Insight RX | WHITE PAPER

The verdict is in

Why pharmacies should rapidly adopt new vancomycin dosing guidelines

Overview

Prescribed to millions of U.S. patients each year, vancomycin is considered the treatment of choice for serious infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and is prescribed for other susceptible Gram-positive organisms.[1] While effective, it can cause nephrotoxicity, which can result in longer lengths of stay, higher costs, and higher mortality rates.

Since dosing guidelines were last issued in 2009, multiple studies have demonstrated that replacing traditional dosing strategies based on vancomycin trough levels with newer area-under-the-curve (AUC) approaches can reduce nephrotoxicity while maintaining or enhancing clinical efficacy.

As a result, new 2020 consensus clinical guidelines call for hospitals to use AUC-based dosing strategies to enhance patient safety. Currently, however, awareness of these guidelines and preparedness to implement them appears to be low.

Key Takeaways

New vancomycin guidelines are intended to reduce kidney toxicity, which impacts an estimated 23% of recipients.

The guidelines recommend replacing simpler pharmacokinetic models and equations based on trough levels with AUC/MIC methodologies.

Studies demonstrate that a Bayesian model provides safer, more efficacious care compared to simplified PK models.

A continuous learning Bayesian model uses machine learning to continually enhance precision dosing for specific patients and populations.

The Problem:
Vancomycin nephrotoxicity is serious and widespread

An estimated 120,000 hospitalized patients per year contract infections due to MRSA, and roughly 20,000 of those patients die from the disease.[2] While vancomycin is the treatment of choice, excessive vancomycin exposure can lead to acute or chronic kidney damage and disease, volume overload, and increased drug resistance. An estimated 23.6% of patients treated with vancomycin suffer from nephrotoxicity and almost 6% (or nearly 10,000 people per year) suffer from Stage 2 or 3 acute kidney injuries (AKIs).[3] AKIs have been shown to increase inpatient mortality rates by 350%[4] as well as length of stay and costs.[5]

Key Terms

Trough levels - The lowest concentration of a drug in the bloodstream before a subsequent dose is given

AUC - Area under the 24-hour concentration-time curve

MIC - The minimum drug concentration needed to inhibit visible bacterial growth

Pharmacokinetics (PK) - How drugs move through the body

Pharmacodynamics (PD) - How a drug interacts with its target (e.g., bacteria)

Bayesian forecasting - A statistical model that enables users to accurately estimate probabilities from limited data

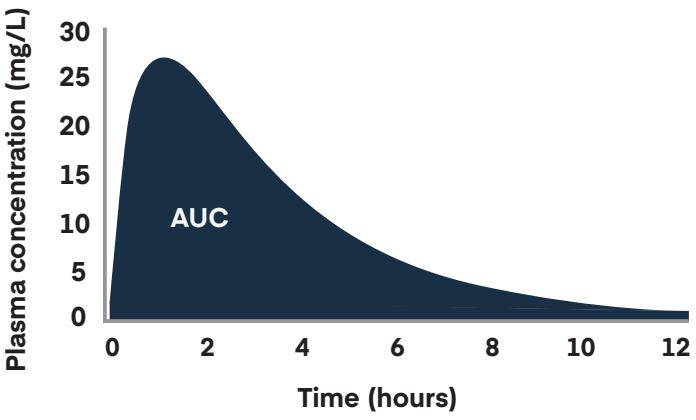
Consensus guidelines for vancomycin therapeutic drug monitoring in place since 2009 called for targeting trough concentrations of greater than 10 mg/L to prevent resistance in all infections and 15-20 mg/L in patients with more complex infections.[6] However, in the decade since these guidelines were published, a growing number of peer-reviewed studies have demonstrated that dosing to these trough targets continues to put patients at undue risk of nephrotoxicity and occasional risk of treatment failure.

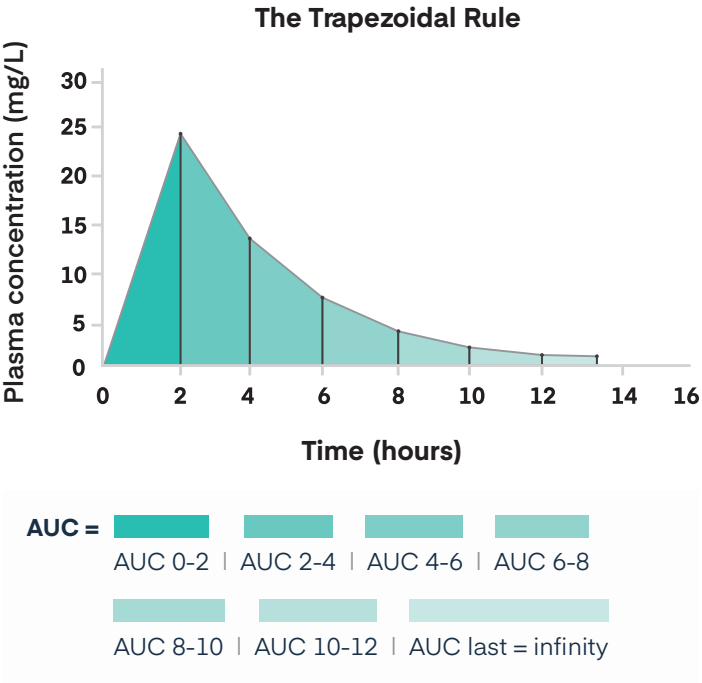
With each new study, it became clearer that updated guidelines were needed to ensure safe vancomycin dosing levels without compromising efficacy.

New guidelines optimize dosing and lower toxicity — but awareness is low

After several years of work to develop new guidelines that would meet these higher standards, the Infectious Diseases Society of America (IDSA), American Society of Health-System Pharmacists, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists published new consensus clinical guidelines in March 2020. These consensus guidelines set targets for empiric dosing in children and adults and recommend AUC-targeted dosing that is ideally calculated using software with MAP-Bayesian forecasting functionality to improve speed and accuracy.

Surprisingly, however, many academic medical center pharmacists aren't well aware of these guidelines — nor do they have the tools they





need to follow them. A 2019 survey found that less than a quarter of academic medical centers performed AUC-based vancomycin monitoring and most were unsure about or not planning to adopt the new monitoring strategy within the next year.[7] About two-thirds of respondents said they use two-point pharmacokinetics, while a minority use either Bayesian software or population-based pharmacokinetics.[8]

> "To optimize vancomycin use for the treatment of serious infections caused by MRSA, we recommend targeting an AUC/MIC_{BMD} ratio of 400-600 for empiric dosing in both adult and pediatric patients to maximize the clinical efficacy and minimize AKI..."

Source: Conclusions page from new 2020 IDSA consensus guidelines, "Therapeutic monitoring of vancomycin: A revised consensus guideline 1 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, and Pharmacists"

Compelling evidence for switching to new AUC-based protocols

The evidence for switching to newer AUC-based protocols for both children and adults is substantial, while evidence continues to mount that the risks of maintaining higher vancomycin trough values outweigh the benefits. Below is a partial list of studies documenting that aggressive vancomycin regimens increase AKI rates and that AUC-based dosing can lower the risk.

Incidence of Vancomycin-associated AKIs

1.7M U.S. patients treated with vancomycin/yr.

10% of vancomycin patients have trough levels > 30 mg/L

23.6% of those patients have AKIs

40,000 AKIs per year (conservative estimate)

* Zonozi R, Wu A, Shin J-I, Secora A, Coresh J, Inker LA, et al. Elevated Vancomycin Trough Levels in a Tertiary Health System: Frequency, Risk Factors, and Prognosis. Mayo Clinic Proceedings. 2019;94(1):17–26.

- A 2013 literature review concluded that vancomycin trough levels ≥ 15 mg/liter were associated with increased odds of nephrotoxicity compared to trough levels below that amount.[9]
- A 2017 study found that AUC-guided dosing was independently associated with lower nephrotoxicity.[10]
- A model-based dosing approach that individualizes empiric vancomycin dosing was predicted to improve achievement of target exposure levels in neonates.[11]
- A 2013 study of 702 children found that using vancomycin AUC/MIC in lieu of trough concentrations provided better dosing calculations in children.[12]

Dosing methodologies: Simple analytic equations vs. the Bayesian method

To estimate vancomycin AUC values more precisely than trough-based methods, pharmacists can use one of several analytic equations based on peak and trough concentrations or a Bayesian methodology.[13] The Rodvold method is often faster and more practical than the trapezoidal method, but tends to underestimate the true AUC value and does not take acute changes in physiology into account.

Manual calculations using the Rodvold equation or trapezoidal methods require two blood levels drawn at specific times with respect to dosing and can be tedious. Because current practice relies on a single trough level, introducing a second blood draw is likely to increase costs, inconvenience patients, and create logistical challenges, as nurses' schedules may not enable collection of both samples at the proper times.

A third method based on Bayes' Theorem—the Bayesian methodology—is gaining popularity. This method combines patient data with population pharmacokinetic models to derive individualized estimates of a patient's pharmacokinetic profile. With a more tailored understanding of the patient's pharmacological disposition, a clinician may adjust the dose after one or more drug concentration levels are collected. This methodology has been shown to improve dosing accuracy by reducing toxicity without compromising efficacy.

Comparison of AUC calculation methods

Manual calculations – require two blood draws and are tedious:

- **Rodvold** – rapid, practical, but underestimates true AUC
- **Trapezoidal** – slower but more individualized than the Rodvold method

Bayesian method – rapid, adaptive and potentially lower cost, with fewer blood draws. Preferred approach when clinical decision support (CDS) dose-optimizing software is used.

The recently published dosing guidelines recommend using a model-informed Bayesian methodology to calculate AUC. Unlike manual methods, the model-informed Bayesian approach can be based on a single blood level that can be drawn at any time between doses. This reduces the operational burden on nursing and other staff because, unlike the manual AUC-based methods, it does not require blood concentrations to be measured precisely at peak or trough time points.

A possible disadvantage of model-informed Bayesian methodology is that it involves complex, potentially time-intensive calculations. This drawback can be overcome by using clinical decision support software to perform the calculations, allowing clinicians to quickly achieve optimal dosing for each patient. The cost of Bayesian software programs may be more than offset by shorter therapy and lower patient care costs.[14]

> "Advantages of the Bayesian approach include adaptive, fast predictions and potential cost savings realized through a reduction in required vancomycin levels. The primary limitation…is the cost of the software, which varies in price depending on the program and selected subscription model."[15]

Several recent studies underscore the value of using the Bayesian approach to make vancomycin dosing more precise. A 2014 study concluded that adjusting vancomycin doses on the basis of trough concentrations without a Bayesian clinical decision support tool fails to achieve safe and effective drug exposures.[16] In a simulated analysis, the use of such a tool was found to be better than clinician judgement in recommending vancomycin dosing regimens in which PK/PD targets would be attained in children.[17] A 2018 study found that the Bayesian method using one or two blood draws produced comparable results to manual equations involving two blood draws.[18]

Looking ahead: Bayesian method with continuous improvement

The evolution of the model-informed Bayesian methodology will likely include a learning mechanism where the underlying population models are optimized over time by leveraging aggregated real-world clinical data.

Progressive healthcare organizations are already beginning to take precision dosing to the next level by incorporating a continuous learning approach — enabling clinicians to dose more accurately across varying patient populations. Such a "continuously learning dosing system" is a concrete and practical step toward the vision of the learning healthcare system described by the Institute of Medicine in 2007.[19]

A continuously learning precision dosing platform helps organizations overcome limitations of static PK models, which are based on populations that may have very different characteristics than a given hospital's *actual* population. Dynamic methodologies that incorporate pharmacometrics and machine learning can prospectively ingest patient data and outcomes from specific sub-populations — even an institution's own patient population — to improve the model's accuracy over time.

> "The Bayesian AUC-guided dosing strategy may be an optimal approach to individualize vancomycin therapy in pediatrics since it can incorporate varying ages, weights, and renal function."*

Source: 2020 IDSA consensus guidelines, page 59

A continuously learning dosing system is especially valuable when treating special populations that are notoriously difficult to dose accurately, such as infants, children, or obese patients. Over time, a hospital pharmacy can further improve AUC target attainment and AKI rates for such special populations with precision dosing, substantially improving patient quality and safety.

Rapid adoption of safer dosing guidelines is recommended

At this time, awareness and adoption of newer vancomycin dosing protocols by hospital pharmacies is low. In the face of compelling evidence for an AUC-based dosing approach, which is supported by the recently published vancomycin dosing guidelines, organizations need to take action. Hospital pharmacy, infectious disease, and safety leaders should urge their organizations to quickly move up the learning curve to adopt AUC-based dosing protocols. That shift will enable them to reduce AKI rates, length of stay, morbidity, and mortality — and likely reduce overall costs.

Among several AUC-based methods, the Bayesian method is the fastest and most precise. The cost of purchasing a software program to deploy this approach should be weighed against potentially greater convenience for nurses and patients, superior patient safety, and a lower cost of care. Applying machine learning to the Bayesian method will allow healthcare organizations to achieve even greater dosing precision over time, which in turn will contribute to continually enhanced patient safety while shortening hospital stays and reducing costs.

To learn more about how to effectively adopt the new vancomycin dosing guidelines, visit us at insight-rx.com or email us at sales@insight-rx.com.

Visit www.insight-rx.com to request a trial.

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