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CLINICAL THERAPEUTICS

Prospective Trial on the Use of Trough Concentration versus Area under the Curve To Determine Therapeutic Vancomycin Dosing

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ABSTRACT We hypothesized that dosing vancomycin to achieve trough concentrations of >15 mg/liter overdoses many adults compared to area under the concentration-time curve (AUC)-guided dosing. We conducted a 3-year, prospective study of vancomycin dosing, plasma concentrations, and outcomes. In year 1, nonstudy clinicians targeted trough concentrations of 10 to 20 mg/liter (infection dependent) and controlled dosing. In years 2 and 3, the study team controlled vancomycin dosing with BestDose Bayesian software to achieve a daily, steady-state AUC/MIC ratio of ≥400, with a maximum AUC value of 800 mg · h/liter, regardless of trough concentration. For Bayesian estimation of AUCs, we used trough samples in years 1 and 2 and optimally timed samples in year 3. We enrolled 252 adults who were ≥18 years old with ≥1 available vancomycin concentration. Only 19% of all trough concentrations were therapeutic versus 70% of AUCs ($P < 0.0001$). After enrollment, median trough concentrations by year were 14.4, 9.7, and 10.9 mg/liter ($P = 0.005$), with 36%, 7%, and 6% over 15 mg/liter ($P < 0.0001$). Bayesian AUC-guided dosing in years 2 and 3 was associated with fewer additional blood samples per subject (3.6, 2.0, and 2.4; $P = 0.003$), shorter therapy durations (8.2, 5.4, and 4.7 days; $P = 0.03$), and reduced nephrotoxicity (8%, 0%, and 2%; $P = 0.01$). The median inpatient stay was 20 days among nephrotoxic patients versus 6 days ($P = 0.002$). There was no difference in efficacy by year, with 42% of patients having microbiologically proven infections. Compared to trough concentration targets, AUC-guided, Bayesian estimation-assisted vancomycin dosing was associated with decreased nephrotoxicity, reduced per-patient blood sampling, and shorter length of therapy, without compromising efficacy. These benefits have the potential for substantial cost savings. (This study has been registered at ClinicalTrials.gov under registration no. NCT01932034.)

KEYWORDS vancomycin, therapeutic drug monitoring, prospective, clinical study, Bayesian

Vancomycin is still a mainstay of therapy for serious Gram-positive infections. Successful treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) is associated with a ratio of ≥400 for the steady-state area under the 24-h vancomycin concentration-time curve (AUC) over the MIC for MRSA (1). However, because ≥2 concentrations are needed to directly estimate an AUC (2), a single trough concentration is a suggested surrogate for AUC in adults with normal renal function (1).

Previously, we predicted that 32% of adults with normal renal function given 1 g every 12 h who achieved an AUC of ≥400 mg · h/liter (appropriate for MIC of 1 mg/liter) would have trough concentrations of <10 mg/liter, which are currently considered

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TABLE 1 Characteristics of all enrolled subjects

Subject parameter	Value(s)			
	Yr 1 control (n = 75)	Yr 2 BestDose—MM (n = 88)	Yr 3 BestDose—MMopt (n = 89)	P
Mean (range) age, yrs	47.7 (19.0–71.0)	48.0 (18.0–93.0)	50.3 (22.0–81.0)	0.42
No. (%) of male sex	61 (81)	67 (76)	67 (75)	0.57
Mean (range) wt, kg	82.4 (47.7–150.9)	81.0 (46.4–193.6)	78.8 (30.3–180.0)	0.64
Mean (range) ht, cm	171.9 (149.9–198.1)	169.1 (149.9–193.0)	168.6 (127.4–188.0)	0.11
No. (%) of indicated race				0.15
Native American	0	0	1 (1)	
Asian	0	4 (5)	4 (4)	
African American	9 (12)	13 (15)	17 (19)	
Caucasian	66 (88)	70 (80)	66 (74)	
Not reported	0	1 (1)	1 (1)	
No. (%) Hispanic				0.002
Yes	54 (72)	61 (69)	49 (55)	
No	21 (28)	19 (22)	39 (44)	
Not reported	0	8 (9)	1 (1)	
Baseline serum creatinine, mg/dl	0.82 (0.36–1.63)	0.84 (0.33–2.71)	0.83 (0.39–2.21)	0.92
Baseline creatinine clearance, ml/min (Cockroft-Gault)	146.9 (36.0–665.5)	131.1 (31.7–281.0)	126.8 (27.8–286.8)	0.14

subtherapeutic for all MRSA infections, and 60% would have trough concentrations of <15 mg/liter (3). Therefore, we believe that targeting trough concentrations, especially >15 mg/liter, overdoses many adults and increases the risk of nephrotoxicity (4).

To test the primary hypothesis that AUC-guided treatment of a patient is more likely to be therapeutic than trough concentration-guided treatment, we conducted a prospective clinical study. Our secondary hypotheses were that vancomycin dosing, concentrations, and nephrotoxicity would be lower with Bayesian estimation-assisted, AUC-guided therapeutic drug management (TDM) than with standard trough concentration-guided TDM. Since *in vitro* data (5–8), animal data (9, 10), and clinical data (11–15) support associations between vancomycin AUC and outcomes, we also expected the efficacy seen with AUC-guided dosing to be the same as or better than that seen with trough concentration-guided dosing.

RESULTS

Study population. We enrolled 252 adults from December 2012 to June 2016. There were 75 patients in year 1 (control), 88 patients in year 2 (multiple-model [MM] BestDose), and 89 patients in year 3 (MM optimal [MMopt] BestDose), as shown in Table 1. Patient characteristics were similar except for ethnicity, which was based on self-reporting. Baseline renal function data, quantified using the Cockcroft-Gault estimator, were similar across the years, with 16%, 10%, and 13% in each year having a calculated estimated glomerular filtration rate (eGFR) of >200 ml/min (P = 0.54, chi-square test), including a 25-year-old morbidly obese (150 kg) male, 177 cm tall, in year 1 with a creatinine level of 0.36 mg/dl and an eGFR of 665.5 ml/min. Because the vancomycin population model uses calculated eGFR regardless of value, we did not correct these extreme outliers, recognizing that the goal was not to describe renal function *per se* but to quantify the kidney-based descriptor of vancomycin kinetics in the context of the model.

The most common indication for vancomycin was a skin and soft tissue infection (46%). In year 3, significantly more patients had pneumonia (6%, 10%, and 27%, P = 0.0002, Fisher's exact test) and bacteremia (5%, 8%, and 19%, P = 0.006, Fisher's exact test) than in the prior 2 years. The isolated organisms differed, with the most common being *S. aureus* (Table 2). There was no significant trend in the variety of species by year (P = 0.45, chi-square test). The majority (88%) of MRSA isolates had a vancomycin MIC that was ≤1 mg/liter, and all were vancomycin susceptible (MIC ≤ 2 mg/liter).

TABLE 2 Isolated bacterial species (unique subjects)

Species	No. (%) of patients		
	Yr 1 control ($n = 75$)	Yr 2 BestDose—MM ($n = 88$)	Yr 3 BestDose—MMopt ($n = 89$)
MSSA	12 (16)	8 (9)	8 (9)
MRSA	11 (15)	7 (8)	8 (9)
CoNS[a]	14 (19)	14 (16)	11 (12)
Enterococcus	1 (1)	3 (3)	4 (4)
S. viridans	0	4 (5)	5 (6)
Total	38 (51)	36 (41)	36 (40)

[a]CoNS, coagulase-negative staphylococci; MSSA, methicillin-sensitive *Staphylococcus aureus*.

Primary outcome. Over the entire study, 19% of trough concentrations versus 70% of associated AUCs were therapeutic ($P < 0.0001$, binomial test), proving the primary hypothesis that treatment of more patients would be therapeutic with the AUC rather than the trough concentration as the target. Furthermore, we found that 40 (31%) of 128 AUCs that were ≥400 mg · h/liter were associated with a trough concentration of <10 mg/liter and that 87 (68%) were associated with a trough concentration of <15 mg/liter, agreeing quite well with our previously published predictions of 32% and 60% determined by simulation (3).

As shown in Table 3, by year, there were 82 (35%) of 231, 84 (44%) of 189, and 33 (16%) of 201 concentrations that could be classified as trough concentrations. There were fewer trough concentrations in year 3 due to the optimal sampling strategy. Of the trough concentrations in each year, 28%, 13%, and 15% were therapeutic overall ($P = 0.02$, chi-square test). In year 1, when the target trough concentration was 10 to <15 mg/liter, only 31% of measured concentrations were in this range, and when the target was 15 to 20 mg/liter, only 25% were in range. These data for year 1 indicate very poor adherence to proper timing of blood sampling and very poor target trough concentration attainment, regardless of the goal. An overall rate of 28% therapeutic trough concentrations is consistent with our prestudy survey finding that 30% trough concentrations were therapeutic. In years 2 and 3, AUCs were the target for MM and MMopt dosing strategies rather than trough concentrations. Hence, the low rates of therapeutic trough concentrations are not surprising. In contrast, 75%, 63%, and 73%

TABLE 3 Trough concentrations versus AUC

Total available concn(s)	Value(s)			
	Yr 1 control ($n = 233$)	Yr 2 BestDose—MM ($n = 189$)	Yr 3 BestDose—MMopt ($n = 201$)	*P*
No. (%) of samples with concn sampled 10 to 12 h postdose ("trough")	84 (36%)	87 (46%)	43 (21%)	0.02
No. (%) of samples with indicated trough concn (mg/liter)				<0.0001
<10	40 (47%)	61 (70%)	17 (40%)	
10 to <15	14 (17%)	19 (22%)	20 (46%)	
15 to 20	22 (26%)	5 (6%)	4 (9%)	
>20	8 (10%)	2 (2%)	2 (5%)	
Proportion within target				
Trough concentrations				
Overall	28%	13%	15%	0.04
Target 10 to <15	13%	11%	9%	
Target 15 to 20	15%	2%	6%	
AUC/MIC ratio				
Overall	75%	63%	73%	0.21
≥400 and <800	68%	56%	70%	
300 to 400[d] and <800	7%	7%	3%	

[a]Data represent the results obtained only when clinical response had already been already documented by enrollment.

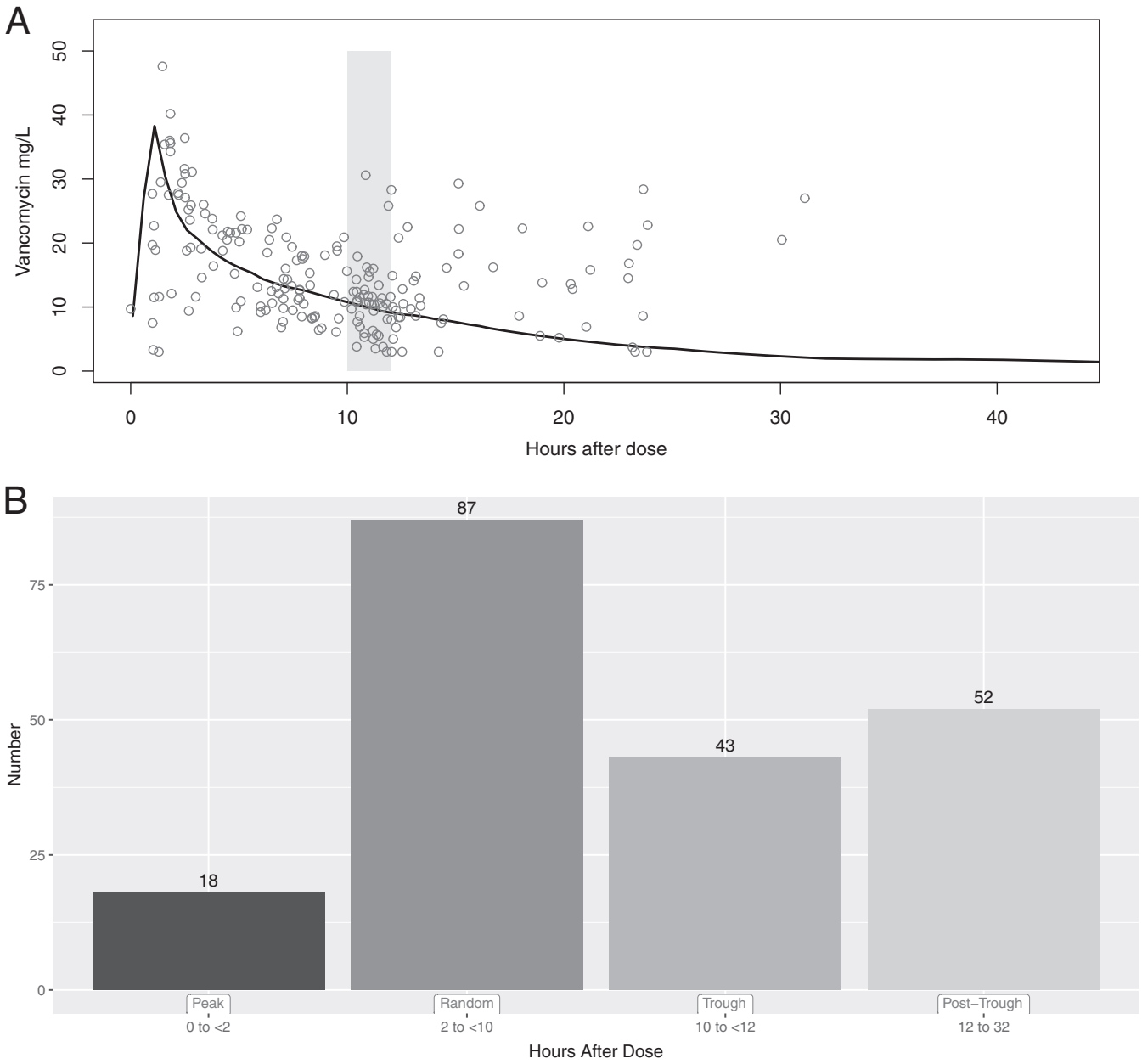

FIG 1 Distribution of optimal sample times in year 3. (A) Actual sample times and measured concentrations are shown as open circles. The dark line shows the median simulated steady-state time-concentration profile for vancomycin administered at 1,000 mg every 12 h to a 75-kg adult with normal renal function. The gray box shows the recommended sampling trough window at 10 to 12 h after a dose at the steady state. One can easily see that optimal sampling times are frequently outside this window and that there is tremendous variability in vancomycin concentrations within a population of adult patients. (B) Categories of optimal sample times relative to the previous dose. Only 43 (21.5%) of the 200 optimally timed samples were trough concentrations.

of the AUC-guided therapies were therapeutic ($P = 0.21$, chi-square test for year-to-year comparison).

As also shown in Table 3, fewer than half the samples in any year were within the trough concentration window of 10 to 12 h postdose. This represented poor adherence to the hospital policy in years 1 and 2 and was by design in year 3. In the first 2 years, 37% of the samples were obtained earlier than 10 h following the previous dose, and 23% were obtained later than 12 h after the preceding dose. In the third year (MMopt), with an optimal rather than a trough concentration-based sampling strategy, 79% of the samples were not trough concentrations, as shown in Fig. 1, highlighting that a trough sampling strategy is rarely optimal from a pharmacokinetic perspective.

TABLE 4 Summary of vancomycin therapy characteristics[a]

Parameter	Value(s)			
	Yr 1 control	Yr 2 MM	Yr 3 MMopt	*P*
Data collected during entire admission				
Mean (minimum–maximum) starting daily dose[a]				
mg	2,000 (270–3,750)	2,000 (500–3,000)	2,000 (500–4,000)	0.47
mg/kg	25.9 (5.4–62.9)	22.5 (7.1–60.1)	24.9 (5.9–76.1)	0.16
Mean (minimum–maximum) avg daily dose				
mg	1,818 (275–2,760)	1,750 (700–3,360)	1,577 (750–4,300)	0.46
mg/kg	24.0 (7.4–52.6)	22.0 (9.5–67.2)	22.6 (8.8–85.7)	0.30
Median (25th percentile, 75th percentile) sample time after dose (h)	10.6 (6.9, 11.9)	11.0 (8.3, 12.0)	9.5 (5.0, 12.0)	0.04
Data collected from date/time second vancomycin concn was obtained (after enrollment)[b]				
Median (25th percentile, 75th percentile) no. of days of vancomycin	7.8 (4.1, 14.3)	5.4 (4.0, 8.6)	4.7 (3.2, 8.7)	0.05
Median (25th percentile, 75th percentile) no. of days until discharge	9.0 (6.0, 21.0)	8.0 (4.0, 15.0)	7.0 (5.0, 16.0)	0.37
Mean (minimum–maximum) no. of samples per patient	3.6 (1–15)	2.1 (1–8)	2.4 (1–12)	0.007
Mean (minimum–maximum) trough concn (mg/liter)	14.4 (3.8–27.2)	9.7 (4.5–29.6)	10.9 (3.5–25.8)	0.005
Mean (minimum–maximum) daily AUC (mg · h/liter)	510 (160–1,050)	459 (154–975)	459 (194–890)	0.29

[a]For year 1 control, $n = 75$; for year 2 BestDose—MM, $n = 88$; for year 3 BestDose—MMopt, $n = 89$.
[b]For year 1 control, $n = 44$; for year 2 BestDose—MM, $n = 51$; for year 3 BestDose—MMopt, $n = 56$.

Secondary therapy and outcomes. (i) Vancomycin therapy. Characteristics of vancomycin dosing by year are shown in Table 4. Starting and average daily doses were not significantly different from year to year, and neither was length of hospitalization after the first vancomycin concentration had been determined. However, the length of vancomycin therapy after the first concentration was significantly shorter in years 2 and 3 than in year 1.

As reported in Table 4, the mean numbers of blood samples for vancomycin concentration measurement after the first, per subject by year, were lower in years 2 and 3, reflecting more-efficient therapeutic management with Bayesian control. The median concentration in samples that were obtained within the trough concentration window after enrollment also dropped significantly after year 1, and there were significantly more patients with trough concentrations over 15 mg/liter and 20 mg/liter in year 1 than in subsequent years.

Estimation of vancomycin AUC for each patient in BestDose depends on fitting the measured concentrations to generate the vancomycin Bayesian posterior model. The median (interquartile) percent prediction error in year 1 was −5.6% (−12.8 to 2.2) compared to −1.4% (−7.0 to 2.8) in year 2 and 0.0% (−1.8 to 0.1) in year 3 with optimal sampling ($P < 0.0001$, Kruskal-Wallis test). Based on these low fitting biases, we were confident that AUC was well estimated by BestDose and our vancomycin population model, even with only one sample corresponding to any given dosing interval.

After the first vancomycin concentration had been obtained, among subjects with defined MRSA infections, the AUC/MIC ratio was over two times higher than required in year 1 with standard trough concentration-based TDM than in years 2 and 3 with Bayesian control and AUC-guided dosing, at 1,069 (441 to 1,310) mg · h/liter, 560 (309 to 1,310) mg · h/liter, and 465 (287 to 879) mg · h/liter, respectively ($P < 0.0001$, Kruskal-Wallis test). The variability of AUCs in year 3 was significantly smaller than in year 1 ($P = 0.0001$, F-test) or even year 2 ($P = 0.002$, F-test), reflecting the tighter control achieved with optimal sampling. This is shown visually in Fig. 2. The proportion of AUCs above 800 mg · h/liter was lowest in year 3 with Bayesian control and optimal sampling (at 10% for year 1, 7% for year 2, and 4% for year 3), but the results of the comparisons were not statistically significant ($P = 0.18$, chi-square test).

(ii) Vancomycin therapeutic outcomes. Table 5 shows therapeutic outcomes for all enrolled subjects. There were no therapeutic failures or deaths in the study. The only relapse occurred in year 1, with a 39-year-old male with hepatitis C and leg cellulitis. He responded to empirical vancomycin initially but was discharged after 4 days of therapy on an oral antibiotic. He returned within 72 h with a culture-negative abscess.

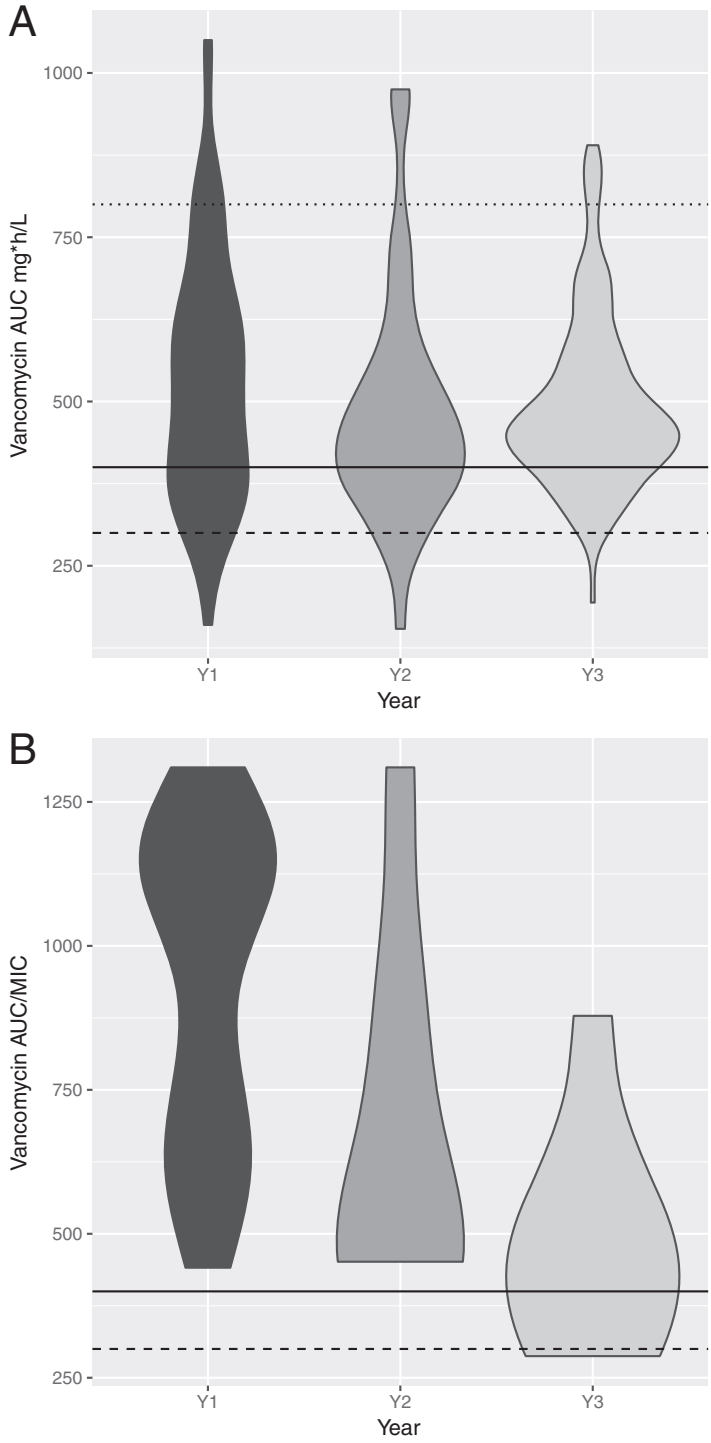

FIG 2 (A) Violin plots by year showing the distribution of AUCs with the second vancomycin concentration and after, which reflects the effect of the method of controlling vancomycin exposure, since enrollment occurred after the first vancomycin concentration was measured. While the distributions are not statistically significantly different from each other ($P = 0.29$, analysis of variance), the tighter control (less variation) of vancomycin AUC is readily seen with Bayesian control in year 2 and even more so with Bayesian control and optimal sampling in year 3 ($P = 0.0001$ versus year 1, F-test). The solid horizontal line represents the target AUC of 400 mg · h/liter for experiments in which the MIC was 1 mg/liter or was unknown or for an organism other than *S. aureus*. The dashed line represents the efficacy target of 300 mg · h/liter for documented clinical response (and unknown MIC) before evaluation with BestDose. The dotted line represents the target toxicity cap of 800 mg · h/liter. These targets were used to control dosing only in years 2 and 3. (B) AUC/MIC ratios by year among subjects with documented MRSA infections and known MICs. The ratios were significantly higher and more varied using trough concen-

(Continued on next page)

TABLE 5 Therapeutic outcomes of vancomycin therapy for all enrolled subjects

Outcome[a]	No. (%) of subjects		
	Yr 1 (n = 75)	Yr 2 (n = 88)	Yr 3 (n = 89)
Resolved	59 (71)	60 (67)	66 (74)
Relapsed	1 (1)	0	0
Failure	0	0	0
Death	0	0	0
Toxicity	2 (2)	0	0
Deescalation	7 (8)	5 (6)	6 (7)
Not indicated	8 (10)	9 (10)	9 (10)
Transferred	6 (7)	16 (18)	9 (10)

[a]Resolved, disappearance or marked improvement of signs and symptoms of acute infection and cessation of vancomycin therapy; Relapsed, return of signs of symptoms of the same infection within 72 h of stopping vancomycin therapy; Failure, persistence of signs and symptoms despite vancomycin therapy for a defined, vancomycin-susceptible infection requiring change of therapy; Death, all-cause death within 72 h of stopping vancomycin therapy; Toxicity, any event thought to be associated with vancomycin that caused cessation of the drug; Deescalation, step down to narrower-spectrum intravenous antibiotics or to oral therapy for defined or presumed organisms; Not indicated, infections with defined organisms resistant to vancomycin (e.g., Gram-negative bacterial infections); Transferred, subjects who were transferred to another inpatient facility while still receiving vancomycin for whom it was not possible to complete 72-hour post-vancomycin therapy follow-up.

Standard practice at our hospital is to measure serum creatinine levels in patients approximately daily while they are receiving vancomycin. Subjects in each year had mean measured serum creatinine levels per day of vancomycin therapy of 0.76, 1.05, and 1.20 mg/dl ($P < 0.0001$). Even with less-intense monitoring, vancomycin-associated nephrotoxicity occurred in 6 (8%) subjects in the first year compared to none in year 2 and 2 (2%) in year 3 ($P = 0.01$, Fisher's exact test). Two of the 6 subjects in year 1 stopped therapy due to the toxicity versus none in years 2 and 3 ($P = 0.09$, Fisher's exact test). The median first measured vancomycin concentration was 15.7 mg/liter in those who developed nephrotoxicity and was 8.7 mg/liter in those who did not ($P = 0.02$, Mann-Whitney test). The median initial vancomycin AUC was 625 mg · h/liter in those who developed nephrotoxicity and was 423 mg · h/liter in those who did not ($P = 0.06$, Mann-Whitney test).

The median length of stay was 20 days for those who developed nephrotoxicity due to vancomycin and was 6 days for those without nephrotoxicity ($P = 0.002$, Mann-Whitney test). Based on the daily rate for a general medicine ward bed at our hospital, admission lasting 2 weeks longer represents an increased cost of approximately $145,000 per patient.

DISCUSSION

This report represents the largest prospective study of Bayesian estimation-controlled, AUC-guided vancomycin dosing in adults thus far published. We proved our primary hypothesis that, for intermittent dosing, far more patients achieve therapeutic success when an AUC/MIC target of 400 is used than when the more usual target trough concentration targets of 10 to 15 and 15 to 20 mg/liter are used, depending on the infection severity (1). Using these trough concentration targets generally results in unnecessarily high levels of vancomycin dosing, thereby increasing the risk of nephrotoxicity, which is consistent with many observations reported in the literature (4). Indeed, we observed significantly higher rates of trough concentrations of >15 mg/liter and vancomycin-associated nephrotoxicity in targeting trough concentrations than

FIG 2 Legend (Continued)
trations to dose vancomycin in year 1 than by Bayesian adaptive control of AUC in years 2 and 3 ($P < 0.0001$, analysis of variance). The solid horizontal line represents the usual efficacy target of 400, and the dashed line represents the acceptable target of 300 for those subjects who had an established clinical response before evaluation with BestDose. The increased exposures in year 1 were not associated with improved outcomes and were associated with increased trough concentrations and more nephrotoxicity, as described in Results.

targeting AUCs, and patients who developed vancomycin-associated nephrotoxicity had higher baseline trough concentrations and AUCs than those who did not develop nephrotoxicity. This increase in renal injury was associated with markedly longer hospital stays, which can increase costs by hundreds of thousands of dollars.

On the efficacy side, we found no compromise in the clinical outcomes of infections treated with vancomycin despite lower average trough concentrations than recommended. Only 10% of the study population had microbiologically proven MRSA infections, but this is the reality of vancomycin use in a tertiary care hospital. Because we included other Gram-positive organisms, 42% of the subjects had a microbiologically proven infection. AUC/MIC targets for these other infections largely do not exist, although for coagulase-negative staphylococcal infections that are not catheter associated, the AUC/MIC target in an animal model was 150 (16). For infections treated with a catheter *in situ*, the AUC/MIC target was 520 (17). Therefore, our empirical target of 400, based on an effective MIC of 1 mg/liter, appeared reasonable. Although MIC levels may differ by up to 2-fold on repeat measurement, which would be associated with AUC targets that are 2-fold different, our data here and those reported by others (11) suggest that the AUC/MIC ratio is still more strongly associated with outcomes than are trough concentrations.

Ironically, although dosing and AUCs tended to be lower in targeting AUCs with BestDose rather than trough concentrations, the average reduction in total daily dose was modest and not statistically significant from year to year. This modest effect was likely because the standard dosing in year 1 was already at the low end of the recommended range (1). However, such lower dosing is adequate for many patients, and an individually tailored approach to vancomycin therapy using AUCs can both preserve efficacy and reduce nephrotoxicity. Institutions that use higher doses to more routinely achieve trough concentrations of 15 to 20 mg/liter will likely see even greater reductions in toxicity and cost savings resulting from a clearer knowledge of which patients can have doses safely lowered to maintain therapeutic AUCs. This was exactly the observation in a recently published retrospective comparison of trough-guided versus AUC-guided vancomycin dosing in almost 1,300 adults at four hospitals within the Detroit Medical Center (18). That hospital system made a wholesale change in 2014 from a trough-guided approach to using two vancomycin samples (peak and trough) to estimate AUC and control dosing (i.e., a non-Bayesian approach). The investigators compared outcomes before and after the change. They found reduced nephrotoxicity and reduced trough concentrations, as we did. They also found that doses were lower because they were no longer targeting aggressively high trough concentrations of 15 to 20 mg/liter in all patients with serious MRSA infections. We have demonstrated that the same benefits can be realized with only one vancomycin concentration per episode if coupled with a capable Bayesian method.

Our study data reveal additional shortcomings of the trough concentration-sampling strategy, despite its apparent simplicity. Even with relatively generous criteria used to identify a sample as representative of a "trough concentration," at best we could only manage to obtain 44% of the samples within this 10-to-12-h postdose window. When a concentration is not a trough concentration, it is erroneous to compare it to targets that represent the assumption that it is a trough concentration. This practice results in over- or underdosing, with associated risks of oversampling and toxicity (as we observed) or therapeutic failure. Even if samples are correctly recognized as having been obtained outside an appropriate time window, manual extrapolation to a trough concentration is impossible without a second concentration (2).

The Bayesian approach resulted in collection of significantly fewer blood samples for vancomycin measurement and dose adjustment. We did not calculate the cost savings, as charges at the county hospital are not itemized in the same way as for private hospitals. However, savings from reduced phlebotomy, laboratory, and pharmacist labor and supplies, in addition to the savings from avoiding nephrotoxicity, could total tens of thousands of dollars per year at a major hospital.

Optimal sampling improved the fit between measured concentrations and the

corresponding concentrations calculated by BestDose based on the vancomycin model. We achieved significantly tighter control of AUCs around our targets using optimal sampling (best visualized in Fig. 2). However, we did not find differences in outcomes whether optimal sampling was used or not when paired with a capable Bayesian method.

Finally, without access to Bayesian software such as BestDose and professionals trained to use it, for intermittent dosing of vancomycin, AUC is best estimated from ≥2 samples (2), with good results (18). An attractive alternative may be continuous-infusion vancomycin therapy, since a single concentration measured at steady state and multiplied by 24 is the daily AUC. Meta-analyses have shown similar or reduced levels of nephrotoxicity using continuous infusion (19–22), but the effect on efficacy is controversial (19).

Strengths of this study included the prospective design, sample size, real-world application, preservation of efficacy, and reduction in nephrotoxicity when AUCs rather than trough concentrations were targeted. Consideration of costs is much needed in this era of value- and evidence-based decisions in health care (23). Our study was not designed or powered to evaluate the treatment efficacy of trough-guided versus AUC-guided vancomycin dosing for defined infections with MRSA. Nevertheless, we felt compelled to collect some information about efficacy-related outcomes in this heterogenous population. Accordingly, our definitions were simple, and the diversity of infections, proven or otherwise, dilutes the infection-specific validity of the concentration targets that we used. The relatively short duration of vancomycin therapy is likely a reflection of the high numbers of patients with skin and soft tissue infections, which are typically treated with vancomycin for shorter durations before therapy is stepped down to the use of an oral agent such as clindamycin. Together, these limitations preclude definitive conclusions about the comparative efficacies of trough-concentration-guided and AUC-guided vancomycin dosing. On the other hand, the lack of any obvious reduced efficacy signal using vancomycin AUC targeting for a prospectively studied, diverse patient population is encouraging.

In summary, we found numerous benefits of AUC-guided, Bayesian estimation-controlled vancomycin dosing compared to the traditional trough concentration-targeted approach, including reduced nephrotoxicity, fewer blood samples, shorter duration of therapy, lower doses overall than current recommendations, and tighter control of vancomycin exposures, all without an obvious compromise in clinical efficacy. These benefits are associated with the potential for substantial cost savings at hospitals that use vancomycin extensively. Trough concentration-guided dosing of vancomycin should be replaced by AUC-guided dosing, preferably with Bayesian estimation-assisted control.

MATERIALS AND METHODS

Study design and population. We conducted a 3-year, prospective, serial cohort study (ClinicalTrials registration no. NCT01932034) among hospitalized patients at the Los Angeles County—University of Southern California (LAC-USC) Medical Center, a 600-bed, tertiary care, university-affiliated county hospital. The study was approved by the USC Institutional Review Board, and all subjects confirmed in writing prior to enrollment that they consented to participate. Inpatients were eligible for enrollment if they were ≥18 years old and had been prescribed intravenous vancomycin therapy with ≥1 measured concentration, indicating continuation of therapy beyond 48 h. Exclusion criteria were any form of renal replacement therapy and expected survival of less than 72 h.

First-year subjects served as controls, with vancomycin dosing, concentration monitoring, and management according to decisions of the treating physician and clinical pharmacy staff. From the vancomycin concentrations and times, dose amounts and times, and patient sex, age, weight, and creatinine level, we estimated daily vancomycin AUCs for each patient using our validated nonparametric population model (3) and BestDose Bayesian software (www.lapk.org) (24, 25). BestDose combines the population model with the data from each individual patient to "update" the model to an individualized, "Bayesian posterior" version, which comprises the most likely probability distribution of "support points" for the patient. Each support point consists of a set of vancomycin pharmacokinetic (PK) parameter values (e.g., volume of distribution) and the probability of that set. Support points which generate predictions that closely match observed concentrations have higher probabilities. This is an iterative process, so that as more data (e.g., vancomycin concentrations) accumulate over time for an individual patient, the model becomes increasingly specific to that patient. From this model, for any given dosage

regimen, the predicted concentration of vancomycin may be calculated by the software at any moment in time. This also permits calculation of the full 24-h steady-state AUC by standard trapezoidal approximation, using concentrations calculated at 6-min intervals. In year 1, we did not use BestDose to adjust vancomycin dosages, and we did not communicate results of BestDose analysis to the primary medical team, all to ensure that we were capturing baseline vancomycin TDM performance.

In year 2, we targeted vancomycin daily AUCs and controlled vancomycin dosing using the multiple-model (MM) Bayesian adaptive control algorithm in BestDose. This algorithm uses the Bayesian posterior model for an individual patient obtained after each concentration is measured. The software finds the dose that minimizes the mean weighted squared error corresponding to the concentrations predicted by each of the support points in the posterior model and the desired target (AUC in this case). We continued the standard practice of attempting to obtain trough concentrations, from which we generated posterior models, but we did not control (target) the trough concentration. The AUC targets that we used to control the vancomycin dose are discussed under "Study definitions" below. As each new concentration was obtained from a patient, we used it and all prior concentrations and dosage history to regenerate the patient's updated Bayesian posterior model, estimate AUC, and calculate the next dosing regimen.

In year 3, we continued to use BestDose for AUC targeting. In addition to calculating the optimal dose, we additionally used the MM optimal (MMopt) sampling function in BestDose (26, 27) to calculate the most informative (optimal) date and time to measure the next vancomycin concentration for each patient. MMopt is a unique optimal sampling algorithm designed to efficiently reveal the drug kinetics for the individual patient. It introduces the important concept that truly optimal sample times are as individual as dosing. MMopt chooses the sample time when all the possible future time-concentration profiles for any planned regimen that arise from a patient's posterior model are the most highly separated. In this way, we minimize the risk of assigning erroneous probabilities to support points in the Bayesian posterior after the next blood sample is collected. MMopt can calculate optimal times for any number of samples, with an asymptotically decreasing risk of misclassification; however, to be consistent with the standard practice of conducting vancomycin TDM on the basis of data from one sample, we restricted our number of MMopt samples to one for each dose adjustment.

In year 1, repeat trough concentrations were sampled at the discretion of the primary team, generally after the fourth new dose if the patient was meant to remain on vancomycin. In years 2 and 3, we recommended repeat sampling after the second dose following any change in dose for patients who were to continue vancomycin, since there is no need to wait for steady state with model-based, Bayesian TDM. However, in all years, the decision to obtain follow-up concentrations was ultimately left to the primary medical team.

Data extraction. We obtained subjects' pertinent demographic and clinical data, including indication for vancomycin, bacterial species isolated from sterile sites, vancomycin MICs, concomitant nephrotoxic medications, length of vancomycin therapy and hospital admission, and evidence for treatment failure or relapse within 72 h of completing vancomycin (further defined below). For all subjects in all years who were discharged prior to the end of the postvancomycin 72-h window, we contacted them once by telephone at least 72 h after stopping vancomycin therapy to verify whether they had evidence of relapse.

Study definitions. "Trough" concentrations were defined as samples obtained 10 to 12 h after the previous dose, since all subjects were prescribed vancomycin twice daily. Because nurses often hold the next dose until a pending concentration is known, it was more reliable to classify trough concentrations by postdose rather than predose interval. "Peak" concentrations, although not routine, represented samples drawn zero to 2 h postinfusion. Samples taken at other times represented "random" concentrations.

For complicated infections such as bacteremia, endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia, a trough concentration was classified as therapeutic if it was between 15 and 20 mg/liter. For all other infections, a concentration of 10 to 15 mg/liter was classified as therapeutic, in accordance with IDSA guidelines (1). Peak and random concentrations were not classified. An AUC/MIC ratio of $\geq$400 was classified as therapeutic (omitting the units of hours for simplicity). For sterile cultures and Gram-positive isolates other than *S. aureus*, our AUC target was 400 mg · h/liter and was based on an "effective" MIC of 1 mg/liter, regardless of the measured MIC. An AUC/MIC ratio of $>$400 has been established only for MRSA, and choosing an MIC of 1 mg/liter is consistent with known vancomycin efficacy against these organisms at standard doses and was also the prestudy MIC_{90} for our hospital reported by the microbiology laboratory. On the basis of data previously reported by Brown et al. (12) and Lodise et al. (11), we accepted a lower AUC/MIC ratio of $\geq$300 as therapeutic for any organism, including *S. aureus*, if clinical response was already present at enrollment (i.e., after at least one vancomycin concentration had been obtained).

In targeting AUC in years 2 and 3, our maximum desired AUC was 800 mg · h/liter. This is consistent with our previous suggestion of 700 mg · h/liter derived by simulation (3) and with an AUC/MIC ratio of 400 for an MIC of 2 mg/liter, which is the current susceptibility breakpoint for *S. aureus*.

We defined vancomycin-associated nephrotoxicity as representing an increase in serum creatinine of $\geq$0.5 mg/dl or $\geq$50% from baseline, confirmed on two consecutive measurements and more highly attributable to vancomycin than to another cause by the primary team. This definition is consistent with other studies of vancomycin-associated nephrotoxicity (4, 28). Treatment failure was defined as the need to add or change therapy to another drug with a similar spectrum of activity (e.g., daptomycin or linezolid) to treat a vancomycin-susceptible organism. Deescalation was not considered representative of treatment failure. Success was defined as resolution/marked improvement of the original signs/symp-

toms of infection and cessation of vancomycin. Relapse was defined as the return of signs/symptoms of the original infection within 72 h after successful therapy.

All data were entered into the secure Research Electronic Data Capture software (REDCap) (29).

Sample analysis. Vancomycin MIC was measured in the LAC-USC Medical Center Clinical Microbiology Laboratory by the use of Vitek2 (bioMérieux, Durham, NC) for MRSA from nonsterile sites and by the use of Etest (bioMérieux) for MRSA from sterile sites. Vitek2 was used for all non-MRSA isolates.

Vancomycin concentrations prior to 11 June 2014 were measured using the Centaur system (Siemens Healthineers USA, PA) in the LAC-USC Medical Center core laboratory, with a lower limit of 0.67 mg/liter. After that date, the laboratory switched to the Abbott Architect i1000SR immunoassay analyzer (Abbott Laboratories, IL), with a lower limit of 3 mg/liter. The laboratory did not verify these limits but censored measured values below them. Average interday assay quality control variance in the laboratory was <10% within the working ranges of both assays.

Statistical analysis. On the basis of a preliminary survey of 20 patients, approximately 30% of appropriately timed vancomycin trough concentrations were noted to be therapeutic prior to the study. To demonstrate that a 50% proportion of therapeutic AUCs would be significantly higher than 30% with an alpha (type I error rate) of 5% and power of 80% (20% type II error rate) in any given year, approximately 90 patients were required in each group, using the Cohen effect size function ("ES.h") and power calculation for two proportions ("pwr.2p.test") in the "pwr" package for R (www.r-project.org). We performed univariate analysis using the Mann-Whitney test for nonnormal continuous data and Student's *t* test for normal continuous data. We used the Kruskal-Wallis test for multivariate analysis of nonnormal data, and we used analysis of variance or linear regression for normal data. For purely categorical data, we used Fisher's exact test or the chi-square test. All statistical tests were two-tailed, and a P value of <0.05 denoted significance. Statistical analyses were performed using R and the Rstudio interface. The primary outcome was determination of the proportion of all available trough concentrations that were therapeutic versus the proportion of all corresponding AUCs. Secondary outcomes evaluated for all enrolled subjects included treatment outcomes and nephrotoxicity. Due to the prospective nature and limited resources of the study, we did not design or power it to look primarily at efficacy, which would have required a multicenter study of a more homogenous population with microbiologically proven infections, such as bacteremia. To evaluate outcomes related to the method of TDM by year, we restricted analyses to subjects who had at least one vancomycin concentration measured after enrollment in addition to the concentration measured prior to enrollment. These TDM-related outcomes included vancomycin dose, number of vancomycin blood samples drawn per patient, vancomycin trough concentration and AUC, length of vancomycin therapy, and length of hospitalization.

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