Pharmacy’s Role in MRSA Prevention and Treatment

It is estimated that there are over 125,000 methicillin-resistant *Staphylococcus aureus* (MRSA) infections that require hospitalization annually in the United States. In fact, *S. aureus* is the number one bacterial organism responsible for causing nosocomial infections according to The Surveillance Network-USA (TSN). Unfortunately, incidences of drug-resistant *S. aureus* infections continue to increase in the intensive care unit (ICU) as well as inpatient non-ICU and outpatient settings, resulting in increased mortality and morbidity rates, length of hospitalization, and health care costs.

**Challenges with Vancomycin Use**

Traditionally, vancomycin has been used to manage MRSA infections. However, concerns have been raised over the efficacy of vancomycin in managing deep-seated infections such as osteomyelitis and invasive MRSA infections caused by isolates with minimum inhibitory concentration (MIC) values of 2 g/mL. It is concerning since these MICs are considered to be in the susceptible range according to the breakpoints established by the Clinical and Laboratory Standards Institute. The Clinical and Laboratory Standards Institute lowered the vancomycin susceptibility breakpoint from 4 μg/mL to 2 μg/mL for *S. aureus* in 2006 and the American Thoracic Society advocated higher vancomycin trough levels of 15 to 20 μg/mL for MRSA pneumonia. It is concerning since these MICs are considered to be in the susceptible range according to the breakpoints established by the Clinical and Laboratory Standards Institute. The Clinical and Laboratory Standards Institute lowered the vancomycin susceptibility breakpoint from 4 μg/mL to 2 μg/mL for *S. aureus* in 2006 and the American Thoracic Society advocated higher vancomycin trough levels of 15 to 20 μg/mL for MRSA pneumonia.

Further complicating the matter is the method of identifying MRSA strains at the breakpoint of susceptibility. There is significant variability among some of the commercially available automated testing systems in demonstrating a correlation between in vitro MRSA vancomycin susceptibility and treatment outcome. However, MRSA strains with MICs at the breakpoint of susceptibility as detected by bioMérieux’s Etest methodology were found to be significantly associated with bloodstream infections and overall treatment failure with vancomycin.

Recently, a position statement on therapeutic monitoring of vancomycin jointly published by the American Society of Health-System Pharmacists (ASHP), Infectious Diseases Society of America (IDSA), and Society of Infectious Diseases Pharmacists (SIDP) endorsed attaining a higher target vancomycin trough over-all of 10-15 μg/mL for most infections and 15-20 μg/mL in severe infections, such as meningitis, osteomyelitis, endocarditis, and hospital-acquired pneumonia, as well as infections caused by MRSA isolates with a MIC >1 μg/mL. Furthermore, it was stated that AUC/MIC is the most effective pharmacodynamic parameter for evaluating the effectiveness of vancomycin in treating MRSA infections, with a target ratio of > 400. Despite these aggressive recommendations, it should be noted that for an MRSA isolate with a MIC of 2 μg/mL, the target AUC/MIC ratio cannot be achieved. Since many hospitals, including our respective institutions: St. Mary Medical Center (SMMC) in Long Beach, California and St. Joseph Hospital (SJH) in Orange, California, have pharmacy protocols that allow pharmacists to dose vancomycin, order labs for monitoring drug concentrations and safety, and make the appropriate dose adjustments, they need to stay informed about the use of vancomycin in treating MRSA infections. In order to manage the MRSA epidemic, hospitals must take a multifaceted approach that includes strategies aimed at the prevention and detection of MRSA, accurate diagnosis and susceptibility testing, appropriate selection and prudent use of antimicrobial agents, and prevention of transmission. By working collaboratively with infection control practitioners, microbiology laboratory personnel, and prescribing clinicians, pharmacists play an integral role in executing these strategies.

**Active Surveillance**

Surveillance is a critical component of MRSA prevention and allows for detection of asymptomatic colonized patients, monitoring of epidemiologic trends, and detection of strains potentially associated with poor treatment outcomes. Using active surveillance of cultures to detect MRSA colonization is a strategy that has found some positive outcomes in various countries including The Netherlands, Finland, Belgium, and Denmark. Consequently, MRSA accounts for a very small percentage of the *S. aureus* isolates in these countries.

Research has shown that active surveillance in combination with isolation of colonized patients and a strictly enforced contact-precautions policy can lead to the decline of a target pathogen. Currently, SMMC performs active surveillance testing for MRSA in patients admitted to the ICU, hemodialysis patients, those from long-term care or skilled nursing facilities, patients who were recently discharged from a hospital within 30 days, and high-risk surgical patients. SJH performs active surveillance for all patients at the time of admission, on transfer from unit to unit, and upon discharge from the hospital. It is important for pharmacists to be aware of these MRSA screening results, especially when we are rec-
ommending antimicrobial therapies for patients in whom S. aureus is a potential pathogen.

Another commonly used form of surveillance is the implementation of antibiograms. When appropriately prepared, an antibiogram can report the:
1) Prevalence of methicillin-resistance among all S. aureus isolates
2) Prevalence of MRSA in infecting cases
3) Unit-specific prevalence of MRSA

Examining unit-specific distribution can provide more insight into the true prevalence of MRSA, especially in high-risk units such as the intensive care unit or the oncology ward. The CDC recommends preparing an antibiogram using the first isolate from an individual over a period of one year. Many of the commercial automated systems available and in use are not able to distinguish first isolates from repeat cultures after a certain period of time. At our respective institutions, we are involved in the development and interpretation of a meaningful antibiogram, and in the distribution of the findings.

Infection Control

Standard precautions and contact precautions are essential to the prevention of MRSA transmission. Adherence to hand hygiene protocol has been associated with control of multi-drug resistant organisms including MRSA, and contact precautions should be implemented for patients who are colonized or infected with MRSA in order to help reduce the spread of this organism. Hand sanitizers should be available in every patient room, on the medical wards, the lobby, and the cafeteria. In addition, displaying signs that promote hand washing throughout the hospital helps educate visitors. At SMMC and SJH, compliance by health care providers with CDC hand hygiene recommendations is routinely monitored and emphasized by the infection control departments. Furthermore, at both institutions, pharmacy has collaborated with the infection control department to provide continuing education lectures on MRSA infection and prevention to health care providers and the lay public.

Collaboration with the Microbiology Department

The relationship between pharmacy and the microbiology department is critical to optimizing antimicrobial therapeutic outcomes. Routine communication with microbiology is key to early detection of resistant organisms and provides an opportunity for research collaborations as well. Collaborations at SMMC and SJH between pharmacists and laboratory personnel have resulted in strategies to discriminate antimicrobial susceptibility reporting and optimize susceptibility testing by converting to more sensitive panels that improve data interpretation. The suppression of select antimicrobial susceptibilities in culture and sensitivity (C&S) reporting is a strategy used to prevent or minimize the inappropriate use of broad-spectrum antibiotics. At our facilities, the C&S report reflects a...
suppressed list of antimicrobial agents, however, the complete report with sensitivities for all agents tested is available to the pharmacy department since the pharmacists serve as the gatekeepers of appropriate drug use and reinforce hospital-approved restrictions of broad-spectrum antibiotics. Additionally, pharmacists are often in discussion with physicians regarding therapeutic antimicrobial options for patients.

Given the increasing reports of vancomycin failure against invasive MRSA infections caused by strains at the borderline of susceptibility, accurate testing and reporting of sensistivities have become even more critical, as the use of alternative agents to treat MRSA infections may need to be considered. Both SMMC and SJH use an automated system in the microbiology laboratory to differentiate MRSA vancomycin susceptibilities below 2 μg/mL. In working with our respective microbiology departments, we have recently converted to a panel that will provide MIC results for vancomycin as low as 0.25 μg/mL. This is a significant change allowing pharmacists to target more aggressive vancomycin troughs based on the infection site, severity of infection, as well as the MIC of the MRSA isolate. More importantly, invasive infections caused by MRSA isolates with MICs >1.5 μg/mL have been associated with poor treatment outcomes,8, 9, 11, 26 which may mean alternative agents need to be considered. However, it should be noted that the correlation of MIC with vancomycin treatment outcomes has only been substantiated using the Etest methodology. As such, we advocate additional testing using Etet methodol-

ogy for invasive MRSA infections to confirm the MIC.

Consider implementing the more involved approach of saving MRSA isolates for further molecular and phenotypic studies. These studies can enhance the understanding of clonal transmission, effect of interventions, accuracy of various susceptibility testing techniques, and correlation of genotype/phenotype with treatment outcomes.

**Pharmacy’s Role in Treatment**

In response to increasing reports of vancomycin failure in invasive infections caused by MRSA isolates with a MIC of 2 μg/mL,8, 26, 27 many institutions sample...
the MIC distribution of a small collection of MRSA isolates. However, it should be noted that in the study by Hidayat, et al, the majority of the invasive infections (i.e., bloodstream and pneumonia) were caused by MRSA isolates with MICs at the breakpoint of susceptibility. Thus, pharmacists should consider advocating a more patient-directed approach by requesting additional susceptibility testing at the point of care when appropriate, providing input on selection of antimicrobial agents and appropriate dosing, and monitoring treatment outcomes for efficacy and safety.

The screening of C&S reports by pharmacists provides opportunities for routine communication with physicians regarding selection, dosing, and monitoring of antimicrobial regimens for the management of MRSA infections. Pharmacists can then target a range of vancomycin troughs for suspected or documented MRSA infections based on physician diagnoses and laboratory data. Several years ago, the antibiotic subcommittee at SMMC endorsed changing the target vancomycin troughs because of the limited reporting of vancomycin MICs at the time. Thus, the pharmacy-driven protocol at SMMC aims for vancomycin troughs of 10-15 μg/mL for most infections and 15-20 μg/mL for hospital-acquired pneumonia, endocarditis, meningitis, and osteomyelitis, which are consistent with the recent recommendations by ASHP, IDSA, and SIDP. However, with the new automated systems in place and the recent data regarding the predictability of Etest results on vancomycin treatment outcomes in MRSA infections, we are working toward an initiative to incorporate supplementation of an Etest MIC confirmation in patients with invasive MRSA infections such as bacteremia, pneumonia, meningitis, endocarditis, or osteomyelitis. The results of the Etest would assist the pharmacist and physician in selecting antimicrobial therapy at the point of care.

Pharmacists play an important role in the consideration of alternative therapies for invasive MRSA infections because of our knowledge of the pharmacokinetics, pharmacodynamics, and safety profiles of these agents. While there are many agents that can be considered for use against MRSA such as daptomycin, linezolid, quinupristin/dalfopristin, and tigecycline, their use has been limited due to high acquisition costs and/or lack of clinical experience. In addition, they are typically restricted for use against specific indications or by physician specialties. Not only should pharmacists serve as gatekeepers for the use of these broader antibiotics, but we should also work with members of the antibiotic subcommittee to create the restrictions that ensure these broader, newer, and more expensive antibiotics are only used for multi-drug resistant pathogens or patients who have failed traditional therapies.

Quality Assurance and Continuing Education

Conducting medication use evaluations (MUEs) on a routine basis has proven to be beneficial in improving treatment of MRSA infections. This quality assurance process allows pharmacists to evaluate the appropriateness of antimicrobial use and compile safety data. The findings of MUEs can identify areas that need improvement, and result in policy changes that optimize the dosing of antibiotics and monitoring of specific labs. It is important to share MUE results with pharmacists, nurses, and physicians to underscore the important principles of specific drug therapies.

When new antibiotics for the treatment MRSA enter the market, MUEs should be performed as part of the formulary evaluation process. Not only is it important for pharmacists to understand the dosing, pharmacokinetics, pharmacodynamics, and potential side effects and drug-drug interactions of these new agents, but it is also very important to know the availability of these new antibiotics on susceptibility panels or the types of susceptibility testing that will be available. Pharmacists should work with the microbiology department to determine what susceptibility testing will be available so that therapies can be assessed and correlated with in...
vitro data. As changes to the anti-infective formu-
lar occur, pharmacists should also conduct con-
tinuing education at nursing in-services, medical
noon conferences, and grand rounds to promote
the safe and judicious use of newer antimicrobial
therapies.

Conclusion
The prevention and management of MRSA
infections pose significant challenges for health
care providers given the prevalence of MRSA,
the wide spectrum of associated infections, dis-
parity in susceptibility testing, and limited
agents available for the treatment of such infec-
tions. In an era where MRSA infections are an
increasing reality, pharmacists must work


together with physicians, nurses, microbiolo-
gists, and epidemiologists to successfully miti-
gate the occurrence of MRSA infections in the
hospital.

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