Methicillin-Resistant Staphylococcus aureus: A Review of Current Antibiotic Therapy

INTRODUCTION

MRSA was first identified in the 1960s.1 Since then, it has become a major cause of serious nosocomial and community-associated infections.1 In 2007, the Centers for Disease Control and Prevention reported 94,000 cases of MRSA infections in US hospitals and has resulted in approximately 18,000 deaths.2 MRSA is a common bacterial pathogen responsible for a variety of infections including: skin and skin-structure infections (SSSI), bone and joint infections, pneumonia, bacteremia, endocarditis, central nervous system (CNS) infections and sepsis syndromes.3, 4 Due to increasing antimicrobial resistance, limited treatment options exist for patients infected with MRSA.

RESISTANCE

Shortly after the introduction of methicillin, the first MRSA isolate was reported. The acquisition of the mecA gene is the major mechanism responsible for conferring resistance to methicillin and other beta-lactam antibiotics.5 Resistance is thought to be mediated by horizontal transfer of the mecA gene.5 The mecA gene is carried on a mobile genetic element called staphylococcal chromosome cassette (SCCmec).1, 5, 6 This gene encodes for an altered penicillin-binding protein (PBP2a) that has a low affinity for beta-lactam antibiotics.6 Five major clinical MRSA clones have emerged, labeled as SCCmec I-V.6

Given the resistance of MRSA to beta-lactams, glycopeptides, such as vancomycin, became the gold standard for the treatment of MRSA infections and have been the drug of choice since the 1960's. Resistance has emerged with glycopeptides due to increased utilization. In 1996, the first vancomycin-intermediate S. aureus was reported in Japan.3 Subsequently, in 2002, the first case of vancomycin-resistant S. aureus (VRSA) was documented, and to date there have been 11 cases reported in the United States.8 The Clinical Laboratory Standards Institute (CLSI), the standardizing body determining antibiotic susceptibility, define vancomycin-intermediate S. aureus as having a minimum inhibitory concentration (MIC) of 4-8 mcg/mL and VRSA is defined as having a MIC of ≥ 16 mcg/mL.7, 8 This mechanism of resistance to glycopeptides is believed to be due to the presence of the vanA gene complex.9 Isolates with this gene complex are noted to have a thicker cell wall with a decreased production of PBPs.9 Heterogeneous vancomycin-intermediate S. aureus (hVISA) is defined as being susceptible to vancomycin, but contain subpopulations of MRSA which confer intermediate resistance to vancomycin.7, 9 It likely precedes the development of vancomycin-intermediate S. aureus. Since screening for hVISA is not routinely performed in the clinical microbiology laboratory, many cases go undetected.7 In recent studies, the rate of hVISA was approximately 6-11% of all MRSA isolates.9 One study determined that hVISA bacteremia infections were associated with prolonged duration of bacteremia and increased number of complications.3 However, infection-related mortality due to hVISA and MRSA was similar.7

OTHER BARRIERS TO EFFECTIVE TREATMENT

The capacity for MRSA to form biofilms on foreign devices such as endotracheal tubes and catheters makes this organism difficult to treat.3 Biofilm facilitates the bacteria’s ability to grow on surfaces,
increases resistance and decreases antibiotic penetration. Certain strains of MRSA carry genes that produce toxins that can increase the severity of the infection. CA-MRSA carries the Panton-Valentine leukocidin (PVL) genes, which are responsible for toxin production and enhanced virulence. These highly resistant infections continue to challenge physicians both in and out of the hospital setting.

COMMUNITY-ASSOCIATED VERSUS HEALTHCARE-ASSOCIATED MRSA

Initially, MRSA infections were almost exclusively found in the healthcare setting. However, over the last decade there has been an emergence of CA-MRSA infections. The SCCmec type IV or V genes are found on the CA-MRSA strains. Most CA-MRSA infections are associated with superficial SSSI, which are usually susceptible to non-beta-lactam antibiotics, such as trimethoprim-sulfamethoxazole (TMP-SMX), doxycycline, and clindamycin. CA-MRSA, however, can cause invasive infections including pneumonia and bacteremia. Risk factors for CA-MRSA are difficult to define, but factors associated with transmission include compromised skin integrity, poor hygiene, and places people may have close contact, such as daycare centers, prisons, dormitories, and athletic facilities.

Healthcare-associated MRSA (HA-MRSA) carry the SCCmec I, II, or III genes and tend to be more resistant to antimicrobials. They are usually associated with severe invasive infections including catheter-related infections, bacteremia, pneumonia and severe SSSIs. Common patient risk factors include prolonged hospitalization, hemodialysis, indwelling catheters, prior antimicrobial use, and enteral nutrition.

TREATMENT OPTIONS

MRSA is associated with numerous types of infections that can be considered either invasive or noninvasive. Invasive MRSA infections require aggressive treatment with intravenous antibiotics in addition to appropriate source control. Some uncomplicated CA-MRSA abscesses may be treated only with incision and drainage provided there are no signs of systemic infection. If there is suspicion of invasive infection, treatment often includes intravenous antibiotics in addition to incision and drainage and/or debridement. Most oral anti-MRSA agents are usually not recommended for initial treatment of severe MRSA infections but still may have a place in therapy. Oral antibiotics, such as TMP-SMX, tetracyclines, and clindamycin, have demonstrated successful clinical outcomes in observational studies. The remainder of this article will focus on the individual agents used to treat MRSA infections.

VANCOMYCIN

Vancomycin is widely considered the antimicrobial agent of choice for the treatment of invasive MRSA infections. It is a glycopeptide antibiotic that exerts its antibacterial effect by inhibiting bacterial cell wall synthesis. This is accomplished by binding to the D-alanyl-D-alanine subunit, which is the precursor to peptidoglycan polymerization. Vancomycin is approved by the FDA for the treatment of MRSA infections and infective endocarditis. The efficacy of vancomycin has been challenged in recent publications due to its slow bactericidal activity, the concern for evolving resistance, and possible “MIC creep”.

The susceptibility of MRSA to vancomycin may be declining and reports of treatment failures are increasing. Unfortunately, the use of vancomycin for S. aureus infections has been associated with an increased risk for recurrent bacteremia and mortality which may be due to inadequate bactericidal activity against S. aureus strains even with an MIC of 1–2 mcg/mL. Prior to 2006, the CLSI defined methicillin resistance in the microbiology laboratory as an oxacillin MIC ≥ 4 mcg/mL. In 2006, the CLSI decreased the MRSA vancomycin breakpoint from ≤ 4 mcg/mL to ≤ 2 mcg/mL for strains that are considered susceptible. Based on tests of more than 400 S. aureus strains with an MIC ≤ 1 mcg/mL, the recommended trough concentrations of 15-20 mcg/mL should achieve the area under the curve (AUC) to MIC ratio of 400, which is required for eradication of invasive infections. This ratio may not be achieved if the MIC is 2 mcg/mL, despite being reported as sensitive by the laboratory. The MRSA guidelines endorsed by the Infectious Diseases Society of America (IDSA) recommend using alternative agents in isolates with an MIC >2 mcg/mL, or if the patient is not clinically responding to treatment, even if the MIC is reported as susceptible. Numerous studies have been conducted to determine the impact of “MIC creep”, though inconsistencies have been noted between methods of MIC laboratory measurements.

Although vancomycin is generally well-tolerated, nephrotoxicity has been examined in a number of studies. Unfortunately, there is lack of definitive data in the literature to support that specific vancomycin concentrations are related to nephrotoxicity. The IDSA has inconsistent definitions of nephrotoxicity, as well as conflicting results. One recent retrospective study noted a significant relationship between nephrotoxicity and vancomycin doses of 4 grams or more per day. Risk factors for vancomycin-induced nephrotoxicity cited in the literature have included underlying renal disease, longer duration of therapy, and concomitant nephrotoxic agents, such as amphotericin B or aminoglycosides. The IDSA vancomycin guidelines state that vancomycin nephrotoxicity should be considered if the patient has been on...
vancomycin. Several days and experiences multiple increases in serum creatinine (by 0.5 mg/dL and/or more than 50% above baseline) and when no other contributing factor can be identified.13

Another side effect of vancomycin is Red Man Syndrome, which is a hypersensitivity reaction due to the release of histamine. Red Man Syndrome is often associated with rapid infusion (less than one hour).30 Symptoms include pruritus, an erythematous rash that involves the face, neck, upper torso and less frequently, hypotension and angioedema can occur.30 Discontinuation of the vancomycin infusion and administration of diphenhydramine can abort most of the reactions. If vancomycin is restarted, a slower infusion of vancomycin should minimize the risk of developing such adverse effects.30

LINEZOLID

Linezolid is an oxazolidinone antibiotic FDA approved for the treatment of complicated MRSA SSSI and nosocomial pneumonia. It has activity against vancomycin-intermediate S. aureus and VRSA.4 Linezolid exerts its antibacterial effects by inhibiting the initiation of protein synthesis by binding to the 50S ribosomal subunit.3, 4 Unlike most anti-MRSA antibiotics, oral linezolid has 100% bioavailability, which is an advantage when transitioning a patient from parental to oral therapy. Oral MRSA treatments are usually not recommended for severe MRSA infections but may have a place in the treatment of noninvasive SSSI.3, 4

The use of linezolid in the treatment of pneumonia has been examined in several studies. Linezolid has excellent penetration into the epithelial lining fluid, which is advantageous in the treatment of pneumonia. Two retrospective analyses concluded that linezolid had better survival and clinical cure rates than vancomycin for the treatment of MRSA nosocomial pneumonia.31, 32 Unfortunately, the study designs of combining two double-blind studies was a limitation, as well as the uncertainty that optimal vancomycin dosing was achieved. Another recent retrospective analysis of 113 patients with MRSA VAP found no difference in survival benefit between linezolid and vancomycin treatment groups; however, they did observe a trend toward a higher cure rate in the linezolid treatment group.33 The first randomized, multicenter, prospective, double-blind, clinical trial (the Zephyr trial) comparing linezolid to vancomycin for the treatment of MRSA nosocomial pneumonia was recently published.34 The primary endpoint was clinical outcome at the end of the study and the secondary endpoint was 60-day all-cause mortality.34 Patients treated with linezolid achieved higher rates of clinical success than those treated with vancomycin (57.6% vs 46.6%; p=0.042) in the per protocol population.34 There was no difference in all-cause mortality at 60 days between linezolid (15.7%) and vancomycin (17%).34 How the results of this trial will impact practice in the clinical setting remains to be seen.

Linezolid may be similar to clindamycin in its ability to suppress bacterial toxin production, but studies have been conflicting. One study suggested that linezolid reduces toxin production by suppressing PVL gene translation and may have a beneficial outcome in severe SSSI.35 In contrast, another study concluded that linezolid failed to inhibit toxin production.36 More frequently, invasive MRSA infections require more aggressive treatment with parental antibiotics. Further research examining clinical outcomes is needed in this area.

Complications with extended use of linezolid include thrombocytopenia, anemia, peripheral and optic neuropathy, and lactic acidosis.3 Thrombocytopenia is generally reversible and same reports indicate that supplementation with pyridoxine may be helpful, while other studies have shown no benefit.37 Linezolid is a weak, nonselective, reversible inhibitor of monoamine oxidase A, an enzyme responsible for the breakdown of serotonin.3 It is believed that when given to patients taking serotonergic medications, serotonin may accumulate leading to potential toxicity. The FDA recently released a warning regarding the potential to cause serotonin syndrome in patients receiving linezolid and serotonergic medications.38 (Table 2) The FDA recommends that if linezolid must be emergently given to a patient receiving a serotonergic drug, the serotonergic drug should be immediately discontinued and the patient should be monitored for symptoms of toxicity until 24 hours after the last dose of linezolid.38

DAPTOMYCIN

Daptomycin is a cyclic lipopeptide antibiotic that binds to components of the cell membrane and causes rapid depolarization leading to the inhibition of protein synthesis.31 Daptomycin is FDA approved for the treatment of severe MRSA infections, including SSSI, bacteremia and right-sided endocarditis. It may be a suitable treatment in invasive MRSA infections but it should not be used for the treatment of pneumonia, due to its inactivation by pulmonary surfactants.3, 4

A prospective, noninferiority trial examined the clinical outcomes of daptomycin 6mg/kg daily versus standard treatment (low-dose gentamicin plus either an anti-staphylococcal penicillin or vancomycin) for the treatment of S. aureus bacteremia (including MRSA) with or without endocarditis.39 The primary end point consisted of treatment success 42 days after completion of therapy. The authors concluded that daptomycin was noninferior compared to the standard treatment for bacteremia and right-sided endocarditis.39

There has been considerable debate over the optimal dosing of daptomycin. The FDA-approved dose is 4 mg/kg once daily for the treatment of complicated SSSI and 6 mg/kg once daily for the treatment of bacteremia and right-sided endocarditis.3 It exhibits concentration-dependent bactericidal activity; therefore, some experts advocate higher
Daptomycin treatment may be associated with myopathy and elevations in creatinine phosphokinase (CPK), which occur more frequently at higher doses.3 Case reports of daptomycin-induced acute eosinophilic pneumonia (AEP) have also emerged prompting a safety warning from the FDA.43, 44 Possible symptoms of AEP may include increased dyspnea, cough, and hypoxia, in combination with ground-glass opacities on computed tomographic scans.43, 44 Resolution of AEP usually occurs after discontinuing daptomycin and initiating steroid therapy.43, 44

TELAVANCIN

Telavancin is a lipoglycopeptide with bactericidal activity against MRSA, vancomycin-intermediate S. aureus and VRSA. Its dual mechanism of action inhibits cell wall synthesis and depolarizes the bacterial membranes disrupting barrier function.11, 45 It is approved by the FDA for complicated SSSI due to Gram-positive bacteria including MRSA.

The pooled ATLAS trials compared telavancin to vancomycin for the treatment of complicated SSSIs.46 Both studies met the criteria for noninferiority of telavancin to vancomycin.46 The telavancin package insert mentions that clinical cure rates were lower with telavancin than vancomycin in patients with an estimated creatinine clearance less than 50 mL/min compared to an estimated creatinine clearance of greater than 50 mL/min.45, 46

While not FDA approved for the treatment of pneumonia, telavancin has good lung penetration. The ATTAIN studies were 2 randomized, double-blind, comparator-controlled, parallel-group phase III trials comparing telavancin to vancomycin in patients with Gram-positive HAP.47 The primary endpoint was clinical response at follow up. Cure rates of telavancin versus vancomycin in the pooled all-treated group were 58.9% versus 59.5%, respectively.47 Telavancin was found to be noninferior to vancomycin in patients with HAP due to MRSA.47 Although overall adverse effects were comparable in both groups, telavancin was found to have more increases in serum creatinine than vancomycin (16% versus 10%, respectively).47

In vitro data suggests that telavancin may have a unique role in biofilm-associated infections.48-50 Infective endocarditis (IE) is difficult to treat due to valvular vegetations that produce biofilms which decreases antibiotic penetration. Although telavancin is not indicated for the treatment of IE, there have been 2 case reports recently published.51, 52 One case reported successful treatment of vancomycin intermediate Staphylococcus aureus IE with telavancin after the patient failed therapy with high-dose daptomycin.51 Upon initiation of telavancin, bacteremia resolved within 48 hours.51 In another case report, telavancin was used successfully to treat a MRSA bacteremia and endocarditis despite 8 days of vancomycin treatment with adequate trough levels.52

The most common adverse effects reported include taste disturbances, nausea, vomiting, insomnia and foamy urine.11, 45, 53 Telavancin has a black box warning on fetal risk due to congenital anomalies found in animal studies; therefore, telavancin should be avoided during pregnancy.45 A pregnancy test should be obtained in women of childbearing potential before initiation of this agent, as well as ensuring that female patients use effective contraception to prevent pregnancy while receiving telavancin.45 The FDA requires Risk Evaluation and Mitigation Strategy (REMS) for telavancin which dictates that a medication guide be provided to patients each time the drug is dispensed.11

Nephrotoxicity has been reported with treatment, which is more likely in patients with underlying renal dysfunction.45 Although it is a derivative of vancomycin, the cross-sensitivity potential is unknown. It should be used with caution in patients with documented hypersensitivity to vancomycin.

Other safety warnings to note with telavancin include the risk of QTc prolongation, and it may interfere with some anticoagulation tests, as it may bind to phospholipids in test assays.45 Recently, the manufacturer of telavancin has discontinued production of this agent.44 At this time there has not been any news of another manufacturer obtaining a license for the production of telavancin.

TIGECYCLINE

Tigecycline, a glycyclcycline antibiotic, is FDA approved for the treatment of complicated SSI, intra-abdominal infections, and community-acquired pneumonia (CAP). It exhibits antibacterial effects by inhibiting the initiation of protein synthesis and binding to the 30S ribosomal subunit.11 It’s structure contains a modified side chain that prevents the major mechanisms of bacterial resistance. Tigecycline has a large volume of distribution and produces high concentrations in tissue. Serum concentrations are relatively low shortly after administration.3, 4 Therefore, tigecycline is not recommended for the treatment of bacteremia.3, 4

A randomized, double-blinded, multicenter phase III trial compared the safety and efficacy of tigecycline with vancomycin or linezolid in 157 hospitalized patients with complicated intra-abdominal infections, complicated SSI, bacteremia or pneumonia due to MRSA or VRE.55 The primary endpoint was the clinical response to treatment. For MRSA infections, the clinical cure rate was 81% with tigecycline and 83.9% with vancomycin.55 The authors concluded that tigecycline is safe and effective in patients with serious MRSA infections.55
The FDA recently issued a warning to consider alternative agents in patients with serious infections due to an increased risk of all-cause mortality reported in a pooled analysis of over 7400 patients from 13 phase III and IV clinical trials. The mortality risk was greatest when tigecycline was used for the treatment of hospital-acquired pneumonia (HAP), particularly VAP. A prospective, randomized, double-blind clinical trial compared tigecycline to imipenem-cilastatin in 945 patients with HAP. In patients with VAP, lower cure rates were reported in the tigecycline group (67.9%) compared to imipenem-cilastatin group (78.2%). In non-VAP cases, similar cure rates were reported. There was an increase in all-cause mortality in VAP patients treated with tigecycline (19.1%) compared to imipenem-cilastatin (12.3%).

Common adverse effects associated with tigecycline from clinical studies include substantial nausea, vomiting, and diarrhea. Cases of acute pancreatitis have also been reported in patients and improvement usually occurs after the drug is discontinued.

**CEFTAROLINE**

Ceftaroline is a new broad-spectrum cephalosporin with activity against multidrug resistant *Staphylococcus aureus* including MRSA, vancomycin-intermediate *S. aureus* and VRSA. With Gram-negative activity limited to mainly respiratory pathogens, ceftaroline is FDA approved for the treatment of CAP and SSSI. Ceftaroline fosamil is an inactive prodrug that rapidly undergoes dephosphorylation in the blood to the active metabolite ceftaroline which binds to PBP, inhibiting mucopeptide synthesis resulting in the formation of an osmotically unstable bacterial cell wall which leads to lysis. The activity against MRSA is due to an ability to bind to modified PBP 2A, encoded by SCCmeC genes.

The CANVAS trials were two phase III, double-blind, randomized, noninferiority trials evaluating ceftaroline’s role in the treatment of complicated SSSI. The primary objective of the CANVAS trials was clinical cure rate of ceftaroline versus aztreonam plus vancomycin. The pooled clinical cure rate for the clinically evaluable patients was 91.6% (554 of 610 patients) in the ceftaroline arm and 92.7% (549 of 592 patients) in the aztreonam and vancomycin arm. The authors concluded that ceftaroline was noninferior to vancomycin plus aztreonam for the treatment of complicated SSSI.

Ceftaroline has a safety profile similar to other cephalosporins. Most common side effects reported include diarrhea, nausea and insomnia. It has been associated with a positive Coombs test, without hemolysis and has rarely been associated with interstitial nephritis.

Ceftaroline’s unique feature is its activity against drug-resistant Gram-positive pathogens, such as MRSA and hVISA. The role, if any, of ceftaroline in the treatment of bacteremia remains unanswered. To date, there are no clinical trials available to answer this question.

**QUINUPRISTIN-DALFORPRISTIN**

Quinupristin-dalfopristin (QPT-DFP) is a combination of two streptogramin antibiotics. Each agent binds at a different site on the 50S ribosomal subunit, resulting in interruption of protein synthesis. QPT-DFP is FDA approved for the treatment of methicillin-susceptible *S. aureus* SSSIs. This agent is bactericidal against most Gram-positive organisms and it has a long post-antibiotic effect. It has been used as salvage therapy for invasive MRSA infections refractory to other antibiotic treatments. Dose-dependent infusion reactions and severe myalgias limit its use.

**TRIMETHOPRIM-SULFAMETHOXAZOLE**

Trimethoprim-sulfamethoxazole is a combination antibiotic that inhibits bacterial folic acid synthesis. Sulfamethoxazole inhibits dihydropteroate synthetase, an enzyme responsible for converting para-aminobenzoic acid to dihydrofolate. Trimethoprim inhibits dihydrofolate reductase, an enzyme responsible for converting dihydrofolate to tetrahydrofolate. The synergistic effect of each agent leads to inhibition of bacterial growth.

TMP-SMX is not FDA approved for the treatment of MRSA infections, although it is commonly used in the treatment of noninvasive CA-MRSA infections since 95-100% of CA-MRSA strains are susceptible in vitro. One of the first studies that demonstrated TMP-SMX efficacy in the treatment for MRSA infections was a double-blind, randomized trial that compared TMP-SMX with vancomycin in 101 patients for the treatment of invasive *S. aureus* infections. Of 101 *S. aureus* isolates, 47% were MRSA. The cure rate was 86% (37/43) in the TMP-SMX group versus 98% (57/58) in the vancomycin group (p=0.02). Six patients failed treatment on TMP-SMX, all of which were infected with methicillin-susceptible *S. aureus* (MSSA), and four of whom had tricuspid valve endocarditis. However, unlike MSSA, both treatment groups had 100% MRSA cure rate regardless of infection location. Authors concluded that although TMP-SMX is not the therapeutic equivalent of vancomycin, it may be considered as an alternative to vancomycin in selected cases of MRSA infections.

TMP-SMX is one of the oral options available to be used as step-down therapy for noninvasive MRSA infections, such as SSSI. The optimum dosing of TMP-SMX has been debated in SSSI. A prospective, observational study examined whether treatment with a higher dose of TMP-SMX (2 double strength tablets twice daily) led to greater clinical resolution in patients with SSSIs caused by MRSA than a standard dose of TMP-SMX (1 double strength twice daily). Infection resolution was similar between the high-dose and standard dose groups (88/121, [72.7%] versus 127/170 [74.7%], p=0.79). The MRSA IDSA guidelines...
recommend a TMP-SMX dose 1 to 2 double strength tablets twice daily for MRSA SSSIs.6\)

Common side effects associated with TMP-SMX include nausea, vomiting, rash, pruritus and transient elevations in serum creatinine.11, 65 Rarely, crystalluria with azotemia, bone marrow suppression, and methemoglobinemia have been reported.65 TMP-SMX contains sulfa and should be avoided in patients with a documented sulfa allergy and caution should be used in patients with chronic renal insufficiency due to increased risk for hyperkalemia.65

TETRACYCLINES

Long-acting tetracyclines (doxycycline and minocycline) are bacteriostatic agents. They inhibit protein synthesis by preventing the association of aminoacyl-tRNA with the bacterial ribosome.3 Doxycycline is FDA approved for the treatment of SSSI due to S. aureus but has a diminished role for HA-MRSA infections due to resistance.66, 67 CA-MRSA resistance to tetracyclines is primarily due to the tetK gene which leads to inducible resistance to doxycycline but has no impact on minocycline.68 Reported tetracycline-resistant strains should be considered resistant to both doxycycline and minocycline unless minocycline susceptibility is confirmed.68 Unlike other tetracyclines, minocycline has a longer half-life, better oral absorption, enhanced tissue penetration and overcomes most tetracycline resistance mechanisms.3, 70

Case studies suggest the effectiveness of long-acting tetracyclines for the treatment of MRSA, but to date, no prospective clinical studies have been conducted.68, 69 A retrospective record review reported a clinical cure rate of 83% in 24 patients treated with doxycycline or minocycline for tetracycline-susceptible MRSA infections.68 Another retrospective cohort study reported higher cure rates with doxycycline or minocycline (95%) compared to a beta-lactams (88%) in 276 patients treated for MRSA SSSI.69

Minocycline was shown to be highly active against MRSA isolates embedded in a biofilm, compared with vancomycin, daptomycin, linezolid and tigecycline.70 Doxycycline is associated with GI intolerance and photosensitivity. Serious side effects include worsening azotemia in patients with renal failure and pancreatitis. Minocycline is generally well-tolerated but vestibular effects occur more frequently with minocycline than with other tetracyclines.70 It has been associated with more serious side effects including autoimmune hepatitis and drug-induced lupus-like-syndrome.70

CLINDAMYCIN

Clindamycin is derivative of lincomycin, which inhibits protein synthesis by binding to 50S ribosomal subunits, interfering with transpeptidation and early chain termination.11 Clindamycin is FDA approved for the treatment of S. aureus infections and is commonly used for the treatment of SSSI.11 Although not FDA approved for the treatment of MRSA infections, clindamycin has been successfully used for the treatment of invasive CA-MRSA infections.11 It has excellent tissue penetration into bone and abscesses but limited CNS penetration.3, 11 Clindamycin is usually not an appropriate treatment option for invasive endovascular MRSA infections in adults since it is bacteriostatic.3

Laboratory susceptibility to clindamycin does not always predict clinical outcomes. MRSA strains that exhibit resistance to erythromycin and susceptibility to clindamycin may have inducible expression of the macrolide–lincosamide–streptogramin B (iMLSb) due to the erm gene. For iMLSB strains, erythromycin will induce the production of methylase resulting in clindamycin resistance.71 A double-disk D-test, is used to confirm susceptibility for erythromycin-resistant, clindamycin-susceptible isolates.3, 11, 71

The factors limiting the use of clindamycin are gastrointestinal adverse effects, including diarrhea, nausea, and vomiting. It has been associated with a higher incidence of Clostridium difficile-associated disease (CDAD) compared to other oral anti-MRSA antibiotics; therefore, caution should be used in patients with a history of CDAD.3, 11

CONCLUSION

MRSA continues to cause a variety of clinical syndromes and is associated with significant morbidity and mortality. It is a significant cause of both healthcare and community-associated infections. Although vancomycin is still commonly used to treat many MRSA infections, concern is rising about vancomycin’s role in MRSA therapy due to emergence of less susceptible strains. Newer therapeutic alternatives, such as daptomycin, linezolid, and tigecycline, are available in cases with less susceptible strains, depending on the type of infection. Telavancin and ceftaroline are the two newest agents to be added to the anti-MRSA armamentarium, however many questions still remain about their place in therapy. Older antimicrobials, such as TMP-SMX, doxycycline, minocycline, and clindamycin continue to be viable treatment options for less severe MRSA infections, such as SSSIs. MRSA infections continue to challenge the medical community, and further clinical research continues to provide better guidance on optimal therapy. Increasing knowledge of resistance will help guide the development of new antibiotics.
and non-members may be charged a fee if available online to non-members. Details will be posted online. Initial Release Date: 11/27/12. Expiration Date: 12/31/14. Questions: Call IPA at (317) 634-4968.

References


Table 1. Summary of Studies Evaluating Vancomycin Minimum Inhibitory Concentration (MIC) and Patient Outcomes

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Study Population</th>
<th>MIC Testing Methodology</th>
<th>Key Results</th>
</tr>
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<tbody>
<tr>
<td>Sakoulas et al</td>
<td>2004</td>
<td>Prospective</td>
<td>MRSA bacteremia</td>
<td>Agar dilution</td>
<td>Treatment for MRSA bacteremia had overall success rate of 55% with vanco MIC ≤ 0.5 mcg/mL, and 9.5% with vanco MIC of 1-2 mcg/mL (p=0.03)</td>
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<tr>
<td>Hidayat et al</td>
<td>2006</td>
<td>Prospective</td>
<td>MRSA infections from any site</td>
<td>Etest</td>
<td>Patients with MRSA bacteremia, pneumonia or both had poorer response with vanco MICs of 1.5 or 2 mcg/mL (62% and 85%, respectively, p=0.02), and higher mortality rates (p=0.16) compared to low-MIC strains (≤ 1 mcg/mL)</td>
</tr>
<tr>
<td>Moise-Broder et al</td>
<td>2007</td>
<td>Retrospective</td>
<td>MRSA bacteremia</td>
<td>Broth Microdilution</td>
<td>Patients with a vancomycin MIC of 2 mcg/mL had higher median days to organism eradication than patients with MIC ≤ 1 mcg/mL (p=0.019)</td>
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<tr>
<td>Lodise et al</td>
<td>2008</td>
<td>Retrospective</td>
<td>MRSA bacteremia</td>
<td>Etest</td>
<td>Patients with a vancomycin MIC &gt; 1.5 mcg/mL had a 21% higher treatment failure rate compared to patients with an MIC &lt; 1 mcg/mL (36.4% vs. 15.4%, p=0.049)</td>
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<td>Hsu et al</td>
<td>2008</td>
<td>Prospective</td>
<td>MRSA Infection</td>
<td>Etest, Vitek, Microscan, and Broth Microdilution</td>
<td>Different MIC testing methodologies produced varied results. Significantly higher treatment failure rates were seen with high MICs (&gt;1 mcg/mL) vs low MICs ≤ 1 mcg/mL (38% vs. 11%; p = 0.034) using the Etest methodology.</td>
</tr>
<tr>
<td>Soriano et al</td>
<td>2008</td>
<td>Prospective</td>
<td>MRSA bacteremia</td>
<td>Etest</td>
<td>Patients with MRSA bacteremia with a vanco MIC = 2 mcg/mL were significantly associated with higher mortality (p=0.001)</td>
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<tr>
<td>Haque et al</td>
<td>2010</td>
<td>Prospective</td>
<td>MRSA pneumonia</td>
<td>Etest</td>
<td>An increase in vancomycin MIC was associated with an increased risk for 28-day mortality (p=0.001)</td>
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<td>Wang et al</td>
<td>2010</td>
<td>Prospective</td>
<td>MRSA bacteremia</td>
<td>Broth Microdilution</td>
<td>Patients with a high MIC = 2 mcg/mL had a 16% higher mortality after 14 days and a 22% higher mortality after 30 days (p=0.014)</td>
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<td>Yoon et al</td>
<td>2010</td>
<td>Retrospective</td>
<td>MRSA bacteremia</td>
<td>Vitek</td>
<td>Mortality was higher with a vancomycin MIC = 2 mcg/mL, compared to MIC ≤ 1 mcg/mL (50.0% versus 19.0%; p=0.027)</td>
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<tr>
<td>Choi et al</td>
<td>2011</td>
<td>Retrospective</td>
<td>MRSA nosocomial pneumonia</td>
<td>Etest</td>
<td>Patients with vancomycin MIC ≥ 1.5 mcg/mL had a higher rate of treatment failure compared to vancomycin MICs ≤ 1 mcg/mL (29.6% versus 6.9%, p = 0.038).</td>
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<tr>
<td>Kullar et al</td>
<td>2011</td>
<td>Retrospective</td>
<td>MRSA bacteremia</td>
<td>Etest and Broth Microdilution</td>
<td>A vancomycin MIC &gt; 1 mcg/mL was found to be an independent predictor of treatment failure (p=0.045)</td>
</tr>
<tr>
<td>Holmes et al</td>
<td>2011</td>
<td>Prospective</td>
<td>MRSA and MSSA bacteremia</td>
<td>Etest and Broth Microdilution</td>
<td>Increased mortality was associated with a vancomycin MIC &gt; 1.5 mcg/mL compared to MIC ≤ 1.5 mcg/mL (26.8% vs. 12.2%, p=0.001)</td>
</tr>
</tbody>
</table>
Table 2. Medications with Serotonergic Properties

<table>
<thead>
<tr>
<th>Class</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRIs</td>
<td>citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, sertraline</td>
</tr>
<tr>
<td>SNRIs</td>
<td>desvenlafaxine, duloxetine, venlafaxine</td>
</tr>
<tr>
<td>TCAs</td>
<td>amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine</td>
</tr>
<tr>
<td>MAOIs</td>
<td>isocarboxazid, phenelzine, selegiline, tranylcypromine</td>
</tr>
<tr>
<td>Other Medications</td>
<td>amoxapine, bupropion, buspirone, levodopa, lithium, maprotiline, meperidine, metoclopramide, mirtazapine, nefazodone, risperidone, sumatriptan, tramadol</td>
</tr>
</tbody>
</table>

Table 3. FDA-Approved Indications for MRSA Infections

<table>
<thead>
<tr>
<th>Complicated SSSI</th>
<th>CAP</th>
<th>Nosocomial Pneumonia</th>
<th>Bacteremia</th>
<th>Infective Endocarditis</th>
<th>Complicated Intra-abdominal Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>x</td>
<td>X</td>
<td>X</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Linezolid</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daptomycin</td>
<td>x</td>
<td></td>
<td>x</td>
<td>x</td>
<td>(right-sided endocarditis)</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Telavancin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftaroline</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SSRI: selective serotonin reuptake inhibitors, SNRI: serotonin norepinephrine reuptake inhibitors, TCA: tricyclic antidepressants, MAOI: monoamine oxidase inhibitors

Table 4. Summary of Antibiotics Used to Treat MRSA Infections

<table>
<thead>
<tr>
<th>Route</th>
<th>Antibiotic</th>
<th>Renal Dose Adjustment: Yes or No?</th>
<th>ADR (incidence)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>Vancomycin</td>
<td>15-20 mg/kg q 8-12 hr (dosing protocols may vary with institution; Individual pharmacokinetic dose adjustment, verification of MIC data and appropriate trough attainment recommended)</td>
<td>Yes Red Man Syndrome (&gt;10%) Hypotension accompanied by flushing (&gt;10%) Nephrotoxicity (5%)</td>
<td>Treatment failures despite susceptible MIC Dosing based on actual body weight</td>
</tr>
<tr>
<td>Route</td>
<td>Antibiotic</td>
<td>Renal Dose Adjustment: Yes or No?</td>
<td>ADR (incidence)</td>
<td>Comments</td>
</tr>
<tr>
<td>---------------------</td>
<td>------------------------------------------------</td>
<td>----------------------------------</td>
<td>-----------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>IV</td>
<td>Quinupristin-dalfopristin</td>
<td>No</td>
<td>Injection site reactions (10-68%) Arthralgia (up to 47%) Myalgia (up to 47%) Hyperbilirubinemia (3-35%)</td>
<td>Not first-line agent; reserved for serious infections in patients intolerant of other agents</td>
</tr>
<tr>
<td>IV, PO</td>
<td>Linezolid</td>
<td>No</td>
<td>Diarrhea (3-11%) Nausea (10%) Vomiting (4%) Thrombocytopenia (10%) Lactic acidosis (2%) Headache (up to 11%)</td>
<td>Bone marrow suppression is common in patients who receive treatment for more than two weeks Patients with renal insufficiency are at higher risk for developing thrombocytopenia Serotonin syndrome reported with coadministration of serotonergic medications Oral formulation has 100% bioavailability</td>
</tr>
<tr>
<td>IV</td>
<td>Daptomycin</td>
<td>Yes</td>
<td>Diarrhea (5-12%) Vomiting (3-12%) Constipation (6-11%) Increase CPK (9%) Hypokalemia (9%) Anemia (2-13%) Acute eosinophilic pneumonia (&lt;1%)</td>
<td>Not indicated for pneumonia Resistant isolates have emerged during therapy leading to treatment failure</td>
</tr>
<tr>
<td>IV</td>
<td>Tigecycline</td>
<td>No</td>
<td>Nausea (26%) Vomiting (18%) Diarrhea (12%) Liver function test abnormalities (up to 5%) Pancreatitis (&lt;2%)</td>
<td>Not recommended for bacteremia due to low concentrations in the serum Not recommended for serious infections due to increased mortality risk Severe hepatic impairment (Child-Pugh class C) dose adjustment required</td>
</tr>
<tr>
<td>IV</td>
<td>Telavancin</td>
<td>Yes</td>
<td>Metallic/soapy taste (33%) Nausea (27%) Vomiting (14%) Foamy Urine (13%) Insomnia (13%) Psychiatric disorder (12%) Headache (11%) Increased serum creatinine (8%) Microalbuminuria (7%) Thrombocytopenia (7%) QT prolongation (&lt;1%)</td>
<td>REMS medication May prolong QTc interval May interfere with tests used to monitor anticoagulation when samples drawn ≤18 hours after drug administration</td>
</tr>
<tr>
<td>IV</td>
<td>Ceftaroline</td>
<td>Yes</td>
<td>Positive Coombs® test without hemolysis (11%) Headache (5%) Rash (3%)</td>
<td>Use with caution in patients with history of penicillin allergy</td>
</tr>
<tr>
<td>IV, PO</td>
<td>Trimethoprim-sulfamethoxazole</td>
<td>Yes</td>
<td>Elevations in serum creatinine (18%) Nausea/vomiting (3.5%) Hypersensitivity reaction (0.5%)</td>
<td>Dosage based off of TMP component 1 DS tablet contains TMP160 mg and SMX 800 mg Administer oral dose with at least 8 ounces of water</td>
</tr>
<tr>
<td>Route</td>
<td>Antibiotic</td>
<td>Renal Dose Adjustment: Yes or No?</td>
<td>ADR (incidence)</td>
<td>Comments</td>
</tr>
<tr>
<td>--------</td>
<td>----------------</td>
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<td>----------</td>
</tr>
<tr>
<td>Minocycline IV, PO</td>
<td>200 mg x 1 then 100 mg q 12 hr</td>
<td>Yes CrCl=&lt;80 mL/min: Do not exceed 200 mg/day</td>
<td>Nausea (10%) Vomiting (1%) Vestibular effects (75%) Autoimmune hepatitis (&lt;1%) Lupus-like-syndrome (&lt;1%)</td>
<td>Not recommended for children &lt; 8 yrs old Worsening azotemia (increased in patients with renal failure) Doxycycline preferred in pts with renal insufficiency May cause photosensitivity: instruct patient to use sunscreen</td>
</tr>
<tr>
<td>Doxycycline IV, PO</td>
<td>100 mg q12 hr</td>
<td>No</td>
<td>Nausea (10%) Vomiting (1%)</td>
<td>Not recommended for children &lt; 8 yrs old Preferred over minocycline in patients with renal failure May cause photosensitivity: instruct patient to use sunscreen</td>
</tr>
<tr>
<td>Clindamycin IV, PO</td>
<td>300-450 mg PO q 6-8 hr 600-900 mg IV q 8 hr</td>
<td>No</td>
<td>Diarrhea (10-30%) C. difficile colitis (6%)</td>
<td>Excellent tissue, bone and abscess penetration but limited CSF penetration The D-zone test recommended for detection of inducible clindamycin resistance</td>
</tr>
</tbody>
</table>

ADR: adverse drug reaction, DDI: drug-drug interactions, IV: intravenous, PO: oral, REMS: risk evaluation and mitigation strategy, SSSI: skin and skin-structure infections
Test name: 2012 Article #7: Methicillin-Resistant Staphylococcus aureus: A Review of Current Antibiotic Therapy

This test is worth: 10 points

INSTRUCTIONS: This page is intended to help participants REVIEW the quiz questions prior to submitting their answers online. Please take the quiz online using the link in the MEMBERS section of the website.

Question 1 of 19

MRSA is associated with which of the following infections?

- A) Bacteremia
- B) Pneumonia
- C) SSSI
- D) All of the above

Question 2 of 19

Which of the following is a (are) true statement(s) regarding MRSA's mechanism of resistance to beta-lactam antibiotics?

- A) The mecA gene encodes for an altered penicillin-binding protein (PBP2a) that has a low affinity for beta-lactam antibiotics
- B) The mecA gene is carried on a mobile genetic element called staphylococcal chromosome cassette (SCCmec)
- C) The vanA gene complex encodes for thicker cell walls with fewer PBP and is thought to be the mechanism of resistance to glycopeptides
- D) All of the above are true statements

Question 3 of 19

Which of the follow is a NOT a true statement regarding CA-MRSA

- A) CA-MRSA as associated with the SCCmec type IV or V genes
- B) CA-MRSA is associated with PVL genes which are responsible for toxin production and enhanced virulence
- C) Most CA-MRSA infections are usually associated with severe invasive infections including catheter-related infections, bacteremia, pneumonia and severe SSSIs
- D) All of the above are true

Question 4 of 19

At what vancomycin MIC do the MRSA IDSA guidelines recommend using another antibiotic?

- A) MIC\(\leq 0.2\) mcg/mL
- B) MIC <0.5 mcg/mL
- C) MIC \(\leq 1\) mcg/mL
D) MIC $> 2 \text{ mg/L}$ or clinical response of the patient, regardless of a susceptible vancomycin MIC should determine whether another agent should be considered

**Question 5 of 19**
Which of the following side effect limits the use of quinupristin-dalfopristin?

A) Nausea and vomiting
B) Thrombocytopenia
C) Interstitial nephritis
D) Dose-dependent infusion reactions and severe myalgias

**Question 6 of 19**
Which of the following is NOT a complication of long-term linezolid use?

A) Thrombocytopenia and anemia
B) Peripheral and optic neuropathy
C) Lactic acidosis
D) Renal failure

**Question 7 of 19**
Daptomycin should NOT be used to treat which of the following types of MRSA infections?

A) Pneumonia
B) Bacteremia
C) Endocarditis
D) All of the above

**Question 8 of 19**
Which of the following antibiotics did the FDA recently issued a warning to consider alternative agents in patients with serious infections due to an increased risk of all-cause mortality?

A) Linezolid
B) Tigecycline
C) Telavancin
D) Ceftaroline

**Question 9 of 19**
Which of the following antibiotics is a REMS medication?

A) a. Linezolid
B) Tigecycline
C) Telavancin
D) Ceftaroline
**Question 10 of 19**

Which of the following cephalosporins has activity against MRSA, vancomycin intermediate Staphylococcus aureus and VRSA?

- [ ] A) Cephalexin
- [ ] B) Ceftriaxone
- [ ] C) Cefepime
- [ ] D) Ceftaroline

**Question 11 of 19**

Did the article help you achieve EACH of the stated objectives? If not, describe in the comment box at the end of this section. Refer to the article for the list of learning objectives.

- [ ] A) Yes
- [ ] B) No

**Question 12 of 19**

Quality of the written material/content?

- [ ] A) Very Good Quality
- [ ] B) Good Quality
- [ ] C) Neutral
- [ ] D) Poor Quality
- [ ] E) Very Poor Quality

**Question 13 of 19**

Overall evaluation of this article?

- [ ] A) Very Good
- [ ] B) Good
- [ ] C) Neutral
- [ ] D) Poor
- [ ] E) Very Poor

**Question 14 of 19**

How much time was required to complete this article?

- [ ] A) 0.5 hours
- [ ] B) 1.0 hours
- [ ] C) 1.5 hours
- [ ] D) 2.0 hours
- [ ] E) 2.5 hours
Question 15 of 19
The learning activities (e.g. case studies, quiz) were effective?

- [ ] A) Strongly Agree
- [ ] B) Agree
- [ ] C) Neutral
- [ ] D) Disagree
- [ ] E) Strongly Disagree

Question 16 of 19
The information in this article will help assist and reinforce my practice/treatment habits?

- [ ] A) Strongly Agree
- [ ] B) Agree
- [ ] C) Neutral
- [ ] D) Disagree
- [ ] E) Strongly Disagree

Question 17 of 19
The author(s) did NOT appear to be promoting a product or company? Please use COMMENT box at end of evaluation to explain or provide comment.

- [ ] A) Strongly Agree
- [ ] B) Agree
- [ ] C) Neutral
- [ ] D) Disagree
- [ ] E) Strongly Disagree

Question 18 of 19
Author(s) communicated material clearly?

- [ ] A) Strongly Agree
- [ ] B) Agree
- [ ] C) Neutral
- [ ] D) Disagree
- [ ] E) Strongly Disagree

Question 19 of 19
Comments. Please use this space to provide comments related to any of the above questions.
If NO COMMENT, please write "NONE " in the box below.