Antimicrobial Stewardship News
Volume 8, Number 4
April 2020

New Vancomycin Dosing Guidelines - Should We Switch?

Vancomycin has been the mainstay of therapy for serious infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) for decades. Unfortunately, appropriate dosing remains challenging with increased observations of elevated serum creatine reported after target trough concentrations were maintained above 15 to 20 mcg/mL.[1–5] In March of 2020, new consensus guidelines were published that recommend transitioning from traditional trough-based dosing to targeting an area under the curve (AUC) to minimum inhibitory concentration (MIC) ratio of ≥ 400 to achieve clinical efficacy and improve patient safety.[6] The question of whether to or how to adopt this new dosing strategy is a key concern for many hospitals nationwide. This newsletter outlines major updates in the guidelines and describes the pros and cons of implementation.

Why Switch?

The primary reason to consider switching to AUC/MIC-based dosing is to improve safety and efficacy. The prior 2009 guidelines recommended targeting trough concentrations of 15 to 20 mcg/mL for most infections as a surrogate marker for AUC/MIC.[1] However, recent evidence has emerged reporting increased acute kidney injury (AKI) without any improvement in clinical outcomes in patients with trough concentrations in this higher range.[7–10] Although the data are limited, some reports suggest the risk of AKI increases as a function of vancomycin trough concentration, and more recent data suggests AKI also increases as a function of AUC, especially when the daily AUC exceeds 650 to 1,300.[7,11–13] Therefore, the current guidelines recommend dosing based on an individualized target AUC/MIC ratio of 400 to 600 (assuming a MIC of 1 mg/L).[6] This new target AUC/MIC ratio can be achieved in many patients with much lower doses than would be required to achieve the previously recommended therapeutic trough concentrations. In regards to efficacy data, the guidelines note the evidence is largely derived from retrospective, single-center studies in patients with MRSA bacteremia.[6]

Which Infection Types/Pathogens Do the New Guidelines Address?

The dosing recommendations in the new guidelines apply only to patients with serious infections caused by MRSA (e.g., bacteremia, sepsis, infective endocarditis, osteomyelitis, and meningitis). The new guidelines exclude nonbacteremic skin and skin structure or urinary tract infections caused by MRSA and any infection caused by methicillin-susceptible *Staphylococcus aureus* (MSSA), coagulase-negative staphylococci, or *Enterococcus spp*.

How Are Doses Calculated and Vancomycin Levels Drawn?

There are two approaches to calculate AUC/MIC-based dosing regimens. The first approach requires the use of first-order pharmacokinetic (PK) equations utilizing two vancomycin concentrations (a 1- to 2-hour post-peak and a trough). There are many examples of hospitals using this approach with a “home grown” calculator in Excel. One advantage of this approach is its low cost; with the major drawback that it requires two separate concentrations drawn at near steady-state, and there is variability in the validity and accuracy of these calculators. The second approach involves use of Bayesian software utilizing either one or two vancomycin concentrations, at least one being a trough. A few advantages of the Bayesian approach include improved accuracy, ability to use concentrations collected within the first 24- to 48-hours, the potential to use a single concentration instead of multiple, and ability to integrate into the electronic health record. The major drawback is cost of the additional software platform. There are several existing platforms available that we will highlight in detail in our upcoming toolkit.

Additional Recommendations in the New Guidelines:[6]

- Pharmacokinetic target and dosing recommendations provided for pediatric patients, including neonates
- Dosing recommendations provided for continuous infusion vancomycin that may be considered when the AUC target cannot be achieved with traditional intermittent dosing
- Dosing recommendations provided for patients receiving hybrid dialysis therapies (e.g., slow-low efficiency dialysis (SLED)) and continuous renal replacement therapy (CRRT)
- Loading doses recommended for critically-ill patients with serious MRSA infections:
  - General: 25 to 35 mg/kg (actual body weight); max 3,000 mg
  - Obesity: 20 to 25 mg/kg (actual body weight); max 3,000 mg

Key Considerations When Determining Whether or Not to Convert:

- It is becoming increasingly clear that trough levels are poor markers of vancomycin safety and efficacy. This new approach to dosing has the potential to optimize efficacy by achieving targets proven with *in vitro* and *in vivo* data while also reducing the potential for vancomycin-induced nephrotoxicity.
- This new approach represents a significant departure from prior dosing calculations, and most clinical pharmacists have not received formal education surrounding AUC/MIC-based dosing. Therefore, extensive training will likely be required for AUC/MIC-based dosing competency.
- Depending upon the approach (e.g., first-order kinetics vs Bayesian), two levels might be required to appropriately calculate an AUC/MIC-based dose. The requirement for additional levels will likely require significant education to clinical staff ordering and collecting vancomycin levels.
- These new dosing recommendations only apply to serious invasive infections caused by MRSA. Therefore, traditional trough-based dosing will still be used certain infection types. The use of two dosing strategies could potentially create confusion upon new starts or handoff to other pharmacists.

Overall, while these new guidelines present an opportunity to improve the safety and efficacy of one the most frequently prescribed antimicrobials in acute care hospitals, this approach departs significantly from current practices at most community hospitals. Therefore, we believe the switch to AUC-based dosing will require a thoughtful, multidisciplinary approach. DASON is currently in the process of developing a full toolkit to provide additional resources to hospitals considering the switch to AUC-based dosing.

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