Treating Central Catheter–Associated Bacteremia Due to Methicillin-Resistant *Staphylococcus aureus:* Beyond Vancomycin

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Methicillin-resistant *Staphylococcus aureus* is a frequent cause of hospital-associated infections, including central catheter–associated bacteremia. Vancomycin has been the drug of choice for treating this type of bacteremia for decades in patients who have no contraindications to the antibiotic. However, resistance to vancomycin is an emerging problem. Newer antibiotics approved by the Food and Drug Administration have activity against methicillin-resistant *S aureus*. Some of the antibiotics also have activity against strains of *S aureus* that are intermediately susceptible or resistant to vancomycin. This article uses a case study to highlight the clinical signs of vancomycin failure and describes the indications for and appropriate use of alternative antimicrobials such as ceftaroline, daptomycin, linezolid, tigecycline, and telavancin. (*Critical Care Nurse*. 2016;36[4]:46-57)

A ccording to the Centers for Disease Control and Prevention, methicillin-resistant *Staphylococcus aureus* (MRSA) is a leading cause of heath care–associated infections. It is responsible for more than 75 000 severe infections and approximately 11 000 deaths each year in the United States.[1] *S aureus* is both a commensal skin organism and a pathogen. Colonization can lead to infection when a breach occurs in the skin or mucosal defense systems because of trauma or common procedures

such as surgery or placement of a central catheter.[2] Several different risk factors have been reported for MRSA infections (Table 1) in inpatients, including patients with central intravenous catheters.[3-6] MRSA is a common cause of bacteremia and is the causative organism reported in 7.4% of central catheter–associated bloodstream infections (CLABSIs) in critical care patients.[1,7] CLABSIs occur in approximately 80 000 critically ill patients annually in the United States. The infections are associated with prolonged stays in the intensive care unit (ICU) and the hospital and with increases in overall health care costs.[8,9] Prevention of CLABSI is necessary to achieve goals for patient safety and maximize hospital reimbursement from the Centers for Medicare and Medicaid Services.[10] Accordingly, the Centers for Disease Control and Prevention collaborated with other organizations to develop guidelines[11] and checklists[12] to help clinicians and health care facilities prevent CLABSIs. This emphasis on preventive measures has contributed to an almost 50% decrease in CLABSIs due to MRSA from 1997 to 2007.[7]

For patients with suspected CLABSI, the guidelines of the Infectious Diseases Society of America (IDSA)[9] recommend starting systemic antimicrobial therapy after blood for culturing has been obtained and, if possible, removing the intravascular catheter. Initial empiric therapy should include drugs effective against gram-positive organisms commonly found on the skin, including *S aureus*. Most patients with suspected CLABSI

Table 1 Risk factors for hospital-acquired infection with methicillin-resistant *Staphylococcus aureus* (MRSA)
Antibiotic treatment in the past 90 days
Hospital stay of 5 or more days within the past 12 months
Residence in a long-term care facility
Open skin wound and/or central intravenous catheter, including hemodialysis patients
Recent major surgery
Medical condition causing immunosuppression
Hospital stay at a health care facility with high rates of MRSA infection

are given vancomycin because of the increased prevalence of MRSA in health care settings, and combination therapy with a drug effective against a broad spectrum of gram-negative organisms should be considered for patients who are critically ill or immunocompromised.[9] Definitive treatment of a CLABSI depends on the causative organism, removal of the infected catheter, patient-specific factors, and complications. Vancomycin remains the first-line option for treatment of documented MRSA bacteremia.[6,9] However, several antimicrobial agents are effective against nosocomial MRSA infections. Each agent differs in the mechanism of action, indications for use, clinical and laboratory monitoring required, and adverse effects. Unfortunately, data are limited on use of these agents in patients with MRSA bacteremia, including CLABSI.

In this article, we present the case study of a patient with CLABSI due to MRSA who required alternative antibiotic therapy to eradicate the infection, and we discuss other agents that may be used to treat MRSA CLABSIs. Identifying information has been changed to protect the patient's privacy and confidentiality.

Vancomycin

Vancomycin has been used to treat penicillin-resistant infections for more than 50 years and is the first-line treatment option for MRSA CLABSI[6,9] (Table 2). Vancomycin is widely available and costs less than newer antibiotics designed to treat MRSA infections.[19] However, determining the best dosage is difficult, tissue penetration is highly variable, routine trough-level monitoring is required, and infusion-related reactions and anaphylaxis can occur. Vancomycin also can be nephrotoxic.[13] In addition to these disadvantages, unsuccessful

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A 71-year-old woman was transferred to a tertiary care center from an outside facility because of acute exacerbation of chronic heart failure and moderate dyspnea. Her medical history included ischemic cardiomyopathy with an ejection fraction of 20%, coronary artery bypass grafting and placement of an automated internal cardioverter defibrillator because of coronary artery disease, type 2 diabetes mellitus, stage III chronic kidney disease with baseline level of serum creatinine 1.2 mg/dL (to convert to micromoles per liter, multiply by 88.4) and glomerular filtration rate 47.9 mL/min per 1.73 m^2. Within a few hours of admission, her condition deteriorated; oxygen saturation was 88% on 100% oxygen via a nonrebreather mask, and she was transferred to the cardiac ICU, where noninvasive positive pressure ventilation was started. A central catheter was placed, and a dobutamine infusion was started for inotropic support. An indwelling bladder catheter was placed for accurate monitoring of fluid intake and output. Furosemide 40 mg was administered intravenously every 8 hours for 3 doses to induce diuresis. The patient responded well to the medications. As her condition improved, she was weaned to 2 L of oxygen via nasal cannula and transferred to the cardiac stepdown unit, where the dobutamine infusion was slowly discontinued during the next 48 hours. The bladder catheter was subsequently removed.

On hospital day 5, she became lethargic and febrile. Vital signs were temperature 103°F (39.4°C), blood pressure 105/48 mm Hg, heart rate 102/min (sinus tachycardia), respirations 22/min, and oxygen saturation 94% on 2 L of oxygen via nasal cannula. Laboratory studies revealed a serum level of creatinine of 2.0 mg/dL and a white blood cell count of 14 500/µL. Severe sepsis and acute-on-chronic kidney failure were suspected. Samples were obtained for pan cultures (ie, pair of blood cultures, urinalysis with culture and sensitivity, sputum sample if a productive cough is present). A chest radiograph revealed mild pulmonary vascular congestion without infiltrates. Central venous pressure was 12 mm Hg. The serum level of lactic acid was 2.4 mg/dL (to convert to millimoles per liter, multiply by 0.111). The patient was empirically started on broad-spectrum antibiotics, including intravenous vancomycin and cefepime. Urinalysis showed no pyuria, and urine culture was negative for microorganisms. Both blood cultures initially showed gram-positive cocci in clusters. Final culture results were positive for MRSA bacteremia, with a minimum inhibitory concentration of 1 µg/mL for vancomycin. Cefepime was discontinued. Peripheral intravenous access was obtained, and the central catheter was removed. Despite treatment with vancomycin, the patient's clinical status did not improve. She remained febrile and had worsening leukocytosis. Vancomycin was discontinued, and daptomycin was started for complicated MRSA bacteremia. The patient's condition rapidly improved with the change in antibiotic. Her fever and leukocytosis resolved. Repeat blood cultures were negative for microorganisms. Daptomycin was continued for 4 weeks after the first blood culture negative for MRSA was obtained. The patient was eventually discharged to acute inpatient rehabilitation.

treatment and increased mortality have been documented in patients who require elevated concentrations of vancomycin to inhibit growth of MRSA isolates. Isolates that require elevated levels of the antibiotic encompass those reported as intermediately susceptible or resistant to vancomycin (minimum inhibitory concentrations [MICs] <2 µg/mL) and those for which the vancomycin MIC is 2 µg/mL; the latter isolates are still reported as sensitive under current laboratory standards.[6,13,20] As a result, the IDSA vancomycin guidelines[13] suggest that an alternative agent should be considered in MRSA infections for which the vancomycin MIC is 2 µg/mL or less, particularly if the patient is not responding to treatment. Alternative agents are also recommended in patients who have persistent bacteremia during therapy with vancomycin regardless of the reported MIC value (vancomycin failures).[6] Although vancomycin remains the drug of choice, alternative agents may be used to treat invasive MRSA infections (Table 2).[6,9,13-19] Alternative MRSA therapy is based on the reported MIC values, bactericidal activity, antibiotic penetration at the infection site, and patient comorbid conditions, including reduced renal function.[6,21] See Table 3 for antibiotic pharmacology definitions.

Alternative Treatments for MRSA Infections
Daptomycin

Daptomycin (Cubicin) is a lipopeptide antibacterial agent that has rapid bactericidal activity against aerobic

Table 2 Treatment options for bacteremia and central catheter–associated bloodstream infections due to methicillin-resistant *Staphylococcus aureus* (MRSA)

Feature	Vancomycin[13]	Linezolid[14]	Daptomycin[15]	Telavancin[16]	Tigecycline[17]	Ceftaroline[18]
Common dosing	15-20 mg/kg every 8-12 h	600 mg every 12 h	6-10 mg/kg every 24 h	10 mg/kg every 24 h	100 mg x1 then 50 mg every 12 h	600 mg every 12 h
Route	Intravenous	Intravenous and oral	Intravenous	Intravenous	Intravenous	Intravenous
Infusion times	Minimum of 60 min	30-120 min	2-min intravenous bolus or 30-min infusion	60 min	30-60 min	60 min
Renal dose adjustment	Yes	No	Yes	Yes	No	Yes
Effect on MRSA	Slowly bactericidal	Bacteriostatic	Bactericidal, concentration dependent	Bactericidal, concentration dependent	Bacteriostatic	Bactericidal, time dependent
Mechanism of action	Inhibits bacterial cell wall synthesis	Inhibits bacterial protein synthesis	Binds the cell membrane and causes rapid depolarization	2 mechanisms: inhibits cell wall synthesis and disrupts cell membrane function	Inhibits bacterial protein synthesis by blocking the binding of transfer RNA to the bacterial ribosome	Inhibits bacterial cell wall synthesis
Recommendations per IDSA MRSA 2011 guidelines[6]	Bacteremia	Persistent bacteremia	Bacteremia Persistent bacteremia	Persistent bacteremia	Not recommended in IDSA MRSA 2011 guidelines because of a study that showed increased risk of death compared with risk with other agents	Not applicable
Recommendations per IDSA CRBSI 2009 guidelines[9]	Preferred empiric and MRSA treatment option	Alternative MRSA treatment option Should not be used empirically	Alternative MRSA treatment option	Not applicable	Not applicable	Not applicable
Laboratory monitoring	SCr routinely At least 1 steady-state trough concentration, repeated as clinically appropriate Periodic WBC, if prolonged therapy	CBC weekly (platelet monitoring)	CPK weekly SCr routinely Can interfere with coagulation tests and falsely increase clotting times	SCr at least every 2-3 days Pregnancy test before start of treatment Can interfere with coagulation tests and falsely increase clotting times	Monitor for increases in INR if patient is receiving warfarin concomitantly	SCr routinely
Drug cost (AWP) per day for a 75-kg patient,[19] $	15.00	501.90 intravenous	425.66	371.36	243.20	303.24

Abbreviations: AWP, average wholesale price; CBC, complete blood cell count; CPK, creatine phosphokinase; CRBSI, catheter-related bloodstream infection; IDSA, Infectious Diseases Society of America; INR, international normalized ratio; SCr, serum creatinine; WBC, white blood cell count.

Table 3 Antibiotic pharmacology definitions[a]	
Term	**Definition**
Bactericidal	Agents that kill bacteria.
Bacteriostatic	Agents that halt bacterial growth.
Minimum inhibitory concentration (MIC)	Smallest concentration of antibiotic required to inhibit the growth of bacteria.
Concentration-dependent killing	Antibiotic activity that depends on the peak blood concentrations of the antibiotic in relation to the MIC for the specific organism, with higher peak concentrations resulting in optimized bacterial killing.
Time-dependent killing	Antibiotic activity that depends on the maintenance of antibiotic blood concentrations greater than the MIC of the specific organism for the specified part of the dosing interval. The optimal amount of time the concentration remains about the MIC varies depending on the antibiotic.
Volume of distribution (V_d)	The theoretical volume or space within the body that a drug occupies, resulting in the measured drug concentration in the patient's serum. Larger volumes of distribution generally indicate that a drug distributes well into various tissues in the body, whereas smaller volumes of distribution indicate that a drug is predominately contained within the intravascular space.

[a] Based on information from Pankey and Sabath.[21]

gram-positive bacteria, including MRSA[15] (Table 2). Daptomycin has been approved by the Food and Drug Administration (FDA) for treatment of MRSA bacteremia, including right-sided endocarditis. In the IDSA guidelines, the antibiotic is recommended as a first-line option for MRSA bacteremia. Daptomycin is a concentration-dependent antibiotic, and higher doses of 8 to 10 mg/ kg per day may be considered for more invasive infections.[6,15] Clinical success rates are similar for daptomycin and vancomycin (44.4% vs 31.8%; $P = .28$) in patients with MRSA bacteremia and endocarditis.[22] In addition, daptomycin may be preferred over vancomycin in MRSA bacteremia caused by isolates with vancomycin MIC values greater than 1 µg/mL because of improved patient outcomes. Murray et al[23] conducted a matched retrospective cohort study (n = 170) in patients with MRSA bacteremia with elevated vancomycin MIC values (for 94.1% of the bacterial isolates, the MIC of vancomycin was 2 µg/mL). Compared with the control group, patients in the daptomycin group had significantly lower rates of unsuccessful treatment (20.0% vs 48.2%; $P < .001$), lower 30-day mortality (3.5% vs 12.9%; $P = .05$), and lower rates of persistent bacteremia (18.8% vs 42.4%; $P = .001$). In patients with persistent bacteremia and unsuccessful treatment with vancomycin, high-dose daptomycin (10 mg/kg per day) in combination with another agent to which the MRSA isolate is susceptible is a recommended option per IDSA guidelines.[6] However, combination therapy is not routinely used in

clinical practice because of the lack of supporting clinical evidence.

Although daptomycin has solid clinical data to support its use in MRSA bacteremia, treatment with this antibiotic has drawbacks. Daptomycin should not be used in patients with suspected pneumonia because the drug is inactivated by pulmonary surfactant. Serious adverse events reported include myopathy and rhabdomyolysis. Serum levels of creatinine phosphokinase should be checked weekly during the treatment to monitor for development of toxic musculoskeletal effects. Concomitant use of other agents that may cause myopathy, including inhibitors of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (statins), may increase the risk of increasing the levels of creatinine phosphokinase and should be avoided if possible.[15] Data are limited on the coadministration of daptomycin and statins, and results of a recent retrospective observational study[24] indicated a slightly higher incidence of elevations in creatinine phosphokinase level when combination therapy was used (6.1% vs 2.9%; $P = .38$). Elevations in phosphokinase level rarely result in discontinuation of therapy. However, discontinuation of therapy should be considered in patients with myopathy and concurrent elevations in the enzyme level (5 times the upper limit of the reference range) or in patients with elevations 10 times or greater than the upper limit of the reference range. Clinicians may also consider stopping administration of statins temporarily while the patient is being treated with daptomycin.[15]

Other rare adverse effects include eosinophilic pneumonia, peripheral neuropathy, and anaphylaxis. In addition, daptomycin may falsely prolong prothrombin time and elevate the international normalized ratio.[15]

Linezolid

Linezolid (Zyvox) was approved by the FDA in 2000. This member of the oxazolidinone class has bacteriostatic activity against aerobic gram-positive bacteria and against multidrug-resistant gram-positive organisms, including MRSA and organisms with reduced susceptibility to vancomycin (Table 2).[14] Although linezolid is recommended for treatment of several different MRSA infections, it is not a first-line empiric or definitive treatment option in MRSA bacteremia, including CLABSIs.[6] Available data do support use of linezolid as an alternative agent in MRSA bacteremia. The effectiveness of linezolid as definitive treatment for MRSA bacteremia was shown in an observational compassionate use program[25] as well as a pooled analysis[26] of data from 5 randomized controlled trials that showed similar clinical cure rates for vancomycin and linezolid (46% vs 56%; odds ratio, 1.47; 95% CI, 0.50-4.31). Additionally, findings of an open-label randomized controlled study[27] published in 2009 indicated that linezolid and vancomycin treatment of MRSA CLABSIs had similar successful clinical outcomes (79% vs 76%; 95% CI, -21 to 27). However, further analysis of data on patients with suspected CLABSIs whose cultures were negative for microorganisms or positive for gram-negative pathogens, the linezolid group had a higher mortality rate than did the comparative group (21.5% vs 16%). Because of these data, the FDA issued an update for the linezolid package insert to state that linezolid should not be used for treatment of CLABSI.[14] In the IDSA guidelines,[6,9] linezolid is recommended solely as an alternative agent for patients with documented or persistent MRSA bacteremia.

Prolonged linezolid therapy may increase the risk for hematological toxic effects (thrombocytopenia, anemia, and neutropenia), peripheral neuropathy, and lactic acidosis.[14] Complete blood cell counts should be monitored in patients receiving linezolid for longer than 2 weeks to assess for myelosuppression. Linezolid is a monoamine oxidase inhibitor that places patients at risk for serotonin syndrome when they are receiving other serotonergic agents. Concurrent use of linezolid and serotonergic agents should be avoided if possible, and the FDA has specific recommendations for handling this drug interaction when simultaneous administration is necessary.[14,28]

Telavancin

Telavancin (Vibativ) is a bactericidal lipoglycopeptide antibiotic approved by the FDA in 2009. It has 2 mechanisms of action against gram-positive organisms, a characteristic that makes it unique[16] (Table 2). The IDSA guidelines for treatment of MRSA infections reserve it for salvage therapy in patients with MRSA bacteremia caused by isolates with reduced susceptibility to vancomycin or patients whose treatment with vancomycin was unsuccessful.[6] In a phase 2 randomized study,[29] telavancin was compared with standard therapy for the treatment of uncomplicated *S aureus* bacteremia. Of the 30 patients with uncomplicated MRSA bacteremia, 29 experienced a clinical cure. In this study with a small number of patients, patients treated with telavancin had a higher incidence of adverse events (90%) than did patients who received standard therapy (72%); nephrotoxic effects were the most common.

Linezolid is recommended only as an alternative agent for patients with documented or persistent MRSA bacteremia.

Telavancin should be used solely as an alternative agent when the anticipated benefits outweigh the risks of exposure to the antibiotic. Adverse events include nephrotoxic effects, taste disturbances, and a prolonged QT interval.[16] Telavancin is contraindicated in patients with prolonged QT intervals, severe left ventricular hypertrophy, and decompensated heart failure. The manufacturer recommends pregnancy testing before treatment with this antibiotic for women who are nonmenopausal and have not had a tubal ligation, hysterectomy, or bilateral oophorectomy because of the risk of fetal harm. Infusions of telavancin should be administered during a period of at least 60 minutes to avoid the risk of reactions, including flushing of the upper part of the body, rash, and pruritus, all of which also can occur with rapid administration of vancomycin. Telavancin does not affect blood coagulation; however, anticoagulation test results are falsely altered, similar to the alterations caused by daptomycin. In order to ensure more accurate results, blood samples for coagulation studies should be obtained just before the next scheduled dose of telavancin to allow the effects on the test results to decrease.[16]

Tigecycline

Tigecycline (Tygacil), a glycylcycline antibiotic approved by the FDA in 2005, has bacteriostatic activity against MRSA[17] (Table 2). The current IDSA MRSA guidelines do not include tigecycline because of its black box warning for increased mortality and the availability of other agents active against MRSA.[6] This black box warning was based on an increased 30-day mortality reported in a meta-analysis with data from phase 3 and 4 trials.[30,31] The highest mortality risk occurred in patients treated with tigecycline for ventilator-associated pneumonia. In addition to the increased mortality, blood levels of tigecycline are low because of its large volume of distribution[32] (Table 2). This pharmacokinetic property of the drug along with its bacteriostatic activity has called into question its effectiveness in patients with bacteremia. No studies on its use for primary MRSA bacteremia have been published.

The effectiveness of tigecycline in patients with secondary bacteremia was evaluated in an analysis of pooled data from 8 multicenter trials.[33] Gardiner et al[33] reported that tigecycline was effective for patients with bacteremia associated with community-acquired bacterial pneumonia, complicated skin/skin-structure infections, and intra-abdominal infections; however, only 6 patients in the tigecycline group had MRSA bacteremia. Adverse effects include severe nausea and vomiting, severe skin reactions, QT prolongation, pancreatitis, and hepatotoxic effects. Drug interactions with tigecycline are uncommon; however, the antibiotic may alter the clearance of warfarin, resulting in an increased international normalized ratio. The international normalized ratio should be monitored when tigecycline and warfarin are administered concomitantly.[17] On the basis of the current literature, tigecycline cannot be recommended for treatment of primary MRSA bacteremia, including MRSA CLABSI.

Ceftaroline may be considered as an alternative antibiotic in instances when patients have disease progression on standard therapy.

Ceftaroline

Ceftaroline (Teflaro) is a bactericidal cephalosporin[18] (Table 2). Ceftaroline's specific affinity for penicillin-binding proteins 2a and 2x makes it effective against *Streptococcus pneumoniae* and *S aureus*, including MRSA.[34]

Ceftaroline is not included in the 2011 IDSA MRSA guidelines because the antibiotic had not been approved by the FDA when the guidelines were published.[6] Since publication of the guidelines, several retrospective studies and case reports on use of this antibiotic, both as monotherapy and in combination with other agents, for treatment of MRSA bacteremia have been published.[35-40] Polenakovik and Pleiman[39] reported clinical success with ceftaroline therapy in 23 of 31 patients (74.2%) with MRSA bacteremia. The sample included 7 patients with intravenous catheter–associated MRSA infections and 10 patients given combination MRSA therapy. The most common reason for use of ceftaroline was elevated MIC values (MIC >1 μg/mL) for vancomycin.

More recently, in a multicenter retrospective case-control study (n = 32),[38] ceftaroline salvage therapy (started after 5 days of vancomycin therapy) was compared with vancomycin alone in treating MRSA bacteremia caused by organisms for which MIC levels for vancomycin were higher (≥2 μg/mL). Time to eradication of MRSA was significantly shorter ($P = .06$) with ceftaroline (4 days) than with vancomycin (8 days), and clinical success at the end of treatment was significantly higher ($P = .06$) for ceftaroline (81%) than for vancomycin (44%).

In another retrospective study, Casapao et al[35] analyzed ceftaroline use at several sites during a 2.5-year period. Of the 527 patients included in the study, 241 (45.7%) had documented MRSA infections. Bacteremia was reported in 48 patients (28.1%); in 10 of the 48, the infections were associated with use of intravenous catheters. The majority of patients (80.1%) were treated with vancomycin before therapy with ceftaroline was started; the median duration of vancomycin therapy was 3 days. Clinical success was achieved in 79% of the bacteremia subgroup (112 of 141 patients). The success rate was 79% with both the standard dosing and the off-label dosing (600 mg intravenously every 8 hours).

Combination therapy with ceftaroline has also been reported. Sakoulas et al[40] used ceftaroline plus daptomycin for 26 patients with documented refractory staphylococcal bacteremia. Patients had persistent bacteremia for median of 10 days with previous therapy. Among the 26 patients, 20 had MRSA infections and 14 had endocarditis. After combination therapy was started, the median time to bacteremia clearance was 2 days (range, 1-6 days).

This increasing amount of evidence helps support the notion that ceftaroline may be considered as an

alternative antibiotic in the treatment of MSRA bacteremia and CLABSIs, including instances when patients have disease progression on standard therapy.

Adverse events reported with ceftaroline are minimal and are similar to those associated with other cephalosporins. Hypersensitivity reactions to penicillins and carbapenems should be considered before therapy with ceftaroline is started because most likely cross-reactivity exists between β-lactam antibiotics.[18] In addition to common adverse events associated with treatment with β-lactam antibiotics, case reports have described the development of eosinophilic pneumonia.[41]

Nursing Care

Although appropriate antibiotic therapy is a key element in managing CLABSI due to MRSA, instituting evidence-based infection control measures is required to prevent the spread of MRSA and other multidrug-resistant organisms. Multiple studies have shown that decreasing the skin's bacterial load with chlorhexidine gluconate (CHG) baths decreases rates of infection with MRSA and other pathogens. CHG is a topical antiseptic active against a large number of both gram-positive and gram-negative microbes. Bathing patients with 2% CHG solution is recommended by the Centers for Disease Control and Prevention for preventing CLABSIs.[11]

In addition to CHG bathing and other methods of decolonization, such as administering mupirocin ointment intranasally, consistently applying infection prevention and control practices can halt the spread of infections due to multidrug- resistant organisms. Research[42] has indicated that implementing use of bundles for insertion of central venous catheters decreases the incidence of CLABSI. Bundle elements include performing hand hygiene, using CHG for skin cleansing, and instituting full-barrier precautions before insertion of the catheter.[43] Having registered nurses assist in insertion of central venous catheters and monitor bundle compliance is an important step in preventing CLABSI. The Joint Commission[44] recommends having nurses complete an insertion checklist that incorporates these bundle elements as a patient safety measure.

Empowering nurses to stop the insertion if breaks in sterile technique occur is critical in minimizing the threat of bacterial migration into the bloodstream. The need for central venous catheters should be reassessed frequently, and any unnecessary devices should be removed

to decrease the risk of CLABSI.[11] Once the catheters are placed, nurses should actively survey the site for signs of infection, including erythema, warmth, and purulent drainage. If the site becomes infected, a physician or a midlevel provider should be notified promptly. In these instances, removal of the catheter is recommended by the Centers for Disease Control and Prevention.[11]

For patients with bacteremia or other severe infections caused by MRSA or other multidrug-resistant organisms, response to treatment must be assessed. Up to 1 week may be required after the start of treatment with appropriate antibiotics before blood cultures indicate eradication of MRSA. If a patient's clinical status is worsening despite antibiotic therapy, the causative organism may be resistant to the current medication.[6] The patient's clinical status should be correlated to laboratory values, especially the white blood cell count. A decrease in the white blood cell count is not always an indication the antibiotic is effective.

Drug-induced neutropenia is associated with some classes of medications, including anti-infectives. The neutropenia usually occurs within 2 to 60 days after administration of a drug.[45] Drug-induced neutropenia increases the risk for sepsis and may predispose patients to hospital-acquired infections. Superinfections can also result from antibiotic use. Monitoring is required for the development of oral thrush, vaginal yeast infections, and other superinfections, as well as *Clostridium difficile*–associated diarrhea.[16] Vancomycin, linezolid, and ceftaroline may decrease bone marrow production. Monitoring the complete blood cell count can help detect neutropenia, anemia, and thrombocytopenia before these blood abnormalities become clinically relevant.

Registered nurses can help prevent CLABSI by assisting in insertion of central venous catheters and monitoring bundle compliance.

The bactericidal activity of vancomycin depends on the ratio of the area under the curve to the MIC of vancomycin for the organism in question. Trough levels are used as a surrogate marker to ensure a target ratio greater than 400. Correct timing is essential in obtaining blood samples to determine trough levels. Measurements of vancomycin troughs are most accurate when the medication has reached its steady state. The blood samples should be obtained just before the fourth dose in patients

with normal renal function.[13] If a blood sample is obtained too early, the level will be higher than it would be if the sample were obtained at the correct time. In a retrospective analysis of 2597 blood samples obtained during a 13-month period, Morrison et al[46] found that more than 41.3% of the samples obtained to measure vancomycin troughs were obtained too early. The samples that were obtained early yielded higher trough levels than did samples obtained at the appropriate time. Measurements that inaccurately indicated elevated levels may prompt the provider or clinical pharmacist to inappropriately adjust subsequent vancomycin doses.[47] Subtherapeutic levels can lead to vancomycin-resistant bacteria and potential treatment failures.[13]

Patient Education

Because MRSA CLABSIs typically require a minimum of 14 days of antibiotic therapy after the first blood culture is negative for the microbe, some patients will be discharged before they complete their course of treatment.[6,11] At the time of discharge, general education for patients taking antibiotics to treat MRSA CLABSIs should focus on reminding the patients to take the drugs as instructed, not skip doses, and not stop the medication until the course of therapy is finished. Discharge education should include information on the potential adverse effects of the antibiotic, including superinfections and *Clostridium difficile*–associated diarrhea. Patients should be educated on the signs and symptoms to look for and when to notify the prescribing health care provider.

Accurate and reliable measurements of vancomycin troughs are achieved with correct timing of previous doses and when the medication has reached its steady state.

Counseling patients on preventing the spread of MRSA to others is important. Hand hygiene keeps MRSA from spreading. Hand washing is preferable, but alcohol-based gel hand sanitizers are also effective, except for *Clostridium difficile*–associated diarrhea. Patients should cover all draining wounds to prevent transmission of the bacteria. Because patients usually have some type of long-term venous access, such as a peripherally inserted central catheter, they and their family members should be instructed on proper care of the catheter and use of aseptic technique before, during, and after each administration of antibiotic. Patients should be educated about the signs of infection at the catheter site and be instructed to notify their provider if infection occurs.[48] Patients and caregivers assisting with dressing changes must wear gloves during wound care and must wash their hands immediately after. Family members should be warned to avoid sharing personal or hygiene items with the patient. Nurses should encourage frequent cleaning of surfaces with which the patient infected with MRSA comes into contact with a product labeled as a disinfectant. The agent must stay in contact with the contaminated surface for 10 minutes. Clothing and linen should be laundered frequently. If wound drainage is present, these items should be washed daily.[6] Additionally, patients with active MRSA infections should avoid participating in contact sports and in exercising at public facilities such as gyms until the patients are cleared by their health care provider.

Conclusions

Vancomycin has remained the agent of choice for treating MRSA bacteremia for several decades.[6,9] Recent research supports use of alternative agents for MRSA bacteremia, but the use of these agents is often reserved for patients who cannot tolerate vancomycin, have persistent bacteremia during treatment with vancomycin, or have MRSA infections for which vancomycin MICs are elevated.[6,9,22,23,25,26,38] Daptomycin has the most data to support its use as an alternative agent in MRSA bacteremia in both the IDSA 2009 CLABSI and 2011 MRSA guidelines. Linezolid should be reserved for salvage therapy.[6,9] In addition, ceftaroline has increasing retrospective clinical data to support its use as an alternative agent in MRSA bacteremia, including CLABSIs, and in patients in whom standard therapy has been unsuccessful.[35-40] Recently, 3 new MRSA-active agents have been approved by the FDA: dalbavancin, oritavancin, and tedizolid. All 3 agents have activity against MRSA, but currently no data are available to support their use in MRSA bacteremia or CLABSIs.[49-51] Unfortunately, resistance to available antibiotics is occurring quicker than new agents are being developed.[52] Antimicrobial stewardship efforts to ensure the optimal prescribing of these available broad-spectrum anti-MRSA antibiotics are needed to help decrease the development of multidrug-resistant organisms.[53] In addition to preventing the development of resistant organisms, evidence-based

practices such as isolation, proper cleaning of high-touch surfaces, and CHG bathing to decrease bacterial load are essential in preventing the spread of MRSA. **CCN**

Financial Disclosures
None reported.

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To learn more about caring for patients with methicillin-resistant *Staphylococcus aureus,* read "Nasal Colonization and Lower Respiratory Tract Infections With Methicillin-Resistant *Staphylococcus aureus*" by Tilahun et al in the *American Journal of Critical Care*, January 2015; 24:8-12. Available at **www.ajcconline.org**.

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Treating Central Catheter–Associated Bacteremia Due to Methicillin-Resistant *Staphylococcus aureus:* Beyond Vancomycin

According to the Centers for Disease Control and Prevention, methicillin-resistant *Staphylococcus aureus* (MRSA) is a leading cause of heath care–associated infections. Colonization can lead to infection when a breach occurs in the skin or mucosal defense systems because of trauma or common procedures such as surgery or placement of a central catheter.

MRSA is a common cause of bacteremia and is the causative organism reported in 7.4% of central catheter–associated bloodstream infections (CLABSIs) in critical care patients. Most patients with suspected CLABSI are given vancomycin because of the increased prevalence of MRSA in health care settings, and combination therapy with a drug effective against a broad spectrum of gram-negative organisms should be considered for patients who are critically ill or immunocompromised.

Vancomycin

- Treatment of a CLABSI depends on the causative organism, removal of the infected catheter, patient-specific factors, and complications. Vancomycin is the first-line option for treatment of documented MRSA bacteremia.
- Determining the best dosage of vancomycin is difficult, tissue penetration is highly variable, routine trough-level monitoring is required, and infusion-rel ated reactions and anaphylaxis can occur.
- The Infectious Diseases Society of America vancomycin guidelines suggest that an alternative agent should be considered in MRSA infections for which the vancomycin minimum inhibitory concentration is 2 µg/mL or less, particularly if the patient is not responding to treatment.
- Although vancomycin remains the drug of choice, alternative agents may be used to treat invasive MRSA infections, including daptomycin (Cubicin), linezolid (Zyvox), telavancin (Vibativ), tigecycline (Tygacil), and ceftaroline (Teflaro).

Nursing Care

- Instituting evidence-based infection control measures is required to prevent the spread of MRSA and other multidrug-resistant organisms. Studies have shown that decreasing the skin's bacterial load with chlorhexidine gluconate baths decreases rates of infection.
- Implementing use of bundles for insertion of central venous catheters decreases the incidence of CLABSI. Bundle elements include performing hand hygiene, using chlorhexidine gluconate for skin cleansing, and instituting full-barrier precautions before insertion of the catheter.
- Having registered nurses assist in insertion of central venous catheters and monitor bundle compliance is an important step in preventing CLABSI.
- Empowering nurses to stop the insertion if breaks in sterile technique occur is critical in minimizing the threat of bacterial migration into the bloodstream.
- Superinfections can result from antibiotic use. Monitoring is required for the development of oral thrush, vaginal yeast infections, and other superinfections, as well as *Clostridium difficile*–associated diarrhea.
- Counseling patients on preventing the spread of MRSA to others is important. Hand hygiene keeps MRSA from spreading. Hand washing is preferable, but alcohol-based gel hand sanitizers are also effective, except for *Clostridium difficile*–associated diarrhea.
- Patients should cover all draining wounds to prevent transmission of the bacteria.
- Patients and their family members should be instructed on proper care of the catheter and use of aseptic technique before, during, and after each administration of antibiotic. Patients should be educated about the signs of infection at the catheter site and be instructed to notify their provider if infection occurs. CCN

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