Vancomycin remains the reference standard for the treatment of invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infections, as a result of its relatively clean safety profile, its durability against the development of resistance, and, for many years, the lack of other approved alternatives. However, the advent and testing of new compounds with anti-MRSA activity, for comparison with vancomycin, have rendered results that call into question the efficacy of vancomycin in the treatment of many serious infections. The reasons for clinical failure of vancomycin are many and have been hypothesized to include poor penetration of the drug to certain tissues [1–3], loss of accessory gene–regulator function in MRSA [4], and potential escalation of vancomycin MICs for MRSA [5]. Additionally, an increasing number of reports of vancomycin-intermediate *S. aureus* (VISA) and vancomycin-resistant *S. aureus* (VRSA) have populated the literature dating back to 1999. Many alternatives for the treatment of MRSA infections, including linezolid, daptomycin, tigecycline, and quinupristin/dalfopristin, are currently approved by the US Food and Drug Administration (FDA). Additionally, there are several investigational compounds with demonstrated in vitro activity against MRSA. The chemical structures of these agents are shown in figure 1.

LINEZOLID

Linezolid is a synthetic oxazolidinone that inhibits the initiation of protein synthesis at the 50S ribosome [6]. It is currently approved by the FDA for the treatment of complicated skin and skin-structure infections (SSSIs) and nosocomial pneumonia caused by susceptible pathogens, including MRSA. Several retrospective analyses of pooled data from randomized trials have compared linezolid with vancomycin in patients with proven MRSA infection. An analysis of 2 double-blind studies of patients with MRSA nosocomial pneumonia found that 75 patients treated with linezolid had survival rates that were significantly higher than those of 85 patients treated with vancomycin (80% vs. 64%; *P* = .03) [7]. The authors hypothesized that a possible explanation for the finding was vancomycin’s poor penetration of the lung, particularly when the standard dosage is 1 g administered every 12 h. However, aggressive dosing strategies for vancomycin (goal trough concentrations of >15 μg/mL, or 4–5× the MIC value) may not offer an advantage over traditional dosing strategies [8, 9]. A follow-up, randomized, double-blind
trial is under way that compares these 2 agents in hospitalized patients with nosocomial pneumonia due to MRSA. Similarly, retrospective evaluations of complicated skin and soft-tissue infections (SSTIs) caused by MRSA have found that, compared with vancomycin, linezolid is associated with significantly higher clinical cure rates and reduced lengths of hospitalization [6, 10]. A retrospective analysis of pooled data from 5 randomized studies did not find linezolid to be superior to vancomycin in patients with secondary MRSA bacteremia [11].

Linezolid should also be considered for necrotizing infections, including skin lesions [12], fasciitis [13], and pneumonia [14] caused by community-associated MRSA, particularly the USA300 strain. The severity of these infections may be associated with allotypes of mobile genetic elements found in USA300 that code for pathogenic toxins, including Panton-Valentine leukocidin, enterotoxin Q, and enterotoxin K [15]. It has been hypothesized that antibiotics with the ability to inhibit protein synthesis may demonstrate efficacy against susceptible toxin-producing strains. Linezolid, along with clindamycin, has recently been found to reduce production of Panton-Valentine leukocidin, α-hemolysin, and toxic-shock syndrome toxin–1, whereas vancomycin and nafcillin have been found to increase such production in an in vitro model [16].

Despite the apparent advantages of linezolid in the treatment of MRSA infections, concerns about safety often limit its use. Of particular concern is the association of linezolid with serotonin toxicity and thrombocytopenia [17, 18]. Linezolid exhibits weak reversible inhibition of monoamine oxidase and can induce toxicity when used in combination with agents that have serotonergic activity, most commonly selective serotonin reuptake inhibitors. Twenty-nine cases of linezolid-associated serotonin toxicity were recently reported. Postmarketing information submitted to the FDA regarding 29 patients with serotonin toxicity showed that 61% had received concomitant treatment with a selective serotonin reuptake inhibitor [17]. Three patients died, possibly because of serotonin toxicity, and another 13 patients required medical treatment [13]. Linezolid used concomitantly with selective serotonin reuptake inhibitors in hospitalized patients has also been evaluated in a retrospective study [19]. This study found a high probability of serotonin toxicity in association with 2 of 72 concomitant uses. The authors suggest that linezolid
<table>
<thead>
<tr>
<th>Drug, authors [reference]</th>
<th>Infection treated (no. of patients in study)</th>
<th>Regimen</th>
<th>Efficacy</th>
<th>Safety</th>
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<tbody>
<tr>
<td><strong>LZD</strong></td>
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<tr>
<td>Wunderink et al. [7]</td>
<td>Nosocomial pneumonia (160 patients with MRSA)</td>
<td>LZD (600 mg q12h) or VM (1 g q12h); both plus ATN for 7–12 days</td>
<td>Clinical cure rate: LZD, 59% (36 of 61 patients); VM, 36% (22 of 62 patients) ((P &lt; .01)). Survival rate: LZD, 80% (60 of 75 patients); VM, 64% (54 of 85 patients) ((P = .03)).</td>
<td>Not reported</td>
</tr>
<tr>
<td>Wiegelt et al. [6]</td>
<td>SSTIs (285 patients with MRSA)</td>
<td>LZD (600 mg iv or po q12h) or VM (1 g q12h)</td>
<td>Clinical cure rate: LZD, 89% (124 of 140 patients); VM, 67% (97 of 145 patients) ((P &lt; .001)).</td>
<td>Drug-related adverse events were reported in similar numbers of patients in both treatment arms.</td>
</tr>
<tr>
<td>Shorr et al. [11]</td>
<td>Bacteremia (53 patients with MRSA)</td>
<td>LZD (600 mg) or VM (1 g each q12h); ATN is added in studies of pneumonia</td>
<td>Clinical cure rate: LZD, 56% (14 of 25 patients); VM, 46% (13 of 28 patients); OR, 1.47 (95% CI, 0.50–4.34)</td>
<td>The rate of adverse events was similar between treatment groups (LZD, 89%; VM, 70%), as were the rate of serious adverse events (LZD, 47%; VM, 39%) and the rate of treatment discontinuation (LZD, 37%; VM, 39%); all differences were NS</td>
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<tr>
<td><strong>TIG</strong></td>
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<td>Breedt et al. [25]</td>
<td>SSTIs (546 patients) [0 with documented MRSA and 8 with presumed MRSA]</td>
<td>TIG (100 mg/day, with an initial 100-mg loading dose); VM (1 g q12h) plus ATN (2 g q12h)</td>
<td>Clinical response rate: TIG, 84%; VM/ATN, 87% ((P = .02)). Pathogen eradication rate: TIG, 85%; VM/ATN, 93% ((P = .02)).</td>
<td>Adverse events similar between 2 groups, but there were increased rates of nausea and vomiting in the TIG group and higher rates of rash and increases in LFT results in the VM/ATN group</td>
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<td><strong>DPT</strong></td>
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<tr>
<td>Arbeit et al. [28]</td>
<td>SSTIs (899 patients) [87 patients with MRSA]</td>
<td>DPT (4 mg/kg iv q24h for 7–14 days); comparators (results pooled) included PRPs (4–12 g/day iv) or VM (1 g iv q12h)</td>
<td>Clinical success rate (all evaluable patients): DPT, 83%; comparators, 84%. Clinical success rate (patients with MRSA): DPT, 75%; comparators, 68%.</td>
<td>Frequency and distribution of adverse events were similar between treatment groups</td>
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<tr>
<td>Fowler et al. [29]</td>
<td>Bacteremia and endocarditis (246 patients) [89 patients with MRSA]</td>
<td>DPT (6 mg/kg iv q24h); OR VM (1 g q12h) or PRPs (2 g q4h) plus GM (1 mg/kg iv q8h)</td>
<td>Clinical success rate at day 42 of treatment: DPT, 44%; comparators, 42%. Clinical success rate (patients with MRSA): DPT, 44%; comparators, 32%.</td>
<td>Overall incidence of adverse events was similar between treatment groups. Rate of serious adverse events: DPT, 52%; comparators, 45%. Increases in creatine kinase levels were more common in the DPT group (7% vs. 1%) ((P = .04)).</td>
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<tr>
<td>DBV</td>
<td>SSTIs [660 patients (287 patients with MRSA)]</td>
<td>DBV (1000 mg on day 1, followed by 500 mg iv on day 8); LZD (600 mg iv or po q12h for 14 days)</td>
<td>Clinical efficacy at test-of-cure: DBV, 89%; LZD, 91%</td>
<td>Adverse events involving the GI tract were the most common adverse events in both treatment groups; a higher proportion of patients receiving LZD had adverse events that were judged by investigators to be treatment related</td>
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<td>Raad et al. [31]</td>
<td>CR-BSIs (75 patients (14 patients with MRSA))</td>
<td>DBV (1000 mg on day 1, followed by 500 mg iv on day 8); VM (1 g q12h for 14 days)</td>
<td>Overall success rate: DBV, 87%; VM, 73%</td>
<td>Adverse events were generally mild and were comparable in the 2 treatment groups</td>
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<td>TLV</td>
<td>SSTIs [167 patients (48 patients with MRSA)]</td>
<td>TLV (7.5 mg/kg/day iv); standard therapy: VM (1 g q12h), NAF or OX (2 g q6h), and Clox (0.5–1 g q6h)</td>
<td>Overall test-of-cure rate: TLV, 80%; standard therapy, 77%. MRSA test-of-cure rate: TLV, 82%; standard therapy, 69%. MRSA microbiological eradication rate: TLV, 84%; standard therapy, 74%</td>
<td>Fewer serious adverse events were noted with TLV; the most common adverse events were similar between treatment groups and included nausea, psychiatric disorder, headache, vomiting, and dyspnea</td>
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<td>CTB</td>
<td>SSTIs due to gram-positive pathogens (784 patients [25% with MRSA])</td>
<td>CTB (500 mg q12h); VM (1 g q12h)</td>
<td>Clinical cure rate: CTB, 93%; VM, 93%. MRSA clinical response rate: CTB, 92%; VM, 90%</td>
<td>There were fewer serious treatment-related adverse events, the incidences of which were similar between treatment groups</td>
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</table>

NOTE. ATN; aztreonam; Clox, cloxacillin; CR-BSIs, catheter-related bloodstream infections; CTB, ceftobiprole; DBV, dalbavancin; DPT, daptomycin; GI, gastrointestinal; GM, gentamicin; iv, intravenously; LFT, liver function test; LZD, linezolid; MRSA, methicillin-resistant Staphylococcus aureus; NAF, nafcillin; NS, not significant; OX, oxacillin; po, by mouth; PRPs, penicillinase-resistant penicillins; q4h, every 4 h; q6h, every 6 h; q8h, every 8 h; q12h, every 12 h; q24h, every 24 h; SSTIs, skin and soft-tissue infections; TIG, tigecycline; TLV, telavancin; VM, vancomycin.

- a Diarrhea, nausea, and thrombocytopenia were most commonly associated with LZD, and anemia, nausea, and pruritus were most commonly associated with VM.
- b Pooled analysis of results from 5 studies.
- c Details regarding the nature of the serious adverse events are not available. Investigators assessed each event as serious or not serious.
- d Clox, flucloxacillin, NAF, and OX.
- e Serious adverse events included infections and infestations, cardiac disorders, respiratory, thoracic, and mediastinal disorders, nervous system disorders, psychiatric disorders, and laboratory abnormalities.
- f Phase 2 study.
may be used concomitantly with selective serotonin reuptake inhibitors, with careful monitoring, and they recommend prompt discontinuation of the serotonergic agent if serotonin syndrome is suspected [19]. The occurrence of thrombocytopenia has proven to be not significantly different than that encountered in patients with nosocomial pneumonia or orthopedic infections. Of note, patients with renal insufficiency may be at higher risk of developing this toxicity [20, 21]. Finally, there have been sporadic reports of peripheral neuropathy, typically in patients with osteomyelitis or other underlying diseases, and lactic acidosis [22, 23].

TIGECYCLINE

Tigecycline is the first drug approved in the class of glycyccyclines, a derivative of minocycline. A modified side chain on tigecycline enhances binding to the 30S ribosomal subunit, inhibiting protein synthesis and bacterial growth across a broad spectrum of pathogens, including MRSA [24]. In addition, this structural modification circumvents resistance mechanisms that plague tetracycline and other antibiotics in this class. Tigecycline is approved in the United States for the treatment of complicated SSSIs due to MRSA. The drug is also approved for the treatment of complicated intra-abdominal infections but only for those caused by methicillin-susceptible S. aureus. At this time, the published experience with tigecycline for the treatment of MRSA infections is limited to 2 double-blind comparison studies of vancomycin and aztreonam in patients with complicated SSSIs and case reports [25, 26]. Tigecycline has a large volume of distribution and produces high concentrations in tissues outside of the bloodstream, including bile, the colon, and the lung. Conversely, serum concentrations of tigecycline rapidly decrease after infusion, and the area under the concentration-time curve (AUC) after administration of multiple 50-mg doses every 12 h is $\sim 3 \mu g \cdot h/mL$ [27]. On the basis of studies of the pharmacodynamic properties of tetracycline, the target AUC for tigecycline should be 2–4 times the MIC, in an effort to optimize efficacy in the treatment of MRSA infections. Given a tigecycline MIC$_{50}$ range of 0.25–0.5 $\mu g/mL$ for MRSA, caution should be used when using tigecycline for the treatment of patients with suspected or proven bacteremia [27]. The results of further clinical evaluation should be cumulated and assessed to determine whether to accept or refute this potential limitation. The approved dose is a 100-mg intravenous loading dose followed by 50 mg given every 12 h. Nausea and vomiting are the predominant adverse events, and they increase in frequency with dose escalation.

DAPTOMYCIN

Daptomycin is a cyclic lipopeptide that causes depolarization of the bacterial cell membrane. The indicated dose for MRSA-associated complicated SSSIs is 4 mg/kg once daily, and that for bloodstream infections, including right-side endocarditis, is 6 mg/kg once daily [28]. Of note, daptomycin should not be used in the treatment of MRSA pneumonia, because the activity of the drug is inhibited by pulmonary surfactant. The results of daptomycin trials in patients with complicated SSSIs and bacteremia/endocarditis are shown in table 1 [28, 29]. In brief, of the patients who had MRSA isolated, 20 (44%) of 45 were successfully treated with daptomycin, and, of the patients in the bacteremia/endocarditis trial, 14 (32%) of 44 patients were successfully treated with vancomycin. The difference between daptomycin and standard therapy in the treatment of MRSA infections was not statistically significant. Significantly, for 6 patients who experienced microbiological failure while receiving daptomycin, it was reported that, during therapy, the MICs for the isolated pathogen increased from 0.25 or 0.5 $\mu g/mL$ to 2 or 4 $\mu g/mL$ [29]. The mechanism for resistance development while receiving therapy is, at present, not understood, but it is likely to be a consequence and a concern in patients who require prolonged courses of daptomycin therapy.

GLYCOPEPTIDES

Dalbavancin. Dalbavancin is a semisynthetic lipoglycopeptide that inhibits cell wall synthesis and has in vitro activity against MRSA [34]. The unique feature of this investigational agent is its long half-life (6–10 days), which allows for once-weekly dosing. In a randomized, double-blind trial, dalbavancin (1000 mg given intravenously on day 1 and 500 mg given intravenously on day 8) has been compared with linezolid in the treatment of SSSIs [30]. Overall clinical success rates are presented in table 1. In this trial, 51% of the isolates were found to be MRSA. In a phase 2, open-label study of the treatment of catheter-related bloodstream infections, once-weekly treatment with dalbavancin was compared with treatment with vancomycin [31]. MRSA was identified at baseline in 5 patients who received dalbavancin, and, in the overall intention-to-treat analysis, dalbavancin was found to result in a success rate significantly higher than that noted with vancomycin (87% vs. 50%; $P < .05$). The most common adverse events included nausea and diarrhea or constipation; however, dalbavancin may also be associated with hypotension, hypokalemia, and increases in alanine aminotransferase and aspartate aminotransferase levels measured in liver function tests, although, to date, the reports of these adverse events are conflicting [34].

Telavancin. Telavancin is another semisynthetic lipoglycopeptide that has a dual mechanism of action, including inhibition of cell wall synthesis and disruption of membrane barrier function [35]. It has a half-life of 7–9 h, which allows once-daily dosing (7.5–10 mg/kg/day). The disruption of membrane barrier function translates to rapid bactericidal ac-
Cell death of staphylococci and enterococci [38]. Oritavancin has a very long half-life of ~100 h, and dosing once daily or every other day is likely to be recommended. The percentage of time above the MIC of the free drug was found to be the determinant of microbiological and clinical response in bacteremia [39]. Studies of oritavancin are being conducted in patients with complicated SSTIs, catheter-related bloodstream infections, and nosocomial pneumonia [38]. Preliminary results of studies of SSTIs showed noninferiority of oritavancin to vancomycin and cephalaxin. Adverse events associated with oritavancin include headache, nausea, and sleep disorders.

**CEFTOBIPROLE AND CEFTAROLINE**

Ceftobiprole is an investigational cephalosporin engineered to bind tightly to penicillin-binding protein 2a, a peptidoglycan transpeptidase that confers β-lactam resistance in *S. aureus* isolates harboring the meca gene [40, 41]. This compound is the first of the β-lactam antibiotics to have activity against MRSA as well as penicillin-resistant streptococci. Importantly, in preclinical, multipassage resistance-selection studies, ceftobiprole demonstrated a low potential to select for resistance; the highest MIC found in the presence of prolonged serial passages with ceftobiprole at subinhibitory concentrations was 8 μg/mL in 1 of 10 strains after 50 passages [42]. Ceftobiprole is administered twice daily by the intravenous route and has been granted fast-track status by the FDA for the indications of complicated SSSIs and health care–associated pneumonia [41]. Two phase 3 trials for complicated SSSIs have been completed (STRAUSS and STRAUSS II), with preliminary results reportedly demonstrating noninferiority of ceftobiprole to comparators overall and in patients with MRSA [40, 33]. The most common adverse effects were nausea and taste disturbances.

Ceftaroline is another broad-spectrum cephalosporin with gram-positive and gram-negative bactericidal activity. Early testing indicates that MRSA and vancomycin-resistant staphylococci are susceptible to ceftaroline [43]. Phase 2 studies of this agent in patients with SSTIs are under way.


