



A CLINICIAN'S ROADMAP TO MRSA MANAGEMENT

Stewardship for Optimal Care

E-NEWSLETTER # 1

Optimized Use of Vancomycin

FROM THE EDITOR'S DESK

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a serious concern for clinicians managing infectious diseases in the healthcare setting. Trends in *S. aureus* epidemiology have demonstrated rising rates of methicillin resistance along with gradually decreasing susceptibility to vancomycin (known as “MIC creep”). This can have a significant impact on clinical outcomes and places added pressure on clinicians to optimally utilize antimicrobial agents to maximize effectiveness while minimizing the potential for adverse events.

This is the first of four electronic newsletters that will tackle specific issues related to the management of MRSA infections. In this issue, the role of vancomycin in managing MRSA infections is discussed. The recently released evidence-based guidelines from the Infectious Diseases Society of America (IDSA) offer important recommendations for dosing and monitoring vancomycin to ensure effective and safe levels are achieved. Though vancomycin has been associated with certain adverse events and toxicity, clinicians can take precautions to minimize their potential risk in patients with serious MRSA infections. I hope you find this and subsequent issues to be relevant and useful in your clinical practice.

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E-NEWSLETTER #1 OPTIMIZED USE OF VANCOMYCIN

TARGET AUDIENCE

This activity is designed for physicians, pharmacists, and other healthcare professionals on the frontline of managing patients with serious MRSA infections.

LEARNING OBJECTIVES

Healthcare professionals participating in this educational activity will be able at its conclusion to:

- Determine the optimal use of vancomycin for MRSA infections
- Identify strategies to minimize the risk of vancomycin-associated adverse events

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The Evolving Role of Vancomycin

Methicillin-resistant *Staphylococcus aureus* (MRSA) is among the leading causes of drug-resistant hospital-acquired infections in the United States and now accounts for approximately 60% of all *S. aureus* isolated from hospitalized patients.¹ In many cases of serious MRSA infections, vancomycin is considered first-line therapy.²

WHAT IS VANCOMYCIN “MIC CREEP”?

Vancomycin has long been considered the mainstay for serious MRSA infections. While the occurrence of vancomycin-resistant *S. aureus* is rare,³ some institutions are reporting vancomycin “MIC creep” or an increasing vancomycin minimum inhibitory concentration (MIC) distribution for hospital *S. aureus* isolates.⁴⁻⁶

In one report, the UCLA Medical Center re-evaluated over 6000 *S. aureus* isolates collected from 2000 to 2004 for MIC values using uniform microbiological protocols.⁷ This study showed an **increase in**

- the percentage of *S. aureus* isolates with vancomycin MIC of 1 µg/mL (19.9% in 2000 to 70.4% in 2004, $P < .01$)
- the number of isolates with vancomycin MIC of 2 µg/mL, regardless of whether the isolate was methicillin-resistant or methicillin-susceptible (2 isolates in 2000 to 12 isolates in 2004).

WHAT ARE THE POTENTIAL CAUSES FOR VANCOMYCIN “MIC CREEP”?

Though the exact cause of vancomycin “MIC creep” is not known, decreased *S. aureus* susceptibility to vancomycin is likely due to (1) overuse and (2) sub-optimal dosing of vancomycin.³

Overuse of vancomycin: Increasing concern about MRSA in the community setting and hospital-acquired infections has been associated with an increase in the overall use of vancomycin.⁸ One study involving 22 medical centers across the United States reported a 43% increase in vancomycin use from 2002 to 2006.⁸

Sub-optimal use of vancomycin: Sub-optimal dosing of vancomycin is prevalent.³ Under-dosing does not eradicate the infection but allows less susceptible *S. aureus* strains, such as heteroresistant vancomycin-intermediate *S. aureus* (hVISA), to survive.⁹



Impact of Vancomycin “MIC Creep” on Outcomes

Vancomycin “MIC creep” has a significant impact on clinical outcomes. For MRSA isolates with vancomycin MIC >1 µg/mL, vancomycin effectiveness diminishes¹⁰⁻¹⁴ as demonstrated by a decrease in MRSA eradication rates¹³ and an increase in mortality risk¹⁴ (Figure 1 and Table 1).

Figure 1. Vancomycin MIC and MRSA eradication rates among patients with bacteremia¹³

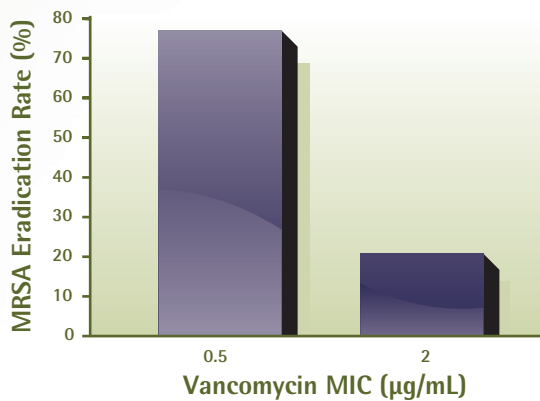


Table 1. Vancomycin MIC and mortality risk among patients with MRSA infections¹⁴

Vancomycin MIC	Mortality Risk: Odds Ratio	} tripled risk of mortality	} six-fold risk of mortality
1.0 µg/mL	1.0		
1.5 µg/mL	2.86		
2 µg/mL	6.39		

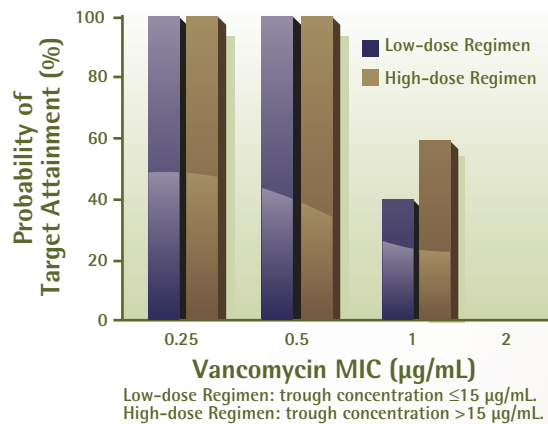
Table 2. Vancomycin MIC (µg/mL) interpretive criteria for *S. aureus*¹⁹

	Susceptible	Intermediate	Resistant
Old Criteria	≤4	8–16	≥32
New Criteria	≤2	4–8	≥16

These poorer outcomes associated with higher vancomycin MICs can be explained by the pharmacokinetic/pharmacodynamic characteristics of vancomycin. Studies using animal models as well as clinical trials demonstrate that clinical outcomes are dependent on the ratio of the area under the concentration-time curve to MIC (AUC/MIC).^{15,16} An AUC/MIC ≥400 is predictive of optimal clinical response for MRSA infections.¹⁷

Recent evidence-based guidelines recommend achieving a vancomycin serum trough concentration of 15–20 µg/mL when treating serious MRSA infections.² By attaining these trough levels, an AUC/MIC ≥400 will likely be reached for isolates with vancomycin MIC <1 µg/mL.¹⁸ However, the probability of attaining an AUC/MIC ≥400 decreases dramatically for MRSA isolates with vancomycin MIC ≥1 µg/mL, even with higher vancomycin dosing regimens (Figure 2).¹⁸

Figure 2. Probability of PK/PD target attainment (AUC/MIC ≥400) with high- versus low-dose vancomycin regimen¹⁸



Given this association between higher vancomycin MICs and poorer outcomes, the Clinical and Laboratory Standards Institute (CLSI) and the Food and Drug Administration changed the vancomycin susceptibility breakpoints for *S. aureus* (Table 2).¹⁹

Optimal Dosing of Vancomycin

Two recent evidence-based guidelines specify dosing recommendations for vancomycin. These include “*Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists*” released in 2009 and “*Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of MRSA infections in adults and children*” released in 2011 (Table 3).^{2,20}

WEIGHT-BASED DOSING

Vancomycin dosing should be based on actual body weight. This is particularly important when treating overweight patients as they are likely to be underdosed with traditional vancomycin dosing regimens (such as 1 g q12h).²¹

LOADING DOSE

A loading dose may be considered for serious infections to hasten achievement of target trough serum concentrations. Though clinical data on the effectiveness of loading doses is lacking, a small clinical study determined that a 25 mg/kg vancomycin loading dose is generally safe.²²

DOSING IN CHILDREN

Data on vancomycin dosing in children are limited. IV vancomycin 15 mg/kg/dose every 6 h is recommended in children with serious or invasive disease.² Pharmacokinetic data suggest that such doses (60 mg/kg/day) are needed to achieve an AUC/MIC ≥ 400 for most MRSA isolates (ie, when vancomycin MIC is ≤ 1 $\mu\text{g/mL}$).²³

Table 3. Vancomycin dosing: recommendations by the IDSA²

Adults	
Patients with normal renal function	IV vancomycin 15–20 mg/kg/dose (actual body weight) every 8–12 h, not to exceed 2 g per dose
Seriously ill patients with suspected MRSA infection (eg, those with sepsis, meningitis, pneumonia, or infective endocarditis)	Consider using a loading dose of 25–30 mg/kg (actual body weight)
Trough serum concentrations	Most accurate and practical method to guide vancomycin dosing
Serious infections due to MRSA (bacteremia, infective endocarditis, osteomyelitis, meningitis, pneumonia, and severe SSTI [eg, necrotizing fasciitis])	Vancomycin trough concentrations of 15–20 $\mu\text{g/mL}$ should be attained
Most patients with SSTI who have normal renal function and are not obese	Traditional doses of 1 g every 12 h adequate Trough monitoring not required
Continuous infusion vancomycin regimens	Not recommended
Pediatrics (data limited)	
Children with serious or invasive disease	IV vancomycin 15 mg/kg/dose every 6 h is recommended
Children with serious infections (bacteremia, infective endocarditis, osteomyelitis, meningitis, pneumonia, and severe SSTI [necrotizing fasciitis])	Efficacy and safety of targeting trough concentrations of 15–20 $\mu\text{g/mL}$ requires additional study but should be considered in children with serious infections

Vancomycin Therapeutic Drug Monitoring

Effective and safe vancomycin therapy depends on appropriate dosing. While dosing vancomycin, it is important to remember that vancomycin pharmacokinetics can be influenced by patient renal function and concomitant medications.²⁴

Vancomycin is predominantly eliminated from the body through the kidneys. As renal function decreases, vancomycin exposure increases warranting dose adjustment.²⁴ Concomitant medications with potential for nephrotoxicity (eg, amphotericin B, aminoglycosides) or alteration in renal function (diuretics) can also impact vancomycin elimination.²⁴

Therapeutic drug monitoring is, therefore, critical in ensuring that effective and safe vancomycin concentrations are attained. The IDSA guidelines recommend that trough vancomycin monitoring is an accurate and practical way to guide therapy since the trough concentration is predictive of AUC/MIC (**Table 4**).²

Table 4. IDSA recommendations regarding vancomycin trough serum concentration monitoring²

Vancomycin Trough Serum Concentration Monitoring	IDSA Recommendations
When?	At steady-state condition, prior to the fourth or fifth dose of vancomycin
Not necessary for?	Patients with skin and soft tissue infections who have normal renal function and are not obese
Recommended for?	Patients with serious infections and who are morbidly obese, have renal dysfunction (including those receiving dialysis), or have fluctuating volumes of distribution

Vancomycin-Associated Adverse Events

Adverse events associated with vancomycin include neutropenia, fever, phlebitis, nephrotoxicity, ototoxicity, thrombocytopenia, and infusion-related reactions (including Red Man Syndrome—flushing of the face, neck, and chest linked to rapid infusion).²⁵⁻²⁷ While fever, chills, and phlebitis were more frequently observed with the earlier formulations of vancomycin that had larger amounts of impurities, today's main concerns are greater risk of toxicity, particularly nephrotoxicity, associated with higher dosing of vancomycin.²⁸⁻³¹

NEPHROTOXICITY

Incidence of nephrotoxicity is generally low with vancomycin dosing of up to 2 g/day. However, the risk for nephrotoxicity increases once vancomycin dosing reaches 4 g/day (correlating to higher trough serum concentrations) or when vancomycin is used concomitantly with other nephrotoxic agents, such as aminoglycosides.

A retrospective cohort study compared clinical outcomes and nephrotoxicity in patients with low (<15 µg/mL) versus high (>15 µg/mL) vancomycin trough concentrations.²⁸ High vancomycin trough concentrations were associated with higher mortality and nephrotoxicity (**Figure 3**).²⁸

Lodise and colleagues evaluated the association between initial vancomycin trough concentrations and nephrotoxicity among 166 patients (**Figure 4**).²⁹ Multivariate analysis demonstrated that vancomycin trough concentration was the best pharmacodynamic indicator for risk of nephrotoxicity.

OTOTOXICITY

Higher vancomycin dosing is associated with an increased risk of ototoxicity as well.³² In a study of 89 patients, high vancomycin doses increased the risk of high-frequency hearing loss. The rate of ototoxicity was greater for older patients (>53 years), with longer exposure to the drug (about 28 days), and with higher trough concentrations (mean, 19 µg/mL). Further studies are needed to better understand the clinical implication of these findings and the reversibility of these effects.

Figure 3. Impact of vancomycin trough serum concentrations on mortality and nephrotoxicity²⁸

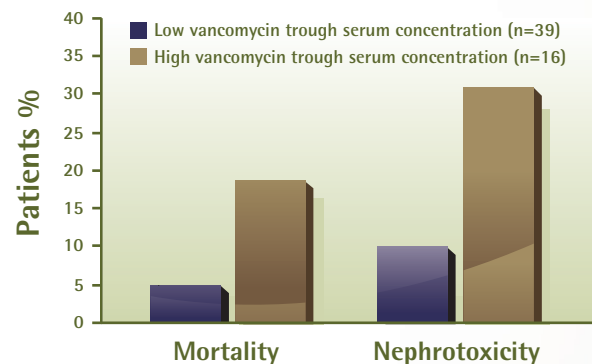
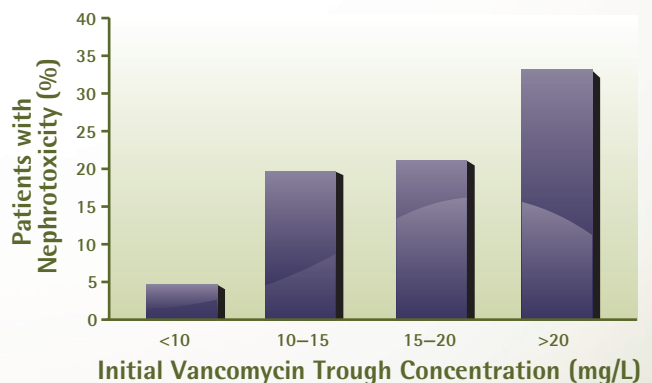


Figure 4. Relationship Between Initial Vancomycin Trough Serum Concentration and Nephrotoxicity²⁹



Minimizing The Risk Of Vancomycin-Associated Adverse Events

AS CLINICIANS, WE CAN TAKE SOME STEPS TO MINIMIZE THE RISK OF ADVERSE EVENTS WHEN USING VANCOMYCIN.

Increase the duration of infusion

to decrease the risk of infusion-related reactions and Red Man Syndrome.

Evaluate all other concomitant agents for their potential for nephrotoxicity, particularly aminoglycosides.

Monitor changes in renal function

to detect early signs of toxicity and act accordingly.

- Consider altering the dose to target a lower trough concentration (10–15 $\mu\text{g}/\text{mL}$ instead of 15–20 $\mu\text{g}/\text{mL}$).
- Consider terminating treatment with concomitant nephrotoxic agents.
- Switch from vancomycin to another effective anti-MRSA agent as per guideline recommendations.

Monitor vancomycin trough concentrations

to ensure that effective, yet safe, levels are attained with the current dosing regimen.



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POST TEST Please select the most appropriate response.

1. Possible causes of "MIC creep" include:

- Overuse of vancomycin Sub-optimal dosing of vancomycin
 More restricted use of vancomycin Overuse of and sub-optimal dosing of vancomycin

2. According to the new CLSI vancomycin interpretive breakpoints, MIC of susceptible *S. aureus* isolates is: ≤0.5 µg/mL ≤1 µg/mL ≤2 µg/mL ≤4 µg/mL

3. What PK/PD parameter is predictive of optimal clinical response with vancomycin for MRSA infections? AUC ≥400 AUC/MIC ≥400 C_{max} ≥50 µg/mL C_{max}/MIC ≥25

4. According to the IDSA guidelines, what is the appropriate vancomycin trough concentration for serious MRSA infections? 5 µg/mL 15 µg/mL 25 µg/mL 50 µg/mL

5. When is vancomycin trough serum concentration monitoring recommended?

- Those with serious infections and morbidly obese Those with serious infections and renal dysfunction
 Those with serious infections and fluctuating volumes of distribution All of these

COMMITMENT TO CHANGE

As an accredited provider of continuing education, Center for Independent Healthcare Education is increasingly focusing on the outcomes of our offerings, particularly as reflected in changes and improvements in clinical practices. Accordingly, we are now asking our learners to reflect on how they might alter their practices as a result of participating in our CE activities. The following request solicits your commitments to change, based on what you have learned. We hope that you will find this exercise useful and thank you in advance for participating.

Do you wish to make commitments to change in your practice?

- Yes No

As a result of what I learned participating in this activity, I intend to make the following practice changes:

OVERALL EVALUATION

	Yes	Somewhat	No
1. The following learning objectives were achieved.			
• Determine the optimal use of vancomycin for MRSA infections	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
• Identify strategies to minimize the risk of vancomycin-associated adverse events	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. The content was relevant to my practice and educational needs.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. The activity format enhanced achievement of learning objectives.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. This activity was fair, balanced, and without commercial bias.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

If you answered "No" to any of the above, please explain.

5. Quality of Guest Editor. Excellent Good Fair Poor

6. Do you have (1) any suggestions for improving this activity or (2) any additional comments?

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