Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: A revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists

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The first consensus guideline for therapeutic monitoring of vancomycin in adult patients was published in 2009. A committee representing 3 organizations (the American Society for Health-System Pharmacists [ASHP], Infectious Diseases Society of America [IDSA], and Society for Infectious Diseases Pharmacists [SIDP]) searched and reviewed all relevant peer-reviewed data on vancomycin as it related to in vitro and in vivo pharmacokinetic and pharmacodynamic (PK/PD) characteristics, including information on clinical efficacy, toxicity, and vancomycin resistance in relation to serum drug concentration and monitoring. The data were summarized, and specific dosing and monitoring recommendations were made. The primary recommendations consisted of eliminating routine monitoring of serum peak concentrations, emphasizing a ratio of area under the curve over 24 hours to minimum inhibitory concentration (AUC/MIC) of ≥400 as the primary PK/PD predictor of vancomycin activity, and promoting serum trough concentrations of 15 to 20 mg/L as a surrogate marker for the optimal vancomycin AUC/MIC if the MIC was ≤1 mg/L in patients with normal renal function. The guideline also recommended, albeit with limited data support, that actual body weight be used to determine the vancomycin dosage and loading doses for severe infections in patients who were seriously ill.[1]

Since those recommendations were generated, a number of publications have evaluated the impact of the 2009 guidelines on clinical efficacy and toxicity in patients receiving vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections. It should be noted, however, that when the recommendations were originally published, there were important issues not addressed and gaps in knowledge that could not be covered adequately because of insufficient data. In fact, adequate data were not available to make recommendations in the original guideline for specific dosing and monitoring for pediatric patients outside of the neonatal age group; specific recommendations for vancomycin dosage adjustment and monitoring in the morbidly obese patient population and patients with renal failure, including specific dialysis dosage adjustments; recommendations for the use of prolonged or continuous infusion (CI) vancomycin therapy; and safety data on the use of dosages that exceed 3 g per day. In addition, there were minimal to no data on the safety and efficacy of targeted trough concentrations of 15 to 20 mg/L.

This consensus revision evaluates the current scientific data and controversies associated with vancomycin dosing and serum concentration monitoring for serious MRSA infections (including but not limited to bacteremia, sepsis, infective endocarditis, pneumonia, osteomyelitis, and meningitis) and provides new recommendations based on recent available evidence. Due to a lack of data to guide appropriate targets, the development of this guideline excluded evaluation of vancomycin for methicillin-susceptible *S. aureus* (MSSA) strains, coagulase-negative staphylococci, and other pathogens; thus, the extrapolation of

guideline recommendations to these pathogens should be viewed with extreme caution. Furthermore, serious invasive MRSA infections exclude nonbacteremic skin and skin structure and urinary tract infections. Since this guideline focuses on optimization of vancomycin dosing and monitoring, recommendations on the appropriateness of vancomycin use, combination or alternative antibiotic therapy, and multiple medical interventions that may be necessary for successful treatment of invasive MRSA infections are beyond the scope of this guideline and will not be presented.

Methods

These are the consensus statements and guideline of ASHP, IDSA, the Pediatric Infectious Diseases Society (PIDS), and SIDP. Guideline panel composition consisted of physicians, pharmacists, and a clinical pharmacologist with expertise in clinical practice and/or research with vancomycin. Committee members were assigned key topics regarding vancomycin dosing and monitoring. A draft document addressing these specific areas was reviewed by all committee members and made available for public comments for 30 days through ASHP, IDSA, PIDS, and SIDP. The committee then met to review and revise the document based on the submitted comments, suggestions, and recommendations. After careful discussion and consideration, the document was revised and circulated among the committee and supporting organizations prior to final approval and publication. A search of PubMed and Embase was conducted using the following search terms: *vancomycin, pharmacokinetics, pharmacodynamics, efficacy, resistance, toxicity, obesity,* and *pediatrics.* All relevant and available peer-reviewed studies in the English-language literature published from 1958 through 2019 were considered. Studies were rated by their quality of evidence, and the subsequent recommendations were graded using the classification schemata described in Table 1.

Table 1. Grading System for Recommendations Based on Quality of Evidence[a]

Category and Grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for or against use
B	Moderate evidence to support a recommendation for or against use
C	Poor evidence to support a recommendation
Quality of evidence	
I	Evidence from 1 or more properly randomized controlled trials
II	Evidence from 1 or more well-designed clinical trials, without randomization; from cohort or case-controlled analytic studies (preferably from more than 1 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

[a]Adapted from the Canadian Task Force on the Periodic Health Examination.[2]

Potential limitations of this review included the fact that there are few published randomized clinical trials of vancomycin dosing and monitoring available in the literature. Most published studies evaluating vancomycin dosing, dosage adjustment, and monitoring were retrospective PK or PD clinical assessments or retrospective observational studies in patients with MRSA infections.

PK/PD efficacy targets. To optimize the dosing of any antimicrobial agent, a firm understanding of the drug's exposure-effect and exposure-toxicity links are required. While a variety of PD indices for vancomycin have been suggested, an AUC/MIC ratio of ≥400 (with the MIC determined by broth microdilution [BMD]) is the current accepted critical PK/PD index in light of our limited experience and studies evaluating AUC/MIC values of <400.[1,3-7] In vitro and in vivo assessments of PK/PD models applicable to human MRSA infection have found that bactericidal activity (ie, a 1- to 2-log reduction in bacterial inoculum in the animal model) is achieved when the vancomycin AUC/

MIC_{BMD} ratio approximates or exceeds 400. Furthermore, in vitro data suggest that an AUC of <400 potentiates the emergence of MRSA resistance and vancomycin-intermediate *S. aureus* strains.[8,9] There are also mounting clinical data, albeit mostly retrospective in nature, in support of this PK/PD target for vancomycin.[10-18] A summary of these investigations and their findings can be found in eTable 1.[10-17,19-23]

Clinical PK/PD Data: Adults

While an AUC/MIC_{BMD} ratio of ≥400 is currently considered the optimal PK/PD "efficacy" target, it is important to recognize that this target has been largely derived from retrospective, single-center, observational studies of patients with MRSA bloodstream infections.[11-17] It is also important to recognize that most of the landmark clinical studies that established the contemporary PK/PD efficacy target relied on simple vancomycin clearance (CL) formulas based on daily vancomycin dose and estimated renal function to determine AUC values.[10,11,13] Current evaluation of these data demonstrates that

these CL formulas provide imprecise estimates of the AUC.[24-26] This finding is not surprising, as there is considerable interpatient variability in vancomycin exposure profiles in clinical practice, and it is not possible to generate valid estimates of exposure variables in a given individual based on CL formulas that are derived from glomerular filtration rate estimation equations alone.[10,11,13] In most cases, the formula-based approach will overestimate vancomycin CL by approximately 40% to 50%.[16]

While it has been cumbersome to estimate AUC in the clinical setting in the past, Neely and colleagues[24] recently demonstrated that Bayesian software programs (refer to Therapeutic Monitoring section) can be used to generate accurate and reliable estimates of the daily AUC values with trough-only PK sampling. However, the accuracy of AUC estimation is higher with peak and trough measurements compared to trough-only PK sampling.[24] Using this validated Bayesian method to estimate the daily AUC in a single-center, retrospective study of patients with MRSA bloodstream infections, Lodise and colleagues[16] found that outcomes were maximized when day 1 and day 2 AUC/MIC$_{BMD}$ ratios exceeded 521 and 650, respectively. Employing the same Bayesian approach to estimate daily AUC values, Casapao and colleagues[17] also noted that the risk of vancomycin treatment failure among patients with MRSA infective endocarditis was greatest among those with an AUC/MIC$_{BMD}$ ratio of ≤600 and that this exposure-failure relationship persisted after adjusting for factors such as intensive care unit (ICU) admission, presence of heteroresistant vancomycin-intermediate *S. aureus*, and other comorbidities. In contrast to the studies by Lodise et al and Casapao et al, several small-scale, retrospective clinical evaluations of vancomycin exposure-response reported lower Bayesian-derived thresholds for AUC/MIC since the AUC was measured at steady-state conditions and indexed to the MIC, as determined by the Etest

(bioMérieux USA, Hazelwood, MO) method, to arrive at an AUC/MIC$_{Etest}$ value.[12,14,15] The MIC$_{Etest}$ value tends to be 1.5- to 2-fold higher than the MIC$_{BMD}$ value; therefore, it is likely that the AUC threshold needed for response from these 3 studies,[12,14,15] if calculated using the MIC$_{BMD}$, would align with the studies by Lodise et al[16] and Casapao et al.[17]

In an effort to surmount the limitations associated with previous single-center, retrospective vancomycin exposure-response clinical analyses, a multicenter, observational prospective study was performed to evaluate the relationship between the prespecified day 2 AUC/MIC ratios (ie, AUC/MIC$_{Etest}$ of ≥320 and AUC/MIC$_{BMD}$ of ≥650) and outcomes in adult patients ($n = 265$) with MRSA bacteremia. In the multivariate analyses, treatment failure rates were not significantly different between the prespecified day 2 AUC/MIC groups. Post hoc global outcomes analyses suggested that patients in the 2 lowest AUC exposure quintiles (ie, those with an AUC of ≤515 mg·h/L) experienced the best global outcome (defined as absence of both treatment failure and acute kidney injury [AKI]). While global outcomes were similar in the 2 lowest AUC-exposure quintiles, only 20% of the study population ($n = 54$) had an AUC of ≤400 mg·h/L, and it is unclear if efficacy outcomes are maintained at an AUC less than this threshold of 400 mg·h/L.[23] Notably, the higher AUC value cited above (515 mg·h/L) provides a new index that incorporates both efficacy and AKI that is still within the recommended AUC range of 400 to 600 mg·h/L (assuming a MIC of 1 mg/L).

Collectively, recent studies highlight the importance of generating valid estimates of the AUC values through Bayesian modeling techniques when conducting vancomycin exposure-outcomes analyses in patients. Current vancomycin exposure-effectiveness data originated largely from studies of MRSA bacteremia, with some studies for pneumonia and infective endocarditis and none for osteomyelitis and meningitis. Furthermore, outcomes

data for a MIC of 2 mg/L are limited, suggesting the need for more studies to ascertain the optimal AUC/MIC target for this MIC value or consideration for the use of alternative antibiotics. The currently available data also highlight the critical need for large-scale, multicenter, randomized, vancomycin dose–optimized clinical outcomes trials. As data from future prospective, multicenter clinical studies emerge, it is important that clinicians recognize that our current understanding of the PK/PD target associated with maximal effect and toxicity is subject to change, and this may ultimately alter the current way we dose vancomycin to optimize effect and minimize toxicity.

Toxicodynamics: AKI

A major concern with vancomycin use is the occurrence of AKI. While multiple definitions of vancomycin-associated AKI have been employed in the literature, most studies defined it as an increase in the serum creatinine (SCr) level of ≥0.5 mg/dL, or a 50% increase from baseline in consecutive daily readings, or a decrease in calculated creatinine CL (CL$_{cr}$) of 50% from baseline on 2 consecutive days in the absence of an alternative explanation.[1] Recently, it has been proposed that a more sensitive threshold (ie, an increase in SCr of ≥0.3 mg/dL over a 48-hour period) may be considered as an indicator of vancomycin-associated AKI. This threshold was adopted from the Acute Kidney Injury Network (AKIN) and the Kidney Disease: Improving Global Outcomes (KDIGO) criteria.[27-29] The incidence of vancomycin-associated AKI has varied across published studies. In a meta-analysis by van Hal and colleagues,[29] the prevalence of vancomycin-associated AKI varied from 5% to 43%. Similarly, a recent meta-analysis of 13 studies by Sinha Ray et al[30] reported that the relative risk of AKI with vancomycin was 2.45 (95% confidence interval, 1.69-3.55), with an attributable risk of 59%. Most episodes of AKI developed between 4 and 17 days after initiation of therapy. Many patients, especially those who are critically ill, do not fully recover renal

function after AKI,[31] and even mild AKI can significantly decrease long-term survival rates, increase morbidity, prolong hospitalizations, and escalate healthcare costs.[22,32]

With any drug, an understanding of its toxicodynamic profile is required for optimal dosing. Several studies, largely retrospective in nature, have attempted to quantify the relationship between vancomycin exposure and probability of AKI.[33,34] Although data are limited, the collective literature suggests that the risk of AKI increases as a function of the trough concentration, especially when maintained above 15 to 20 mg/L.[29] Similarly, there are recent data to suggest that the risk of AKI increases along the vancomycin AUC continuum, especially when the daily AUC exceeds 650 to 1,300 mg·h/L.[24,33-35] Furthermore, animal studies corroborate the finding that increased AUC rather than trough concentration is a strong predictor of AKI.[36,37]

Suzuki et al[33] evaluated the mean vancomycin AUC in relation to AKI. Most patients who developed AKI had AUC values between 600 and 800 mg·h/L, compared with 400 to 600 mg·h/L in those without AKI ($P = 0.014$). Furthermore, Lodise and colleagues[34] showed that the probability of AKI increased 2.5-fold among patients with AUC values above 1,300 mg·h/L compared with patients with lower values (30.8% vs 13.1%, $P = 0.02$). Although AUC values above 1,300 mg·h/L were associated with a substantial increase in AKI, an AUC exposure-response relationship appeared to exist, and the probability of a nephrotoxic event increased as a function of the daily AUC and patient's body weight.[38] A study by Zasowski et al[21] also reported a similar relationship between Bayesian-estimated vancomycin AUC thresholds and AKI in 323 patients; AUC values of ≥1,218 mg·h/L for 0 to 48 hours, ≥677 for 0 to 24 hours, and ≥683 for 24 to 48 hours or troughs of ≥18.2 mg/L were associated with a 3- to 4-fold increased risk of nephrotoxicity. Similarly, the aforementioned multicenter, prospective study of patients with MRSA bloodstream infections found that AKI

increased along the day 2 AUC continuum in a stepwise manner and that patients with day 2 AUC values of ≥793 mg·h/L were at the greatest risk for AKI.[23]

Given the understanding about potential toxic concentrations, there are also data to suggest that AUC-guided vancomycin dosing may reduce the occurrence of vancomycin-associated AKI. In a retrospective, quasi-experimental study of 1,280 hospitalized patients, Finch et al[20] compared the incidence of nephrotoxicity in patients monitored by individualized AUC vs trough concentration. AUC-guided dosing was found to be independently associated with a significant decrease in AKI (odds ratio [OR], 0.52; 95% CI, 0.34-0.80; $P = 0.003$).[20] Median Bayesian-estimated AUC was significantly lower with AUC-guided dosing vs trough monitoring (474 [SD, 360-611] mg·h/L vs. 705 [SD, 540-883] mg·h/L; $P < 0.001$). In the prospective study by Neely et al,[22] 252 patients were monitored via troughs of 10 to 20 mg/L in year 1 vs Bayesian-estimated AUC values of ≥400 mg·h/L in years 2 and 3 of the investigation. Nephrotoxicity occurred in 8% of subjects in year 1 and in 0% and 2% of subjects in years 2 and 3, respectively ($P = 0.01$). The median trough concentration and AUC values associated with AKI were 15.7 mg/L and 625 mg·h/L, as compared with values of 8.7 mg/L and 423 mg·h/L in subjects without AKI ($P = 0.02$).[22]

Collectively, the published clinical exposure-response analyses suggest that a daily AUC of ≥400 is the driver of effectiveness and that the risk of AKI is related to AUC and trough values. More importantly, these data provide the foundation for the current understanding of the therapeutic window for vancomycin. When evaluating the toxicodynamics of vancomycin, it is important to recognize other factors that may complicate or exacerbate the risk of AKI. Host-related factors associated with nephrotoxicity include increased weight, pre-existing renal dysfunction, and critical illness. Concurrent administration of nephrotoxic agents such as aminoglycosides, loop diuretics, amphotericin B, intravenous

(i.v.) contrast dye, and vasopressors has been shown to increase the risk of nephrotoxicity. Recently, piperacillin/tazobactam and flucloxacillin have been reported to increase the risk for AKI in patients receiving vancomycin.[39-44] It is unclear if the threshold for vancomycin-induced AKI varies according to these covariates, but clinicians should be mindful of the potential for additional risk when prescribing vancomycin to patients when these conditions are present.[34,40-50]

Based on the current best available evidence, daily vancomycin AUC values (assuming a MIC of 1 mg/L) should be maintained between 400 and 600 mg·h/L to minimize the likelihood of nephrotoxicity and maximize efficacy for suspected or definitive serious invasive MRSA infections. Once culture results or the clinical presentation rule out invasive MRSA infection, the empiric use of vancomycin at guideline-recommended exposures should be de-escalated, either by a decrease in vancomycin exposure or initiation of alternative antibiotics. Extrapolation of guideline recommendations to noninvasive MRSA and other pathogens should be viewed with extreme caution.

Therapeutic Monitoring

Therapeutic monitoring has centered on maintaining trough concentrations between 15 and 20 mg/L for serious infections due to MRSA. Previous expert guidelines recommended monitoring trough concentrations as a surrogate marker for the AUC/MIC ratio based on the historical difficulty in estimating the AUC in clinical practice.[1,5] In the past, calculation of AUC in clinical practice involved collection of multiple vancomycin serum concentrations during the same dosing interval, with subsequent use of PK software that was not readily available at all institutions. As such, the guideline viewed trough-directed dosing as a more practical alternative to AUC/MIC-guided dosing in clinical practice.

Although the recommendation to maintain trough values between 15 and 20 mg/L for serious infections

due to MRSA has been well integrated into practice, the clinical benefits of maintaining higher vancomycin trough values have not been well documented.[38,51-55] From a PK/PD perspective, it is not surprising that there are limited clinical data to support the range of 15 to 20 mg/L. Recent studies have demonstrated that trough values may not be an optimal surrogate for AUC values.[26,56,57] While trough attainment ensures achievement of a minimum cumulative exposure, a wide range of concentration-time profiles can result in an identical trough value. Patel et al[26] reported a wide range of AUC values from several different dosing regimens yielding similar trough values. The therapeutic discordance between trough and AUC values is not surprising, as the AUC is the integrated quantity of cumulative drug exposure (ie, the serum drug concentration–time curve over a defined interval). In contrast, the trough represents a single exposure point at the end of the dosing interval. In clinical practice, monitoring of trough concentrations will translate into achievement of one specific minimum daily AUC value, whereas the 24-hour AUC (AUC_{24}) largely represents the average concentration during that time period [AUC_{24} (mg·h/L) = average concentration (mg/L) x 24 (hours)]. For troughs of 15 to 20 mg/L, this typically equates to a daily AUC in excess of 400 mg·h/L. However, there is considerable variability in the upper range of AUC values associated with a given trough value. Although trough-only monitoring is practical, the potential limitations surrounding the practice suggest that trough monitoring may be insufficient to guide vancomycin dosing in all patients.

Although the AUC/MIC ratio is considered the PK/PD driver of efficacy for vancomycin, clinicians trying to optimize vancomycin treatment for patients with serious MRSA infections may be best advised to use AUC-guided dosing and assume a MIC_{BMD} of 1 mg/L (unless it is known, through BMD, to be greater or less than 1 mg/L). The MIC value is of less importance for several reasons.

First, the range of vancomycin MIC values among contemporary MRSA isolates is narrow, and the BMD MIC_{90} in most institutions is 1 mg/L or less.[58-62] Second, measurement of MIC values is imprecise, with dilution of ±1 $\log_2$ and variation of 10% to 20% considered acceptable; therefore, the variability of reported MIC values encountered in routine clinical practice is likely to reflect measurement error.[63] Third, there is a high degree of variability between commercially available MIC testing methods relative to the BMD method (see Vancomycin Susceptibility Testing section). Last, MIC results are typically not available within the first 72 hours of index culture collection, yet current data indicate that the vancomycin AUC/MIC ratio needs to be optimized early in the course of infection.

Daily AUC values (assuming a MIC_{BMD} of 1 mg/L) should be maintained between 400 and 600 mg·h/L to maximize efficacy and minimize the likelihood of AKI. In the past, AUC monitoring required the collection of multiple concentrations over the same dosing interval. With these data, a clinician would calculate the AUC using the linear-trapezoid rule. This approach required precise collection of vancomycin concentrations, making it largely impractical outside of a research setting. However, this is no longer the case. It is now possible to accurately estimate the AUC with limited PK sampling. One such approach involves the use of Bayesian software programs to estimate the vancomycin AUC value with minimal PK sampling (ie, 1 or 2 vancomycin concentrations) and provide AUC-guided dosing recommendations in real time. An alternative approach involves use of 2 concentrations (peak and trough) and simple analytic PK equations to estimate AUC values.[57,64]

Bayesian-derived AUC monitoring. Bayesian-guided dosing is based in part on Bayes' Theorem, as it quantifies the sequential relationship between the estimated probability distribution of an individual patient's PK parameter values (eg, volume [V_d] or CL) prior to administering the drug

based on the way the drug behaved in a population of prior patients (the Bayesian prior) and the revised probability distribution of a specific patient's PK parameter values using exact dosing and drug concentration data (the Bayesian conditional posterior). In short, Bayesian dose optimization software uses a well-developed vancomycin population PK model as the Bayesian prior, together with the individual patient's observed drug concentrations in the data file, to calculate a Bayesian posterior parameter value distribution for that patient. The dose optimization software then calculates the optimal dosing regimen based on the specific patient's profile.[65-67]

An advantage of the Bayesian approach is that vancomycin concentrations can be collected within the first 24 to 48 hours rather than at steady-state conditions (after the third or fourth dose), and this information can be used to inform subsequent dosing (adaptive feedback control). As part of their output, Bayesian dosing programs provide innovative treatment schemes, such as front-loading doses with subsequent transition to a lower maintenance dosing regimen, to rapidly achieve target concentrations within the first 24 to 48 hours among critically ill patients. The Bayesian approach also provides the ability to integrate covariates, such as CL_{cr}, in the structural PK models (the Bayesian prior density file) that account for the pathophysiological changes that readily occur in critically ill patients. Incorporation of covariates that account for these "dynamic" changes serves as a way to identify dosing schemes that optimize effect and predict future dosing in a patient who has an evolving PK profile.[67]

Bayesian dose-optimizing software programs are now readily available and can be used in real time to identify the optimal vancomycin dosage that readily achieves the AUC target (assuming a MIC_{BMD} of 1 mg/L).[66,68] Bayesian programs offer numerous advantages over the traditional first-order equation software programs. Using richly

sampled vancomycin PK data from 3 studies comprising 47 adults with varying renal function, Neely and colleagues[24] demonstrated that Bayesian software programs, embedded with a PK model based on richly sampled vancomycin data as the Bayesian prior, can be used to generate accurate and reliable estimates of the daily AUC values with trough-only PK sampling. Of note, there was limited inclusion of special populations in this study, and it is unclear if this trough-only Bayesian AUC estimation approach can be applied to obese patients, critically ill patients, pediatric patients, and patients with unstable renal function. A randomized controlled study of 65 subjects by Al-Sulaiti et al[69] showed that estimating AUC using both peak and trough concentrations (vs trough-only estimates) may improve vancomycin-associated therapeutic cure. Until more data are available, it is preferred to estimate the Bayesian AUC using 2 vancomycin concentrations (peak and trough).

First-order PK analytic equations. Alternatively, the AUC can be accurately estimated based on the collection of 2 timed steady-state serum vancomycin concentrations and the use of first-order PK equations.[57] The equations used to compute AUC from 2 samples are based in part on an original approach proposed by Begg, Barclay, and Duffull[70] for aminoglycosides and modified by Pai and Rodvold.[57] It is preferred that a near steady-state, postdistributional peak (1 to 2 hours after end of infusion) and trough concentrations within the same dosing interval (if possible) are used when estimating the AUC with the equation-based methods.

The major advantage of this approach is that it is simpler and relies on fewer assumptions than the Bayesian approach. The first-order PK equations used to estimate the AUC are also familiar to most clinicians, facilitating ease of use in practice. Once the AUC_{24} is estimated, the clinician simply revises the total daily dose to achieve the desired AUC_{24}, as alterations of total daily dose will provide proportional changes in observed AUC_{24}.[6,71-73] The major limitation of this approach is that it is not adaptive like the Bayesian approach, as it can only provide a snapshot of the AUC for the sampling period. As such, this AUC calculation will not be correct if a physiologic change such as renal dysfunction occurs during or after the sampling period. Furthermore, it is extremely difficult to estimate the vancomycin AUC_{24} with the equation-based method in patients who receive multiple dosing regimens within a 24-hour period. If the vancomycin dosing interval is more frequent than once a day, the AUC_{24} will be a function of the number of identical doses administered during that interval (eg, AUC must be multiplied by 2 for a 12-hour dosing interval to calculate the true AUC_{24}). It is also highly preferred that concentrations are collected near steady-state conditions.

Despite its drawbacks, this estimate of AUC is a clear step above trough-only or peak-only concentration interpretation and is familiar to most clinicians. Several large medical centers within the United States have already adopted this approach of acquiring 2 postdose serum concentration estimates of the AUC to perform routine vancomycin dosing and monitoring and have demonstrated a considerable improvement in safety over the current trough-only concentration monitoring method.[37,64]

PK sampling time. Timing of achievement of targeted AUC values (assuming a MIC_{BMD} of 1 mg/L) remains unclear. The early AUC/MIC target ratios derived in animal models were based on the AUC value from 0 to 24 hours.[3,4] More recent clinical assessments that identified a link between AUC/MIC ratio and outcomes also assessed the AUC values achieved early in the course of therapy.[1,3,5-7,10,13,20-22] The 2009 vancomycin guideline stated that the trough should be assessed prior to steady-state conditions (ie, prior to the fourth dose).[1,5] In fact, steady-state conditions are difficult to determine in clinical practice, and the timing of the fourth dose is more dependent on the dosing interval (ie, 12 vs 24 hours) than steady-state conditions. Given the importance of early, appropriate therapy,[74] targeted AUC exposures should be achieved early during the course of therapy, preferably within the first 24 to 48 hours. If monitoring is initiated after the first dose, the contribution of the loading dose to the actual AUC may vary depending on the magnitude of the loading dose vs maintenance doses. The decision to delay therapeutic monitoring beyond 48 hours should be based on severity of infection and clinical judgment.

Summary and recommendations:

1. *In patients with suspected or definitive serious MRSA infections, an individualized target of the AUC/MIC_{BMD} ratio of 400 to 600 (assuming a vancomycin MIC_{BMD} of 1 mg/L) should be advocated to achieve clinical efficacy while improving patient safety (A-II). Doses of 15 to 20 mg/kg (based on actual body weight) administered every 8 to 12 hours as an intermittent infusion are recommended for most patients with normal renal function when assuming a MIC_{BMD} of 1 mg/L (A-II). In patients with normal renal function, these doses may not achieve the therapeutic AUC/MIC target when the MIC is 2 mg/L.*

2. *Given the narrow vancomycin AUC range for therapeutic effect and minimal AKI risk, the most accurate and optimal way to manage vancomycin dosing should be through AUC-guided dosing and monitoring (A-II). We recommend to accomplish this in one of two ways.*
   a. *One approach relies on the collection of 2 concentrations (obtained near steady-state, postdistributional peak concentration [C_{max}] at 1 to 2 hours after infusion and trough concentration [C_{min}] at the end of the dosing interval), preferably but not required during the same dosing interval (if possible) and utilizing first-order PK equations to estimate the AUC (A-II).*

b. *The preferred approach to monitor AUC involves the use of Bayesian software programs, embedded with a PK model based on richly sampled vancomycin data as the Bayesian prior, to optimize the delivery of vancomycin based on the collection of 1 or 2 vancomycin concentrations, with at least 1 trough. It is preferred to obtain 2 PK samples (ie, at 1 to 2 hours post infusion and at end of the dosing interval) to estimate the AUC with the Bayesian approach (A-II). A trough concentration alone may be sufficient to estimate the AUC with the Bayesian approach in some patients, but more data are needed across different patient populations to confirm the viability of using trough-only data (B-II).*

3. *When transitioning to AUC/MIC monitoring, clinicians should conservatively target AUC values for patients with suspected or documented serious infections due to MRSA assuming a vancomycin MIC_{BMD} of 1 mg/L or less at most institutions. Given the importance of early, appropriate therapy, vancomycin targeted exposure should be achieved early during the course of therapy, preferably within the first 24 to 48 hours (A-II). As such, the use of Bayesian-derived AUC monitoring may be prudent in these cases since it does not require steady-state serum vancomycin concentrations to allow for early assessment of AUC target attainment.*

4. *Trough-only monitoring, with a target of 15 to 20 mg/L, is no longer recommended based on efficacy and nephrotoxicity data in patients with serious infections due to MRSA (A-II). There is insufficient evidence to provide recommendations on whether trough-only or AUC-guided vancomycin monitoring should be used among patients with noninvasive MRSA or other infections.*

5. *Vancomycin monitoring is recommended for patients receiving vancomycin for serious MRSA infections to achieve sustained targeted AUC values (assuming a MIC_{BMD} of 1 mg/L unless it is known to be greater or less than 1 mg/L by BMD). Independent of MRSA infection, vancomycin monitoring is also recommended for all patients at high risk for nephrotoxicity (eg, critically ill patients receiving concurrent nephrotoxins), patients with unstable (ie, deteriorating or significantly improving) renal function, and those receiving prolonged courses of therapy (more than 3 to 5 days). We suggest the frequency of monitoring be based on clinical judgment; frequent or daily monitoring may be prudent for hemodynamically unstable patients (eg, those with end-stage renal disease), with once-weekly monitoring for hemodynamically stable patients (B-II).*

Vancomycin Susceptibility Testing

With the MIC being a component of the vancomycin AUC/MIC targeted surrogate for efficacy, it is important to be aware of local and national vancomycin susceptibility patterns for MRSA. Although in some centers there has been a steady increase in the average vancomycin MIC over several decades, recent national and international studies that have evaluated MRSA susceptibility to glycopeptides, lipopeptides, and beta-lactams have demonstrated that vancomycin MICs have remained constant over time, with a MIC of ≤1 mg/L demonstrated for more than 90% of isolates.[58-62] A meta-analysis of 29,234 MRSA strains from 55 studies revealed that the MIC determinations performed by BMD, Etest, and automated systems were predominately 1 mg/L and that there was no evidence of a MIC creep phenomenon.[75] Furthermore, a global surveillance program reported that 95% of 57,319 MRSA isolates had MICs of 1 mg/L, with no signs of MIC creep over 20 years.[76] While there does not seem to be a large number of organisms with a vancomycin MIC of ≥2 mg/L when reference methods are used, there is considerable variability in MIC results between the susceptibility testing methods.

The challenge is that, according to the Clinical Laboratory Standards Institute (CLSI), acceptable variability for MIC measurement methods is within ±1 doubling dilution (essential agreement), such that current susceptibility testing methods are unable, with high reproducibility, to distinguish MICs of 1 mg/L from MICs of 0.5 mg/L or 2 mg/L. Most institutions routinely perform MIC testing using automated systems: BD Phoenix (BD, Franklin Lakes, NJ), MicroScan WalkAway (Beckman Coulter, Brea, CA), or Vitek 2 (bioMérieux), and in some cases the Etest methodology (bioMérieux). In a study of 161 MRSA blood isolates, when using the essential agreement definition of ±1 log_2 dilution error, Vitek 2 and MicroScan WalkAway demonstrated a 96.3% agreement with BMD, whereas BD Phoenix demonstrated an 88.8% agreement.[77] The Etest method had the lowest agreement with BMD, at 76.4% (results were consistently higher by 1 to 2 dilutions). The Etest will likely produce a higher value (0.5 to 2 dilutions higher) than BMD. In another study, 92% of the strains were demonstrated to have a vancomycin MIC of 1 mg/L by BMD; corresponding figures were 70% for MicroScan WalkAway and Etest and 41% for Vitek 1.[78]

Rybak et al[79] compared MicroScan WalkAway, Vitek 2, BD Phoenix, and Etest to BMD methods among 200 MRSA strains. In contrast to previous studies, these investigators used an absolute agreement definition of ±0 log_2 dilution error to better characterize the precision. Using this definition, results with BD Phoenix and MicroScan WalkAway had the highest agreement with BMD (66.2% and 61.8%, respectively), followed by Vitek 2 (54.3%). As noted above, Etest tended to produce results that were 1 to 2 dilutions higher (agreement with BMD was 36.7%). However, when compared to BMD, Etest identified a MIC of 2 mg/L 80% of the time. When compared to BMD, MicroScan WalkAway (prompt method)

overcalled MIC values of 1 mg/L by 74.1%, and BD Phoenix and Vitek 2 undercalled MIC values of 2 mg/L by 76% and 20%, respectively.

The high variability of MIC results among the 4 systems compared to BMD clearly poses a challenge to the clinician making treatment decisions based on MIC and poses questions as to the most relevant MIC method.[79] This variability between MIC values and testing methods routinely performed at most institutions further supports the use of AUC (assuming a MIC_{BMD} of 1 mg/L) to guide vancomycin empiric dosing. For nonserious infections, this variability may be inconsequential. In a critically ill patient infected by MRSA, who may require prompt achievement of the target AUC/MIC, it is imperative to verify the MIC by a standardized method (preferably BMD, as Etest may result in a higher MIC than BMD) as soon as possible to avoid a delay in effective therapy. An AUC/MIC_{BMD} of 400 to 600 is approximately equivalent to an AUC/MIC_{Etest} of 200 to 400, reflecting values that are 1 to 2 dilutions higher than those yielded by Etest. Furthermore, there are no data to support decreasing the dose to achieve the targeted AUC/MIC of 400 to 600 if the MIC is less than 1 mg/L.

Summary and recommendations:

6. *Based on current national vancomycin susceptibility surveillance data, under most circumstances of empiric dosing, the vancomycin MIC should be assumed to be 1 mg/L. When the MIC_{BMD} is >1 mg/L, the probability of achieving an AUC/MIC target of ≥400 is low with conventional dosing; higher doses may risk unnecessary toxicity, and the decision to change therapy should be based on clinical judgment. In addition, when the MIC_{BMD} is <1 mg/L, we do not recommend decreasing the dose to achieve the AUC/MIC target. It is important to note the limitations in automated susceptibility testing methods, including*

the lack of precision and variability in MIC results depending on method used (B-II).

Continuous Infusion vs Intermittent Infusion

Administration of vancomycin by continuous infusion (CI) has been evaluated as an alternative to intermittent infusion (II) with potential advantages of earlier target attainment, less variability in serum concentrations, ease of drug level monitoring (less dependence on sampling time or multiple concentrations to calculate AUC), and lower the potential risk of AKI.

Comparative studies. Published studies that compared intermittent to continuous administration primarily focused on 2 distinct populations, adult critically ill patients in the ICU with suspected or documented infections and those receiving outpatient antimicrobial therapy (OPAT) for bone and joint infections.[80-89] Most studies compared CI to II for the risk of AKI and attainment of target serum concentrations; only 4 studies included other outcome endpoints such as treatment failure and mortality.[80,84,87,89] Measures of vancomycin drug exposure reported in clinical trials include trough and average steady-state concentrations and AUC_{24}. One challenge when comparing clinical outcomes between CI and II is the lack of consistent reporting of exposure parameters between groups treated using the 2 dosing strategies. For CI, the most commonly reported drug exposure parameter was the steady-state concentration, while for II it was the trough concentration. For future investigations it would be beneficial to report AUC and/or average steady-state concentration for both CI and II groups to enable direct comparison of drug exposure between groups and correlate with efficacy and safety endpoints.

Critically ill patients. A total of 7 studies compared CI vs II of vancomycin in critically ill patients.[81-87] Only one study, by Wysocki et al,[80] evaluated both efficacy and safety in a prospective randomized trial comparing

vancomycin CI ($n = 61$) and II ($n = 58$) in 119 patients. Most patients had pneumonia or bacteremia, mostly due to MRSA. Mean serum steady-state and trough concentrations attained were 24 mg/L and 15 mg/L, respectively, for both the CI and II groups. AUC_{24} values were comparable between the CI and II groups, with significantly less variability in the CI group ($P = 0.026$). Clinical failure rates were similar in the CI and II groups on day 10 (21% vs 26%) and at end of treatment (21% vs 19%), although the mean AUC_{24} was shown to be lower in the CI group than in the II group (596 [SD, 159] mg·h/L vs 685 [SD, 260] mg·h/L, $P < 0.05$). Nephrotoxicity occurred in 18% of patients overall, with similar rates in the CI and II groups (16% vs 19%). However, dialysis was required more often in those who received CI vs II (6 of 10 patients vs 3 of 11 patients). Risk factors for nephrotoxicity such as diabetes and concomitant diuretic, aminoglycoside, and iodine use were similar between groups. It is notable that the study only had 23% power to detect a difference in clinical outcomes between groups.[1]

Another study compared mortality among critically ill burn patients receiving CI ($n = 90$) or II ($n = 81$).[84] Mortality rates in the hospital and on days 14 and 28 were numerically higher for those receiving CI, but the differences did not reach statistical significance (10% vs 6.2%, 18.9% vs 11%, and 32% vs 21%, respectively). However, when mortality was compared by treatment indications, those who received CI for non–gram-positive sepsis had significantly higher mortality (70% vs 16.7%, $P = 0.001$); nearly half of this subgroup had gram-negative bacteremia or candidemia. It is possible that the difference in outcome may be attributed to differences in the management of those infections and not directly related to vancomycin administration. Nephrotoxicity occurred numerically less frequently in the CI group than in the II group (percentage of patients with increase in Scr of 0.5 mg/dL at end of therapy, 6.7% vs 14.8%). While higher mean vancomycin concentrations were noted in the CI

group relative to the II group (20 [SD, 3.8] mg/L vs 14.8 [SD, 4.4] mg/L, $P < 0.001$), which would be expected when comparing steady-state and trough concentrations, AUC_{24} was not reported, thereby precluding comparison of drug exposure between the CI and II groups.

Five other studies compared serum drug concentrations achieved and the risk of nephrotoxicity between CI and II in critically ill patients.[81-83,85,86] As expected, the ranges of measured vancomycin concentrations from the studies were significantly higher in the CI groups than in the II groups (steady-state concentrations of 20-25 mg/L vs troughs of 10-15 mg/L, respectively). Another study showed that a higher percentage of patients attained a vancomycin concentration of >20 mg/L at least once during the treatment course with CI vs II administration (63.2% vs 44.9%, $P = 0.065$).[82] One study reported lower mean AUC_{24} with CI vs II (529 [SD, 98] mg·h/L vs 612 [SD, 213] mg·h/L, P value not stated), and increased steady-state concentration compared with trough (25 ± 4 vs 17 ± 4.7 mg/L, respectively, $P = 0.42$) with CI vs. II.[83] The discordance observed in the relationship of trough concentration and AUC_{24} underscores the importance of measuring AUC_{24} to compare relative drug exposure with CI vs II in future studies.

In general, the rate of nephrotoxicity was reported to be similar or numerically lower with CI vs II administration (range, 4%-16% vs 11%-19%); the same trend but higher rates were reported in studies that applied the AKIN criteria for nephrotoxicity (26%-28% vs 35%-37%).[81-83,85,86] In addition, Saugel et al[85] noted significantly less frequent need for renal replacement therapy (RRT) during vancomycin treatment for patients in the CI group than for those in the II group (7% [7 of 94 patients] vs 23% [12 of 52 patients] required RRT; $P = 0.007$). Of interest, in the largest retrospective study comparing CI and II, conducted in 1,430 ICU patients, Hanrahan et al[86] reported a higher rate of nephrotoxicity in those receiving CI vs II (25% [161 of 653 patients] vs 20% [77 of 390 patients]; $P = 0.001$); bivariate analysis indicated that every

1-mg/L increase in serum concentration was associated with an 11% increase in the risk of nephrotoxicity, with lower odds in those receiving II. However, logistic regression analysis indicated the contrary in that II was associated with an 8-fold higher odds of nephrotoxicity (95% confidence interval, 2.87-23.41). The lack of information provided on confounding variables such as receipt of concomitant nephrotoxins and relative AUCs between treatment groups preclude drawing a definitive conclusion regarding the safety of CI, especially in light of the disparate results of bivariate and logistic regression analyses.

Patients receiving OPAT. To date there have been 2 studies comparing the efficacy of vancomycin administration by CI vs II in patients whose therapy was initiated in the hospital and continued as OPAT. Duration of therapy ranged from 30 days to 14 weeks.[87,89] Most patients were treated for bone and joint and skin structure–related infections. In a small prospective study, rates of osteomyelitis cure, defined as remaining asymptomatic 12 months after completion of therapy, did not differ significantly between groups (94% vs 78%, $P = 0.3$), but only 27 patients were evaluable.[87] Another study retrospectively evaluated the efficacy of vancomycin in patients with MRSA infections; most had bone and joint and skin structure–related infections, while 10% had bloodstream infections or endocarditis.[89] Rates of clinical failure were similar in the CI and II groups (19% [25 of 133 patients] vs 25% [9 of 36], $P = 0.41$) after excluding 29% of study patients who had subtherapeutic serum vancomycin concentrations for more than 1 week. However, it is not clear how frequent serum concentrations were monitored, if in-hospital treatment duration before OPAT differed between groups, and whether treatment success rates differed by type of infection.

In studies that evaluated the safety of CI vancomycin as OPAT, treatment duration ranged from 4 to 14 weeks, with a reported average mean steady-state serum concentration of 13 to 30 mg/L.[87,88] In a retrospective matched cohort study

of 80 patients, a trend towards less frequent occurrence of nephrotoxicity was observed in the CI group vs the II group (10% vs 25%, $P = 0.139$), and when nephrotoxicity did occur it had a later onset in the CI group ($P = 0.036$).[88] Patients were matched by age, comorbid conditions, gender, baseline Scr, and receipt of concurrent nephrotoxins; those who had an Scr of ≥1.5 mg/dL at baseline, developed nephrotoxicity as inpatients prior to OPAT, or experienced hypotension resulting in renal dysfunction were excluded. In another retrospective study,[90] the same investigators identified a steady-state average concentration of 28 mg/L as the threshold breakpoint for the development of nephrotoxicity using CART (classification and regression tree) analysis: Nephrotoxicity occurred in 71.4% (5 of 7) and 11.6% (11 of 95) patients with steady-state concentrations of ≥28 mg/L and <28 mg/L, respectively. In one prospective study of an elderly cohort (mean age, 70 years) receiving high-dose vancomycin therapy by CI, with targeting of a steady-state concentration of 30 to 40 mg/L for a median duration of 6 weeks, nephrotoxicity occurred in 32% of patients. Additionally, 4 patients in that study developed leukopenia.[91]

Dosing and other considerations for use of CI. Most published studies of critically ill patients receiving vancomycin CI employed a loading dose of 15 to 20 mg/kg followed by daily maintenance infusions at doses of 30 to 40 mg/kg (up to 60 mg/kg) to achieve a target steady-state concentration of 20 to 25 mg/L. By simply multiplying the steady-state concentration by 24, a target steady-state concentration of 20 to 25 mg/L would equate to an AUC_{24}/ MIC of 480 to 600 (assuming a MIC of 1 mg/L). Of note, the PK/PD target for CI has not been validated. All of the PK/ PD data supporting an AUC_{24}/MIC ratio of >400 as the best correlate for clinical outcomes were derived from patients who received II vancomycin dosing.

Rapid attainment of target serum concentrations has been cited as a potential advantage of CI over II when treating acute infections, particularly

in ICU patients early during the course of infection. In 2 comparative studies, target steady-state concentrations of 20 to 25 mg/L were achieved more rapidly with use of CI vs II: in a mean time of 36 (SD, 31) hours vs 51 (SD, 39) hours ($P = 0.03$) in one study and 16 (SD, 8) hours vs 50 (SD, 21) hours ($P < 0.001$) in the other.[81,83] Importantly, less variability in the steady-state concentration and fewer blood samples (a single steady-state concentration vs both peak and trough concentrations) are required to calculate AUC_{24} among patients receiving CI vs II. Timing of blood sampling for trough determinations is critical during II, whereas steady-state concentration can be measured any time after steady state has been reached during CI. In addition, vancomycin administration by CI in patients receiving OPAT has the theoretical advantage of a need for less frequent access to the i.v. catheter and thus less complications resulting from thrombus formation or infections. On the other hand, incompatibility of vancomycin with certain drugs (particularly at high concentrations), that are commonly administered in the critical care setting is a notable challenge of vancomycin CI.[92,93] The use of proper concentration, alternative agents, independent lines, or multiple catheters may be warranted if vancomycin is to be administered by CI.

Summary and recommendations:

7. *The pharmacokinetics of CI suggest that such regimens may be a reasonable alternative to conventional II dosing when the AUC target cannot be achieved (B-II). Based on currently available data, a loading dose of 15 to 20 mg/kg, followed by daily maintenance CI of 30 to 40 mg/kg (up to 60 mg/kg) to achieve a target steady-state concentration of 20 to 25 mg/L may be considered for critically ill patients (B-II). AUC_{24} can be simply calculated by multiplying the steady-state concentration (ie, the desired therapeutic range of 20 to 25 mg/L throughout the entire dosing interval) by a factor of 24. Attaining the desired drug exposure may be more readily accomplished given the ease of sampling time and dosage adjustment by changing the rate of infusion, which is a highly desirable feature in critically ill patients (B-II).*

8. *The risk of developing nephrotoxicity with CI appears to be similar or lower than that with intermittent dosing when targeting a steady-state concentration of 15 to 25 mg/L and a trough concentration of 10 to 20 mg/L (B-II). Definitive studies are needed to compare drug exposure based on measured AUC_{24} and factors that predispose to development of nephrotoxicity, such as receipt of concomitant nephrotoxins, diuretics, and/or vasopressor therapy in patients receiving CI vs II of vancomycin.*

9. *Incompatibility of vancomycin with other drugs commonly coadministered in the ICU requires the use of independent lines or multiple catheters when vancomycin is being considered for CI (A-III).*

Loading Doses

Loading doses of vancomycin have been evaluated in several studies during the past decade.[94-109] Providing loading doses of 20 to 35 mg/kg based on actual body weight rapidly achieves targeted ranges of serum vancomycin concentrations and decreases the risk of subtherapeutic concentrations during the first days of therapy. Loading doses are recommended in patients who are critically ill or in the ICU,[95-102] require dialysis or renal replacement therapy,[102-106] or are receiving vancomycin CI therapy.[94-98,105,108] 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. Vancomycin should be administered in a dilute solution (eg, concentrations of no more than 5 mg/mL) and infused over a period of not less than 60 minutes or at a rate of 10 to 15 mg/min (≥1 hour per 1,000 mg) to minimize infusion-related adverse events. An infusion rate of 10 mg/min or less is associated with fewer infusion-related events. Loading doses of 25 to 35 mg/kg will require infusion times of at least 2 to 3 hours.[99] After administration of the loading dose, the initiation of the maintenance dose should occur at the next dosing interval (eg, an interval of every 6 hours indicates initiating the maintenance dose 6 hours after the start of the loading dose).

In most studies that have employed loading doses, vancomycin dosing was based on actual body weight. While this practice is commonplace, dosing by actual body weight assumes there is a linear relationship between key population PK parameters (ie, V_d and clearance) and the body size descriptor employed. While a wide variety of actual weight–based estimates of V_d (for example, 0.4 to 1 L/kg) have been reported in the literature,[6] mounting data suggest that it is not entirely accurate to describe vancomycin V_d as being proportional to body weight, particularly among obese patients (refer to Dosing in Obesity section). As noted in several recent articles discussing vancomycin PK in obesity, as weight increases the coefficient used to calculate V_d decreases.[48,110,111] At this point, dosing should be based on actual body weight, with doses capped at 3,000 mg (refer to Dosing in Obesity section.[112] More intensive therapeutic monitoring should also be performed in obese patients.

Summary and recommendations:

10. *In order to achieve rapid attainment of targeted concentrations in critically ill patients with suspected or documented serious MRSA infections, a loading dose of 20 to 35 mg/kg can be considered for intermittent-infusion administration of vancomycin (B-II).[1]*

11. *Loading doses should be based on actual body weight and not exceed 3,000 mg (refer to Dosing in Obesity section). More intensive and early therapeutic monitoring should*

also be performed in obese patients (B-II).

Dosing in Obesity

The original vancomycin dosing strategies predate our current definitions of obesity and understanding of drug pharmacokinetics in obesity. Obesity is defined as a body mass index (BMI) of ≥30 kg/m² and is currently divided into 3 tiers: class I obesity (30.0-34.9 kg/m²), class II obesity (35.0-39.9 kg/m²), and class III, or morbid, obesity (≥40 kg/m²).[113] The prevalence of obesity increased from approximately 10% in the 1950s to 39.8% in 2015-2016, and the average US adult weighs approximately 83 kg, compared to the historical standard of 70 kg.[114,115] This shift in the distribution of body size is relevant to the calculation of vancomycin doses based on patient body weight. Obesity may be associated with an increased risk of vancomycin-induced nephrotoxicity, in part due to supratherapeutic exposure resulting from maintenance doses calculated using actual body weight.[45,116]

The selection of vancomycin loading dose is dependent on the estimated V_d. Pharmacokinetic studies have repeatedly demonstrated that the vancomycin V_d increases with actual body weight; however, this PK parameter does not increase with actual body weight in a proportionate manner and is not reliably predictable in obese individuals.[111,117-121] Blouin and colleagues[111] demonstrated a statistically significant difference in weight-indexed V_d between obese and nonobese patients. Similarly, using data from 704 patients, Ducharme and colleagues[118] found that mean weight-indexed vancomycin V_d decreased with increasing body size. The average weight-indexed V_d in a study by Bauer and colleagues[119] was much lower in 24 morbidly obese patients (0.32 L/kg) than in 24 patients of normal weight (0.68 L/kg, $P < 0.001$). Recent studies in obese adults corroborate these findings and suggest that lower V_d estimates of approximately 0.5 L/kg or weight-independent central

tendency estimates approaching 75 L are observed in obese adults.[112,120,121] The nonlinear relationship between vancomycin V_d and body weight can be resolved with piecewise functions of alternate weight descriptors, allometric scaling, use of lower mg/kg doses with increasing body size, or capping the dose at a threshold.[118,122] The underlying rationale for a loading dose is rapid attainment of therapeutic concentrations. Therefore, using actual body weight–based loading doses of 20 to 25 mg/kg (doses lower than previously recommended), with consideration of capping doses at 3,000 mg, is the most practical strategy in obese patients with serious infections.[112] For example, this strategy would result in calculated loading doses of 1,500 to 2,500 mg in patients weighing 80 to 99 kg, 2,000 to 3,000 mg in those weighing 100 to 119 kg, and 2,500 to 3,000 mg in patients with a weight of ≥120 kg (doses rounded to the nearest 250 mg). The decision of whether or not to employ a loading dose, as well as the magnitude of this dose, should be driven by the severity of infection and the urgency to achieve a therapeutic concentration rather than by body size alone.

Empiric maintenance dosing of vancomycin is reliant on estimated CL. Vancomycin CL is predicted by kidney function, which is most commonly estimated as CL_{cr} with the Cockcroft-Gault equation using patient age, sex, Scr, and body size.[123] There is considerable controversy regarding the optimal body size metric for this calculation in obese patients.[124] The Cockcroft-Gault equation predates the global standardization of Scr measurement traceable to isotopic-dilution mass spectrometry (IDMS) standards advocated to reduce intralaboratory and interlaboratory measurement variability.[124] A recent population PK study by Crass and colleagues[112] of obese patients (n = 346) with BMI values of 30.1 to 85.7 kg/m² and body weights of 70 to 294 kg provided an equation to estimate vancomycin CL based on age, sex, Scr (IDMS traceable), and allometrically scaled body weight. This model or similar

approaches to estimating vancomycin CL, such as that defined by Rodvold and colleagues,[125] can be used to estimate the total daily maintenance dose. The population model–estimated vancomycin CL multiplied by the target AUC estimates the initial daily maintenance dose.[112,120,122] For example, studies report an average vancomycin CL of approximately 6 L/h in obese patients that equates to achieving an AUC of approximately 500 mg·h/L with a daily dose of 3,000 mg. Empiric vancomycin maintenance dosages above 4,500 mg/day are not expected in obese adults, because vancomycin CL rarely exceeds 9 L/h.[112,120,121]

Population PK models of vancomycin cannot account for more than 50% of the interindividual variability, which supports therapeutic drug monitoring (TDM) in this population.[117,118,120,122] A reliable estimate of vancomycin V_d is necessary for AUC estimation when AUC is based solely on a trough concentration measurement.[24,121,126,127] This bias is addressed and precision is improved by measurement of both a peak (collected at least 1 hour after the end of infusion) and a trough concentration to estimate AUC accurately in obese patients.[126] Once a reliable PK estimate of vancomycin elimination is determined by using these 2 concentration measurements, subsequent vancomycin AUC estimation is achievable with trough-only measurements by Bayesian methods in physiologically stable patients.[57] For critically ill obese patients with unstable physiology, additional work to design adaptive feedback models to tailor doses is needed.

Summary and recommendations:

12. *A vancomycin loading dose of 20 to 25 mg/kg using actual body weight, with a maximum dose of 3,000 mg, may be considered in obese adult patients with serious infections (B-II). Initial maintenance doses of vancomycin can be computed using a population PK*

estimate of vancomycin clearance and the target AUC in obese patients. Empiric maintenance doses for most obese patients usually do not exceed 4,500 mg/day, depending on their renal function (B-II). Early and frequent monitoring of AUC exposure is recommended for dose adjustment, especially when empiric doses exceed 4,000 mg/day (A-II). Measurement of peak and trough concentrations is recommended to improve the accuracy of vancomycin AUC estimation and maintenance dose optimization in obese patients, aligning with recommendations 2 and 5 for nonobese adults.

Renal Disease and Renal Replacement Therapies

Intermittent hemodialysis. Despite the common use of vancomycin in patients receiving hemodialysis, there are few published outcome studies that provide guidance on the optimal PK/PD targets in this population. Previously published drug dosing recommendations generally targeted a predialysis serum concentration, even though other PD targets may be more appropriate. Predialysis vancomycin concentration to MRSA MIC ratios of >18.6 have been associated with improved bacteremic patient outcomes, suggesting that serum concentration monitoring is essential throughout the course of therapy.[128] Dosing to achieve predialysis vancomycin concentrations of 10 to 20 mg/L, as has been done clinically,[129] results in mean AUC_{24} values ranging from 250 to 450 mg·h/L, with some values below the AUC/MIC goals recommended in other populations.[130] Outcome studies validating the AUC_{24h} goal of 400 to 600 mg·h/L used in other patient populations have not been conducted in the hemodialysis population. Nonetheless, the maintenance doses recommended in this section aim to reach this AUC_{24} target (ie, 400-600 mg·h/L), as recommended throughout this document.

Many dialysis-related factors affect the degree of vancomycin exposure in

these patients. These considerations include the amount of time between vancomycin dose administration and the scheduled time of the next dialysis session,[104] whether the dose is given during dialysis or after hemodialysis has ended, and the dialyzer's permeability if the dose is administered intradialytically.[131] Dialysis frequency also plays a role in dosing decisions. For non–critically ill patients receiving hemodialysis, 2 or 3 days is the most common interdialytic period. Some critically ill patients with severe catabolism and AKI may require more than thrice-weekly hemodialysis for optimal metabolic control, and their maintenance vancomycin doses should be based on serum concentration monitoring.[132]

Vancomycin dosing in patients with acute or chronic kidney failure has transformed over time due to the changes in dialysis technology and techniques.[133] Older (pre-1990s) hemodialyzers were not very permeable to large molecules. Vancomycin (with a molecular weight of 1,450 Da) was not considered "dialyzable" because it poorly crossed the hemodialysis membranes of the era. Indeed, even today's vancomycin package insert, based on PK studies conducted in the 1980s, states that "vancomycin is poorly removed by dialysis."[134] As hemodialysis membrane technology has improved, dialyzers have become far more permeable. Vancomycin is cleared substantially by contemporary high-permeability hemodialyzers[135,136]; consequently, vancomycin dosing strategies have changed substantially as well. For example, in spite of the package insert statement "In anuria, a dose of 1000 mg every 7 to 10 days has been recommended" and the statement that "vancomycin is poorly removed by dialysis,"[134] far more frequent doses are needed to maintain therapeutic serum concentrations in patients receiving hemodialysis. The extent of vancomycin removal by dialysis is dependent on the permeability of the hemodialyzer used[131]; consequently, investigators have developed

and published a wide variety of vancomycin dosing protocols in an attempt to compensate for the increase in vancomycin dialytic CL caused by increases in dialyzer permeability.

An added complication of appropriate vancomycin dosing in patients receiving hemodialysis is the prevailing practice of administering the drug during the final hours of the hemodialysis process, thus resulting in some of the infused drug being removed immediately by the hemodialyzer. This practice started back when low-permeability dialyzers were used and little vancomycin was eliminated by hemodialysis. The practice has persisted at most dialysis units because most dialysis units treat 3 shifts of patients per day, and holding a dialysis chair for 60 to 90 additional minutes while vancomycin infuses into a patient is not cost-effective. Indeed, it is more cost-effective to infuse "extra" vancomycin during the hemodialysis session to compensate for intradialytic loss than it is to keep a dialysis unit open later to allow vancomycin infusions. Intradialytically infused vancomycin results in reduced delivery of drug to the patient, similar to a first-pass phenomenon. The extent of intradialytic drug removal is variable and depends on patient and dialysis system factors, the most important of which is dialyzer membrane permeability.[135,137-139] Approximately 20% to 40% of an intradialytically administered vancomycin dose is removed by the simultaneous hemodialysis, with the highly permeable dialyzers tending to the higher end of this range.[137,140,141]

Maintenance dosing strategies that do not provide a dose with every hemodialysis session (eg, a maintenance dose is given with every second or third hemodialysis session) have been studied,[102,142,143] but none have been found to meet vancomycin exposure goals in the last day of the dosing interval without giving massive doses that result in very high peak concentrations. Consequently, maintenance vancomycin doses are recommended to be administered with each hemodialysis session to ensure therapeutic serum concentrations throughout the dosing interval. In the typical

thrice-weekly hemodialysis schedule, 25% larger doses are needed for the 3-day interdialytic period (eg, Friday to Monday) to maintain sufficient vancomycin exposure on the third day.[130,144]

Dosing that is weight based appears to be superior to standard dosing schemes that do not account for patient size. Further, doses should be based on actual body weight rather than a calculated body weight (see Dosing in Obesity section for considerations on how to dose morbidly obese patients). Because vancomycin is water soluble, vancomycin dosing in fluid overloaded patients should also be based on actual body weight at the time of dosing rather than on some calculated adjusted weight.[102-105]

Serum concentration monitoring is a valuable tool to guide vancomycin dosing in patients receiving dialysis, provided that serum concentrations are obtained and interpreted correctly. For example, blood sampling for assessment of vancomycin concentrations should not occur during or for at least 2 hours after a hemodialysis treatment. These samples will not be reflective of the true vancomycin body load because of the dialytic removal of vancomycin. Vancomycin serum concentrations will be low immediately following a dialysis treatment but will rebound substantially as drug redistributes from the tissues back to the blood over the next few hours.[131,142,145] Dosing decisions based on serum concentrations obtained during or soon after hemodialysis will be inherently incorrect and could result in administration of doses higher than necessary.[145] Serum concentration monitoring performed with blood samples obtained prior to the hemodialysis treatment is recommended to guide dosing, although other serum concentration monitoring techniques have been suggested.[146]

Dosing to achieve predialysis vancomycin concentrations of 10 to 20 mg/L, as has been conducted clinically,[129] results in mean AUC_{24} values ranging from 250 to 450 mg·h/L, often below the AUC/MIC goals recommended in other populations.[130] Outcome studies validating the AUC target of 400 to 600 mg·h/L used in

other patient populations have not been conducted in the hemodialysis population. While determination of AUC/MIC attainment is recommended, limited serum concentration monitoring is possible in patients receiving hemodialysis in the outpatient setting for 2 reasons. The first reason is that frequent phlebotomy must be avoided in order to preserve future hemodialysis vascular access needs; the second is that it is impractical to obtain blood samples aside from the predialysis sample that is obtained from the blood catheter inserted for use in the dialysis process. Patients leave the dialysis unit after hemodialysis and do not return until the next dialysis session days later. Consequently, since data are unavailable for an optimal AUC target in these patients, and no data are available to demonstrate efficacy below an AUC threshold value of 400, the goal should be to attain the AUC target of 400 to 600 mg·h/L used in other patient populations. It is most practical to continue monitoring based on predialysis concentrations and extrapolate these values to estimate AUC. Maintaining predialysis concentrations between 15 and 20 mg/L is likely to attain the AUC target of 400 to 600 mg·h/L in the previous 24 hours, with higher AUC/MIC values occurring on days prior.

Summary and recommendations:

13. *The following tabulation outlines recommended vancomycin loading and maintenance doses for patients receiving hemodialysis, with accounting for permeability of the dialyzer and whether the dose is administered intradialytically or after dialysis ends (B-II).*

Timing and Dialyzer Permeability	Vancomycin Dose, mg/kg[a]
After dialysis ends	
Low permeability	Loading: 25 Maint.: 7.5[b]
High permeability	Loading: 25 Maint.: 10[b]

Timing and Dialyzer Permeability	Vancomycin Dose, mg/kg[a]
Intradialytic	
Low permeability	Loading: 30 Maint.: 7.5-10[b]
High permeability	Loading: 35 Maint.: 10-15[b]

[a]From references 104, 129, 130, 137, 138, 140, and 147.
[b]Thrice-weekly dose administration.

14. *Since efficacy data are unavailable for AUC values of <400 mg·h/L, monitoring based on predialysis serum concentrations and extrapolating these values to estimate AUC is most practical. Maintaining predialysis concentrations between 15 and 20 mg/L is likely to achieve the AUC of 400 to 600 mg·h/L in the previous 24 hours (C-III). Predialysis serum concentration monitoring should be performed not less than weekly and should drive subsequent dosing, as opposed to a strict weight-based recommendation, although these recommended doses provide a useful starting point until serum concentrations have been determined (B-II).*

Hybrid hemodialysis therapies. Contemporary renal replacement therapies used to treat kidney disease have expanded well beyond thrice-weekly, 3- to 4-hour hemodialysis sessions. In the outpatient setting, shorter, more frequent home hemodialysis treatments are used in a growing number of patients. In the inpatient setting, various types of "hybrid" hemodialysis therapies are employed. These hybrid treatments go by many names, including prolonged intermittent renal replacement therapy (PIRRT) and slow-low efficiency dialysis (SLED). Essentially these hybrid therapies use standard hemodialysis machines that run at slower blood and dialysate flow rates and for longer durations (usually 6 to 12 hours per day). Even hemodialysis itself differs in the inpatient and outpatient settings, as patients with AKI

are often hemodynamically unstable and lack sufficient vascular access for robust blood flow through the dialysis vascular access. All these hybrid dialysis therapies clear vancomycin to a different extent than standard intermittent hemodialysis.[148,149] The timing of the vancomycin dose in relation to the hybrid hemodialysis session is essential in determining a dosing regimen. If hybrid hemodialysis is started soon after the dose is administered, much of the dose will be removed, whereas the same vancomycin dose given after the dialysis session ends will yield a much larger AUC_{24} and much higher average serum concentrations. As is the case with any hemodialysis therapy, serum concentrations obtained during or within 2 hours from the end of hemodialysis will be artificially low because dialysis will have efficiently removed vancomycin from the blood, and vancomycin located in the tissues will not have had time to redistribute back into the bloodstream. Calculation of maintenance doses based on an intra- or postdialytic vancomycin serum concentration may result in doses that are too high. Caution is recommended in basing any maintenance dosing on these serum concentration values.

Little has been published on the patient outcomes achieved when vancomycin is used in patients receiving hybrid dialysis. Authors of one small case series of 27 courses of vancomycin given to patients receiving a hybrid hemodialysis therapy reported that prescribers have tried a wide variety of dosing schemes.[150] By these authors' criteria, 89% of the prescribed vancomycin doses in their institution were too low. Given the absence of outcome data in patients receiving these therapies, it seems prudent to use the same vancomycin AUC goal recommended throughout this document (400 to 600 mg·h/L assuming a MIC of 1 mg/L).

Summary and recommendations:

15. *Loading doses of 20 to 25 mg/kg actual body weight should be used,* *recognizing that these hybrid dialysis therapies efficiently remove vancomycin (B-III). Initial doses should not be delayed to wait for a dialysis treatment to end. Maintenance doses of 15 mg/kg should be given after hybrid hemodialysis ends or during the final 60 to 90 minutes of dialysis, as is done with standard hemodialysis (B-III).[130] Concentration monitoring should guide further maintenance doses.*

Continuous renal replacement therapies. The use of continuous renal replacement therapy (CRRT) modalities like continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF) has grown in popularity in critically ill patients with AKI because of their superior ability to provide fluid and solute balance. Provided these therapies operate in an uninterrupted fashion, vancomycin CL is relatively constant over the dosing interval, although CL may decline as the hemodiafilter clogs over time.[151] Vancomycin is removed by CRRT and its CL is related closely to the rate of ultrafiltrate/dialysate flow,[105] with hemodiafilter type being of lesser importance, because contemporary hemodiafilters are all very permeable to the drug.

In patients on CRRT, serum concentration attainment goals often are not met with conventional dosing.[84,152] Although outcomes studies specific to patients receiving CRRT have not been conducted, it seems prudent to apply the same vancomycin AUC/MIC target (ie, 400-600) in these critically ill patients as is recommended throughout this document.

Summary and recommendations:

16. *Loading doses of 20 to 25 mg/kg by actual body weight should be used in patients receiving CRRT at conventional, KDIGO-recommended effluent rates of 20 to 25 mL/kg/h (B-II).[153] Initial maintenance dosing for CRRT with effluent rates of 20 to 25 mL/kg/h should be 7.5* *to 10 mg/kg every 12 hours (B-II). Maintenance dose and dosing interval should be based on serum concentration monitoring, which should be conducted within the first 24 hours to ensure AUC/MIC targets are met.[154] In fluid overloaded patients, doses may be reduced as patients become euvolemic and drug V_d decreases. The use of CI of vancomycin in patients receiving CRRT appears to be growing,[84,105] and this method could be used in place of intermittent vancomycin dosing, especially when high CRRT ultrafiltrate/dialysate flow rates are employed (B-II).*

Pediatric Patients

In 2011, prior to the availability of alternative agents for MRSA in pediatrics, vancomycin was recommended as the drug of choice for invasive MRSA infections in children.[5] Although there are limited prospective, comparative data on the value of vancomycin therapeutic monitoring in adults with respect to improving outcomes and decreasing toxicity, virtually no prospectively collected data on outcomes of MRSA infection in newborns, infants and children exist. Further, for newborns (particularly premature infants) compared with older infants, immature renal elimination mechanisms and a relative increase in V_d by body weight further complicate dosing guidelines during the first several weeks of life. Additional complexity for dosing strategies during early childhood is based on a continual maturation of glomerular filtration, which is directly related to vancomycin CL. The glomerular filtration rate increases through the first years of life to rates in school-aged children that are greater than those in adults, with subsequent decline during the teen years to adult normal rates. Such a diversity of PK parameter values based on developmental pharmacology from neonates to adolescents provides a challenge to develop generalized vancomycin dosing. However, this has improved with the application of population-based PK models using allometric scaling and renal maturation

covariates. In a population-based PK study by Colin and colleagues[155] that evaluated vancomycin PK throughout the entire age continuum from infancy to geriatric years using pooled data from 14 studies, age, weight, and kidney function were important factors in estimating clearance. Careful monitoring in the pediatric population is prudent, especially with the evident dynamic changes in renal function in this population. As with adults, comorbidities and concurrent medications can influence vancomycin tissue distribution, elimination, and toxicity.

Limitation of outcomes data. Recent retrospective studies on bacteremic *S. aureus* infections (both MRSA and MSSA strains) in children treated with vancomycin suggest that trough concentrations of >15 mg/L were not associated with improved outcomes, yet an increase in AKI was observed.[156-158] Furthermore, another retrospective pediatric study evaluating outcomes of MRSA bacteremia as a function of an AUC/MIC$_{BMD}$ of ≥400 did not show improved outcomes.[159] Similarly, vancomycin trough concentrations of <10 mg/L, as compared with concentrations of >10 mg/L, were not associated with increased 30-day mortality and recurrent bacteremia in children, although the lower concentrations were associated with prolonged bacteremia.[160]

In the absence of prospective, comparative outcomes data in children regarding unique AUC/MIC exposures necessary for clinical and microbiologic success in treating serious MRSA infections in different neonatal and pediatric populations to validate the observations reported in adults (see Clinical PK/PD Data: Adults section), dosing in children should be designed to achieve an AUC of 400 mg·h/L and potentially up to 600 mg·h/L (assuming a MIC of 1 mg/L). This PD target range, specifically a range closer to an AUC/MIC of 400 rather than 600, has been widely used by investigators to model pediatric dosing and therapeutic monitoring. With inadequate PK studies

and outcomes data to support the higher end of the AUC target range in pediatrics, it is prudent to aim for an AUC/MIC of 400 in pediatrics to limit the development of exposure-related AKI. Furthermore, in pediatrics, an AUC/MIC target of 400 is more readily achievable than it is in adults and correlates to trough concentrations of 7 to 10 mg/L rather than concentrations of 15 to 20 mg/L as are reported in adults. This wide variability in trough concentrations between these populations with regard to achieving an AUC/MIC of 400 corroborates the need for an AUC-guided approach to dosing and monitoring. It is possible that in otherwise healthy children with fewer comorbidities than are typically seen in adults, a lower target may yield outcomes equivalent to an AUC of 400 to 600 mg·hr/L. The decision to retain or increase AUC target exposure should be based on clinical judgment in the management of these patients.

With use of currently recommended vancomycin dosages of 45 to 60 mg/kg/day, widespread treatment failures in children have not been reported in the literature, which may be reflective of a younger host with a more robust systemic and immunologic response to infection, a different management approach (surgical and antibiotic) to invasive MRSA infection, lack of associated comorbidities, or publication bias. Prospective comparative clinical trials involving children with documented infections treated with different vancomycin dosages or exposures have not been published.

Empiric maintenance regimen. Published retrospective PK/PD data in children suggest that current vancomycin dosing of 45 to 60 mg/kg/day (in divided doses administered every 6 to 8 hours) may be insufficient to achieve currently recommended targets for adults of an AUC of 400 to 600 mg·h/L (assuming a MIC of 1 mg/L).[1] In fact, higher dosages, ranging from 60 to 80 mg/kg/day and given in divided doses every 6 hours, may be needed to achieve these targets for MRSA strains with a vancomycin MIC

of 1 mg/L or less, presumably as a result of greater vancomycin CL than is seen in adults.[1,161-164] For children infected by MRSA pathogens with a MIC of >1 mg/L, it is unlikely that the target exposure can be reliably achieved with previously investigated dosages of vancomycin in children.

Le and colleagues[164] utilized population-based PK modeling to analyze 1,660 vancomycin serum concentrations obtained at 2 institutions from 2003 to 2011 among 702 children older than 3 months of age with varying comorbidities. They demonstrated that 4 important factors (age, weight, renal function as assessed by SCr, and MIC) contributed to vancomycin exposure. Monte Carlo simulations were created using population-based PK modeling with Bayesian estimation and MICs of clinical isolates as determined by Etest, with 85% of clinical isolates demonstrated to have a MIC$_{Etest}$ of 1 mg/L or less. To achieve an AUC/MIC$_{Etest}$ of ≥400 in 90% of subjects, a dosage of 80 mg/kg/day was necessary, particularly in those less than 12 years of age with normal renal function. At a dosage of 80 mg/kg/day, the median AUC and median trough concentration were 675 mg·h/L and 16 mg/L, respectively. As expected, subjects 12 years of age or older achieved similar exposure at lower dosages of 60 to 70 mg/kg/day. At a dosage of 60 to 70 mg/kg/day (divided doses administered every 6 hours), an AUC of 400 mg·h/L correlated to a mean trough of 8 to 9 mg/L.[164] The clinical applicability of this PK model for vancomyin CL estimation to determine AUC exposure was validated in a small study by Ploessl et al.[165]

Other studies corroborated Le and colleagues' findings regarding the need to use higher dosages, ranging from 60 to 80 mg/kg/day, depending on age and renal function.[162,164,166,167] Using the literature for vancomyin CL published in or before 2000 and Bayesian estimation for one 25-kg base subject, Frymoyer et al[163] evaluated the relationship between AUC and trough concentrations, showing that a dosage of 60 mg/kg/day achieved trough concentrations of 7 to 10 mg/L and an AUC/MIC of ≥400 in

90% of children for MRSA pathogens with a MIC of 1 mg/L. However, their finding may not be extrapolatable to the entire pediatric population given the variable ages and renal function. In a second study, these investigators demonstrated that a dosage of 60 mg/kg/day achieved AUC/MIC$_{BMD}$ values between 386 and 583 (assuming a MIC$_{BMD}$ of 1 mg/L) in children 2 to 12 years of age, indicating that some younger children may require higher doses to achieve target AUC/MIC$_{BMD}$.[162] The probability of target attainment was not provided, and dosages above 60 mg/kg/day were not evaluated in this study.

Two retrospective studies that utilized non-Bayesian methods evaluated trough concentration targets of 10 to 20 mg/L (a higher range than that used by Le et al[164] and Frymoyer et al[163], who also assessed AUC) in children 1 month to 18 years of age. An interesting finding of the study of Madigan et al[166] was that a dosage of 60 mg/kg/day achieved the target trough concentration in only 17% of preschool-aged children 2 to 5 years old, which was the lowest attainment for any pediatric age group. Eiland and colleagues[161] showed that dosages of 70 to 80 mg/kg/day were necessary to achieve trough concentrations of 10 to 20 mg/L. Another study, by Abdel et al,[168] demonstrated that dosages higher than 60 mg/kg/day were necessary to achieve an AUC/MIC of ≥400 in children with cancer. The mean age in this study cohort was 6 (SD, 2.5) years; it is possible that young age with greater CL may have been a contributing factor for the need for an increased dose, an observation uncovered in studies by Le et al[164] and Madigan et al.[166]

As a drug that demonstrates renal elimination, vancomycin requires dosage adjustment in children with acute or chronic renal insufficiency. Le and colleagues[169] conducted a population-based PK analysis with Bayesian methods that evaluated 63 case-control pairs (matched by age and weight) with 319 vancomycin serum concentrations. The mean age of this study cohort was 13 (SD, 6) years. The investigators reported that a vancomycin dosage of 45 mg/kg/day (ie, 15 mg/kg every 8 hours) in renally impaired children achieved AUC exposure similar to that achieved with a dosage of 60 mg/kg/day in children with normal renal function. Notably, they showed that in 87% of children with initial renal impairment, vancomycin CL improved (with a lag in the recovery of renal function as assessed by SCr) within the first 5 days of therapy, indicating some degree of renal function recovery, a finding that provides support for ongoing vancomycin TDM. In addition, vancomycin CL does not always correlate well with renal function (as assessed by creatinine CL) in children, particularly in those who are acutely ill in the ICU setting and have varying degrees of renal dysfunction. Rapid return of renal function may occur over the first few days after ICU admission. As such, therapeutic monitoring of both serum concentrations and renal function should be conducted during vancomycin therapy.[170,171]

Loading doses. Loading doses of 25 to 30 mg/kg for critically ill adults have been suggested to achieve steady-state concentrations more quickly, but preliminary data on pediatric patients suggest that the benefit of a loading dose of 30 mg/kg is quickly lost if the maintenance dose is insufficient to provide adequate ongoing exposure.[167] However, the concept of a loading dose accompanied by a daily maintenance dose sufficient to achieve the target exposure and initiated at a specified time after the loading dose should be investigated.

Minimizing AKI risk. Similar to the literature on adults, the literature in pediatrics suggests, in aggregate, that the risk of AKI increases as a function of vancomycin exposure, especially when the trough concentration exceeds 15 to 20 mg/L. In fact, Fiorito and colleagues[158] reported in a recent meta-analysis of 10 pediatric studies that troughs of ≥15 mg/L increased the OR for AKI by 2.7-fold (95% confidence interval, 1.82-4.05) and that AKI was further correlated with a stay in the pediatric ICU. McKamy and colleagues[172] published results of the first study that uncovered the association between vancomycin trough concentrations greater than 15 to 20 mg/L and AKI in pediatric patients. In addition, they showed that children who received concurrent nephrotoxic drugs (particularly furosemide) and stayed in the pediatric ICU were also more likely to experience AKI. Four studies published later corroborated these findings, indicating that the interplay of multiple factors in addition to vancomycin exposure contributed to AKI.[173-176] Interestingly, Sinclair et al[174] reported that a 5-mg/kg dose augmentation or each additional day of vancomycin use increased the risk of AKI. Knoderer and colleagues[173] evaluated late-onset AKI (defined as occurring after 7 days of vancomycin therapy) and observed that young age (<1 year) was independently associated with late AKI.

One pediatric study evaluated the relationship of AKI with vancomycin AUC and trough concentrations, both derived by Bayesian estimation. Le and colleagues[19] conducted a large population-based PK analysis using 1,576 serum concentrations collected from 680 pediatric subjects. A continuous exposure-response relationship was observed, with 10%, 33%, and 57% of patients who respectively achieved AUC values of ≥400, 800, and 1,000 mg·h/L experiencing AKI. Even after adjusting for ICU stay and concomitant use of nephrotoxic drugs, an AUC of ≥800 mg·h/L and trough concentrations of ≥15 mg/L were independently associated with a greater than 2.5-fold increased risk of AKI. The linkage of AUC to AKI, along with the strong correlation between AUC and trough concentrations (Spearman's coefficient, 0.963; $P < 0.001$), reinforces AUC as a plausible PK/PD parameter for therapeutic monitoring that encompasses both therapeutic and toxic responses. Vancomycin exposure should be maintained at an AUC of <800 mg·h/L to minimize AKI risk. As such, vancomycin dosages of ≥100 mg/kg/day should be avoided given that the projected median AUC and trough values are 843 mg·h/L and 21 mg/L, respectively, at a dosage of 100 mg/kg/day.[164] However, enhanced renal clearance of

vancomycin may transiently occur in specific situations in children, in which case the dose of vancomycin may need to be higher than is usually prescribed to achieve an AUC of 400 mg·h/L, highlighting the need for therapeutic monitoring.

Therapeutic monitoring. Recent literature on vancomycin in pediatrics has focused primarily on PK analysis to support optimal dosing. Le and colleagues[177] conducted a population-based PK analysis in 138 pediatric subjects who were more than 3 months of age, evaluating 712 serum vancomycin concentrations (collected mostly after the third or fourth dose). They showed that both accuracy and precision for estimating AUC_{24} (calculated by total daily dose over vancomycin CL, with the integration of Bayesian estimation) were improved using 2 concentrations (peak and trough), compared with trough-only monitoring. Furthermore, the 2-concentration approach improved the prediction of future AUC exposure in patients.[177] Another study, by Stockmann et al,[178] evaluated AUC-based vancomycin monitoring in 23 pediatric patients with cystic fibrosis. The researchers demonstrated that 2 concentrations calculated using a standard PK equation and a trough concentration calculated using a Bayesian population-based PK model produced similar AUC estimations. Despite the availability of limited studies on vancomycin monitoring in pediatrics, the findings appear congruent with adult data supporting AUC-guided therapeutic monitoring that incorporates the Bayesian method, especially if only a single trough concentration is available. Furthermore, this AUC-guided monitoring approach also appears prudent in order to predict toxicity in light of AKI data in pediatrics.

Overall, there are limited pediatric outcomes data to support the AUC target correlated with drug effectiveness in adults. Some of the differences found between adults and children treated for MRSA infections with vancomycin include the complexity of vancomycin CL

in the various pediatric age groups, and the differences in tissue site-of-infection drug exposure (eg, common occurrence of multifocal complicated osteomyelitis in children requiring therapeutic bone concentrations, with rare occurrence of MRSA endocarditis) suggest that further studies in children that incorporate prospective assessment of clinical outcomes and large sample size are needed to identify the optimal dosing strategies for MRSA infections in pediatrics. Until additional data are available, the AUC target used in adults (ie, from 400 up to 600 mg·h/L [assuming a MIC of 1 mg/L]) appears to be the most appropriate initial target for vancomycin exposures in all pediatric age groups. For most children across the pediatric age groups, assuming a vancomycin MIC of 1 mg/L, published data suggest that a dosage of 60 to 80 mg/kg/day (given in divided doses every 6 hours) is required to achieve an AUC target of 400 to 600 mg·h/L.

Summary and recommendations:

17. *Based on an AUC target of 400 mg·h/L (but potentially up to 600 mg·hr/L, assuming a vancomycin MIC of ≤1 mg/L for MRSA) from adult data, the initial recommended vancomycin dosage for children with normal renal function and suspected serious MRSA infections (including pneumonia, pyomyositis, multifocal osteomyelitis, complicated bacteremia, and necrotizing fasciitis) is:*

    - *60 to 80 mg/kg/day, in divided doses given every 6 hours, for children ages 3 months to less than 12 years or*
    - *60 to 70 mg/kg/day, in divided doses given every 6 to 8 hours, for those ≥12 years old (A-II).*

The maximum empiric daily dose is usually 3,600 mg in children with adequate renal function (C-III). Most children generally should not require more than 3,000 mg/day, and doses should be adjusted based on observed

concentrations to achieve the AUC/MIC target. Early monitoring of observed concentrations is recommended when doses exceed 2,000 to 3,000 mg/day (A-III). Furthermore, close monitoring of observed concentrations and renal function is prudent in patients with poor or augmented renal clearance, as resolution of their renal function abnormalities may occur within the first 5 days of therapy.

18. *AUC-guided therapeutic monitoring for vancomycin, preferably with Bayesian estimation, is suggested for all pediatric age groups, based on developmental changes of vancomycin CL documented from the newborn to the adolescent. Based on current available data, the suggestion for AUC-guided monitoring in pediatrics aligns with the approach for adults, including the application of Bayesian estimation for 1 trough concentration or first-order PK equations with 2 concentrations (B-II). The Bayesian AUC-guided dosing strategy may be an optimal approach to individualize vancomycin therapy in pediatrics since it can incorporate varying ages, weights, and renal function. Both serum concentrations of vancomycin and renal function should be monitored since vancomycin CL and CL_{cr} are not always well correlated in pediatrics. Furthermore, aggressive dosing to maintain target AUC exposure and decrease the risk of potential AKI in treatment of MRSA infection necessitates drug monitoring.*

19. *Therapeutic monitoring may begin within 24 to 48 hours of vancomycin therapy for serious MRSA infections in children, as in adults (B-III). Any delay in therapeutic monitoring should be based on severity of infection and clinical judgment. Dosing adjustment should be made for those with renal insufficiency, those with obesity (see Pediatric Obesity), and those receiving concurrent nephrotoxic drug therapy. Following the initial dose, dosing adjustment is*

*important for those with acute renal insufficiency, but subsequent adjustment (particularly within the first 5 days of therapy) may be necessary for those experiencing recovery of renal function. Sustained or subsequent decreases in dosage may be needed, particularly for those with chronic renal insufficiency and those receiving concurrent nephrotoxic drug therapy (**B-III**).*

20. *Vancomycin exposure may be optimally maintained below the thresholds for AUC of 800 mg·h/L and for trough concentrations of 15 mg/L to minimize AKI (**B-II**). The safety of vancomycin dosages above 80 mg/kg/day has not been prospectively evaluated. Avoiding vancomycin dosages of ≥100 mg/kg/day is suggested since they are likely to surpass these thresholds (**B-III**).*

21. *Insufficient data exist on which to base a recommendation for a loading dose among the nonobese pediatric population. Loading doses from adult studies may be considered, but further studies are needed to elucidate the appropriate dose for the various pediatric populations from the neonate to adolescent (**C-III**).*

Pediatric obesity. Vancomycin is a large glycopeptide molecule that is hydrophilic, suggesting that distribution into tissues with high lipid concentrations, such as adipose tissue, is decreased, as noted above for adults (see Dosing in Obesity section). When vancomycin dosing is based on total body weight (mg/kg) for both obese and nonobese children, serum concentrations have been documented to be higher in obese children, assuming that renal CL is similar between the 2 populations.[179] Moffett retrospectively compared vancomycin pharmacokinetics in 24 obese children who were matched with 24 nonobese control children.[180] Vancomycin dose administration per child was slightly higher in the obese children, which resulted in increased trough concentrations. Similarly, 2 retrospective non-Bayesian

studies by Heble et al[181] and Miller et al[182] documented higher vancomycin trough concentrations in overweight and obese children, as compared to normal-weight children, with dosing based on total body weight. No increase in AKI was noted in the overweight children.[182]

Collectively, non-Bayesian studies of obese children have evaluated maintenance regimens ranging from 40 to 80 mg/kg/day (calculated using total body weight), with some instituting maximum doses of 1 to 2 g over 1 to 2 hours.[180,181,183,184] As an alternative to total body weight, one study recommended the use of body surface area to dose vancomycin, which necessitates establishing a different dosing regimen and obtaining height measurements that may not always be readily available in clinical practice.[185] Body surface area is not typically used for dosing medications in children, except for chemotherapeutic agents.[186]

Using a Bayesian population-based PK analysis of 389 vancomycin serum concentrations collected from 87 pairs of obese and nonobese children (matched by age and baseline SCr), Le and colleagues[187] showed that the V_d was strongly correlated with actual or total body weight and that CL correlated with allometric weight (ie, weight x 0.75) and body surface area. Using this PK model, Nguyen and colleagues[164,166] concluded, using Monte Carlo simulations with Bayesian estimation, that vancomycin 60 mg/kg/day dosed by total body weight, as compared with other weight measures, resulted in the highest rate of achievement of the target AUC/MIC of ≥400 in obese children (ie, the target was achieved in 76% when vancomycin was given by total body weight, in 66% when given by adjusted body weight, and in 31% when given by allometric weight). Furthermore, when given dosages of vancomycin of 60 mg/kg/day by total body weight, fewer obese children of <12 vs ≥12 years of age achieved an AUC/MIC of ≥400 (70% and 84%, respectively), an age-based observation also identified in nonobese children.[164,166] Interestingly,

the use of a 20-mg/kg loading dose based on total body weight in obese children increased achievement of an AUC/MIC of ≥400, especially within the first 12 hours of therapy. In addition, 1 of every 5 obese children had an AUC of ≥ 800 mg·h/L, indicating that routine therapeutic and safety monitoring is prudent.[188]

Summary and recommendations:

22. *Data suggest that obese children are likely to have vancomycin exposures that may be statistically greater than those in normal-weight children when doses are calculated on a mg/kg basis, but these differences are not known to be of sufficient clinical importance to suggest different mg/kg empiric vancomycin dosages in obese children at this time. Similar to nonobese children, obese children < 12 years old, compared with those ≥ 12 years, may require a higher mg/kg dose (**B-II**).*

23. *Therapeutic monitoring is likely to be of particular value in obese children, both for therapeutic response and the risk of AKI. The specific recommendations for therapeutic monitoring in nonobese children may also apply for obese children (**B-II**).*

24. *A loading dose of 20 mg/kg by total body weight is recommended in obese children (**A-III**).*

Neonates. Vancomycin therapeutic monitoring is important in neonates, based on developmental considerations of prominent increasing renal function that occurs over the first several weeks of life.[189] Models to predict vancomycin dosing have variously incorporated weight-based dosing, chronologic age–based dosing, postmenstrual age–based dosing, SCr-based dosing (except for the first week of life, when transplacental maternal creatinine in the neonatal circulation renders neonatal SCr values inaccurate in estimating renal function), or combinations of these strategies. Regardless of which model is used, therapeutic monitoring in the neonate is essential due to

the rapid maturation of renal function over the first weeks of life.

Mehrotra et al[190] compared 4 models for predicting vancomycin serum concentrations, based on their population PK model, using a standard weight-based dose, a postmenstrual age–based dose, a postmenstrual and postnatal age–based dose, and a SCr-based dose. Serum creatinine–based dosing predicted trough concentrations with the smallest variability in both term and preterm neonates. However, for those who wish to achieve a target exposure based on high trough concentrations within a narrow range of 15 to 20 mg/L, it should be noted that only 13% to 21% of neonates were within this range across the 4 dosing regimens. Marqués-Miñana et al[191] also developed a population PK model and proposed dosing based on postmenstrual age. SCr-based rather than postmenstrual or postconceptional age–based dosing has been supported by Irikura et al[192] and Capparelli et al.[193] However, when evaluating published neonatal PK models, no consensus on an optimal dosing regimen was achieved by experts on neonatal vancomycin, Zhao et al reported.[194] After evaluating the predictive performance of 6 models, Zhao et al concluded the importance of evaluating analytical techniques for SCr and vancomycin concentrations best explained the variability of predictions between the models. Zhao et al found that the Jaffé method overestimated SCr concentrations when compared to the enzymatic method and that for vancomycin concentrations, the fluorescence polarization immunoassay method and enzyme-multiplied immunoassay method assays showed different predictive performances as well.[194]

With the knowledge that AUC, as compared with trough concentrations, is a more achievable target in pediatrics, Frymoyer and colleagues[195] evaluated the association between AUC and trough concentrations in neonates. Using 1,702 vancomycin concentrations (measured by the homogenous particle-enhanced turbidimetric inhibition immunoassay) collected from 249 neonates up to 3 months of age, population

PK analysis was conducted to create a model for vancomycin CL that was based on weight, postmenstrual age, and SCr (measured by a modified kinetic Jaffé reaction). Monte Carlo simulations with Bayesian estimation demonstrated that trough concentrations ranging from 7 to 11 mg/L were highly predictive of an AUC_{24} of >400 mg·h/L in at least 90% of neonates. Dosages to achieve this PK/PD target ranged from 15 to 20 mg/kg every 8 to 12 hours, depending on postmenstrual age and SCr.[194] Stockmann et al[196] later supported the predictive performance and generalizability of this model in their study of 243 neonates with 734 vancomycin concentrations. While a trough concentration of 11 mg/L predicted the attainment of an AUC of ≥400 mg·h/L in 93% of neonates, Stockmann and colleagues noted that a trough concentration alone did not precisely predict AUC and concluded that Bayesian approaches to support vancomycin dosing decisions for neonates in the clinical setting are needed.[196] Furthermore, Cies et al[197] reported differences in vancomycin pharmacokinetics, in particular rapid vancomycin CL, in neonates with extracorporeal oxygenation life support, reiterating the need for Bayesian-derived dosing decision support in this vulnerable population. Lastly, Leroux et al[198] demonstrated the success of the clinical integration of a model-based vancomycin dosing calculator, developed from a population PK study, that was successful in improving the rate of attainment of a serum concentration of 15 to 25 mg/L from 41% to 72% without any cases of AKI.

As an alternative to intermittent administration, CI of vancomycin has been evaluated in infants. In a multicenter, randomized controlled trial involving 111 infants less than 90 days of age, Gwee et al[199] showed that the use of CI resulted in fewer dose adjustments and a lower mean daily dose than intermittent administration. The target trough concentrations were 10 to 20 mg/L for II, and the steady-state concentrations were 15 to 25 mg/L for CI. The AUC and clinical outcomes, including nephrotoxicity, could

not be evaluated rigorously in this study due to the small sample size. Overall, the clinical utility of CI in neonates requires further evaluation, as the most common pathogen causing late-onset sepsis requiring vancomycin therapy is *Staphylococcus epidermidis*, with limited cases of *S. aureus* sepsis. While the optimal AUC/MIC target for *S. epidermidis* is not well studied, a lower target may be reasonable, but further data to support this recommendation are needed.

The incidence of vancomycin-associated AKI reported in neonates has been low, ranging from 1% to 9%.[200] Nonetheless, a positive correlation between increasing vancomycin trough concentrations and AKI has been reported by Bhargava et al.[201] Furthermore, in a large, retrospective, multicenter, propensity score–matched cohort study of 533 neonates receiving vancomycin and gentamicin and 533 receiving gentamicin alone, Constance et al[202] concluded that AKI was not associated with vancomycin alone but may occur in the presence of other recognized risk factors, including patent ductus arteriosus, concomitant nonsteroidal anti-inflammatory drug use, 1 or more positive blood cultures, low birth weight, and higher scores for severity of illness and risk of mortality.

Summary and recommendations:

25. *Doses recommended to achieve an AUC of 400 mg·h/L (assuming a MIC of 1 mg/L) in neonates and infants up to 3 months old range from 10 to 20 mg/kg every 8 to 48 hours, depending on postmenstrual age, weight, and SCr (A-II). AUC-guided therapeutic dosing and monitoring, preferably with Bayesian estimation, can best achieve the target vancomycin exposure likely to be required for a successful outcome of treatment for a MRSA infection for all neonates, regardless of gestational and chronologic age. The specific recommendations for AUC-guided therapeutic monitoring in children*

Table 2. Primary Recommendations for Vancomycin Dosing and Therapeutic Drug Monitoring

A. ADULTS AND PEDIATRIC PATIENTS

1. In patients with suspected or definitive serious MRSA infections, an individualized target AUC/MIC$_{BMD}$ ratio of 400 to 600 (assuming a vancomycin MIC$_{BMD}$ of 1 mg/L) should be advocated to achieve clinical efficacy while improving patient safety **(A-II)**.

2. When transitioning to AUC/MIC monitoring, clinicians should conservatively target AUCs for patients with suspected or documented serious infections due to MRSA, assuming a vancomycin MIC$_{BMD}$ of 1 mg/L or less at most institutions. Given the importance of early, appropriate therapy, vancomycin targeted exposure should be achieved early during the course of therapy, preferably within the first 24 to 48 hours **(A-II)**. As such, the use of Bayesian-derived AUC monitoring may be prudent in these cases since it does not require steady-state serum vancomycin concentrations to allow for early assessment of AUC target attainment.

3. Trough-only monitoring, with a target of 15 to 20 mg/L, is no longer recommended, based on efficacy and nephrotoxicity data in patients with serious infections due to MRSA **(A-II)**. There is insufficient evidence to provide recommendations on whether trough-only or AUC-guided vancomycin monitoring should be used among patients with noninvasive MRSA or other infections.

4. Vancomycin monitoring is recommended for patients receiving vancomycin for serious MRSA infections to achieve a sustained targeted AUC (assuming a MIC$_{BMD}$ of 1 mg/L unless it is known to be greater or less than 1 mg/L by BMD). Independent of MRSA infection, vancomycin monitoring is also recommended for all patients at high risk for nephrotoxicity (eg, critically ill patients receiving concurrent nephrotoxins), patients with unstable (ie, deteriorating or significantly improving) renal function, and those receiving prolonged courses of therapy (more than 3 to 5 days). We suggest the frequency of monitoring be based on clinical judgment; frequent or daily monitoring may be prudent for hemodynamically unstable patients (eg, those with end-stage renal disease), with once-weekly monitoring for hemodynamically stable patients **(B-II)**.

5. Based on current national vancomycin susceptibility surveillance data, under most circumstances for empiric dosing, the vancomycin MIC should be assumed to be 1 mg/L. When the MIC$_{BMD}$ is greater than 1 mg/L, the probability of achieving an AUC/MIC target of ≥400 is low with conventional dosing; higher doses may risk unnecessary toxicity, and the decision to change therapy should be based on clinical judgment. In addition, when the MIC$_{BMD}$ is less than 1 mg/L, we do not recommend decreasing the dose to achieve the AUC/MIC target. It is important to note the limitations in automated susceptibility testing methods, including the lack of precision and variability in MIC results depending on the method used **(B-II)**.

6. The pharmacokinetics of continuous infusion suggest that such regimens may be a reasonable alternative to conventional intermittent infusion dosing when the AUC target cannot be achieved **(B-II)**.

7. Incompatibility of vancomycin with other drugs commonly coadministered in the ICU requires the use of independent lines or multiple catheters when vancomycin is being considered for continuous infusion **(A-III)**.

B. ADULTS

8. Given the narrow vancomycin AUC range for therapeutic effect and minimal associated risk of acute kidney injury (AKI), the most accurate and optimal way to manage vancomycin dosing should be through AUC-guided dosing and monitoring **(A-II)**. We recommend to accomplish this in one of two ways:

   a. One approach relies on the collection of 2 concentrations (obtained near the steady-state, post-distributional peak concentration at 1 to 2 hours after infusion and trough at end of dosing interval), preferably but not required during the same dosing interval (if possible) and utilizing first-order pharmacokinetic (PK) equations to estimate the AUC **(A-II)**.

   b. The preferred approach to monitor AUC involves the use of Bayesian software programs, embedded with a PK model based on richly sampled vancomycin data as the Bayesian prior, to optimize the delivery of vancomycin based on the collection of 1 or 2 vancomycin concentrations, with at least 1 trough. It is preferred to obtain 2 PK samples (ie, 1 to 2 hours post infusion and at the end of the dosing interval) to estimate the AUC with the Bayesian approach **(A-II)**. A trough concentration alone may be sufficient to estimate the AUC with the Bayesian approach in some patients, but more data across different patient populations are needed to confirm the viability of using trough-only data **(B-II)**.

9. Doses of 15 to 20 mg/kg (based on actual body weight) administered every 8 to 12 hours as an intermittent infusion are recommended for most patients with normal renal function, assuming a MIC$_{BMD}$ of 1 mg/L **(A-II)**. In patients with normal renal function, these doses may not achieve therapeutic AUC/MIC targets when the MIC is 2 mg/L.

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Table 2. Primary Recommendations for Vancomycin Dosing and Therapeutic Drug Monitoring

B. ADULTS

10. *Continuous Infusion:* Based on current available data, a loading dose of 15 to 20 mg/kg, followed by daily maintenance CI of 15 to 20 mg/kg may be considered for critically ill patients (**B-II**). AUC$_{24}$ can be simply calculated when multiplying the steady-state concentration (ie, desired therapeutic range of 20 to 25 mg/L throughout the entire dosing interval) by a factor of 24 (**B-II**). Attaining the desired drug exposure may be more readily accomplished, given the ease of sampling time and dosage adjustment, by changing the rate of infusion, which is a highly desirable feature in critically ill patients (**B-II**).

11. The risk of developing nephrotoxicity with CI appears to be similar or lower compared to intermittent dosing when targeting a steady-state concentration of 15 to 25 mg/L and a trough concentration of 10 to 20 mg/L, respectively (**B-II**). Definitive studies are needed to compare drug exposure based on measured AUC$_{24}$ and factors that predispose to development of nephrotoxicity, such as receipt of concomitant nephrotoxins, diuretics, and/or vasopressor therapy in patients receiving continuous vs intermittent infusion of vancomycin.

12. In order to achieve rapid attainment of targeted concentrations in critically ill patients with suspected or documented serious MRSA infections, a loading dose of 20 to 35 mg/kg can be considered for intermittent administration of vancomycin (**B-II**). Loading doses should be based on actual body weight and not exceed 3,000 mg. More intensive and early therapeutic monitoring should also be performed in obese patients (**B-II**).

13. *Adult Obesity:* A vancomycin loading dose of 20 to 25 mg/kg using actual body weight, with a maximum of 3,000 mg, may be considered in obese adult patients with serious infections (**B-II**). Empiric maintenance doses for most obese patients usually do not exceed 4,500 mg/day, depending on their renal function (**B-II**). Early and frequent monitoring of AUC exposure is recommended for dose adjustment, especially when empiric doses exceed 4,000 mg/day (**A-II**).

14. *Intermittent Hemodialysis:* Since efficacy data are unavailable for an AUC of <400 mg · h/L, monitoring based on predialysis serum concentrations and extrapolating these values to estimate AUC is most practical. Maintaining predialysis concentrations between 15 and 20 mg/L is likely to achieve the AUC of 400 to 600 mg · h/L in the previous 24 hours (**C-III**). Predialysis serum concentration monitoring should be performed not less than weekly and should drive subsequent dosing rather than a strict weight-based recommendation, although these recommended doses provide a useful starting point until serum concentrations have been determined (**B-II**).

15. *Hybrid Dialysis Therapies (eg, Slow-Low Efficiency Dialysis [SLED]):* Loading doses of 20 to 25 mg/kg actual body weight should be used, recognizing that these hybrid dialysis therapies efficiently remove vancomycin (**B-III**). Initial doses should not be delayed to wait for a dialysis treatment to end. Maintenance doses of 15 mg/kg should be given after hybrid hemodialysis ends or during the final 60 to 90 minutes of dialysis, as is done with standard hemodialysis (**B-III**). Concentration monitoring should guide further maintenance doses.

16. *Continuous Renal Replacement Therapy (CRRT):* Loading doses of 20 to 25 mg/kg by actual body weight should be used in patients receiving CRRT at conventional, KDIGO-recommended effluent rates of 20 to 25 mL/kg/h (**B-II**). Initial maintenance dosing for CRRT with effluent rates of 20 to 25 mL/kg/h should be 7.5 to 10 mg/kg every 12 hours (**B-II**). Maintenance dose and dosing interval should be based on serum concentration monitoring, which should be conducted within the first 24 hours to ensure AUC/MIC targets are met. In fluid overloaded patients, doses may be reduced as patients become euvolemic and drug V$_d$ decreases. The use of CI vancomycin in patients receiving CRRT appears to be growing, and this method could be used in place of intermittent vancomycin dosing, especially when high CRRT ultrafiltrate/dialysate flow rates are employed (**B-II**).

C. PEDIATRIC PATIENTS

17. Based on an AUC target of 400 mg · h/L (but potentially up to 600 mg · h/L assuming a MIC of ≤1 mg/L) from adult data, the initial recommended vancomycin dosage for children with normal renal function and suspected serious MRSA infections is 60 to 80 mg/kg/day, divided every 6 to 8 hours, for children ages 3 months and older (**A-II**).

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Table 2. Primary Recommendations for Vancomycin Dosing and Therapeutic Drug Monitoring

C. PEDIATRIC PATIENTS

18. The maximum empiric daily dose is usually 3,600 mg/day in children with adequate renal function **(C-III)**. Most children generally should not require more than 3,000 mg/day, and doses should be adjusted based on observed concentrations to achieve the AUC/MIC target. Early monitoring of observed concentrations is recommended when doses exceed 2,000 to 3,000 mg/day **(A-III)**. Furthermore, close monitoring of observed concentrations and renal function is prudent in patients with poor or augmented renal clearance as resolution of their renal function may occur within the first 5 days of therapy.

19. AUC-guided therapeutic monitoring for vancomycin, preferably with Bayesian estimation, is suggested for all pediatric age groups, based on developmental changes of vancomycin CL documented from the newborn to the adolescent. Based on current available data, the suggestion for AUC-guided monitoring in pediatrics aligns with the approach for adults, including the application of Bayesian estimation for 1 trough concentration, or first-order PK equations with 2 concentrations **(B-II)**. The Bayesian AUC-guided dosing strategy may be an optimal approach to individualize vancomycin therapy in pediatrics since it can incorporate varying ages, weights, and renal function. Both serum concentrations of vancomycin and renal function should be monitored since vancomycin CL and creatinine CL are not always well correlated in pediatrics. Furthermore, aggressive dosing to maintain target AUC exposure and decrease the risk of potential AKI in treatment of MRSA infection necessitates drug monitoring.

20. Therapeutic monitoring may begin within 24 to 48 hours of vancomycin therapy for serious MRSA infections in children, as in adults **(B-III)**. Any delay in therapeutic monitoring should be based on severity of infection and clinical judgment. Dosing adjustment should be made for those with renal insufficiency, or those with obesity, or for those receiving concurrent nephrotoxic drug therapy. Following the initial dose, dosing adjustment is important for those with acute renal insufficiency, but subsequent adjustment (particularly within the first 5 days of therapy) may be necessary for those experiencing recovery of renal function. Sustained or subsequent decreases in dosage may be needed, particularly for those with chronic renal insufficiency and those receiving concurrent nephrotoxic drug therapy **(B-III)**.

21. Vancomycin exposure may be optimally maintained below the thresholds for AUC of 800 mg · h/L and for trough concentrations of 15 mg/L to minimize AKI **(B-II)**. The safety of vancomycin above 80 mg/kg/day has not been prospectively evaluated. Avoiding vancomycin dosages of ≥100 mg/kg/day is suggested since they are likely to surpass these thresholds **(B-III)**.

22. Insufficient data exist on which to base a recommendation for a loading dose among the nonobese pediatric population. Loading doses from adult studies may be considered, but further studies are needed to elucidate the appropriate dose for the various pediatric populations, from neonates to adolescents **(C-III)**.

23. *Pediatric Obesity:* Data suggest that obese children are likely to have vancomycin exposures that may be statistically greater than in normal-weight children when doses are calculated on a mg/kg basis, but these differences are not known to be of sufficient clinical importance to suggest different mg/kg empiric vancomycin dosages in obese children at this time. Similar to nonobese children, obese children < 12 years old, compared with those ≥ 12 years old, may require higher mg/kg doses **(B-II)**.

24. *Pediatric Obesity:* Therapeutic monitoring is likely to be of particular value in obese children, both for therapeutic response and to minimize the risk of AKI. The specific recommendations for therapeutic monitoring in nonobese children may also apply for obese children **(B-II)**. A loading dose of 20 mg/kg by total body weight is recommended in obese children **(A-III)**.

25. *Neonates:* Dosages recommended to achieve an AUC of 400 mg · hr/L (assuming a MIC of 1 mg/L) in neonates and infants up to 3 months old range from 10 to 20 mg/kg every 8 to 48 hours depending on postmenstrual age, weight, and SCr **(A-II)**.

Abbreviations (not defined in body of table): AUC, area under the curve; BMD, broth microdilution; CL, clearance; ICU, intensive care unit; KDIGO, Kidney Disease: Improving Global Outcomes; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; SCr, serum creatinine; V$_d$, volume of distribution.

should also apply for neonates (see recommendation 18, A-III).

Conclusion

To optimize vancomycin use for the treatment of serious infections caused by MRSA, we recommend targeting an AUC/MIC_{BMD} ratio of 400 to 600 (assuming an MIC_{BMD} of 1 mg/L) for empiric dosing in both adult and pediatric patients to maximize clinical efficacy and minimize AKI risk. Furthermore, the AUC should be therapeutically monitored using 1 or 2 postdose concentrations (ie, a peak concentration measured after the early vancomycin tissue distribution phase and a trough level measured prior to the next dose), preferably integrating the Bayesian approach. The primary recommendations are summarized in Table 2. The successful use of these guideline recommendations to positively impact patient outcomes may require multifaceted interventions, including educational meetings, guideline implementation, and dissemination of educational material on vancomycin dosing, monitoring, and nephrotoxicity.[203,204] While valuable literature pertaining to adults, children, and neonates has emerged since the last vancomycin guideline, future studies in all patient populations are necessary to address existing gaps, including (1) efficacy data to support vancomycin use in specific patient populations (including neonates and pediatric patients and patients with renal disease and obesity) and for other types of infections, (2) efficacy data for specific pathogens, including coagulase-negative staphylococcus and *Streptococcus* species; (3) robust pediatric efficacy data for MRSA and other gram-positive pathogens causing different types of serious infections; (4) optimal loading and maintenance dosing regimens for patients with obesity and renal insufficiency; (5) efficacy benefit and the need for a dosing algorithm (specifically incorporating a loading dose followed by maintenance infusion); and (6) toxicodynamics of vancomycin CI in critically ill patients.

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eTable 1. Summary of Adult and Pediatric Studies With Outcome Assessment

Authors(Year Published)	Population, Design, Infection Type(s)	Method to Determine AUC[24]	Method to Determine MIC	AUC/MIC Breakpoint/ Target	Outcome(s) Measured	Reference
Moise-Broder et al (2004)	Adults; retrospective; *S. aureus* lower respiratory infections (n = 107)	Dose$_{24h}$/clearance	BMD	$\geq350_{BMD}$	Bacterial eradication	10
Kullar et al (2011)	Adults; retrospective; MRSA bacteremia (n = 320)	Dose$_{24h}$/clearance	BMD/Etest	$\geq421_{BMD}$	Composite failure (based on 30-day mortality and persistent signs & symptoms of infection, >7 days of bacteremia)	11
Holmes et al (2013)	Adults; retrospective; MRSA bacteremia (n = 182)	Dose$_{24h}$/clearance	BMD/Etest	$>373_{BMD}/271.5_{Etest}$	30-day all-cause mortality	13
Jung et al (2014)	Adults; retrospective; MRSA bacteremia (n = 76)	Dose$_{24h}$/clearance	BMD/Etest	$<430_{BMD}/398.5_{Etest}$	30-day all-cause mortality	15
Brown et al (2012)	Adults; retrospective; MRSA bacteremia (n = 50)	Bayesian	Etest	≥211	Attributable mortality	12
Gawronoski et al (2013)	Adults; retrospective; MRSA bacteremia & osteomyelitis (n = 59)	Bayesian	Etest	>292	Time to bacterial clearance	14
Lodise et al (2014)	Adults; retrospective; MRSA bacteremia (n = 123)	Bayesian	BMD/Etest	$521_{BMD}/303_{Etest}$	Composite failure (based on 30-day mortality, >7 days of bacteremia, recurrence of bacteremia within 60 days of discontinuation of therapy)	16
Casapao et al (2015)	Adults; retrospective; MRSA bacteremia & endocarditis (n = 139)	Bayesian	BMD	>600	Composite failure (based on >7 days of bacteremia and/or 30-day attributable mortality)	17
Le et al (2015)	Pediatric patients; retrospective; all pediatric infection types (n = 680)	Bayesian	NA	≥800	Nephrotoxicity	19
Finch et al (2017)	Adults; retrospective, quasi-study design; all infection types except UTI, SSSI, meningitis; surgical prophylaxis (n = 1,300)	AUC derived from multiple samples	NA	<400	Nephrotoxicity	20

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eTable 1. Summary of Adult and Pediatric Studies With Outcome Assessment

Authors(Year Published)	Population, Design, Infection Type(s)	Method to Determine AUC[24]	Method to Determine MIC	AUC/MIC Breakpoint/ Target	Outcome(s) Measured	Reference
Zasowski et al (2017)	Adults; retrospective; pneumonia or bloodstream infection (n = 323)	Bayesian	NA	>700	Nephrotoxicity	21
Neely et al (2018)	Adults; prospective; all infection types (n = 252)	Bayesian	NA	≥400	Nephrotoxicity, resolution or improvement in signs & symptoms, relapse, and mortality	22
Lodise et al (2019)	Adults; multicenter, observational, prospective; MRSA bacteremia	Bayesian	BMD/Etest	No threshold identified, but only 20% of study population had AUC/MIC_{BMD} ratio of <420	Composite failure (based on >7 days of bacteremia and/or 30-day mortality)	23

Abbreviations: AUC, area under the curve; BMD, broth microdilution; MRSA, methicillin–resistant *Staphylococcus aureus*; NA, not applicable; SSSI, skin and skin structure infection; UTI, urinary tract infection.