Journal of the Pediatric Infectious Diseases Society

EXECUTIVE SUMMARY/GUIDELINE

Executive Summary: Therapeutic Monitoring of Vancomycin for Serious Methicillin-Resistant *Staphylococcus aureus* Infections: 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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Keywords. nephrotoxicity; pharmacokinetics and pharmacodynamics; target attainment; vancomycin; vancomycin consensus guidelines.

The revised consensus guidelines for dosing and monitoring vancomycin are 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 Guidelines Committee. The following is an executive summary of key recommendations contained in this document [1]. The grading system for evaluating the literature can be found in Table 1.

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 concentrations (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/MIC (target 400 mg × h/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 × h/L and thereby increase efficacy. However, since implementation of these recommendations, there have been numerous reports of increased nephrotoxicity in adults and pediatric patients when trough level monitoring using these targets has been applied. Recent PK/PD and toxicodynamic studies have demonstrated a significant reduction in vancomycin exposure and nephrotoxicity rates when AUC/MIC monitoring has been used vs traditional trough monitoring approaches.

When AUC/MIC-guided empiric dosing is used, 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

Received 6 May 2020; editorial decision 8 May 2020; accepted 12 May 2020.

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Journal of the Pediatric Infectious Diseases Society 2020;9(3):281–4

DOI: 10.1093/jpids/piaa057

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].

susceptibility testing (±1 log2 dilutions). Specific information regarding MIC evaluation and automated susceptibility testing can be found under the MIC susceptibility section of the full guidelines [1]. A target AUC between 400 and 600 mg × h/L is suggested for methicillin-resistant *Staphylococcus aureus* (MRSA) invasive infections in adults and pediatric patients based on clinical efficacy and safety data. These AUC targets should be evaluated early in the course of treatment (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, require renal replacement therapy, or are 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 MRSA infections. Further, the majority of the data have been derived from patients with complicated

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

A. Adults and pediatric patients

1. In patients with suspected or definitive serious MRSA infections, an individualized target of the AUC/MIC_{BMD} ratio of 400 to 600 (assuming a vancomycin MIC_{BMD} of 1 mg/L) should be advocated to achieve clinical efficacy while improving patient safety (A-II).
2. When transitioning to AUC/MIC monitoring, clinicians should conservatively target AUCs for patients with suspected or documented serious infections due to MRSA assuming a vancomycin MIC_{BMD} of 1 mg/L or less at most institutions. Given the importance of early, appropriate therapy, vancomycin-targeted exposure should be achieved early during the course of therapy, preferably within the first 24 to 48 hours (A-II). As such, the use of Bayesian-derived AUC monitoring may be prudent in these cases since it does not require steady-state serum vancomycin concentrations to allow for early assessment of AUC target attainment.
3. Trough-only monitoring, with a target 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.
4. Vancomycin monitoring is recommended for patients receiving vancomycin for serious MRSA infections to achieve a sustained targeted AUC (assuming a MIC_{BMD} of 1 mg/L, unless it is known to be greater or less than 1 mg/L by BMD). Independent of MRSA infection, vancomycin monitoring is also recommended for all patients at high risk 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 to 5 days). We suggest the frequency of monitoring be based on clinical judgment; frequent or daily monitoring may be prudent for hemodynamically unstable patients (eg, end stage renal disease) and once-weekly monitoring for hemodynamically stable patients (B-II).
5. Based on current national vancomycin susceptibility surveillance data, under most circumstances for empiric dosing, the vancomycin MIC should be assumed to be 1 mg/L. When the MIC_{BMD} is >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_{BMD} is <1 mg/L, we do not recommend decreasing the dose to achieve the AUC/MIC target. It is important to note the limitations in automated susceptibility testing methods, including the lack of precision and variability in MIC results depending on the method used (B-II).
6. 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).
7. Incompatibility with vancomycin and other drugs commonly coadministered in the intensive care unit requires the use of independent lines or multiple catheters when vancomycin is being considered for continuous infusion (A-III).

B. Adults

8. Given the narrow vancomycin AUC range for therapeutic effect and minimal AKI, the most accurate and optimal way to manage vancomycin dosing should be through AUC-guided dosing and monitoring (A-II). We recommend that this be accomplished in 1 of 2 ways:

a. One approach relies on the collection of 2 concentrations (obtained near steady-state, post-distributional 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 using first-order PK equations to estimate the AUC (A-II).

b. The preferred approach for monitoring the AUC involves the use of Bayesian software programs embedded with a PK model that is 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 that 2 PK samples be obtained (ie, 1–2 hours post-infusion and at the end of the dosing interval) to estimate the AUC with the Bayesian approach (A-II). A trough concentration alone may be sufficient to estimate the AUC with the Bayesian approach in some patients, but more data are needed across different patient populations to confirm viability of using trough-only data (B-II).

9. Doses of 15–20 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 an MIC_{BMD} of 1 mg/L (A-II). In patients with normal renal function, these doses may not achieve a therapeutic AUC/MIC target when the MIC is 2 mg/L.
10. *Continuous infusion:* Based on current available data, a loading dose of 15–20 mg/kg followed by daily maintenance clearance of 30–40 mg/kg up to 60 mg/kg to achieve a target steady-state concentration of 20–25 mg/L may be considered for critically ill patients (B-II). AUC_{24} 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).

Table 2. Continued

B. Adults

11. The risk of developing nephrotoxicity with continuous infusion appears to be similar or lower compared with intermittent dosing when targeting the steady-state concentration of 15–25 mg/L and trough of 10–20 mg/L, respectively (B-II). Definitive studies are needed to compare drug exposure based on measured AUC_{24} and factors that predispose to development of nephrotoxicity, such as receipt of concomitant nephrotoxins, diuretics, and/or vasopressor therapy in patients receiving continuous infusion vs intermittent infusion of vancomycin.
12. In order to achieve rapid attainment of targeted concentrations in critically ill patients with suspected or documented serious MRSA infections, a loading dose of 20–35 mg/kg can be considered for intermittent administration of vancomycin (B-II). Loading doses should be based on actual body weight and should 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 pre-dialysis serum concentrations and extrapolating these values to estimate AUC is most practical. Maintaining pre-dialysis concentrations between 15 and 20 mg/L is likely to achieve the AUC of 400–600 mg × h/L in the previous 24 hours (C-III). Pre-dialysis 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 until the completion of dialysis treatment. 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. *CRRT:* Loading doses of 20–25 mg/kg by actual body weight should be used in patients receiving CRRT at conventional, Kidney Disease Improving Global Outcomes-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). The maintenance dose and dosing interval should be based on serum concentration monitoring, which should be conducted within the first 24 hours to ensure AUC/MIC targets are met. In fluid-overloaded patients, doses may be reduced as patients become euvolemic and drug volume of distribution 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 used (B-II).

C. Pediatric patients

17. Based on an AUC target of 400 mg × h/L (but potentially up to 600 mg × h/L assuming an MIC of ≤1 mg/L) from adult data, the initial recommended vancomycin dosage for children with normal renal function and suspected serious MRSA infections is 60–80 mg/kg/day, divided every 6–8 hour, for children aged ≥3 months (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 in the newborn to the adolescent. Based on current available data, the suggestion for AUC-guided monitoring in pediatric patients aligns with the approach for adults, including the application of Bayesian estimation with 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 pediatric patients since it can incorporate varying ages, weights, and renal function. Both vancomycin serum concentration and renal function should be monitored since vancomycin CL and creatinine CL are not always well correlated in pediatric patients. Furthermore, aggressive dosing to maintain target AUC exposure and decrease the risk of potential AKI in treatment of MRSA infections necessitates drug monitoring.
20. Therapeutic monitoring may begin within 24–48 hours of vancomycin therapy for serious MRSA infections in children, as in adults (B-III). Any delay in therapeutic monitoring should be based on the 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 a trough concentration 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 ≥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 additional 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 those of normal-weight children when doses are calculated on a milligram per kilogram basis. However, these differences are not known to be of sufficient clinical importance to suggest different milligram per kilogram empiric vancomycin dosages in obese children at this time. Similar to nonobese children, obese children aged <12 years, compared with those aged ≥12 years, may require a higher milligram per kilogram 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 aged ≤3 months are 10–20 mg/kg every 8–48 hours, depending on post-menstrual age, weight, and serum creatinine (A-II).

Abbreviations: AKI, acute kidney injury; AUC, area under the curve; BMD, broth Micro Dilution, clearance; CL, CRRT, continuous renal replacement therapy; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; PK, pharmacokinetic.

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 are the most accurate and safest ways to dose vancomycin. The recommendations in this document should not circumvent sound clinical judgment in managing patients who require vancomycin therapy (Table 2). Specific details for each section of the document, including references, can be found in the primary publication [1].

The complete vancomycin guideline paper can be cited and accessed at: https://academic.oup.com/ajhp/advance-article/doi/10.1093/ajhp/zxaa036/5810200

Note

Financial support. A. W.-B. received a grant from Merck & Co. and consulted for Rempex Pharmaceuticals, INSMED, Merck & Co., Nabriva Therapeutics, GlaxoSmithKline, Paratek Pharmaceuticals, Achaogen, Inc., Bayer HealthCare, and SIGA Technologies. J. B. served on a planning committee for the US Food and Drug Administration and European Medicines Agency at the American College of Clinical Pharmacy's annual meeting; participated in the design of a pediatric clinical trial; served on an executive committee for the United States Committee on Antimicrobial Susceptibility Testing; and consulted for Achaogen, Allergan, ContraFect, GlaxoSmithKline, Janssen, Melinta, Merck, Nabrive, Pfizer, Theravance, and Zavante. C. L. received a research grant from Nohla Therapeutics and was a member of an Independent Efficacy Adjudication Committee with Theravance. J. L. received research awards from the Sternfels Prize for Drug Safety Innovation, Duke University, the National Institutes of Health (NIH) and National Institute of Child Health and Human Development, and JMI Laboratories; was an invited advisory board member for FDA, the Asian Pacific Health Foundation, and Infectious Diseases and Therapy journal. D. L. served on the data safety monitoring board for Contrafect and served on an adjudication panel for Novartis. T. L. received grants from the Antibiotic Resistance Leadership Group (ARLG), Merck & Co, and Motif Bio PLC; served as a health outcomes project consultant for Paratek Pharmaceuticals, Allergan, Merck & Co., and Melinta Therapeutics; served on advisory boards for Paratek Pharmaceuticals, Motif Bio PLC, Achaogen, Nabriva, and Tetraphase; served as a consultant to Paratek Pharmaceuticals, ARLG, Allergan, Merck & Co., Melinta Therapeutics, Motif Bio PLC, Achaogen, Nabriva, and Tetraphase; and was a speaker for Melinta Therapeutics, Tetraphase, and Sunovion. H. M. served as an international working group member for the European Cystic Fibrosis Society and North American Cystic Fibrosis Society, served on an advisory panel for the Centers for Disease Control and Prevention and Pew Charitable Trust, and was on a committee for the Arkansas Health Department. M. B. received research grants from Merck & Co. and Hope Pharmaceutical and served on an advisory board for NxStage and Baxter. M. P. received a grant from Merck, Inc., served on an advisory board for Shinogi and Paratek Pharmaceuticals, and served on the meet the professor program for Merck. K. R. received a grant from Theravance Biopharm, NIH, ARLG, and Allergan; consulted for BLC, Entasis, Merck, Paratek Pharmaceuticals, Shionogi, Tetraphase, and Wockhardt; was a speaker at the American Society for Microbiology and European Society for Clinical Microbiology and Infectious Diseases ASM/ESCMID conference; served on the 2015–2019 Program Committee and was 2016–2018 Program Co-Chairperson for the American Microbiology Society; and was a member of the 2017–2019 Antimicrobial Resistance Committee for IDSA. M. J. R. received research grants from Bayer Pharmaceuticals, the NIH Research Project Grant (RO1) Program, Merck, Allergan, the Michigan Department of Health and Human Services, Accelerate Diagnostics, Inc., NIH, Contrafect, Motif Biosciences, and the Michigan Translational Research and Commercialization Program; and served as a grant review panel member for NIH. The other authors have declared no potential conflicts of interest.

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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