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 χ² 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.

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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. 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 AUC0–24 divided by the MIC for a given pathogen ≥ 400 is considered to be the best predictor of vancomycin efficacy. During routine clinical care, vancomycin serum trough concentrations are used as a surrogate marker for AUC, aiming to
achieve trough levels above 10 mg/L during intermittent intravenous administration. 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 1). 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, 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. 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 cardiopulmonary, 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

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**Table 1**

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® 20114 and | ≤ 29 | 0–14 | | 10 (bacteremia), | 8 | | |
| The Harriet Lane Handbook 2012 and | > 14 | | | 12 | | | |
| The Sanford guide 2012–2013 | 30–36 | 0–14 | | 12 | | | |
| | 37–44 | 0–7 | | 8 | | | |
| | ≥ 45 | > 7 | | 8 | | | |
| British National Formulary for children 2011 | ≤ 29 | | | 24 | | | |
| | 29–35 | | | 12 | | | |
| | > 35 | | | 8 | | | |
| Neonatal Formulary 2011 | ≥ 29 GA | 0–7 | | 24 | | | |
| | > 7 | | | 12 | | | |
| | 29–35 | | | 8 | | | |
| | 36–44 | | | 6 | | | |
| Dutch Children’s Formulary | | c < 7 | | 12 | | | |
| | 7–28 | | | 8 | | | |
| Nelson’s textbook of Pediatrics 2007 | ≤ 7 | | | 24 | | | |
| | ≤ 1200 | 15 | | 12 | | | |
| | > 1200 | | | 12 | | | |
| | 1200–2000 | 15 | 7.5–11.3 | 12 | | | |
| | Any weight | | | 24 | | | |
| | > 7 | | | 12 | | | |
| | ≤ 1200 | 15 | 5–7.5 | 8–12 | | | |
| | > 2000 | 15 | | 8 | | | |
| | Any weight | | | 8 | | | |
| Red Book 2012 | 7–28 | | | 12 | | | |
| | < 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 | | | | | | | |
| (Drug formulary for the newborn) | | | | | | | |
| | < 7 | | | 24 | | | |
| | ≤ 1200 | 15 | | 12 | | | |
| | > 1200–2000 | | | 12 | | | |
| | > 2000 | | | 8–12 | | | |
| | < 2000 | | | 8–12 | | | |
| | > 2000 | | | 8 | | | |

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

* Data are adapted to mg/kg/dose.
Vancomycin indication, administration, and TDM assay

Vancomycin (Vancocin, Elly Lilly, Brussels, Belgium)\(^6\) 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 postmenstrual age (PMA) and serum creatinine, published by Anderson et al.\(^7\)) was used as standard therapy for (suspected) late onset sepsis. Therefore, only first trough levels were included. The ethics board of our hospital approved the study protocol.

### Vancomycin indication, administration, and TDM assay

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

As trough levels were collected at the end of the dosing interval (ie, after 24 hours of treatment initiation), therefore only first trough levels were included. The ethics board of our hospital approved the study protocol.

### 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.

### Vancomycin serum trough levels and clinical characteristics

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

### 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 \(\chi^2\) 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 \(\chi^2\) 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).

### 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.
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 (i.e., 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 gestational age) and postnatal age, it was used as a covariate in the regression analysis.

### Table IIIA

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 (i.e., 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 gestational age) and postnatal age, it was used as a covariate in the regression analysis.

| 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 (12–121)                 | 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.

‡ $n = 164$.

§ $n = 89$.

|| $n = 178$.

¶ $n = 93$. 

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### Table IIB

Indications to start vancomycin therapy. Differences in incidences between both dosing regimens were explored using χ² test.

| Vancomycin indication | Previous dosing regimen (n = 193) | New dosing regimen (n = 101) | $P$  |
|-----------------------|----------------------------------|-----------------------------|------|
| 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|
| (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|
| (Sub)cutaneous wound infection | 4 (2.07) | 2 (1.98) | 0.7031|
| Pneumonia              | 8 (4.15) | 1 (0.99) | 0.2564|

EOS = early onset sepsis; LOS = late onset sepsis; $n =$ number of observations.

* $P < 0.05$ was considered statistically significant.

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Figure 1. Flowchart of included vancomycin therapeutic drug monitoring (TDM) observations.
prenatal maturation) and PNA (representing postnatal matura-
tion), 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 rewarminh 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, administra-
tion, 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 matu-
ration but also disease characteristics22 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

| Covariates | All TDM data (n = 294) | TDM < 10 mg/L (n = 205) | TDM ≥ 10 mg/L (n = 89) | Test  | P     |
|------------|-----------------------|------------------------|-----------------------|-------|-------|
|            |                       |                        |                       | k     |       |
| Continuous |                       |                        |                       |       |       |
| 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 (440–6860)       | 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 (0.13–119)      | 0.43 (0.23–118)        | 0.43 (0.13–119)       | 2.55  | 0.1103 |
|            |                       |                        |                       |       |       |
| Dichotomous |                       |                        |                       |       |       |
| 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                 | 2.635 | 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 |

*χ²* 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 χ² was used.
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 AUC₀–₂₄/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 AUC₀–₂₄/MIC ratio ≥ 400, if the MIC is < 1 mg/L.²³,²⁴,²⁵ 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 spectrometry (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.³¹ 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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**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        | 0.0363        | 0.0308| 0.0344†| 1.3885| 1.0478–3.4075 |

OR = odds ratio.

* Degrees of freedom were equal to 1 for all covariates.
† P < 0.05 was considered statistically significant.
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