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BRIEF REPORT

In Outpatients Receiving Parenteral Vancomycin, Dosing Adjustments Produced by Area Under the Curve-Based and Trough-Based Monitoring Differ Only at the Extremes of the Therapeutic Trough Range

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Area under the curve (AUC)-based vancomycin dosing reduces nephrotoxicity but is burdensome. Reviewing 115 adults receiving ≥2 weeks of outpatient vancomycin, we found AUC-based and trough-based dose adjustments discordant only for troughs <12 or >16 mg/L. Selective versus universal outpatient AUC calculation would likely offer similar benefit with reduced workload.

Keywords. monitoring; nephrotoxicity; OPAT; therapeutic dose monitoring; vancomycin.

Vancomycin is frequently used for definitive treatment of methicillin-resistant *Staphylococcus aureus* (MRSA). Current guidelines for therapeutic vancomycin monitoring for serious MRSA infections recommend targeting a 24-hour area under the curve (AUC) to minimum inhibitory concentration (MIC) ratio of 400–600 (eg, 400–600 mg*h/L for isolates with an MIC of ≤1 mg/L) rather than using a surrogate serum trough target [1]. The rationale for this is reduction of vancomycin-induced kidney injury (VIKI) rather than improved efficacy, because data comparing AUC and trough-based dosing more strongly supports a difference in the former outcome [2]. Following these guidelines' release, some colleagues have argued against AUC-based dosing, pointing to evidence that vancomycin troughs and AUCs correlate well, questioning the validity of research suggesting AUC-based dosing reduces VIKI, citing the cost of Bayesian dosing software, recognizing AUC calculations increase pharmacist workload, and suggesting a relaxed trough target of 10–20 mg/L as a simpler alternative [3, 4].

Data on vancomycin dosing in outpatient parenteral antimicrobial therapy (OPAT) are scant. In 2021, Rees et al [5] reported a 17.4% lower risk of acute kidney injury with AUC-based dosing among 118 outpatients receiving at least of 1 week of vancomycin; in this study, however, rather than regular AUC monitoring, the authors performed a single AUC calculation once steady-state vancomycin levels had been achieved, determining an individualized target trough range for subsequent therapeutic dose monitoring (TDM). A recent Canadian cohort found that VIKI necessitating treatment discontinuation complicated just 5% of vancomycin courses administered via OPAT, which suggests limited opportunity for further reduction of vancomycin nephrotoxicity in the OPAT setting [6]. Beyond this, little has been reported on AUC- versus trough-based vancomycin TDM in OPAT. Our center's OPAT program uses AUC-based vancomycin TDM for all patients based on a single serum concentration and a commercially available, clinically validated Bayesian modeling platform (DoseMe Pty Ltd., Brisbane, Australia). Obtaining reports of weekly laboratory tests and performing dosing calculations takes up the majority of the time our OPAT team spends on vancomycin TDM; therefore, we examined the weekly vancomycin troughs and AUCs of patients who received AUC-dosed vancomycin via OPAT to evaluate how frequently AUC-based and trough-based dosing strategies prompted different dose adjustments.

METHODS

We conducted a retrospective cohort study using the University of Nebraska Medical Center (UNMC) OPAT database, including adults who received outpatient intravenous vancomycin between March 1, 2019 and March 1, 2021. We included patients who received 2 or more consecutive weeks of vancomycin via OPAT during the study period; more than 1 episode of vancomycin treatment per patient could be included in the study so long as all included courses of vancomycin treatment via OPAT occurred during the study period and lasted 2 weeks or more. For each patient, we collected additional clinical data from the medical record including demographics, the type of infection, the treatment regimen, and the vancomycin trough, vancomycin 24-hour AUC, and serum creatinine

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for each week that both a serum vancomycin trough level and calculated AUC were documented. We defined acute kidney injury (AKI) using the fold change component of the 2012 KDIGO definition of AKI (ie, a >1.5-fold increase in serum creatinine over 7 days), to which we added a weekly serum creatinine increase ≥0.3 mg/dL, adapted from the 48-hour change component of the KDIGO definition [7]. We excluded patients receiving hemodialysis or peritoneal dialysis.

Our primary outcome of interest was discordance in vancomycin dose adjustment prompted by the patient's vancomycin 24-hour AUCs, compared with theoretical trough level management, considered as a 3-step ordinal variable (ie, a recommendation could be to either decrease the dose, keep the same dose, or increase the dose of vancomycin). Dose adjustment recommendations for 24-hour AUC were determined using a goal range of 400–600 mg*h/L. Vancomycin trough-based dosing recommendations were evaluated by the traditional goal trough target for serious infections (15–20 mg/L), as well as the relaxed trough target of 10–20 mg/L that Jorgensen et al [3, 4] have suggested as a simpler alternative to AUC-based dosing.

We performed statistics in IBM's SPSS Statistics for Windows version 26 (2019; Armonk, NY) and Microsoft Excel (2022; Redmond, WA). We report Pearson's correlation for the association between vancomycin trough and 24-hour AUC pairs; otherwise, the statistics reported are entirely descriptive.

Patient Consent Statement

This study was exempted from UNMC's institutional review board review after being deemed a quality improvement project involving retrospective, deidentified patient data. The requirement to obtain and document patient consent was waived by the institutional review board.

RESULTS

We included 115 patients in the study, whose baseline demographics, indications for OPAT, pathogens under treatment, and intravenous and oral antimicrobial regimens are summarized in Table 1. The mean total duration of vancomycin therapy was 5.8 (standard deviation [SD], 2.7) weeks, and the mean duration of vancomycin via OPAT was 3.9 (SD, 2.0) weeks. Twenty-two patients (19.1%) were readmitted during antimicrobial therapy; 12 (10.4%) of these were determined to be infection-related, with reasons including worsening infection (5 of 22), preplanned procedure (3 of 22), vancomycin drug rash (2 of 22), and catheter thrombosis or phlebitis (2 of 22). The other readmissions were not clearly related to the initial infection and included new and unrelated infection (eg, coronavirus disease 2019 [COVID-19]) (2 of 22) and other acute issues (eg, decompensated heart failure, gout flare, gastrointestinal bleeding) (8 of 22). With AUC-based vancomycin dosing, 8 patients had AKI on vancomycin (2 by formal KDIGO criteria), none requiring hospitalization or emergency department evaluation. Each of these patients had AUCs at goal, half with troughs 10–15 and half with troughs 15–20; in 5 cases, no changes to the vancomycin dose were made and in 3 cases the dose was reduced, with 1 patient eventually switching to daptomycin.

Our patients received 447 patient-weeks of vancomycin therapy. Of these, weekly laboratory tests were either missing or uninterpretable (eg, due to errors in vancomycin administration) in 32 cases, and a specific OPAT note including the calculated AUC was not documented in another 184 cases. It is notable that, for part of the study period, a single pharmacist was handling all outpatient vancomycin TDM in addition to their

Table 1. Patient Characteristics (n = 115)

Characteristics	Mean (SD)/No. (%)
Age, year	61.7 (16.1)
Weight, kg	91.0 (23.6)
Male	51 (44.0%)
Serum creatinine, mg/dL	1.0 (0.4)
Total daily vancomycin dose, mg	2230 (1026)
Total duration of therapy, weeks	5.8 (2.7)
Duration of vancomycin OPAT, weeks	3.9 (2.0)
Indications for OPAT, No. (%)	
Osteomyelitis	38 (33.0%)
PJI	30 (26.1%)
Endovascular device infection	8 (7.0%)
CNS infection	7 (6.1%)
CRBSI or primary bacteremia	6 (5.2%)
SSTI	5 (4.3%)
Native joint septic arthritis	4 (3.5%)
Endocarditis	4 (3.5%)
Other infections	8 (7.0%)
Pathogens Being Treated, No. (%)	
MRSA	32 (27.8%)
Culture negative	32 (27.8%)
Polymicrobial	22 (19.1%)
Coagulase-negative staphylococci	18 (15.7%)
Enterococcus	2 (1.7%)
Other	9 (7.8%)
IV Antibacterial Regimens	
Vancomycin alone	78 (67.8%)
Vancomycin plus ceftriaxone	25 (21.7%)
Vancomycin plus cefepime	7 (6.1%)
Vancomycin plus ertapenem	3 (2.6%)
Vancomycin plus piperacillin/tazobactam	1 (0.9%)
Concomitant PO Antibacterials	
Nothing	85 (73.9%)
Rifampin	14 (12.2%)
Metronidazole	10 (8.7%)
Levofloxacin	5 (4.3%)
Doxycycline	1 (0.9%)

Abbreviations: CNS, central nervous system; CRBSI, catheter-related bloodstream infection; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; OPAT, outpatient parenteral antimicrobial therapy; PJI, prosthetic joint infection; SD, standard deviation; SSTI, skin and soft tissue infection.

inpatient and COVID-19-related duties, making documentation of all AUCs infeasible, although AUCs were consistently calculated and used to guide vancomycin dosing throughout. Thus, a total 231 patient-weeks of vancomycin treatment via OPAT in which both serum vancomycin troughs and calculated 24-hour AUCs were included in this study, with overall high correlation between these values (Pearson's r = 0.888; scatter plot shown in Supplementary Figure 1).

Discordance between 24-hour AUC 400–600 mg*hour/L and the traditional trough target for severe infections of 15–20 mg/L was 51%; relaxing the vancomycin trough target to 10–20 mg/L reduced discordance to 16%. When we stratified vancomycin 24-hour AUC distributions by serum trough ranges (Supplementary Table 1), we found that a substantial portion of AUCs fell below goal when the trough was <12 mg/L and above goal when the trough was >16 mg/L. When we stratified dose adjustment recommendations from the 24-hour AUC and 10–20 mg/L trough TDM strategies by these vancomycin trough cutoffs (Supplementary Figure 2), we found the 2 TDM strategies had near-perfect (97.6%) agreement when troughs ranged 12–16 mg/L. However, AUC-based dosing recommended a higher dose for over one third of instances when troughs were <12 mg/L and a lower dose for over one fifth of instances with troughs >16 mg/L.

DISCUSSION

To our knowledge, this is the largest reported cohort of AUC-directed vancomycin dosing in OPAT. With AUC-based vancomycin dosing in OPAT, AKI occurred in 8 of 115 patients (7%) with no AKI-associated readmissions or emergency department visits over 2 years; only 1 patient required a change to an alternate agent due to AKI. Our nephrotoxicity findings are similar to those in recent cohorts using continuous infusion vancomycin as a renal-sparing OPAT strategy, and 1 smaller AUC-directed dosing evaluation [5, 8]. Calculating vancomycin AUCs and documenting vancomycin dose adjustments currently represents a substantial portion of our OPAT team's pharmacist workload; this study suggests that streamlined patient care workflow with selective calculation of AUCs could dispense with much of that workload, freeing up pharmacist time for more consistent documentation and other more value-added OPAT activities.

When evaluating discordance between trough-based and 24-hour AUC-based vancomycin TDM strategies in OPAT patients, we found that although vancomycin troughs and AUCs correlated highly overall, agreement between AUC-based and trough-based dosing adjustment recommendations varied substantially based on the trough values, and this discordance was only partially resolved by relaxing the trough target from 15–20 to 10–20 mg/L. Specifically, widening the range to 10–20 mg/L still led to a significant number of situations in which AUC calculation indicated that either lower troughs would have been acceptable (12 instances) or that higher troughs might be necessary (18 instances). That said, the dosing strategies produced nearly identical recommendations when the serum trough was in the range of 12–16 mg/L, which occurred in 36.4% of patient-weeks, suggesting vancomycin AUC calculation in the OPAT setting could often be dispensable. Moreover, because the data for value of AUC-based vancomycin TDM primarily concerns safety rather than efficacy, and arguably AUC calculation is useful primarily for reducing vancomycin doses, we note that dispensing with AUC calculations for vancomycin troughs <16 mg/L would have avoided most (67.5%) of our cohort's calculation workload.

Two important caveats deserve mention. First, AUC calculation occasionally facilitates more convenient vancomycin-dosing intervals despite lower troughs; for example, in 19 of 231 patient-weeks in this study, patients had 24-hour AUCs ≥400 despite troughs ≤12 mg/dL with once-daily vancomycin. We believe AUC calculation to confirm the patient is receiving therapeutic drug levels in this setting is reasonable. Second, AUC still varied considerably within narrow trough ranges, and AUC calculations would be far less dispensable given narrower AUC targets. For example, if the therapeutic AUC target range was narrowed to 400–515 mg*hour/L (eg, to fall under the increased nephrotoxicity risk threshold defined in the PROVIDE cohort), 24 of 84 (28.6%) of vancomycin troughs 12–16 mg/L would have corresponding AUCs out-of-range [9].

This study has multiple limitations. It was single-center and retrospective. Our focus on the OPAT population, most of whom likely had a stable vancomycin dose determined in the hospital, limits our findings' generalizability to inpatients who are starting vancomycin or in whom renal function is actively changing. A significant proportion of undocumented AUC calculations due to high OPAT team workload may have biased our dataset to disproportionately include patient-weeks in which dosing regimens were changed. Although we report paired troughs and AUCs, the actual vancomycin dose management was made based on the AUC throughout; thus, this study does not directly compare vancomycin-dosing strategy outcomes. We used a 1-concentration Bayesian estimation model throughout, and discordance with trough-based TDM could be modestly different with other AUC calculation methods, because agreement between methods is high but not complete [10]. Finally, due to the small sample size and low rates of nephrotoxicity observed in the entire cohort, we were unable to ascertain whether certain risk factors (eg, underlying kidney disease or obesity) might particularly predispose to trough-AUC discordance and represent a subpopulation more likely to benefit from AUC-directed vancomycin dosing; this could be the subject of a subsequent, larger study.

CONCLUSIONS

In conclusion, correlation between vancomycin troughs and AUCs in OPAT is high but varies based on trough level, with more discordance at the extremes of the vancomycin trough range. We conclude that selective versus universal calculation of AUCs in patients receiving vancomycin via OPAT would likely offer equivalent reduction in VIKI while substantially reducing OPAT program workload.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Potential conflicts of interest. All authors: no reported conflicts of interest.

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