New Vancomycin Dosing Guidelines for Hemodialysis Patients:

Rationale, Caveats, and Limitations

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Vancomycin continues to be the most frequently prescribed antibiotic in end stage kidney disease (ESKD) patients 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 hemodialysis patients has 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 based on individual clinicians’ preference and experience. Consequently, a wide range of vancomycin dosing regimens with different TDM and drug infusion approaches have been utilized in hemodialysis patients (2) with 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 hemodialysis patients and 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 based on accumulating data raising safety concerns related to vancomycin-associated acute kidney injury (AKI). The previous 2009 vancomycin consensus guidelines recommended trough-only TDM, based on the premise that a serum vancomycin concentration of 15 to 20 mg/L was a surrogate marker for attaining the efficacy
target [i.e., the 24-hour area under the serum concentration-time curve to minimum inhibitory concentration (AUC:MIC) ratio of $\geq 400$] 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 has 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 non-dialysis patients (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 to 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 better understanding of the vancomycin 24-hour AUC upper threshold associated with AKI ($\geq 650$ 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 of 400 to 600, which would balance efficacy target attainment and AKI risk in non-dialysis patients. Of note, AUC estimation using a Bayesian approach requires 1 to 2 serum vancomycin concentration samples, and preferably 2 samples (e.g., peak and trough) to improve the estimation.

Importantly, the revised guidelines specifically address vancomycin dosing in dialysis patients with some important caveats. While still acknowledging limited outcomes data related to the optimal efficacy target in hemodialysis patients, the revised guidelines provide initial dosing recommendations and a corresponding TDM strategy for use in the common thrice
The goal of these initial dosing recommendations is to attain a vancomycin target AUC:MIC 400 to 600 extrapolated from non-dialysis patients 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 dialysis patients. In addition, the guidelines address logistical challenges associated with blood sampling and determination of AUC, especially in the outpatient setting, in order to implement newly recommended AUC monitoring in hemodialysis patients. Currently, there is a lack of available user friendly pharmacokinetic software utilizing Bayesian methods that contain bundled models for dialysis patients and are practical for routine use in the clinical setting. A non-Bayesian method to determine the AUC using simple trapezoidal estimates based on 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 hemodialysis patients.

While 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 of 400-600 have not been conducted in hemodialysis patients. Moreover, optimal predialysis serum concentrations have not been widely evaluated. The predialysis monitoring
approach was adapted from trough monitoring recommended in the 2009 guidelines (4).

Typically, ESKD patients receiving hemodialysis exhibit negligible vancomycin clearance via the kidneys, and predialysis concentrations observed during post-dialysis 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 mg·h/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 outcome in hemodialysis patients with MRSA bacteremia (9). Given the available data, the new guidelines recommend a narrow predialysis serum concentration range of 15-20 mg/L that 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, though the upper AUC threshold of 650 mg·h/L associated with AKI may be of less concern in ESKD patients receiving hemodialysis except for those with residual kidney function.

Other practical but important considerations in applying the new vancomycin recommendations to hemodialysis patients relate to timing of blood sampling and vancomycin infusion time. The guidelines assume that the predialysis concentration is assessed immediately prior to 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 utilized 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 since approximately 20-40% of a vancomycin doses 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 gram/hour, but a much shorter infusion time may be employed to minimize the intradialytic drug loss in some places, raising safety concern. In order 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 exhibits large interindividual variability that is compounded by the aforementioned dialysis-related factors. Common vancomycin fixed post-hemodialysis doses (e.g., 750 mg, 1000 mg) are not likely to yield adequate drug exposure in hemodialysis patients that 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 non-dialysis patients. Recommendations to individualize vancomycin therapy in hemodialysis patients based on the revised guidelines are presented in Table 1 (2). The recommended vancomycin efficacy target is the 24-hour AUC:MIC ratio of 400 to 600 (2). However, with many logistic issues in determining AUC and a lack of data in hemodialysis patients, the revised guidelines recommend monitoring based on predialysis serum concentrations and extrapolating these values to estimate AUC. Maintaining predialysis concentrations between 15 and 20 mg/L will likely translate to a 24-hour AUC of <600 mg*h/L, which will achieve the target AUC:MIC ratio of 400 to 600 assuming the MIC is ≤1 mg/L. The relationship between predialysis serum vancomycin concentrations and
24-hour AUC in hemodialysis patients was modelled 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 hemodialysis patients, the general dosing recommendations for obesity in the revised guidelines that place caps on the maximal doses (i.e., 3 gram for a loading dose) should be considered. TDM is recommended to determine and/or confirm individualized maintenance doses in all dialysis patients. When infusing the drug intradialytically, 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 intradialytically. Diligent vancomycin prescribing and monitoring in hemodialysis patients based on 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.

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REFERENCES


Table 1. Recommendations for Hemodialysis Patients based on the Revised Vancomycin Concensus Guidelines (3)

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<th>Dosing Recommendations</th>
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<td>• Weight-based initial dosing recommendations with actual body weight should be used.</td>
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<td>• A maximal loading dose of 3,000 mg is recommended for obese patients.</td>
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<td>• A 30% larger vancomycin dose should be considered if infused intradialytically.</td>
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<td>• Vancomycin infusion rate should not exceed 1 gram/hour even if infused intradialytically.</td>
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<th>Monitoring Recommendations</th>
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<td>• TDM should be performed for all patients to individualize maintenance doses.</td>
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<tr>
<td>• Targeting predialysis concentrations between 15 to 20 mg/L is likely to attain the efficacy target 24-hour AUC:MIC ratio of 400 to 600 assuming an MIC of ≤1 mg/L.</td>
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TDM : therapeutic serum drug concentration monitoring; AUC:MIC: area under the serum concentration-time curve to minimum inhibitory concentration ratio
FIGURE LEGEND

Figure 1. Predicted relationship between predialysis serum vancomycin concentrations and 24-hour AUC in modelled hemodialysis patients receiving a guideline recommended dosing regimen (2,8). The model assumed patients with end stage kidney disease (n=500) weighing 40-139 kg (mean 76 kg) receiving 25 mg/kg loading dose, 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 will translate to a 24-hour AUC of <600 mg*h/L and will likely achieve the target AUC:MIC ratio of 400 to 600 assuming the MIC is ≤1 mg/L.
Figure 1

24-hour AUC (mg*hr/L)

Predialysis Vancomycin Serum Concentration (mg/L)