

## ***Methicillin-Resistant Staphylococcus Aureus (MRSA)***

Over the past several decades, the incidence of resistant gram-positive organisms has risen in the United States. MRSA strains, first identified in the 1960s in England, were first observed in the U.S. in the mid 1980s.<sup>1</sup> Resistance quickly developed, increasing from 2.4% in 1979 to 29% in 1991.<sup>2</sup> The current prevalence for MRSA in hospitals and other facilities ranges from <10% to 65%. In 1999, MRSA accounted for more than 50% of all *Staphylococcus aureus* isolates within U.S. intensive care units.<sup>3,4</sup> The past years, however, outbreaks of MRSA have also been seen in the community setting, particularly among preschool-age children, some of whom have attended day-care centers.<sup>5,6,7</sup>

MRSA does not appear to be more virulent than methicillin-sensitive *Staphylococcus aureus*, but certainly poses a greater treatment challenge. MRSA also has been associated with higher hospital costs and mortality.<sup>8</sup> Within a decade of its development, methicillin resistance to *Staphylococcus aureus* emerged.<sup>9</sup> MRSA strains generally are now resistant to other antimicrobial classes including aminoglycosides, beta-lactams, carbapenems, cephalosporins, fluoroquinolones and macrolides.<sup>10,11</sup> Most of the resistance was secondary to production of beta-lactamase enzymes or intrinsic resistance with alterations in penicillin-binding proteins.

*Staphylococcus aureus* is the most frequent cause of nosocomial pneumonia and surgical-wound infections and the second most common cause of nosocomial bloodstream infections.<sup>12</sup> Long-term care facilities (LTCFs) have developed rates of MRSA ranging from 25%-35%. MRSA rates may be higher in LTCFs if they are associated with hospitals that have higher rates.<sup>13</sup>

Transmission of MRSA generally occurs through direct or indirect contact with a reservoir. Some authors suggest MRSA strains appear in LTCFs after admitting patients who became infected or colonized in an acute-care facility prior to transfer.<sup>14</sup> Alternatively, other studies suggest that patients entering an acute-care facility colonized with MRSA were transferred from a LTCF.<sup>15,16</sup> Those with MRSA surgical wound infections or receiving hemodialysis may pose a greater risk than nasal carriers. Other risk factors include intravascular catheters, tracheostomy, gastrostomy, indwelling urinary catheters and decubitus ulcers. Strict adherence to infection control practices is imperative to prohibit further spread of MRSA.

### **TREATMENT**

Basic infection-control measures are critical to success. Another important consideration is careful evaluation of culture and sensitivity reports. Infection is often confused with colonization and can lead to unnecessary utilization of antimicrobial agents. Potential anatomical sites of colonization include the anterior nares, axillae, upper extremities, urinary tract and perineum. Consultation with an infectious-disease specialist is advised regarding management when there is question as to infection versus colonization.

MRSA is of special concern in regards to treatment because it is usually multi-drug resistant. In addition to most beta-lactams, MRSA is also commonly resistant to erythromycin, clindamycin, aminoglycosides, fluoroquinolones, co-trimoxazole and rifampin. However, some strains remain sensitive to minocycline and recently, strains acquired outside of health-care settings remain susceptible to agents, such as clindamycin and gentamicin.

Vancomycin continues to be the drug of choice for treating most MRSA infections caused by multi-drug resistant strains. Clindamycin, co-trimoxazole, fluoroquinolones or minocycline may be useful when patients do not have life-threatening infections caused by strains susceptible to these agents. For serious infections caused by strains that are susceptible to rifampin, adding this agent to vancomycin or fluoroquinolone may contribute to improved outcomes. Rifampin should not be used alone to treat MRSA infections due to the rapid development of resistance. The infecting strain always should be tested for susceptibility prior to initiating any of these therapies.<sup>17</sup> The two newest antimicrobials, quinupristin-dalfopristin (Synecid<sup>®</sup>) and linezolid (Zyvox<sup>™</sup>), also are effective for MRSA infections, although routine use is generally discouraged to prevent further resistance to these agents. Other investigational agents are in research stages but not yet approved for use.

Most strains of MRSA are inhibited by concentrations of vancomycin ranging from 0.5-2.0 mcg/mL, although strains have been reported with intermediate sensitivity (MIC=8 mcg/mL) that have been called glycopeptide-intermediate *Staphylococcus aureus* (GISA) or vancomycin-intermediate *Staphylococcus aureus* (VISA).<sup>19</sup> Such infections are likely to be seen with increasing frequency, particularly among patients who receive prolonged courses of vancomycin or have risk factors for acquiring MRSA. The GISA strains reported have been variably sensitive to other antimicrobials such as chloramphenicol, gentamicin, rifampin, co-trimoxazole and tetracycline. Quinupristin-dalfopristin and linezolid are also active against GISA. Combinations of these agents and others have been used successfully to treat cases involving GISA, though assistance from an infectious disease specialist is strongly advised.<sup>17</sup>

## ***Vancomycin-Resistant Enterococcus (VRE)***

Enterococci are opportunistic pathogens that are normal inhabitants of human gastrointestinal and genitourinary tracts. Enterococci are generally not particularly pathogenic in humans and have traditionally been classified as relatively harmless commensals. Enterococci alone rarely colonize or cause infection of the respiratory tract or cause primary cellulitis, unlike other gram-positive organisms such as *Staphylococcus aureus*.<sup>19</sup>

Though over a dozen different species of enterococci have been identified, two species, *Enterococcus faecalis* and *Enterococcus faecium*, are the most prevalent in human infections. *Enterococcus faecalis*, which comprises 85%-90% of all human enterococcal infections, is typically considered the most pathogenic. The remaining 5%-10% of enterococcal infections are due to *Enterococcus faecium*, which is increasingly resistant to vancomycin and is now considered a major nosocomial pathogen.<sup>19</sup> Other less common *Enterococcus* species include *E. durans*, *E. gallinarum*, *E. avium*, *E. raffinosus* and others. Enterococci typically are associated with causing urinary tract infections, intra-abdominal and pelvic sepsis, surgical wound infections and bacteremia, in descending order of frequency. However, they now are emerging as highly-resistant organisms and nosocomial pathogens.<sup>19</sup>

Enterococci have been identified as the third most common cause of nosocomial, hospital-acquired pneumonia.<sup>20</sup> The Centers for Disease Control and Prevention (CDC) reported that the incidence of VRE increased from 0.3% in 1989 to 7.9% in 1993. During the same time period, VRE rates in the intensive care unit (ICU) setting increased from 0.4% to 13.6%.<sup>21</sup> Since its identification in U.S. hospitals in the 1980s, VRE rates have continued to increase and now account for more than 25% of ICU enterococci, according to the NNIS system.<sup>22</sup> Mortality rates for VRE bacteremia and sepsis have been reported to exceed 30%.<sup>22, 23</sup>

Enterococci are intrinsically resistant to a number of antibiotics and antibiotic classes. They do not possess exotoxins or enzymes that allow invasion and destruction of tissues. They can, however, readily acquire resistance genes that are capable of transfer to other bacteria. Resistant enterococcus can be isolated from patients who have been institutionalized for long periods of time. Other risk factors for acquiring a resistant enterococcal infection include severity of underlying illness, presence of invasive devices, prolonged antibiotic use and prior colonization. Those at higher risk include immunosuppressed hosts such as renal dialysis, transplant and oncology patients.

Since vancomycin use is a factor that has been linked with the development of VRE, appropriate use guidelines have been established by the Hospital Infection Control Practices Advisory Committee (HICPAC) of the CDC (Table 1<sup>25</sup>).

<b>TABLE 1. Recommendations for Preventing the Spread of Vancomycin Resistance<sup>25</sup></b>
<p style="text-align: center;"><b>SITUATIONS IN WHICH THE USE OF VANCOMYCIN IS APPROPRIATE</b></p> <ol style="list-style-type: none"> <li>1. Treatment of serious infections due to beta-lactam resistant gram-positive organisms.</li> <li>2. Treatment of serious infections due to gram-positive organisms in patients with serious beta-lactam allergies.</li> <li>3. Treatment of antibiotic-associated colitis (AAC) when treatment with metronidazole has failed or if the AAC is potentially life-threatening.</li> <li>4. Prophylaxis for endocarditis for certain procedures based on American Heart Association recommendations.</li> <li>5. Prophylaxis for certain surgical procedures involving implantation of prosthetic materials in hospitals with a high rate of MRSA or MRSE.</li> </ol>
<p style="text-align: center;"><b>SITUATIONS IN WHICH THE USE OF VANCOMYCIN SHOULD BE DISCOURAGED</b></p> <ol style="list-style-type: none"> <li>1. Routine surgical prophylaxis unless the patient has a severe allergy to beta-lactam antibiotics.</li> <li>2. Empiric treatment for febrile neutropenic patients unless a gram-positive infection is suspected and the institution has a high rate of MRSA.</li> <li>3. Treatment of one positive blood culture for coagulase-negative staphylococcus if other blood cultures drawn at the same time are negative (i.e., likely contamination).</li> <li>4. Continued empiric use in patients whose cultures are negative for beta-lactam resistant gram-positive organisms.</li> <li>5. Prophylaxis for infection or colonization of indwelling central or peripheral intravenous catheters.</li> <li>6. Selective decontamination of the gastrointestinal tract.</li> <li>7. Eradication of MRSA colonization.</li> <li>8. Primary treatment of AAC</li> <li>9. Routine prophylaxis for infants with very low birth weight.</li> <li>10. Routine prophylaxis for patients on continuous ambulatory peritoneal dialysis or hemodialysis.</li> <li>11. Treatment of infection due to beta-lactam sensitive gram-positive microorganisms in patients with renal failure (for ease of dosing schedule).</li> <li>12. Use of vancomycin solution for topical application or irrigation.</li> </ol>

Enterococcus has developed intrinsic resistance to many antibiotics, including cephalosporin antibiotics. They exhibit low-level resistance to aminoglycosides, which can be overcome by adding a cell-wall active agent such as ampicillin or vancomycin. These combinations can provide a bactericidal effect, sometimes referred to as a synergistic effect. Unfortunately, enterococci also have developed high-level resistance to aminoglycosides (MIC >500 to gentamicin), in which case they will not produce a synergistic, bactericidal effect.<sup>20</sup> Resistance to beta-lactams occurs secondary to either enzyme production or altered penicillin-binding proteins. Beta-lactamase producing strains for *Enterococcus faecalis*, which are typically rare, can be treated with ampicillin/sulbactam ± an aminoglycoside. *Enterococcus faecium*, which produce an enzyme different from penicillinase that is not inhibited by penicillin, are now commonly resistant to many beta-lactams although there are reports of success with combination therapy using double and or triple combination regimens.<sup>20, 26</sup> Enterococci develop resistance via three phenotypes, which are outlined in Table 2.<sup>19, 27</sup>

<b>Phenotype</b>	<b>Characteristics</b>
VanA	<ul style="list-style-type: none"> <li>• MIC (vancomycin) 64 to &gt;1,000 mcg/mL</li> <li>• High-level vancomycin resistance</li> <li>• Resistant to teicoplanin</li> <li>• Most commonly seen with <i>E. faecium</i></li> <li>• Transferable between organisms</li> <li>• Inducible by antibiotics</li> </ul>
VanB	<ul style="list-style-type: none"> <li>• MIC (vancomycin) 4 to &gt;1,000 mcg/mL</li> <li>• Moderately resistant to vancomycin</li> <li>• Susceptible to teicoplanin</li> <li>• Transferable between organisms</li> </ul>
VanC	<ul style="list-style-type: none"> <li>• MIC (vancomycin) 2 -32 mcg/mL</li> <li>• Low-level vancomycin resistance</li> <li>• Susceptible to teicoplanin</li> <li>• Not observed in <i>E. faecalis</i> or <i>E. faecium</i></li> <li>• Not transferable</li> </ul>

### TREATMENT

An important aspect for controlling VRE is implementation of strict infection control practices. Without utilization of appropriate infection control practices, it will be difficult to prevent VRE from becoming endemic. In addition to infection control policies and procedures, health-care facilities should have guidelines in place to manage actual or suspected cases of VRE in regards to antimicrobial therapy. Steps may include:

- A comprehensive antimicrobial utilization plan that includes education of all staff (medical, nursing and other ancillary services).
- Understanding of antimicrobial use for surgical prophylaxis (if pertinent).
- Guidelines for appropriate antibiotic use (as applicable to the institution).

A comprehensive group of individuals, which may consist of infection control, infectious disease, medical, surgical, nursing, microbiology, pharmacy, epidemiology, quality assurance, administration staff and all other pertinent entities, should develop its own protocols for each individual institution.

Fortunately, VRE is not a highly-virulent organism. Therefore, other measures besides antimicrobial therapy also must be considered. For line-related bacteremia, simply removing the intravenous device may be sufficient. Surgical debridement and drainage may be adequate for cases of soft tissue infections, surgical site infections and abscesses. Urinary tract infections may respond spontaneously or with removal of indwelling catheters. For severe infections such as endocarditis and meningitis, utilization of bactericidal antibiotics is advised.

Until recently, most of the data for treating VRE infections with antibiotics has been limited and primarily derived from experimental animal models, case reports or small series of cases. Reasons for limited clinical data include lack of comparator arms in clinical trials, high mortality rates with advanced illness and complex treatment

requirements. Under most circumstances, consultation with an infectious disease specialist is recommended to treat and control VRE infections.

A number of different combination antimicrobial drug regimens have been used to treat clinically important VRE infections resistant to both ampicillin and vancomycin. For strains of VRE not isolated from the urinary tract, regimens have consisted of high-dose ampicillin or ampicillin-sulbactam plus gentamicin, doxycycline or chloramphenicol and including  $\pm$  other drugs, ampicillin + imipenem  $\pm$  gentamicin, a beta-lactam + vancomycin  $\pm$  gentamicin, ampicillin + fluoroquinolone (unless quinolone resistant), rifampin + fluoroquinolone + gentamicin, quinupristin-dalfopristin, or linezolid. Nitrofurantoin, amoxicillin, or ampicillin have been used selectively to treat VRE strains isolated from the urinary tract when the MIC to ampicillin is  $\leq 64$  mcg/mL.<sup>27</sup> Nitrofurantoin, ampicillin, and amoxicillin have been effective for treating urinary tract infections because they achieve high concentrations in urine. However, nitrofurantoin should be used with caution in the elderly and those with impaired renal function.

Two newer antimicrobial agents are approved for VRE infections: quinupristin-dalfopristin (Synercid<sup>®</sup>) and linezolid (Zyvox<sup>™</sup>). Quinupristin-dalfopristin is a streptogramin that is active against *Enterococcus faecium* but not *Enterococcus faecalis*. Linezolid, an oxazolidinone, has activity against both *Enterococcus faecium* and *Enterococcus faecalis*. Linezolid is available in both intravenous and oral formulations. Other investigational agents are being studied but are not yet approved for use.

Based on surveillance data and current trends, it appears VRE will continue to escalate as a problem not only in acute-care settings, but also in long-term care facilities and the community. Treatment options, though limited, are available and newer agents are being studied. Besides quinupristin-dalfopristin and linezolid, use of older agents, usually in combination, have been effective. Strict adherence to infection control policies and consultation with infectious disease specialists are important.

