

New Vancomycin Dosing Guidelines for Hemodialysis Patients: Rationale, Caveats, and Limitations

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KIDNEY360 2: 1313–1315, 2021. doi: <https://doi.org/10.34067/KID.0000192021>

Vancomycin continues to be the most frequently prescribed antibiotic in patients with ESKD who are receiving hemodialysis due to the high prevalence of infections with methicillin-resistant *Staphylococcus aureus* (MRSA) (1). Despite decades of clinical experience and routine performance of therapeutic serum drug concentration monitoring (TDM), vancomycin dosing in patients receiving hemodialysis remains challenging. Limited data and corresponding recommendations in the 2009 guidelines related to vancomycin dosing and monitoring in patients on hemodialysis have resulted in a lack of standardization of vancomycin dosing protocols among institutions and dialysis centers. In fact, it is not uncommon for vancomycin dosing regimens to be prescribed on the basis of individual clinicians' preference and experience. Consequently, a wide range of vancomycin dosing regimens with different TDM and drug infusion approaches have been used in patients on hemodialysis (2), and there is a legitimate risk of therapeutic failure, toxicity, and drug resistance when suboptimal dosing regimens are prescribed. For instance, development of vancomycin-intermediate or vancomycin-resistant *S. aureus* is common in patients on hemodialysis and is likely attributed to suboptimal vancomycin therapy (3).

Recently published vancomycin consensus guidelines provide updated recommendations for the treatment of serious MRSA infections, with the goal of attaining clinical efficacy (pharmacodynamic) targets while ensuring patient safety (2). The updated guidelines reflect a paradigm shift in TDM on the basis of accumulating data raising safety concerns related to vancomycin-associated AKI. The previous 2009 vancomycin consensus guidelines recommended trough-only TDM, based on the premise that a serum vancomycin concentration of 15–20 mg/L was a surrogate marker for attaining the efficacy target (*i.e.*, the 24-hour area under the serum concentration-time curve/minimum inhibitory concentration [AUC/MIC] ratio of ≥ 400) in patients with normal kidney function (4). Trough-only monitoring was thought to be a reasonable alternative to avoid cumbersome AUC estimation in clinical settings. However, recent data have demonstrated that a trough concentration is a poor surrogate of true AUC and that targeting higher trough serum concentrations, especially 15–20

mg/L for serious infections, significantly increases the risk of AKI in patients who are not receiving dialysis (5). As such, the revised guidelines now recommend AUC-guided dosing and monitoring in lieu of the trough-only approach. The currently recommended vancomycin efficacy target is the 24-hour AUC/MIC ratio of 400–600 (2). AUC monitoring appears to perform better than trough-based monitoring for the purposes of decreasing incident vancomycin-associated AKI (6). Recent studies have also provided a better understanding of the vancomycin 24-hour AUC upper threshold associated with AKI (≥ 650 mg·h/L) (7). Hence, the new guidelines promote the implementation of AUC-based TDM, preferably using pharmacokinetic modeling software (*i.e.*, a Bayesian forecasting program) to facilitate individualized dosing regimens and a higher likelihood of achieving a vancomycin AUC/MIC ratio of 400–600, which would balance efficacy target attainment and AKI risk in patients not receiving dialysis. Of note, AUC estimation using a Bayesian approach requires one to two serum vancomycin concentration samples, and preferably two samples (*e.g.*, peak and trough) to improve the estimation.

Importantly, the revised guidelines specifically address vancomycin dosing in patients receiving dialysis with some important caveats. Although still acknowledging limited outcomes data related to the optimal efficacy target in patients on hemodialysis, the revised guidelines provide initial dosing recommendations and a corresponding TDM strategy for use in the common thrice-weekly hemodialysis setting. The goal of these initial dosing recommendations is to attain a vancomycin target AUC/MIC ratio of 400–600, extrapolated from patients who are not on dialysis and to account for important dialysis-related factors (*e.g.*, dialyzer permeability, interdialytic period after vancomycin administration, and vancomycin infusion either during or after hemodialysis) that can alter drug exposure. Of note, a weight-based dosing approach using actual body weight is recommended over fixed dosing to account for patient size and fluid overload in patients on dialysis. In addition, the guidelines address logistic challenges associated with blood sampling and determination of AUC, especially in the outpatient setting, to implement the newly

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recommended AUC monitoring in patients on hemodialysis. Currently, there is a lack of available user-friendly pharmacokinetic software using Bayesian methods that contain bundled models for patients on dialysis and are practical for routine use in the clinical setting. A non-Bayesian method to determine the AUC using simple trapezoidal estimates on the basis of two serum concentrations obtained at steady state is a potential alternative, but this approach is complicated by dialytic drug removal and redistribution after hemodialysis. Consequently, the revised guidelines favor predialysis concentration monitoring as an alternative in patients receiving hemodialysis.

Although the revised guidelines offer useful vancomycin dosing and monitoring recommendations, the presence of ESKD and hemodialysis present unique challenges that should be considered when providing individualized vancomycin therapy to these patients. For example, outcomes studies validating the newly recommended pharmacodynamic target AUC/MIC ratio of 400–600 have not been conducted in patients receiving hemodialysis. Moreover, optimal predialysis serum concentrations have not been widely evaluated. The predialysis monitoring approach was adapted from trough monitoring, which was recommended in the 2009 guidelines (4). Typically, patients with ESKD receiving hemodialysis exhibit negligible vancomycin clearance *via* the kidneys, and predialysis concentrations observed during postdialysis maintenance dosing appear to correlate with vancomycin exposure as measured by the AUC. Commonly used predialysis concentration targets of 10–20 mg/L generally reflect mean 24-hour AUC values of 250–450 mgh/L, often below the AUC/MIC target of 400–600 recommended in the revised guidelines (8). Predialysis concentrations of >18.6 mg/L have been linked to improved patient outcomes in patients on hemodialysis who have MRSA bacteremia (9). Given the available data, the new guidelines recommend a narrow predialysis serum concentration range of 15–20 mg/L, which is more likely to attain the pharmacodynamic AUC/MIC target of 400–600. The upper limits of the optimal predialysis concentration target and corresponding AUC need to be elucidated, although the upper AUC threshold of 650 mgh/L associated with AKI may be of less concern in patients with ESKD who are receiving hemodialysis, except for those with residual kidney function.

Other practical, but important, considerations in applying the new vancomycin recommendations to patients on

hemodialysis relate to timing of blood sampling and vancomycin infusion time. The guidelines assume the predialysis concentration is assessed immediately before initiating hemodialysis with subsequent dose adjustment at the end of the same hemodialysis session. Although ideal, such practice is not feasible in most clinical settings, especially outpatient dialysis units where simplified fixed dosing protocols are often used and routine TDM proves cumbersome. In addition, many dialysis centers administer vancomycin during dialysis, but the dose prescribed may not take intradialytic drug loss into consideration and, thus, may be subtherapeutic because approximately 20%–40% of a vancomycin dose infused during dialysis is subject to dialytic removal (2). Furthermore, vancomycin infusion time may vary between centers. Due to the risk of developing “red man syndrome,” it is generally recommended that the vancomycin infusion rate not exceed 10–15 mg/min or 1 g/h, but a much shorter infusion time may be used to minimize the intradialytic drug loss in some places, raising safety concerns. To address these practical issues, efforts have been made to identify an optimal vancomycin regimen that is applicable to most patients receiving outpatient dialysis for the purpose of attaining predialysis targets (10). However, one ideal dosing regimen may not exist, given that vancomycin pharmacokinetics exhibit large interindividual variability that is compounded by the aforementioned dialysis-related factors. Common vancomycin fixed posthemodialysis doses (*e.g.*, 750 mg, 1000 mg) are not likely to yield adequate drug exposure in patients on hemodialysis who are increasingly affected by obesity and/or fluid overload.

In summary, the revised vancomycin consensus guidelines now recommend AUC-guided dosing and monitoring in lieu of the trough-only approach in patients who are not receiving dialysis. Recommendations to individualize vancomycin therapy in patients on hemodialysis on the basis of the revised guidelines are presented in Table 1 (2). The recommended vancomycin efficacy target is the 24-hour AUC/MIC ratio of 400–600 (2). However, with many logistic issues in determining AUC and a lack of data in patients on hemodialysis, the revised guidelines recommend monitoring on the basis of predialysis serum concentrations and extrapolating these values to estimate the AUC. Maintaining predialysis concentrations between 15 and 20 mg/L will likely translate to a 24-hour AUC of <600 mgh/L, which will achieve the target AUC/MIC ratio of 400–600, assuming the MIC is ≤ 1 mg/L. The relationship between predialysis

Table 1. Recommendations for patients receiving hemodialysis on the basis of the revised vancomycin consensus guidelines (3)

Dosing Recommendations	Monitoring Recommendations
<ul style="list-style-type: none"> ■ Weight-based initial dosing recommendations with actual body weight should be used. ■ A maximal loading dose of 3000 mg is recommended for patients who are obese. ■ A 30% larger vancomycin dose should be considered if infused intradiallytically. ■ Vancomycin infusion rate should not exceed 1 g/h, even if infused intradiallytically. 	<ul style="list-style-type: none"> ■ TDM should be performed for all patients to individualize maintenance doses. ■ Targeting predialysis concentrations between 15–20 mg/L is likely to attain the efficacy target 24-hour AUC/MIC ratio of 400–600, assuming an MIC of ≤ 1 mg/L.
<p>TDM, therapeutic serum drug concentration monitoring; AUC/MIC, area under the serum concentration-time curve/minimum inhibitory concentration.</p>	

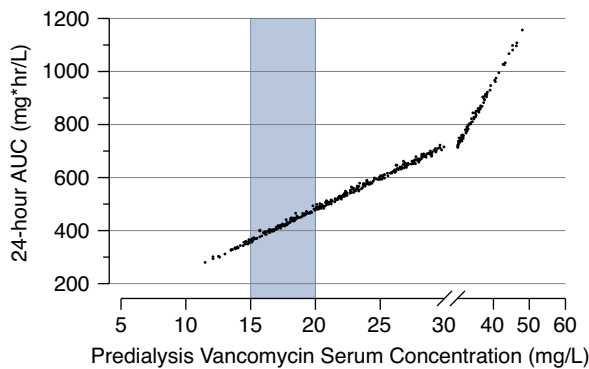


Figure 1. | Target predialysis serum vancomycin concentrations of 15–20 mg/L are predicted to attain the target AUC/MIC ratio in modeled patients on hemodialysis receiving a guideline-recommended dosing regimen (2,8). The model assumed patients with ESKD ($n=500$) weighing 40–139 kg (mean, 76 kg) receiving a 25 mg/kg loading dose, and then 10 mg/kg after each thrice-weekly, high-flux hemodialysis session. Blue vertical lines indicate the target predialysis vancomycin concentrations of 15–20 mg/L that will translate to a 24-hour AUC of <600 mgh/L, and will likely achieve the target AUC/MIC ratio of 400–600, assuming the MIC is ≤ 1 mg/L. AUC, area under the serum concentration-time curve; AUC/MIC, AUC/minimum inhibitory concentration.

serum vancomycin concentrations and 24-hour AUC in patients on hemodialysis was modeled as previously described (8), and is presented in Figure 1. In addition, the weight-based initial dosing recommendations incorporating actual body weight should be used. In the absence of data specific for patients on hemodialysis, the general dosing recommendations for obesity in the revised guidelines that place caps on the maximal doses (*i.e.*, 3 g for a loading dose) should be considered. TDM is recommended to determine and/or confirm individualized maintenance doses in all patients receiving dialysis. When infusing the drug intradiallytically, administration of a 30% larger vancomycin dose should be considered to compensate for the dialytic removal. Without further safety data, the vancomycin infusion rate should not exceed the generally recommended rate, even if infused intradiallytically. Vigilant vancomycin prescribing and monitoring in patients receiving hemodialysis, on the basis of the best available evidence, will increase the likelihood of safe and effective therapy, and clinicians are encouraged to adopt the recommendations set forth in the revised vancomycin guidelines.

Disclosures

T.D. Nolin reports serving on the American College of Clinical Pharmacology Board of Regents, on the editorial board of *CJASN*, on the scientific advisory board of Healthmap Solutions, and as an editor for McGraw Hill; having consultancy agreements with CytoSorbents and MediBeacon; and having ownership interest in Healthmap Solutions. The remaining author has nothing to disclose.

Funding

None.

Acknowledgments

The content of this article reflects the personal experience and views of the author(s) and should not be considered medical advice or recommendation. The content does not reflect the views or opinions of the American Society of Nephrology (ASN) or *Kidney360*. Responsibility for the information and views expressed herein lies entirely with the author(s).

Author Contributions

S.J. Lewis wrote the original draft; and T.D. Nolin reviewed and edited the manuscript.

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Received January 12, 2021 Accepted May 21, 2021

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