Burden of Methicillin-Resistant *Staphylococcus aureus*: Focus on Clinical and Economic Outcomes

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Infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) are a major public concern. Hospital-acquired MRSA rates have steadily increased over the past 25 years, and the bacterial strain is making inroads to the community. The morbidity and mortality burden of MRSA infection is compounded by delayed or inappropriate antibiotic treatment, taking a toll on health care resources that are already stretched thin. Vancomycin has historically been the drug of choice for this pathogen because its broad spectrum can address the multidrug resistance of most MRSA infections. Despite its sustained in vitro microbiologic inhibitory activity, researchers are beginning to question the continued utility of vancomycin for MRSA infections. Evidence against vancomycin is most notable with regard to nosocomial pneumonia and skin and soft tissue infections. In addition, because vancomycin must be administered intravenously, patients typically require prolonged hospitalization, which further increases the cost of MRSA treatment and exposes patients to additional nosocomial infections. Recent studies have shown that antibiotics with good bioavailability, such as linezolid, can be given orally to facilitate early hospital discharge, thus alleviating the economic burden of MRSA infections. Several agents have been developed over the past decade that have excellent in vitro activity against MRSA. Further studies are needed to determine if these drugs can better eradicate MRSA than vancomycin and remedy the adverse outcomes frequently observed with this organism.

Key Words: MRSA, mortality, outcomes, vancomycin, linezolid, daptomycin.
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With the welcome advent of antimicrobial agents in the last century came the emergence of resistant organisms. These pathogens threaten the viability of our current antimicrobial options and present a major therapeutic challenge for clinicians worldwide. Of the 2 million annual nosocomial infections in the United States, more than 50% are caused by drug-resistant strains of bacteria.[1, 2] Drug resistance has a considerable impact on patient morbidity and mortality and is a major economic burden for society, with yearly expenditures in the United States ranging from $4 billion–$30 billion.[1–3]

One organism of particular concern is methicillin-resistant *Staphylococcus aureus* (MRSA). Methicillin resistance in *S. aureus*

infections is mediated by the *mecA* gene, which encodes a penicillin-binding protein (PBP2a) that has low affinity for β-lactam–type antibiotics and renders all β-lactams inactive.[4] This particular strain was first observed shortly after the introduction of semisynthetic penicillins in the 1960s. By just 2 decades later, MRSA had become endemic in many hospitals throughout the world.[5] Since then, MRSA rates have been steadily climbing in both the intensive care unit (ICU) and non-ICU hospital settings. Among U.S. hospitals, MRSA is the most commonly isolated antibiotic-resistant pathogen. It accounts for more than half of all *S. aureus* isolates in many institutions.[6, 7] In numerous ICUs, the MRSA rate exceeds 70%.[6]

Historically, MRSA infections have occurred primarily among hospitalized patients or among those with a history of extensive hospitalization and other predisposing risk factors, such as indwelling catheters, past antimicrobial use, decubitus ulcers, postoperative surgical wounds, or treatment with enteral feedings or dialysis.[8–24] The epidemiology of MRSA, however, is evolving; the drug-resistant strain is no longer exclusively confined to hospitals or limited to patients with traditional predisposing risk factors.[25–27] A growing number of reports document nascent community-associated MRSA (CA-MRSA) infections among previously healthy individuals without known risk factors for MRSA. Outbreaks of CA-MRSA have been reported in close-contact settings, such as prisons, child day-care centers, sports teams, and Native American communities.[28–40] In certain areas, CA-MRSA is endemic. This pathogen is now the predominant cause of community-acquired staphylococcal infections.[25, 28, 30]

The strains responsible for CA-MRSA infections are genotypically distinct from those responsible for MRSA infections acquired in health care settings. Thus, CA-MRSA is not merely a hospital-acquired strain that has escaped into the community. Pulsed-field gel electrophoresis and other strain-typing methods have identified a small number of molecular types that account for most CA-MRSA isolates characterized in the United States.[26, 30, 41–45] Compared with health care–associated MRSA (HA-MRSA), CA-MRSA isolates carry a different type of the gene complex known as the staphylococcal cassette chromosome *mec* (SCC*mec*), which contains the *mec*A methicillin-resistance gene. Another difference is that CA-MRSA isolates tend to be resistant to fewer antimicrobial classes than HA-MRSA. Genomic studies have consistently shown that CA-MRSA strains carry a range of virulence genes that are distinct from virulence genes in typical HA-MRSA strains.[26, 27, 30, 41–45] Thus far, CA-MRSA seems to preferentially infect children and young adults. The spectrum of disease caused by CA-MRSA appears to be similar to that caused by methicillin-susceptible *S. aureus* (MSSA). Infections caused by CA-MRSA range from minor skin and soft tissue infections to rapidly fatal, necrotizing pneumonia and overwhelming sepsis. Skin and soft tissue infections, specifically furuncles and carbuncles, are the most frequently reported presentation of CA-MRSA infections.[25, 27–40, 42, 44, 46, 47]

Public Health Threat

Clinicians and public health officials now see MRSA as a major public health threat because of its rising rate of occurrence in both hospital and community settings and the dearth of proven treatment options available.[1–3, 48] Most HA-MRSA infections are cross-resistant to many non–β-lactam antibiotics, which further complicates treatment decisions.[7, 25] Cross-resistance is less common among CA-MRSA strains than HA-MRSA strains. Nevertheless, CA-MRSA strains are a significant threat because they carry a range of virulent genes and other genes that are distinct from typical HA-MRSA strains. Collectively, these factors may enhance the transmissibility of CA-MRSA and account for the faster growth and higher infection burden associated with CA-MRSA versus HA-MRSA. Moreover, CA-MRSA is being found in hospitals and is the predominant MRSA clone in some institutions. This is alarming because of the more virulent nature of CA-MRSA strains compared with the traditional HA-MRSA strains.[26, 43, 45]

Vancomycin emerged as the drug of choice for serious MRSA infections against this backdrop of resistance, and it has remained highly active against MRSA at the currently defined minimum inhibitory concentration (MIC) breakpoints.[6] Within the past 10 years, however, multiple reports have described MRSA strains with intermediate susceptibility or high-level resistance to vancomycin, and some researchers have questioned vancomycin's activity against MRSA strains with MICs at the high end of the susceptible range.[49–51] Based on changing vancomycin susceptibility and an increased appreciation of clinical failures involving MRSA strains with high vancomycin MICs, the Clinical

and Laboratory Standards Institute (CLSI) lowered the susceptibility breakpoint from 4 mg/L or lower to 2 mg/L or lower in January 2006.[52] Often, a history of vancomycin use preceded the development of vancomycin-intermediate *S. aureus* (VISA) and vancomycin-resistant *S. aureus* (VRSA).[50, 51] Many experts view the emergence of VISA, heteroresistant glycopeptide-intermediate *S. aureus*, and VRSA as a public health crisis.[48]

Mortality Rates

In addition to the resistance threat, public health officials are concerned about the deleterious outcomes associated with MRSA infections, particularly MRSA bloodstream infections. Before the advent of penicillin, mortality rates associated with *S. aureus* bloodstream infections were extremely high. In a 1941 study of 122 patients with *S. aureus* bloodstream infections, the overall fatality rate was 82%, and fatalities exceeded 97% for patients older than 50 years.[53] The introduction of effective antibiotics was associated with a dramatic drop in the mortality rate related to *S. aureus* bloodstream infections. Although contemporary mortality rates are much lower than those of the preantibiotic era, there has been a steady rise in fatality rates associated with *S. aureus* bloodstream infections,[5] and the current mortality rate is 15–60%.[8, 10, 11, 13–15, 17, 18, 20, 21, 23, 24, 54–60] The mortality rate is usually higher for patients with MRSA bloodstream infections than for patients with MSSA bloodstream infections; these findings contribute to the growing public health concern about MRSA and fuel the debate on how to improve MRSA treatment outcomes.

Despite the higher crude mortality rates observed with MRSA bloodstream infections than with bloodstream infections involving MSSA, the role of MRSA in patient survival has been a contentious issue.[8, 10, 11, 13–15, 17, 18, 20, 21, 23, 24, 54–59] Many believe that the association between MRSA and mortality can be explained by factors other than drug resistance. It is well known that certain medical and comorbid conditions predispose patients to MRSA infection.[8, 10, 11, 13–15, 17, 18, 20, 21, 23, 24, 54–59] For example, patients with MRSA infections typically have greater severity of illness, more comorbid conditions, and a longer hospital stay before onset of infection than patients infected with MSSA. These patient factors may independently contribute to adverse clinical outcomes and obviate assessments of the relationship between methicillin resistance and patient outcome; indeed, this relationship has been studied extensively with varying conclusions.[8, 10, 11, 13–15, 17, 18, 20, 21, 23, 24, 54–59]

To clarify the role of MRSA in patient outcomes, a research group performed a meta-analysis that compared mortality rates associated with bloodstream infections caused by MRSA versus MSSA.[13] Using the MEDLINE database, the researchers reviewed studies that reported mortality rates associated with both MRSA and MSSA bloodstream infections from January 1980–December 2000. They identified 31 cohort studies with a total of 3963 patients with *S. aureus* bloodstream infections. The etiology of infection was assigned to MSSA for 2603 (65.7%) of the total patients and to MRSA for 1360 (34.3%) patients. Although 24 (77.4%) of the 31 studies did not identify a statistically significant association between methicillin susceptibility and death, the pooled analysis revealed a statistically significant increase in mortality among patients with MRSA versus MSSA bacteremia (36.4% vs 23.4%, $p<0.01$), with a pooled odds ratio (OR) of 1.93 (95% confidence interval [CI] 1.54–2.42, $p<0.001$). Of no surprise, the authors tried to overcome the inherent heterogeneity among the studies by creating homogenous subgroups of studies, including a cohort of studies that controlled for disease severity. They subsequently examined the relationship between MRSA and death in the comparable subgroups. In all of the subgroup analyses, the OR between MRSA and death remained at 1.56–2.2. This association persisted even when adjustments were made for severity of illness. Based on their findings, the authors cited type II error as the primary reason for heterogeneity among results of previous studies.

Another research group performed a similar meta-analysis but limited its focus to nosocomial bloodstream infections caused by *S. aureus*.[59] After comprehensively reviewing all studies published from 1978–2000, they selected nine studies encompassing 2209 nosocomial *S. aureus* bloodstream infections. All but one study found a significant relationship between MRSA and death. As with the meta-analysis described above,[13] the relative risk of death was significantly higher for patients with bloodstream infections due to MRSA (29%) versus MSSA (12%) (OR 2.12, 95% CI 1.76–2.57, $p<0.001$)[59] Although further, large-scale studies are needed to determine the definitive contribution of methicillin resistance to observed mortality rates

from MRSA bloodstream infections, these meta-analyses support the notion that the mortality rate difference between MRSA and MSSA is real, even after adjustment for severity of illness and comorbid conditions, and cannot be solely explained by differences in patient factors.

Economic Outcomes

Despite the ongoing debate over the impact of MRSA on the rate of mortality, studies have consistently demonstrated that MRSA infections are associated with increased morbidity relative to MSSA infections.[8, 16, 20, 54, 56, 58, 60–63] Studies have shown that the increased hospitalization costs attributable to methicillin resistance range from $5000 to as much as $40,000.[8, 16, 20, 56, 60, 61] Although the absolute difference of cost has varied between investigations, studies have consistently demonstrated that MRSA is associated with a 1.2–2.0-fold increase in length of hospital stay and hospitalization costs. Disparities in study results are most likely secondary to differences in study populations and costing structures.[64]

Methicillin resistance is not restricted to the acute care setting. It also has significant effects on costs and charges associated with management of *S. aureus* surgical site infections,[62] *S. aureus* bloodstream infections among community-dwelling patients who require hemodialysis,[63] and *S. aureus* infections in long-term care facilities.[54] In a study of patients with surgical site infections, MRSA was associated with 1.2-fold higher median hospital charges (p=0.03) compared with MSSA in a multivariate analysis.[62] In a prospective study of patients undergoing dialysis who had either MRSA bloodstream infections or MSSA bacteremia, adjusted costs were 1.5-fold higher for those with MRSA.[63] Similarly, the median overall cost associated with MRSA infections in a long-term care facility was reported to be twice that of MSSA infections.[54] It also appears that CA-MRSA infections are associated with increased morbidity, but few dedicated studies have addressed that issue.[65] Collectively, these studies establish the gravity of MRSA compared with MSSA with respect to overall costs (Table 1).[8, 20, 54, 56, 58, 60–63]

It is important to note that the above morbidity and cost estimates are conservative and do not account for additional costs incurred by implementation of infection control measures. A research group estimated that the cost for isolation and management of patients with MRSA infections in one Canadian hospital was $1363/admission (Can $).[66] The same researchers found that the hospital's annual screening cost for MRSA was $109,813 (Can $). Assuming a modest MRSA infection rate of 10–20%, they determined that the cost associated with MRSA in all Canadian hospitals would be $42–59 million (Can $) annually. Obviously, this would be substantially higher if extrapolated to U.S. hospitals, where the average MRSA rate is approximately 50% of all nosocomial *S. aureus* infections.[6] In addition, it is well documented that patients isolated for infection control precautions experience more preventable adverse events, express greater dissatisfaction with their treatment, and have less documented care than other patients.[67]

Because the morbidity and cost statistics for most of these studies were derived from the hospital perspective, they provide a limited assessment of the impact of resistance.[64] In addition, most of these figures do not account for the cost of managing MRSA infection outside the hospital, which may include the cost of rehabilitation, extended care facilities, or home intravenous therapy.[68] As mentioned above, vancomycin has historically been the drug of choice for MRSA but can only be administered intravenously to treat MRSA infections because the oral formulation is not absorbed. From the payer's standpoint, it is beneficial to treat patients with MRSA in the outpatient setting. Nevertheless, costs for providing vancomycin to outpatients, including drug acquisition, nursing time, supplies, laboratory tests, as well as intravenous line placement, replacement, and management, are high. A study showed these costs to be substantially higher than the average daily reimbursement of approximately $300 estimated from four different health care payers.[68] In addition, these costs do not quantify the effects on patients, which include the emotional toll of having a drug-resistant infection requiring a hospital isolation room, lost time from work and family due to a prolonged hospitalization and recovery period, and the long-term health consequences of having an MRSA infection.[64]

In summary, MRSA adversely affects both morbidity and the rate of mortality. Its impact can be seen in both hospitalized patients and outpatients. Given the continuing increase in the spread of MRSA and the evolution of CA-MRSA strains, this pathogen is likely to remain a major challenge for clinicians.

Table 1. Comparison of Hospital Costs and Charges for MRSA versus MSSA Infections

		Hospital Costs and Charges	
Type of Infection	End Point	MRSA ($)	MSSA ($)
Nosocomial bloodstream infection[8]	Median total cost of hospitalization attributable to bloodstream infection	27,083	9661
Infections in a long-term care facility[54]	Median infection cost	2607	1332
Nosocomial bloodstream infection[56]	Median hospital charges after onset of bloodstream infection	26,212	19,212
Surgical site infection[62]	Median hospital charges attributable to surgical site infection	92,363	52,791
Nosocomial bloodstream infection[60]	Adjusted mean cost after onset of bloodstream infection	21,577	11,668
Nosocomial bloodstream infection[20]	Mean cost/patient-day of hospitalization	5878	2073
Bloodstream infection in patients undergoing dialysis[63]	Adjusted mean cost of first hospitalization	21,251	13,978
	Adjusted mean cost 12 wks after first hospitalization	25,518	17,354
All infections[58]	Attributable mean cost	34,000	31,500
Nosocomial infections[58]	Attributable mean cost	31,400	27,700
Nosocomial infections[61]	Mean total cost of hospitalization directly attributable to infection	7481	2377

MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*.

Factors Contributing to Clinical and Economic Outcomes

The causal pathway for MRSA is complex, and outcomes reflect a confluence of factors related to the organism, treatment, and the patient.[64] Although differences in organism fitness may explain differences in outcomes,[69–73] several treatment-related factors provide plausible explanations for the heightened morbidity, mortality, and cost associated with MRSA infections versus infections caused by other pathogens. Patients with MRSA infections are at risk for delayed administration of effective antimicrobial therapy due to the rising prevalence of multidrug-resistant MRSA strains.[7, 25] In a study that examined the relationship between adequacy of antimicrobial treatment for bloodstream infections and clinical outcomes of patients requiring ICU admission, 32.9% of patients with MRSA bloodstream infections did not receive antibiotics that were microbiologically active against their pathogens at the time of organism identification and antibiotic susceptibility reporting.[74] Similarly, an assessment of 398 patients with *S. aureus* bloodstream infections revealed that inappropriate empiric therapy was started in 141 (35.4%) patients with MRSA bacteremia,[75] and an outcomes study involving 353 patients found that 42.9% of patients with MRSA infections did not receive appropriate therapy within 45 hours of onset of *S. aureus* bacteremia compared with only 9.8% of patients with MSSA.[57]

These high rates of inadequate empiric therapy are alarming because numerous investigators in various practice settings have correlated the risk of a poor outcome with treatment delays.[23, 57, 74–76] A study of patients with nosocomial *S. aureus* bloodstream infections revealed that patients with treatment delays exceeding 45 hours were at an almost 3-fold higher risk of mortality compared with patients who received adequate antimicrobial therapy within 45 hours[57]; this study corroborated findings of several other investigations.[23, 24] In addition to the increased mortality risk, delayed treatment drives up hospital length of stay (LOS) and cost. The study of patients with nosocomial *S. aureus* bloodstream infections found an adjusted mean LOS of 20.2 days for patients with delayed treatment, compared with only 14.3 days for those treated effectively within 45 hours of onset of bloodstream infection (p=0.05).[57] In a retrospective *S. aureus* bloodstream infection case-control study, MRSA was significantly associated with infection-related mortality and 30-day mortality in the bivariate analysis, but this relationship did not persist after adjustment for delayed appropriate treatment in the multivariate analyses. Delayed treatment was highly predictive of both infection-related mortality (OR 2.2, 95% CI 1.0–4.5, p=0.04) and 30-day mortality (OR 2.1, 95% CI 1.0–4.5, p=0.04) in the multivariate analyses.[60] The findings in these studies underscore the importance of selecting

the appropriate antibiotic early in the course of infection and may partially explain negative MRSA outcomes.

A recent study that examined the impact of methicillin resistance on patients with *S. aureus* ventilator-associated pneumonia reinforces the importance of appropriate empiric therapy to prevent poor MRSA outcomes.[12] In this study, initial antibiotic therapy was appropriate for every patient, and MRSA was not a significant predictor of 28-day mortality in the logistic regression analysis. These findings further highlight the need for early MRSA detection and treatment delivery to improve MRSA outcomes, and investigators should continue to monitor the role of such improvements in determining patient outcomes.

Beyond the complications caused by treatment delays, differences in antibiotics play a role in patient outcomes for MRSA and MSSA infections. As previously mentioned, vancomycin has been the drug of choice for MRSA, and all of the studies above evaluated MRSA outcomes in the "vancomycin era." Despite the sustained in vitro microbiologic inhibitory activity of vancomycin, researchers are beginning to question whether it is appropriate for all MRSA infections.[73] In the past 10 years, multiple reports have described MRSA strains with intermediate susceptibility or high-level resistance to vancomycin.[49–51, 73] There is also growing concern that vancomycin resistance to *S. aureus* is underappreciated because the susceptibility breakpoint designated by the CLSI is still too high (MIC ≤ 2 mg/L).[73, 77] Data, albeit limited, suggest that vancomycin has reduced activity against MRSA infections with vancomycin MICs at the high end of the range deemed susceptible by the CLSI.[73, 77] A post hoc examination of 30 patients with MRSA bacteremia from multicenter, prospective vancomycin-refractory compassionate use studies revealed that clinical success was highly dependent on the vancomycin MIC within the CLSI susceptibility range.[77] For MRSA isolates with vancomycin MICs of 0.5 mg/L or lower, vancomycin was successful in the treatment of 55.6% of patients with bacteremia, whereas it was only effective in 9.5% of cases in which vancomycin MICs were 1–2 mg/L.

A prospective study of adult patients infected with MRSA and treated with vancomycin revealed that the high vancomycin MIC group (vancomycin MIC ≥ 1.5 mg/L) was significantly less responsive to vancomycin than the low vancomycin MIC group (vancomycin MIC < 1.5 mg/L) by bivariate analysis (62% vs 85%; p=0.02).[78] The same study showed that the MIC of infecting strains (high vs low) was an independent predictor of poor treatment response when controlled for Acute Physiology and Chronic Health Evaluation (APACHE) II score, age, ICU admission, site of infection, and target trough attainment in the multivariate analysis. A case-control study of patients undergoing hemodialysis who had MRSA bacteremia found that the mortality rate was significantly higher in those with high vancomycin MICs compared with low vancomycin MICs and a control group (35% vs 24% and 15%, respectively, p=0.02). Furthermore, mean ± SD hospitalization costs were significantly higher in the high-MIC group compared with the low-MIC group and control group ($47,624 ± $80,534 vs $26,792 ± $25,167 and $13,185 ± $15,568, respectively; p<0.001).[79]

Collectively, these studies suggest that patients with MRSA infections who have elevations in vancomycin MICs may have suboptimal clinical responses to vancomycin.[78–81] Furthermore, these studies have raised additional questions about the optimal vancomycin dosage for MRSA infections with high vancomycin MICs.

As mounting data raise concerns about vancomycin's efficacy against high-MIC MRSA strains, other types of studies have provoked questions about which antibiotic class yields the best results against *S. aureus*. In vitro data show that vancomycin is actually inferior to the β-lactams with respect to bactericidal activity against MSSA.[82] Moreover, a growing amount of clinical evidence suggests that glycopeptides are inferior to β-lactam antibiotics as therapy for serious staphylococcal infections.[15, 55, 83, 84]

Important data were provided by a large-scale, prospective, multicenter, observational study of MSSA bloodstream infections that followed patients for 6 months after completion of therapy to assess rates of recurrence.[55] In this study, nafcillin was superior to vancomycin with respect to preventing bacteriologic failure and relapse; moreover, vancomycin use was highly predictive of relapse in the multivariate analysis (OR 6.5, 95% CI 1.0–52.8, p=0.048). Similarly, patients dependent on hemodialysis who had MSSA bacteremia treated with vancomycin had a higher risk of experiencing treatment failure than those who received cefazolin (31.2% vs 13%, p=0.02), and a multivariate analysis of these findings showed vancomycin to be independently associated with treatment failure (OR 3.53, 95%

CI 1.15–13.45).[85] A case-control study of patients with bacteremic pneumonia found the mortality rate to be significantly higher for patients with MSSA infections treated with vancomycin than for those treated with cloxacillin (47% vs 0, p<0.01).[15] In this study, the relationship between vancomycin therapy and mortality (OR 14, p<0.01) persisted in the multivariate analysis that adjusted for other variables associated with mortality.

The substandard clinical cure rates observed with vancomycin for MRSA pneumonia may be related to suboptimal dosing or the inability of vancomycin to achieve sufficient concentrations in the lungs and epithelial lining fluid.[86, 87] In a study of vancomycin's penetration into the lung tissue, the lung tissue:serum concentration ratio was 0.24 at 1 hour and 0.41 at 12 hours after a 1-g dose of vancomycin infused over 30 minutes.[86] More concerning was the fact that nearly half of patients who had samples measured 12 hours after the dose had undetectable levels of vancomycin in lung tissue. The study also showed the ratio of vancomycin's penetration of blood versus epithelial lining fluid to be 6:1.

Another problem with vancomycin is the need for intravenous administration, which can increase the economic burden by prolonging the duration of hospitalization or necessitating costly arrangements for administration in the outpatient setting.[68] Intravenous administration not only increases the cost of treatment but also places patients at risk for other nosocomial infections. In a recent survey, internal medicine and infectious diseases doctors indicated that they would be more inclined to discharge patients with MRSA infections earlier if a high-bioavailability oral formulation existed.[88]

Clinical and Economic Benefits of Newly Approved Antimicrobials

Despite the recent approval of several new agents—linezolid, daptomycin, tigecycline, and quinupristin-dalfopristin—for treatment of MRSA infections, surprisingly few clinical studies in the peer-reviewed literature document any advantage of vancomycin over these drugs. The reported experience with linezolid for treatment of MRSA infections has been more extensively documented than any of the other agents. Data from two studies suggest that vancomycin is inferior to linezolid for treatment of nosocomial pneumonia secondary to MRSA.[89, 90] In a post hoc analysis of two prospective, double-blind studies of patients with hospital-acquired pneumonia,[91] clinical cure rates were significantly higher in the linezolid group compared with the vancomycin group (59.0% vs 35.5%, p<0.01) in the MRSA subgroup, and this effect persisted in the logistic regression analysis (OR 3.3, 95% CI 1.3–8.3, p=0.01).[90] A similar post hoc analysis limited to patients with ventilator-associated pneumonia also noted significant differences in favor of linezolid over vancomycin in both the *S. aureus* subgroup (48.9% vs 35.2%, p=0.06) and the MRSA subgroup (62.2% vs 21.2%, p=0.001).[89] It should be noted, however, that subgroup analyses are associated with several difficulties (e.g., nonrandomization of subgroups, unknown biases, and chance findings due to multiple comparisons). Clinicians should exercise care in drawing conclusions based on subgroup analyses alone. Prospective clinical studies are ongoing to determine definitively if linezolid is superior to vancomycin for treatment of MRSA pneumonia.[92]

Linezolid also has higher clinical and microbiologic success rates for MRSA surgical site infections and complicated skin and soft tissue infections than vancomycin.[93, 94] In an open-label, comparator-controlled, multicenter study that included patients with suspected or proven MRSA-complicated skin and soft tissue infections, linezolid clinical cure rates were similar to vancomycin at the test of cure visit planned 7 days after the end of treatment in the intent-to-treat population (all randomized patients that received one or more doses of study drug), and superior to vancomycin (88.6% and 66.9%, respectively, p<0.001) at the test of cure visit for patients with documented MRSA (p<0.001).[93] In another open-label, comparator-controlled study that involved patients with known or suspected MRSA surgical site infections, linezolid produced significantly more microbiologically cured patients than vancomycin (87% vs 48%, 95% CI 16.51–60.27, p=0.0022).[94]

Another demonstrated advantage is that linezolid can be obtained as a 100% bioavailable oral treatment for MRSA infection. Before the emergence of linezolid, no proven oral treatment option existed for patients with MRSA, who are typically treated with intravenous vancomycin and remain hospitalized for the duration of their treatment. Linezolid's highly bioavailable oral formulation enables clinicians to switch their patients to oral dosing, thereby allowing for an earlier discharge. Examination of the economic

outcomes of patients with known or suspected MRSA infections treated with linezolid or vancomycin in phase III and IV trials has validated this approach.[93–97] These studies have consistently demonstrated the economic benefits of linezolid compared with vancomycin due to decreased LOS, duration of intravenous therapy, and cost of care. In the above-mentioned study that compared vancomycin with linezolid in the treatment of complicated skin and soft tissue MRSA infections, treatment with linezolid versus vancomycin shortened the duration of intravenous therapy from 12.6 to 1.8 days and reduced hospital LOS from 10.7 to 8.1 days.[98] Furthermore, the investigators observed a cost difference of $1125/patient in favor of linezolid ($4881 for linezolid vs $6006 for vancomycin) when costs of antibiotic, concomitant drugs, procedures, and hospitalization were analyzed for a U.S. subset of patients with MRSA-complicated skin and soft tissue infections.[99]

Another antibiotic with promising activity against MRSA is daptomycin. Daptomycin is a recently approved, first-in-class lipopeptide antibiotic that is rapidly bactericidal against MRSA. It is approved for treatment of complicated skin and skin structure infections and *S. aureus* bloodstream infections, including right-sided endocarditis, caused by MSSA and MRSA.[100] In clinical trials involving patients with complicated skin and skin structure infections, daptomycin demonstrated noninferiority to the semisynthetic penicillins and vancomycin. Of interest, a statistically significant 63% of patients treated with daptomycin required only 4–7 days of therapy, whereas 67% of those receiving a semisynthetic penicillin or vancomycin required therapy for at least 8 days.[101]

Other favorable data emerged from a more recent, prospective, open-label study that matched each study patient who received daptomycin to four historical control patients treated with vancomycin.[99] This study revealed that patients who received daptomycin had a significantly faster clinical response, shorter duration of intravenous antibiotics, and shorter LOS than patients given vancomycin. Although all patients in both study arms achieved clinical success (resolution or improvement) at the end of therapy, those given daptomycin were more likely to achieve complete resolution of symptoms and required an average of 4 days less of antimicrobial therapy and hospitalization than those who received vancomycin. In a recent *S. aureus* bacteremia and infective endocarditis study, daptomycin demonstrated noninferiority to semisynthetic penicillin plus gentamicin and to vancomycin plus gentamicin.[100] In the MRSA subset (intent-to-treat population), there was an 11.8% higher success rate in daptomycin group compared with the group given vancomycin plus gentamicin, but the difference was not statistically significant. Daptomycin therapy, however, was associated with a higher rate of microbiologic failure than standard therapy (15.8% vs 9.6%, p=0.17). Although the findings for daptomycin are promising, further study is needed to evaluate the impact of daptomycin on patient outcomes and costs associated with MRSA infections. We are unaware of any improved outcomes data with tigecycline and quinupristin-dalfopristin for MRSA.

Although the initial MRSA outcomes data with linezolid and daptomycin are highly favorable, clinicians should temper their enthusiasm about these new agents. Drug acquisition costs for linezolid and daptomycin are higher than those for vancomycin. In addition, other possible adverse outcomes of antibiotic use, such as toxicity and resistance, should be considered. Toxicity concerns with these new agents include thrombocytopenia associated with linezolid and skeletal myopathy with daptomycin. Staphylococci have already been reported with resistance to both linezolid and daptomycin.[102–113] In the *S. aureus* bacteremia and infective endocarditis study, a daptomycin MIC shift to 2 mg/L or greater was found in 5.8% of patients who received daptomycin and in 13.2% of the patients given vancomycin.[100] Although most of these shifts occurred in patients who did not or could not receive adjunctive surgery, clinicians should be cognizant that resistance has been observed and should closely follow patients who receive these agents. Furthermore, institutions should routinely perform antibiotic susceptibility testing for these agents and closely monitor for emergence of resistance.

Conclusion

High morbidity, mortality, and health care resource utilization have elevated MRSA to a significant public health concern. Studies of the clinical and economic impact of MRSA compared with MSSA have consistently identified divergent patient outcomes for the two pathogens. Numerous investigations have attempted to control for factors that may contribute to such systematic differences, yet none have controlled

for all variables, including delayed treatment, antibiotic selection, and severity of illness. Although the data are not definitive, it appears that treatment-related factors may be primarily responsible for the negative outcomes observed with MRSA.

Despite its sustained in vitro microbiologic inhibitory activity, the role of vancomycin in the treatment of MRSA infections has recently been questioned, and a growing amount of clinical evidence confirms the suboptimal response of MRSA to vancomycin, particularly for nosocomial pneumonia and skin and soft tissue infections. Antibiotics with good bioavailability, such as linezolid, can facilitate early discharge and alleviate the economic burden of hospitalization for MRSA infections. In the era of newer agents such as linezolid, daptomycin, and tigecycline, we will begin to learn more about treatment-related factors, specifically antibiotic selection, that affect patient outcomes. Further studies are needed to determine if these new agents will replace vancomycin as the drug of choice for MRSA infections and remedy the adverse clinical and economic outcomes frequently associated with MRSA.

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