug treatment regimens and serve to achieve synergistic bacterial killing or to prevent the emergence of bacterial resistance. *S aureus* endocarditis is the treatment indication for which the addition of an aminoglycoside is most often considered.

In vitro and animal model studies from the 1970s demonstrated the addition of gentamicin to nafcillin afforded synergistic killing of *S aureus* compared with nafcillin alone. In a randomized trial comparing 4 weeks of β-lactam monotherapy with 2 weeks of gentamicin plus 4 weeks of β-lactam in 25 patients with *S aureus* native-valve endocarditis related to IV drug use, however, there were no differences in the two treatment groups in terms of time to defervesence, rates of bacteriologic failure, or mortality. Similarly, in a study evaluating patients with either right- or left-sided MSSA endocarditis (with or without a history of IV drug use), although the addition of 2 weeks of gentamicin to a 6-week course of nafcillin resulted in decreased duration of bacteremia (by 1–1.5 days), there was no overall mortality benefit and there was increased nephrotoxicity observed in the non-IV drug use patients with predominantly left-sided endocarditis. When specifically evaluating native-valve, right-sided *S aureus* endocarditis in the IV drug use population, a 2-week course of low-dose
tobramycin plus β-lactam therapy was found to achieve high cure rates (94%). Subsequent data revealed, however, that the addition of the aminoglycoside to 2 weeks of β-lactam (cloxacillin) did not improve treatment success rates (86% for combination therapy versus 89% for cloxacillin alone). Several of these studies have also been evaluated as part of a recent meta-analysis, which confirmed that addition of aminoglycosides failed to improve treatment success rates or mortality of *S aureus* native-valve endocarditis. Guidelines for the treatment of endocarditis issued by the American Heart Association are reflective of the lack of clear efficacy of aminoglycosides in the management of either left-sided or non–IV drug use–associated, right-sided native-valve endocarditis caused by MSSA, and state that the addition of gentamicin (3 mg/kg IV or intramuscularly daily in divided doses) to a β-lactam is an optional consideration and should not be continued beyond the first 3 to 5 days of therapy. Furthermore, in the setting of uncomplicated, IV drug use–associated right-sided MSSA endocarditis, these guidelines note that treatment with 2 weeks of β-lactam therapy, irrespective of the addition of aminoglycoside, seems to be sufficient. The role of aminoglycosides in the treatment of native-valve endocarditis caused by MRSA is limited because of higher rates of aminoglycoside resistance among MRSA; the potential for synergistic nephrotoxicity and ototoxicity when combining an aminoglycoside with vancomycin; and high clinical failure rates when used in short-course (2-week) therapy with vancomycin for the treatment of right-sided endocarditis.

The use of aminoglycosides for the treatment of *S aureus* PVE derives from studies of coagulase-negative staphylococcal PVE. In a study comparing a 6-week regimen of vancomycin plus rifampin with a 6-week regimen of these two agents plus 2 weeks of gentamicin, the cure rates were similar in the two arms. A total of 37% of patients receiving the dual antibiotic regimen developed rifampin-resistant staphylococci, however, necessitating adjustment of the antibiotic regimen (addition of a prolonged course of gentamicin to vancomycin). No patients in the triple antibiotic arm developed rifampin resistance. Extrapolating from these data, American Heart Association guidelines recommend the addition of an initial 2 weeks of gentamicin (3 mg/kg/d in divided doses) to 6 weeks of rifampin plus a semisynthetic penicillin (or vancomycin for methicillin-resistant staphylococci) in the treatment of adult or pediatric PVE caused by gentamicin-susceptible staphylococci, including *S aureus*. Gentamicin dosing should be adjusted (interval and dose) as necessary to achieve a peak serum concentration of approximately 3 μg/mL and a trough concentration of less than 1 μg/mL.

**FLUOROQUINOLONES**

Fluoroquinolones are bactericidal agents that inhibit bacterial DNA gyrase and topoisomerase IV. Side effects that may be associated with this class include gastrointestinal distress, neuropsychiatric changes, cardiac conduction disturbances, abnormalities in liver enzymes, hypoglycemia or hyperglycemia, and drug rashes. A recent report noted that more than other frequently used fluoroquinolones (including ciprofloxacin and levofloxacin), moxifloxacin was associated with one of the highest frequency of estimated emergency department visits (per prescription visit) for antibiotic-associated adverse drug reactions. A recent FDA-issued alert focused on the risk of fluoroquinolone-associated tendonitis and tendon rupture, with increased risk among older patients (greater than 60); recipients of corticosteroids; or patients status-post kidney, heart, or lung transplant. Based on studies in juvenile animals, fluoroquinolones may result theoretically in cartilage damage in children and are not
presently FDA-approved agents in pediatric populations except in specified cases, which are general exclusive of staphylococcal infections. Clinically available fluoroquinolones in the United States include norfloxacin, ofloxacin, ciprofloxacin, levofloxacin, moxifloxacin, and gemifloxacin. Against MSSA and MRSA, the MIC90 for ciprofloxacin and ofloxacin are lower than that of norfloxacin. Time-kill assays have demonstrated bactericidal activity (>3 log killing at 24 hours), however, for all three agents at concentrations 5 \times \text{MIC}. Of note, rapid development of ciprofloxacin resistance has been demonstrated among clinical S aureus, particularly in MRSA. Although in vitro data suggest improved staphylococcal activity for levofloxacin, moxifloxacin, and gemifloxacin compared with that of ciprofloxacin, the presence of ciprofloxacin resistance in S aureus does seem to confer some cross-resistance to even these newer generation fluoroquinolones.

In a study evaluating ciprofloxacin for the treatment of either MRSA SSTI or colonization (750 mg ciprofloxacin orally twice daily for 5, 10–14, or 21 days, with the 21-day course being coadministered with rifampin), treatment with ciprofloxacin resulted in clinical improvement in all treatment arms. Among patients treated with 5 or 10 to 14 days of ciprofloxacin, however, MRSA eradication was achieved in only 50% of patients at the end of treatment and all patients subsequently became recolonized. Among the patients treated with the combination of ciprofloxacin and rifampin, all five patients infected with fluoroquinolone- and rifampin-susceptible MRSA demonstrated clinical improvement and eradication of MRSA at the end of therapy and 1 month posttherapy. Comparing moxifloxacin with piperacillin–tazobactam (with the option of transitioning to oral amoxicillin–clavulanate) for the treatment of diabetic foot infections, Lipsky and colleagues demonstrated that among the microbiologically evaluable cases of S aureus infection, moxifloxacin eradicated 81% of S aureus infection (13 of 16 cases) compared with 67% (12 of 18 cases) for the \(\beta\)-lactam comparator. This trial allowed for the use of narrow-spectrum agents, however, such as vancomycin to treat resistant gram-positive pathogens, such as MRSA, and the authors note that because of its lack of consistent activity against MRSA, the role for moxifloxacin in the treatment of diabetic foot infections is limited. As a corollary to these reports, the role of fluoroquinolone monotherapy for the treatment of contemporary SSTI may be continuing to shrink given the rising rates of community-associated MRSA infections, which in some ambulatory populations has been also associated with high rates of ciprofloxacin resistance (>75%).

Multiple other investigators have further evaluated the efficacy of combining a fluoroquinolone with rifampin for the treatment of S aureus infections, including orthopedic infections and endocarditis (see also the section on rifampin). In a prospective, randomized trial comparing a 28-day oral course of ciprofloxacin (750 mg twice daily) plus rifampin (300 mg twice daily) with oxacillin (2 g IV every 4 hours) or vancomycin (1 g every 12 hours) plus 5 days of gentamicin (2 mg/kg IV every 8 hours) for right-sided S aureus endocarditis in injection drug users, Heldman and colleagues demonstrated equivalent microbiologic cure rates in both study arms (95% versus 88%) using test-of-cure blood cultures obtained approximately 1 week after discontinuation of antibiotic therapy. It is important also to note that there was approximately a 50% attrition rate in this study, however, with only 19 of 40 patients available for test-of-cure analysis in the oral treatment group and 25 of 45 patients evaluable in the parenteral treatment group. Schrenzel and colleagues conducted the largest clinical trial to date studying the combination of a fluoroquinolone and rifampin. These investigators compared the efficacy of the oral fluoroquinolone, fleroxacin (not available in the United States), plus rifampin with parenteral flucloxacillin (or vancomycin) for the treatment of S aureus bacteremia or deep-seated infection (including bone and joint
infection, pneumonia, right-sided endocarditis, or urinary tract infection). Cure rates were equivalent for both treatment arms among clinically evaluable patients (79% for the fluoroquinolone-rifampin combination and 76% for parenteral therapy) and among the microbiologically evaluable cases (84% for oral combination and 82% for parenteral therapy arm). Of note, although patients receiving the oral regimen had significantly shorter median length of stay (12 versus 23 days), they also had significantly more adverse drug effects compared with the patients receiving parenteral antibiotics therapy.

With rising rates of MRSA in both the community and hospital setting, the role for fluoroquinolone monotherapy in \textit{S. aureus} infections may be decreasing. Combination therapy with a fluoroquinolone and rifampin may be appropriate in certain infections caused by susceptible \textit{S. aureus}, however, particularly when attempting to salvage an infected orthopedic device or in cases of right-sided endocarditis when a transition from parenteral to oral therapy is necessary.

\textbf{RIFAMPIN}

Rifampin is a potent, bactericidal antistaphylococcal agent with data from the early 1980s establishing a rifampin MIC\textsubscript{90} of 0.015 \textmu g/mL for \textit{S. aureus}.\textsuperscript{164,165} Although there are no recent publications reporting the susceptibility of large collections of clinical isolates, the drug seems to be maintaining reliable in vitro activity against target isolates including CA-MRSA.\textsuperscript{1} Rifampin acts by inhibiting the bacterial RNA polymerase.\textsuperscript{166} Because it is highly bioavailable, rifampin can be administered orally. Rapid resistance can emerge among \textit{S. aureus} on exposure to this drug, however, at frequency of approximately $10^{-8}$.\textsuperscript{167} In most clinical applications rifampin is used in conjunction with another antibiotic agent to prevent the development of resistance and may be best reserved for situations when the organism burden has already been reduced by prior treatment or surgery. Rifampin is associated with a wide spectrum of side effects and clinicians must also be cognizant of the potential risk for drug-drug interactions caused by rifampin-associated induction of the hepatic cytochrome P-450 system.\textsuperscript{168}

Rifampin has been shown to be highly effective in eradicating staphylococcal infections associated with foreign bodies.\textsuperscript{169} As such, it is used in the treatment of staphylococcal PVE and orthopedic hardware-related infections.

In patients being treated for \textit{Staphylococcus epidermidis} PVE, the addition of rifampin to vancomycin increased serum bactericidal activity by more than eightfold compared with serum bactericidal activity of patients treated with vancomycin alone.\textsuperscript{170} The clinical correlate of these data was the finding that among patients with \textit{S. epidermidis} PVE the addition of rifampin, an aminoglycoside, or both rifampin and an aminoglycoside to vancomycin therapy resulted in significantly greater cure rates than among patients receiving vancomycin monotherapy.\textsuperscript{171} Extrapolating from these data, treatment with rifampin (900 mg/d for adults or 20 mg/kg/d for pediatric patients, in three equally divided doses, and administered either orally or parenterally) in combination with a \beta-lactam or vancomycin is now recommended for the entire 6-week duration of therapy for staphylococcal PVE, including that caused by \textit{S. aureus} (with an aminoglycoside administered during the initial 2-week period).\textsuperscript{21}

Rifampin in combination with a fluoroquinolone\textsuperscript{30,172-174} has been efficacious in the treatment of staphylococcal orthopedic hardware-related infections. Zimmerli and colleagues\textsuperscript{30} conducted a randomized, controlled trial comparing outcomes in patients with hardware-associated orthopedic infections treated with an antistaphylococcal \beta-lactam (or vancomycin) plus either rifampin (orally dosed at 450 mg twice
daily) or placebo for 2 weeks followed by ciprofloxacin plus either rifampin or placebo for 3 to 6 months. Enrollment criteria included early onset infection, absence of prosthesis loosening, and adequate initial surgical debridement before antibiotic therapy. With follow-up extending to nearly 3 years, all 12 patients receiving rifampin were cured (based on clinical, radiographic, and laboratory parameters) compared with only 58% of the placebo arm (7 of 12 patients).

The use of rifampin plus a fluoroquinolone has been investigated by multiple investigators for other staphylococcal infections (see the section on fluoroquinolones). Caution must be used, however, in extrapolating from the aforementioned studies to other drug combinations with rifampin and other clinical scenarios. For example, there was no benefit to the addition of rifampin to vancomycin in treatment of primarily right-sided MRSA native-valve endocarditis in a small randomized trial by Levine and colleagues. A more recent retrospective cohort analysis of cases of S. aureus native-valve endocarditis (predominantly right-sided and MRSA) found that in addition to hepatotoxicity and drug interactions, there was more prolonged bacteremia and increased mortality in patients treated with rifampin in addition to standard therapy. Overall, the role of rifampin in the treatment of staphylococcal infections other than staphylococcal PVE or orthopedic hardware infection remains less well defined by clinical trials. Although some data may support a rifampin-based antibiotic regimen in these settings, other considerations that may weigh against the use of rifampin include risk of adverse drug reaction, possible drug-drug interactions, and the potential development of drug resistance.

Because of the ability to attain high nasopharyngeal drug levels, rifampin has also been used to eradicate S. aureus nasal colonization. Oral rifampin has been shown to achieve nasal secretion concentrations exceeding 20 times the MIC₉₀ for MRSA in healthy volunteers. Rifampin monotherapy, however, fails to achieve a durable S. aureus decolonization response. Other investigators have evaluated the efficacy of staphylococcal decolonization when combining rifampin with TMP-SMX, ciprofloxacin, or minocycline and have demonstrated mixed results. More recently, Simor and colleagues showed that MRSA-colonized patients who received 7-day combined regimen of intranasal mupirocin, topical chlorhexidine, plus oral rifampin plus doxycycline were significantly more likely to remain free of MRSA colonization (64 [74%] of 87 treated patients) at 3 months follow-up compared with patients who did not receive this treatment (8 [32%] of 25 patients). Side effects attributable to treatment were noted in 25% of cases, but were reported to be mild in nature. The authors noted that 54% of patients available for follow-up 8 months after the decolonization treatment remained MRSA-free. Of note, because this study included multiple interventions it is difficult to determine the contribution of the rifampin plus doxycycline. Based on these data, if the decision is made to use rifampin in a staphylococcal decolonization regimen, consideration should be given to including an additional antistaphylococcal antibiotic and a topical antibiotic and antiseptic agent maximally to ensure eradication. Irrespective of the regimen used, there seems to be a time-dependent risk for reacquisition of nasal colonization.

MACROLIDES, KETOLIDES, CLINDAMYCIN, QUINUPRISTIN-DALFOPRISTIN

The macrolides-lincosamide-streptogramin (MLS) antibiotics currently in clinical use for staphylococcal infections include several macrolides (erythromycin, clarithromycin, and the azalide azithromycin), the lincosamide drug clindamycin, and streptogramin B antibiotic quinupristin, which is combined with the streptogramin A antibiotic dalfopristin in the drug Synercid. The MLS group of drugs shares a common
mechanism of action (ie, they bind to the bacterial ribosome and block protein elongation). Acquired resistance to the MLS drugs in staphylococci is typically conferred by target alteration, specifically *erm*-mediated methylation of the ribosomal target, but drug efflux is also prominent. The *erm*-mediated resistance may be constitutively or inducibly expressed. Constitutive expression results in cross-resistance to all macrolides, lincosamides, and type B streptogramins (MLS<sub>B</sub> phenotype). When inducibly expressed in staphylococci, *erm*-mediated macrolide resistance is induced by erythromycin, but not by clindamycin or streptogramin B antibiotics, which retain in vitro activity. In isolates that are resistant to erythromycin, inducible resistance to clindamycin may be detected in the clinical microbiology laboratory by the “D-test.”<sup>182</sup> Isolates that show inducible resistance to clindamycin may develop resistance to that drug on treatment; hence, CLSI’s suggested cautionary notice for reporting of these isolates, “This *S. aureus* is presumed to be resistant based on detection of inducible clindamycin resistance. Clindamycin may still be effective in some patients.”<sup>182,183</sup> This phenotype is fairly common and was found in 39% of erythromycin-resistant clindamycin-susceptible *S. aureus* isolates in a recent large survey.<sup>90</sup> The in vitro susceptibility of *S. aureus* and coagulase-negative staphylococci to macrolides and clindamycin is often correlated with methicillin susceptibility. For example, in a large recent survey including *S. aureus* isolates, 66% and 93% of MSSA were susceptible to erythromycin and clindamycin, whereas only 5% and 55% of MRSA were susceptible to these drugs.<sup>184</sup> Most CA-MRSA are resistant to the macrolides, and although clindamycin has been used successfully against CA-MRSA in some populations, isolates from the highly successful USA300 clone are often resistant.<sup>1,184</sup> After *erm*-encoded methylation, the most common mechanism of resistance to macrolides in staphylococci is the Msr ATP-binding cassette pumps that confer resistance to 14-membered ring macrolides (eg, erythromycin and clarithromycin) and type B streptogramins,<sup>185,186</sup> although the prevalence and relative proportion of these resistance determinants varies depending on the isolates sampled.

This group of drugs is generally bacteriostatic against staphylococci, with the noted exception of quinupristin-dalfopristin, which offers the potential for bactericidal activity against staphylococci that are not constitutively resistant to quinupristin.<sup>187,188</sup> Unfortunately, such resistance is fairly common, particularly among MRSA isolates.<sup>188</sup>

### Macrolides

Macrolides available for oral treatment of minor SSTI caused by susceptible *S. aureus* include erythromycin, clarithromycin, and azithromycin. The available parenteral agents in the United States are IV erythromycin and azithromycin, but these are rarely used for treatment of staphylococcal infection. Because of the prevalence of resistance in MRSA and many MSSA (as noted previously),<sup>184</sup> currently available macrolides are rarely if ever appropriate empiric agents. Given their relatively limited role, dosing for the variety of available macrolides is beyond the scope of this article, but can be found elsewhere.<sup>189</sup> Renal failure that is moderate to severe warrants a dose reduction of clarithromycin.<sup>190</sup> These drugs share some degree of gastrointestinal toxicity, primarily abdominal cramping, nausea, vomiting, and diarrhea, which is a less prominent side effect of the newer agents than for erythromycin.<sup>190</sup> A wide range of significant drug interactions result from the effects of erythromycin, and to a lesser extent clarithromycin on the hepatic cytochrome P-450 system, more precisely inhibition of CYP 3A4.<sup>190,191</sup> Azithromycin, however, has only limited hepatic metabolism and few drug interactions.
Clindamycin

As compared with the macrolides, clindamycin is more widely used to treat staphylococcal infections. It has specific use in patients with β-lactam hypersensitivity, in the treatment of infections caused by isolates resistant to alternative agents, and in the treatment of staphylococcal toxin-mediated disease. Although most nosocomial and many CA-MRSA are clindamycin-resistant, clindamycin has activity against most methicillin-susceptible isolates. Many coagulase-negative staphylococci, particularly nosocomial isolates, are resistant to clindamycin.

Clindamycin (along with sulfonamides and moxifloxacin) was one of the drugs associated with the highest frequency of estimated emergency department visits (per prescription visit) in a recent study. The most common adverse reactions caused by clindamycin involve the gastrointestinal system. Antibiotic-associated diarrhea is not uncommon in patients receiving clindamycin, and in a subset of those patients is caused by the overgrowth of toxigenic *Clostridium difficile*, resulting in antibiotic-associated colitis with pseudomembrane formation. Clindamycin is one of many antimicrobial drugs that have been found to be risk factors for *C difficile*-associated diarrhea, but despite being often invoked as a high-risk agent, some recent studies have not found it to be a greater risk factor than numerous other agents.

Clindamycin causes relatively few significant drug interactions, but may potentiate neuromuscular blocking agents and may reduce the levels of cyclosporine. Clindamycin may be administered orally, intramuscularly, or parenterally. The standard oral preparation is clindamycin hydrochloride, which may be given in doses ranging from 150 to 450 mg every 6 hours. Another oral preparation of clindamycin is a palmitate ester suspension. Oral preparations are absorbed rapidly and have approximately 90% bioavailability. For intravenous delivery, 600 to 900 mg of clindamycin phosphate is infused every 6 to 8 hours. This preparation may also be administered intramuscularly in doses as high as 600 mg. This agent penetrates into most tissues and fluids except cerebrospinal fluid. Like the macrolides, although not to the same extent as azithromycin, it is concentrated in polymorphonuclear neutrophils and macrophages, but the clinical significance of this property is unclear. Because the metabolites of clindamycin are cleared through the urine and feces, significant dose reduction is recommended only for patients with severe hepatic failure or combined renal and hepatic dysfunction. Clindamycin levels are not reduced by either hemodialysis or peritoneal dialysis.

Clindamycin is an agent with several well-defined niches in antimicrobial chemotherapy. SSTI caused by *S aureus* are often treatable with clindamycin. Because of its activity against predominant clones of CA-MRSA in some geographic locales, clindamycin has been used for empiric and directed treatment of SSTI, particularly in pediatric patients, but this strategy is ill-advised in other areas where circulating clones of CA-MRSA, particularly multidrug-resistant USA-300, are prevalent. Close attention to the local antibiogram is critical to this consideration. Because of its good penetration into bone, clindamycin is sometimes used in the treatment of osteomyelitis caused by staphylococci or streptococci or may be combined with other agents for polymicrobial osteomyelitis, such as diabetic foot infections or decubitus ulcers. Clindamycin is also included in some surgical antibiotic prophylaxis regimens for β-lactam–allergic patients. Because it inhibits ribosomal protein synthesis clindamycin has been used, in practice often combined with a cell-wall active agent, to stop toxin production in patients with infections caused by toxin-producing *S aureus* (eg, staphylococcal toxic shock syndrome). Clindamycin has additional theoretic advantages over β-lactams in that it is less affected by the large inoculum of organisms.
present in serious infections, such as necrotizing fasciitis; is active against slowly growing organisms; and may also have beneficial immunomodulatory effects.\textsuperscript{199}

**Quinupristin-Dalfopristin**

Quinupristin-dalfopristin is a combination of two semisynthetic derivatives of pristinamycin (pristinamycin streptogramin A and B drugs), providing the potential for synergistic bactericidal activity against staphylococci. Quinupristin, the streptogramin B component, is derived from pristinamycin I, and the streptogramin A antibiotic dalfopristin is derived from pristinamycin IIa. The binding of the type A streptogramin induces a conformational change in the ribosome that increases the affinity of the ribosome for type B drugs.\textsuperscript{200} Synercid has in vitro activity against gram-positive organisms including MSSA and MRSA and \textit{S epidermidis}. It is available only as an intravenous drug, and has significant toxicity liabilities including phlebitis (42\% of patients in comparative clinical trials had inflammation at the IV site) and the not uncommon occurrence of moderate or severe arthralgias and myalgias.\textsuperscript{201} It causes a plethora of potential drug interactions because of its inhibition of cytochrome \textit{P-450 3A4}. At the dose of 7.5 mg/kg every 12 hours, this drug is approved for treatment of complicated SSTI caused by \textit{S aureus}, although the indication is limited to MSSA, and also for \textit{S pyogenes} for the same indication. Clinically, the relative toxicity of this drug limits its use, but Synercid may be considered as an option for patients with resistance to second-line drugs or multiple drug hypersensitivities.

**Telithromycin**

The ketolide drug telithromycin has good activity against \textit{S aureus} that are not constitutively resistant to MLS\textsubscript{B} drugs, and one global survey of community respiratory tract isolates of \textit{S aureus} from 1999 to 2000 found that 95\% of MSSA, but only 18\% of MRSA, were susceptible to telithromycin.\textsuperscript{202} In addition to significant toxicity liabilities, such as hepatotoxicity (including rare cases of fulminant hepatitis) and QTc prolongation, the drug carries the sole indication of treatment of mild to moderate community-acquired pneumonia caused by organisms other than \textit{S aureus}.\textsuperscript{190,203,204}

MLS drugs continue to have a role in the treatment of \textit{S aureus} infections, often when ß-lactam agents cannot be used because of methicillin resistance or hypersensitivity; however, this role is increasingly limited by unfavorable trends in antimicrobial drug resistance. Clindamycin remains a potentially useful drug for MSSA and CA-MRSA SSTI in settings where local antibiograms show susceptibility (including attention to D-testing for erythromycin-clindamycin discordant results).

**SUMMARY**

The treatment of staphylococcal infections continues to vex clinicians, in no small part because of the constantly evolving drug resistance of this virulent and durable pathogen. Additional research may help to understand how best to preserve the existing drugs, including recycling some older drugs for which there are currently only limited clinical data for the treatment of staphylococcal infections. Clinicians can look forward to additional studies of newer FDA-approved agents to understand better their place in treatment algorithms versus currently existing standards of care; and to approval of additional drugs with activity against MRSA that are in late-stage clinical trials.
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