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Prospective validation of neonatal vancomycin dosing regimens is urgently needed

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ABSTRACT

Background: Although vancomycin is frequently used to treat neonatal late-onset sepsis, there is no consensus on the optimal dosing regimen. Because many neonates needed dosing adaptation due to suboptimal trough values, the vancomycin dosing regimen in our neonatal department was changed during 2012.

Objective: We aimed to document the need for validation of neonatal vancomycin dosing by exploring serum trough levels achieved using 2 published dosing regimens (previous regimen: based on postmenstrual age and serum creatinine and new regimen: based on postmenstrual age and postnatal age) and to identify covariates associated with suboptimal vancomycin trough levels (< 10 mg/L).

Methods: Routine therapeutic drug monitoring serum trough levels quantified after initiation of intravenous vancomycin therapy and clinical covariates were retrospectively collected. Median vancomycin trough levels of both dosing regimens were compared using the Mann-Whitney *U* test. The influence of continuous and dichotomous covariates on achieving a suboptimal trough level was explored using the Van Elteren test (stratified Mann-Whitney *U* test) and Mantel-Haenszel test (stratified χ^2 test), respectively. Covariates significant in monovariate analysis were subsequently included in a logistic regression analysis.

Results: In total, 294 observations (median current weight 1870 g [range = 420–4863 g] and median postmenstrual age 35.07 weeks [range = 25.14–56.00 weeks]) were included. Using the previous and new dosing regimens, 66.3% and 76.2% of trough levels, respectively, were below 10 mg/L. Overall, suboptimal vancomycin trough values were significantly associated with lower weight (birth weight and current weight) and age (gestational age and postmenstrual age).

Conclusions: The majority of vancomycin trough levels in neonates achieved using 2 published dosing regimens did not reach the target of 10 mg/L. This illustrates the urgent need for prospective validation of neonatal vancomycin dosing regimens. We anticipate that dosing regimens integrating covariates reflecting general physiological maturation and renal maturation, as well as disease characteristics, could improve vancomycin exposure in neonates.

Introduction

According to the Neonatal Research Network of the National Institute of Child Health and Human Development, 21% of very–low-birth weight infants experience at least 1 episode of late-onset sepsis (LOS), a major cause of morbidity and mortality in this specific population. Gram-positive bacteria are the most common isolated pathogens (70%) causing LOS, with coagulase-negative staphylococci accounting for 48% of the isolates.[1] Vancomycin, a glycopeptide antibiotic, is frequently used to treat these pathogens. However, an optimal vancomycin dosing regimen for neonates is not available and prospective validation of published dosing guidelines is lacking.

In adults, an AUC_{0-24} divided by the MIC for a given pathogen ≥ 400 is considered to be the best predictor of vancomycin efficacy.[2,3] During routine clinical care, vancomycin serum trough concentrations are used as a surrogate marker for AUC, aiming to

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Table I
Intermittent vancomycin dosing regimens* for neonates as retrieved in reference handbooks.[4–12]

Reference	PMA (wk)	PNA (d)	Current weight (g)	Creatinine (mg/dL)	Dose (mg/kg)	Interval (h)
Neofax® 2011[4] and	≤ 29	0–14			10 (bacteremia),	18
The Harriet Lane Handbook 2012[5] and		> 14			15 (meninigitis)	12
The Sanford guide 2012-2013[6]	30–36	0–14				12
		> 14				8
	37–44	0–7				12
		> 7				8
	≥ 45	any PNA				6
British National Formulary for children 2011[7]	< 29				15	24
	29–35					12
	> 35					8
Neonatal Formulary 2011[8]	< 29 GA	0–7			15	24
		> 7				12
	29–35					12
	36–44					8
	> 44					6
Dutch Children's Formulary[9]		< 7			10	12
		7–28				8
Nelsons's texbook of Pediatrics 2007[10]		≤ 7	< 1200		15	24
			1200–2000		7.5–11.3	12–18
			> 2000		15	12
			Any weight			12 (Meningitis)
		> 7	< 1200			24
			1200–2000		5–7.5	8–12
			> 2000		15	8
		7–28	Any weight		10 -15	8 (Meningitis)
Red Book 2012[11]				< 0.7	15	12
				0.7–0.9	20	24
				1–1.2	15	24
				1.3–1.6	10	24
				> 1.6	15	48
Neonatal and pediatric pharmacology 2011		< 7	< 1200		15	24
(Drug formulary for the newborn)[12]			1200–2000		10–15	12–18
			> 2000			8–12
		> 7	< 2000			8–12
			> 2000		15–20	8

GA = gestational age in the footnote, PMA = postmenstrual age, PNA = postnatal age.

* Data are adapted to mg/kg/dose.

achieve trough levels above 10 mg/L during intermittent intravenous administration.[3] In neonates, there is no firm correlation between serum trough levels and vancomycin efficacy. Consequently serum vancomycin target levels for this special population are derived from adults. However, neonates differ from adults based on their body composition, maturation aspects, specific physiology, and diseases. Furthermore, neonates are considered immunocompromised hosts due to the immaturity of their innate immune system.

The fact that we have been using vancomycin in neonatal care for more than half a century, but are still searching for the optimal dosing regimen and efficacy targets confirms the complexity of neonatal vancomycin pharmacology. These deficits can also be noticed in daily clinical care. First of all, clinicians are confronted with a diversity of dosing regimens presented in commonly used handbooks (Table I).[4–12] Second, subtherapeutic vancomycin trough levels are still frequently observed in neonates.

Because many neonates displayed vancomycin trough levels below the target value (needing subsequent dosing adaptation) when using a previously published postmenstrual age (PMA) and serum creatinine-based dosing regimen,[13] we decided to introduce the PMA and postnatal age (PNA)-based Neofax® dosing approach in our neonatal department during 2012 as new vancomycin dosing regimen.[4] To illustrate the need for prospective validation of neonatal vancomycin dosing regimens, we explored serum trough levels achieved using both dosing approaches and, by pooling all observations, we aimed to identify covariates associated with vancomycin serum trough levels below 10 mg/L in neonates and young infants.

Patients and Methods

Study population, data collection, and ethics

Vancomycin therapeutic drug monitoring (TDM) observations of neonates and young infants treated with intravenous vancomycin, mainly for (suspected) LOS (ie, > 72 hours after birth), in the neonatal intensive care unit of the University Hospitals Leuven, Leuven, Belgium, between June 2011 and December 2012, were considered for inclusion in our retrospective study. Our patient population consists of (pre)term neonates, inborn or transferred, in need of specialized care related to prematurity, infections, perinatal asphyxia, congenital diseases (eg, surgery for cardiopathy, congenital diaphragmatic hernia, or esophageal atresia), or other diseases. Clinical characteristics at birth (eg, gestational age [GA] in weeks, birth weight in grams), as well as characteristics at the moment of TDM (PMA in weeks), PNA (in days), current weight (in grams), concurrent treatment with ibuprofen (yes/no) or dopamine (yes/no), respiratory support (continuous positive airway pressure or mechanical ventilation) (yes/no), mechanical ventilation (conventional or high frequency) (yes/no), patent ductus arteriosus (yes/no), positive blood culture (yes/no), serum creatinine concentration (in milligrams per deciliter), serum

Table II
The 2 vancomycin dosing regimens evaluated in this study. (A) Previous dosing regimen (2011) based on postmenstrual age (PMA) and serum creatinine, published by Anderson et al.[13] B) New dosing regimen (2012, Neofax®[4]) based on PMA and postnatal age (PNA) and limited to sepsis indication.

(A)

PMA (wk)	Creatinine (mg/dL)	Dose (mg/kg)	Interval (h)
< 29		15	24
29–35	< 0.6	15	12
	> 0.6		24
> 35	< 0.6	15	8
	> 0.6		12

(B)

PMA (wk)	PNA (d)	Dose (mg/kg)	Interval (h)
≤ 29	0–14	10	18
	> 14		12
30–36	0–14	10	12
	> 14		8
37–44	0–7	10	12
	> 7		8
> 45	All	10	6

albumin concentration (in grams per liter), and serum vancomycin concentration (in milligrams per liter) were extracted from the patient files. The daily nursing progress reports were used to collect data regarding vancomycin prescription (dose and interval). Results were excluded if data regarding vancomycin prescription could not be obtained or in case of an administration or sampling time error. We aimed to document early vancomycin exposure (ie, after 24 hours of treatment initiation), therefore only first trough levels were included. The ethics board of our hospital approved the study protocol.

Vancomycin indication, administration, and TDM assay

Vancomycin (Vancocin, Elly Lilly, Brussels, Belgium)® combined with amikacin, is used as standard therapy for (suspected) late onset sepsis in our department and administration occurs as an intravenous infusion over 60 minutes. Add-on therapy of vancomycin for other indications (eg, severe early onset sepsis or prophylaxis) is limited. The previous vancomycin dosing regimen (based on PMA and creatinine) (Table II**A**) was used between June 2011 and June 2012.[13] The new dosing regimen (based on PMA and PNA) (Table II**B**) was introduced during June 2012.[4] Because we noticed no improvement in trough levels during clinical practice, we believed it to be inappropriate to continue with this new regimen. Therefore, only data up to December 2012 were available for inclusion. As part of routine clinical care, blood samples for TDM were collected at the end of the dosing interval, in most cases 24 hours after treatment onset. Serum vancomycin assay was performed either with a particle-enhanced turbidimetric inhibition immunoassay method (Siemens Dimension; Dade Behring, Deerfield, Illinois) (June 2011–October 2012) or with an enzyme multiplied immunoassay technique (Cobas c702; Roche Diagnostics, Basel, Germany) (November 2012–December 2012). During November 2012, the assay was changed throughout the entire hospital for unrelated (ie, no clinical) reasons. The hospital laboratory has a quality system that conforms to ISO15189. This implies clinical interchangeability of results is verified when changing from 1 assay to another. To avoid censoring of values below the lower limit of quantification (2 mg/L), these concentrations were replaced by a lower limit of quantification/2 (ie, 1 mg/L) as suggested in the literature.[14] An enzymatic technique (Cobas c702 module) was used to quantify serum creatinine levels.[15] A colorimetric method (bromcresol green) was used to quantify serum albumin concentrations.

Statistical analysis

Comparison of continuous clinical characteristics as well as median vancomycin serum trough level between observations of both dosing regimens was determined using the Mann-Whitney *U* test. Comparison of dichotomous covariates was done by χ^2 test.

On the total dataset, the influence of continuous and dichotomous covariates on achieving suboptimal trough levels (< 10 mg/L) was explored using the Van Elteren test (stratified Mann-Whitney *U* test) and Mantel-Haenszel test (stratified χ^2 test), respectively. Stratification was done for dosing regimen. Covariates significantly associated with suboptimal vancomycin trough levels in monovariate analysis were entered in a logistic regression analysis. Spearman correlation was used to evaluate relations between continuous variables before inclusion in the logistic regression analysis. A P value < 0.05 was considered statistically significant.

Vancomycin serum trough levels and clinical characteristics were presented as median and range or incidence. Statistical analyses were performed using MedCalc12 (MedCalc Software, Mariakerke, Belgium) and the coin package in R version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Dataset

In total, 593 TDM observations were obtained in 223 patients. Sixty-one observations were excluded based on criteria summarized in **Figure 1**. Another 238 observations, collected after dosing adjustments, were also excluded. The final dataset comprised 294 vancomycin TDM observations: 193 observations of the previous (2011) dosing regimen, 101 of the new (2012) dosing regimen. Both cohorts had comparable clinical characteristics, but differences for serum albumin and creatinine were documented (**Table IIIA**). Taking into account the 294 vancomycin treatment episodes, indications to start vancomycin were (suspected) sepsis (87.7%, of which 8.8% were early onset cases [≤ 72 hours after birth] and 78.9% were late onset cases), presence of foreign body material (eg, thoracic drain or pacemaker [2.4%], prophylaxis such as perforation umbilical catheter or disconnection ventricular-external drain [2.7%], [sub]cutaneous wound infection [3.4%], pneumonia [3.1%], or unknown [0.7%]. Incidences of indications stratified by dosing regimen and by age at initiation of therapy are presented in **Table IIIB**.

Sixteen vancomycin trough values were below the lower limit of quantification. Median vancomycin concentration of samples achieved using the same dosing regimen (Neofax®), but with different vancomycin quantification assays used during the study period, were compared and did not differ significantly (5.9 mg/L Behring vs 5.5 mg/L Roche; Mann-Whitney *U* test, $P = 0.773$).

Previous versus new dosing regimen

The previous dosing regimen (Table II) resulted in a significantly higher vancomycin trough concentration compared with the new regimen (median 7.8 mg/L [range = 1–37.8 mg/L] vs median 5.8 mg/L (range = 1–20.1 mg/L) (**Figure 2**). In the previous regimen, 128 out of 193 (66.32%) of observations were < 10 mg/L and 65 out of 193 (33.68%) were ≥ 10 mg/L. In the new regimen, 77 out of 101 (76.24%) of observations were < 10 mg/L and 24 out of 101 (23.76%) reached levels ≥ 10 mg/L.

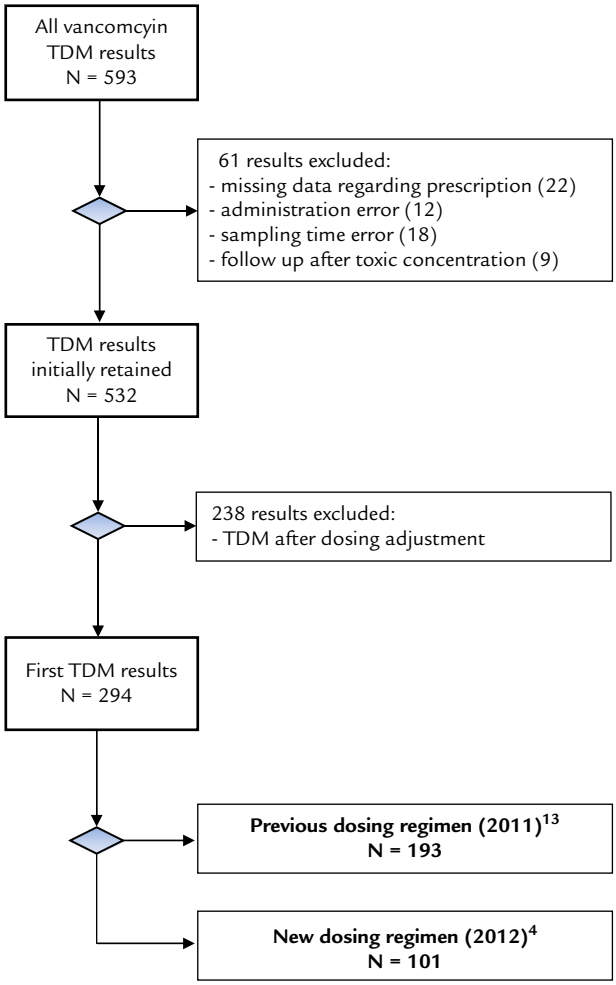

Figure 1. Flowchart of included vancomycin therapeutic drug monitoring (TDM) observations.

Table IIIB
Indications to start vancomycin therapy. Differences in incidences between both dosing regimens were explored using χ^2 test.

Vancomycin indication	Previous dosing regimen (n = 193)	New dosing regimen (n = 101)	P*
	Incidence (%)		
Early (≤ 72 h after birth)	26/193 (13.47)	15/101 (14.85)	0.8830
Foreign body material	4 (2.07)	3 (2.97)	0.9388
Prophylaxis	2 (1.04)	2 (1.98)	0.8939
(Suspected) EOS	16 (8.29)	10 (9.90)	0.8059
(Sub)cutaneous wound infection	4 (2.07)	0	0.3541
Late (> 72 h after birth)	167/193 (86.53)	86/101 (85.15)	0.8830
Prophylaxis	3 (1.55)	1 (0.99)	0.8939
(Suspected) LOS	150 (77.72)	82 (81.19)	0.5880
(Sub)cutaneous wound infection	4 (2.07)	2 (1.98)	0.7031
Pneumonia	8 (4.15)	1 (0.99)	0.2564
Unknown	2 (1.04)	0	0.7799

EOS = early onset sepsis; LOS = late onset sepsis; n = number of observations.
* $P < 0.05$ was considered statistically significant.

Clinical characteristics associated with (sub)optimal trough levels

Overall, 205 out of 294 (69.73%) vancomycin trough levels were < 10 mg/L, whereas 89 out of 294 (30.27%) reached levels ≥ 10 mg/L. Clinical characteristics of both groups (ie, trough level < 10 vs ≥ 10 mg/L) are presented in Table IV. Lower age (GA and PMA), lower weight (birth weight and current weight), and higher PNA were significantly associated with suboptimal trough levels and these covariates were considered for inclusion in a logistic regression analysis. High correlation coefficients were documented between PMA and GA ($r = 0.83$), and between birth weight and current weight ($r = 0.89$). Because PMA combines GA (representing

Table IIIA
Clinical characteristics of included vancomycin trough concentrations achieved by the previous versus the new dosing regimen. To explore continuous and dichotomous covariates between both cohorts, Mann–Whitney *U* test and χ^2 test were used, respectively.*

Covariate	Previous dosing regimen (n = 193)	New dosing regimen (n = 101)	P†
Continuous			
Gestational age (wk)	32.86 (24.57–41.43)	32.14 (24.86–41)	0.9862
Postnatal age (d)	13 (1–169)	12 (2–121)	0.4445
Postmenstrual age (wk)	34.71 (25.14–49.86)	35.29 (25.43–56)	0.5950
Birth weight (g)	1540 (420–4680)	1850 (440–4150)	0.3821
Current weight (g)	1818 (500–4715)	2060 (420–4863)	0.9237
Albumin (g/dL)	31.95 (17.40–50.40)‡	31 (12.90–39.70)§	0.0290
Creatinine (mg/dL)	0.43 (0.14–1.18)‖	0.49 (0.13–1.19)¶	0.0429
Dichotomous			
Patent ductus arteriosus	12/153	5/80	0.8581
Concurrent ibuprofen	10/193	6/101	0.9985
Concurrent dopamine	22/193	11/101	0.9494
Positive blood culture	64/192	30/101	0.6163
Respiratory support	130/193	71/101	0.7020
Invasive respiratory support	80/193	42/101	0.9183

n = number of observations.
* Data are presented as median and range (continuous covariates) or incidence (dichotomous covariates).
† $P < 0.05$ was considered statistically significant.
‡ n = 164.
§ n = 89.
‖ n = 178.
¶ n = 93.

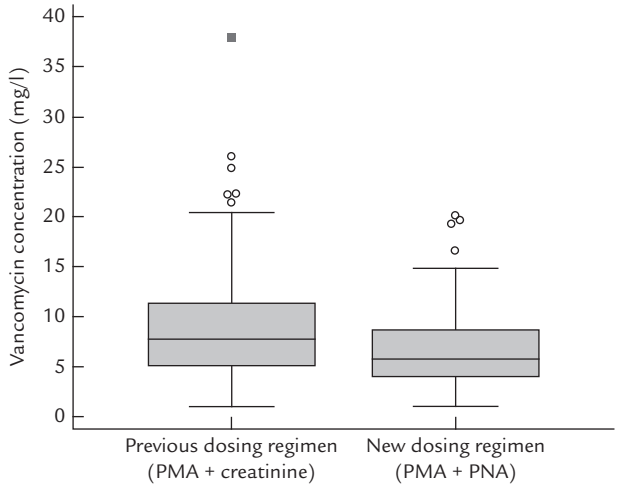

Figure 2. Vancomycin serum trough concentrations (in milligrams per liter) achieved by the 2 vancomycin dosing regimens used in our neonatal department, presented as boxplots (Mann-Whitney *U* test, $P < 0.05$). PMA = postmenstrual age; PNA = postnatal age.

prenatal maturation) and PNA (representing postnatal maturation), GA was retained for inclusion instead of PMA. Because vancomycin is usually not administered in the first days of life, current weight was chosen instead of BW. The final covariates entered in the logistic regression analysis were GA, PNA, current weight, and dosing regimen. Results of the analysis are presented in Table V.

Discussion

Up to 70% of vancomycin serum trough levels in neonates and young infants, achieved using 2 published dosing regimens for intermittent intravenous vancomycin administration, were below the target level of 10 mg/L. This finding illustrates the urgent need for optimization with subsequent prospective validation of suggested vancomycin dosing regimens in this specific population.

We documented that weight (birth weight and current weight) and age (GA, PMA, and PNA)—both reflecting ontogeny—were major covariates associated with vancomycin serum trough levels in neonates (Table IV). This can be explained by the fact that developmental changes in physiology are most prominent in early life and influence drug disposition (ie, pharmacokinetics).[16,17] Especially small (low birth weight, current weight) and immature (low GA, PMA) babies showed vancomycin trough concentrations below 10 mg/L. Their higher body water content, resulting in a larger distribution volume for hydrophilic drugs (eg, vancomycin) compared with older neonates, infants, and adults, can in part contribute to the low TDM values observed. Besides changes in body composition with increasing age, also renal function (and consequently renal drug clearance) displays maturation. This maturation is related to conditions at birth (eg, birth weight and GA) and conditions after delivery (eg, PNA, ibuprofen administration, and perinatal asphyxia).[18,19] The role of renal tubular functions on neonatal drug clearance—and more specifically on vancomycin clearance—is at present not yet unveiled.

The same holds true for the influence of specific diseases on vancomycin disposition in neonates. To illustrate this, the vancomycin trough value of 37.8 mg/L (outlier on **Figure 2**) was documented in a girl with GA 39 weeks and PNA 4 days, during the rewarming phase after hypothermia therapy for severe perinatal asphyxia. Because C-reactive protein levels increased while receiving amikacin and amoxicillin, vancomycin was added on day 3. Serum creatinine was normal and amikacin trough level was only slightly elevated (4.1 mg/L). Vancomycin prescription, administration, and TDM sampling times were in line with our local procedures, but an error in drug handling before administration cannot be excluded. Although asphyxia itself can impair renal function and hypothermia can reduce renal blood flow (and consequently renal drug clearance)[20,21] the influence of these events on neonatal vancomycin disposition is at present unknown.

We anticipate that optimized neonatal vancomycin dosing regimens should take into account covariates representing maturation but also disease characteristics[22] and coadministration of drugs influencing renal function, but these covariates are not yet well considered in the currently proposed dosing regimens.

Besides the above-mentioned patient-specific characteristics, the absence of optimal vancomycin efficacy targets, drug-specific characteristics, and quantification assays used can also contribute to variability in neonatal vancomycin exposure and can complicate

Table IV
Clinical characteristics of all included vancomycin trough concentrations as well as for the subgroups with trough concentrations < or ≥ 10 mg/L. To explore the influence of continuous and dichotomous covariates on achieving vancomycin trough concentrations < or ≥ 10 mg/L, the Van Elteren test (stratified Mann-Whitney *U* test) and Mantel-Haenszel test (stratified χ^2 test) was used, respectively. Stratification was done for dosing regimen.*

Covariates	All TDM data (n = 294)	TDM < 10 mg/L (n = 205)	TDM ≥ 10 mg/L (n = 89)	Test	*P*
Continuous				*k*	
Gestational age (wk)	32.29 (24.57–41.43)	31 (24.57–41)	35.71 (24.86–41.43)	23.95	< 0.0001†
Postnatal age (d)	13 (1–169)	15 (1–169)	10 (1–102)	8.25	0.0041†
Postmenstrual age (wk)	35.07 (25.14–56)	33.28 (25.14–56)	38.28 (25.43–53.28)	14.11	0.0002†
Birth weight (g)	1575 (420–4680)	1435 (420–4150)	2380 (440–4680)	26.51	< 0.0001†
Current weight (g)	1870 (420–4863)	1567 (487–4715)	2535 (420–4863)	21.03	< 0.0001†
Albumin (g/dL)	31.60 (12.90–50.40)	32 (12.9–50.4)	31.15 (18.4–42.9)	1.38	0.2399
Creatinine (mg/dL)	0.43 (0.13–1.19)	0.43 (0.23–1.18)	0.43 (0.13–1.19)	2.55	0.1103
Dichotomous				χ^2	
Patent ductus arteriosus	17/233 (7.3%)	13/172	4/61	0.0001	0.9939
Concurrent ibuprofen	16/294 (5.4%)	11/205	5/89	0.027	0.8688
Concurrent dopamine	33/294 (11.2%)	23/205	10/89	0.037	0.8478
Positive blood culture	94/293 (32.1%)	72/205	22/88	2.655	0.1032
Dosing regimen (previous/new)	193 (65.6%) / 101(34.4%)	128/77	65/24	2.628	0.1044‡
Respiratory support	201/294 (68.4%)	136/205	65/89	1.1052	0.2931
Invasive respiratory support	122/294 (41.5%)	77/205	45/89	3.8257	0.0505

χ^2 = test statistic Mantel-Haenszel test; *k* = test statistic Van Elteren test; n = number of observations; TDM = therapeutic drug monitoring.

* Data are presented as median and range (continuous covariates) or incidence (dichotomous covariates). In all tests, degrees of freedom were equal to 1.

† Statistically significant at $P < 0.05$.

‡ To explore the impact of dosing regimen on achieving trough concentrations < or ≥ 10 mg/L, standard χ^2 was used.

Table V
Logistic regression analysis with vancomycin serum trough levels < 10 mg/L ($= 1$) or ≥ 10 mg/L ($= 0$) as the dependent variable. Two hundred ninety-four vancomycin serum trough levels were included.*

Covariate	Coefficient β	SE	*P*	OR	95% CI
Constant	2.8523	1.6130	0.0770	17.327	
Gestational age	−0.0486	0.0616	0.4296	0.9525	0.8443–1.0747
Postnatal age	0.0220	0.0088	0.0113†	1.0222	1.0050–1.0397
Current weight	−0.0005	0.0003	0.1049	0.9995	0.9990–1.0001
Dosing regimen	0.6363	0.3008	0.0344†	1.8895	1.0478–3.4075

OR = odds ratio.

* Degrees of freedom were equal to 1 for all covariates.

† $P < 0.05$ was considered statistically significant.

the development of adequate dosing regimens.[23,24] First, there is no clear relationship between clinical response and indices of systemic vancomycin exposure in neonates. Based on studies in adults, an AUC_{0-24}/MIC ratio ≥ 400 has been recommended to achieve effectiveness. In clinical practice, vancomycin trough concentrations are used as surrogate marker and should be kept above 10 mg/L to correspond with an AUC_{0-24}/MIC ratio ≥ 400, if the MIC is < 1 mg/L.[3,24,25] This assumption is derived from adults receiving 12-hourly vancomycin dosing. Moreover, trough concentrations depend on dose frequency.[26] In neonates, it is unknown what the optimal trough targets should be. Although some authors recommend directly monitoring AUC, the optimal parameter for vancomycin efficacy in neonates and young children remains unresolved.[26–29]

It should be emphasized that the staphylococcal targets (coagulase-negative staphylococci) for vancomycin use in neonates and their corresponding local MIC values are not comparable with the adult setting in which vancomycin is predominantly used to cure methicillin-resistant *Staphylococcus aureus* infection.[30] Second, vancomycin is bound to albumin and immunoglobulin A in plasma and only the unbound drug is pharmacologically active. However, data in neonates concerning the extent of protein binding as well as the disposition of vancomycin in deep body compartments are limited. We would like to stress that these pharmacokinetic aspects need further research to improve insight into the behavior of vancomycin in neonates. Finally, currently used analytical methods for vancomycin quantification contribute to variability in TDM results and limit the transferability of vancomycin pharmacokinetic models—and subsequently model-derived dosing regimens—to other centers.[31,32] Therefore, the introduction of a more precise method, such as liquid chromatography-tandem mass spectroscopy (LC-MS/MS), which is considered to be the gold standard reference method, should be considered.[33,34] The high specificity, sensitivity, and accuracy of LC-MS/MS makes it more suitable for pharmacokinetic studies compared with immunoassays, which in general suffer from nonspecific interference from related compounds or matrix effects[33,35,36] or, in the case of vancomycin, its crystalline degradation products. High instrument costs, greater technical complexity, speed, and turnaround of sample analysis, are considered as the main disadvantages of LC-MS/MS. However, careful choice of sample preparation method and internal standard, and validation of assays, should be able to avoid the majority of pitfalls.[33] Bijleveld et al[36] recently reported that LC-MS/MS documented slightly lower vancomycin concentrations than Fluorescence Polarization Immunoassay. However, the applicability of their LC-MS/MS was only tested in 3 neonatal patients.[36] Therefore, paired analysis of neonatal vancomycin plasma concentrations using immunoassay versus LC-MS/MS in a large neonatal cohort is currently not yet available, but could be of relevance to optimize neonatal vancomycin dosing.

During the past decade, several neonatal vancomycin dosing regimens have been proposed. The previous dosing regimen used in our unit seemed to be slightly better than the Neofax® regimen, but both were unable to reach sufficient median vancomycin trough levels. As soon as preliminary results of our study were available, we decided to reintroduce the previous approach (based on PMA and serum creatinine) until prospectively validated improved dosing appears. Our observations are, to a certain extent, in line with Badran et al,[37] who documented that only 51% of neonates attained a predefined vancomycin trough level between 5 and 10 mg/L using the Neofax® vancomycin dosing regimen and 33% of their trough concentrations were below 5 mg/L.

We are aware that our analysis is only based on trough levels quantified after initiation of therapy because we aimed to achieve drug levels in the target range within a short time. We consider our covariate analysis as exploratory. More precise and predictive analyses require a population pharmacokinetic modelling approach in which available pharmacokinetic data can be used for the exploration of the most optimal vancomycin pharmacodynamic target in neonates, as well as for Monte Carlo simulations exploring different vancomycin administration modes (eg, loading dose in intermittent dosing) to achieve early targeted vancomycin exposure. However, this is beyond the intention of our study. Nevertheless, the large study size and the comparison of 2 recently published vancomycin dosing regimens to document the emergence of prospective validation of neonatal vancomycin dosing are relevant strengths.

We conclude that 66.3% and 76.2% of vancomycin trough levels in neonates achieved using 2 published dosing regimens did not reach the target of 10 mg/L. This is relevant, but just 1 of the problems related to vancomycin treatment of neonates. Prospective validation of vancomycin dosing regimens, but also further exploration of pharmacokinetic (eg, protein binding, influence of renal [tubular] functions on clearance) and pharmacodynamic (eg, optimal exposure targets) aspects of vancomycin in neonates is urgently needed.

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Conflicts of Interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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