# Optimizing Therapy for MRSA Pneumonia

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## ABSTRACT

With its remarkable armamentarium of resistance and virulence factors, *Staphylococcus aureus* has emerged as a dominant pathogen causing pneumonia of all classifications. Rates of methicillin resistance are increasing as clinicians struggle to find ways to prevent the acquisition of methicillin-resistant *Staphylococcus aureus* (MRSA) and to effectively treat MRSA pneumonia. Community-associated MRSA has been identified as an important subset of MRSA with unique characteristics. Vancomycin remains a recommended first-line therapy for MRSA pneumonia, but resistance and therapeutic failures with vancomycin are being increasingly reported. Factors associated with vancomycin success or failure have been identified, including the genetics of the MRSA isolate, vancomycin lung penetration, minimum inhibitory concentration, and pharmacokinetic and pharmacodynamic variables. Retrospective analyses suggest that linezolid may provide improved outcomes compared with vancomycin for MRSA pneumonia, but validation in a prospective trial is currently lacking. Other treatment options are limited, but new prospects are being investigated. This paper reviews the epidemiology and pharmacotherapy of MRSA pneumonia.

**KEYWORDS:** Methicillin-resistant *Staphylococcus aureus,* pneumonia, health care–associated

## MRSA AS A PATHOGEN

*Staphylococcus aureus* is a gram-positive coccus that has a remarkable armamentarium of resistance and virulence factors.[1–3] *S. aureus* also has a large number of mobile DNA elements that are able to perform gene exchange; as a result of these characteristics this organism has evolved as a major pathogen. *S. aureus* can be found as part of the normal flora on the skin and mucosal surfaces, with a proclivity for the nares. Colonization is enhanced by biofilm formation, antiphagocytotic microcapsules, and surface adhesions. Surface proteins that bind extracellular matrix molecules are referred to as microbial surface components recognizing adhesive matrix molecules (MSCRAMM). MSCRAMMs are anchored to the cell wall peptidoglycan and aid in colonization of host tissues.[1–3]

Once an inoculum is established, *S. aureus* can produce a variety of virulence factors to cause disease, including exoenzymes and toxins.[1–3] Exoenzymes include proteases, lipases, and hyaluronidases, which can cause tissue destruction and may facilitate spread of infection. The toxins that can be produced are numerous and include hemolysins, leukocidins, exfoliative toxins, Panton-Valentine leukocidin (PVL) toxin, toxic shock syndrome toxin (TSST-1), enterotoxins, and α-toxin. These toxins are associated with specific diseases and are capable of eliciting severe local and systemic responses.[1–3]

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Expression of virulence factors is regulated by *agr*, an accessory gene regulator.[1,2,4] *agr* is able to alter virulence gene expression and generally upregulates production of secreted virulence factors and downregulates production of cell surface virulence factors. Polymorphisms of *agr* account for the four major *agr* groups (I to IV) and the different groups appear to be associated with different clinical scenarios.[4] Examples include associations of the *agr* II polymorphism with glycopeptide intermediate *S. aureus* (GISA)[4] and the *agr* III polymorphism with community-associated methicillin-resistant *S. aureus* (CA-MRSA).[5]

Another important genetic element of *S. aureus* is the genomic island SCC*mec*. SCC stands for staphylococcal chromosomal cassette and *mec* is the gene encoding methicillin resistance. The *mec*A gene encodes PBP2A, a penicillin-binding protein with reduced affinity for β-lactams. The *mec* gene must be present for *S. aureus* to be resistant to extended-spectrum penicillins and cephalosporins. There are five types of SCC*mec* (I to V). SCC*mec* I, II, and III are larger elements that are more difficult to mobilize and are present in hospital-acquired clones. SCC*mec* IV is a smaller, easier to mobilize genetic element that is present in CA-MRSA.

As already eluded to, MRSA can be further differentiated into hospital-acquired MRSA (HA-MRSA) and CA-MRSA. These names imply a difference in genetic elements, resistance patterns, location of acquisition, and possibly clinical presentation. The genetics of both HA-MRSA and CA-MRSA have now been described and eight distinct genetic clusters have been recognized (USA100 to USA800).[6] CA-MRSA strains contain the USA300 or USA400 genotype, whereas the remaining genotypes are found in HA-MRSA strains. Identification of CA-MRSA infections in the clinical setting is practically done through careful scrutiny of the sensitivity report for each MRSA isolate. Compared with HA-MRSA, CA-MRSA isolates are more likely to be susceptible to non-β-lactam antibiotics, including trimethoprim-sulfamethoxazole (TMP-SMX), clindamycin, fluoroquinolones, gentamicin, erythromycin, and tetracyclines with geographic variability.[5,7–10] CA-MRSA are also more likely to carry Panton-Valentine leukocidin genes. Differentiation based on the location of acquisition is becoming increasingly less distinct because recent findings suggest that the CA-MRSA is effectively integrating into the hospital environment.[10,11]

## EPIDEMIOLOGY OF MRSA PNEUMONIA

Pneumonia is classified based on time of infection acquisition and risk for drug-resistant pathogens as community-acquired (CAP), health care–associated (HCAP), hospital-acquired (HAP), or ventilator-associated (VAP).[12] Regardless of the classification, MRSA is a major cause of pneumonia. In a recent analysis of over 4500 hospitalized patients with culture-positive pneumonia, the most frequently isolated organism was *S. aureus*, and MRSA was a causative pathogen in 8.9, 26.5, 22.5, and 14.6% of patients with CAP, HCAP, HAP, and VAP, respectively.[13] In the SENTRY database, *S. aureus* was the most frequent cause of lower respiratory tract infection, and patients with pneumonia had the highest rates of methicillin resistance.[14] Rates of pneumonia due to *S. aureus* have been increasing in the past 2 decades; an analysis of over 410,000 isolates from the National Nosocomial Infection Surveillance (NNIS) system reported that pneumonia due to *S. aureus* had more than doubled from 13.4% in 1975 to 27.8% in 2003.[15] At the same time, rates of methicillin resistance are increasing such that MRSA now accounts for $>50\%$ of *S. aureus* isolates in many intensive care unit (ICU) settings.[16,17] These data establish MRSA as an important cause of pneumonia in all settings.

As a result of the increasing incidence of MRSA as a causative pathogen in pneumonia and the association between inappropriate antimicrobial therapy and increased mortality,[18–20] it is imperative to identify patients at risk for MRSA infection upon presentation. Community-dwelling patients at risk for MRSA infection are those with recent health care exposures, including home intravenous therapy, hospitalization within the past 90 days, receipt of hemodialysis in a clinic or hospital setting, residence in a nursing home or long-term care facility, home wound care in the past 30 days, antimicrobial therapy in the preceding 90 days, and an immunosuppressive therapy or disease, or those presenting to an institution with high MRSA frequencies.[12] Additionally, patients presenting with lung abscesses, injection drug abusers, those with structural lung disease, and those living in communities where influenza is active are at risk for MRSA infection.[21] Significant morbidity and mortality are associated with MRSA pneumonia. Studies investigating outcomes in patients with VAP due to MRSA compared with patients with MSSA found patients with MRSA infection are older, have higher severity of illness, have longer durations of mechanical ventilation prior to the onset of VAP, and often have higher mortality rates.[22–24]

Recently, several case reports have described CA-MRSA as the cause of severe, necrotizing pneumonia.[25–27] Patients often present with hemoptysis, leukopenia, high fever, and a cavitary picture on chest radiograph.[28] CA-MRSA pneumonia has been linked as a secondary bacterial infection in patients with influenza infection.[25] Consequently, the Centers for Disease Control and Prevention (CDC) has recommended empirically covering for MRSA in community-dwelling hosts that present with this viral infection.[29] The severity of CA-MRSA pneumonia may be linked to the production of Panton-Valentine leukocidin (PVL), a bicomponent

exotoxin with the ability to create lytic pores in neutrophil cell membranes, causing release of neutrophil chemotactic factors, including interleukin-8 and leukotriene B4.[30] Although the importance of PVL as a determinant of virulence in CA-MRSA murine models of sepsis with abscess formation has recently been called into question,[31] this is not the case in models of PVL-positive pneumonia. Lung tissue of mice infected with PVL-positive *S. aureus* develop massive neutrophilic infiltration, lung parenchyma infiltration, hemorrhage, and tissue necrosis.[32] Comparatively, the lungs of mice infected with PVL-negative *S. aureus* remain normal. Additionally, PVL induces expression of adhesion proteins (specifically staphylococcal protein A), which block the actions of phagocytic immune cells and elicit a proinflammatory response. Thus the clinical presentation of pneumonia caused by PVL-positive CA-MRSA is likely due to this dual mechanism of PVL virulence—lysis/apoptosis of host cells and enhanced adhesion expression.

## TREATMENT OF MRSA PNEUMONIA

### Vancomycin

Vancomycin has long been considered the drug of choice for MRSA infections and is recommended as a first-line therapy for HCAP, HAP, and VAP in the most recent guidelines.[12] Given the increasing incidence of infections due to MRSA, vancomycin use has greatly increased. Although vancomycin has been considered a reliable agent and MRSA susceptibilities to vancomycin have remained fairly stable, isolates with intermediate (VISA [vancomycin-intermediate *S. aureus*], hVISA [heteroresistant VISA]) and full (VRSA [vancomycin-resistant *S. aureus*]) levels of resistance have been reported. Furthermore, numerous reports have emerged describing vancomycin treatment failure for infections due to MRSA with vancomycin minimum inhibitory concentrations (MIC) in the "susceptible" range.[33–35] For these reasons the study of outcomes for patients with MRSA infections treated with vancomycin has become an important area of research. Through these investigations several factors associated with vancomycin success or failure have been identified, including genetics of the MRSA isolate, vancomycin lung penetration, MRSA inoculum size, MIC, and pharmacokinetic and pharmacodynamic (PK/PD) variables.

Vancomycin is a large-molecular-weight compound that inhibits bacterial cell wall synthesis by binding tightly to the D-alanyl-D-alanine portion of cell wall precursors and subsequently inhibiting glycopeptide polymerization and transpeptidation.[36] This mechanism of action results in slowly bactericidal activity with time-dependent killing. Vancomycin has a large volume of distribution (0.5 to 0.9 L/kg) and is 10 to 50% protein bound. The drug is eliminated primarily via the kidneys and has an elimination half-life of 6 to 12 hours.[37]

Recently an association between certain MRSA genotypes and vancomycin resistance with treatment failure has been observed. Moise-Broder and colleagues investigated the relationship between the *agr* II polymorphism and clinical outcomes in 87 patients with MRSA infection treated with vancomycin as part of two clinical trials.[33] Through multivariate logistic regression analysis, the presence of *agr* II polymorphism and renal insufficiency were found to be predictors of treatment failure. However, a potential selection bias exists in this analysis because patients were included if glycopeptide treatment failure had occurred. The group of investigators observed *agr* II polymorphism with loss of *agr* functionality was associated with glycopeptide intermediate-level resistance in seven strains of *S. aureus* and thus hypothesized that lack of *agr* function may be a factor in determining vancomycin resistance.[38]

In order for vancomycin to be active, free drug must be present at the site of the infection. As mentioned previously vancomycin is a large compound that displays protein binding, which may reduce its penetration into lung tissue. Cruciani and colleagues measured vancomycin lung tissue concentrations after a one-time dose of 1 g in 30 patients undergoing lung resection.[39] Mean lung tissue concentrations at 1, 2, 6, and 12 hours were 9.6, 5.7, 2.4, and 2.8 mg/kg, respectively. One out of six and three out of seven patients had undetectable levels at 6 and 12 hours, respectively. Lamer and colleagues measured steady-state vancomycin trough concentrations in bronchoscopically obtained epithelial lining fluid (ELF) and serum for 14 mechanically ventilated critically ill patients.[40] The mean ELF vancomycin concentration was 18% of the mean serum concentration. Drug penetration was improved in patients who had inflammation as was defined by ELF albumin concentrations. Although there are some limitations to these methods of estimating lung penetration, it is clear that the pulmonary distribution of vancomycin is limited.

Knowledge of the isolate MIC may be an important variable when making treatment decisions. In 2006, the Clinical and Laboratory Standards Institute (CLSI) lowered the vancomycin MIC breakpoints for MRSA as follows: susceptible, $\leq 2$ μg/mL; intermediate, 4 to 8 μg/mL; resistant, $\geq 16$ μg/mL. Intermediate-level resistance [glycopeptide intermediate *S. aureus* (GISA) and hetero-GISA] appears to be mediated via a thickened cell wall and sequestration of vancomycin.[41] Three isolates of glycopeptide-resistant *S. aureus* (GRSA) have now been reported in Michigan, New York, and Pennsylvania.[42–44] High-level resistance to vancomycin in *S. aureus* is mediated via the VanA gene, which encodes for D-ala-D-lac and has reduced affinity for vancomycin.[36] Importantly, the CA-MRSA USA300 strain contains a conjugative plasmid (pUSA03) found to be more than

99% homologous to the genetic architecture identified in GRSA strains containing the vancomycin-resistant transposon (VanA), and thus emergence of CA-GRSA has the potential to develop.[45]

It has also been observed that higher MICs within the "susceptible" range may result in increased rates of treatment failure. In the previously mentioned analysis of the *agr* II polymorphism, vancomycin failure rates were 48, 70, and 92% for patients who had MRSA infection with MIC values of 0.5, 1.0, and 2.0, respectively.[33] A subgroup analysis of this population consisting of 30 patients with MRSA bacteremia revealed response rates of 55.6% among patients with MRSA isolates having vancomycin MICs of $\leq 0.5$ μg/mL compared with a 9.5% response rate for patients with MRSA isolates having vancomycin MICs of 1 to 2 μg/mL ($p = .01$).[38] Similarly, end-of-treatment responses were recently found to be significantly lower in a heterogeneous sampling of MRSA infections caused by isolates with an MIC $\geq 2$ μg/mL compared with isolates with an MIC $< 2$ μg/mL [62% (24/39) vs 85% (34/40); $p = .02$], when target vancomycin troughs were achieved.[46]

Given these findings, the incidence of MRSA isolates with MIC values $\geq 2$ μg/mL is of great interest. An analysis of $> 240{,}000$ *S. aureus* isolates compiled in U.S. laboratories by the Surveillance Network found 16.2% had an MIC of 2 μg/mL and 0.2% had an MIC of $\geq 4$ μg/mL.[47] Despite this report, globally it does not appear the incidence of *S. aureus* isolates with a vancomycin MIC of 2 μg/mL or greater is on the rise as reported in the SENTRY database spanning 1998 to 2003.[48] However, Rhee and colleagues found a threefold increase in the proportion of MRSA isolates with a minimum bactericidal concentration (MBC) $\geq 1.6$ μg/mL at a single center between 1994 and 1999, and MBC may be a better predictor of vancomycin success than MIC.[49]

Given the poor lung penetration of vancomycin, the presence of VISA and hVISA, and the association between elevated MICs within the "susceptible" range and worse outcomes, optimization of vancomycin PK/PD parameters may yet be another variable necessary for treatment success. The most recent American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) guidelines for HAP, VAP, and HCAP recommend targeting vancomycin trough concentrations of 15 to 20 μg/mL for the treatment of pneumonia.[12] If one considers the lung penetration of vancomycin to be ~20% of serum concentrations this would result in a concentration of 4 μg/mL in the lung tissue, not taking protein binding into account. Although no prospective trials have investigated targeting PD indices or elevated troughs, this has been the subject of several retrospective analyses.

Moise-Broder and colleagues have performed two retrospective analyses of the relationship between area under the inhibitory curve (AUIC) and clinical response in hospitalized patients with *S. aureus* infection. In the initial investigation of 70 patients with both methicillin-susceptible *S. aureus* and MRSA lower respiratory tract infection, clinical success with vancomycin was more common in patients who had a predicted AUIC of $\geq 345$ mg(hr)/L versus $< 345$ mg(hr)/L (78% vs 24%, respectively, no *p*-value provided).[50] A second analysis of 108 patients with *S. aureus* lower respiratory tract infection treated with vancomycin found an AUIC of $\geq 400$ mg(hr)/L to be predictive of clinical and microbiological outcome.[51] Of the 108 patients, only 63 patients received vancomycin, of which 37 had MRSA and 26 MSSA infection. Neither investigation utilized bronchoalveolar lavage (BAL) confirmation for diagnosis.

Two recent studies have investigated the relationship between targeting higher vancomycin troughs and clinical outcomes. Hidayat and colleagues evaluated the effects of attaining serum trough concentrations of four times the MIC of the infecting organism in 95 patients with MRSA infections, 49 (52%) of which were due to pneumonia.[46] Although significantly more patients who achieved the target trough concentration had a response at 72 hours compared with those who failed to achieve the target trough, this difference did not exist at the end of therapy. A study at our institution evaluated 102 patients with BAL-confirmed MRSA HCAP treated with vancomycin for $\geq 72$ hours.[52] The mean vancomycin trough concentrations ($13.6 \pm 5.9$ vs $13.9 \pm 6.7$ μg/mL, respectively) and AUC values ($351 \pm 143$ vs $354 \pm 109$ μg/hr/mL, respectively) were not different between survivors and nonsurvivors, and similar results were obtained when the patients were stratified according to vancomycin trough concentrations or AUC values. Renal toxicity is reported to be a relatively infrequent complication of vancomycin administration occurring in about 5% of patients and is usually reversible.[53] However, associations between elevated trough concentrations and increased rates of nephrotoxicity have recently been observed.[46,54] Thus it is not clear that optimizing vancomycin PK/PD parameters will optimize outcomes for patients with MRSA pneumonia, and only a prospective randomized trial can fully address this issue.

## Linezolid

Linezolid is a synthetic oxazolidinone that inhibits the initiation of protein synthesis at the 50s ribosome. It is currently approved by the U.S. Food and Drug Administration (FDA) for treating nosocomial pneumonia caused by susceptible pathogens, including MRSA, and is listed as a first-line option by the ATS/IDSA

guidelines for the treatment of HCAP, HAP, or VAP. Much attention has been given to the question surrounding whether linezolid is superior to vancomycin for the treatment of MRSA pneumonia. The debate stems from two retrospective analyses of pooled data from randomized trials that compared linezolid to vancomycin for nosocomial pneumonia. The first analysis evaluated a subgroup of nosocomial pneumonia patients that had MRSA isolated from respiratory specimens.[55] Seventy-five patients treated with linezolid had significantly higher survival rates compared with 85 patients treated with vancomycin (80% vs 63.5%; $p = .03$).[55] Logistic regression analysis also found an association between linezolid-treated patients and in-hospital survival (adjusted odds ratio 2.2, 95% confidence interval 1.0 to 4.8; $p = .05$). The authors hypothesized the outcome difference may be a consequence of vancomycin's poor lung penetration, particularly when a standard dose of 1 g every 12 hours is administered, which may not be reason alone given the aforementioned data. Linezolid, in contrast, has been observed to achieve mean epithelial lining fluid (ELF) concentrations (peak and trough) that are 100% of the simultaneous mean concentrations in plasma 2 days after the initiation of therapy in critically ill patients with VAP.[56] A second retrospective analysis utilized the same group of patients as the first post hoc analysis but limited the sample to patients with VAP caused by MRSA.[57] In this subset of patients, significantly higher in-hospital survival rates were observed in patients treated with linezolid compared with vancomycin [37/44 (84.1%) vs 29/47 (61.7%); $p = .02$]. Similar to the first analysis, linezolid therapy was found to be an independent factor associated with survival. A randomized, double-blind trial is under way in an effort to confirm these findings in hospitalized patients with nosocomial pneumonia due to MRSA. A case could be made to preferentially use linezolid in cases of CA-MRSA pneumonia. Linezolid along with clindamycin has recently been found to reduce production of PVL, α-hemolysin, and toxic-shock syndrome toxin 1, in contrast to vancomycin and nafcillin, which were found to increase production in an in vitro model.[58]

Despite the potential advantage of linezolid in the treatment of MRSA pneumonia, safety concerns often limit its use. Linezolid exhibits weak reversible inhibition of monoamine oxidase (MAO) and can induce serotonin toxicity when used in combination with agents that have serotonergic activity, most commonly selective serotonin reuptake inhibitors (SSRIs). Twenty-nine cases of linezolid-associated serotonin toxicity were recently described.[59] Postmarketing information submitted to the FDA from 29 patients with serotonin toxicity showed that 60.5% had concomitant treatment with an SSRI. Three patients died, possibly due to serotonin toxicity, and another 13 required medical treatment. Linezolid use concomitantly with SSRIs in hospitalized patients has also been evaluated in a retrospective study.[60] This study found a high probability of serotonin toxicity in two out of 72 concomitant uses. The authors suggest that linezolid may be used concomitantly with SSRIs with careful monitoring and recommend prompt discontinuation of the serotonergic agent if serotonin syndrome is suspected. 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.[61,62] Finally, there have been sporadic reports of peripheral neuropathy, typically in patients with osteomyelitis or other underlying disease, and lactic acidosis.[63,64]

## Tigecycline

Tigecycline is the first drug approved in the class of glycylcyclines, a derivative of minocycline. A modified side chain on tigecycline enhances binding to the 30s ribosomal subunit, inhibiting protein synthesis and bacterial growth against a broad spectrum of pathogens, including MRSA. Tigecycline is approved in the United States for the treatment of complicated MRSA skin and skin structure infections. The drug is also approved for the treatment of complicated intra-abdominal infections, but for methicillin-sensitive *S. aureus* only. Tigecycline has a large volume of distribution and produces high concentrations in tissues outside of the bloodstream, including the lung where epithelial lining fluid and alveolar macrophage concentrations are manyfold higher than achieved in the serum.[65] Conversely, tigecycline serum concentrations rapidly decline after infusion and the area under the curve (AUC) after multiple 50 mg doses administered every 12 hours is ~3 μg(hr)/mL.[66] Based on tetracycline PD studies, the AUC target for tigecycline should be two to four times the MIC in an effort to optimize efficacy in the treatment of MRSA infections. Given an $MIC_{90}$ range of 0.25 to 0.5 μg/mL for MRSA, caution should be used in patients with suspected or proven bacteremia. Further clinical evaluation should be cumulated to accept or refute this potential limitation and to assess the potential role of this agent in the treatment of pneumonia. The dose approved is a 100 mg intravenous loading dose followed by 50 mg every 12 hours. Nausea and vomiting are the predominant side effects and increase in frequency with dose escalation.

## Daptomycin

Daptomycin should not be used in the treatment of MRSA pneumonia because the drug's activity is inhibited by pulmonary surfactant.[67]

### Quinupristin-Dalfopristin

Quinupristin-dalfopristin is a mixture of two streptogramin antibiotics. The site of action is the bacterial ribosome, and collectively quinupristin-dalfopristin act synergistically to inhibit protein synthesis. A multicenter study compared quinupristin-dalfopristin and vancomycin in the treatment of nosocomial pneumonia by gram-positive pathogens.[68] Similar clinical success rates were observed, including the MRSA subgroup, although very low response rates were seen (30.9% in the quinupristin-dalfopristin group vs 44.4% in the vancomycin group) in the bacteriologically evaluable population ($n = 38$). These data suggest that quinupristin-dalfopristin is probably not a better option than vancomycin, with both agents seemingly having limited efficacy against MRSA pneumonia in this study. Additionally, quinupristin-dalfopristin is limited by its propensity to induce severe myalgia, which has led many practitioners to abandon use of this agent altogether.

## INVESTIGATIONAL AGENTS

### Ceftobiprole

Ceftobiprole is a unique cephalosporin that has been engineered to have a strong affinity for the penicillin-binding protein PBP2a, which confers activity against MRSA.[69,70] Ceftobiprole, administered two to three times daily by the intravenous route[71,72] is currently under investigation for the treatment of HCAP, HAP and VAP due to suspected or proven MRSA, all indications granted fast-track status by the FDA.

### Glycopeptides

A new generation of glycopeptide antibiotics have also been developed and are currently in clinical trials. Dalbavancin, televancin, and oritavancin all inhibit cell wall synthesis in an identical manner to vancomycin. These new compounds also have additional modes of action, including directly blocking enzymes involved in peptidoglycan synthesis, disruption of the *S. aureus* cell membrane, and possibly affecting fatty acid synthesis in *S. aureus* isolates, which could result in a more rapidly bactericidal effect compared with vancomycin.[73] Each of these new entities have exceptionally long elimination half-lives, which makes extended interval dosing possible.

Telavancin's clinical effectiveness against MRSA has been evaluated in two randomized, double-blind phase 2 trials for the treatment of complicated skin/skin structure infections. Dosed at 10 mg/kg IV every 24 hours, telavancin demonstrated similar clinical cure and microbiological eradication rates compared with standard therapy, generally vancomycin.[74,75] In a murine model of pneumonia caused by MRSA, telavancin has demonstrated superior reduction in lung bacterial titer and mortality compared with vancomycin and linezolid at doses equivalent to the area under the AUC associated with efficacy in humans.[76]

Dalbavancin's uniqueness stems from its long terminal elimination half-life, on the order of 250 hours, which has translated into a weekly dosing interval when treating MRSA infections.[77] Clinical success against MRSA has been demonstrated in patients with skin and soft tissue infections and catheter-related bloodstream infections. The usefulness of this agent for the treatment of pneumonia remains unknown but might be limited as a result of the dosing regimen.

Oritavancin is also a semisynthetic glycopeptide in development. This drug's mechanism of action involves disruption of transmembrane potential, and it has demonstrated activity against vancomycin-resistant strains of staphylococci and enterococci.[78] Oritavancin has a very long half-life of ~100 hours, and once-daily or every other day dosing is likely.[79] Studies are being conducted in complicated SSTIs (skin/soft tissue infections), CR-BSI (catheter-related bloodstream infection), and nosocomial pneumonia.

## CONCLUSION

Methicillin-resistant *Staphylococcus aureus* pneumonia is a serious infection associated with significant mortality and health care costs. Antibiotic choices for the treatment of MRSA pneumonia are limited, particularly as data emerge regarding vancomycin's relative lack of efficacy for this infection. Many novel compounds with activity against MRSA are being evaluated for the treatment of pneumonia.

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