PHARMACOTHERAPY

Conversion from Vancomycin Trough Concentration–Guided Dosing to Area Under the Curve–Guided Dosing Using Two Sample Measurements in Adults: Implementation at an Academic Medical Center

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Study Objective The optimal pharmacodynamic parameter for the prediction of efficacy of vancomycin is the area under the concentration–time curve (AUC), and current published data indicate that dosing based on vancomycin trough concentrations is an inaccurate substitute. In this study, our objective was to compare the achievement of therapeutic target attainment after switching from a trough-based to an AUC-based dosing strategy as a part of our institution's vancomycin-per-pharmacy protocol.

Design Prospective observational quality assurance study.

Setting Academic medical center.

Patients A total of 296 hospitalized adults who received vancomycin and monitoring under our institution's vancomycin-per-pharmacy protocol were included in the analysis. The preimplementation retrospective comparison group consisted of 179 patients in whom vancomycin was initiated using a trough-based dosing strategy between November 22, 2017, and January 22, 2018. The postimplementation group included 117 patients in whom vancomycin was initiated using an AUC-based dosing strategy using two-point sampling between June 19, 2018, and July 19, 2018, after hospital-wide implementation of this protocol on June 19, 2018.

Measurements and Main Results AUC values were calculated from two vancomycin concentrations (peak and trough). The primary outcome was achievement of therapeutic AUC values (400–800 mg·hr/L) in the postimplementation group or therapeutic trough level values (10–20 mg/L) in the preimplementation group. Only 98 (55%) of 179 initial trough values were therapeutic in the preimplementation group (trough-only dosing method) versus 86 (73.5%) of 117 initial AUC values in the postimplementation group (AUC-based dosing method) ($p=0.0014$). A lower proportion of supratherapeutic AUC values was observed in the postimplementation group compared with supratherapeutic trough concentrations in the preimplementation group (1.7% vs 18%, $p<0.0001$). Overall, 62% of patients with initially therapeutic AUC values had subsequent trough value increases of 25% or greater, occurring at a median of 6 days of vancomycin therapy. Nephrotoxicity occurred in 11% of patients in the preimplementation versus 9.4% in the postimplementation group ($p=0.70$).

Conclusion Compared with a trough concentration–based dosing strategy, AUC-based dosing using two-point sampling improved therapeutic target attainment. Implementation is feasible at any hospital that performs vancomycin peak concentration testing and is a workable alternative to using Bayesian software for estimating AUC. This approach should also be directly compared with AUC-based dosing using Bayesian software.

KEY WORDS vancomycin, antimicrobial stewardship, therapeutic drug monitoring, clinical pharmacy services, dosing strategies.
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A 24-hour vancomycin area under the concentration–time curve (AUC_{24}) to minimum inhibitory concentration (MIC) ratio of 400 or greater is the pharmacokinetic (PK) target predictive of the antibacterial efficacy of vancomycin in the treatment of invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infections.[1] The 2009 vancomycin dosing guidelines recommend maintaining trough concentrations of 15–20 mg/L in patients with serious infections to approximate achievement of this target.[1] More recently, however, trough concentrations were found to underestimate AUC by 23% and therefore may lead to excessive dosing and inadvertent increases in nephrotoxicity.[2] Studies describing switches from a trough concentration–guided to an AUC-guided dosing strategy demonstrated reduced drug exposure and nephrotoxicity while maintaining AUC_{24} of 400 mg·hour/L or greater.[3, 4] AUC can be estimated by using Bayesian software, two or more serum concentrations, or continuous infusions. A recent study performed AUC-guided dosing using single vancomycin levels and Bayesian-controlled software (BestDose, Los Angeles, CA; available at http://www.lapk.org/).[4] However, implementation of such software may require expertise and extensive training, and it may be cost ineffective for some institutions. AUC estimates calculated from two vancomycin levels were shown to have good precision and accuracy when compared with AUC estimates derived from Bayesian software using a single vancomycin level.[2, 5] Thus the objective of this study was to compare the achievement of therapeutic target attainment after switching from a trough-based to an AUC-based dosing strategy using two sample measurements (peak and trough levels) as a part of our institution's vancomycin-per-pharmacy protocol.

Methods

Study Design, Setting, and Patient Population

This prospective observational quality assurance study of hospitalized adults in whom vancomycin was initiated took place between June 2018 and July 2018 at Stanford Health Care–Stanford Hospital (Stanford, CA), an academic medical center and level 1 trauma center with 613 inpatient beds of which 67 are intensive care unit beds. This study was reviewed by the Stanford Research Compliance Office and determined to be for quality improvement; therefore, submission to the institutional review board was not required.

Hospital-wide implementation of an AUC-based vancomycin-per-pharmacy dosing protocol using two-point sampling (peak and trough) using the trapezoidal rule[6] occurred on June 19, 2018. The preimplementation retrospective comparison group consisted of patients in whom vancomycin was initiated under the pharmacy protocol using a trough-based dosing strategy between November 22, 2017, and January 22, 2018. The postimplementation group included patients in whom vancomycin was initiated under an AUC-based dosing strategy between June 19, 2018, and July 19, 2018. Patients were included if they were at least 18 years old and had one or more trough concentrations measured after at least three vancomycin doses were administered in the preimplementation group and had at least one calculated AUC value in the postimplementation group. Exclusion criteria were renal replacement therapy (RRT) or acute kidney injury (AKI) at initiation of vancomycin, and nonprotocol patients. AKI was defined as a serum creatinine (S_{cr}) concentration increase of at least 0.3 mg/dl within 48 hours or 50% increase from baseline within 7 days, creatinine clearance (Cl_{cr}) change of more than 25–50%, or urine output less than 0.5 ml/kg/hour over 6 hours. Nonprotocol patients were those who received a one-time vancomycin dose, pediatric patients, and those with an anticipated duration of therapy less than 2 days (mainly surgical or perioperative prophylaxis).

Conflict of interest: The authors have declared no conflicts of interest for this article.

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Study Outcomes and Definitions

The primary outcome was achievement of therapeutic AUC values (400–800 mg·hr/L) in the postimplementation group or therapeutic trough level values (10–20 mg/L) in the preimplementation group. We chose to target AUC and not AUC:MIC given limited published data on this method and due to issues with MIC laboratory testing methodology.[7] Secondary outcomes included repeat trough concentrations higher than 25% of initial values in those with therapeutic initial AUC values, subsequent therapeutic AUC values after initial dose revision, and nephrotoxicity rates. Trough concentrations were defined as samples obtained 6.5–9.5, 10.5–13.5, and 22–26 hours after the previous dose for 3 times/day, twice/day, and once/day dosing, respectively. Vancomycin-associated nephrotoxicity was defined as an increase in S_{cr} of 0.5 mg/dl or 50% from baseline, and more highly attributable to vancomycin than to another cause by the primary team.[1, 4]

We built a dose calculator using Microsoft Excel (Microsoft Corp., Redmond, WA) based on the PK equations in our protocol (Appendix S1).[8] Its three functions include calculation of initial dosing regimens (Figure 1), AUC, and revised dosing regimens (Figure 2).

Statistical Analysis

Analysis consisted of descriptive statistics including median ± SD and interquartile range (IQR), where appropriate. For categorical data, the Fisher exact test was used to evaluate the differences between groups. For continuous data, we used the Mann-Whitney *U* test. All tests of significance were 2-tailed; $p<0.05$ was considered to indicate a significant difference. Statistical analyses were performed with GraphPad Prism v.6.0 (GraphPad Software, San Diego, CA).

Data Acquisition

Data were obtained from patients' electronic medical records (Epic, Verona, WI). Data variables included age, sex, indication for vancomycin, weight, body mass index (BMI), S_{cr}, concomitant use of piperacillin-tazobactam, medication administration data, and vancomycin serum concentration data.

Vancomycin-Per-Pharmacy Protocol

The pharmacist determines if a trough-based or AUC-based dosing strategy is appropriate based on the protocol criteria: patients receiving RRT or those with AKI or fluctuating renal function continue with a trough-based protocol, but they may switch to an AUC-based protocol once these conditions no longer exist.[8] For most indications, the target AUC is 400–700 mg·hour/L or trough 10–20 mg/L, except in patients with meningitis or confirmed MRSA infections with a vancomycin MIC of 2 mg/L, in which case the goal AUC is 600–800 mg·hour/L or trough

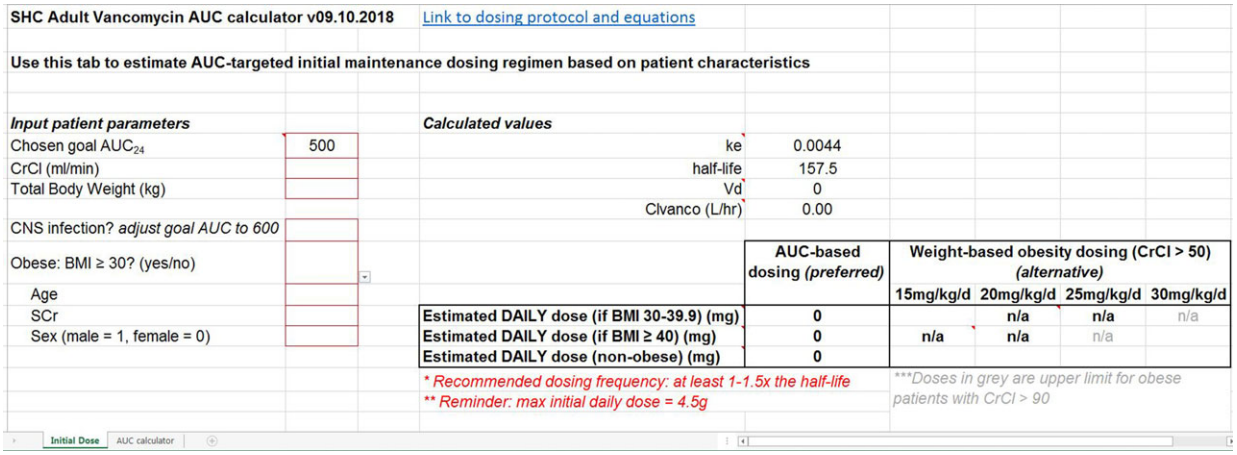

Figure 1. Stanford Health Care (SHC) Calculator: Initial Maintenance Dose Advice. On the first tab of the SHC Calculator on Microsoft Excel, end users enter the goal AUC, creatinine clearance, and total body weight to obtain initial dose estimates that are either AUC targeted or weight based. The default AUC target is 500 mg·hr/L for a goal AUC of 400–700 mg·hr/L but may be customized by the end user. The maximum daily vancomycin dose is capped at 4.5 g. AUC_{24} = area under the concentration–time curve; BMI = body mass index; Cl_{vanco} = vancomycin clearance; CNS = central nervous system; CrCl = creatinine clearance; k_e = elimination constant; mg/kg/d = milligrams per kilogram per day; Scr = serum creatinine concentration; SHC = Stanford Health Care; Vd = volume of distribution.

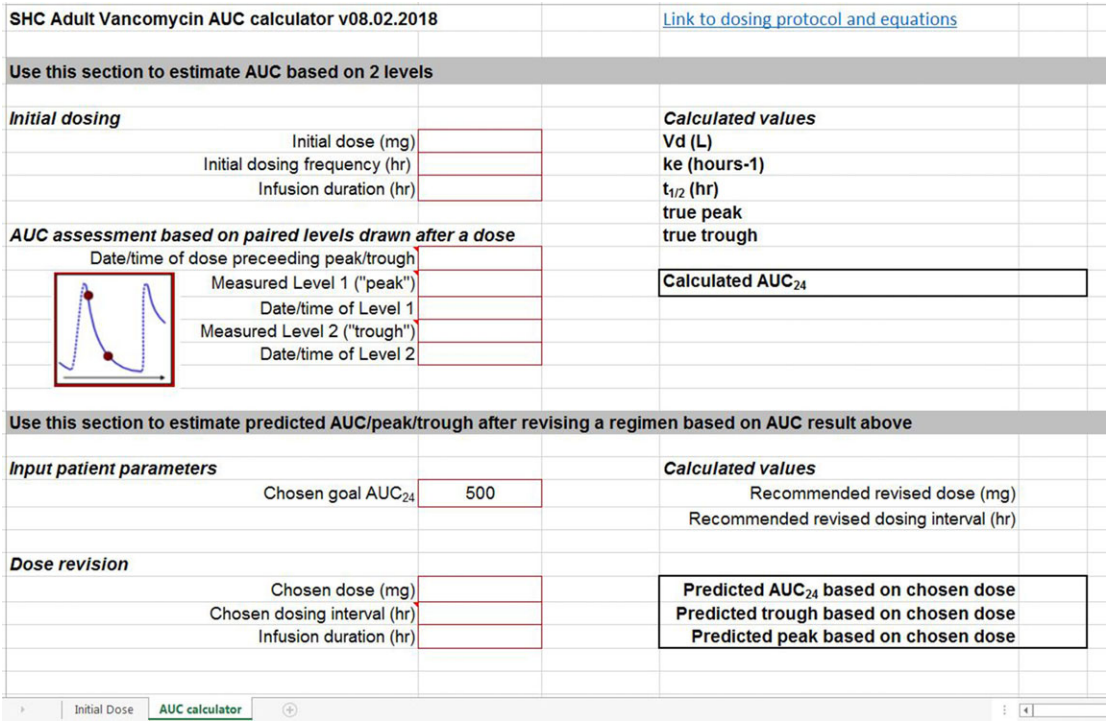

Figure 2. Stanford Health Care Calculator: AUC Estimate and Dose Revisions. On the second tab of the SHC Calculator on Microsoft Excel, users enter dosing regimen data and date/time/value of paired levels drawn after a dose. The calculated AUC and other pharmacokinetic values are calculated on the right side. On the bottom section, users have the option to view recommended revised dosing regimens or input a different dosing regimen and their corresponding AUC, peak, and trough values. AUC, AUC_{24} = area under the concentration–time curve; k_e = elimination constant; SHC = Stanford Health Care; $t_{1/2}$ = elimination half-life; V_d = volume of distribution.

15–20 mg/L. We selected the upper AUC thresholds of 800 mg·hour/L based on its high positive predictive value for nephrotoxicity in a recent study.[9] Peak and trough levels were scheduled at estimated steady state based on renal function (Appendix S1).

Pharmacists enter dosing and vancomycin serum concentration information into a Stanford hospital–specific spreadsheet calculator with prebuilt pharmacokinetic equations using Microsoft Excel (Appendix S1; also available at http://med.stanford.edu/bugsanddrugs.html) to obtain AUC values and revised dosing recommendations, if applicable.[8] If the initial AUC is within goal range and renal function remains stable, a repeat trough level is obtained every 2–5 days.

Sample Analysis

Vancomycin MIC is measured in the Stanford Clinical Microbiology Laboratory by the use of the Microscan broth microdilution method (Beckman Coulter, Miami, FL) for all staphylococci and enterococci isolates. Vancomycin serum concentrations were measured in the Stanford Clinical Pre-Analytical Laboratory using the EXL and RXL Dimension platform (Siemens Healthcare Diagnostics, Inc., Tarrytown, NY), with a lower limit of 0.8 mg/L and SD less than 1.49 mg/L.

Results

AUC-Based Vancomycin Dosing Protocol Implementation

Planning and initial implementation occurred from February to June 2018. A summary and timeline are provided in Table 1.

Study Population

The preimplementation group was composed of 179 patients. In the postimplementation group, vancomycin-per-pharmacy orders were placed for 371 patients, but only 117 were included in the analysis. Reasons for exclusion of the remaining 254 were as follows: 150 vancomycin orders were discontinued before any vancomycin peak and trough concentrations, 72

Table 1. Timeline of Implementation of the AUC-Based Vancomycin Dosing Protocol

February 2018	Discussed protocol changes with Antimicrobial Stewardship Team members and the Pharmacy Clinical Effectiveness Manager
March 2018	An infectious diseases pharmacist–led workgroup was formed, consisting of pharmacy leadership representatives and one representative from each satellite pharmacy
April 2018	Pharmacy workgroup reviewed protocol specifics and Epic electronic health record software modifications
	Meeting was held with Clinical Preanalytical Laboratory supervisors to review laboratory procedures for vancomycin serum concentrations and revise Epic orders
May 2018	Pharmacy and Therapeutics Committee and Antimicrobial Subcommittee approvals were obtained for the revised Vancomycin-Per-Pharmacy Protocol
	Epic modifications began
	Joint meeting was held with pharmacy, nursing, and information technology members from Stanford Health Care–Palo Alto and Stanford Health Care–ValleyCare to align Epic changes to the vancomycin laboratory because the Epic laboratory codes are shared between the two hospitals
	Presentations given at the hospital's nursing education council, the intensive care unit continuous quality improvement meeting, the Surgery Quality meeting, and the Infectious Diseases Department meeting
	Educational flyers e-mailed to hospital list-serves for house staff, residents, fellows, and various medical specialties including medicine, cystic fibrosis, solid organ transplantation, hematology, nephrology, critical care, and surgery
June 2018	Laboratory changes were approved by the institution's prioritization committee and implemented hospital-wide on June 19, 2018
	Six live 45-minute in-services were held by pharmacists
	Vancomycin-Per-Pharmacy protocol competency created
	June 4–June 18: 2-wk pilot test of protocol was conducted on patients on medicine wards and those receiving infectious diseases consultation services. Adjustments were made to the Excel calculator to simplify user inputs.
	June 19: Protocol was implemented hospital-wide
	June 19–July 3: Real-time audit with feedback was performed by the infectious diseases pharmacist
July 2018	Interim analysis was conducted and reported at the Pharmacy Department staff meeting
	Protocol revisions: pharmacist intervention occurred if repeat serum creatinine concentration or area under the concentration–time curve (AUC) values changed by > 25% from the previous value (or < 25% if the last AUC value was at the upper or lower limit of the therapeutic range). Pharmacists were also cautioned regarding drug accumulation after 7 days of vancomycin therapy.
	"Frequently asked questions" document was circulated to provide guidance on ways to address discordant AUC and trough level values, missed vancomycin laboratory blood draws, and clarification on exclusion criteria from AUC-based dosing for patients with unstable renal function or acute kidney injury
August 2018	Nursing and laboratory staff were re-messaged regarding protocol and timing of vancomycin serum concentration laboratory blood draws
September 2018	Audit completed with feedback to pharmacy department
	Excel calculator revised to remove estimation of vancomycin clearance by Ducharme equation[19]
	Excel calculator revised to include initial weight-based dose advice option in obese patients and vancomycin clearance equation from Crass and colleagues[10]

patients had unstable renal function or AKI, 26 were receiving RRT, and 6 were not on protocol or refused blood draws. Baseline characteristics were similar between the pre- and postimplementation groups (Table 2). The most common indication for vancomycin was pulmonary infections (26–32%), followed by skin and soft tissue infections (23–27%) (Table 2). In patients dosed by AUC, 57 (49%) of patients had positive cultures. The most commonly isolated pathogen was methicillin-sensitive *S. aureus* (11%), followed by MRSA (9%), all of which had vancomycin MICs of 1 mg/L. Additionally, at our institution in 2018, the MIC for 90% of tested isolates (MIC_{90}) was 1 mg/L or lower for *S. aureus*. In fact, nearly all *S. aureus* isolates (99.6%) exhibited vancomycin MICs of 1 mg/L or lower.

Primary Outcome

Achievement of therapeutic initial AUC values was attained in 73.5% of the postimplementation group compared with attainment of therapeutic initial troughs in only 55% of the preimplementation group (p=0.0014) (Table 3). Only two patients (1.7%) had a supratherapeutic initial AUC value compared with 33 (18%) of patients with a supratherapeutic initial trough value in the preimplementation group (p<0.0001). Additionally, of the observed AUC values that were 400 mg·hour/L or higher, 49 (55%) of the 89 corresponding troughs were lower than 15 mg/L, 88% were lower than 20 mg/L, and 75% were 10–20 mg/L. Those with AUC values ranging from 600–800 mg·hour/L had a median

Table 2. Baseline Demographic and Clinical Characteristics of the Study Patients

Characteristic	Preimplementation group (n=179)	Postimplementation group (n=117)	p Value
Age, yrs	58 ± 17 (46–67)	62 ± 17 (46–68)	0.33
Male	98 (55)	67 (57)	0.72
Weight, kg	78 ± 24 (65–100)	75 ± 23 (63–91)	0.08
Body mass index ≥ 30 kg/m^2	55 (31)	36 (31)	1.00
Age > 65 yrs	53 (30)	46 (39)	0.10
Serum creatinine concentration, mg/dl	0.76 ± 0.3 (0.6–1.0)	0.80 ± 0.3 (0.6–1.0)	0.66
Indication for vancomycin therapy			
Pulmonary	57 (32)	31 (27)	0.36
Skin and soft tissue infection	48 (27)	27 (23)	0.50
Osteoarticular	12 (7)	17 (15)	0.04
Febrile neutropenia	8 (5)	11 (9)	0.14
Abdominal, pelvic, intrathoracic	13 (7)	11 (9)	0.52
Bacteremia	13 (7)	7 (6)	0.81
Central nervous system	12 (7)	6 (5)	0.63
Endocarditis, cardiovascular implantable electronic device infections, vascular graft	4 (2)	5 (4)	0.33
Other or undifferentiated	12 (7)	2 (2)	0.05

Data are median ± SD (interquartile range) values or no. (%) of patients.

corresponding trough of 18.7 (IQR16.4–21.3), with 13 (52%) between 15 and 20 mg/L and 44% above 20 mg/L.

Secondary Outcomes

In those with therapeutic initial AUC values and a follow-up trough measurement performed (21/86 patients [24%]), 13 (62%) had a repeat trough level higher than 25% of the initial trough level. Of these repeat trough values, all were less than 10 mg/L, and 6 (46%) were supratherapeutic. All instances occurred at a median of 6 days (IQR 5–6 days) of therapy, despite stable S_{cr} in most cases. In patients with subtherapeutic or supratherapeutic initial AUC values who received dose revisions, subsequent AUC values were therapeutic in 14 patients (89%).

Subgroup analyses were performed in select populations. Patients older than 65 years and those with cystic fibrosis achieved therapeutic initial AUC values more frequently than the overall group (Table 4). In 31 patients with a BMI of 30–39.9 kg/m^2, all AUC values were under 800 mg·hour/L, achieved with a median daily dose of 25 mg/kg (IQR 18–28 mg/kg). In

Table 3. Vancomycin AUC, Trough Concentration Values, and Therapy Characteristics

Characteristic	Preimplementation group (n=179)	Postimplementation group (n=117)	p Value
Initial AUC			
Therapeutic range, 400–800, mg·hr/L	NA	86 (74)[a]	NA
AUC, mg·hr/L	NA	505 ± 141 (403–595)	NA
Initial peak, mg/L	NA	28.9 ± 7.8 (22.9–34)	NA
Supratherapeutic, > 800 mg·hr/L	NA	2 (1.7)[b]	NA
Initial trough concentration, mg/L			
Therapeutic range, 10–20	98 (55)[a]	70 (60)	0.40
10 to < 15	56 (31)	41 (35)	0.53
15–20	42 (23)	29 (25)	0.89
Subtherapeutic, < 10	48 (27)	36 (31)	0.51
Supratherapeutic, > 20	33 (18)[b]	11 (9)	0.04
Initial trough concentration	13.8 ± 7 (9.5–18.7)	13.1 ± 5.2 (9.2–16.4)	0.12
Total initial vancomycin daily dose, mg	2000 ± 821 (2000–2500)	2000 ± 809 (1500–3000)	0.10
Vancomycin-associated nephrotoxicity	20 (11)	11 (9)	0.70

Data are no. (%) of patients or median ± SD (interquartile range) values.
AUC = area under the concentration–time curve; NA = not applicable.
[a]Therapeutic initial AUC values in the postimplementation group vs therapeutic initial trough concentrations in the preimplementation group: 73.5% vs 55%, p=0.0014.
[b]Supratherapeutic AUC values in the postimplementation group vs supratherapeutic trough concentrations in the preimplementation group: 1.7% vs 18%, p<0.0001.

Table 4. Postimplementation Group AUC and Trough Concentration Values in the Subgroup Analysis

	All patients (n=117)	Patients > 65 yrs of age (n=46)	Patients with body mass index ≥ 30 kg/m^2 (n=36)	Patients with cystic fibrosis (n=7)
Initial AUC, mg·hr/L				
400–800	86 (74)	37 (80)	25 (69)	6 (86)
< 400	29 (25)	9 (20)	10 (28)	0
> 800	2 (2)	0	1 (3)	1 (14)
Initial trough concentration, mg/L				
Subtherapeutic, < 10	36 (31)	8 (17)	10 (28)	1 (14)
Target attainment, 10–20	70 (60)	34 (74)	20 (56)	6 (86)
10 to < 15	41 (35)	21 (46)	10 (28)	3 (43)
15–20	29 (25)	13 (28)	10 (28)	3 (43)
Supratherapeutic, > 20	11 (9)	4 (9)	6 (17)	0
Total initial daily dose, mg/kg	28 ± 11 (21, 35)[a]	23 ± 7 (17, 27)[a]	24 ± 9 (20, 28)	34 ± 13 (29, 41)

Data are no. (%) of patients or median ± SD (interquartile range) values.
AUC = area under the concentration–time curve.
[a]Total initial daily dose in all patients vs those > 65 yrs of age: 28 vs 23 mg/kg, p=0.01.

five morbidly obese patients (BMI 40 kg/m^2 or higher), the median dose was 20 mg/kg (20–22 mg/kg), and three (60%) had therapeutic AUC values.

Nephrotoxicity occurred in 11 (9.4%) of patients in the AUC-based dosing group at a median of day 4 of vancomycin therapy (Table 5). This was numerically lower than the nephrotoxicity rate in the trough-only dosing group (20 patients [11%], p=0.70). Of those with an AUC value of 600 mg•hour/L or higher, 4 (3.4%) experienced nephrotoxicity versus 7 (6%) of those with an AUC lower than 600 mg•hour/L (p=0.25). Of these 11 patients, 9 (82%) received concomitant piperacillin-tazobactam. However, among 59 patients who received concomitant piperacillin-tazobactam, 9 (15%) experienced nephrotoxicity versus 50 (85%) who did not (p=0.053).

Excel Calculator

Pharmacist override of initial dose advice was common in patients with cystic fibrosis because many of them had historic vancomycin dosing information at our hospital from prior admissions. In obese patients, the calculator originally generated initial dosing advice targeting AUC using vancomycin clearance (CLv) estimates from volume of distribution multiplied by the elimination rate constant. Since implementation of the protocol, we have replaced the CLv estimate in obese patients with a recently published equation[10] and added a secondary recommendation using weight-based obesity dosing to align with our protocol (Appendix S1).

Impact on Clinical Laboratory and Nursing

A total of 122 peak concentrations were ordered within 1 month in the postimplementation group. During this time, inappropriate vancomycin concentration laboratory draws (i.e., due to incorrect timing or those missed completely) occurred in 16 patients (14%). These were levels deemed to be inaccurate and unusable for the calculation of AUC values.

Discussion

This early report shows that implementation of AUC-based dosing using two sample

Table 5. Characteristics of Patients with Nephrotoxicity in the Postimplementation Group

	Nephrotoxicity (n=11)	No nephrotoxicity (n=106)	p Value
Day of vancomycin therapy	4 ± 2.5 (3.5, 6)	–	
Age, yrs	51 ± 19 (37, 62)	63 ± 17 (50, 69)	0.07
Baseline serum creatinine concentration, mg/dl	0.83 ± 0.2 (0.7, 1.1)	0.80 ± 0.3 (0.6, 1.0)	0.63
Maximum serum creatinine concentration, mg/dl	1.77 ± 0.7 (1, 1.9)	0.85 ± 0.4 (0.7, 1.1)	0.0006
Concomitant piperacillin-tazobactam use	9 (82)	50 (47)	0.0533
Initial AUC, mg·hr/L	586 ± 130 (386, 609)	485 ± 143 (404, 593)	0.60
Initial trough concentration, mg/L	13.1 ± 5.4 (10.6, 18.4)	13.1 ± 5.2 (9.2, 16.3)	0.67
Total initial daily dose, mg	2500 ± 1073 (1500, 3000)	2000 ± 772 (1500, 2500)	0.53
Duration of vancomycin, days	5 ± 3.6 (4, 8.5)	4 ± 4.2 (3, 7)	0.23

Data are median ± SD (interquartile range) values or no. (%) of patients.
AUC = area under the concentration–time curve.

measurements is feasible in less than 6 months and better able to achieve therapeutic targets compared with trough-based dosing. An earlier pilot study comparing these two methods in 50 patients with complicated MRSA infections looked at the frequency of vancomycin dosing alterations required but not target attainment rates.[11] Additionally, we include understudied or excluded populations such as patients with neutropenia, cystic fibrosis, or meningitis.[3, 5, 9, 11–13]

Achievement of Pharmacodynamics Targets

We found that AUCs greater than 400 mg•hour/L were achieved with troughs less than 15 mg/L in 55% of cases, which supports the argument that dosing by troughs, particularly targeting 15–20 mg/L, leads to excessive dosing.[2–4] A lower proportion of patients had troughs less than 10 mg/L compared with another study,[4] which may be explained by their exclusive use of twice/day vancomycin dosing. It is possible that a considerable number of our patients could have achieved a lower trough concentration if dosing had been decreased from 3 times/day to twice/day while maintaining the same total daily dose and AUC. We observed a large proportion of patients (62%) with therapeutic initial AUC values but a subsequent trough that was over 25% above the initial trough. One explanation is that the standard practice of sampling troughs before the fourth dose in those with normal renal function may represent pre–steady-state values in some patients. It is also possible that dosing frequencies were high relative to the observed half-life, contributing to drug accumulation. Bayesian software may be particularly helpful in these cases, whereas in those with stable renal function requiring dose revisions, we achieved therapeutic repeat AUCs in 89% of cases using linear PK dose revisions via the Excel calculator alone.

Clinical data are lacking on the optimal target AUC in patients with central nervous system infections. This population was either excluded or included in very low numbers in prior studies.[2–4, 9] Our protocol uses an AUC goal of 600–800 mg•hour/L that corresponded to troughs higher than 15 mg/L 96% of the time and frequently (44%) led to troughs above those recommended for meningitis.[1] In such cases, our protocol directs dose adjustments to maintain troughs under 20 mg/L (usually achieved by reducing the dosing frequency while maintaining the same total daily dose).

Clinical data are also lacking for non–*S. aureus* infections. Although targeting an AUC of 700 mg•hour/L may be excessive for *S. aureus* at our institution, where 99.6% of isolates have vancomycin MICs of 1 mg/L or lower, reducing the target may not be appropriate for enterococcus with a proposed AUC:MIC_{Etest} of 389 mg•hour/L.[14]

Vancomycin-Associated Nephrotoxicity

We observed higher nephrotoxicity rates than two centers using AUC-based dosing (9.4% vs 0–5.4%),[3, 4] but rates similar to a study exclusively focused on MRSA bacteremia (13%).[12] Unlike these first two studies,[3, 4] we did not observe significantly lower rates of nephrotoxicity. This may be explained by differences in study populations, protocol targets, dosing regimens, and our already low rates of nephrotoxicity (11%) with a trough-based protocol compared with 12–43%[15, 16] reported previously. Furthermore, one center targeted AUCs of 400–600 mg•hour/L and excluded patients with concomitant piperacillin-tazobactam therapy, baseline S_{cr} of 2 mg/dl or greater, and meningitis.[3]

Several studies recommend an AUC nephrotoxicity threshold between 600 and 800 mg•hour/L based on 3- to 7-fold increases in the rate of nephrotoxicity with AUCs above this range.[7, 9, 12] Given our institution's vancomycin MIC_{90} of 1 mg/L or lower for *S. aureus*, targeting AUCs of 700 mg•hour/L may be excessive and could have contributed to increased nephrotoxicity, but we were unable to detect a significant increase. We observed a numerically higher rate of nephrotoxicity in patients with an AUC of 600–800 mg•hour/L compared with those with an AUC of 600 mg•hour/L or lower (6% vs 3.4%, p=0.25), correlating to a number needed to harm of 38.5. Overall, we had a relatively small number of patients with nephrotoxicity (11/117 [9.4%]) compared with another study[9] (20/323 [6.2%]) but larger than a third study[12] (6/46 [13%]).

Interestingly, we observed a low rate of nephrotoxicity (15%) in those who received concomitant piperacillin-tazobactam compared with previous reports that range from 11–37%, although uncontrolled variables likely contributed to the observed rates at our institution such as use of extended-infusion piperacillin-tazobactam, lower vancomycin exposure, concomitant nephrotoxic medications, severity of

illness, length of therapy, and use of intravenous contrast dye.[17]

Lastly, the rate of nephrotoxicity may have been higher with the use of AUC rather than AUC:MIC; for example, double the AUC might have been achieved in those with *S. aureus* with an MIC of 0.5 mg/L compared with 1 mg/L. Our protocol intentionally targets AUC and not AUC:MIC in isolates with a MIC of 0.5 mg/L due to the lack of published safety and efficacy data on this strategy and due to methodological issues with determining MIC.[7]

Excel Calculator Initial Dose Advice Assessment

The AUC-based estimates using weight-based dosing or the equation for CLv[10] may improve dosing accuracy in obese patients, but this needs prospective validation. These two methods should be explored further for AUC-based dosing using two samples in obese populations because previous studies using two samples used alternative dosing methods.[18] Additionally, more studies are needed in the cystic fibrosis population[19] because we only included seven patients with cystic fibrosis.

Laboratory Workload and Hospital Costs

At our institution, we anticipate more than 1400 vancomycin peak concentration tests per year, which, at an approximate cost of $35 per test, exceeds $49,000 per year. Software utilizing Bayesian analysis would result in fewer vancomycin levels and would also provide additional PK data even with single levels.

Study Limitations

Data on concomitant nephrotoxins or contributors to nephrotoxicity with vancomycin other than piperacillin-tazobactam were not collected, and therefore the nephrotoxicity rate may be higher than secondary to the administration of vancomycin alone. In addition, our definition for nephrotoxicity was different from recent studies that evaluated AUC or AUC:MIC versus nephrotoxicity, which may have also influenced our results or made it difficult to compare results between studies. In the preimplementation group, 20 patients received every-8-hour vancomycin regimens and had troughs drawn 6.5–9.5 hours after the previous dose, but this range could have been too wide in patients with short half-lives (e.g., less than 4 hrs). Thus we calculated the expected true trough 8 hours after the previous dose in all 20 patients, which led to only two values being reclassified from supratherapeutic to therapeutic. Second, with our protocol, pharmacists may override guidelines based on clinical discretion, contributing to interpharmacist variability in dosing. Lastly, we did not assess clinical outcomes or compare treatment efficacy due to low numbers.

Conclusion

This is an early report that compares attainment of initial therapeutic AUC and trough values using AUC-based dosing with two-point sampling compared with a trough-based dosing strategy. Compared with the latter, AUC-based dosing more frequently achieved initial therapeutic values and less frequently achieved supratherapeutic values. The anticipated impact on the laboratory is over 1400 vancomycin peak concentrations measured per year or four peak concentrations measured daily at an academic medical center with more than 600 beds. Further studies are needed in special populations such as the elderly, obese patients, and patients with cystic fibrosis, neutropenia, and infections of the central nervous system. Bayesian software using single levels should be considered to decrease the number of vancomycin levels and optimize dosing. Vancomycin AUC-based dosing using two samples is a feasible alternative to Bayesian-controlled software, although, to our knowledge, no direct comparisons have been performed to date.

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Supporting Information

The following supporting information is available in the online version of this paper:

Appendix S1. Stanford Health Care Vancomycin Dosing Guide.