

# Therapeutic Monitoring of Vancomycin for Serious Methicillin-resistant *Staphylococcus aureus* Infections: A Revised Consensus Guideline and Review by the American Society of Health-system Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists

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Recent clinical data on vancomycin pharmacokinetics and pharmacodynamics suggest a reevaluation of current dosing and monitoring recommendations. The previous 2009 vancomycin consensus guidelines recommend trough monitoring as a surrogate marker for the target area under the curve over 24 hours to minimum inhibitory concentration (AUC/MIC). However, recent data suggest that trough monitoring is associated with higher nephrotoxicity. This document is an executive summary of the new vancomycin consensus guidelines for vancomycin dosing and monitoring. It was developed by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists vancomycin consensus guidelines committee. These consensus guidelines recommend an AUC/MIC ratio of 400–600 mg\*hour/L (assuming a broth microdilution MIC of 1 mg/L) to achieve clinical efficacy and ensure safety for patients being treated for serious methicillin-resistant *Staphylococcus aureus* infections.

**Keywords.** vancomycin consensus guidelines; vancomycin; pharmacokinetics and pharmacodynamics; target attainment; nephrotoxicity.

## EXECUTIVE SUMMARY

The revised vancomycin consensus guidelines for dosing and monitoring vancomycin is an updated version of the 2009 guidelines developed by the American Society of Health-Systems Pharmacists, the Infectious Diseases Society of

America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists vancomycin consensus guidelines committee. The following is an executive summary of key recommendations and grading system used for this document (Tables 1, 2) [1, 2].

Despite more than 61 years of clinical use of vancomycin, knowledge gaps regarding the most appropriate approach for optimizing therapy and minimizing toxicity still exist. The area under the curve over 24 hours to minimum inhibitory concentration ratio (AUC/MIC) has been documented as the primary pharmacokinetic/pharmacodynamic (PK/PD) target for glycopeptides, including vancomycin. The previous consensus guidelines in 2009 recommended the use of trough monitoring (target 15–20 mg/L) as a surrogate marker of the AUC/

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**Table 1. Grading System for Recommendations Based on Quality of Evidence**

Category and Grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for or against use
B	Moderate evidence to support a recommendation for or against use
C	Poor evidence to support a recommendation
Quality of evidence	
I	Evidence from 1 or more properly randomized controlled trials
II	Evidence from 1 or more well-designed clinical trials, without randomization; from cohort or case-controlled analytic studies (preferably from > 1 center); from multiple time-series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

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

**Table 2. Primary Recommendations for Vancomycin Dosing and Therapeutic Drug Monitoring****A. ADULTS AND PEDIATRICS**

- In patients with suspected or definitive serious MRSA infections, an individualized target of the AUC/MIC<sub>BMD</sub> ratio of 400 to 600 (assuming a vancomycin MIC<sub>BMD</sub> of 1 mg/L) should be advocated to achieve clinical efficacy while improving patient safety **(A-II)**.
- When transitioning to AUC/MIC monitoring, clinicians should conservatively target AUCs for patients with suspected or documented serious infections due to MRSA assuming a vancomycin MIC<sub>BMD</sub> of 1 mg/L or less at most institutions. Given the importance of early, appropriate therapy, vancomycin targeted exposure should be achieved early during the course of therapy, preferably within the first 24 to 48 hours **(A-II)**. As such, the use of Bayesian-derived AUC monitoring may be prudent in these cases since it doesn't require steady-state serum vancomycin concentrations to allow for early assessment of AUC target attainment.
- Trough-only monitoring, with target between 15 and 20 mg/L, is no longer recommended based on efficacy and nephrotoxicity data in patients with serious infections due to MRSA **(A-II)**. There is insufficient evidence to provide recommendations on whether trough-only or AUC-guided vancomycin monitoring should be used among patients with noninvasive MRSA or other infections.
- Vancomycin monitoring is recommended for patients receiving vancomycin for serious MRSA infections to achieve sustained targeted AUC (assuming a MIC<sub>BMD</sub> of 1 mg/L, unless it is known to be greater or less than 1 mg/L by BMD). Independent of MRSA infection, vancomycin monitoring is also recommended for all patients at high risk of nephrotoxicity (eg, critically ill patients receiving concurrent nephrotoxins), patients with unstable (ie, deteriorating or significantly improving) renal function, and those receiving prolonged courses of therapy (more than 3–5 days). We suggest the frequency of monitoring be based on clinical judgement; frequent or daily monitoring may be prudent for hemodynamically unstable patients (eg, end-stage renal disease) and once-weekly monitoring for hemodynamically stable patients **(B-II)**.
- Based on current national vancomycin susceptibility surveillance data, under most circumstances for empiric dosing, the vancomycin MIC should be assumed to be 1 mg/L. When the MIC<sub>BMD</sub> is > 1 mg/L, the probability of achieving an AUC/MIC ≥ 400 target is unlikely with conventional dosing; higher doses may risk unnecessary toxicity and the decision to change therapy should be based on clinical judgment. In addition, when MIC<sub>BMD</sub> < 1 mg/L, we do not recommend decreasing the dose to achieve the AUC/MIC target. It is important to note the limitations in automated susceptibility testing methods, including the lack of precision and variability in MIC results depending on method used **(B-II)**.
- The PK of continuous infusion suggest that such regimens may be a reasonable alternative to conventional intermittent infusion dosing when the AUC target cannot be achieved **(B-II)**.
- Incompatibility with vancomycin and other drugs commonly coadministered in the ICU requires the use of independent lines or multiple catheters when vancomycin is being considered for continuous infusion **(A-III)**.

**B. ADULTS**

- Given the narrow vancomycin AUC range for therapeutic effect and minimal AKI, the most accurate and optimal way to manage vancomycin dosing should be through AUC-guided dosing and monitoring **(A-II)**. We recommend to accomplish this in 1 of 2 ways.
  - One approach relies on the collection of 2 concentrations (obtained near steady-state, postdistributional peak concentration at 1–2 hours after infusion and trough at end of dosing interval) preferably but not required during the same dosing interval (if possible) and utilizing first-order PK equations to estimate the AUC **(A-II)**.
  - The preferred approach to monitor AUC involves the use of Bayesian software programs, embedded with a PK model based on richly sampled vancomycin data as the Bayesian prior, to optimize the delivery of vancomycin based on the collection of 1 or 2 vancomycin concentrations, with at least 1 trough. It is preferred to obtain 2 PK samples (ie, 1–2 hours postinfusion and at end of dosing interval) to estimate the AUC with the Bayesian approach **(A-II)**. A trough concentration alone may be sufficient to estimate the AUC with the Bayesian approach in some patients, but more data are needed across different patient populations to confirm viability of using trough only data **(B-II)**.
- Doses of 15 to 20 mg/kg (based on actual body weight) administered every 8–12 hours as an intermittent infusion are recommended for most patients with normal renal function when assuming MIC<sub>BMD</sub> of 1 mg/L **(A-II)**. In patients with normal renal function, these doses may not achieve therapeutic AUC/MIC target when the MIC is 2 mg/L.
- Continuous infusion*: Based on current available data, a loading dose of 15–20 mg/kg, followed by daily maintenance CI of 30–40 mg/kg up to 60 mg/kg, to achieve target steady-state concentration of 20–25 mg/L may be considered for critically ill patients **(B-II)**. AUC<sub>24</sub> can be simply calculated when multiplying steady-state concentration (ie, desired therapeutic range of 20–25 mg/L throughout entire dosing interval) by a factor of 24 **(B-II)**. Attaining the desired drug exposure may be more readily accomplished given the ease of sampling time and dosage adjustment by changing the rate of infusion which is a highly desirable feature in critically ill patients **(B-II)**.
- The risk of developing nephrotoxicity with continuous infusion appears to be similar or lower compared to intermittent dosing when targeting steady-state concentration 15–25 mg/L and trough 10–20 mg/L, respectively **(B-II)**. Definitive studies are needed to compare drug exposure based on measured AUC<sub>24</sub> and factors that predispose to development of nephrotoxicity such as receipt of concomitant nephrotoxins, diuretics, and/or vasopressor therapy in patients receiving continuous infusion vs intermittent infusion of vancomycin.

**Table 2. Continued**

12. In order to achieve rapid attainment of targeted concentrations in critically ill patients with suspected or documented serious MRSA infections, a loading dose of 20–35 mg/kg can be considered for intermittent administration of vancomycin (**B-II**). Loading doses should be based on actual body weight and not exceed 3000 mg. More intensive and early therapeutic monitoring should also be performed in obese patients (**B-II**).
13. *Adult obesity*: A vancomycin loading dose of 20–25 mg/kg using actual body weight with a maximum of 3000 mg may be considered in obese adult patients with serious infections (**B-II**). Empiric maintenance doses for most obese patients usually do not exceed 4500 mg/day, depending on their renal function (**B-II**). Early and frequent monitoring of AUC exposure is recommended for dose adjustment, especially when empiric doses exceed 4000 mg/day (**A-II**).
14. *Intermittent hemodialysis*: Since efficacy data are unavailable for AUC < 400 mg\*h/L, monitoring based on predialysis serum concentrations and extrapolating these values to estimate AUC is most practical. Maintaining predialysis concentrations between 15 and 20 mg/L are likely to achieve the AUC of 400–600 mg\*h/L in the previous 24 hours (**C-III**). Predialysis serum concentration monitoring should be performed not less than weekly and should drive subsequent dosing rather than a strict weight-based recommendation, although these recommended doses provide a useful starting point until serum concentrations have been determined (**B-II**).
15. *Hybrid dialysis therapies (eg slow-low efficiency dialysis)*: Loading doses of 20–25 mg/kg actual body weight should be used, recognizing that these hybrid dialysis therapies efficiently remove vancomycin (**B-III**). Initial doses should not be delayed to wait for a dialysis treatment to end. Maintenance doses of 15 mg/kg should be given after hybrid hemodialysis ends or during the final 60–90 minutes of dialysis, as is done with standard hemodialysis (**B-III**). Concentration monitoring should guide further maintenance doses.
16. *Continuous renal replacement therapies*: Loading doses of 20–25 mg/kg by actual body weight should be used in patients receiving CRRT at conventional, KDIGO-recommended effluent rates of 20–25 mL/kg/h (**B-II**). Initial maintenance dosing for CRRT with effluent rates of 20–25 mL/kg/h should be 7.5–10 mg/kg every 12 hours (**B-II**). Maintenance dose and dosing interval should be based on serum concentration monitoring, which should be conducted within the first 24 hours to ensure AUC/MIC targets are met. In fluid-overloaded patients, doses may be reduced as patients become euvoletic and drug Vd decreases. The use of continuous infusion vancomycin in patients receiving CRRT appears to be growing, and could be used in place of intermittent vancomycin dosing, especially when high CRRT ultrafiltrate/dialysate flow rates are employed (**B-II**).
- C. PEDIATRICS**
17. Based on an AUC target of 400 mg\*h/L (but potentially up to 600 mg\*h/L assuming MIC of  $\leq 1$  mg/L) from adult data, the initial recommended vancomycin dosage for children with normal renal function and suspected serious MRSA infections is 60–80 mg/kg/day, divided every 6 to 8 hours, for children ages 3 months and older (**A-II**).
18. The maximum empiric daily dose is usually 3600 mg/day in children with adequate renal function (**C-III**). Most children generally should not require more than 3000 mg/day and doses should be adjusted based on observed concentrations to achieve the AUC/MIC target. Early monitoring of observed concentrations is recommended when doses exceed 2000–3000 mg/day (**A-III**). Furthermore, close monitoring of observed concentrations and renal function is prudent in patients with poor or augmented renal clearance as resolution of their renal function may occur within the first 5 days of therapy.
19. AUC-guided therapeutic monitoring for vancomycin, preferably with Bayesian estimation, is suggested for all pediatric age groups, based on developmental changes of vancomycin CL documented from the newborn to the adolescent. Based on current available data, the suggestion for AUC-guided monitoring in pediatrics aligns with the approach for adults, including the application of Bayesian estimation for 1 trough concentration, or first-order PK equations with 2 concentrations (**B-II**). The Bayesian AUC-guided dosing strategy may be an optimal approach to individualize vancomycin therapy in pediatrics since it can incorporate varying ages, weights, and renal function. Both serum concentrations of vancomycin and renal function should be monitored since vancomycin CL and creatinine CL are not always well correlated in pediatrics. Furthermore, aggressive dosing to maintain target AUC exposure and decrease the risk of potential AKI in treatment of MRSA infection necessitates drug monitoring.
20. Therapeutic monitoring may begin within 24 to 48 hours of vancomycin therapy for serious MRSA infections in children, as in adults (**B-III**). Any delay in therapeutic monitoring should be based on severity of infection and clinical judgment. Dosing adjustment should be made for those with renal insufficiency, obesity, or for those receiving concurrent nephrotoxic drug therapy. Following the initial dose, dosing adjustment is important for those with acute renal insufficiency, but subsequent adjustment (particularly within the first 5 days of therapy) may be necessary for those experiencing recovery of renal function. Sustained or subsequent decreases in dosage may be needed, particularly for those with chronic renal insufficiency and those receiving concurrent nephrotoxic drug therapy (**B-III**).
21. Vancomycin exposure may be optimally maintained below the thresholds for AUC of 800 mg\*h/L and trough concentrations of 15 mg/L to minimize AKI (**B-II**). The safety of vancomycin above 80 mg/kg/day has not been prospectively evaluated. Avoiding vancomycin doses  $\geq 100$  mg/kg/day is suggested since they are likely to surpass these thresholds (**B-III**).
22. Insufficient data exist on which to base a recommendation for a loading dose among the nonobese pediatric population. Loading doses from adult studies may be considered, but further studies are needed to elucidate the appropriate dose for the various pediatric populations from the neonate to adolescent (**C-III**).
23. *Pediatric obesity*: 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 nonobese children, obese children < 12 years old, compared with those  $\geq 12$  years, may require higher mg/kg dose (**B-II**).
24. *Pediatric obesity*: Therapeutic monitoring is likely to be of particular value in obese children, both for therapeutic response and the risk of AKI. The specific recommendations for therapeutic monitoring in nonobese children may also apply for obese children (**B-II**). A loading dose of 20 mg/kg by total body weight is recommended in obese children (**A-III**).
25. *Neonates*: Doses recommended to achieve an AUC of 400 mg\*h/L (assuming an MIC of 1 mg/L) in neonates and infants up to 3 months old range from 10 to 20 mg/kg every 8 to 48 hours, depending on postmenstrual age, weight, and SCr (**A-II**).

Abbreviations: AKI, acute kidney injury; AUC, area under the curve; AUC<sub>24</sub>, area under the curve over 24 hours; CL, clearance; CRRT, continuous renal replacement therapy; ICU, intensive care unit; KDIGO, Kidney Diseases Improving Global Outcomes; MIC<sub>BMID</sub>, minimum inhibitory concentration, broth microdilution; MRSA, methicillin-resistant *Staphylococcus aureus*; PK, pharmacokinetics; SCr, serum creatinine; Vd, volume of distribution.

MIC (target 400 mg\*hour/L) for ease of managing therapy and simplifying dose adjustments and monitoring. At that time, the primary reason for increasing the exposure of vancomycin via specific trough monitoring targets was to improve the

likelihood of achieving the AUC/MIC target of 400 mg\*hour/L and thereby increasing efficacy. However, since the implementation of these recommendations, there have been numerous reports of increased nephrotoxicity in adults and pediatrics

when trough level monitoring using these targets has been applied. Recent PK/PD and toxicodynamic studies have demonstrated a significantly reduction in vancomycin exposure and nephrotoxicity rates without compromising outcomes when AUC/MIC monitoring has been employed vs traditional trough monitoring approaches.

When using AUC/MIC-guided empiric dosing, the MIC should be assumed to be 1 mg/L based on broth microdilution methods, extensive antibiotic susceptibility data, and the inaccuracies or variability of automated susceptibility testing ( $\pm 1 \log_2$  dilutions). Specific information regarding MIC evaluation and automated susceptibility testing can be found under the MIC susceptibility section of the full guideline [1]. A target AUC between 400 and 600 mg\*hour/L is suggested for methicillin-resistant *Staphylococcus aureus* (MRSA) invasive infections in adults and pediatrics based on clinical efficacy and safety data. These AUC targets should be achieved early in the course of therapy (24–48 hours) given the importance of early and appropriate therapy. Loading doses based on actual body weight are suggested for patients who are critically ill, requiring renal replacement therapy, or receiving continuous infusion therapy. Specific recommendations for patients with obesity on renal replacement therapy and, for the first time, pediatric patients are now included in the revised guidelines [1].

It should be noted that almost all data available on vancomycin PK/PD and toxicodynamics have been derived from patients who have been treated for serious infections of MRSA. Furthermore, the majority of the data have been derived from patients with complicated bloodstream infections. Therefore, caution should be applied when extrapolating this information to mild noninvasive infections or other bacterial species susceptible to vancomycin. These guidelines conclude that

AUC-guided dosing and monitoring is the most accurate and safest way to dose vancomycin. The recommendations in this document should not circumvent sound clinical judgment in managing patients who require vancomycin therapy. Specific details for each section of the document, including references, can be found in the primary publication [1].

## Note

**Potential conflicts of interest.** T. P. L. is a board member of Motif; is a consultant for Paratek, Melinta, Merck, and Motif; has received grants from Merck and Motif; and is on the speaker's bureaus of Melinta and Sunovion. B. A. M. has received grants from NxStage and Merck, and personal fees from Wolters-Kluwer. M. P. P. reports personal fees from Paratek and grants from Merck. K. A. R. is a consultant, on the speaker's bureau, and/or served on advisory boards for the following companies: Achaogen, Allergan, Bayer, BLC USA, Entasis Therapeutics, GSK, Janssen Pharmaceuticals, Meiji, Melinta Therapeutics, Medicine Company, Merck, Motif Bio PLC, Nabriva Therapeutics, Qpex Biopharma, Rempex, Shionogi, Spero Therapeutics, Theravance Biopharma, Tetrphase, Wockhardt, and Zavante Therapeutics; and has received research grants and contracts (paid to the University of Illinois at Chicago) from Theravance Biopharma and Allergan. M. J. R. has received grants and personal fees from Allergan, Melinta, Merck, Motif, Paratek, Shionogi, and Tetrphase; personal fees from InsightRx; and grants from Contrafact. A. W.-B. has received grants from Merck and Allergan, and from Nabriva Therapeutics and Paratek Pharmaceuticals. All other authors report no potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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