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

MICHAEL RYBAK, BEN LOMAESTRO, JOHN C. ROTSCHAFER, ROBERT MOELLERING JR., WILLIAM CRAIG, MARIANNE BILLETER, JOSEPH R. DALOVISIO, AND DONALD P. LEVINE

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Vancomycin is a glycopeptide antibiotic that has been in clinical use for nearly 50 years as a penicillin alternative to treat penicillinase-producing strains of *Staphylococcus aureus*. It is one of the most widely used antibiotics in the United States for the treatment of serious gram-positive infections involving methicillin-resistant *S. aureus* (MRSA).[1] Early use of vancomycin was associated with a number of adverse effects, including infusion-related toxicities, nephrotoxicity, and possible ototoxicity. Upon further investigation, it appears that the impurities in early formulations of vancomycin caused many of these adverse events.[1-4] Its overall use was curtailed significantly with the development of semisynthetic penicillins (e.g., methicillin, oxacillin, nafcillin) that were considered less toxic.[1-4] However, the steady rise in the number of MRSA infections since the early 1980s has once again brought vancomycin into the forefront as the primary treatment for infections caused by this organism.

Over the years, vancomycin has been one of the most studied antibiotics. Extensive pharmacokinetic studies in a variety of patient populations and the availability of commercial drug assays have allowed clinicians to target serum vancomycin concentrations precisely in a relatively nar-

MICHAEL RYBAK, PHARM.D., M.P.H. is Professor of Pharmacy and Medicine, and Director, Anti-Infective Research Laboratory, Eugene Applebaum College of Pharmacy and Health Science, Wayne State University (WSU), Detroit, MI. BEN LOMAESTRO, PHARM.D., is Senior Clinical Pharmacy Specialist in Infectious Diseases, Albany Medical Center, Albany, NY. JOHN C. ROTSCHAFER, PHARM.D., is Professor, Department of Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, Minneapolis. ROBERT MOELLERING JR., M.D., is Shields Warren-Mallinckrodt Professor of Medical Research, Harvard Medical School, and Physician, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA. WILLIAM CRAIG, M.D., is Professor Emeritus, University of Wisconsin School of Medicine and Public Health, School of Medicine and Public Health, University of Wisconsin, Madison. MARIANNE BILLETER, PHARM.D., BCPS, is Manager of Clinical Pharmacy Services at Ochsner Medical Center, New Orleans, LA. JOSEPH R. DALOVISIO, M.D., Chairman, Department of Infectious Diseases, Ochsner Health System, New Orleans. DONALD P. LEVINE, M.D., is Professor of Medicine and Chief, Division of General Internal Medicine, WSU.

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Address correspondence to Ms. Cindy Reilly at the American Society of Health-System Pharmacists, 7272 Wisconsin Avenue, Bethesda, MD 20814 (creilly@ashp.org).

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row range. This approach has been advocated to lessen the potential for nephrotoxicity and ototoxicity and to achieve therapeutic concentrations. However, it should be noted that the practice of routine monitoring and adjusting of serum vancomycin drug concentrations has been the subject of intense debate for many years.[5-9] The controversy has resulted from conflicting evidence regarding the use of serum vancomycin concentrations to predict and prevent drug-induced toxicity and as a measure of effectiveness in treating infections. Further, data derived from more recent studies appear to suggest that vancomycin has little potential for nephrotoxicity or ototoxicity when used at conventional dosages (e.g., 1 g every 12 hours [15 mg/kg every 12 hours]), unless it is used concomitantly with known nephrotoxic drugs or at very high dosages.[10-12] This consensus review evaluates the scientific data and controversies associated with serum vancomycin monitoring and provides recommendations based on the available evidence.

This is a consensus statement of the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), and the Society of Infectious Diseases Pharmacists (SIDP). Consensus committee members were assigned key topics regarding vancomycin that contribute to current knowledge about patient monitoring. A draft document addressing these areas that included specific recommendations was reviewed by all committee members. After peer review by members of ASHP, IDSA, and SIDP, the committee met to review the submitted comments and recommendations. After careful discussion and consideration of these suggestions, the document was revised and circulated among the committee and supporting organizations for final comment. This consensus review represents the opinion of the majority of committee members.

A search of PubMed was conducted using the following search terms: vancomycin pharmacokinetics, pharmacodynamics, efficacy, resistance, and toxicity. All relevant and available peer-reviewed studies in the English language published between 1958 and 2008 were considered. Studies were rated by their quality of evidence, and the subsequent recommendations were graded using the classification schemata of the Canadian Medical Association (Table 1).[13] Recommendations of the expert panel are presented in Table 2.

Potential limitations of this review include the facts that few prospective or randomized trials of vancomycin monitoring were available and that most of the published literature regarding vancomycin monitoring described observational studies in patients with *S. aureus* infection. Vancomycin monitoring in pediatric patients is beyond the scope of this review.

Overview of vancomycin pharmacokinetic and pharmacodynamic properties

Sophisticated pharmacokinetic techniques such as Bayesian and noncompartmental modeling have been used to derive pharmacokinetic parameters for vancomycin. The serum vancomycin concentration–time profile is complex and has been characterized as one-, two-, and three-compartment pharmacokinetic models. In patients with normal renal function, the α-distribution phase ranges from 30 minutes to 1 hour, and the β-elimination half-life ranges from 6 to 12 hours. The volume of distribution is 0.4–1 L/kg.[14-18]

While reports of the degree of vancomycin protein binding have varied, a level of 50–55% is most often stated.[19,20] Penetration of vancomycin into tissues is variable and can be affected by inflammation and disease state. For example, with uninflamed meninges, cerebral spinal fluid vancomycin concentrations ranging from 0 to approximately 4 mg/L have been reported, whereas concentrations of 6.4–11.1 mg/L have been reported in the presence of inflammation.[21] Penetration into skin tissue is significantly lower for patients with diabetes (median, 0.1 mg/L; range, 0.01–0.45 mg/L) compared with nondiabetic patients

Table 1.
Definitions of Levels and Grades for Recommendations[13]

Quality Indicator	Type of Evidence
Level of evidence	
I	Evidence from at least one properly randomized, controlled trial
II	Evidence from at least one well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from more than one center); from multiple time series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees
Grade of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation

Table 2.
Summary of Expert Panel Recommendations for Vancomycin Therapeutic Drug Monitoring (TDM)[a]

Variable	Recommendation	Level of Evidence and Grade of Recommendation	Section of Consensus Review
Recommended TDM Parameters			
Optimal monitoring parameter	Trough serum vancomycin concentrations are the most accurate and practical method for monitoring efficacy.	IIB	Therapeutic vancomycin drug monitoring, Peak versus trough concentrations
Timing of monitoring	Troughs should be obtained just prior to the next dose at steady-state conditions (just before the fourth dose).	IIB	Therapeutic vancomycin drug monitoring, Peak versus trough concentrations
Optimal trough concentration (see also Optimal trough concentration—complicated infections)	Minimum serum vancomycin trough concentrations should always be maintained above 10 mg/L to avoid development of resistance. For a pathogen with an MIC of 1 mg/L, the minimum trough concentration would have to be at least 15 mg/L to generate the target AUC:MIC of 400.	IIIB	Therapeutic vancomycin drug monitoring, Optimal trough concentrations
Optimal trough concentration—complicated infections (bacteremia, endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia caused by *Staphylococcus aureus*)	Vancomycin serum trough concentrations of 15–20 mg/L are recommended to improve penetration, increase the probability of obtaining optimal target serum concentrations, and improve clinical outcomes.	IIIB	Therapeutic vancomycin drug monitoring, Optimal trough concentrations
Dosing Regimen			
Dosing to achieve optimal trough concentrations	Doses of 15–20 mg/kg (as actual body weight) given every 8–12 hr are recommended for most patients with normal renal function to achieve the suggested serum concentrations when the MIC is ≤1 mg/L. In patients with normal renal function, the targeted AUC:MIC of >400 is not achievable with conventional dosing methods if the MIC is ≥2 mg/L in a patient with normal renal function.	IIIB	Therapeutic vancomycin drug monitoring, Optimal trough concentrations
Loading doses—complicated infections	In seriously ill patients, a loading dose of 25–30 mg/kg (based on actual body weight) can be used to facilitate rapid attainment of target trough serum vancomycin concentration.	IIIB	Therapeutic vancomycin drug monitoring, Optimal trough concentrations
Continuous vs. intermittent dosing	Continuous infusion regimens are unlikely to substantially improve patient outcome when compared to intermittent dosing.	IIA	Impact of dosing strategies on pharmacokinetic and pharmacodynamic parameters
TDM for Vancomycin-Induced Nephrotoxicity			
Definition	A minimum of two or three consecutive documented increases in serum creatinine concentrations (defined as an increase of 0.5 mg/dL or a ≥50% increase from baseline, whichever is greater) after several days of vancomycin therapy.	IIB	Vancomycin toxicity; Incidence, mechanism, and definition of nephrotoxicity

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Table 2 (*continued*)

Variable	Recommendation	Level of Evidence and Grade of Recommendation	Section of Consensus Review
Criteria for monitoring	Data do not support using peak serum vancomycin concentrations to monitor for nephrotoxicity.	IIB	Vancomycin toxicity, Role of therapeutic drug monitoring in preventing nephrotoxicity
	Trough monitoring is recommended for patients receiving aggressive dosing (i.e., to achieve sustained trough levels of 15–20 mg/L) and all patients at high risk of nephrotoxicity (e.g., patients receiving concurrent nephrotoxins).	IIIB	Vancomycin toxicity, Role of therapeutic drug monitoring in preventing nephrotoxicity
	Monitoring is also recommended for patients with unstable (i.e., deteriorating or significantly improving) renal function and those receiving prolonged courses of therapy (more than three to five days).	IIB	Vancomycin toxicity, Role of therapeutic drug monitoring in preventing nephrotoxicity
Frequency of monitoring	Frequent monitoring (more than one trough before the fourth dose) for short course or lower intensity dosing (to attain target trough concentrations below 15 mg/L) is not recommended.	IIB	Vancomycin toxicity, Role of therapeutic drug monitoring in preventing nephrotoxicity
	All patients on prolonged courses of vancomycin (exceeding three to five days) should have at least one steady-state trough concentration obtained no earlier than at steady state (just before the fourth dose) and then repeated as deemed clinically appropriate.	IIB	Vancomycin toxicity, Role of therapeutic drug monitoring in preventing nephrotoxicity
	There are limited data supporting the safety of sustained trough concentrations of 15–20 mg/L. Clinical judgment should guide the frequency of trough monitoring when the target trough is in this range. Once-weekly monitoring is recommended or hemodynamically stable patients. More frequent or daily trough monitoring is advisable in patients who are hemodynamically unstable.	IIIB	Vancomycin toxicity, Role of therapeutic drug monitoring in preventing nephrotoxicity
TDM for Vancomycin-Induced Ototoxicity			
Criteria for monitoring	Monitoring for ototoxicity is not recommended for patients receiving vancomycin monotherapy.	IIIB	Vancomycin toxicity, Incidence of ototoxicity and role of therapeutic drug monitoring for prevention of vancomycin-induced hearing loss
	Monitoring should be considered for patients receiving additional ototoxic agents, such as aminoglycosides.	IIIB	Vancomycin toxicity, Incidence of ototoxicity and role of therapeutic drug monitoring for prevention of vancomycin-induced hearing loss

[a]MIC = minimum inhibitory concentration, AUC = area under the concentration-versus-time curve.

based on the median ratio of tissue vancomycin to plasma vancomycin concentrations (median, 0.3 mg/L; range, 0.46–0.94 mg/L).[21] Vancomycin concentrations in lung tissue ranging from 5% to 41% of serum vancomycin concentrations have been reported in studies of healthy volunteers and patients.[5,6,22,23] Epithelial lining fluid (ELF) penetration in critically injured patients is highly variable, with an overall blood:ELF penetration ratio of 6:1.[23,24]

Selection of pharmacokinetic and pharmacodynamic monitoring parameters

A variety of pharmacokinetic and pharmacodynamic monitoring parameters have been proposed for vancomycin, including time (*t*) the concentration of vancomycin remains above the minimum inhibitory concentration (MIC), the ratio of the area under the serum drug concentration-versus-time curve and the MIC, and the ratio of the maximum serum drug concentration (C_{max}) and the MIC. These parameters are abbreviated *t*>MIC, AUC/MIC, and C_{max}/MIC, respectively. Reviews of pharmacokinetics and pharmacodynamics have recommended the AUC/MIC as the preferred parameter based in part on data from animal models, in vitro studies, and limited human studies.[6,25-28] Studies by Ackerman et al.,[29] Löwdin et al.,[30] and Larsson et al.[31] demonstrated that vancomycin kills *S. aureus* and *Staphylococcus epidermidis* in a concentration-independent fashion. By simulating free vancomycin peak concentrations of 40, 20, 10, and 5 mg/L in an in vitro chemostat model with a normal vancomycin terminal half-life of six hours, Larsson et al.[31] found no difference in the corresponding bacterial kill curves for *S. aureus*.

Using neutropenic mouse models, investigators have concluded that the AUC/MIC is the pharmacodynamically linked parameter for measuring vancomycin's effectiveness in treating *S. aureus*, including methicillin-susceptible *S. aureus* (MSSA), MRSA, and vancomycin-intermediate *S. aureus* (VISA) strains.[6,25] (Note: The total AUC/MIC and the free vancomycin AUC/MIC [AUC × 50% protein binding/MIC] have been interchangeably reported for vancomycin. Unless designated *f*AUC/MIC, this consensus review refers to total AUC/MIC.)

Craig and Andes[32] recently evaluated the use of free vancomycin AUC_{0-24hr}/MIC (*f*AUC/MIC) as the primary parameter for predicting vancomycin activity against VISA, heteroresistant VISA (hVISA), and MSSA in the murine neutropenic mouse model. They found that the *f*AUC/MIC requirement varied depending on the vancomycin MIC and was a function of bacterial density at the site of infection, with a lower *f*AUC/MIC needed for a lower bacterial inoculum. Of interest, the dose required for a 2 log colony-forming unit/g kill was 2.5 times higher for hVISA strains than for VISA and vancomycin-susceptible *S. aureus* strains. The researchers concluded that vancomycin dosages of 500 mg every 6 hours or 1 g every 12 hours provide *f*AUC/MIC values of 100–250 and suggested that values around 500 may enhance the therapeutic effectiveness of vancomycin in humans.

Moise-Broder et al.[33] explored the use of AUC/MIC in predicting clinical and microbiological success in treating ventilator-associated *S. aureus* pneumonia. These investigators suggested an average AUC/MIC of 345 for a successful clinical outcome and a ratio of 850 for a successful microbiological outcome. For pathogens with an MIC of 1 mg/L, an AUC/MIC of approximately 250 can be achieved in most patients with 1 g every 12 hours based on a patient with an actual body weight (ABW) of 80 kg and normal renal function (i.e., creatinine clearance [CL_{cr}] = 100 mL/min), but obtaining a target AUC/MIC of 850 would require much higher dosages for most patients.

Summary: *Based on these study results, an AUC/MIC ratio of ≥400 has been advocated as a target to achieve clinical effectiveness with vancomycin. Animal studies and limited human data appear to demonstrate that vancomycin is not concentration dependent and that the AUC/MIC is a predictive pharmacokinetic parameter for vancomycin.*

Impact of dosing strategies on pharmacokinetic and pharmacodynamic parameters

The initial clinical dosing strategies for vancomycin were developed in the late 1950s before the emergence of antibiotic pharmacodynamics.[34] Published data on the pharmacodynamics of vancomycin against specific bacterial pathogens or infections are very limited, with much of the available data generated from in vitro or animal models. This is partly due to the drug's generic status, which discourages manufacturers from conducting well-controlled scientific investigations that would provide additional and clarifying pharmacodynamic data. It is recommended that dosages be calculated based on ABW. There are limited data on dosing in obese patients; however, initial dosages should be based on ABW and adjusted based on serum vancomycin concentrations to achieve therapeutic levels.[17]

Vancomycin is ideally suited from a pharmacokinetic and pharmacodynamic perspective for intermittent administration based on the usual susceptibility of staphylococci and streptococci (MIC values of ≤1 mg/L), the most commonly used dosage regimen for vancomycin (1 g every 12 hours), and the concentration-independent nature of the drug. As a result, the likelihood of maintaining free or unbound serum vancomycin concentrations in excess of the bacterial MIC for the entire dosing interval is usually 100% with standard intermittent i.v. infusions for typical staphylococci and streptococci.

Despite the absence of clinical data supporting *t*>MIC as a predictive parameter for clinical effectiveness, continuous-infusion strategies have been suggested as a possible means to optimize the serum vancomycin concentration and improve effectiveness. Using a randomized crossover study design in intensive care unit (ICU) patients, James et al.[35] found no significant difference between intermittent and continuous administrations when measuring killing activity in vitro, although the ability to maintain serum bactericidal titers above 1:8 was better with a continuous infusion. In a similarly designed study in healthy subjects, Lacy et al.[36] found virtually no difference in activity as measured by bactericidal titers between continuous and intermittent infusions. Further, in a randomized study, Wysocki et al.[37,38] evaluated 160 patients with severe staphylococcal infections. No difference in patient outcome was observed between those receiving intermittent or continuous infusion vancomycin. Vancomycin differs from β-lactam antibiotics, which typically have short half-lives and often require shorter dosage intervals or continuous infusion to optimize therapy. Therefore, based on the available evidence, there does not appear to be any difference in patient outcomes between vancomycin administered by continuous infusion or by intermittent administration.

Summary and recommendations: *Vancomycin dosages should be calculated on ABW. For obese patients, initial dosing can be based on ABW and then adjusted based on serum vancomycin concentrations to achieve therapeutic levels. Continuous infusion regimens are unlikely to substantially improve patient outcome when compared with intermittent dosing. (Level of evidence = II, grade of recommendation = A.)*

Therapeutic vancomycin drug monitoring

Peak versus trough concentrations. Over the years, serum vancomycin concentration monitoring practices have varied. Early suggestions, such as those of Geraci,[39] who recommended peak serum vancomycin concentrations of 30–40 mg/L and trough concentrations of 5–10 mg/L, likely did not appreciate the multiexponential decline in the serum vancomycin concentration-versus-time curve.

How Geraci defined peak concentration is unclear. In addition, the pharmacodynamic properties of vancomycin had not been evaluated at the time these recommendations were made. Because the AUC/MIC has been found to correlate with efficacy in experiments conducted with in vitro or animal models, this evidence has led some clinicians to question the relevance of monitoring peak serum vancomycin concentrations.[6] Consequently, some clinicians have decreased the extent of pharmacokinetic monitoring for this antibiotic.[40] However, because it can be difficult in the clinical setting to obtain multiple serum vancomycin concentrations to determine the AUC and subsequently calculate the AUC/MIC, trough serum concentration monitoring, which can be used as a surrogate marker for AUC, is recommended as the most accurate and practical method to monitor vancomycin.

Summary and recommendation: *Trough serum vancomycin concentrations are the most accurate and practical method for monitoring vancomycin effectiveness. Trough concentrations should be obtained just before the next dose at steady-state conditions. (Level of evidence = II, grade of recommendation = B.) (Note: Steady-state achievement is variable and dependent on multiple factors. Trough samples should be obtained just before the fourth dose in patients with normal renal function to ensure that target concentrations are attained.)*

Optimal trough concentrations. While Geraci's[39] recommendation for trough concentration was not based on prospective clinical trial data, the benchmark total drug concentration of 5–10 mg/L is likely to fall short of achieving the desired overall vancomycin exposure in many types of infection and isolates with higher (but susceptible) MICs. Therefore, targeting higher trough serum vancomycin concentrations should increase the likelihood of achieving more effective overall antibiotic exposures (i.e., AUC/MIC) and assist in addressing the trend of higher vancomycin MIC values in these organisms.

In recently published guidelines for hospital-acquired, ventilator-associated, and health-care-associated pneumonia, the American Thoracic Society (ATS) suggested an initial vancomycin dosage of 15 mg/kg every 12 hours in adults with normal renal function.[41] ATS acknowledged that vancomycin was a concentration-independent (time-dependent) killer of gram-positive pathogens but had lower penetration into the ELF and respiratory secretions. ATS further recommended that trough serum vancomycin concentrations be maintained at 15–20 mg/L. However, based on pharmacokinetic dosing principles for patients with a normal body weight and normal renal function, it is unlikely that vancomycin 15 mg/kg every 12 hours will produce trough concentrations of 15–20 mg/L. Furthermore, there are no data indicating that achieving these trough concentrations over time is well tolerated and safe.

In an attempt to evaluate the use of targeted trough concentrations of 15–20 mg/L, Jeffres et al.[42] retrospectively evaluated 102 patients

with health-care-associated MRSA pneumonia. Overall mortality was 31% (32 patients). There were no significant differences in mean ± S.D. calculated trough serum vancomycin concentrations (13.6 ± 5.9 mg/L versus 13.9 ± 6.7 mg/L) or mean ± S.D. calculated AUC (351 ± 143 mg · hr/L versus 354 ± 109 mg · hr/L) between survivors and nonsurvivors. In addition, no relationship was found between trough serum vancomycin concentrations or AUC and hospital mortality. Although no significant differences were found between survivors and nonsurvivors in terms of trough serum vancomycin concentrations and AUCs, several factors should be noted. For instance, a sample size calculation was not predetermined; therefore, the potential for a Type II error is possible. There was also large variability in both vancomycin trough concentrations (range, 4.2–29.8 mg/L) and AUCs (range, 119–897 mg · hr/L), which may account for the lack of significant findings. Time to achieve targeted serum vancomycin concentrations was not measured and may be a critical factor in determining patient outcome. In addition, because a disk-diffusion method was used for susceptibility testing, organism MIC could not be determined. Therefore, only the AUC, not the AUC/MIC, was evaluated as a potential predictor of success or failure. Although the results of this study are of interest, additional prospective studies are needed to confirm these data.

Relationship between trough vancomycin concentrations, resistance, and therapeutic failure. While vancomycin is considered a bactericidal antibiotic, the rate of bacterial kill is slow when compared with that of β-lactams, and vancomycin's activity is affected by the bacterial inoculum. Large bacterial burdens in the stationary growth phase or in an anaerobic environment pose a significant challenge to the speed and extent of vancomycin's bactericidal activity.[43-46]

In recent years, VISA or glycopeptide-intermediate susceptible *S. aureus* (GISA) and vancomycin-resistant *S. aureus* (VRSA) have appeared and raised questions about the overall utility of this antibiotic. (Note: The terms VISA and GISA are often used interchangeably. For the purpose of this consensus review, VISA will be used throughout.) Although infection with these organisms is infrequent, there is fear that the organisms could become more prevalent if the high rate of use and exposure pressure of vancomycin continues.[47] The discovery of inducible hVISA (i.e., strains with MIC values in the susceptible range of 0.5–2 mg/L in patients whose therapy with standard dosages of vancomycin has failed) raises further questions regarding current dosing guidelines and the overall use of this antibiotic. Concerns are related to treatment failures and the inability to easily detect hVISA isolates in clinical settings.[48-50]

In 2006, the Clinical and Laboratory Standards Institute (CLSI) lowered the susceptibility and resistance breakpoints for the MIC of vancomycin from ≤4 to ≤2 mg/L for "susceptible," from 8–16 to 4–8 mg/L for "intermediate," and from ≥32 to ≥16 mg/L for "resistant."[51] The decision to move the breakpoints was primarily based on clinical data indicating that patients were less likely to be successfully treated with vancomycin if the *S. aureus* MIC was ≥4 mg/L.[51] Despite the change in susceptibility and resistance breakpoints, two reports have suggested that patients with *S. aureus* isolates having vancomycin MICs of 1–2 mg/L are less likely to be successfully treated with vancomycin compared with patients with *S. aureus* isolates that demonstrate greater susceptibility.[52,53] However, this information alone does not address whether the use of higher concentrations of vancomycin would improve overall effectiveness. Low serum vancomycin concentrations may also create problems, as there appears to be a direct correlation between low serum vancomycin levels and the emergence of hVISA, VISA, or both, at least with certain genotypes of MRSA.[54] In addition, studies have suggested that trough serum vancomycin concentrations of <10 mg/L may predict therapeutic failure and the potential for the emergence of VISA or VRSA.[54,55]

Studies of MRSA and hVISA bacteremia have revealed significantly higher rates of morbidity in patients infected with hVISA.[50,55,56] These patients were more likely to have high bacterial load infections, low initial trough serum vancomycin concentrations, and treatment failure.[56] Jones[57] recently reported that approximately 74% of hVISA strains and 15% of wild-type *S. aureus* strains were tolerant (minimum bactericidal concentration of ≥32 mg/L) to the effects of vancomycin, which contributes to a low probability of success in patients harboring these organisms.

Sakoulas et al.[52] reported a significant correlation between vancomycin susceptibilities and patient outcome. Treatment of bloodstream infections caused by MRSA strains having a vancomycin MIC of ≤0.5 mg/L had an overall success rate of 55.6%, while treatment of patients infected with MRSA strains having a vancomycin MIC of 1–2 mg/L had a success rate of only 9.5% ($p = 0.03$). (Treatment failure was defined as persistent signs or symptoms of infection [e.g., fever, leukocytosis], new signs or symptoms of infection, or worsening of signs or symptoms of infection in patients receiving at least five days of therapy with targeted trough serum vancomycin concentrations of 10–15 mg/L). However, this was a relatively small study ($n = 30$) of MRSA bacteremic patients who were refractory to vancomycin therapy and were enrolled in compassionate-use drug trials. In a more recent study of patients with MRSA bacteremia ($n = 34$), Moise et al.[58] demonstrated that patients with

MRSA isolates with a vancomycin MIC of 2 mg/L had significantly higher median days to organism eradication, longer treatment with vancomycin, and a significantly lower overall likelihood of organism eradication. Hidayat et al.[53] evaluated the use of high-dosage vancomycin intended to achieve unbound trough serum vancomycin concentrations of at least four times the MIC in patients with MRSA infections. Of the 95 patients evaluated with MRSA pneumonia or bacteremia, or both, 51 (54%) had vancomycin MIC values of 1.5 or 2 mg/L. Although an initial response of 74% was demonstrated in patients achieving the desired target MIC, a high percentage of patients infected with strains having an MIC of 1.5 or 2 mg/L had a poorer response (62% versus 85%) and significantly higher infection-related mortality (24% versus 10%) compared with patients infected with low-MIC strains (0.5, 0.75, or 1 mg/L), despite achieving target trough serum vancomycin concentrations of 15–20 mg/L. The data from these two studies suggest that *S. aureus* isolates with MICs of 1–2 mg/L that are still within the susceptible range may be less responsive to vancomycin therapy. Soriano et al.[59] evaluated the influence of vancomycin MIC on outcome in a total of 414 episodes of MRSA bacteremic patients. MIC evaluations were determined by Etest methodology. Among several factors that predicted poor outcome, *S. aureus* isolates with an MIC of 2 mg/L were significantly associated with increased mortality. Based on the low probability of achieving an appropriate targeted vancomycin concentration exposure (AUC/MIC), the authors suggested that vancomycin should not be considered an optimal treatment approach for infection due to strains with a vancomycin MIC of >1 mg/L when using trough serum vancomycin concentrations of >10 mg/L as a target.

Lodise et al.[60] evaluated the relationship between vancomycin MIC and treatment failure among 92 adult nonneutropenic patients with MRSA bloodstream infections. Vancomycin failure was defined as 30-day mortality, 10 or more days of bacteremia on vancomycin therapy, or recurrence of MRSA bacteremia within 60 days of vancomycin discontinuation. Classification and regression tree analysis found that a vancomycin MIC breakpoint of ≥1.5 mg/L was associated with an increased probability of treatment failure. The 66 patients with a vancomycin MIC of ≥1.5 mg/L had a 2.4-fold higher rate of treatment failure compared with patients with a vancomycin MIC of ≤1 mg/L (36.4% versus 15.4%, respectively; $p = 0.049$). Poisson regression analysis determined that a vancomycin MIC of ≥1.5 mg/L was independently associated with treatment failure ($p = 0.01$). Based on these findings, the investigators suggested that an alternative therapy should be considered.

An analysis of a large surveillance database of 35,458 *S. aureus* strains by Jones[57] found that the MIC required to inhibit the growth of 50% of organisms or the MIC required to inhibit the growth of 90% of organisms (MIC_{90}) for vancomycin is 1 mg/L.[57] The Centers for Disease Control and Prevention 2005 U.S. Surveillance Network data of vancomycin susceptibility reported that 16.2% of 241,605 *S. aureus* isolates had an MIC of 2 mg/L.[51] Regional variability exists, and an MIC_{90} of 2 mg/L has recently been reported by several institutions. For example, Mohr and Murray[61] reported that as many as 30% of 116 MRSA blood culture isolates collected from the Texas Medical Center over a one-year period had a vancomycin MIC of 2 mg/L. There have been recent reports of significant shifts in bacterial susceptibility to vancomycin over a five-year surveillance period.[62-64] Increasing *S. aureus* MIC values, coupled with reports of failure rates associated with a vancomycin MIC of 2 mg/L, have raised the question of whether the breakpoint for vancomycin resistance should be lowered even further.[65]

New information is emerging regarding the importance of the accessory gene regulator (*agr*), a global quorum-sensing regulator in *S. aureus* that is responsible for orchestrating the expression of adherence factors, biofilm production, tolerance to vancomycin, and virulence factors.[66] The *agr* locus has been a subject of intense study because there appears to be a relationship between polymorphism in this gene cluster and patient response to vancomycin therapy. Several studies have determined that all VISA strains reported to date from the United States belong to *agr* group II. The *agr* group II includes the USA 100 MRSA clones that are predominately associated with nosocomial infections, and these strains have been associated with vancomycin treatment failure.[33,67] Sakoulas et al.[67,68] have determined in in vitro studies that the emergence of hVISA or VISA may occur when *S. aureus* isolates with a down-regulated or defective *agr* locus are exposed to suboptimal vancomycin concentrations. In a series of in vitro experiments, MRSA belonging to *agr* group II with a defective *agr* locus exposed to vancomycin concentrations of <10 mg/L produced heteroresistant-like characteristics similar to VISA strains with subsequent MIC increases from 1 to 8 mg/L.[67] This phenomenon was recently demonstrated in a patient with chronic renal failure undergoing hemodialysis who experienced recurrent MRSA bacteremia over a 30-month period.[54] The patient was treated repeatedly with vancomycin at trough serum concentrations that always exceeded 10 mg/L. Despite frequent recurrences of bacteremia with the same isolate, the isolate remained susceptible to vancomycin. The genetic background of this organism was found to be similar to other VISA strains belonging to

agr group II. When the isolate was subjected to vancomycin concentrations of <10 mg/L under laboratory conditions, it quickly demonstrated characteristics similar to VISA strains with a subsequent increased MIC.

Tsuji et al.[69] used an in vitro pharmacodynamic model to evaluate *S. aureus agr* groups I–IV exposed to optimal and suboptimal vancomycin doses over a three-day period. In this study, low vancomycin exposures equivalent to total trough serum vancomycin concentrations of 1.5–10 mg/L and an AUC/MIC of 31–264 produced increases in the MIC to the range considered to be VISA by the current CLSI vancomycin breakpoints. Although resistance was produced in both *agr* functional and defective strains, the likelihood of resistance was fourfold to fivefold higher in *agr*-defective isolates. Subsequently, the investigators determined that as many as 48% of hospital-associated MRSA had a dysfunctional *agr* locus, making this finding potentially clinically relevant and warranting further evaluation.[70]

Summary and recommendation: *Based on evidence suggesting that* S. aureus *exposure to trough serum vancomycin concentrations of <10 mg/L can produce strains with VISA-like characteristics, it is recommended that trough serum vancomycin concentrations always be maintained above 10 mg/L to avoid development of resistance. (Level of evidence = III, grade of recommendation = B.)*

Correlating dosing with optimal AUC/MIC and trough concentrations. As mentioned previously, an isolate's vancomycin MIC is an important parameter for determining the potential success of a given dosage regimen. Therefore, an actual vancomycin MIC value should ideally be obtained from the clinical microbiology laboratory. Currently, some clinical microbiology laboratories may be limited in their ability to report vancomycin MIC values, depending on the methodology (disk diffusion or automated microdilution) used to determine antimicrobial susceptibility. In some instances, supplemental Etest methods may be used to obtain this information.

As previously stated, an AUC/MIC of ≥400 has been promoted as the target predictive of successful therapy (i.e., organism eradication). Based on this information, a simple evaluation of standard dosing practices (e.g., 1 g every 12 hours) for an individual with normal renal function (CL_{cr} of ≥100 mL/min) and average weight (80 kg) would only yield a 24-hour drug AUC of approximately 250 mg · hr/L. Unless the pathogen had a vancomycin MIC of ≤0.5 mg/L, this dosage regimen would not generate the targeted AUC/MIC of ≥400. For a pathogen with an MIC of 1 mg/L, the minimum trough serum vancomycin concentration would have to be at least 15 mg/L to obtain the target AUC/MIC. Using the vancomycin pharmacokinetic data generated by Jeffres et al.[42] in patients receiving vancomycin for the treatment of MRSA pneumonia, Mohr and Murray[61] determined by Monte Carlo simulation that the probability of achieving an AUC/MIC of ≥400 would be 100% if the *S. aureus* MIC for vancomycin was 0.5 mg/L but 0% if the MIC was 2 mg/L. Using a similar one-compartment model of vancomycin and a Monte Carlo simulation integrating *S. aureus* MIC values, del Mar Fernández de Gatta Garcia et al.[71] reported that a daily dosage of 3–4 g of vancomycin would be required to provide 90% probability of attaining a target AUC/MIC of 400 with an MIC of 1 mg/L. For VISA strains, a vancomycin daily dose of ≥5 g would be required to provide a high probability of target AUC/MIC attainment for this pathogen. For susceptible *S. aureus*, total daily doses of ≥40 mg/kg would likely be required for typical patients. Use of these larger dosages of vancomycin should be carefully monitored for the desired clinical outcome and the absence of drug-induced toxicity. The use of a nomogram is an alternative method for dosage adjustments; however, the majority of published nomograms in clinical use have been proven to be inaccurate, and most have not been clinically validated.[72] In addition, no published nomogram to date has been constructed to achieve trough serum vancomycin concentrations of 15–20 mg/L.

Loading doses have also been suggested for critically ill patients to attain target trough serum vancomycin levels earlier. In a small study of critically ill patients with serious *S. aureus* infections, a vancomycin loading dose of 25 mg/kg infused at a rate of 500 mg/hr was found to be safe without producing toxic peak serum drug levels.[73] While this approach is not currently supported by evidence from large randomized clinical trials, vancomycin loading doses can be considered in the treatment of serious MRSA infections.[63,74]

Summary and recommendations: *Based on the potential to improve penetration, increase the probability of optimal target serum vancomycin concentrations, and improve clinical outcomes for complicated infections such as bacteremia, endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia caused by* S. aureus, *total trough serum vancomycin concentrations of 15–20 mg/L are recommended. Trough serum vancomycin concentrations in that range should achieve an AUC/MIC of ≥400 in most patients if the MIC is ≤1 mg/L. (Level of evidence = III, grade of recommendation = B.)*

In order to achieve rapid attainment of this target concentration for seriously ill patients, a loading dose of 25–30 mg/kg (based on ABW) can be considered. (Level of evidence = III, grade of recommendation = B.)

A targeted AUC/MIC of ≥400 is not achievable with conventional dosing methods if the vancomycin MIC is ≥2 mg/L in a patient with normal renal function (i.e., CL_{cr} of 70–100 mL/min). Therefore, alternative therapies should be considered.

Vancomycin dosages of 15–20 mg/kg (based on ABW) given every 8–12 hours are required for most patients with normal renal function to achieve the suggested serum concentrations when the MIC is ≤1 mg/L. It should be noted that currently available nomograms were not developed to achieve these targeted endpoints. Individual pharmacokinetic adjustments and verification of serum target achievement are recommended. When individual doses exceed 1 g (i.e., 1.5 and 2 g), the infusion period should be extended to 1.5–2 hours. (Level of evidence = III, grade of recommendation = B.)

Vancomycin toxicity

Vancomycin was initially dubbed "Mississippi mud" because of the brown color of early formulations, which were about 70% pure. The impurities are thought to have contributed to the incidence of adverse reactions.[7,75,76] In the 1960s, purity increased to 75% and in 1985 to 92–95% for Eli Lilly's vancomycin product.[74] Concurrently, a decrease in the reporting of serious adverse events occurred.

The most common vancomycin adverse effects are unrelated to serum drug concentration and include fever, chills, and phlebitis.[7] Red man syndrome may be associated with histamine release and manifests as tingling and flushing of the face, neck, and upper torso. It is most likely to occur when larger dosages are infused too rapidly (>500 mg over ≤30 minutes).[7,77,78] Vancomycin should be administered intravenously over an infusion period of at least 1 hour to minimize infusion-related adverse effects. For higher dosages (e.g., 2 g), the infusion time should be extended to 1.5–2 hours. Less frequent adverse events, such as neutropenia, also appear unrelated to serum drug concentrations.[79,80]

Vancomycin has long been considered a nephrotoxic and ototoxic agent. Excessive serum drug concentrations have been implicated, and it was assumed that monitoring of serum concentrations would allow interventions that decrease toxicity.

Incidence, mechanism, and definition of nephrotoxicity. A review of the literature published from 1956 through 1986 identified 57 cases of vancomycin-associated nephrotoxicity, with over 50% of those cases identified within the first six years of vancomycin use when the product was relatively impure.[75] The rate of nephrotoxicity attributable to vancomycin monotherapy varied from 0% to 17% and from 7% to 35% with concurrent administration of aminoglycosides.[81-85] A review of the literature available through 1993, conducted by Cantu et al.,[8] identified 167 cases of vancomycin-related nephrotoxicity. However, the lack of clear-cut examples of vancomycin-induced nephrotoxicity (when the drug was used alone) was striking. The researchers determined that the frequency of nephrotoxicity due to vancomycin monotherapy was 5–7%. No evidence supported maintaining serum vancomycin concentrations within a given range to prevent nephrotoxicity. However, another study identified older age, longer treatment courses, and higher trough serum vancomycin concentrations (30–65 mg/L) as risk factors for vancomycin-induced nephrotoxicity.[81] Although the definition of vancomycin-induced nephrotoxicity has varied, a reasonable composite from the literature defines this adverse effect as an increase of >0.5 mg/dL (or a ≥50% increase) in serum creatinine over baseline in consecutively obtained daily serum creatinine values or a drop in calculated CL_{cr} of 50% from baseline on two consecutive days in the absence of an alternative explanation.[10,12,53,86-88]

The exact mechanism and incidence of vancomycin nephrotoxicity have been investigated in animals and humans. The filtration and energy-dependent transport mechanisms found in the proximal tubular epithelium render the kidneys susceptible to toxicant-induced injury.[89] Vancomycin exposure in renal proximal tubule epithelial cells results in increased cell proliferation. The stimulation of oxygen consumption and the increase in ATP concentrations support the role of vancomycin as a stimulant of oxidative phosphorylation.[89] In rats, antioxidants protect kidneys against vancomycin-induced injury, in theory, by inhibiting free oxygen radical production.[90] Human data suggest toxicity from vancomycin (or aminoglycosides) is not confined to the proximal tubule but may also involve the medullary region (loop of Henle and collecting duct) of the nephron.[91] Vancomycin destruction of glomeruli and necrosis of the proximal tubule are thought to be due to oxidative stress.[92]

In humans, nephrotoxicity due to vancomycin monotherapy with typical dosage regimens is uncommon, is usually reversible, and occurs with an incidence only slightly above what is reported with other antimicrobials not considered to be nephrotoxic.[11,83,93-96] Investigators have administered a wide dosing range of vancomycin monotherapy to rats without appreciable renal injury.[97,98] Renal impairment in rats was observed when concurrent aminoglycosides were administered[97-99] or if very high dosages of vancomycin were used (350 mg/kg twice daily for four days).[98] Wood et al.[100] investigated the influence of vancomycin on tobramycin-induced nephrotoxicity in rats and found that toxicity occurred earlier and was more severe with concurrent aminoglycoside and vancomycin therapy. Histological evidence of tubular necrosis occurred

earlier and the percentage of necrotic cells was higher in rats receiving combination therapy compared with animals administered tobramycin alone. Indeed, animals receiving vancomycin alone lacked evidence of nephrotoxicity. Enhanced renal accumulation of tobramycin was not evident in animals receiving both vancomycin and tobramycin. In fact, animals receiving the combination had lower renal tobramycin concentrations than did animals receiving tobramycin alone. Increased enzymuria and crystalluria were seen in rats and may suggest toxicity after vancomycin administration.[101-104] However, these markers are very sensitive and could reflect transient hypotension due to rapid administration rather than toxicity.[8] Enzymuria in humans was minimally affected during five days of vancomycin therapy.[105]

Data regarding concurrent vancomycin and aminoglycoside administration in humans provide conflicting information, with some reports indicating that the combination augments aminoglycoside-induced nephrotoxicity,[11,76,81,83,91,94,106,107] and others indicating no effect.[81,83,85,86,96,108-111] Rybak et al.[10] found that patients given vancomycin and an aminoglycoside were 6.7-fold more likely to develop nephrotoxicity than those receiving vancomycin alone. Vancomycin administration for more than 21 days was an additional risk factor ($p = 0.007$). Bertino et al.[107] found vancomycin to be an independent risk factor for aminoglycoside nephrotoxicity in a review of 1489 patients who prospectively received individualized pharmacokinetic monitoring. However, vancomycin use was not associated with increased risk when assessed in a multivariate model in this study. Most of the available data suggest a 3- to 4-fold increase in nephrotoxicity when aminoglycosides are combined with vancomycin.[81,83,93,94] Synergistic toxicity may also occur when vancomycin is used with other nephrotoxic agents (e.g., amphotericin B, certain chemotherapy agents) or used to treat certain diseases (e.g., sepsis, liver disease, obstructive uropathy, pancreatitis).[40,86,93]

Vancomycin administered either as a single, large, 30-mg/kg once-daily dose or in two divided doses did not influence nephrotoxicity significantly ($p = 0.71$).[112] However, "high-dose" (defined as a total daily dose of 40 mg/kg, either as a continuous infusion or divided every 12 hours, resulting in a mean ± S.D. concentration of 24.4 ± 7.8 mg/L) was found to be less nephrotoxic than "standard-dose" intermittent therapy (defined as 10 mg/kg every 12 hours, resulting in a mean ± S.D. trough serum vancomycin concentration of 10.0 ± 5.3 mg/L) ($p = 0.007$) by other investigators.[113] It should be noted that the average age of patients in this later investigation was 60 years; their average weight was not provided.

Human trials have suggested that trough serum vancomycin concentrations of >10 mg/L are associated with an increased risk of nephrotoxicity.[10,76,83,85,86] No correlation has been observed between peak vancomycin concentrations and nephrotoxicity.[10] Zimmermann et al.[114] found no correlation between nephrotoxicity and initial serum creatinine concentration, length of hospital stay, or duration of vancomycin therapy. However, the researchers did find that serum vancomycin concentrations were significantly higher in those patients who eventually developed nephrotoxicity. In that study, no patient who maintained trough serum vancomycin concentrations of <20 mg/L developed nephrotoxicity. It is noteworthy that 21 (57%) of 37 patients consistently had trough serum vancomycin concentrations of >20 mg/L and yet did not develop nephrotoxicity. Recent guidelines have recommended target trough serum vancomycin concentrations of 15–20 mg/L.[41] However, the safety of higher trough vancomycin concentrations over a prolonged period has not been sufficiently studied.

Lee-Such et al.[115] conducted a retrospective chart review of patients over age 18 years who received vancomycin for at least 14 days and had an available baseline serum creatinine concentration and a CL_{cr} of >30 mL/min (calculated by Cockroft-Gault equation). Patients were categorized by trough serum vancomycin concentrations (≤15 mg/L [$n = 19$] or ≥15.1 mg/L [$n = 40$]). Nephrotoxicity was defined as a rise in serum creatinine of ≥0.5 mg/dL above baseline. The median maximum serum creatinine percentage increase was 0.0% (range, –31.3 to 30.0) in the low-trough-concentration group and 17.2% (range, –36.4 to 133) in the high-concentration group ($p = 0.0045$). There were no significant correlations between percent change in serum creatinine and duration of vancomycin therapy, highest trough concentration, or average daily dose. The frequency of nephrotoxicity was 0% in the low-trough-concentration group and 15% in the high-trough-concentration group. The investigators could not discern if higher vancomycin levels were a cause or an indicator of worsening renal function. In addition, a single trough vancomycin concentration of >15 mg/L placed a patient in the high-concentration group, but such a level could be due to a variety of clinical or operational factors not related to vancomycin-induced toxicity. Finally, the use of pressors and concurrent nephrotoxins was poorly described but could provide additional concurrent risk for renal dysfunction. Further details are lacking, as the data are currently available only in abstract form.

Jeffres et al.[87] conducted a similar but prospective investigation of 94 patients with health-care-associated pneumonia. Nephrotoxicity was defined as a 0.5-mg/dL increase from baseline in serum creatinine or an increase of ≥50% in serum creatinine

from baseline during vancomycin therapy. Patients were stratified based on vancomycin trough concentrations of <15 mg/L (n = 43) or ≥15 mg/L (n = 51). Overall, 40 patients (42.6%) met the criteria for nephrotoxicity. The maximal serum creatinine concentration observed occurred after the maximum serum vancomycin concentration by at least 24 hours in 34 patients (85.0%). Patients who developed nephrotoxicity were more likely to have higher steady-state mean trough serum vancomycin concentrations (20.8 mg/L versus 14.3 mg/L, respectively; p < 0.001), trough serum vancomycin concentrations of >15 mg/L (67.5% versus 40.7%, p = 0.01), and a longer duration (≥14 days) of vancomycin therapy (45.0% versus 20.4%, p = 0.011) than those who did not develop nephrotoxicity.

Hidayat et al.[53] prospectively investigated the efficacy and toxicity of adjusting vancomycin troughs to achieve an unbound concentration of at least four times the MIC. Patients received vancomycin for 72 hours or more. Nephrotoxicity was defined as a 0.5-mg/dL or ≥50% increase from the baseline serum creatinine concentration in two consecutive laboratory analyses. For nephrotoxicity analysis, groups were divided based on trough serum vancomycin concentrations (<15 or ≥15 mg/L). Nephrotoxicity occurred only in the ≥15-mg/L group (11 of 63 patients [12%] versus 0 of 24 patients in the <15-mg/L group [p = 0.01]) and was predicted by the use of concurrent nephrotoxic agents (p < 0.001). By controlling for age, admission to ICUs, Acute Physiology and Chronic Evaluation II score, trough serum vancomycin level, and duration of therapy, multivariate analysis demonstrated concurrent nephrotoxins to be the strongest predictor of vancomycin nephrotoxicity. Without concurrent nephrotoxins, nephrotoxicity occurred in only 1 (2%) of 44 patients with a trough concentration of ≥15 mg/L versus 0 of 24 patients in the <15-mg/L group.

Lodise et al.[12] retrospectively examined the relationship between vancomycin dosage and rate of nephrotoxicity at a single institution. Nephrotoxicity was defined as an increase in serum creatinine of 0.5 mg/dL or an increase of 50%, whichever was greater, on at least two consecutive days during the period from initiation of vancomycin or linezolid therapy to 72 hours after completion of therapy. Linezolid usage was also included as a nonvancomycin comparator group. A significant difference in nephrotoxicity was noted among patients receiving vancomycin ≥4 g/day (34.6%), vancomycin <4 g/day (10.9%), and linezolid (6.7%) (p = 0.001). The relationship between high-dosage vancomycin and nephrotoxicity persisted in the multivariate analyses that controlled for potential confounding covariates. The multivariate analyses also demonstrated that patient total weight of ≥101.4 kg, estimated CL_{cr} of ≤86.6 mL/min, and ICU residence at the start of therapy each independently influenced the time to nephrotoxicity. In a secondary analysis, a significant relationship was found between the vancomycin AUC and nephrotoxicity. Specifically, a vancomycin AUC of ≥952 mg · L/hr was associated with a higher probability of vancomycin-related nephrotoxicity.

Nguyen et al.[88] retrospectively investigated patients receiving vancomycin between January and December 2006 at a single institution. Patients included were age ≥18 years, receiving vancomycin for at least 72 hours, and had at least one serum vancomycin value obtained. Hemodialysis patients were excluded. Nephrotoxicity was defined as an increase of >0.5 mg/dL over baseline in serum creatinine for two consecutive assays. Creatinine levels were followed until patient discharge. Patients were divided based on trough serum vancomycin concentration attainment of 5–15 mg/L (n = 130) or >15 mg/L (n = 88). The rate of nephrotoxicity was 6.2% in the lower-trough group and 18.2% in the higher-trough group (p < 0.01). Multivariate analysis indicated that the main predictors of nephrotoxicity were an elevated overall average trough concentration and duration of therapy.

Investigations, such as those described herein, are intriguing but often limited by small sample size, retrospective design, and questionable methodology. Additional data are needed, including the timing of the relationship between high vancomycin levels and nephrotoxicity (i.e., which one precedes the other). In addition, while statistically relevant, the clinical significance of minor and transient changes in creatinine or CL_{cr} can be debated. The effect of a 0.5-mg/dL increase in serum creatinine concentration would be greater in a patient with a lower initial CL_{cr} value than in one with a higher baseline CL_{cr} value.

Summary and recommendation: *There are limited data suggesting a direct causal relationship between toxicity and specific serum vancomycin concentrations. In addition, data are conflicting and characterized by the presence of confounding nephrotoxic agents, inconsistent and highly variable definitions of toxicity, and the inability to examine the time sequence of events surrounding changes in renal function secondary to vancomycin exposure.*

A patient should be identified as having experienced vancomycin-induced nephrotoxicity if multiple (at least two or three consecutive) high serum creatinine concentrations (increase of 0.5 mg/dL or ≥50% increase from baseline, whichever is greater) are documented after several days of vancomycin therapy in the absence of an alternative explanation. (Level of evidence = II, grade of recommendation = B.)

Role of therapeutic drug monitoring in preventing nephrotoxicity. Because vancomycin is eliminated via glomerular filtration, a decrease in the glomerular filtration rate from any cause will increase the serum vancomycin concentration and make the association between renal dysfunction and trough concentrations difficult to assess.[8]

Some investigators have found vancomycin therapeutic drug monitoring to be associated with decreased nephrotoxicity. Other factors associated with decreased toxicity include shorter courses of therapy, less total dosage in grams of the drug, and a decreased length of hospital stay.[7,12,116,117] However, Darko et al.[7] found therapeutic drug monitoring to be cost-effective only in patients in ICUs, those receiving other nephrotoxins, and, possibly, oncology patients.

Summary and recommendations: *Available evidence does not support monitoring peak serum vancomycin concentrations to decrease the frequency of nephrotoxicity. (Level of evidence = I, grade of recommendation = A.)*

Monitoring of trough serum vancomycin concentrations to reduce nephrotoxicity is best suited to patients receiving aggressive dosing targeted to produce sustained trough drug concentrations of 15–20 mg/L or who are at high risk of toxicity, such as patients receiving concurrent nephrotoxins. (Level of evidence = III, grade of recommendation = B.)

Monitoring is also recommended for patients with unstable renal function (either deteriorating or significantly improving) and those receiving prolonged courses of therapy (over three to five days). (Level of evidence = II, grade of recommendation = B.)

All patients receiving prolonged courses of vancomycin should have at least one steady-state trough concentration obtained (just before the fourth dose). Frequent monitoring (more than a single trough concentration before the fourth dose) for short-course therapy (less than five days) or for lower-intensity dosing (targeted to attain trough serum vancomycin concentrations below 15 mg/L) is not recommended. (Level of evidence = II, grade of recommendation = B.)

There are limited data to support the safety of sustained trough serum vancomycin concentrations of 15–20 mg/L. When this target range is desired, obtaining once-weekly trough concentrations in hemodynamically stable patients is recommended. Frequent (in some instances daily) trough concentration monitoring is advisable to prevent toxicity in hemodynamically unstable patients. The exact frequency of monitoring is often a matter of clinical judgment. (Level of evidence = III, grade of recommendation = B.)

Data on comparative vancomycin toxicity using continuous versus intermittent administration are conflicting and no recommendation can be made.

Incidence of ototoxicity and role of therapeutic drug monitoring for prevention of vancomycin-induced hearing loss. Vancomycin-induced hearing loss is controversial. Vancomycin has not been found to be ototoxic in animal models.[97,98,100,118,119] Early literature attributed ototoxic events to impurities or to concurrent ototoxic agents.[119] Early studies indicated that other ototoxic agents, such as the aminoglycosides kanamycin and streptomycin, may have additive or synergistic toxicity when used in combination with vancomycin.[120] The frequency of ototoxicity in humans has been reported to range from 1% to 9%[3,8,48,121-124] and to be associated with serum vancomycin concentrations above 40 mg/L.[7,125] This most likely represents an inflated occurrence rate due to impurities associated with the older formulation or poor documentation of cause and effect as they relate to serum concentrations. The true risk of ototoxicity from vancomycin monotherapy is low without concurrent therapy with ototoxic agents.[77]

Severe ototoxicity induced by vancomycin is rare and characterized as damage to the auditory nerve that initially affects high-frequency sensory hairs in the cochlea, then the middle- and low-frequency hairs, and eventually can lead to total hearing loss.[75] High-tone deafness occurs before low-tone deafness at all frequencies and is permanent. Inability to hear high-frequency sounds and tinnitus are ominous signs that should result in discontinuation of vancomycin.[126,127] Also rare is reversible ototoxicity such as tinnitus, which can occur with or without high-tone deafness.[33,120,127] Investigation of pediatric pneumococcal meningitis noted that early vancomycin administration (relative to ceftriaxone administration) was associated with a substantially increased risk of hearing loss due to the effects of rapid bacterial killing by both antimicrobials and the resultant host inflammatory response.[128] However, toxicity did not correlate with vancomycin concentrations.

In 1958, Geraci et al.[129] described hearing loss in two patients with serum vancomycin concentrations of 80–100 mg/L. That report generated an impetus to monitor peak serum concentrations. However, Cantu et al.[8] reviewed 53 published cases of vancomycin-attributed ototoxicity and concluded that vancomycin was rarely ototoxic as a single agent. In addition, ototoxicity was fully reversible when other ototoxic agents were not involved.

Bailie and Neal[75] reviewed 28 cases of ototoxicity reported between 1956 and 1986, most of which involved vancomycin preparations with higher levels of impurities. Patients with severe renal dysfunction were found

to be more susceptible to developing ototoxicity when their dosage regimen was not adjusted. The researchers were unable to correlate mild ototoxicity with excessive peak or trough serum vancomycin concentrations or prevention of ototoxicity by monitoring serum concentrations.

A lack of correlation between serum vancomycin levels and the development of ototoxicity has also been observed in cancer patients.[75] Of 742 patients analyzed, ototoxicity occurred in 18 (6%) of 319 patients (95% CI, 4–9%) who were receiving concurrent ototoxic agents (including aminoglycosides, cisplatin, loop diuretics, aspirin, and nonsteroidal antiinflammatory agents) and in 12 (3%) of 423 patients (95% CI, 2–5%) not treated with other ototoxic agents. All clinical ototoxicity resolved within three weeks after vancomycin discontinuation.

Summary and recommendation: *Monitoring serum vancomycin levels to prevent ototoxicity is not recommended because this toxicity is rarely associated with monotherapy and does not correlate with serum vancomycin concentrations. Monitoring may be more important when other ototoxic agents, such as aminoglycosides, are administered. (Level of evidence = III, grade of recommendation = B.)*

Summary

In general, pharmacodynamic dosing of antibiotics may significantly augment antibiotic performance. There seems to be little difference in the pharmacodynamics of intermittently or continuously dosed vancomycin. This consensus panel review supports that vancomycin is a concentration-independent killer of gram-positive pathogens and that the AUC/MIC is likely the most useful pharmacodynamic parameter to predict effectiveness. In many clinical settings where it may be difficult to obtain multiple serum vancomycin concentrations to determine the AUC and subsequently the AUC/MIC, trough serum vancomycin concentration monitoring can be recommended as the most accurate and practical method to monitor serum vancomycin levels. Increasing trough serum vancomycin concentrations to 15–20 mg/L to obtain an increased AUC/MIC of ≥400 may be desirable but is currently not supported by clinical trial data. Target attainment of an AUC/MIC of ≥400 is not likely in patients with *S. aureus* infections who have an MIC of ≥2 mg/L; therefore, treatment with alternative agents should be considered. Higher trough serum vancomycin levels may also increase the potential for toxicity, but additional clinical experience will be required to determine the extent of this potential.

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