Optimization of Vancomycin Dosing to Achieve Target Area Under the Curve in Pediatrics

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OBJECTIVE Vancomycin dosing requirements to achieve a target area under curve/minimum inhibitory concentration (AUC/MIC) of 400 to 600 mg•hr/L have not been established in pediatrics. Dose modeling studies and recent guidelines suggest dosing higher than historical recommendations. This study examines dosing requirements to achieve target AUC/MIC in human pediatric patients.

METHODS This retrospective study includes 77 patients, aged 1 month to 18 years, at a single center, who received at least 2 days of intravenous vancomycin with a pharmacokinetic monitoring note and calculated AUC/MIC. Dosing to achieve target AUC/MIC was evaluated by age and indication. Nephrotoxicity was also assessed.

RESULTS The mean dose required to achieve target AUC/MIC for all patients was 67.7 mg/kg/day. Adjusting for age, the mean dose required to achieve target AUC/MIC of 400 to 600 mg•hr/L was found to be statistically significantly different among 3 age cohorts: 1 month to 5 years, 6 to 12 years, and 13 to 18 years [$F(2,74) = 15.32$, $p < 0.001$], with mean requirements of 79 ± 14.1 , 65.6 ± 21.1 , and 53.9 ± 17.1 mg/kg/day, respectively. Dosing requirements were also found to be statistically significantly different across indications [$F(6,70) = 4.84$, $p < 0.001$]. Acute kidney injury was identified in 5 patients (6.5%).

CONCLUSIONS The vancomycin dose required to achieve target AUC/MIC in pediatrics was significantly higher in younger pediatric patients and ranged from 53.9 to 79 mg/kg/day, confirming recent guideline recommendations. Doses can be further adjusted for indication. Nephrotoxicity rates remain low compared with historical rates with single trough monitoring.

ABBREVIATIONS AKI, acute kidney injury; ANOVA, analysis of variance; AUC, area under the curve; eGFR, estimated glomerular filtration rate; EHR, electronic health record; HEENT, head eyes ears nose throat; IDSA, Infectious Diseases Society of America; IV, intravenous; KDIGO, Kidney Disease: Improving Global Outcomes; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*

KEYWORDS AUC; dosing; pediatric; pharmacokinetics; target attainment; vancomycin

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Introduction

Vancomycin is a glycopeptide antibiotic widely used in hospital settings for the treatment of Gram-positive bacterial infections. Because of its bactericidal activity, it has been considered the agent of choice for invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infections in both adult and pediatric patients.¹ Routine serum concentration monitoring is required with vancomycin therapy to ensure efficacy and prevent toxicity, most notably nephrotoxicity, which occurs at higher rates with elevated trough concentrations.^{2–5} While therapeutic drug monitoring is required, an optimal monitoring strategy in pediatrics has yet to be established.

Historically, single trough concentrations have been used as a surrogate for target 24-hour area under the curve (AUC) to minimum inhibitory concentration (MIC) ratios for pediatric patients on vancomycin therapy for

serious bacterial infections.^{6,7} In recent years, evidence has suggested^{8,9} that single trough concentrations are not the most accurate estimation of AUC/MIC, and a number of other methods, including use of 2-sample serum concentrations, have been suggested as a strategy to improve safety and efficacy.

Efficacy and safety data for AUC/MIC monitoring are limited in pediatrics. Previous research^{8,10,11} in pediatrics has focused on determining the most appropriate and beneficial AUC/MIC coupled with correlating a trough concentration with a targeted AUC/MIC goal. While no definitive AUC/MIC goal range has been established in pediatrics, adult literature¹⁰ would suggest targeting ≥ 400 mg•hr/L. Additionally, multiple adult studies^{5,12,13} have identified an AUC/MIC of >600 mg•hr/L as being correlated with increased risk of nephrotoxicity, although total incidence of nephrotoxicity is decreased with AUC/MIC monitoring as compared with single-trough

Table 1. Institutional Dosing Guidelines Used to Achieve Goal AUC of 400 to 600 mg•hr/L

Age	Goal Trough Serum Concentration	
	10–15 mg/L	15–20 mg/L
1 mo–12 yr	70 mg/kg/day ÷ every 6 hr	90 mg/kg/day ÷ every 6 hr
13–16 yr	60 mg/kg/day ÷ every 8 hr	70 mg/kg/day ÷ every 6 hr
>16 yr	15–20 mg/kg every 8–12 hr	

monitoring.

Dosing requirements to achieve an AUC/MIC of 400 to 600 mg•hr/L have not been established in pediatrics. Utilizing population-based modeling, Le et al⁹ concluded that a dosing range of 60 to 70 mg/kg/day may be required. The Infectious Diseases Society of America (IDSA) has historically recommended⁷ lower dosing of 60 mg/kg/day for all pediatric patients with serious or invasive disease caused by MRSA. However, newly published vancomycin monitoring guidelines¹⁴ for serious MRSA infections published by the American Society of Health-System Pharmacists, the IDSA, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists recommend AUC/MIC monitoring (assuming a MIC ≤ 1 mg/L), with a goal of 400 to 600 mg•hr/L, for pediatric patients, and higher dosing of 60 to 80 mg/kg/day is recommended to meet these goals based on modeling data.

Although human patient data are limited, Olson et al¹⁵ found that a vancomycin dose of 55 to 65 mg/kg/day in patients <18 years resulted in an AUC of > 400 mg•hr/L in 75% of courses. The study also noted lower rates of attainment in patients aged 1 to 3 years of age but did not provide dosing recommendations for all ages. To the best of our knowledge, there have been no dosing recommendations by age or indication for achievement of an AUC/MIC of 400 to 600 mg•hr/L in pediatric patients provided in the literature based on human patient data.

The primary objective of this study was to determine appropriate dosing to achieve an AUC/MIC of 400 to 600 mg•hr/L in pediatric patients using human patient data. Secondary objectives were to assess dosing requirements by indication to achieve an AUC/MIC of 400 to 600 mg•hr/L and an examination of risk factors and incidence of nephrotoxicity.

Materials and Methods

Approval for this retrospective study was obtained through the institutional review board at the University of Kentucky. Patients aged 1 month to 18 years admitted to Kentucky Children's Hospital who received at least 2 days of vancomycin therapy from October 2017 through March 2019 and who had a documented pharmacokinetic monitoring note with a calculated AUC/MIC were eligible for inclusion. Patients were excluded if they were admitted to the neonatal inten-

sive care unit, had renal dysfunction on admission (as defined by an estimated glomerular filtration rate [eGFR] ≤ 50 mL/min/1.73 m²), or did not have baseline or follow-up serum creatinine values reported during admission. The Bedside Schwartz equation was used to calculate eGFR.

All MRSA isolates were assumed to have a MIC of 1 mg/L for the purpose of AUC/MIC calculations. Similar to what has historically been done for trough monitoring, a MRSA MIC of 1 mg/L was then extrapolated to other organisms and used for all pharmacokinetic assessments. This allows AUC to be considered equivalent to AUC/MIC, and, therefore, AUC/MIC will be reported as AUC within our results. Target AUC was defined as 400 to 600 mg•hr/L.

Initial vancomycin dosing was based on an institutional guideline described in Table 1. Patients admitted to the oncology service may have been empirically dosed lower secondary to service preference. Two concentrations were applied to the Sawchuk-Zaske equation to estimate AUC.¹⁶ This method was chosen because of an expected high accuracy in AUC/MIC estimation using 2 concentration kinetic evaluations as well as institutional experience with the Sawchuk-Zaske equation.¹⁴ Timing of steady-state serum concentrations were at the discretion of the pharmacist, taking into consideration the dosing interval and infusion time. Serum concentrations were collected around the fourth dose (±1 dose) of a new regimen.

Dosing to achieve target AUC is defined as the dose (in mg/kg/day) a patient was receiving at the time during which an AUC of 400 to 600 mg•hr/L was recorded within the EHR or as the dose determined by the pharmacist to be required to achieve target AUC for any AUC outside of the goal range of 400 to 600 mg•hr/L following initial dosing. Dosing requirements were compared across 3 age cohorts: 1 month to 5 years, 6 to 12 years, and 13 to 18 years. These age range groupings were selected in an attempt to equally distribute patients across the cohorts.

Dosing to achieve target AUC was also assessed by indication. Indication was identified by EHR order documentation, which is required to be specified within any vancomycin order at time of submission. Documented indications of “*Bacteremia*” and “*Sepsis*” were consolidated to “*Bacteremia*” within our results.

Table 2. Baseline Characteristics (N = 77)

Characteristic	Results
Age, mean $\pm$ SD (range), yr	8.2 $\pm$ 6.2 (0.1–18.4)
Sex, n (%), male	40 (51.9)
Height, mean $\pm$ SD (range), cm	119.6 $\pm$ 39.7 (46–181)
Weight, mean $\pm$ SD (range), kg	36.1 $\pm$ 34.5 (3.1–204)
Glomerular filtration rate, mean $\pm$ SD (range), mL/min/1.73 m ²	135.5 $\pm$ 42 (64–269.7)
Initial vancomycin dose, mean $\pm$ SD (range), mg/kg/day	68.9 $\pm$ 16.3 (19.61–93.2)
Indication, n (%)	
Bacteremia	22 (28.5)
Pneumonia	17 (22.1)
Cystic fibrosis exacerbation	15 (19.5)
Skin and soft tissue	10 (13)
Bone/joint	8 (10.4)
Meningitis	3 (3.9)
Head, eyes, ears, nose, throat	2 (2.6)
Antibiotic use, mean $\pm$ SD, days	
Vancomycin	5.1 $\pm$ 4.0
IV antibiotics	7.3 $\pm$ 5.3
Hospitalization, mean $\pm$ SD, days	
ICU	3.3 $\pm$ 9.7
Total	13.8 $\pm$ 19.2

All other indications are listed as defined within the EHR vancomycin order.

Acute kidney injury (AKI) was assessed based on serum creatinine values and the Kidney Disease: Improving Global Outcomes (KDIGO) criteria.¹⁷ Urine output as a marker of AKI per KDIGO criteria was not used in the analysis because urine output could not be confirmed as consistently charted within the EHR because of both patient-related variables and variability in output monitoring orders. Cystatin C values were not routinely available and were not included in the data. Concomitant nephrotoxic medications, administered within the 12 hours prior to or after a vancomycin dose, and supplemental IV fluid administration were evaluated.

For statistical analysis, the primary endpoint of required dosing to achieve target AUC was assessed using descriptive statistics for all patients and 1-way analysis of variance (ANOVA) assessment for age-adjusted comparison. For secondary endpoints, indication-based dosing requirements were also assessed utilizing descriptive statistics for each indication and 1-way ANOVA for comparison between indications. Mean ages of indication cohorts were evaluated using 2-sample *t*-tests. Comparisons to baseline values for nephrotoxicity were also evaluated using 2-sample *t*-tests. Baseline characteristics and nephrotoxicity markers were also evaluated using descriptive statistics.

Results

A total of 77 patients were included in the final analysis. A description of the study population can be found in Table 2. The mean AUC following initial dosing was 534 $\pm$ 157.5 mg•hr/L, with 43 patients (55.8%) achieving target AUC and 34 patients (44.2%) having a documented AUC outside of the target range. Of the 34 patients outside of the target range, 11 (14.3%) had AUC of <400 mg•hr/L and 23 (30%) had AUC of >600 mg•hr/L.

Dosing Required for Target AUC Achievement. The mean dose required to achieve target AUC of 400 to 600 mg•hr/L for all 77 patients was 67.7 $\pm$ 20 mg/kg/day. Adjusting for age, numerically lower mean daily doses were required with increasing age. For patients aged 1 month to 5 years, the mean dose required to achieve target AUC was 79 $\pm$ 14.1 mg/kg/day. For patients aged 6 to 12 years, the mean dose required was 65.6 $\pm$ 21.1 mg/kg/day. For patients aged 13 to 18 years, the mean dose required was 53.9 $\pm$ 17.1 mg/kg/day. A 1-way ANOVA showed that the effect of age on dose required to achieve target AUC was statistically significant [*F*(2,74) = 15.32, *p* < 0.001]. The absolute difference in mean dose required for target AUC achievement from the youngest age cohort and oldest age cohort was 25.4 mg/kg/day.

Indication-Based Dosing Required for Target AUC Achievement. Assessment of indication-based dosing requirements found differences in the dosing required

Table 3. Age-Adjusted Mean Dosing Requirements Based on Indication

Indication	Age			Total*
	1 mo–5 yr*	6–12 yr*	13–18 yr*	
All indications	79 (33)	65.6 (20)	53.9 (24)	67.7 (77)
Meningitis	89.4 (1)	79.2 (1)	93.2 (1)	87.3 (3)
Pneumonia	85.7 (11)	53.7 (2)	57.0 (4)	75.2 (17)
Bone/joint	97.2 (3)	73.8 (3)	36.6 (2)	73.3 (8)
Skin/soft tissue	78.7 (1)	75.4 (7)	37.6 (2)	68.2 (10)
Bacteremia	70.7 (15)	49.5 (3)	42.2 (4)	62.6 (22)
Cystic fibrosis	80.9 (1)	65.4 (3)	59.5 (11)	62.1 (15)
HEENT	63.2 (1)	30.4 (1)	—	46.8 (2)

HEENT, head, ears, eyes, nose and throat

* Mean dose in mg/kg/day (n).

to achieve target AUC. Mean dosing required to achieve target AUC is described in Table 3. A 1-way ANOVA showed that the effect of indication on dose required to achieve target AUC was statistically significant [$F(6,70) = 4.84, p < 0.001$].

The indications of bacteremia, cystic fibrosis exacerbation, and head, ears, eyes, nose, throat (HEENT) infections each required lower dosing than the total sample mean and were more likely to have an AUC > 600 mg·hr/L (41% of patients with these indications) following initial dosing with the institutional guideline. The indications of bone and joint infections, pneumonia, meningitis, and skin and soft tissue infection each required higher dosing than the sample mean and had lower rates of AUC > 600 mg·hr/L (18.4 % of patients for these indications). When comparing the mean age of the 2 indication cohorts, the lower dose indication cohort mean age of 8.4 ± 6.7 years and the higher dose indication cohort mean of 7.9 ± 5.6 years were not found to be statistically significant ($p = 0.6943$; 95% CI: -2.26 – 3.37).

Nephrotoxicity. Post-vancomycin mean eGFR was not found to be statistically significantly different from baseline, at 124.1 ± 34.1 mL/min/m², with an absolute mean decrease per patient of 11.4 mL/min/m² ($p = 0.0662$; 95% CI: -0.77 – 23.57). Acute kidney injury was identified in 5 patients (6.5%). All 5 patients were considered KDIGO stage 1, with a mean increase in serum creatinine of 1.59 ± 0.06 times baseline. No patients with AKI required vancomycin to be discontinued, and the mean AUC for these patients was 507 mg·hr/L. Only one patient with AKI had an AUC > 600 mg·hr/L, with a value of 613 mg·hr/L. The mean initial dosing of patients with AKI was 76.5 ± 18.8 mg/kg/day, with a mean age of 4.8 ± 5.0 years.

The mean number of nephrotoxic medications per patient for the sample was 2.2. The most common con-

comitant nephrotoxic medications were antihistamines ($n = 44, 57.1\%$), non-steroidal anti-inflammatory agents ($n = 42, 54.5\%$), and proton pump inhibitors ($n = 24, 31.2\%$) (Table 4). Other agents historically considered to be highly nephrotoxic in combination with vancomycin were much less frequent, such as piperacillin/tazobactam ($n = 5, 6.5\%$), aminoglycoside antibiotics ($n = 4, 5.2\%$), and amphotericin B ($n = 1, 1.3\%$). All 5 patients meeting criteria for AKI were receiving 3 or more concomitant nephrotoxic medications. Fluid administration showed no impact on risk of AKI. Sixty-five (84.4%) patients were receiving supplemental IV fluids, with the majority receiving continuous IV fluids ($n = 47, 72\%$) as opposed to daily IV boluses ($n = 18, 28\%$). Of the 5 patients with AKI, 3 were receiving maintenance IV fluids, 1 received a daily IV fluid bolus, and 1 did not have supplemental IV fluids ordered.

Discussion

In 3 studies^{6,8,11} published between 2015 and 2017, researchers found that an AUC/MIC of 400 mg·hr/L was equivalent to a trough concentration of approximately 11 mg/L, and an AUC/MIC < 400 mg·hr/L was predictive of potential treatment failure. Further research¹⁸ in pediatric vancomycin AUC/MIC monitoring was conducted in 2018, suggesting that an AUC/MIC > 400 mg·hr/L may be clinically beneficial in pediatric patients, noting an improvement in early clinical response but no difference in mortality or microbiological outcomes. Toxicity profiles with AUC/MIC > 600 mg·hr/L, while noted in the adult literature, have not been explicitly identified in pediatric data.

The dosing required to achieve an AUC/MIC of 400 to 600 mg·hr/L in pediatrics has not been well established through human patient data. Previous literature¹⁹ noted that at a MIC of 1 mg/L for MRSA infections, a dose of 60 mg/kg/day was needed to achieve an AUC/MIC > 400

Table 4. Concomitant Nephrotoxic Agents

Agent/Drug Class	Patients With Medication Order, n
Antihistamines	44
Non-steroidal anti-inflammatory drugs	42
Proton pump inhibitors	24
Loop diuretics	20
Ranitidine	11
Piperacillin/tazobactam	5
Aspirin	5
Herbal supplements	5
Aminoglycoside antibiotics	4
Sulfonamides	3
ACE inhibitors	2
Acyclovir	1
Amphotericin B	1
Pentamidine	1
Calcineurin inhibitors	1
Thiazide diuretics	1
Allopurinol	1
Phenytoin	1
Lithium	1

mg•hr/L for 4 of 7 dosing models across all pediatric ages. The same study¹⁹ noted a trend toward better AUC/MIC achievement with increasing patient age at the same dose. One study,¹⁵ which involved human patient data for patients receiving a standard 55 to 65 mg/kg/day, indicated that 75% of patients were able to achieve an AUC > 400 mg•hr/L, but this study did not provide the dosing required across all ages. Our study would support previous modeling studies showing decreasing dose requirements for AUC/MIC achievement with increasing age while providing dosing recommendations for specified age ranges. We were able to identify similar dose requirements when compared with previous modeling studies and recommendations made in recent consensus guidelines for dosing significantly higher than 60 mg/kg/day, particularly in younger children.¹⁴ Our data indicate a wide dosing range when adjusting for age, with a dosing range of about 50 to 80 mg/kg/day across all ages.

The data from this study allow for dose optimization based on age in combination with indication. Assessment of dosing requirements adjusted for indication

showed wide variability in likelihood of achievement of target AUC with similar initial dosing per our protocol. There were, however, parallels that were able to be drawn across indications, such as higher mean dosing required for cases involving bone and joint infections, meningitis, pneumonia, and skin and soft tissue infections. Bacteremia, cystic fibrosis exacerbations, and HEENT infections required comparatively lower mean doses, closer to historical IDSA recommendations of 60 mg/kg/day. The mean age of patients in the indication cohort requiring higher dosing than the sample mean and the mean age of those in the indication cohort requiring lower dosing than the sample mean were not statistically different, indicating that age likely did not play a role in dosing requirements when adjusted for indication. These trends in dosing would suggest the use of an age-directed dosing protocol, with initial dosing based on indication as opposed to trough goals, similar to most common current practice.

In our study, patients with cystic fibrosis, a population traditionally expected to require higher empiric dosing, required dosing more similar to historical recommendations of 60 mg/kg/day. While not entirely expected, it can be noted that recent data²⁰ have supported similar dosing in this population. Oncology patients appear to require similar doses to attain target AUC, as compared with the remainder of the population, even with lower initial dosing at our institution, but this group only accounted for 7 of the 77 patients.

While roughly a third of patients had an initial AUC > 600 mg•hr/L, the risk of AKI remained low. Historical incidence of AKI in pediatric patients treated with vancomycin suggests a 5% to 44% risk.¹⁷ This risk has been shown¹⁷ to increase when concomitant nephrotoxic agents are used in combination with vancomycin, as well as with increasing vancomycin dosing requirements targeting higher trough concentrations. Despite an average of 2.2 nephrotoxic agents, our incidence of 6.5% falls at the lower end of the incidence reported in previous literature. Supplemental fluid administration did not appear to have an impact on nephrotoxicity, although the majority of the population were receiving supplemental IV fluids.

Of the 5 patients identified with AKI per KDIGO criteria in this study, all of them met criteria for stage 1 injury, and none required vancomycin dosing adjustment or discontinuation because of nephrotoxicity. These patients had objectively higher numbers of concomitant nephrotoxic medications as compared with the mean of the sample, including each having concomitant non-steroidal anti-inflammatory agents, which may have contributed to their risk of AKI. Of the 5 patients, 2 patients were treated as “infection rule out” for 2 to 3 days, and 3 patients received a complete 7 to 10-day treatment course of vancomycin. This suggests that age and indication targeted dosing, coupled with AUC/MIC monitoring, provides a safe method for vancomycin

dosing, monitoring, and adjustment.

While the results of this study are reassuring relative to the use of AUC/MIC monitoring in pediatrics, we recognize a number of limitations. This is a single-center retrospective study with a limited number of age and indication assessment groups, yielding low patient numbers, making conclusions more challenging. Patients were not randomized, and there is no true comparator group outside of guideline-recommended dosing and previous modeling studies. Neither urine output, which may be a better indicator of renal function in younger pediatric patients, nor Cystatin C values were used to assess for the risk of AKI, which may have allowed for lower detection of nephrotoxicity in the sample. Although the reported incidence of nephrotoxicity remained low, IV contrast agents were not readily reported and were therefore not included in the nephrotoxin assessment.

Further research and prospective analysis of AUC/MIC versus traditional trough monitoring in larger human sample sizes is still needed to confirm the results of the current study. Higher dosing requirements continue to be reported in the literature and guidelines and are supported here, but these requirements are most commonly reported through dose modeling when assessed in the context of AUC/MIC.⁹ This study is the first to use pediatric human patient data with AUC monitoring.

Conclusion

Monitoring of vancomycin therapy in pediatric patients continues to be an area of research designed to determine the most appropriate method. The data provided in the current study reinforce the use of 2-concentration AUC/MIC calculations in pediatric patients as safe and efficacious. The mean dose required to achieve an AUC of 400 to mg·hr/L in this study was approximately 70 mg/kg/day, with a mean range of 50 to 80 mg/kg/day. The dosing range found in our study closely aligns with those of previous modeling studies and recommendations made in recent consensus guidelines. In addition, AUC/MIC monitoring with age-appropriate dosing adjusted for indication showed a low risk of nephrotoxicity. Dose optimization should take into consideration age and indication.

Article Information

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and the accuracy of the data analysis.

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References

1. Choo EJ, Chambers HF. Treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *Infect Chemother.* 2016;48(4):267–273.
2. Balch AH, Constance JR, Thorell EA, et al. Pediatric vancomycin dosing: trends over time and the impact of therapeutic drug monitoring. *J Clin Pharmacol.* 2015;55(2):212–220.
3. Finch NA, Zasowski EJ, Murray KP, et al. A quasi-experiment to study the impact of vancomycin area under the concentration-time-curve-guided dosing on vancomycin-associated nephrotoxicity. *Antimicrob Agents Chemother.* 2017;61(12):e01293–17.
4. Moffett B, Morris J, Kam C, et al. Vancomycin associated acute kidney injury in pediatric subjects. *PLoS One.* 2018;13(10):e0202439.
5. Van Hal SJ, Paterson DL, Lodise TP. Systematic review of vancomycin-induced nephrotoxicity associated with dosing schedules that maintain troughs between 15 and 20 milligrams per liter. *Antimicrob Agents Chemother.* 2013;57(2):734–744.
6. Hahn A, Frenck RW, Vinks AA. Validation of pediatric population pharmacokinetic model for vancomycin. *Ther Drug Monit.* 2015;37(3):413–416.
7. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: executive summary. *Clin Infect Dis.* 2011;52(3):285–292.
8. Kishk OA, Lardieri AB, Heil EL, et al. Vancomycin AUC/MIC and corresponding troughs in a pediatric population. *J Pediatr Pharmacol Ther.* 2017;22(1):41–47.
9. Le J, Bradley JS, Murray W, et al. Improved vancomycin dosing in children using area under the curve exposure. *Pediatr Infect Dis J.* 2013;32(4):e155–e163.
10. Neely MN, Kato L, Youn G, et al. Prospective trial of the use of trough concentration versus area under the curve to determine therapeutic vancomycin dosing. *Antimicrob Agents Chemother.* 2018;62(2):e02042–17.

11. Ploessl C, White C, Manasco K. Correlation of a vancomycin pharmacokinetic model and trough serum concentrations in pediatric subjects. *Pediatr Infect Dis J*. 2015;34(10):e244–e247.
12. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult subjects: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2009;66(1):82–98.
13. Zasowski EJ, Murray KP, Trinh TD, et al. Identification of vancomycin exposure-toxicity thresholds in hospitalized subjects receiving intravenous vancomycin. *Antimicrob Agents Chemother*. 2017;62(1):e01684–17.
14. Rybak M, Le J, Lodise T, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2020;77(11):835–864.
15. Olson J, Hersh A, Sorensen J, et al. Intravenous vancomycin therapeutic drug monitoring in children: evaluation of a pharmacy-driven protocol and collaborative practice agreement. *J Pediatr Dis Soc*. 2020;9(3):334–341.
16. Sawchuk RJ, Zaske DE. Pharmacokinetics of dosing regimens which utilize multiple intravenous infusions: gentamicin in burn patients. *J Pharmacokinet Biopharm*. 1976;4(2):183–195.
17. Sutherland SM, Byrnes JJ, Kothari M, et al. AKI in hospitalized children: comparing the pRIFLE, AKIN, and KDIGO definitions. *Clin J Am Soc Nephrol*. 2015;10(4):554–561.
18. Ruiz J, Garcia-Robles A, Marques MR, et al. Influence of pharmacokinetic/pharmacodynamic ratio on vancomycin treatment response in paediatric subjects with *Staphylococcus aureus* bacteremia. *Minerva Pediatr*. 2018. doi: 10.23736/S0026-4946.18.04978-2
19. Frymoyer A, Hersh A, Benet L, et al. Current recommended dosing of vancomycin for children with invasive methicillin-resistant *Staphylococcus aureus* infections is inadequate. *Pediatr Infect Dis J*. 2011;28(5):398–402.
20. Stockmann C, Olson J, Rashid J, et al. An evaluation of vancomycin area under the curve estimation for children treated for acute pulmonary exacerbations of cystic fibrosis due to methicillin-resistant *Staphylococcus aureus*. *J Clin Pharmacol*. 2019;59(2):198–205.