Therapeutic monitoring of vancomycin: A revised consensus guideline and review of 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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Background – Vancomycin has been in clinical use since 1958. Despite this vast clinical experience with this agent, there are still major gaps in knowledge regarding the most appropriate approach for optimizing patient therapy and avoiding potential adverse reactions. The area-under-the-curve to minimum inhibitory concentration (AUC/MIC) has been identified as the most appropriate pharmacokinetic/pharmacodynamic (PK/PD) target for all glycopeptides, including vancomycin. However, in recent years, controversies regarding vancomycin susceptibility have called into question the ability of current recommended therapy to achieve the most optimized AUC/MIC ratio. In addition, the current recommendations for higher vancomycin trough concentrations and the potential for elevated nephrotoxicity rates have generated considerable concern. More recent vancomycin PK/PD and toxicodynamic studies enable a reassessment of the current dosing and monitoring guidelines in an attempt to further optimize the efficacy and safety of vancomycin therapy.

Methods and Results – This document is an update to the 2009 vancomycin consensus guidelines for dosing and monitoring vancomycin therapy and was developed by the American Society of Health Systems Pharmacists, Infectious Diseases Society of America, Pediatric Infectious Diseases Society and the Society of Infectious Diseases Pharmacists vancomycin consensus guidelines committee.

Conclusions – The vast majority of PK/PD data generated on vancomycin has focused on treatment of serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections. Therefore, extrapolation of these recommendations to methicillin-susceptible strains, coagulase-negative staphylococci, and other pathogens should be viewed with extreme caution. Treatment of serious infections secondary to MRSA are complicated; combination antibiotic therapy and

multiple medical interventions beyond antibiotic therapy may be necessary to improve patient outcomes. The recommendations provided in this document are intended to assist the clinician in optimizing vancomycin therapy in adult and pediatric patients. However, these recommendations should not circumvent sound clinical judgment in the management of these patients.

Key Words: vancomycin consensus guidelines, vancomycin, pharmacokinetics and pharmacodynamics, target attainment, nephrotoxicity

Introduction

The first consensus guidelines for therapeutic monitoring of vancomycin in adult patients was published in 2009. A committee representing three organizations (American Society for Health-System Pharmacists, Infectious Diseases Society of America and the Society for Infectious Diseases Pharmacists) 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 as it related 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 serum peak concentrations, emphasizing an area-under-the-curve over 24 hours to minimum inhibitory concentration by broth microdilution (AUC/MIC_{BMD}) $\geq$ 400 as the primary PK/PD predictor of vancomycin activity, and promoting serum trough concentrations of 15-20 mg/L as a surrogate marker for the optimal vancomycin AUC/MIC if the MIC was $\leq$ 1 mg/L in patients with normal renal function. The guidelines also recommended, albeit with limited data, 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 generating these recommendations, a number of publications have evaluated the impact of these guidelines on clinical efficacy and toxicity in patients receiving vancomycin for the treatment of MRSA infections. It should be noted however, when originally published there were important issues not addressed and gaps in knowledge regarding the recommendations that could not be covered adequately because of inadequate data. These included the lack of specific dosing and monitoring guidelines for pediatric patients outside of the neonatal age

group; specific recommendations for vancomycin dosage adjustment and monitoring in morbidly obese patient populations, patients with renal failure, including specific dialysis dosage adjustments; recommendations for the use of prolonged or continuous infusion vancomycin therapy, and safety data on the use of dosages that exceed three grams per day. In addition, there were little to no data on the safety and efficacy of targeted trough concentrations of 15-20 mg/L. This consensus revision re-evaluates the scientific data and controversies associated with vancomycin dosing and serum concentration monitoring for serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections and provides new recommendations based on recent available evidence.

Methods

These are the consensus statements and guidelines of the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), the Pediatric Infectious Diseases Society (PIDS) and the Society for Infectious Diseases Pharmacists (SIDP). Consensus committee members were assigned key topics regarding vancomycin dosage and monitoring. A draft document addressing these specific areas was reviewed by all committee members. After peer review by members of ASHP, IDSA, PIDS and SIDP, the committee 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 for final comment and approval.

A search of PubMed was conducted using the following search terms: vancomycin, pharmacokinetics, pharmacodynamics, efficacy, resistance, toxicity and pediatrics. All relevant

and available peer-reviewed studies in the English literature published between 1958 and 2018 were considered. Studies were rated by their quality of evidence, and the subsequent recommendations were graded using the classification schemata of Table 1.

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

Table 1. Grading of Evidence and Recommendation

Grading Evidence[2,3]			
Grade	**Description**	**Assessment of Evidence**	**Potential Effect of Further Research**
High (A)	Large or small well conducted randomized controlled trials or large well conducted observational cohorts	Very confident that estimate of effects lies close to true effect	Unlikely to change estimate of effect
Moderate (B)	Large cohort studies; well conducted case-control studies	Moderately confident that estimate of effect lies close to true effect	May change estimate of effect
Low (C)	Uncontrolled studies not well conducted; conflicting evidence that favors a direction; conflicting or unclear literature	Limited Confidence that estimate of effect lies close to true effect	Likely to change estimate of effect
Insufficient (D)	Expert opinion; extrapolated data	No sufficient evidence to estimate effect	May not permit conclusion

Recommendations	
Strength	**Direction**
Strong (I)	For (+)
Weak (II)	Against (-)
No Recommendation (0)	

[2]Owens D., Lohr K., Atkins, D. Grading the strength of a body of evidence when comparing medical interventions. Rockville Maryland: AHRQ; 2009.

[3] Balshem H., Helfand M., Schunemann H.J., et al. GRADE guidelines: 3. Rating the quality of evidence. *Journal of Clinical Epidemiology*. 2011; 64(4):401-406.

PK/PD Efficacy Targets

To optimize the dosing of any antimicrobial agent, a firm understanding of the drug exposure-effect and exposure-toxicity links are required. While a variety of pharmacodynamic indices have been suggested for vancomycin, an AUC/MIC_{BMD} ratio ≥ 400 is the current accepted critical PK/PD index[1, 4-8]. *In vitro* and *in vivo* assessment of PK/PD models applicable to human MRSA infection has found that bactericidal activity is achieved (i.e., 1- to 2-log reduction in bacterial inoculum in the animal model) when the vancomycin AUC/MIC_{BMD} ratio approximates or exceeds 400. There are also mounting clinical data, albeit mostly retrospective in nature, in support of this PK/PD target for vancomycin.[9-17] A summary of these investigations and their findings can be found in Supplement Table 1.

Clinical PK/PD Data: Adults

While an AUC/MIC_{BMD} ratio ≥ 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[10-16]. It is

144 also important to recognize that most of the landmark clinical studies that established the
145 contemporary efficacy PK/PD target relied on simple vancomycin clearance (CL) formulas based
146 on daily vancomycin dose and estimated renal function to determine AUC values [9, 10, 12]
147 Current evaluation of these data demonstrates that these CL formulas provide imprecise
148 estimates of the AUC [18-20]. This finding is not surprising as there is considerable inter-patient
149 variability in vancomycin exposure profiles in clinical practice and it is not possible to generate
150 valid estimates of exposure variables in a given individual based on CL formulas that are derived
151 from glomerular filtration rate estimation equations alone [9, 10, 12]. In most cases, the
152 formula-based approach will overestimate vancomycin CL by ~40-50% [15].

153 While it is has been cumbersome to estimate AUC in the clinical setting in the past,
154 Neely and colleagues recently demonstrated that Bayesian software programs (refer to
155 Therapeutic Monitoring section) can be used to generate accurate and reliable estimates of the
156 daily AUC values with trough-only PK sampling[18]. However, the accuracy of AUC estimation is
157 higher with peak and trough measurements compared to trough-only PK sampling [18]. Using
158 this validated Bayesian method to estimate the daily AUC in a single-center, retrospective study
159 of patients with MRSA bloodstream infections, Lodise and colleagues found that outcomes
160 were maximized when day 1 and 2 AUC/MIC_{BMD} ratios exceeded 521 and 650, respectively[15].
161 Employing the same Bayesian approach to estimate daily AUC values, Casapao and colleagues
162 also noted that the risk of vancomycin failure among patients with MRSA infective endocarditis
163 was greatest among those with an AUC/MIC_{BMD} ratio ≤ 600 and this exposure-failure
164 relationship persisted after adjusting for factors such as intensive care unit (ICU) admission,
165 presence of hVISA, and other comorbidities[16]. In contrast to the studies by Lodise and

Casapao, several other 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 by the Etest method (AUC/MIC_{Etest})[11, 13, 14]. The MIC_{Etest} value tends to be 1.5-2 fold higher than the MIC_{BMD} value; therefore, it is likely that the AUC threshold needed for response from these three studies[11, 13, 14], if calculated using the MIC_{BMD}, would align with the studies by Lodise and Casapao[15, 16].

In an effort to surmount the limitations associated with previous single-center, retrospective vancomycin exposure-response clinical analyses, a multi-center prospective study was performed to evaluate the relationship between the pre-specified day 2 AUC/MIC ratios and outcomes in adult patients (N=265) with MRSA bacteremia. In the multivariate analyses, failure was not significantly different between the pre-specified day 2 AUC/MIC groups. Post-hoc global outcomes analyses suggested that patients in the two lowest AUC/MIC_{BMD} exposure quintiles (i.e., $AUC/MIC_{BMD} \leq 562$) experienced the best global outcome (defined as absence of both treatment failure and acute kidney injury), compared with the three highest-exposure quintiles. While global outcomes were similar between the two lowest AUC/MIC_{BMD} exposure quintiles, only 20% of the study population (n=54) had an $AUC/MIC_{BMD} \leq 425$ and it is unclear if efficacy outcomes are maintained at AUC/MIC_{BMD} less than this threshold of 425[21].

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. The data also highlight the critical need for large-scale, multi-centered future randomized, vancomycin dose-optimized outcomes clinical trials. As data from

future prospective, multi-center clinical studies become available, 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: Acute Kidney Injury

A major concern with vancomycin is the occurrence of acute kidney injury (AKI). While multiple definitions of vancomycin-associated AKI have been employed in the literature, most studies used an increase in SCr level $\geq$ 0.5 mg/dL or 50% increase from baseline in consecutive daily readings, or a decrease in calculated creatinine CL of 50% from baseline on two consecutive days in the absence of alternative explanation.[1] Recently, a more sensitive threshold of an increase in SCr of $\geq$ 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 AKI Network and the Kidney Disease Improving Global Outcomes (KDIGO) criteria.[22-24] The incidence of vancomycin-associated AKI has varied across published studies. In a meta-analysis by van Hal and colleagues, the prevalence of vancomycin-associated AKI varied from 5% to 43%. Similarly, a recent meta-analysis of 13 studies by Sinha Ray et al reported that the relative risk of AKI with vancomycin was 2.45 (95% CI 1.69 to 3.55), with an attributable risk of 59%.[25] Most episodes of AKI developed between 4.3 and 17 days after initiation of therapy. Many patients, especially those who are critically-ill, fail to fully recover renal function after acute kidney injury (AKI), [26] and even mild AKI can significantly decrease long-term survival rates, increase morbidity, prolong hospitalizations, and escalate healthcare costs.[27, 28]

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 [29, 30]. Although data are limited, the collective literature suggests that the risk of AKI increases as a function of trough concentration, especially when maintained above 15-20 mg/L[24]. Similarly, there are recent data to suggest that risk of AKI increases along the vancomycin AUC continuum, especially when the daily AUC exceeds 700 –1300 mg-h/L[18, 29, 30].

Suzuki et al [29] evaluated the mean vancomycin AUC in relation to AKI. Most patients who developed AKI had AUC values between 600-800 mg*h/L, compared with 400-600 mg*h/L in those without AKI ($p = 0.014$). Furthermore, Lodise and colleagues showed that the probability of AKI increased 2.5-fold among patients with AUCs above 1300 mg*hr/L compared with those below (30.8% vs. 13.1%, $p = 0.02$)[30]. Although AUC values above 1300 mg*hr/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 [31]. A study by Zasowski et al also reported similar relationship between Bayesian-estimated vancomycin AUC thresholds and AKI in 323 patients; AUCs $\geq$ 1,218 mg*hr/L for 0-48 h, $\geq$ 677 for 0-24 h and $\geq$ 683 for 24-48 h or troughs $\geq$ 18.2 mg/L were associated with 3-4 fold increased risk of nephrotoxicity [32]. Similarly, the aforementioned multi-center, prospective study of patients with MRSA bloodstream infections found that AKI increased along the day 2 AUC continuum in a stepwise manner and patients with day 2 AUCs $\geq$ 793 mg*h/L were at the greatest risk for AKI[21].

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. compared the incidence of nephrotoxicity in patients monitored by individualized AUC versus trough concentration. AUC-guided dosing was found to be independently associated with a significant decrease in AKI (OR, 0.52; 95% CI, 0.34-0.80; $P = 0.003$)[33]. Median Bayesian-estimated AUC was significantly lower in the AUC-guided dosing compared with trough monitoring (474 [360-611] vs. 705 [540-883]; $P < 0.001$). In the prospective study by Neely et al., 252 patients were monitored via troughs 10-20 mg/L in year 1 versus estimated-Bayesian AUCs of $\geq$ 400 mg*hr/L in years 2 and 3 of the investigation. Nephrotoxicity occurred in 8% of subjects in year 1 compared to 0 and 2% of subjects in years 2 and 3 (P = 0.01). The median trough concentrations and AUC associated with AKI were 15.7 mg/L and 625 mg*hr/L versus 8.7 mg/L and 423 mg*hr/L in those without AKI (P = 0.02).[28]

Collectively, the published clinical exposure-response analyses suggest that the daily AUC is the driver of effectiveness and the risk of AKI is related to trough, and potentially AUC. 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 which 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, and vasopressors has been shown to increase the risk of nephrotoxicity. Recently, piperacillin-tazobactam has also been reported to increase

the risk of AKI in patients receiving vancomycin[34-38]. 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.[30, 34-44]

Therapeutic Monitoring

Therapeutic monitoring has centered on maintaining trough concentrations between 15-20 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, 6]. 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 a PK software that was not readily available at all institutions. As such, the guidelines 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 15-20 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 [31, 45-49]. From a PK/PD perspective, it is not surprising that there are limited clinical data to support the range of 15–20 mg/L. Recent studies have demonstrated that trough values may not be an optimal surrogate for AUC values [20, 50, 51]. While a trough ensures achievement of a minimum cumulative exposure, a wide range of concentration-time profiles can result in an identical trough value. Patel et al. reported a wide range of AUC values from several different

dosing regimens yielding similar trough values [20]. The therapeutic discordance between trough and AUC values is not surprising as the AUC is the integrated quantity of cumulative drug exposure (i.e., 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 AUC_{24h} largely represents the average concentration during that time period [AUC_{24h} (mg*hr/L) = average concentration (mg/L)*24 (hours)]. For troughs of 15-20 mg/L, this typically equates to a daily AUC in excess of 400 mg*hr/L. However, there is considerable variability in the upper range of AUC values associated with a given trough value. Although practical, the limitations surrounding trough-only monitoring suggest that trough monitoring may be insufficient to guide vancomycin dosing in all patients.

Although the AUC/MIC 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_{BMD90} of 1 mg/L (unless it is known to greater 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. Second, measurement of MIC values is imprecise with ± 1-log_2 dilution and variation of 10-20% considered acceptable; therefore, the variability of reported MIC values encountered in routine clinical practice is likely to reflect measurement error.[52] Third, there is a high degree of variability between commercially available MIC testing methods relative to the BMD MIC method (see MIC 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.

Based on the current best available evidence, daily AUCs (assuming a MIC_{BMD90} of 1 mg/L) should be maintained between 400 and 600 mg*hr/L to maximize efficacy and minimize the likelihood of nephrotoxicity. 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 (i.e., one or two vancomycin concentrations) and provide AUC-guided dosing recommendations in real-time. An alternative approach involves use of two concentrations (peak and trough) and simple analytic PK equations to estimate AUC values [51, 53].

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 (e.g. volume [Vd] or CL) prior to administering the drug based on the way the drug behaved in a population of prior patients (Bayesian prior) and the revised probability distribution of a specific patient's PK parameter values using exact dosing and drug concentration data (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 exposure profile[54-56].

With the Bayesian approach, vancomycin concentrations can be collected within the first 24 to 48 hours, rather than waiting till steady-state conditions (after the 3rd or 4th 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 a 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 creatinine CL, in the structural PK models (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 [56].

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_{BMD90} of 1 mg/L) [55]. Bayesian programs offer numerous advantages over the traditional first-order equation software programs. Using richly sampled vancomycin pharmacokinetic data from three studies comprising 47 adults with varying renal function, Neely and colleagues[18], 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 were limited specialized 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, pediatrics, and patients with unstable renal function. Until more data are available, it is preferred to estimate the Bayesian AUC on two vancomycin concentrations (peak and trough).

First-Order Pharmacokinetic Analytic Equations

Alternatively, the AUC can be accurately estimated based on the collection of two timed steady-state serum vancomycin concentrations and use of first-order PK equations [51]. The equations used to compute AUC from two samples are based in part on an original approach proposed by Begg, Barclay, and Duffull for aminoglycosides[57]and modified by Pai and Rodvold[51]. It is preferred that a near steady-state, post-distributional peak (1-2 hours after end of infusion) and trough concentrations 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}.[7, 58-60] 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 (e.g., 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 U.S. have already adopted this two post-dose serum concentration estimates of the AUC to perform their routine dosing and monitoring of vancomycin and have demonstrated a considerable improvement over the current trough-only concentration monitoring method.[33, 53]

Pharmacokinetic Sampling Time

Timing of achievement of targeted AUC values (assuming a MIC_{BMD90} of 1 mg/L) remains unclear. The early AUC/MIC target ratios derived in animal models were based on the AUC value from 0-24 hours [4, 5]. More recent clinical assessments that identified a link between AUC/MIC and outcomes also assessed the AUC values achieved early in the course of therapy [1, 4, 6-9, 12, 28, 32, 33]. The previous vancomycin guidelines stated that trough should be assessed prior to the steady-state conditions (prior to 4^{th} dose)[1, 6]. In fact, steady-state conditions are difficult to determine in clinical practice and the timing of the 4^{th} dose is more

dependent on the dosing interval (i.e., every 12 vs. 24 hours) than steady-state conditions. Given the importance of early, appropriate therapy [61], targeted AUC exposures should be achieved early during the course of therapy, preferably within the first 24 to 48 hours.

Summary and Recommendations:

1. Based on the current body of evidence of vancomycin PK/PD and clinical outcomes in patients with serious MRSA infections, a Bayesian-derived AUC/MIC_{BMD} ratio of 400 to 600 (assuming a vancomycin MIC_{BMD90} of 1 mg/L) should be advocated as the target to achieve clinical efficacy while improving patient safety **(IA+)**.
2. Given the potential narrow vancomycin AUC range for maximal effect and minimal AKI, the most accurate and optimal way to manage vancomycin dosing is through AUC-guided dosing and monitoring **(IB+)**. This can be accomplished in one of two ways. One approach relies on the collection of two concentrations (one near steady-state, post-distributional Cmax at 1-2 hours post infusion and trough) during the same dosing interval and utilizing first-order PK equations to estimate the AUC.
3. 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 one or two vancomycin concentrations, with at least one trough. It is preferred to obtain two PK samples (i.e., shortly after the end of infusion and at end of dosing interval) to estimate the AUC with the Bayesian approach. However, 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 viability of using trough only data **(IIC+)**.

4. When transitioning to AUC/MIC monitoring, clinicians should conservatively target AUCs for patients with suspected or documented serious infections due to MRSA that provide adequate coverage against the common vancomycin MIC_{BMD} values observed in their practices since exact MIC values are largely unknown until day 3 of therapy. The most common MIC_{BMD} will be 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 **(IIB+)**. As such, the use of Bayesian-derived AUC monitoring may be prudent in these cases since it doesn't require steady-state serum vancomycin concentrations to allow for early assessment of AUC target attainment.
5. Trough only monitoring, with target between 15-20 mg/L, is no longer recommended for patients with serious infections due to MRSA **(IIB-).**
6. Vancomycin monitoring is recommended for patients receiving aggressive dosing for MRSA infections to achieve sustained targeted AUC (assuming a MIC_{BMD90} of 1 mg/L, unless it is known to be greater than 1 mg/L) and all patients at high risk of nephrotoxicity (e.g., critically-ill patients receiving concurrent nephrotoxins). Monitoring is also recommended for patients with unstable (i.e., deteriorating or significantly improving) renal function and those receiving prolonged courses of therapy (more than three to five days). Once-weekly monitoring is recommended for hemodynamically stable patients. More frequent or daily monitoring is advisable in patients who are hemodynamically unstable **(IIB+)**.

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429 **Supplement Table 1. Summary of Adult and Pediatric Studies with Outcome Assessment**

Author(s)/ year	Study Design/Population	Method to determine AUC_{24h}	MIC method	AUC/MIC Breakpoint/ Target	Outcome measurement	Refer-ence
Moise-Broder et al. 2004	Retrospective/*S. aureus* lower respiratory infections (n=107)	$Dose_{24h}$/Clearance	BMD	$\geq 350_{BMD}$	Bacterial eradication	7
Kullar et al. 2011	Retrospective/MRSA bacteremia (n=320)	$Dose_{24h}$/Clearance	BMD/Etest	$\geq 421_{BMD}$	Composite failure (based on 30-day mortality and persistent signs & symptoms of infection > 7 days of bacteremia)	8
Holmes et al. 2013	Retrospective/MRSA bacteremia (n=182)	$Dose_{24h}$/Clearance	BMD/Etest	$>373_{BMD}$/ 271.5_{Etest}*	30-day all-cause mortality	10
Jung et al. 2014	Retrospective/MRSA bacteremia (n=76)	$Dose_{24h}$/Clearance	BMD/Etest	$<430_{BMD}$/ 398.5_{Etest}	30-day all-cause mortality	12
Brown et al. 2012	Retrospective/MRSA bacteremia (n=50)	Bayesian	Etest	≥ 211	Attributable mortality	9
Gawronoski et al. 2013	Retrospective/MRSA bacteremia & Osteomyelitis (n=59)	Bayesian	Etest	>292	Time to bacterial clearance	11
Lodise, et al. 2014	Retrospective/MRSA bacteremia (n=123)	Bayesian	BMD/Etest	$521_{BMD}/303_{Etest}$	Composite failure (based on 30-day mortality, >7 days of bacteremia, and recurrence of bacteremia within 60 days of discontinuation of therapy)	13

Casapao et al. 2015	Retrospective/MRSA bacteremia-endocarditis (n=139)	Bayesian	BMD	>600	Composite failure (based on > 7 days of bacteremia, and/or 30-day attributable mortality)	14
Le et al. 2015	Retrospective/All infection types in pediatrics (n=680)	Bayesian	Not applicable	≥800	Nephrotoxicity	
Finch et al. 2017	Retrospective, quasi-study design/All infection types except UTI, SSSI, meningitis, surgical prophylaxis (n=1300)	AUC derived from multiple samples	Not applicable	< 400	Nephrotoxicity	
Zasowski et al. 2017	Retrospective/Pneumonia or bloodstream infection (n=323)	Bayesian	Not applicable	≥ 700	Nephrotoxicity	
Neely et al. 2017	Prospective/All infection types (n=252)	Bayesian	Not applicable	≥400	Nephrotoxicity, resolution or improved signs & symptoms, relapse, and mortality	
Lodise et al. 2017	Multi-center Prospective study of adult hospitalized patients with MRSA bloodstream infections	Bayesian	BMD/Etest	No threshold was identified but only 20% of study population had an AUC/MIC_{BMD} ratio <420	Composite failure (based on > 7 days of bacteremia, and/or 30-day mortality)	

Vancomycin MIC 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 more than 90% of isolates

demonstrating an MIC $\leq$ 1 mg/L.[62-66] A meta-analysis of 29,234 MRSA strains from 55 studies revealed the MIC performed by BMD, Etest and automated systems was predominately 1 mg/L and that there was no evidence of an MIC creep phenomenon.[67] While there does not seem to be a large number of organisms with a vancomycin MIC ≥ 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 Clinical Laboratory Standards Institute (CLSI), acceptable variability for MIC 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, Franklan Lakes, NJ, USA, MicroScan WalkAway; Dade Behring, Deerfield, IL, USA or Vitek 2; bioMeieux, Hazelwook, MO, USA) and, in some cases, the Etest methodology (bioMeieux, Hazelwook, MO, USA). In a study of 161 MRSA blood isolates, when using the essential agreement definition of ± 1 $\log_2$ dilution error, Vitek-2 and MicroScan demonstrated a 96.3% agreement with BMD whereas Phoenix demonstrated an 88.8% agreement[68]. The Etest method had the lowest agreement (with results consistently higher by 1-2 dilutions) compared with BMD at 76.4%. The Etest will likely produce a higher value (0.5-2 dilutions higher) than BMD. In another study, 92% of the strains demonstrated a vancomycin MIC of 1 mg/L by BMD, with over 70% by MicroScan and Etest and 41% by Vitek-1 [69].

Rybak et al. compared MicroScan, Vitek-2, Phoenix and Etest to BMD methods among 200 MRSA strains [70]. In contrast to previous studies, these authors used an absolute

agreement definition of ± 0 $\log_2$ dilution error to better characterize the precision. Using this definition, Phoenix (66.2%) and MicroScan (61.8%) produced the highest agreement results with BMD, followed by Vitek-2 (54.3%). As noted above, Etest tended to produce results that were 1-2 dilutions higher (36.7% agreement). However, when compared to BMD, Etest identified an MIC of 2.0 mg/L 80% of the time. When compared to BMD, MicroScan (prompt method) overcalled MIC values of 1 mg/L by 74.1% and Phoenix and Vitek-2 under called MIC values of 2 mg/L by 76 and 20%, respectively.

The high variability of MIC results among the four systems compared to BMD clearly poses a challenge to the clinician making treatment decisions based on MIC and questions the most relevant MIC method.[71] Given this variability between MIC values and testing methods routinely performed at most institutions, it further supports the use of AUC (assuming a MIC_{BMD90} of 1 mg/L) to guide vancomycin empiric dosing. For non-serious 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, either BMD or Etest, as soon as possible to avoid a delay in effective therapy.

Summary and Recommendations:

7. Based on current national vancomycin susceptibility surveillance data, under most circumstances for empiric dosing, the vancomycin MIC can be assumed to be 1 mg/L. When the MIC_{BMD90} method is > 1 mg/L, the probability of achieving an AUC/MIC ≥ 400 target is unlikely with conventional dosing; higher doses may risk unnecessary toxicity. However, it is

important to note limitations in automated susceptibility testing methods, including the lack of precision and variability in MIC results depending on method used **(IIA+)**.

Vancomycin Continuous Infusion (CI) vs Intermittent Infusion (II)

Since the initial guideline publication in 2009, additional clinical studies have provided further support to AUC_{24}/MIC rather than time above the MIC (T>MIC) as the best predictive parameter for efficacy and AUC_{24} rather than serum trough concentration as a better marker of drug exposure for vancomycin-induced AKI. 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 dependent on sampling time or multiple concentrations to calculate AUC), and lower risk of nephrotoxicity.

Comparative studies

Published studies that compared intermittent to continuous administration primarily focused on two 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.[72-81] Most studies compared CI to II for the risk of nephrotoxicity and attainment of target serum concentrations; only four studies included other outcome endpoints such as treatment failure and mortality.[72, 76, 79, 81] Measures of vancomycin drug exposure reported in clinical trials include trough, steady-state concentration, and AUC_{24}. One challenge when comparing clinical outcomes between CI and II is the lack of consistent

reporting of exposure parameters between groups receiving the two dosing strategies. For CI, the most commonly reported drug exposure parameter was steady-state concentration while for II it was trough. For future investigations it would be beneficial to report AUC and/or 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.[72-78] Only one study by Wysocki et al evaluated both efficacy and safety in a prospective randomized trial comparing CI (n=61) to II (n=58) of vancomycin in 119 patients.[72] Most patients had pneumonia or bacteremia mostly due to MRSA. Mean serum concentrations attained were steady-state concentration 24 mg/L and trough 15 mg/L for CI and II groups, respectively. AUC_{24} was comparable between CI and II groups, but with significantly less variability in the CI group ($p=0.026$); only the variance values were shown. Clinical failure was similar between the groups on day 10 (21 vs 26%) and at end of treatment (21 vs 29%), although AUC_{24} was shown to be lower in the CI group (596 ± 159 vs 685 ± 260, $p<0.05$). Nephrotoxicity occurred in 20% of patients and was similar between CI and II groups (16% vs 19%). However, dialysis was required more often in those who received CI than II (6/10 vs 3/11 patients). Risk factors for nephrotoxicity such as diabetes and concomitant diuretics, aminoglycoside, and iodine 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) vs II (n=81).[76] Mortality rates in-hospital and on days 14 and 28 were numerically higher for those receiving CI, but the difference did not reach statistical significance (10 vs 6.2%; 18.9 vs 11%; 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 compared to II group (increase of Scr 0.5mg/dL at end of therapy: 6.7% vs 14.8%). While higher mean vancomycin concentrations were noted in the CI group which is expected when comparing steady-state concentration to trough (20 ± 3.8 vs 14.8 ± 4.4 ug/ml, $p<0.001$), AUC_{24} was not reported to allow comparison of drug exposure between 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.[73-75, 77, 78] As expected, the range of measured vancomycin concentrations from the studies was significantly higher in CI than II group (steady-state concentration 20-25 mg/L vs trough 10-15 mg/L). Another study showed that more patients attained vancomycin concentration > 20 mg/L at least once during the treatment course with CI than II administration (63.2% vs 44.9%, p=0.065).[74] One study reported lower AUC_{24} (529 ± 98 vs 612 ± 213, p-value not stated) with increased respective steady-state concentration compared to trough achieved between CI and II groups (steady-state concentration 25 ± 4 vs trough 17 ± 4.7 mg/L, p=0.42).[75] The discordance observed

between trough and AUC_{24} relationship underscores the importance of measuring AUC_{24} to compare relative drug exposure between CI and II in future studies.

In general, the rate of nephrotoxicity was reported to be similar or numerically lower with CI than 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%).[73-75, 77, 78] In addition, Saugel et al noted significantly less frequent need for renal replacement therapy during vancomycin treatment for patients in the CI than II group (7%, 7/94 vs 23%, 12/52; p=0.007).[77] Of interest, in the largest retrospective study conducted in 1,430 ICU patients comparing CI vs II, Hanrahan et al. reported a higher rate of nephrotoxicity in those receiving CI vs II (25%, 161/653 vs 20%, 77/390; p=0.001) and that every 1mg/L increase in serum concentration was associated with an 11% increased risk of nephrotoxicity, with lower odds in those receiving II.[78] However, logistic regression analysis indicates the contrary in that II infusion was associated with an 8-fold higher odds of nephrotoxicity (CI: 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 a definitive conclusion to be drawn regarding safety of CI, in light of the disparate results between bivariate and logistic regression analysis.

Patients Receiving OPAT

Two studies have been published thus far comparing efficacy of vancomycin by CI vs II in patients whose therapy was initiated in hospital and continued on as OPAT. Duration of therapy ranged between 30 days to 14 weeks.[79, 81] Most patients were treated for bone and

joint and skin structure-related infections. In a small prospective study, cure rates for osteomyelitis did not differ between groups defined as remaining asymptomatic 12 months after completion of therapy (94% vs 78%, p=0.3), but only 27 patients were evaluable.[79] 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.[81] Clinical failure was similar between groups (19%, 25/133 vs 25%, 9/36, p=0.41) after excluding 29% of study patients who had subtherapeutic serum vancomycin concentrations for more than a week. However, it is not clear how frequent serum concentration was monitored, if treatment duration in hospital before OPAT differs between groups, and whether treatment success differs by type of infection.

In studies that evaluated safety of vancomycin CI as OPAT, treatment duration ranged from 4 to 14 weeks with reported mean steady state average serum concentration at 13 – 30 mg/L.[79, 80] A retrospective matched cohort study of 80 patients observed a trend towards less frequent occurrence of nephrotoxicity in the CI group (10% vs 25%, p=0.139) and later onset (p=0.036).[80] Patients were matched by age, comorbid conditions, gender, baseline Scr, and receipt of concurrent nephrotoxins; those who had Scr ≥ 1.5mg/dL at baseline, developed nephrotoxicity as inpatients prior to OPAT, or experienced hypotension resulting in renal dysfunction were excluded. In another retrospective study[82], the same investigators identified steady state average concentration of 28 mg/L as the threshold breakpoint for the development of nephrotoxicity using CART analysis: nephrotoxicity occurred in 71.4% (5/7) compared to 11.6% (11/95) for patients with steady-state concentration ≥ 28mg/L vs < 28 mg/L, respectively. In one prospective study of an elderly cohort (age 70 years) receiving high dose

vancomycin therapy by CI targeting steady-state concentration of 30-40mg/L for a median duration of 6 weeks, nephrotoxicity occurred in 32% of patients. Additionally, four patients in that study developed leukopenia.[83]

Dosing and Other Considerations for Use of Continuous Infusion

Most published studies in critically-ill patients receiving vancomycin CI employed a loading dose of 15-20mg/kg, followed by daily maintenance infusion at 30-40mg/kg up to 60mg/kg to achieve target steady-state concentration of 20-25mg/L. By simply multiplying steady-state concentration by 24, a target steady-state concentration of 20-25mg/L would equate to AUC_{24}/MIC of 480 to 600 assuming MIC of 1 ug/ml. Of note, the PK/PD target for CI has not been established. All of the PK/PD data supporting an AUC_{24}/MIC ratio >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 with CI when treating acute infections, particularly in ICU patients early during the course of infection. In two comparative studies, target steady-state concentration of 20-25mg/L: 36$\pm$31 h vs 51$\pm$39 h, p=0.03[72] and 16$\pm$8h vs 50$\pm$21h was achieved more rapidly in the CI group, p<0.001.[75] Importantly, less variability in steady-state concentration and fewer blood samples (single steady-state concentration vs peak and trough concentrations) are required to calculate AUC_{24} among patients receiving CI. Timing of blood draw for trough is critical during II, whereas steady-state concentration can be measured any time after steady state has been reached during CI. In addition, administration by CI in patients receiving OPAT

has the theoretical advantage of needing less frequent access to the IV catheter and thus less complications resulting from clots or infections.

On the other hand, incompatibility of vancomycin with drugs commonly administered in the critical care setting is a notable challenge for vancomycin CI. In particular, all β-lactams with broad spectrum Gram-negative activity (including piperacillin-tazobactam, ceftazidime, cefepime, imipenem, cefotaxime, and ceftriaxone) are incompatible with vancomycin along with moxifloxacin, propofol and furosemide.[84] Since a β-lactam agent with Gram-negative activity is commonly prescribed with vancomycin for empiric therapy in critically-ill patients, the use of alternative agents (e.g. ciprofloxacin) or independent lines or multiple-catheters should be considered if vancomycin is to be administered by CI.

Summary and Recommendations:

8. The pharmacokinetics of continuous infusions suggest that such regimens may be a reasonable alternative to conventional dosing and provide a convenient way to readily achieve the desired vancomycin therapeutic range (i.e., steady-state concentration of 20 – 25 mg/L) throughout the entire dosing period. Attaining the desired drug exposure may be more readily accomplished given the ease of sampling time for serum level monitoring and dosage adjustment by changing the rate of infusion which is a highly desirable feature in critically-ill patients. AUC_{24} can be simply calculated when multiplying steady-state concentration by a factor of 24. **(IIB+)**

9. The risk of developing nephrotoxicity with continuous infusion appears to be similar or lower compared to intermittent dosing when targeting steady-state concentration 15-25mg/L and trough 10-20 mg/L respectively. **(IIB+)** 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.
10. Incompatibility with vancomycin and other drugs commonly co-administered in the ICU such as β-lactam agents with broad spectrum Gram-negative activity requires the use of independent lines or multiple-catheters when vancomycin is being considered for continuous infusion.**(IB+)**

Loading Doses

Loading doses of vancomycin have been evaluated in several studies during the past decade.[85-100] Providing loading doses of 25-30 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 intensive care unit[85-92], requiring dialysis or renal replacement therapy[93-97], or receiving continuous infusion therapy of vancomycin[85-89, 96, 99]. 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 such as sepsis, meningitis, bacteremia, infective endocarditis, pneumonia, and osteomyelitis. Vancomycin should be administered in a dilute solution (e.g., concentrations of no more than 5 mg/mL) and infused over a period of not less than 60 minutes

or at a rate of 10–15 mg/minute (≥1 hour per 1000 mg) to minimize infusion-related adverse events (e.g., red man syndrome, hypotension). An infusion rate of 10 mg/min or less is associated with fewer infusion-related events. Loading doses of 25-30 mg/kg will require infusion times of at least 2–3 hours.[90]

Most studies that have employed loading doses were based on actual body weight. While this practice is commonplace, dosing on actual body weight assumes there is a linear relationship between key population PK parameters (i.e., volume of distribution and clearance) and the body size descriptor employed. While a wide variety of actual weight-based estimates of V_D (for example: 0.4 – 1 L/kg) have been reported in the literature[7], mounting data suggest that it is not entirely accurate to describe vancomycin V_D as being proportional to body weight, particularly among obese patients (please refer to Vancomycin Dosing in Obesity section). As noted in several recent articles of vancomycin PK in obesity, as weight increases the coefficient used to calculate volume of distribution decreases.[42, 101, 102] At this point, dosing should be based on actual body weight with doses capped at 3000 mg (please refer to Vancomycin Dosing in Obesity section)[103]. More intensive therapeutic monitoring should also be performed in obese patients.

Summary and Recommendations:

11. In order to achieve rapid attainment of targeted concentrations in critically-ill patients with suspected or documented serious MRSA infections, a loading dose of 25-35 mg/kg can be considered for intermittent and continuous infusion administration of vancomycin **(IC+)**. [1]

12. Loading doses should be based on actual body weight and not exceed 3000 mg (refer to Vancomycin Dosing in Obesity section). More intensive therapeutic monitoring should also be performed in obese patients.

Vancomycin Dosing in Obesity

The original dosing strategies of vancomycin predate our current definitions of obesity and understanding of drug pharmacokinetics in obesity. Obesity is defined as a body mass index (BMI) ≥30 kg/m^2 and is currently divided into three tiers: class I obesity (30 – 34.9 kg/m^2), class II obesity (35 – 39.9 kg/m^2), and class III or morbid obesity (≥40 kg/m^2).[104] The prevalence of obesity has increased from approximately 10.0% 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.[105, 106] 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 supra-therapeutic exposure from maintenance doses calculated using actual body weight.[39, 107]

The selection of vancomycin loading dose is dependent on the estimated volume of distribution (Vd). Pharmacokinetic studies have repeatedly demonstrated that the vancomycin Vd increases with actual body weight; however, this pharmacokinetic parameter does not increase in a proportionate manner with actual body weight and is not reliably predicted in obese individuals.[102, 108-112] Blouin and colleagues demonstrated a statistically significant difference in weight-indexed Vd between obese and non-obese patients.[102] Similarly, using data from 704 patients, Ducharme and colleagues found that mean weight-indexed vancomycin

690 Vd decreased with increasing body size.[109] The average weight-indexed Vd in a study by
691 Bauer and colleagues was much lower (0.32 L/kg) in 24 morbidly obese patients compared to
692 24 patients of normal weight (0.68 L/kg, $p < 0.001$).[110] Recent studies in obese adults
693 corroborate these findings and suggest that lower Vd estimates of approximately 0.5 L/kg, or
694 weight-independent central tendency estimates approaching 75 L are observed in obese adults.
695 [103, 111, 112]The non-linear relationship between vancomycin Vd and body weight can be
696 resolved with piece-wise functions of alternate weight descriptors, allometric scaling, using
697 lower mg/kg doses with increasing body size, or capping the dose at a threshold.[109, 113] The
698 underlying rationale for a loading dose is rapid attainment of therapeutic concentrations.
699 Therefore, using actual body weight loading doses of 20-25 mg/kg (lower than previous
700 recommendations) with consideration for capping doses at 3000 mg is the most practical
701 strategy in obese patients with serious infections. This leads to calculation of 1500-2500 mg
702 (80-99 kg), 2000-3000 mg (100-119 kg), and 2500-3000 mg (≥120 kg) loading doses (rounded to
703 the nearest 250 mg) as examples. The decision of whether or not to employ a loading dose, as
704 well as the magnitude of this dose, should be driven by the severity of infection and the
705 urgency to achieve a therapeutic concentration rather than body size alone.

706 Empiric maintenance dosing of vancomycin is reliant on estimated clearance (CL).
707 Vancomycin CL is predicted by kidney function that is most commonly estimated as creatinine
708 clearance with the Cockcroft-Gault equation using patient age, sex, serum creatinine, and body
709 size.[114] Considerable controversy exists regarding the optimal body size metric for this
710 calculation in obese patients.[115] The Cockcroft-Gault equation predates the global
711 standardization of serum creatinine measurement traceable to isotopic-dilution mass-

712 spectrometry (IDMS) standards that has been advocated to reduce intra-laboratory and inter-
713 laboratory measurement variability.[115] A recent population pharmacokinetic study by Crass
714 and colleagues of obese patients (n=346) with BMI values between 30.1 to 85.7 kg/m^2 and body
715 weights of 70 to 294 kg provides an equation to estimate vancomycin CL based on age, sex,
716 serum creatinine (IDMS traceable), and allometrically scaled body weight.[103] This model or
717 similar approaches to estimating vancomycin CL, such as that defined by Rodvold and
718 colleagues, can be used to estimate the total daily maintenance dose.[116] The population
719 model estimated vancomycin CL multiplied with the target AUC estimates the initial daily
720 maintenance dose.[103, 111, 113] For example, studies report an average vancomycin CL of
721 approximately 6 L/h in obese patients that equates to achieving an AUC of approximately 500
722 hr-mg/L with a daily dose of 3000 mg. Empiric vancomycin maintenance doses above 4500
723 mg/day are not expected in obese adults because vancomycin CL rarely exceeds 9 L/h.[103,
724 111, 113]

725 Population pharmacokinetic models of vancomycin cannot account for more than 50%
726 of the inter-individual variability, which supports TDM in this population.[108, 109, 111, 113] A
727 reliable estimate of vancomycin Vd is necessary to estimate AUC when based solely on a trough
728 concentration measurement.[18, 112, 117, 118] This bias is addressed and precision is
729 improved by measurement of both a peak (collected at least 1 hour after the end of infusion)
730 and trough concentration to estimate AUC accurately in obese patients.[117] Once a reliable
731 pharmacokinetic estimate of vancomycin is defined by this two sample measurement,
732 subsequent vancomycin AUC estimation is achievable with trough only measurements by
733 Bayesian methods in physiologically stable patients.[51] For critically-ill obese patients with

unstable physiology, additional work to design adaptive feedback models to tailor doses are needed.

Summary and Recommendations:

13. A vancomycin loading dose of 20-25 mg/kg using actual body weight with a maximum of 3000 mg may be considered in obese adult patients with serious infections **(IIA+)**. Initial maintenance doses of vancomycin can be computed using a population pharmacokinetic estimate of vancomycin clearance and the target AUC in obese patients. Empiric maintenance doses ≤4500 mg/day are expected for the majority of obese patients. Measurement of peak and trough concentrations is recommended to improve the accuracy of vancomycin AUC estimation and maintenance dose optimization in obese patients **(IIA+)**.

Renal Disease and Patients Receiving Renal Replacement Therapies

Intermittent Hemodialysis

Despite the common use of vancomycin in patients receiving hemodialysis, few published outcome studies exist to determine the optimal pharmacokinetic/pharmacodynamic targets in this population. Previously published drug dosing recommendations generally targeted a pre-dialysis serum concentration, even though other pharmacodynamic targets may be more appropriate. Pre-dialysis vancomycin trough concentrations/MRSA MIC ratios >18.6 have been associated with improved patient outcomes suggesting that serum concentration monitoring is essential throughout the course of therapy.[119] Dosing to achieve pre-dialysis vancomycin concentrations of 10-20mg/L, as has been done clinically,[120] results in mean AUC_{24h} ranging from 250-450 mg*h/L, with some values below the AUC/MIC goals

recommended in other populations.[121] Outcome studies validating the 400-600 mg*h/L AUC_{24h} goal 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 400-600 mg*h/L AUC_{24h} target 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 when the vancomycin dose is given and when the next dialysis session is scheduled,[95] whether the dose is given during dialysis or after hemodialysis has ended, and the dialyzer's permeability if the dose is administered intradialytically.[122] Dialysis frequency also plays a role in dosing decisions. For non-critically-ill patients receiving hemodialysis, two or three days is the most common interdialytic period. Some critically-ill patients with severe catabolism and acute kidney injury may require more than thrice weekly hemodialysis for optimal metabolic control [123]and their maintenance vancomycin doses should be based on serum concentration monitoring.

Serum concentration monitoring is a valuable tool to guide vancomycin dosing in patients receiving dialysis, provided serum concentrations are obtained and interpreted correctly. For example, blood sampling for assessment of vancomycin concentrations should not occur during or for at least 1-2 hours after a hemodialysis treatment. These samples will not be reflective of true vancomycin body load because of the dialytic removal of vancomycin. Vancomycin serum concentrations will be quite 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[124-127].[123][122] Dosing decisions based on serum concentrations obtained during or soon after hemodialysis ends will be inherently incorrect and could result in higher

than necessary doses to be administered.[125] Serum concentration monitoring from blood samples obtained prior to the hemodialysis treatment is recommended to guide dosing, although other serum concentration monitoring techniques have been suggested.[126]

Vancomycin dosing in patients with acute or chronic kidney failure has transformed over time due to the changes in dialysis technology and techniques.[127] Older (pre-1990s) hemodialyzers were not very permeable to large molecules. Vancomycin (molecular weight 1450 Daltons) was not considered "dialyzable" because it poorly crossed the hemodialysis membranes of the era. Indeed, even today's vancomycin package insert, based on pharmacokinetic studies conducted in the 1980s, states "vancomycin is poorly removed by dialysis."[128] As hemodialysis membrane technology has improved, dialyzers have become far more permeable. Vancomycin is cleared substantially by contemporary, high permeability hemodialyzers,[129, 130] consequently vancomycin dosing strategies have changed substantially as well. For example, in spite of the package insert's statement of "In anuria, a dose of 1000 mg every 7 to 10 days has been recommended" and that "vancomycin is poorly removed by dialysis"[128], 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;[122] 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 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 three shifts of patients/day, and holding one dialysis chair for 60-90 additional minutes while vancomycin infuses into a patient is not cost-effective. Indeed, it is cheaper 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 a 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.[129, 131-133] Approximately 20-40% 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.[131, 134, 135]

Maintenance dosing strategies that do not provide a dose with every hemodialysis session have been studied (e.g. maintenance dose given with every second or third hemodialysis session),[93, 123, 136] but none have been found to meet vancomycin exposure goals in the last day of the dosing interval without giving massive doses that achieve 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 (e.g. Friday→Monday) to maintain sufficient vancomycin exposure on the third day.[121]

Dosing that is weight based appears to be superior to standard doses that ignore patient size. Further, doses should be based on actual body weight rather than a calculated body weight (See 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[94-96].[94][93]

Summary and Recommendations

14. The following tables outline recommended vancomycin loading doses for patients receiving hemodialysis, with accounting for permeability of the dialyzer and whether the dose is administered intradialytically or after dialysis ends **(IIB+).**

LOADING DOSE RECOMMENDATION

Time of infusion	Dialyzer Permeability	Vancomycin loading dose
After dialysis ends	Low	25 mg/kg
After dialysis ends	High	25 mg/kg
Intradialytic	Low	30 mg/kg
Intradialytic	High	35 mg/kg

[121, 131, 132, 134]

THRICE WEEKLY HEMODIALYSIS MAINTENANCE DOSE RECOMMENDATION

Time of infusion	Dialyzer Permeability	Maintenance dose
After dialysis ends	Low	7.5 mg/kg
After dialysis ends	High	10 mg/kg
Intradialytic	Low	7.5-10 mg/kg
Intradialytic	High	10-15 mg/kg

[95, 120, 121, 137]

15. 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 **(IB+).**

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 (6-12 hours/day). Even hemodialysis itself differs in the inpatient setting from the outpatient setting, 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 and to a different extent than standard intermittent hemodialysis.[138, 139] 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_{24h} and much higher average serum concentrations. As is the case with any hemodialysis therapy, serum concentrations obtained during or within 1-2 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 a peridialytic 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 series of 27 courses of vancomycin given to patients receiving a hybrid hemodialysis therapy reported prescribers have tried a wide variety of dosing schemes.[140] By these authors' criteria, 89% of the prescribed vancomycin doses were under-dosed in their institution. Given the absence of outcome data in patients

receiving these therapies, it seems prudent to use the same vancomycin AUC goal (400-600 mg*h/L) as is recommended throughout this document.

Summary and Recommendations

16. Loading doses of 20-25 mg/kg actual body weight should be used, recognizing that these hybrid dialysis therapies efficiently remove vancomycin. 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 60-90 minutes of dialysis, as is done with standard hemodialysis.[121] Frequent serum concentration monitoring should guide further maintenance doses **(IIC+).**

Dosing in Continuous Renal Replacement Therapies

The use of continuous renal replacement therapies (CRRT) like continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF) have grown in popularity in critically-ill patients with acute kidney injury 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.[141] Vancomycin is removed by CRRT and its CL is related closely to the rate of ultrafiltrate/dialysate flow[96] with hemodiafilter type being of lesser importance, because contemporary hemodiafilters are all very permeable to the drug.

In patients on CRRT, achieving targeted serum concentration often are not met with conventional dosing.[76, 142] Although outcomes studies specific to patients receiving CRRT

have not been conducted, it seems prudent to apply the same vancomycin AUC/MIC target (i.e., 400-600) in these critically-ill patients as is recommended throughout this document.

Summary and Recommendations

17. Loading doses of 20-25 mg/kg by actual body weight should be used in patients receiving CRRT. Maintenance dose and dosing interval should be based on serum concentration monitoring. An initial 12 hour dosing interval has been suggested to achieve trough concentrations of 15-20 mg/L, which will likely achieve the desired 400-600 mg*h/L AUC/MIC target.[143] In fluid overloaded patients, doses may be reduced as patients become euvolemic and drug Vd decreases. The use of CI of vancomycin in patients receiving CRRT appears to be growing,[76, 96] and could be used in place of intermittent vancomycin dosing, especially when high CRRT ultrafiltrate/dialysate flow rates are employed **(IB+).**

Pediatrics

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, similar to adults.[6] Although limited prospective, comparative data on the value of vancomycin therapeutic monitoring in adults exist with respect to improving outcomes and decreasing toxicity, virtually no prospectively collected data on outcomes of MRSA infection exist in newborns, infants and children. Further, for newborns, particularly premature infants, immature renal elimination mechanisms and relative increase in Vd per bodyweight, compared with older infants, 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 adults, with subsequent decline during the teens 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, but careful monitoring in this patient population is prudent. 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 methicillin-susceptible strains) in children treated with vancomycin suggest that trough concentrations of > 15 μg/mL were not associated with improved outcomes, yet an increase in AKI was observed. [144-146] Furthermore, another retrospective pediatric study evaluating outcomes of MRSA bacteremia as a function of $AUC/MIC_{BMD} \geq 400$ did not show improved outcomes.[147] Similarly, vancomycin trough concentrations < 10 μg/mL, as compared with > 10 μg/mL, were not associated with increased 30-day mortality and recurrent bacteremia in children, although the lower concentrations were associated with prolonged bacteremia. [148]

In the absence of prospective outcomes data on serious MRSA infections in children to validate the observations reported in adults, dosing in children should be designed to achieve an AUC of 400 to 600 μg-hr/mL (assuming MIC of 1 μg/mL). This pharmacodynamic target,

specifically closer to AUC 400, rather than 600, has been used by pediatric investigators to model both dosing and therapeutic monitoring. However, it is possible that in otherwise healthy children with fewer comorbidities than adults, a lower target may yield equivalent outcomes to an AUC of 400 to 600 µg-hr/mL. Using currently recommended dosages of 45-60 mg/kg/day, widespread failures in treatment have not been published for children, which may reflect the younger host with a more robust systemic and immunologic response to infection, a different management approach (surgical and antibiotic) of invasive MRSA infection, lack of associated comorbidities, or publication bias. Prospective comparative clinical trials of documented infections, treated with different dosages of vancomycin, have not been published for children.

Empiric Maintenance Regimen

Published retrospective PK/PD data in children suggest that current dosing of 45 to 60 mg/kg/day divided every 6 to 8 h may be insufficient to achieve currently recommended targets for adults of an AUC 400 to 600 µg-hr/mL (assuming MIC of 1 µg/mL).[1] In fact, higher dosages ranging from 60 to 80 mg/kg/day every 6 h may be needed to achieve these targets for MRSA with an MIC of 1 µg/mL or less to vancomycin, presumably a result of greater CL of vancomycin compared with adults.[1, 149-152] For children infected by MRSA pathogens with a MIC of > 1 µg/mL, it is unlikely that the target exposure can be reliably achieved with previously investigated dosages of vancomycin in children.

Le and colleagues utilized population-based PK modeling on 702 children > 3 months old with varying comorbidities from two institutions to analyze 1660 vancomycin serum

964 concentrations obtained between 2003 and 2011. They demonstrated that four important
965 factors (including age, weight, renal function as assessed by SCr, and MIC) contributed to
966 vancomycin dosing. Monte Carlo simulations were created using population-based PK
967 modeling with Bayesian estimation and MICs of clinical isolates as determined by Etest with
968 85% of clinical isolates demonstrated to have an $MIC_{E\text{-}test}$ of 1 µg/mL or less. A dose of 80
969 mg/kg/day was necessary to achieve an AUC/$MIC_{E\text{-}test}$ ≥ 400 in approximately 90% of subjects,
970 particularly those < 12 years of age with normal renal function. At 80 mg/kg/day, the median
971 AUC was 675 µg-hr/mL and trough was 16 µg/mL. As expected, those ≥ 12 years of age
972 achieved similar exposure at lower dosages of 60 to 70 mg/kg/day.[152] The clinical
973 applicability of this PK model for vancomyin CL estimation to determine AUC exposure was
974 validated by Ploessl et al. [153]

975 Other studies corroborated Le and colleagues' findings—the need to use higher dosages
976 ranging from 60 to 80 mg/kg/day, depending on age and renal function.[150, 151, 154] Using
977 the literature for vancomyin CL published on or before 2000 and Bayesian estimation for one
978 25-kg base subject, Frymoyer et al evaluated the relationship between AUC and trough
979 concentrations, and showed that 60 mg/kg/day achieved trough concentrations of 7-10 µg/mL
980 and AUC/MIC of ≥ 400 in 90% of children, for MRSA pathogens with an MIC of 1 µg/mL.[151]
981 However, their finding may not be extrapolatable to the entire pediatric population with
982 varying ages and renal function. In a second study, these investigators demonstrated that 60
983 mg/kg/day achieved AUC/MIC_{BMD} values between 386 and 583 for MIC_{BMD} of 1 µg/mL in
984 children 2 to 12 years of age, indicating that some younger children may require higher doses

985 to achieve target AUC/MIC_{BMD}.[150] The probability of target attainment was not provided and
986 doses above 60 mg/kg/day were not evaluated in this study.

987 Two retrospective studies, that utilized non-Bayesian methods, evaluated trough
988 concentration targets of 10-20 µg/mL (a higher range than that used by Le and Frymoyer who
989 also assessed AUC) in children 1 month to 18 years of age. An interesting finding of Madigan's
990 study showed that 60 mg/kg/day achieved the target trough concentration in only 17% of
991 preschool-aged children 2 to 5 years old, which was the lowest attainment compared with all
992 other pediatric age groups.[154] Eiland and colleagues showed that doses of 70 to 80
993 mg/kg/day were necessary to achieve trough concentrations of 10-20 µg/mL.[149] Another
994 study by Abdel et al demonstrated that doses higher than 60 mg/kg/day were necessary to
995 achieve an AUC/MIC of ≥ 400 in children with cancer. Mean age in this study cohort was 6 ± 2.5
996 years; it is possible that young age with greater CL may have been a contributing factor for the
997 need for an increased dose, an observation uncovered in studies by Le and Madigan.[155]

998 As a drug that demonstrates renal elimination, vancomycin requires dosage adjustment
999 in children with acute or chronic renal insufficiency. Le and colleagues conducted a population-
1000 based PK analysis with Bayesian method that evaluated 63 case-control pairs (matched by age
1001 and weight) with 319 vancomycin serum concentrations. The mean age of this study cohort
1002 was 13 ± 6 years old. The investigators reported that a vancomycin dose of 45 mg/kg/day (i.e.,
1003 15 mg/kg every 8 h) in renally-impaired children achieved similar AUC exposure to 60
1004 mg/kg/day in children with normal renal function. Notably, they showed that in 87% of
1005 children with initial renal impairment, vancomycin CL improved (with a lag in the recovery of
1006 renal function as assessed by SCr) within the first 5 days of therapy, indicating some degree of

renal function recovery, supporting the need for ongoing therapeutic drug monitoring of vancomycin. [156] In addition, vancomycin CL does not correlate well with creatinine CL in children, particularly in those who are acutely-ill in the ICU setting with varying degrees of renal dysfunction. Rapid return of renal function may occur over the first few days after ICU admission. As such, both therapeutic monitoring of serum concentrations as well as renal function should be conducted during vancomycin therapy.[157, 158]

Loading Dose

Loading doses of 25 to 30 mg/kg in critically-ill adults have been suggested to achieve steady-state concentrations more quickly, but preliminary data in pediatrics suggests 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.[159] However, the concept of a loading dose accompanied by a sufficient daily maintenance dose required to achieve the target exposure, initiated at a specified time after the loading dose, should be investigated.

Acute Kidney Injury

Similar to adults, the aggregate literature in pediatrics suggests that the risk of AKI increases as a function of vancomycin exposure, especially when trough concentration exceeds 15-20 µg/mL. In fact, Fiorito and colleagues reported in a recent meta-analysis of 10 pediatric studies that troughs ≥ 15 µg/mL increased AKI by 2.7-fold (95% CI: 1.82–4.05) and AKI was further correlated with stay in the pediatric ICU. [146] McKamy and colleagues published the first study that uncovered the association between trough concentrations > 15-20 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.[160] Four studies published later corroborated these findings in which the interplay of multiple factors, in addition to vancomycin exposure, contributed to AKI.[161-164] Interestingly, Sinclair et al reported that a 5 mg/kg dose augmentation or each additional day of vancomycin use increased the risk of AKI.[162] Knoderer and colleagues 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.[161]

One pediatric study evaluated the relationship between AKI and vancomycin AUC and trough concentrations, both derived by Bayesian estimation. Le and colleagues conducted a large population-based PK analysis using 1576 serum concentrations collected from 680 pediatric subjects. A continuous exposure-response relationship was observed, where 10%, 33% and 57% of patients who achieved AUC $\geq$ 400, 800, and 1000 µg-hr/mL, respectively, experienced AKI. Even after adjusting for ICU stay and concomitant use of nephrotoxic drugs, AUC ≥ 800 µg-hr/mL and trough concentrations ≥15 µg/mL were independently associated with a > 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.[165] Vancomycin AUC exposure should be optimally maintained at < 800 µg-hr/mL to minimize AKI. As such, vancomycin doses $\geq$ 100 mg/kg/day should be avoided since the projected median AUC and trough concentrations are 843 µg-hr/mL and 21 µg/mL, respective, for 100 mg/kg/day.[152]

Therapeutic Monitoring

Recent literature on vancomycin in pediatrics focused primarily on PK analysis to support optimal dosing. Data on vancomycin therapeutic monitoring in pediatrics are limited to one study. Le and colleagues conducted a population-based PK analysis in 138 pediatric subjects who were > 3 months of age with 712 vancomycin serum concentrations (collected mostly after the 3rd or 4th 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 two concentrations (peak and trough), compared with trough-only monitoring. Furthermore, the two-concentration approach improved the prediction of future AUC exposure in patients.[166] Despite the availability of only one study on vancomycin monitoring in pediatrics, the findings appear congruent with adult data supporting AUC-guided therapeutic monitoring that incorporates the Bayesian method. Furthermore, this AUC-guided monitoring approach also appears prudent to predict toxicity in light of AKI data in pediatrics.

Overall, limited outcomes data exist in pediatrics to support the AUC target found in adults for drug effectiveness. Some of the differences found between adults and children for MRSA infections treated with vancomycin include the complexity of vancomycin CL in the various pediatric age groups, and the differences in tissue site-of-infection drug exposure (e.g., common occurrence of acute hematogenous osteomyelitis in children requiring therapeutic bone concentrations, but rare occurrence of MRSA endocarditis) suggest that further studies in children that incorporate prospective assessment of clinical outcomes, are needed to identify the optimal dosing strategies for MRSA infections in pediatrics. Until additional data are available, the AUC target used in adults of 400 to 600 µg-hr/mL (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 ug/mL, published data suggest that 60 to 80 mg/kg/day divided every 6 hours is required to achieve an AUC target of 400 to 600 μg-hr/mL.

Summary and Recommendations:

18. Based on an AUC target of 400 to 600 μg-hr/mL (assuming MIC of MRSA of ≤ 1 μg/mL) from adult data, the initial recommended vancomycin dosage for suspected serious MRSA infections (including pneumonia, pyomyositis, multifocal osteomyelitis, complicated bacteremia and necrotizing fasciitis) is:
    - 60 to 80 mg/kg/day, divided every 6 h, for children ages 3 months to 12 years and
    - 60 to 70 mg/kg/day, divided every 6 h, for those ≥ 12 years old.

    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. Dosing adjustment should be made for those with renal insufficiency, are obese (see Pediatric Obesity), or for those receiving concurrent nephrotoxic drug therapy. The safety of vancomycin above 80 mg/kg/day has not been prospectively evaluated (**IB+**).
19. AUC-guided therapeutic monitoring for vancomycin, preferably with Bayesian estimation, is recommended for all pediatric age groups, based on developmental changes of vancomycin CL documented from the newborn to the adolescent. Both serum concentrations 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 necessitates drug monitoring. Therapeutic monitoring should begin within 24 to 48 hours of vancomycin therapy for serious MRSA

infections in children, as in adults. 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 (**IB+**).

20. Vancomycin exposure should be optimally maintained below the thresholds for AUC of 800 μg-hr/mL and trough concentrations of 15 μg/mL to minimize AKI. Vancomycin doses ≥ 100 mg/kg/day should be avoided since they are likely to surpass these thresholds (**IB+**).
21. Insufficient data exist on which to base a recommendation for a loading dose. 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.

Pediatric Obesity

Vancomycin is a large glycopeptide molecule that is hydrophilic, suggesting the distribution into tissues with high lipid concentrations such as adipose tissue, is decreased, as noted above for adults (see Obesity). When vancomycin dosing is based on total body weight (mg/kg) for both obese and non-obese children, serum concentrations have been documented to be higher in obese children, assuming that renal CL is similar between the two populations.[167] Moffett retrospectively compared vancomycin PK in 24 obese children who were matched with 24 control non-obese children.[168] Vancomycin dose administration per

child was slightly higher in the obese children, which resulted in increased trough concentrations. Similarly, two other retrospective non-Bayesian studies by Heble and Miller et al documented higher vancomycin trough concentration in overweight and obese children, compared with normal-weight children, with dosing based on total body weight.[169, 170] No increase in AKI was noted in the overweight children.[170]

Collectively, non-Bayesian studies of obese children have evaluated maintenance regimens ranging from 40 to 80 mg/kg/day using total body weight, with some instituting maximum doses of 1 to 2 grams over 1 to 2 hours.[168, 169, 171, 172] 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 measurement that may not always be readily available in clinical practice. [173] Body surface area is not typically used for dosing medications, except for chemotherapeutic agents.[174]

Using a Bayesian population-based PK analysis of 389 vancomycin serum concentrations collected from 87 pairs of obese and non-obese children (matched by age and baseline SCr), Le and colleagues showed that the Vd was strongly correlated with actual or total body weight and CL correlated with allometric weight (by 0.75) and body surface area.[175] Using this PK model, Nguyen and colleagues 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 ≥ 400 in obese children (i.e., target achieved in 76% when given by total body weight, in 66% when given by adjusted body weight, and 31% when given by allometric weight). Furthermore, fewer obese children < 12 years old, compared with those ≥ 12 years, achieved AUC/MIC ≥ 400 dosed at 60

mg/kg/day by total body weight (i.e., 70% vs 84%), an observation identified in non-obese children.[152, 154] Interestingly, the use of a 20 mg/kg loading dose based on total body weight in obese children increased achievement of AUC/MIC ≥ 400, especially within the first 12 hours of therapy. In addition, one of every five obese children had AUC ≥ 800 µg-hr/mL, indicating that routine therapeutic and safety monitoring is prudent.[176]

Summary and Recommendations:

22. Published, retrospective data suggest that obese children are likely to have vancomycin exposures that may be statistically greater than 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 non-obese children, obese children < 12 years old, compared with those ≥ 12 years, may require higher mg/kg dose. (**IIB+**)
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 non-obese children should also apply for obese children (**IC+**).
24. A loading dose of 20 mg/kg by total body weight may be warranted in obese children (**IC+**).

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[177], as well as the increased vancomycin Vd seen in the most premature and youngest infants. Models to predict vancomycin dosing have variously incorporated weight-based

dosing, chronologic age-based dosing, post-menstrual age-based dosing, SCr-based dosing (except for the first week of life when transplacental maternal creatinine in the neonatal circulation renders the 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 compared four 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, when the target was high trough concentrations within a narrow range of 15–20 μg/mL, only 13–21% of patients were within this range across the four dosing regimens.[178] Marqués-Miñana also developed a population PK model, and proposed dosing based on post-menstrual age.[179] SCr-based, rather than post-menstrual or post-conceptional age-based, dosing has been supported by Irikura[180] and Capparelli.[181] However, when evaluating published neonatal PK models, no consensus on an optimal dosing regimen was achieved by experts on neonatal vancomycin as reported by Zhao et al. After evaluating the predictive performance of six 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 the Jaffé method overestimated SCr concentrations when compared to the enzymatic method and for vancomycin concentrations, the fluorescence polarization immunoassay method and enzyme-

multiplied immunoassay method assays showed different predictive performances as well. [182]

With the knowledge that AUC, as compared with trough concentrations, is a more achievable target in pediatrics, Frymoyer and colleagues 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, population PK analysis was conducted to create a model for vancomycin CL that was based on weight, post-menstrual age, and SCr (measured by a modified kinetic Jaffe reaction). Monte Carlo simulations with Bayesian estimation demonstrated that trough concentrations ranging from 7 to 11 μg/mL were highly predictive of an AUC_{24} of >400 μg-hr/mL in at least 90% of neonates. Doses to achieve this PK/PD target ranged from 15 to 20 mg/kg every 8 to 12 h, depending on post-menstrual age and SCr.[183] Stockmann et al later supported the predictive performance and generalizability of this model in 243 neonates with 734 vancomycin concentrations. While a trough concentration of 11 μg/mL predicted the attainment of an AUC ≥ 400 μg-hr/mL in 93% of neonates, Stockmann noted that a trough concentration alone did not precisely predict AUC and concluded the need for Bayesian approaches to support vancomycin dosing decisions for neonates in the clinical setting.[184] Furthermore, Cies et al reported differences in vancomycin PK, particularly impacted by rapid vancomycin CL, in neonates with extracorporeal oxygenation life support, reiterating the need for Bayesian-derived dosing decision support in this vulnerable population.[185] Lastly, Leroux et al demonstrated the success of the clinical integration of a model-based vancomycin dosing

calculator, developed from a population PK study, in augmenting the attainment of target trough concentrations from 41% to 72% without any cases of AKI.[186]

The incidence of vancomycin-associated AKI reported in neonates has been low, ranging from 1 to 9%.[187] Nonetheless, a positive correlation between increasing vancomycin trough concentrations and AKI has been reported by Bhargava et al.[188] Furthermore, in a large, retrospective, multi-centered, propensity score-matched cohort study of 533 neonates receiving vancomycin and gentamicin compared with 533 receiving gentamicin, Constance et al 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 non-steroidal anti-inflammatory drug use, ≥1 positive blood cultures, low birth weight and higher severity of illness and risk of mortality scores.[189]

Summary and Recommendations:

25. Doses to achieve an AUC of 400 μg-hr/mL (assuming an MIC of 1 μg/mL) in neonates may range from 15 to 20 mg/kg every 8 to 12 hours, depending on post-menstrual age and SCr. 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 from an MRSA infection for all neonates, regardless of gestational and chronologic age. A lower AUC/MIC target may be reasonable for neonatal coagulase-negative staphylococcal infections. The specific recommendations for therapeutic monitoring in pediatrics children should also apply for neonates (**IB+**).

Conclusion

To optimize vancomycin use for the treatment of serious infections caused by MRSA, we recommend targeting an AUC/MIC_{BMD} ratio of 400-600 (assuming an MIC_{BMD} of 1 mg/L) for empiric dosing in both adult and pediatric patients to maximize the clinical efficacy and minimize AKI. Furthermore, the AUC should be therapeutically monitored using one or two post dose concentrations (i.e., a peak after the early vancomycin tissue distribution phase, and trough, prior to the next dose), preferably integrating the Bayesian approach. While valuable literature in adults, children and neonates have emerged since the last vancomycin guideline, future studies in all patient populations are necessary to address gaps including: 1) efficacy data to support certain patient populations (including pediatrics, renal disease and obesity) and other types of infections; 2) efficacy data on specific pathogens, including coagulase-negative staphylococcus and *Streptococcus* spp.; 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 in patients with obesity and renal insufficiency; 5) efficacy benefit, dosing algorithm (specifically incorporating a loading dose followed by maintenance infusion), and 6) toxicodynamics for continuous infusion in critically-ill patients.

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