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Pediatric Vancomycin Dosing: Trends Over Time and the Impact of Therapeutic Drug Monitoring

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Abstract

Monitoring of vancomycin trough concentrations is recommended for pediatric patients in the product label and by several professional societies. However, among a network of freestanding children's hospitals vancomycin therapeutic drug monitoring (TDM) practices were reported to be highly variable. In this study, we sought to evaluate whether trends in vancomycin use and TDM changed across a large healthcare delivery system in Utah and Idaho from 2006 to 2012. Children 18 years who received 2 vancomycin doses were included. Overall, vancomycin TDM was performed during 5,035 (80%) of 6,259 hospital encounters, in which 85,442 doses were administered and 7,935 concentrations were obtained. Across this time period, the median trough concentration increased from 10.9 to 13.7 µg/mL ($P < .001$), which temporally coincided with recommendations published by the Infectious Disease Society of America that recommend targeting higher trough concentrations. Two or more abnormally low trough concentrations were accompanied by an increase in the dose 75% of the time. Similarly, 2 abnormally high trough concentrations were followed by a decrease in the dose 35% of the time. In aggregate, these data suggest that vancomycin TDM is commonly performed among children and the majority of abnormal trough concentrations were associated with an appropriate modification to the dosing regimen.

Keywords

vancomycin; pediatrics; therapeutic drug monitoring

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Declaration of Conflicting Interests

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Supporting Information

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For pediatric patients, monitoring of vancomycin serum concentrations is recommended in the product label and “close monitoring” for neonatal (<28.0 days) patients is suggested.¹ A report published by Moffett and Edwards found that vancomycin monitoring practices were highly variable among children admitted to a network of 40 children’s hospitals.² In this study, we explored the extent to which vancomycin therapeutic drug monitoring (TDM) is performed among neonatal and pediatric patients and additionally define how that information influences vancomycin prescribing patterns.

Vancomycin dosing presents a challenge in the neonatal and pediatric populations due to its adverse effect profile and the requirement to achieve high concentrations to maintain effective antimicrobial activity.³ Rashes, chills, and fever are common; and in rare instances, hypersensitivity reactions including anaphylaxis and red man syndrome may occur.⁴ Moreover, vancomycin may adversely affect auditory, vestibular, and renal function, adding further complexity to dosing.⁵ Available evidence suggests that high vancomycin trough concentrations may be associated with a heightened risk for developing nephrotoxicity.⁶ Currently, for children, 15 mg/kg/dose IV every 6 hours is recommended for the treatment of bacteremia and infective endocarditis, which is an increase in both the amount and frequency when compared to earlier recommendations from the Infectious Disease Society of America (IDSA).^{7,8} Consequently, vancomycin TDM continues to be recommended to ensure adequate, effective, and safe levels of drug exposure.^{7,8}

The use of vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections has increased due to the emergence of community-associated strains.⁹ Vancomycin use in pediatrics in recent years has been the subject of much debate regarding its optimal use due to the perceived need for higher doses and the availability of alternative antibiotics (eg, linezolid) for the treatment of invasive MRSA infections.^{10,11} Historically, it was thought that conventional dosing regimens in children resulted in low initial trough concentrations leading to potential treatment failure.^{2,12} Consequently, over the last decade recommended vancomycin dosages have increased for children. However, Frymoyer et al determined that many currently prescribed regimens achieve adequate exposure targets in pediatric patients.¹³

The objectives of this retrospective study were to review and assess (1) the long-term population trends in vancomycin dosing frequency and amounts among neonatal and older pediatric patients; (2) evaluate patient dosing and TDM patterns with respect to published professional society guidelines; (3) assess vancomycin TDM use among different hospital types (community versus quaternary care pediatric hospitals); (4) measure physician responsiveness to abnormally high and low trough concentrations, as established by professional society guidelines; and (5) establish the frequency with which modifications to prescribed vancomycin dosing regimens occurred in the context of abnormally high and low trough concentrations. For each of these objectives, we also examined the temporal trends in the incidence of MRSA detection to determine if epidemiologic changes were altering pediatric vancomycin prescribing patterns.

Methods

Setting and Study Population

In this retrospective study, the incidence of vancomycin use and patterns of TDM in the Intermountain Healthcare (IH) network were evaluated using an electronic medical records database. Children 18 years of age who received 2 or more doses of vancomycin between January 1, 2006 and December 31, 2012 were included. Data were collected for children hospitalized at Primary Children's Hospital (a quaternary care children's hospital) and 16 additional community hospitals within Utah and Idaho (Table S1).

Demographics, pharmacy data, laboratory records, and microbiologic data were reviewed for all included subjects. This study was reviewed and approved by the Institutional Review Board (IRB) at the University of Utah. A waiver of informed consent was granted for the data collected.

TDM was performed as part of standard of care at IH laboratory facilities using automated immunofluorescence polarization assays.¹⁴ Vancomycin peak, random and trough concentrations were all measured from serum. The linear range for the assay was 1.1–100 µg/mL, and the limit of quantitation (LOQ) was 1.1 µg/mL.

Statistical Analysis

Statistical analyses were performed using SASTM version 9.3 and RTM version 3.0.2. Linear mixed effects model analyses were performed using SASTM PROC MIXED software (version 5.04) (Cary, NC). Descriptive statistics were used to (1) characterize the study population; (2) calculate rates of vancomycin use over the study period in comparison to the incidence of MRSA and to the number of admissions; (3) determine the rate of vancomycin TDM at study hospitals and assess overall trends in dosing and vancomycin trough concentrations; and (4) assess physician responses to abnormally high and low vancomycin trough concentrations.

Patient characteristics, excepting age, are summarized per patient, whereas vancomycin monitoring and age are summarized at the level of the patient encounter (admission). In what follows, unless otherwise specified, encounter level data were analyzed and described to reflect a summary of physician actions for a particular admission with regard to drug monitoring and drug administration. Additionally, graphical and summary measurements are used to characterize time and dosing-epoch trends. A dosing epoch was defined to be a period in which a dose was administered immediately after a measured vancomycin serum concentration but before the next, subsequent, vancomycin concentration was taken. To assess an individual physician's response to the vancomycin concentration, three things were required: (1) the patient must have had a concentration measured; (2) the concentration must have had a preceding dose history; and (3) there must have been a subsequent dose history. In a 3 dose/day regimen with daily monitoring, this would mean 3 doses would be given, then a concentration was measured, then 3 more doses were administered, then another concentration was obtained, and so on. The total dose per day (mg/day) was used assessing physician responses to normal, abnormally high, and abnormally low vancomycin trough concentrations. The total dose per day was then scaled by the patient's weight (kilograms) to

create a variable of scaled dose: Dose/Wt/Day (mg/kg/day). A linear mixed-effects regression model was constructed to evaluate differences in the impact of TDM on vancomycin prescribing among the study hospitals. A P -value $< .05$ was considered to be statistically significant.

Patients were included in the analysis population if they had at least one trough concentration, a dose interval < 36 hours, and if the gap between all administered doses was 1 and < 36 hours. Within patients, the pharmacy data were divided into dosing epochs that were separated by vancomycin trough measurements. The effect was assessed by measuring the change in dose within an epoch following each trough concentration.

For the purposes of assessing physician response to TDM, vancomycin trough concentrations were analyzed according to intensive care unit (ICU) status and date. Specifically, if the admission year was 2006–2011 and the patient was not admitted to the ICU then a trough concentration of $5 \mu\text{g/mL}$ was considered to be in accordance with professional society recommendations.^{8,15} If a patient was admitted to the ICU during this time period then a trough concentration $> 10 \mu\text{g/mL}$ was used as the therapeutic cut-off.^{8,15} After publication of the pediatric guidelines in 2011, to maintain agreement with professional society guidelines we defined abnormally low trough concentrations as those $< 15 \mu\text{g/mL}$ for ICU patients and $< 10 \mu\text{g/mL}$ for all other patients.⁷ In all cases, troughs $> 20 \mu\text{g/mL}$ were flagged as abnormally high.

A linear regression model was developed to statistically assess physician response to abnormally high and low vancomycin trough concentrations. The ratio of the geometric mean (total daily dose/weight) before and after a trough concentration was modeled based on whether the vancomycin trough concentration was within the target range. For this purpose, a trivariate categorical variable for concentration status, “Concstatus,” indicating epoch trough concentration status with three values (“High,” “Normal,” “Low”) was defined. Concstatus = “High” if a trough concentration was $> 20 \mu\text{g/mL}$. Concstatus = “Low” indicates that a concentration was below guideline recommendations and was updated in 2011 to reflect publication of the pediatric guidelines.⁸ The low trough flag reflects these changing recommendations and classifies any patient in the ICU as seriously ill.

A general linear mixed effects model was constructed with a categorical fixed effect, a random subject effect, and Gaussian residuals. Fixed effects were fitted with a cell means model where all combinations of the levels were estimated directly. The marginal effects of variables were then estimated via contrasts, which average the estimators of the combined estimates at each level of the variable of interest. Fixed effects were as follows: The patient population effect; N_i was included as a binary variable that indicates whether a patient was < 28.0 days of age; likewise, a fixed hospital-type effect was modeled with a binary variable H_j that indicates whether hospital j was a quaternary care pediatric or community hospital; finally, a fixed concentration status variable, C_k models whether the most recent observed patient concentration was high, low, or within normal limits. An independent Gaussian random subject effect for each subject i was included in the model as an independent Gaussian error for each observation. The resulting cell means statistical predicted model for observation m was therefore defined as:

$$\Delta_{\log(\text{daily dose})}_{\{ijklm\}} = (\text{NHC})_{\{ijk\}} + B_{\{i\}} + \varepsilon_{\{ijklm\}}$$

$\Delta_{\log(\text{daily dose})}$ corresponds to the average change in $\log(\text{dose}/\text{Wt})$ for an epoch of doses immediately preceding and immediately following the sample and resulting concentration. In this model of physician response, subjects are nested within their hospital type and concentrations were drawn repeatedly from each subject.

Results

Patient Distribution in Hospitals

Eleven of the 19 hospitals had 5 patients who received vancomycin from 2006 to 2012 (Table S1). The largest number of patients were hospitalized at Primary Children's Hospital, a quaternary care facility in Salt Lake City, Utah (4,139 encounters; 66%).

Trends in MRSA Infection and Vancomycin Use

Figure 1a,b and Table S2 show the temporal trends in vancomycin use and MRSA infection rates from 2006 to 2012. Over the study period, the total number of hospital admissions throughout IH remained stable. The highest number of MRSA cases occurred in 2009, while vancomycin use was highest in 2011.

Demographics, Patient Characteristics, and Extent of TDM

Of 4,983 total patients meeting the inclusion criteria for the study, 2,133 (43%) were female and 2,850 (57%) were male (Table 1). The majority of patients (>78%) were white; however, racial data were not available for 15%. Ethnicity was tallied separately as Hispanic/ Non-Hispanic. Neonates comprised 30% ($n = 1,881$) of patient encounters. TDM was less frequently performed among patients hospitalized 3 days and among neonatal patients. TDM was performed in 5,035 (80%) of 6,259 hospital encounters (Table 2). Of these, 4,970 encounters had 1 trough concentrations measured (Tables S3 and S4). The number of doses before collection of the first vancomycin concentration ranged from 1 to 26 doses, with a median of 3 doses (Table S5). The frequency of TDM differed between community hospitals (68%) and the quaternary care pediatric hospital (85%; $P < .0001$). Overall, 18,355 samples consisting of 5,320 peaks, 12,686 troughs, and 349 random serum vancomycin concentrations were quantitated. The relative distribution of peak, trough, and random samples collected was similar between the community and pediatric hospitals (Tables S3 and S4).

Patient dosing regimens were characterized by the dosing frequency and the amount of drug administered (Tables 2 and 3). Steady-state dosing trends during the study period are shown in Table 2. Overall, the median trough concentration increased from 10.9 to 13.7 $\mu\text{g}/\text{mL}$ ($P = .0043$) for pediatric patients and from 6.9 to 12.3 $\mu\text{g}/\text{mL}$ ($P < .001$) for neonatal patients. The daily dose and frequency increased for neonatal patients ($P < .001$). The daily dose did not increase for older pediatric patients, although the dosing frequency did ($P = .021$).

From 2006 to 2012, neonates experienced a larger increase in the average daily vancomycin dose when compared to older pediatric patients. In spite of this, higher dosing frequencies for older children resulted in higher trough concentrations for older children as compared to neonates (Table 2). Neonatal patients received a median of 2–3 vancomycin doses per day and pediatric patients received a median of 3–4 doses per day.

Summary statistics for the daily vancomycin dose (mg/kg/day) and trough concentration ($\mu\text{g/mL}$) are stratified by dosing epoch in Table 3 and in Figure 1C–F. In both Tables 3 and 4, the percent coefficient of variation (CV%) for the daily dose was large (68%–108%) necessitating a log transformation for the statistical analysis and geometric means for epoch dose ratio, the results of which are summarized with rank statistics in Table 3. With the exception of a small group in 2006, both dose amount and trough concentrations increased steadily over time. Neonatal patients had longer dosing intervals. Considered on an epoch-to-epoch basis, the largest increases in both doses administered and trough concentrations were observed early in the course of treatment (Figure 1E). Figure 1C and D shows the increase in dose and concentration in the early epochs for both pediatric and neonatal patients. The number of patients in later epochs is fewer (Table 3), contributing to a more variable trajectory in Figure 1C and D after 8 concentrations.

On the average, daily doses were about 16% lower ($P < .0001$) immediately after an abnormally high trough concentration was measured (Table 5). Similarly, immediately following an abnormally low trough concentration, on average the mean daily dose was increased by 11%. This effect was seen in both pediatric and neonatal patient subgroups, and for both hospital types. There was a difference in the response to low trough concentrations, such that pediatric hospitals were more likely to increase the dose following an abnormally low trough concentration when compared to community hospitals ($P < .0001$).

To assess the probability of altering the vancomycin dosing regimen in response to an abnormal trough concentration, Table S7 presents the individual responses for patients with 2 abnormal trough measurements. Two or more abnormally high trough concentrations were associated with a decrease in the daily vancomycin dose of 10% in just 39 (35%) of 112 cases. In contrast, 2 abnormally low trough concentrations were associated with a 10% increase in the daily vancomycin dose in 1,147 (75%) of 1,520 cases. Median doses decreased an average of 41% when there were 2 abnormally high trough concentrations and increased an average of 24% when there were 2 abnormally low trough concentrations. There were 5 patients with trough concentrations $>50 \mu\text{g/mL}$, which represented 0.11% of all pediatric patients who received vancomycin. All of these children had evidence of renal dysfunction (serum creatinine $>1.5 \text{ mg/dL}$); however, all three children for whom complete follow-up data were available had returned to normal creatinine reference ranges at the time of discharge, which is consistent with previous reports documenting reversible nephrotoxicity associated with high vancomycin trough concentrations. One patient was lost to follow-up because they were transferred to another hospital system. The last child had a history of trisomy 21, asplenia, hypothyroidism, pre-B cell acute lymphoblastic leukemia, and fungal pneumonia necessitating resection of his right lower lobe. The decision was ultimately made to withdraw support after he developed acute respiratory distress syndrome (ARDS) and multi-organ failure.

Discussion

Nationally, the United States Centers for Disease Control and Prevention (CDC) has reported that the incidence of invasive MRSA infection among children has increased an average of 10.2% each year from 2005 to 2010.¹⁶ Although relatively little is known about the temporal trends of vancomycin use in children, among 22 adult academic medical centers, total vancomycin use increased 43% from 2002 to 2006.⁹ This builds on a historic trend, in which the rate of vancomycin usage increased 20-fold from 1981 to 1991 at a 900 bed adult academic medical center.¹⁷ In this study, we found that despite relatively stable rates of MRSA infection, vancomycin usage increased markedly from 2006 to 2012. Over this period, there was an increase in the average daily dose of vancomycin administered to neonates; however, dosages among older children remained stable. Additionally, TDM was performed for 80% of children who received vancomycin. Overall, the median trough concentration also increased, which temporally coincided with published pediatric-specific guidelines from the IDSA that recommend targeting trough concentrations $>15 \mu\text{g/mL}$ for critically-ill children and $>10 \mu\text{g/mL}$ for all other pediatric patients.⁷ We found that changes in vancomycin dosing commonly occurred in response to abnormally low and high trough concentrations. In aggregate, these findings suggest that appropriate dosing modifications frequently occur to ensure that children achieve guideline recommended vancomycin trough concentration targets.

TDM affords clinicians the opportunity to assess whether the dose they are providing is achieving the expected serum concentration, which may be particularly useful for drugs with narrow therapeutic windows. Originally, vancomycin dosing was entirely empirical with serum concentrations produced by the “standard” 2 grams/day adult dosage “generally accepted as therapeutic and minimally toxic.”¹⁸ Subsequently, Moellering et al developed a vancomycin dosing nomogram for patients with impaired renal function that targeted a mean steady-state vancomycin concentration of $15 \mu\text{g/mL}$.¹⁹ Within a few years, sensitive and reproducible methods to establish serum vancomycin concentrations emerged in clinical laboratories across the country and it became the standard of care to perform vancomycin TDM.¹⁸ In the last decade, it has been determined that the most predictive pharmacodynamic target for efficacy among adult patients with lower respiratory tract infections is a ratio of the vancomycin area under the concentration–time curve to the minimum inhibitory concentration (AUC/MIC) value >400 .²⁰ For MRSA isolates with an MIC $<1 \mu\text{g/mL}$, this was found to correlate with trough concentrations of $15\text{--}20 \mu\text{g/mL}$ among adults.²¹ Subsequently, the American Thoracic Society (ATS) published guidelines for the treatment of hospital-acquired, ventilator-associated, and healthcare-associated pneumonia and suggested that trough vancomycin concentrations should be maintained at $15\text{--}20 \mu\text{g/mL}$ among adults.¹⁵ More recently, a consensus statement authored by the American Society of Health-System Pharmacists, the Society of Infectious Diseases Pharmacists, and the IDSA proposed the same trough target of $15\text{--}20 \mu\text{g/mL}$ for an expanded range of conditions, including the treatment of *S. aureus* bacteremia, endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia.⁸ In 2011, these adult guidelines were revisited by the IDSA and pediatric-specific guidance was offered, although the authors acknowledged that their recommendation for a target trough concentration of $15\text{--}20$

µg/mL for critically-ill children required additional study and was supported by moderate evidence from respected authorities and expert opinions (Quality of Evidence Grade B-III).⁷

Optimal vancomycin dosing requires appropriate adjustments to drug doses and intervals in response to abnormal serum trough concentrations.⁸ Few studies to date have systematically examined the rate at which dosing modifications occur in response to abnormal vancomycin trough concentrations. In this study, we found that three-quarters of patients with 2 abnormally low trough concentrations had an appropriate increase in their average daily vancomycin dose. Among children with 2 abnormally high trough concentrations, 35% of children had an appropriate decrease in their vancomycin dose. As concentrations trended upward during treatment, it is possible that trough sampling may have missed the second higher concentration, or that the decision was postponed pending more information. As a statistical trend, high trough concentrations drove more frequent dose reductions than increases. Although other clinical factors that could not be captured in this retrospective, observational study likely influenced clinical decision making, it appears that providers are responsive to abnormal vancomycin trough concentrations and frequently implement dosing modifications to achieve guideline recommended trough targets.

This retrospective, observational study features several limitations. First, the study was conducted using data derived from a single large healthcare delivery system in Utah and Idaho, which may not reflect national or international trends in pediatric vancomycin use and monitoring. Additionally, the duration of vancomycin therapy was variable, such that the sample size available at later epochs became small, thereby limiting our ability to conduct statistical comparisons at later time points. Lastly, despite the overall increase in vancomycin use, MRSA rates were stable throughout the study period, which differs from nationally reported trends. However, it is well established that the incidence of MRSA infection varies according to geographic region.^{22–24}

Conclusions

From 2006 to 2012, vancomycin use increased substantially among hospitalized children despite stable rates of MRSA infection. Over the same period, TDM was performed for 80% of children who received vancomycin. Coincident with published pediatric-specific professional society guidelines, the median trough concentration also increased. Critically, abnormal serum trough concentrations were frequently followed by an appropriate dosing modification. Among patients with 2 abnormally low trough concentrations, 75% of children had an immediate increase in their daily vancomycin dose. For those with 2 abnormally high trough concentrations, dose decreases were slightly less common (35%). Although, overall, these data suggest that vancomycin prescribing patterns are responsive to abnormal trough concentrations, there is clearly room for improvement in response to high trough concentrations. Future studies are needed to establish the epidemiologic drivers responsible for the marked increase in vancomycin use; however, this study has established that TDM is frequently performed and the results are often used to improve clinical care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Trends in vancomycin dosing, trough concentrations, and methicillin-resistant *Staphylococcus aureus* (MRSA) infections among 6,259 pediatric hospitalizations from 2006 to 2012.

Table 1**Characteristics of Patients and Vancomycin Monitoring**

Characteristic	No. (%)
Sex (n = 4,983 total patients)	
Female	2,133 (43%)
Male	2,850 (57%)
Race (n = 4,983 total patients)	
American Indian	62(1%)
Asian	47(1%)
Black	88 (2%)
Native Hawaiian/Pacific Islander	132 (3%)
Other/Not given	750(15%)
White	3,904 (78%)
Ethnicity (n = 4,983 total patients)	
Hispanic/Latino	477(10%)
Non-Hispanic/Non-Latino	2,483 (50%)
Patient declined	9(<1%)
Unavailable/Missing	1,951 (39%)
Unknown to patient	63 (1%)
Age (n = 6,259 total admissions)	
Neonate (<28 days)	1,881 (30%)
Infant (28 days to 6 months)	685 (11 %)
Toddler (6 months to 2 years)	909 (15%)
Young child (2 years to 5 years)	878(14%)
Older child (5 years to 12 years)	909 (15%)
Adolescent (12 years)	997(16%)
Vancomycin monitoring (by admission)	
Neonate with hospital stay <3 days	42 (56%)
Child with hospital stay <3 days	655 (66%)
Neonate with hospital stay 3 days	1,404 (78%)
Child with hospital stay 3 days	2,934 (87%)
Vancomycin monitoring by hospital type (by admission)	
Community hospital	1,445 (68%)
Children's hospital	3,525 (85%)

Table 2

Vancomycin Dosing Trends Among Neonates and Pediatric Patients

Population	Parameter	Percentile	Year						
			2006	2007	2008	2009	2010	2011	2012
Neonates	Number	-	77	88	120	123	165	207	179
	Daily dose (mg/kg/day) ^a	50	28.56	27.21	28.82	35.1	38.46	38.85	40.38
		25	22.12	20.12	21.55	27.2	29.61	29.14	30.57
		75	39.02	42.26	39.43	45.53	49.33	51.77	54.04
	First dose (mg/kg) ^a	50	10.49	18.41	14.62	15.00	15.14	15.15	15.55
		25	10.00	10.27	10.12	14.10	14.47	14.58	15.00
		75	17.47	21.78	15.52	18.92	18.60	18.57	20.00
	Dose amount (mg/kg)	50	13.98	18.45	14.56	15.65	16.59	16.15	17.31
		25	10.92	12.46	12.29	14.19	14.59	14.29	14.72
		75	19.23	23.81	18.03	19.26	19.36	18.63	20.00
Pediatrics	Dose frequency (daily)	50	1.46	1.62	1.85	2.01	2.39	2.46	2.57
		25	1.10	1.21	1.33	1.65	1.91	1.92	1.96
		75	1.99	2.00	2.25	2.90	3.00	3.01	3.01
	Trough concentration (mcg/mL) ^a	50	6.9	7.1	10.2	11.7	12.4	13.6	12.3
		25	4.2	4.3	6.0	8.0	9.5	11.0	9.5
		75	9.2	9.7	12.4	14.7	14.5	15.8	15.1
	Number	-	146	172	172	252	290	395	269
	Daily dose (mg/kg/day)	50	69.5	64.94	61.29	65.30	69.53	65.77	70.26
		25	52.51	49.45	42.46	53.42	53.03	52.64	54.25
		75	83.96	80.09	80.05	82.76	81.76	81.12	84.19
	First dose (mg/kg)	50	15.00	14.72	14.12	15.00	15.34	16.2	18.87
		25	12.98	12.80	11.61	13.33	13.95	14.71	15.00
		75	19.51	18.93	15.94	19.70	19.86	19.93	20.00
	Dose amount (mg/kg)	50	20.67	19.67	18.52	19.48	19.82	19.68	19.87
		25	16.33	16.21	14.81	15.44	16.01	15.99	16.67
		75	24.89	22.69	21.56	22.30	22.59	21.67	22.22
	Dose frequency (daily) ^a	50	3.34	3.38	3.60	3.61	3.61	3.64	3.61

Population	Parameter	Percentile	Year						
			2006	2007	2008	2009	2010	2011	2012
Trough concentration (mcg/mL) ^a		25	2.87	2.97	2.84	3.01	2.99	2.96	3.02
		75	3.96	3.92	3.98	3.98	3.96	3.99	3.94
		50	10.9	11.2	11.1	11.6	12.7	13.7	12.7
		25	7.8	8.4	8.5	9.3	9.9	10.9	10.1
		75	13.5	14.1	14.3	14.9	15.5	16.3	16.2

^aSignificant Time Trend $P = .05$.

Table 3

Vancomycin Dosing Trends Among Neonates and Pediatric Patients

Population	Parameter	Concentration Epoch							
		0	1	2	3	4	5	6	7
Neonates	Number	1,417	1,344	674	391	253	175	126	80
	Median dose (mg/kg/day)	36.67	35.62	38.44	38.86	43.54	45.36	46.94	51.97
	25th percentile	26.28	26.57	27.81	26.95	29.19	32.86	33.51	38.93
	75th percentile	46.39	45.56	48.53	53.08	57.48	57.89	60.18	66.22
	Median delta dose (mg/kg/day)		0.59	2.96	2.31	3.59	2.94	1.73	2.39
	25th percentile		-3.09	-2.01	-2.99	-1.79	-1.41	-1.82	-2.65
	75th percentile		7.07	8.38	9.47	9.73	10.18	8.10	9.71
	Median daily frequency/day	2.05	2.01	2.13	2.30	2.72	2.89	2.96	3.00
	25th percentile	1.38	1.51	1.71	1.86	1.97	2.01	2.01	2.34
	75th percentile	3.00	2.95	3.00	3.01	3.05	3.12	3.57	3.76
Pediatrics	Median percent change		1.83	8.67	7.29	9.68	7.23	6.99	3.65
	25th percentile		-8.64	-5.22	-7.16	-4.49	-3.39	-3.71	-5.68
	75th percentile		24.91	26.32	28.88	28.88	26.66	18.53	25.60
	Median trough concentration (mcg/mL)		10.6	12.9	12.9	12.5	13.2	13.1	13.0
	25th percentile		6.7	9.0	7.9	9.6	8.7	10.4	10.1
	75th percentile		14.9	16.8	16.2	16.5	16.8	16.4	17.5
	Number	3,471	3,211	1,664	766	419	254	180	118
	Median dose (mg/kg/day)	53.46	57.94	68.61	70.35	68.88	63.27	61.86	59.62
	25th percentile	41.35	45.58	54.35	50.99	47.08	44.80	43.39	42.13
	75th percentile	61.55	68.75	82.71	88.22	90.92	86.59	88.60	89.63
	Median delta dose (mg/kg/day)		4.08	7.66	2.83	1.71	-0.13	-0.15	0.88
	25th percentile		-2.39	0.33	-5.79	-5.35	-7.1	-6.6	-4.99
	75th percentile		13.41	15.77	10.48	9.85	8.70	6.58	7.30
	Median daily frequency/day	3.10	3.20	3.71	3.63	3.39	3.10	3.08	3.07
	25th percentile	2.87	2.93	2.99	2.97	2.87	2.76	2.84	2.72
	75th percentile	3.83	3.83	4.00	3.98	3.98	3.93	3.93	3.95
	Median percent change		8.47	12.93	4.22	2.73	-0.19	-0.27	1.58

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Population	Parameter	Concentration Epoch							
		0	1	2	3	4	5	6	7
	25th percentile		-4.35	0.54	-9.37	-8.13	-11.04	-8.37	-8.03
	75th percentile		28.1	27.47	17.2	16.25	13.46	12.54	13.25
	Median trough concentration (mcg/mL)		8.2	12	13.4	14.3	14.3	14.2	15.0
	25th percentile		5.4	9.1	10.2	11	10.6	11.0	11.4
	75th percentile		12.0	15.4	17.1	17.8	17.4	18.0	18.6

Table 4

Comparison of the Effects of High and Low Trough Concentrations Upon Vancomycin Dosing Stratified by Patient Population and Care Setting

Comparison	Dose Ratio ^a	95% Confidence Interval	P-Value
High concentration vs. low concentration	0.75	0.72–0.79	<.001
High concentrations vs. normal concentration	0.84	0.80–0.87	<.001
Neonatal patients	0.87	0.82–0.91	<.001
Pediatric patients	0.81	0.76–0.86	<.001
Community hospital	0.84	0.79–0.91	<.001
Pediatric hospital	0.83	0.80–0.86	<.001
Difference in hospital response to high concentration (pediatric vs. community)	0.99	0.91–1.07	.73
Difference in response to high concentration (neonatal vs. pediatric patients)	1.07	0.99–1.16	.09
Low concentration vs. normal concentration	1.11	1.09–1.13	<.001
Neonatal patients	1.10	1.07–1.14	<.001
Pediatric patients	1.12	1.09–1.15	<.001
Community hospital	1.14	1.10–1.18	<.001
Pediatric hospital	1.08	1.06–1.10	<.001
Difference in hospital response to high concentration (pediatric vs. community)	0.93	0.90–0.97	.001
Difference in response to high concentration (neonatal vs. pediatric patients)	1.00	0.96–1.04	.07

^aCompares dose ratios from the current dosing epoch to the next dosing epoch (a value of 1.0 indicates no effect on the next dose).

Table 5**Modifications to Vancomycin Therapy in Response to Repeated Abnormal Trough Concentrations**

Parameter	2 Abnormally High ^a Trough Concentrations	2 Abnormally Low ^b Trough Concentrations
All pediatric patients (< 18 years)	n = 112	n = 1,520
Dose increase	30 (27%)	1,147(75%)
Dose increase and decrease	5 (4%)	69 (5%)
Dose decrease	39 (35%)	63 (4%)
No change in dose	38 (34%)	241 (16%)
Neonates (<28 days)	n = 24	n = 404
Dose increase	6 (25%)	289 (72%)
Dose increase and decrease	3 (12%)	32 (8%)
Dose decrease	6 (25%)	28 (7%)
No change in dose	9 (38%)	55 (14%)
Children (> 28 days-18 years)	n = 88	n = 1,116
Dose increase	24 (27%)	858 (77%)
Dose increase and decrease	2 (2%)	37 (3%)
Dose decrease	33 (38%)	35 (3%)
No change in dose	29 (33%)	186(17%)

^a Abnormally high trough concentrations were defined as a serum vancomycin concentration >20 µg/mL.

^b Abnormally low trough concentrations were established based on guideline recommendations. Prior to publication of the 2011 pediatric guidelines, trough concentrations < 10 µg/mL for critically-ill patients and <5 µg/mL for all other patients were defined as abnormally low.^{8,15} Following publication of the 2011 pediatric guidelines, trough concentrations < 15 µg/mL for critically-ill patients and < 10 µg/mL for all other patients were defined as abnormally low.⁷