Critical Care

MATTERS ARISING Open Access

Trough concentrations of 10–15 mg/L of vancomycin are generally sufficient to achieve pharmacodynamic targets, whereas higher troughs can result in unnecessary nephrotoxicity: we respectfully disagree

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Keywords Vancomycin, Trough concentration, AUC, Nephrotoxicity, Critically ill patients

The recent letter by Movahedan et al., entitled "Reconsidering vancomycin trough targets in critically ill patients" [1], raises an important issue regarding the optimal therapeutic monitoring of vancomycin in critically ill patients. We commend the authors for stimulating discussion on this clinically relevant topic. However, we respectfully disagree with their conclusion that trough concentrations of 10–15 mg/L are generally sufficient to achieve pharmacodynamic targets and that higher trough concentrations primarily result in unnecessary nephrotoxicity.

The authors state that "trough concentrations of 10–15 mg/L are generally sufficient to achieve pharmacodynamic targets, whereas higher troughs can result in unnecessary vancomycin exposure (with AUC/MIC > 600 mg·h/L), with potential for increased nephrotoxicity risk" [1]. Although several pharmacokinetic studies support this hypothesis, the available clinical evidence suggests that the relationship between vancomycin exposure and nephrotoxicity is considerably more complex than implied.

A dose–response relationship between vancomycin exposure and nephrotoxicity has been reported repeatedly [2]. Nevertheless, the available evidence does not support a simple toxicity threshold at a trough concentration of 15 mg/L. In the study by Kullar et al., nephrotoxicity occurred in 17% of patients with trough concentrations of 10–15 mg/L, 13% in those with trough concentrations of 15–20 mg/L, and 15% in patients with trough concentrations below 10 mg/L. A significantly higher incidence of nephrotoxicity was observed only when trough concentrations exceeded 20 mg/L (27%, $P = 0.032$) [3]. These findings suggest that trough concentrations within the currently recommended therapeutic range of 15–20 mg/L are not, by themselves, associated with a significantly increased risk of nephrotoxicity.

This reply refers to the comment available online at https://doi.org/10.1186/s13054-025-05820-x.

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Furthermore, the causal relationship between elevated vancomycin trough concentrations and kidney injury remains uncertain. As discussed by Filippone et al. [2], an important unanswered question is whether higher vancomycin exposure directly induces nephrotoxicity or whether worsening renal function reduces vancomycin clearance, thereby resulting in elevated serum trough concentrations. Consequently, increased trough concentrations may represent a consequence rather than the primary cause of acute kidney injury.

Similar uncertainty exists regarding AUC-guided monitoring. Although AUC is widely recognized as the most appropriate pharmacodynamic parameter for predicting antimicrobial efficacy, its role as an independent predictor of nephrotoxicity remains less well established. In a retrospective study of 166 hospitalized patients, Lodise et al. identified an AUC threshold of approximately 1,300 mg·h/L, above which nephrotoxicity occurred significantly more frequently (26% versus 10%, $P = 0.05$) [4]. However, as highlighted by Filippone et al. [2], multivariable analyses have not consistently demonstrated AUC to be an independent predictor of nephrotoxicity after adjustment for potential confounding variables, whereas trough concentration has remained significantly associated with renal injury. Therefore, while AUC-guided monitoring undoubtedly represents an important tool for optimizing efficacy, its superiority over trough concentrations for predicting toxicity remains open to debate.

In addition, vancomycin-associated nephrotoxicity should not be interpreted in isolation. Critically ill patients frequently receive multiple concomitant nephrotoxic agents, including aminoglycosides, amphotericin B, intravenous contrast media, calcineurin inhibitors, loop diuretics, vasopressors, and renin–angiotensin system blockers [2]. Sepsis-related hypotension, hemodynamic instability, and pre-existing renal dysfunction further contribute to the development of acute kidney injury. Consequently, attributing nephrotoxicity solely to vancomycin exposure may oversimplify a multifactorial process.

Finally, while Movahedan et al. emphasize minimizing toxicity, the potential consequences of insufficient vancomycin exposure should also be considered. Kullar et al. demonstrated that adequate vancomycin exposure was associated with improved outcomes in patients with methicillin-resistant Staphylococcus aureus bacteremia, supporting the importance of maintaining sufficient drug exposure in severe infections [3]. Likewise, Hidayat et al. reported that although higher-dose vancomycin therapy was associated with increased nephrotoxicity, it was introduced to improve target attainment in serious MRSA infections, highlighting the need to balance efficacy against toxicity rather than prioritizing one at the expense of the other [5].

In conclusion, although excessive vancomycin exposure—particularly trough concentrations exceeding 20 mg/L—should undoubtedly be avoided, the currently available evidence does not conclusively demonstrate that maintaining trough concentrations between 15 and 20 mg/L independently increases nephrotoxicity compared with concentrations of 10–15 mg/L. Given the multifactorial nature of acute kidney injury in critically ill patients and the continued importance of achieving adequate antimicrobial exposure, we believe that recommending a universal reduction of trough targets to 10–15 mg/L may be premature. Further prospective studies are needed to better define the optimal balance between efficacy and safety before revising current therapeutic targets.

Acknowledgements
None.

Author contributions
PMH , YB & CYM, designed the paper. PMH , YB & CYM participated in drafting and reviewing. PMH , YB & CYM read and approved the final version of the manuscript.

Funding
None.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 6 August 2026 / Accepted: 13 August 2026
Published online: 14 August 2026

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