Methicillin-Resistant *Staphylococcus aureus* Therapy: Past, Present, and Future

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Methicillin-resistant *Staphylococcus aureus* (MRSA) continues to be associated with significant morbidity and mortality. Vancomycin was the “gold standard” of treatment for serious MRSA infections; however, the emergence of less-susceptible strains, poor clinical outcomes, and increased nephrotoxicity with high-dose therapy are challenging its current role as first-line therapy. Linezolid is recommended for PO or IV treatment of skin and skin structure infections (SSSIs) and pneumonia caused by MRSA. Daptomycin (IV) should be considered in patients with MRSA bacteremia and right-sided endocarditis as well as in complicated SSSIs, but should not be used to treat MRSA pneumonia. Tigecycline and telavancin are alternative (IV) treatments for SSSIs caused by MRSA; however, safety concerns have limited use of these agents. Ceftaroline is the newest of the approved parenteral agents for SSSIs caused by MRSA. Several investigational agents with activity against drug-resistant gram-positive pathogens are being developed primarily for treatment of MRSA infections, including tedizolid, dalbavancin, and oritavancin.

Methicillin-resistant *Staphylococcus aureus* (MRSA) remains a major public health problem worldwide and a therapeutic challenge to treat [1–3]. The changing epidemiology of MRSA infections, varying resistance to commonly used antibiotics, and involvement of MRSA in community-associated (CA-MRSA) and hospital-associated infections are influencing the use and clinical outcomes of currently available antiinfective agents.

MRSA remains one of the difficult-to-treat ESRAPE pathogens (*Enterococcus faecium*, *S. aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) despite the introduction of several new antiinfective agents during the past decade [4]. Many of these newer agents are associated with dose-limiting adverse events, emerging resistance issues, and high drug costs. In addition, linezolid is currently the only oral agent available for outpatient and step-down therapy [5]. A significant number of investigational agents with activity against MRSA are currently being developed [6]. While most of these are targeted for treatment of acute bacterial skin and skin structure infections (ABSSIS), new and novel agents are urgently needed for treatment and prevention of invasive MRSA infections.

**OLDER AGENTS FOR MRSA**

Oral agents such as clindamycin, trimethoprim-sulfamethoxazole (TMP-SMX), doxycycline, and minocycline are recommended for empiric outpatient therapy of ABSSIS associated with CA-MRSA [2, 7]. Rifampin is no longer recommended for monotherapy or adjunctive therapy of ABSSIS because of the rapid development of resistance. Tetracyclines and TMP-SMX have limited activity against beta-hemolytic streptococci. Consequently, when empiric coverage is needed for both CA-MRSA and beta-hemolytic streptococci, these agents should be combined with a beta-lactam agent. Alternatively, clindamycin alone could be considered, but resistance is a concern. A D-zone test with erythromycin can be used to detect inducible clindamycin resistance in patients, which may result in clinical failure. Doxycycline...
and minocycline are also limited to use in adolescents and adults due to the risks of staining of dental enamel in children aged <12 years. Tetracyclines also have potential photosensitization potential. The high rates of drug rash and hypersensitivity reactions associated with TMP-SMX may limit clinical utility. *Clostridium difficile*-associated diarrhea and potentially life-threatening pseudomembranous colitis are concerns associated with all antibiotics.

After more than 50 years of clinical use, treatment guidelines and surveys indicate vancomycin remains the workhorse of parenteral antiinfective agents for MRSA infections despite the ongoing debate of whether it is obsolete [2, 8–11]. Most clinicians use vancomycin for the empiric and definitive therapy of systemic MRSA infections as outlined in current Infectious Diseases Society of America (IDSA) treatment guidelines [3]. Vancomycin should be continued as long as the patient is clinically and microbiologically responding to therapy, other foci of infection have been adequately debrided and removed, and susceptibility testing shows a minimal inhibitory concentration (MIC) of 2 µg/mL or less (Clinical and Laboratory Standards Institute [CLSI] susceptible breakpoint).

While the CLSI breakpoint defines the upper limit of the laboratory-defined susceptibility range, recent reviews [12] have drawn attention to increased treatment failures at MICs <2 and suggest that alternative therapy be considered when an isolate vancomycin MIC is >1 µg/mL [2]. Global surveillance studies have suggested a gradual rise in vancomycin MIC, further challenging the routine use of vancomycin. Several other key observations reported in the past few years suggest and/or confirm the following: (1) vancomycin MIC values are method specific [13]; (2) higher vancomycin MIC values for isolates of methicillin-susceptible *S. aureus* (MSSA) and MRSA appear to influence clinical outcomes associated with beta-lactam agents and vancomycin, respectively [14, 15]; (3) clinical outcomes with vancomycin are a function of bacterial load at the site of infection [16]; (4) targeting of higher vancomycin trough concentrations (eg, 15–20 µg/mL) is associated with modest improvements in clinical outcomes of selected patients [17]; (5) targeted trough concentrations of 15–20 µg/mL, however, do not consistently attain area under (concentration-time) curve (AUC)/MIC ratios ≥400 when the vancomycin MIC is 2 µg/mL [18]; and (6) higher rates of nephrotoxicity (eg, 20%–30%) are associated with high-dose vancomycin therapy [19]. It has become obvious that no single factor can serve as a predictor of success or failure for vancomycin therapy [17]. As suggested in the treatment guidelines [3], a number of questions remain unanswered, and further clinical studies will be required to determine the most effective treatment regimens for MRSA infections.

Quinupristin-dalfopristin has limited utility (eg, salvage therapy) in patients with serious MRSA infections in light of limited and equivocal data, issues of resistance (eg, with *E. faecium*), increased risk of adverse events (eg, myalgias, arthralgias, infusion-related and injection-site reactions), multiple drug-drug interactions, and high cost of therapy [2, 7, 20]. TMP-SMX can be considered an alternative to vancomycin for selective cases of invasive MRSA infections. In a recent retrospective chart review of MRSA infections with a vancomycin MIC ≥ 2 µg/mL, TMP-SMX was effective but tended to be used in less severe infections [21]. A small, retrospective study provides further evidence that TMP-SMX and vancomycin have similar safety and efficacy in patients with MRSA bacteremia [22].

**NEWER AGENTS FOR MRSA**

The following 5 antiinfective agents have been approved by the US Food and Drug Administration (FDA) for the treatment of MRSA based on well-controlled clinical trials in SSSIs: linezolid, daptomycin, tigecycline, telavancin, and ceftaroline. Among the newer agents, only linezolid is available in both an oral and an intravenous formulation and could be considered for empiric monotherapy of both CA-MRSA and beta-hemolytic streptococci. However, its clinical use has been limited to selective patients secondary to its high drug costs. Table 1 provides a summary of these agents compared to vancomycin [6, 7].

Linezolid is the first available oxazolidinone antimicrobial agent [23]. Linezolid is 100% bioavailable and demonstrates extensive tissue penetration, including into the epithelial lining fluid of the lungs and infected skin and soft tissues of diabetic patients [3, 23, 24]. The published guidelines for the treatment of MRSA consider linezolid an alternative first-line agent for MRSA pneumonia [3]. Although several studies (including the recent ZEPHYR trial [25]) have found higher cure rates for linezolid compared to vancomycin, it remains controversial whether linezolid is superior to vancomycin for its approved indications (complicated and uncomplicated SSSI and nosocomial pneumonia). Likewise, numerous studies have provided support for clinical use of linezolid in complicated MRSA SSSIs, including diabetic foot infections without osteomyelitis. The most common drug-related side effects observed with linezolid were diarrhea, nausea, headache, and abnormal liver function tests [24]. Reversible myelosuppression (including thrombocytopenia, leucopenia, pancytopenia, and anemia) has been reported with linezolid therapy, and complete blood counts should be monitored weekly in patients receiving linezolid for longer than 2 weeks [24]. Other rare but serious adverse events observed during postmarketing experience include lactic acidosis, peripheral neuropathy, and optic neuropathy, mostly with prolonged therapy (>28 days) [24]. Linezolid is a weak, nonselective monoamine oxidase inhibitor, and serotonin syndrome has been reported in cases with concomitant administration of selective serotonin reuptake inhibitors. While rare, sporadic clinical reports of linezolid resistance, associated with either point mutations or acquisition of the cfr

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<th>Adverse Events</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tr>
<td>Vancomycin</td>
<td>&quot;Slow&quot; bactericidal activity (concentration independent); cell wall inhibition</td>
<td>IV: 500 mg q6h or 1000 mg q12h; high-dose therapy (15 to 20 mg/kg total body weight q8 to 12 h) currently recommended when MIC values are 1 µg/mL</td>
<td>Renal: Dosing adjustments are necessary; dosing nomograms and monitoring trough serum vancomycin concentration recommended Hepatic: no adjustment needed</td>
<td>Nephrotoxicity; red man syndrome</td>
<td>Inexpensive; &gt;50 y of clinical experience</td>
<td>VISA, hVISA, VRSA; increasing MIC values associated with poor outcomes; nephrotoxicity with higher doses</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Bacteriostatic; protein synthesis inhibition (23S RNA at 50S ribosomal subunit)</td>
<td>IV or PO: 600 mg q12h</td>
<td>Renal: None Hepatic: No specific recommendations</td>
<td>Thrombocytopenia and anemia (duration dependent); peripheral and optic neuropathy; lactic acidosis; serotonin syndrome</td>
<td>100% bioavailable oral formulation; good drug penetration into lung; active against VRE</td>
<td>Bacteriostatic; serious adverse events with long-term use (&gt;14 d); increasing linezolid-resistant S. aureus; high drug cost</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>Bactericidal (concentration dependent); membrane depolarization (Ca++ dependent)</td>
<td>IV: cSSSI: 4 mg/kg (total body weight) q24h; S. aureus bacteremia: 6 mg/kg (total body weight) q24h; some experts recommend higher doses (8 to 10 mg/kg) for bacteremia/infective endocarditis indications</td>
<td>Renal: For CrCl &lt;30 mL/min, q48h Hepatic: No specific recommendations</td>
<td>CPK elevation; myopathy; peripheral neuropathy; case reports of rhabdomyolysis and eosinophilic pneumonia</td>
<td>Rapidly bactericidal; effective for MRSA bloodstream infections and right-side endocarditis; active against VRE; extensive published literature on treatment experiences for a wide range of MRSA infections</td>
<td>Inactivated by pulmonary surfactant and should not be used to treat pneumonia; increasing MIC values correlated to vancomycin increasing MIC values; suboptimal clinical outcomes in patients with reduced renal function; high drug cost</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>Bacteriostatic; protein synthesis inhibition (at 30S ribosomal subunit)</td>
<td>IV: loading dose of 100 mg followed by 50 mg q12h</td>
<td>Renal: None Hepatic: Child-Pugh class C. 100 mg single dose, maintenance 25 mg q12h</td>
<td>GI side effects (nausea and vomiting are common)</td>
<td>Active against VRE</td>
<td>Bacteriostatic; low serum and ELF drug concentrations; not approved for HAP/VAP; high rates of GI adverse events; higher risk of mortality than comparator agents; high drug cost</td>
</tr>
<tr>
<td>Telavancin</td>
<td>Bactericidal (concentration dependent); cell wall inhibition and membrane depolarization</td>
<td>IV: 10 mg/kg (total body weight) q24h</td>
<td>Renal: CrCl 30 to 50 mL/min, 7.5 mg/kg q12h; CrCl 10 to &lt;30, 10 mg/kg q48h; CrCl &lt;10, limited data Hepatic: No specific recommendations</td>
<td>GI side effects (including dysgeusia); mild QT prolongation; nephrotoxicity</td>
<td>Rapidly bactericidal against MRSA, VISA, and VRSA; active against MRSA strains resistant to vancomycin, linezolid, and daptomycin</td>
<td>Nephrotoxicity; lower clinical outcomes in patients with reduced renal function; REMS and avoid use during pregnancy; coagulation test interference; manufacturing issues limit its current availability</td>
</tr>
</tbody>
</table>
Daptomycin or when organisms have a high vancomycin MIC combination with other antibiotics has been recommended for mSSSI caused by MRSA with high vancomycin MIC values (>1 µg/mL) [30]. High-dose daptomycin (10 mg/kg once daily) in cases of native-valve, right-sided infective endocarditis [2]. Some experts recommend still higher doses (eg, 8–10 mg/kg once daily) to minimize the emergence of elevated daptomycin MIC values, as was observed in a randomized, controlled trial [2, 29]. A recent case-control study by Moore and colleagues provides supportive evidence for switching to daptomycin in patients with bacteremia caused by MRSA with high vancomycin MIC values (>1 µg/mL) [30]. High-dose daptomycin (10 mg/kg once daily) in combination with other antibiotics has been recommended for persistent MRSA bacteremia when isolates are susceptible to daptomycin or when organisms have a high vancomycin MIC (eg, >1 µg/mL) or for vancomycin-resistant strains [2]. The role of combination MRSA therapy has been mainly limited to in vitro testing, and clinical trials are urgently needed. An increase in the vancomycin MIC (eg, ≥2 µg/mL) and heteroresistant (hVISA) phenotype have been associated with an increased daptomycin MIC [31]. When MRSA isolates are not susceptible to daptomycin, alternative agents should be used. Although daptomycin penetrates into the lungs, it is inactivated by pulmonary surfactant and should not be used for the treatment of pneumonia [28]. Overall, daptomycin appears to be well tolerated and serious adverse events (eg, rhabdomyolysis, peripheral neuropathy, and eosinophilic pneumonia) have been limited to case reports. Elevations in serum levels of creatine phosphokinase (CPK) as well as drug-induced myopathy have been reported with daptomycin. The incidence of CPK elevation has ranged from 2.8% to 6.7% in phase 3 clinical studies and is reported to be reversible once daptomycin is discontinued [32]. Bhavnani and coworkers demonstrated an increased probability of a CPK elevation with daptomycin trough concentrations of 24.3 µg/mL or greater [33]. Baseline and periodic monitoring of CPK levels and assessment of myopathy should be pursued in all patients prescribed daptomycin. Because rates of CPK elevation appear to increase with frequency of dosing, dosing with daptomycin should be limited to once daily [32].

Tigecycline is a semisynthetic derivative of minocycline and the first licensed drug from the glycyclycline class of antimicrobial agents [34]. It has a broad spectrum of activity that includes aerobic and anaerobic gram-positive and gram-negative pathogens as well as atypical pathogens. The recent MRSA guidelines did not include tigecycline because of the FDA’s September 2010 safety statement describing increased overall mortality among patients with serious infections treated with tigecycline (4%) vs comparator therapy (3%) [35]. This finding was based on pooled data from 13 randomized phase 3 and 4 clinical trials of
both FDA-approved and off-label indications (eg, hospital-acquired pneumonia, ventilator-associated pneumonia, and diabetic foot infections). Further evidence comes from 4 recently published metaanalyses [36–39]. Although no significant differences in efficacy have been observed between tigecycline and comparator agents in complicated SSSIs [36–38, 40], tigecycline is often recommended as a second- or third-line agent for MRSA infections when alternative agents cannot be used. Because of its low plasma drug concentrations and bacteriostatic activity [41] and higher mortality rates, tigecycline should not be used in patients with MRSA bacteremia and it has not been included in the recent IDSA MRSA treatment guidelines [3].

Telavancin is a once-daily parenteral lipoglycopeptide approved for the treatment of adult patients with complicated SSSIs, including MSSA and MRSA [42]. Two phase 3, randomized, double-blind clinical trials (ATTAIN I and II) have investigated telavancin for the treatment of nosocomial pneumonia [43]. The FDA Anti-Infective Drugs Advisory Committee recently reviewed the New Drug Application of telavancin for the indication of nosocomial pneumonia (including ventilator-associated pneumonia) caused by gram-positive bacteria, including MRSA, and has advised for limited use when no other options are available [44]. The FDA approved telavancin for this indication in June 2013. This indication had been previously approved in Europe and limited to known or suspected cases of MRSA for which alternative agents are not appropriate. Careful consideration is required before using telavancin for ABSSSIs in light of the following warnings and precautions: (1) more frequent increases in serum creatinine to 1.5 times baseline values (15% vs 7%) and higher rates of renal impairment (3.1% vs 1.1%) vs vancomycin; (2) decreased efficacy in patients with reduced renal function vs vancomycin; (3) lack of data and unknown efficacy in life-threatening bloodstream infections; and (4) teratogenicity with an FDA-mandated risk evaluation and mitigation strategy (REMS) requiring pregnancy testing in woman of childbearing potential (pregnancy category C) before administering telavancin [42]. Until more clinical information becomes available, telavancin should be reserved for serious infections caused by MRSA with a vancomycin MIC of 1 µg/mL or greater, infections caused by hVISA, MRSA infections that do not respond to vancomycin, and gram-positive bacteremia in patients who are unable to tolerate other proven antimicrobials [2, 42]. During the past year, telavancin use has been limited because of manufacturing problems announced in November 2011. The manufacturing process has been revised, and commercial supplies of telavancin became available for clinical use in August 2013.

Ceftaroline fosamil is the first FDA-approved cephalosporin with any activity against MRSA [45]. Two phase 3, noninferiority-designed clinical trials (CANA 1 and II) have demonstrated that 5 to 14 days of intravenous ceftaroline 600 mg administered every 12 hours is comparable to vancomycin plus aztreonam for the treatment of ABSSSIs [46]. Pooled clinical cure rates in microbiologically evaluable patients with MRSA were similar: 93.4% for ceftaroline and 94.3% for vancomycin plus aztreonam. Ceftaroline fosamil was well tolerated, with <5% incidence of adverse effects. The most common adverse reactions occurring in >2% of patients were diarrhea, nausea, and rash. A higher rate of Coombs’ test seroconversion was noted during clinical trials for ceftaroline vs comparators (10.8% vs 4.4%), but no episodes of hemolytic anemia were observed. As with other cephalosporins, hypersensitivity reactions, including anaphylaxis, are also a

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<th>Route of Administration</th>
<th>Developer</th>
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<tr>
<td>Ceftobiprole</td>
<td>Cephalosporin</td>
<td>Intravenous</td>
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<td>EDP-420</td>
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<tr>
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<td>Oritavancin</td>
<td>Lipoglycopeptide</td>
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<tr>
<td>TD-1792</td>
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<tr>
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<td>Linopristin/Flopristin (NXL-103)</td>
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</tr>
<tr>
<td>JNJ-Q2</td>
<td>Fluoroquinolone</td>
<td>Oral and intravenous</td>
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<tr>
<td>Delafloxacin (ABT 492)</td>
<td>Fluoroquinolone</td>
<td>Oral and intravenous</td>
<td>Melinta Therapeutics</td>
</tr>
<tr>
<td>Radezolid</td>
<td>Oxazolidinone</td>
<td>Oral and intravenous</td>
<td>Melinta Therapeutics</td>
</tr>
<tr>
<td>Tedizolid (formerly torezolid)</td>
<td>Oxazolidinone</td>
<td>Oral and intravenous</td>
<td>Cubist Pharmaceuticals</td>
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<tr>
<td>BC-3781</td>
<td>Pleuromutilin</td>
<td>Oral and intravenous</td>
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<td>Fusidane</td>
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potential risk with ceftaroline. Although ceftaroline is also approved for the treatment of community-acquired bacterial pneumonia, the 2 randomized, double-blind clinical trials performed for this indication (FOCUS I and II) excluded patients with MRSA [46]. Clinical experience with ceftaroline in other types of invasive infections caused by MRSA has been limited.

FUTURE AGENTS FOR MRSA

Development of new antiinfective agents has significantly decreased during the past 10 to 15 years [4, 47–49]. The antibiotic pipeline has dramatically declined for several key reasons: (1) difficulties in discovering new agents with novel mechanism(s) of action; (2) substantial changes and challenges in regulatory guidance and decision-making; and (3) lower financial return on corporate investment compared to other therapeutic classes in medicine [47, 49]. Several recent initiatives (eg, the IDSA 10 × 20 Initiative and the Innovative Medicine Initiative) as well as ongoing changes to regulatory guidance documents have been implemented to encourage development of new antibiotics to treat antibacterial-resistant infections [50, 51].

Table 2 provides a list of investigational antiinfective agents being considered for the treatment of MRSA [4, 5, 6, 48, 52, 53]. Many are familiar derivatives of antibiotic classes currently used to treat MRSA (eg, glycopeptides, oxazolidinones, cephalosporins, tetracyclines) [47, 48], have been in development for several years [52, 53], and/or were recently not approved following regulatory actions [49]. Many have significant antibacterial and pharmacologic benefits compared to MRSA agents currently used. For example, tedizolid (formerly known as torezolid, TR-701, DA-7218) is a novel oxazolidinone that has completed a phase 2 study in ABSSSI, has reported findings from a phase 3 trial, and has recently completed enrollment for a second phase 3 trial for ABSSSI. Results from the first phase 3 trial confirm noninferior response (compared to linezolid) at 48–72 hours after the start of therapy and when the outcome from 6 days of tedizolid is compared to 10 days of linezolid (see results in this supplement). Tedizolid differs from linezolid by having in vivo bactericidal activity, activity against linezolid-resistant strains associated with the cfr gene, once-daily dosing, a shorter duration of therapy for treating ABSSSI, and a lower incidence of gastrointestinal and myelosuppressive adverse events [5]. Tedizolid, dalbavancin, and oritavancin are currently completing phase 3 clinical trials for the treatment of ABSSSI caused by MRSA. The new FDA draft guidance for ABSSSI includes a new primary endpoint of clinical response at 48–72 hours after initiating antimicrobial therapy, with endpoint criteria outlined by the Biomarkers Consortium of the Foundation for the National Institutes of Health [51, 54], that will likely reshape the conduct and outcomes of future product development.

CONCLUSIONS

Vancomycin remains the “gold standard” of parenteral therapy for the treatment of serious MRSA infections. During the past decade, linezolid and daptomycin have established significant roles as first-line agents in selective patients. Limitations in clinical efficacy data, unavailability of drug product, and safety risks have limited the use of other older and newer agents. The changing epidemiology of MRSA infections and design of clinical trials will continue to shape the landscape for the management of serious MRSA infections. The current pipeline of investigational agents for the treatment of MRSA infections is promising and will hopefully yield several new options for the antibacterial armamentarium.

Notes

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