Should Therapeutic Monitoring of Vancomycin Based on Area under the Curve Become Standard Practice for Patients with Confirmed or Suspected Methicillin-Resistant *Staphylococcus aureus* Infection?

THE "PRO" SIDE

The pharmacokinetic-pharmacodynamic parameter best correlated with efficacy of vancomycin in the treatment of infections with methicillin-resistant *Staphylococcus aureus* (MRSA) is the 24-h ratio of area under the curve (AUC) to minimum inhibitory concentration (MIC).[1,2] Given the need for multiple measurements of vancomycin level and complex calculations, the trough level has historically been used as a surrogate marker. In the 2009 guidelines for therapeutic monitoring of vancomycin,[3] troughs of 15–20 µg/mL were recommended, on the basis that these levels should correlate with an AUC/MIC of at least 400 mg*h/L, the true efficacy target. Since the implementation of these recommendations, reports of increased toxic effects have raised concerns about overly aggressive dosing, and clinicians have attempted to identify strategies to better balance targeted clinical efficacy with the risk of toxic effects.

There is known interpatient variability in the correlation between measured trough, which is a single point estimate, and target AUC/MIC.[4-6] Pai and others[5] detailed the mathematical relation between trough and AUC and demonstrated, through Monte Carlo simulations, that only 50% of interindividual variability in exposure is explained by trough values. Pragmatically, Hale and others[6] evaluated vancomycin levels in 100 patients in an attempt to correlate trough concentrations with AUC/MIC of at least 400. They found that troughs less than 10 µg/mL were unlikely to achieve an AUC of at least 400 (p = 0.045); however, there was no difference between troughs of 10–14.9 µg/mL and 15–20 µg/mL (p = 0.817). Therefore, without the corresponding AUC, a trough value alone is minimally useful.

Data regarding the vancomycin trough level as a surrogate marker for AUC/MIC in the context of MRSA bacteremia also highlight that troughs of 15–20 µg/mL are likely to attain the pharmacokinetic-pharmacodynamic target, but may also lead to unnecessary exposure and risk of toxicity.[4,7,8] In their meta-analysis, van Hal and others[7] reviewed 15 studies and found that vancomycin trough levels of 15 µg/mL or above were associated with increased odds of nephrotoxicity relative to trough levels below 15 µg/mL (odds ratio [OR] 2.67, 95% confidence interval [CI] 1.95–3.65), a difference that persisted after adjustment for clinically relevant covariates. Bosso and others[9] came to a similar conclusion when evaluating vancomycin levels in 291 patients across 7 sites. Fifty-five patients met the definition for nephrotoxicity, of whom 76.4% had troughs above 15 µg/mL. In a multivariable analysis, relative to lower trough values, troughs above 15 µg/mL were independently associated with increased risk of nephrotoxicity. These findings are supported by the quasi-experimental study of Finch and others,[10] who examined the impact of changing from trough-based to AUC/MIC-based monitoring. In a study of more than 1000 patients, AUC/MIC-based monitoring was independently associated with lower odds of nephrotoxicity relative to trough-based monitoring (OR 0.53, 95% CI 0.34–0.8).

Data correlating attainment of the target vancomycin trough with improved clinical outcomes are lacking.[11] Jung and others[12] evaluated vancomycin treatment failure in patients with MRSA bacteremia and found no difference in the proportion of treatment failures between those who did and those who did not achieve troughs of 15–20 µg/mL. They did determine that AUC/MIC below 430 was associated with more treatment failure than AUC/MIC above 430 (50% versus 25%, p = 0.039). Kullar and others[11] found a similar result. Among 320 patients, they reported a 52.5% failure rate and found that patients with AUC/MIC below 421 had an increased risk of failure relative to those with AUC/MIC above 421 (61.2% versus 48.6%, p = 0.038). Brown and others[13] found a significant 4-fold increased risk of death with AUC/MIC below 211 (with MIC determined by Etest) relative to AUC/MIC above 211 in patients with MRSA bacteremia and infective endocarditis (63% versus 19%, p = 0.02). Admittedly, most of the literature supporting the use of AUC as a marker of clinical outcomes is based on AUC approximations; nonetheless, these studies still provide more evidence than is available for trough-based monitoring. As outlined above, data supporting either measure to improve clinical outcomes are lacking; however, AUC/MIC-based monitoring to limit toxic effects is more robust than trough-based monitoring. This conclusion is supported by a recent, prospective evaluation of vancomycin AUC/MIC exposures in 265 patients with MRSA bacteremia. Lodise and others[14] were not able to identify an AUC/MIC threshold associated with treatment success but did find that patients with AUC/MIC less than or equal to 515 experienced the best global outcomes, including a limited risk of nephrotoxicity.

As mentioned, vancomycin troughs of 15–20 µg/mL have been recommended as a surrogate marker because of challenges in estimating AUC in clinical practice.[3] The consensus guidelines for therapeutic monitoring of vancomycin have recently been updated to recommend target attainment based on AUC/MIC, stating that use of 2-level AUC calculators or Bayesian software programs now makes quick and reliable calculations feasible.[15] There remains considerable hesitation among clinical pharmacists, however, regarding the practical application of AUC/MIC-based monitoring.[16-18] As reported by those surveyed, common concerns have included unclear benefit of and lack of familiarity with AUC/MIC-based monitoring, training requirements, and resource allocation in terms of pharmacist time and laboratory costs. The paradigm of trough-based monitoring has been so long engrained in clinical practice that the need for extensive education to address the lack of familiarity with AUC/MIC-based monitoring is a valid concern.

To assist others, several clinicians have published their experiences with implementing AUC/MIC-based monitoring.[19-21] These publications highlight the need for extensive education of not only clinical pharmacists, but also front-line nurses, phlebotomists, and ordering providers. This culture change does not happen overnight, but successful implementation of this strategy has proven feasible across numerous and varied practice sites. Although resource allocation related to the number of levels measured per patient is a justifiable concern, recent publications have not supported this.[18,19,22] In a prospective trial investigating a transition from trough-based to AUC/MIC-based monitoring using Bayesian software, Neely and others[23] reported fewer blood samples per patient, shorter duration of therapy, and decreased nephrotoxicity. Numerous programs are now available that utilize richly sampled patient populations and Bayesian-based mathematical modelling to assist in optimizing AUC/MIC without the need to measure vancomycin level numerous times for each patient.[24] Additionally, if the cost of these programs is a concern, 2-level AUC-based calculators, either developed separately or integrated with the electronic medical record, have been commonly used to implement AUC/MIC-based monitoring.[19-21] It is also important to note that among those who have changed to AUC/MIC-based monitoring, the perception of clinical relevance shifts from "unknown" to "of clinical importance", evidence that a paradigm shift is in fact possible.[18,21]

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THE "CON" SIDE

New practices in infectious disease pharmacotherapy are often promoted because they should work, according to our understanding of pathophysiology, microbiology, and pharmacokinetics and pharmacodynamics. However, theoretical advantages frequently fail to produce tangible benefit and occasionally result in harm.[1] Recent examples of failures in the translation from theory to practice include inhaled antibiotics for ventilator-associated pneumonia,[2] combination therapy for methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia[3,4] and carbapenem-resistant *Acinetobacter baumannii* infections,[5] and—of particular relevance to the topic of this Point Counterpoint debate—the use of vancomycin troughs of 15 to 20 mg/L to guide treatment for invasive MRSA infections.[6,7] When the first iteration of the vancomycin monitoring guideline was published in 2009,[6] concerns over the emergence of *S. aureus* strains with reduced vancomycin susceptibility led some researchers and clinicians to advocate for an aggressive dosing approach in the absence of high-quality data.[8,9] Since then, evidence has suggested that trough levels of at least 15 mg/L may not be necessary to achieve the guideline target for area under the curve (AUC) of at least 400.[10] Furthermore, the described "creep" in vancomycin minimum inhibitory concentration (MIC) may be an artifact of the testing method, and changes in pathogen virulence and/or lack of source control may often be responsible for antibiotic failure.[11-15] In addition, the clinical benefit of maintaining trough levels between 15 and 20 mg/L has not been well documented, and available data indicate that levels within this range are associated with an increase in nephrotoxicity.[7,16]

The updated vancomycin guideline, published earlier this year, now recommends AUC/MIC monitoring for serious MRSA infections, with abandonment of trough-based monitoring.[17] This recommendation creates a significant shift in how clinicians mange vancomycin therapy and may have substantial monetary and opportunity costs. These costs are justified only if AUC-based monitoring improves clinical or safety outcomes. Below we outline our view that the recommendation for AUC-based monitoring is drawn from weak evidence, which is not sufficient to justify widespread adoption.

The threshold AUC/MIC value of 400 originates from a single-centre, retrospective study of *S. aureus* pneumonia from the early 2000s.[18,19] In that study, an AUC/MIC value greater than or equal to 350, as determined by classification and regression tree analysis (CART) in 50 clinically evaluable patients, was associated with a greater likelihood of clinical success, whereas an AUC/MIC value greater than or equal to 400 (n = 34 patients) was associated with bacterial eradication.[18,19] Several points pertaining to this study deserve emphasis: first, the estimated AUC was calculated on the basis of *all* anti-staphylococcal antibiotics administered during the course of therapy, including combination therapy with ß-lactams and aminoglycosides, for which AUC/MIC is not the relevant pharmacokinetic-pharmacodynamic index; second, the majority (63%) of *S. aureus* isolates were methicillin-susceptible; and finally, the outcome of bacterial eradication from respiratory samples has uncertain clinical value.

Many studies have since examined the relationship between vancomycin AUC/MIC and clinical outcomes in patients with MRSA infections, coming to divergent conclusions and identifying a wide range of thresholds.[20-44] Most have been small (fewer than 100 participants),[23,25,28,30,32,33,35,36,38-40] retrospective,[23-25,27-30,32,33,35,36,38,40-42] single-centre[23,24,27-30,32,33,35,36,38,40,42] studies in which vancomycin dosing was managed by assessment of trough levels.[23,24,27,29,32,34-36,39-43] Study registration, planned analyses, and power calculations were rarely discussed in the published reports. Vancomycin MIC was determined by a variety of testing methods, and many of the studies used formulas to estimate AUC that were based on daily vancomycin dose, population pharmacokinetics, and estimated renal function.[25,27,32,39,42] The guideline authors acknowledged technical issues with determination of vancomycin MIC and suggested the assumption that MIC = 1 mg/L.[17] However, using this assumption for dosing decisions in individual patients is problematic because most studies have not assumed MIC = 1 mg/L. High MIC on its own may be predictive of response, and when used as the denominator, a higher value of MIC drives down the AUC/MIC value, creating a spurious correlation.[45] In addition, in many studies CART was used as an exploratory method to identify cut points for dichotomizing AUC/MIC data without validation in an independent external data set.[23-25,27,28,33,34,38,40] Threshold values

identified by CART have ranged from as low as 211[22] to as high as 667,[28] with some studies identifying multiple thresholds.[21,24,27,29,30] In the only study to date that attempted to validate alternative CART-derived AUC/MIC thresholds (day-2 AUC/MIC ≥ 650 and ≥ 320, with MIC determined by broth microdilution and Etest, respectively) in a multicentre, prospective study of an external population, there was no significant difference in mortality or persistent bacteremia using these vancomycin exposure thresholds.[31] Additionally, that study did not identify alternative thresholds or confirm AUC/MIC of at least 400 as predictive of clinical failure.[31]

Among studies assessing the relationship between clinical outcomes and a prespecified AUC/MIC threshold of 400,[11,32,35,36,39] only one, which involved 51 pediatric patients with *S. aureus* bacteremia, found a statistically significant relationship between AUC/MIC of at least 400 and clinical response[32]; however, no significant association was found between AUC/MIC of at least 400 and mortality or microbiological response. Interestingly, one study found no significant reduction in 30-day mortality among patients with *S. aureus* bacteremia who achieved AUC/MIC of at least 400, but found that an alternative CART-derived threshold of 373 was statistically significant.[44] In another study, patients who experienced clinical failure paradoxically had a significantly higher mean vancomycin AUC than those who experienced clinical success.[37] Many other studies also found no statistically significant relationship between AUC (or AUC/MIC) and outcomes, and therefore the authors did not go on to perform CART (or other) analyses.[35,36,38-43,46] None of these studies reported a formal power calculation, so type II errors cannot be excluded.[11,32,35,36,39] Surprisingly, many studies with negative or nonsignificant results[35,38-43,46] were not mentioned in the guideline update, even though the guideline methods suggested that all relevant literature published in English had been reviewed.[17]

AUC-based vancomycin monitoring may still be valuable if it is a safer alternative than trough-based monitoring. A large body of observational literature collectively suggests that the incidence of nephrotoxicity increases as a function of vancomycin exposure, whether measured by trough level or AUC.[11,31,37,46-57] A wide range of threshold AUC values have been identified (563–1300 mg*h/L),[33,47,54,56,57] and the observational data are conflicting with regard to which pharmacokinetic parameter—trough level or AUC—is most closely correlated with nephrotoxicity.[47,56,57] In some studies, which used Monte Carlo simulation or population pharmacokinetic data to estimate AUC, trough levels have been only moderately correlated with AUC.[10,52] However, recent clinical studies using human data (rather than simulation) have found remarkably high correlation between trough level and AUC (R^2 = 0.88–0.95).[47,49,50,53,58,59] Such high correlation makes distinguishing a "better" measure of exposure a fool's errand, since one predictor can easily and reasonably accurately be approximated by the other.

Two recent observational studies reported lower rates of nephrotoxicity with the implementation of AUC-based monitoring relative to previously used trough-based monitoring.[48,51] Importantly however, all[48] or many[51] patients in the trough-based monitoring arms of these studies received vancomycin regimens targeting trough levels of 15 to 20 mg/L, an approach to vancomycin therapy that is known to be harmful.[7,16] Average doses and trough levels were significantly lower in the AUC-based groups, which reaffirms that lower vancomycin exposure confers a decreased risk of nephrotoxicity, regardless of the monitoring method. An important knowledge gap is the issue of whether AUC-based monitoring is safer than trough-based monitoring that targets pre–guideline era troughs between 5 and 15 mg/L. We hypothesize that there would be little observable difference.

In summary, the collective evidence on vancomycin AUC-based therapeutic drug monitoring for MRSA infections is primarily hypothesis-generating and inconsistent. Although AUC-based monitoring may have appeal because of its perceived sophistication, it has not met the stated criteria of improving clinical outcomes or safety. In fact, the multiple blood samples required for AUC-based monitoring will affect patient comfort and convenience and may cause harm. Pharmacists and other clinicians should advocate for interventions that are valuable to patients and the health care system, rather than assuming that newer, more complex, more expensive, and more time-consuming strategies will lead to better outcomes.

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