

## REVIEW

# Clinical pharmacokinetics of vancomycin in the neonate: a review

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Neonatal sepsis is common and is a major cause of morbidity and mortality. Vancomycin is the preferred treatment of several neonatal staphylococcal infections. The aim of this study was to review published data on vancomycin pharmacokinetics in neonates and to provide a critical analysis of the literature. A bibliographic search was performed using PubMed and Embase, and articles with a publication date of August 2011 or earlier were included in the analysis. Vancomycin pharmacokinetic estimates, which are different in neonates compared with adults, also exhibit extensive inter-neonatal variability. In neonates, several vancomycin dosing schedules have been proposed, mainly based on age (i.e., postmenstrual and postnatal), body weight or serum creatinine level. Other covariates [e.g., extracorporeal membrane oxygenation (ECMO), indomethacin or ibuprofen, and growth restriction] of vancomycin pharmacokinetics have been reported in neonates. Finally, vancomycin penetrates cerebrospinal fluid (range=7-42%). Renal function drives vancomycin pharmacokinetics. Because either age or weight is the most relevant covariate of renal maturation, these covariates should be considered first in neonatal vancomycin dosing guidelines and further adjusted by renal dysfunction indicators (e.g., ECMO and ibuprofen/indomethacin). In addition to the prospective validation of available dosing guidelines, future studies should focus on the relevance of therapeutic drug monitoring and on the value of continuous vancomycin administration in neonates.

**KEYWORDS:** Pharmacokinetics; Vancomycin; Neonate; Developmental pharmacology; Covariates.

Pacifici GM, Allegaert K. Clinical pharmacokinetics of vancomycin in the neonate: a review. Clinics. 2012;67(7):831-837.

Received for publication on November 22, 2011; First review completed on January 11, 2012; Accepted for publication on March 5, 2012

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## INTRODUCTION

Neonates have a higher risk of nosocomial infections due to humoral, cellular and myeloid cell functions combined with the use of invasive techniques (e.g., central venous catheter and endotracheal intubation) (1). Because neonatal bacterial sepsis has mortality rates of 10-20% and causes morbidity in 25-30% of survivors (2,3), effective and tolerated antimicrobiologic treatment regimens are required. Coagulase-negative *Staphylococci* and *Staphylococcus aureus* are common nosocomial bacterial pathogens, and vancomycin is the first-choice antibiotic to treat these pathogens, especially in methicillin-resistance settings (4). Vancomycin is active against gram-positive bacteria. *Staphylococcus epidermidis*, including methicillin-resistant strains, are inhibited by vancomycin concentrations of 1-4 µg/ml. *Staphylococcus pyogenes*, *Streptococcus pneumoniae*, and *Streptococcus viridans* are susceptible to 2 µg/ml vancomycin. *Bacillus spp.* are inhibited by 2 µg/ml, *Corynebacterium spp.* by 0.04-3.1 µg/ml and *Clostridium spp.* by 0.39-6 µg/ml vancomycin (5). Peak and trough concentrations of vancomycin should be <40 µg/ml

and <10 µg/ml, respectively, to both be effective and avoid oto- or nephrotoxicity in adults (6,7,8). Because vancomycin activity is primarily time-dependent, the 24-h area under the curve (AUC<sub>0-24h</sub>) divided by the minimum inhibitor concentration (MIC) value (AUC<sub>0-24h</sub>/MIC) is a better predictor of efficacy. In adults with MIC values less than 1 µg/ml, trough concentrations greater than 10 µg/ml result in AUC<sub>0-24h</sub>/MIC values >400.

In subsequent analyses addressing clinical pharmacology, it is important to note that vancomycin is water-soluble, has a limited plasma protein binding capacity (i.e., IgA and albumin) and is mainly eliminated renally by glomerular filtration, although its elimination is further modulated by renal tubular transport (4). Compared with adults, neonates have a higher extracellular fluid volume and a limited renal elimination capacity (4,9). Consequently, vancomycin pharmacokinetics are different in neonates and undergo significant alterations as neonates mature. We aimed to provide a summary of published observations on vancomycin pharmacokinetics in neonates and a subsequent discussion on areas of further research.

## BIBLIOGRAPHIC SEARCH

The bibliographic search was performed electronically using PubMed and Embase. Searches were performed with the following keywords: "pharmacokinetics vancomycin neonate"; "continuous infusion vancomycin neonate";

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No potential conflict of interest was reported.

**Table 1 - Vancomycin dosage guidelines developed by Grimsley and Thomson (10).**

Serum creatinine concentration (µmol/l)	Vancomycin (mg/kg)	Interval (h)
20-29	20	8
30-39	20	12
40-49	15	12
50-59	12	12
60-79	15	18
80-100	15	24
>100	15	Check trough level at 24 h

“ECMO vancomycin neonate”; “indomethacin vancomycin neonate”; “ibuprofen vancomycin neonate”; “vancomycin penetration CSF neonate” and “vancomycin toxicity neonate” with the limit of “human”. All studies published in August 2011 or earlier were included in the analysis. The bibliography of each article was examined, and selected articles were read carefully. In addition, the book *Neofax: a Manual of Drugs Used in the Neonatal Care*, by Young and Mangum (8), was consulted. The bibliographic search resulted in 60 original articles, 10 review articles, and two book chapters; the publication year range was from 1961 to 2011.

**RESULTS**

Seventy-two studies were considered in this review. Table 1 summarizes vancomycin dose guidelines based on serum creatinine levels (10). Table 2 provides two neonatal vancomycin-dosing strategies that are based on either postmenstrual age or serum creatinine levels (11). Table 3 provides dosage guidelines based on postmenstrual age and weight (12). Finally, Table 4 summarizes demographic and pharmacokinetic parameters of vancomycin in neonates as reported in the literature (12-27).

**Median estimates of vancomycin pharmacokinetics in neonates**

Compared with pharmacokinetic estimates in adults, the median distribution volume is higher in neonates, and the highest estimates are in the most preterm neonates (Table 4). In contrast, vancomycin clearance is significantly lower in neonates compared with adults after correcting for body surface area (27). When expressed in ml/min/kg, the clearance estimates are lowest in the most preterm neonates (0.98 ml/min/kg) (15). In addition, Table 4 illustrates that there is at least a 2- to 3-fold difference in vancomycin clearance within the neonatal age range, which in part reflects maturation and other renal functions that are related to co-morbidity characteristics in neonates (12-27).

**Covariates that reflect maturation: creatinine, age and/or weight**

Vancomycin is almost exclusively cleared by renal glomerular filtration because renal tubular functions are still immature in neonates (4,9). Either postmenstrual age or weight is a covariate of vancomycin clearance, presumably because these covariates serve as indicators of glomerular filtration rate maturation (28). Vancomycin clearance is positively affected by weight, gestational age, postnatal age and postmenstrual age and negatively affected by creatinine levels (10-28). However, these covariates are interrelated because postmenstrual age is the sum of gestational and postnatal ages, whereas the correlation between weight and age is self-evident. Finally, a progressive decline in creatinine levels is associated with an increase in age (Tables 1-4).

**Covariates reflect comorbidity characteristics**

The level of creatinine does not only reflect maturational changes, but it may also in part reflect renal impairment. At present, the use of neonatal creatinine levels to predict renal function is controversial due to residual maternal creatinine and bio-analytical issues (see the discussion section). Other comorbidity characteristics that affect vancomycin clearance are related to renal impairment, which are either primarily caused by a drug-related reduction in renal clearance or a lower endogenous renal clearance capacity or secondarily caused by a disease-related decrease in renal function (Table 4).

As documented by Frattarelli et al., growth restriction affects vancomycin clearance capacity (17) in neonates (<28 days old), but this reduction in vancomycin clearance is limited (16-20%) and related to the reduced renal elimination capacity of these neonates (19,29).

The association between patent ductus arteriosus (PDA) and reduced vancomycin clearance is likely related to pharmacological treatment with either ibuprofen or indomethacin. Either indomethacin or ibuprofen is administered to induce PDA closure. Asbury et al. (26, Table 4) quantified the impact of indomethacin on vancomycin clearance. Basically, indomethacin administration for PDA closure reduced vancomycin clearance by 50% (26). Allegaert (30) aimed to quantify the impact of indomethacin or ibuprofen on neonatal vancomycin clearance. Allegaert et al. confirmed the effect of indomethacin on vancomycin clearance (-40%), whereas ibuprofen reduced clearance by 28%. Therefore, indomethacin has a much higher effect on vancomycin clearance compared with ibuprofen (30,31).

Seay et al. (21) reported on the population pharmacokinetics of vancomycin in 192 patients and documented that dopamine reduced vancomycin clearance (Table 4). In contrast, when dopamine was evaluated as one of the covariates of

**Table 2 - Two neonatal vancomycin dosing strategies (postnatal age <60 days) developed by Capparelli et al. (11).**

Postmenstrual age (PMA)			Serum creatinine concentration (Scr)		
PMA (weeks)	Dose (mg/kg)	Interval (h)	Scr (mg/dl)	Dose (mg/kg)	Interval (h)
≤29	20	24	≥1.7	15	48
30-33	20	18	1.3-1.6	10	24
34-37	20	12	1.0-1.2	15	24
38-44	15	8	0.7-0.9	20	24
≥45	10	6	≤0.6	15	12

**Table 3** - Initial vancomycin dosage guidelines in neonates based on postmenstrual age (PMA) or weight, developed by McDougal et al. (12).

PMA (weeks)	Weight (g)	Dose (mg/kg)	Interval (h)
<27	<800	18	36
27-30	800-1200	16	24
31-36	1200-2000	18	18
≥37	>2000	15	12

vancomycin clearance in a data set of 214 preterm neonates, size, renal function and PMA, but neither dopamine nor respiratory support, were major contributors to clearance variability in premature neonates, which caused 18% of the variability to be unexplained (28). Extra-corporeal membrane oxygenation (ECMO) provides cardiopulmonary support for patients with potentially reversible respiratory and cardiac failure. Vancomycin clearance is decreased and its distribution volume is increased in neonates on ECMO (Table 4) (24,25). Finally, an interaction at the level of competitive binding or inhibition of renal tubular transport processes likely explains the increase in vancomycin clearance during amoxicillin-clavulanic acid co-administration in a cohort of 70 neonates (22).

### Cerebrospinal fluid (CSF) pharmacokinetics of vancomycin

Little is known concerning the penetration of vancomycin in neonatal CSF. Reiter and Doron (32) reported CSF concentrations in three vancomycin-treated neonates. The case 1 subject was a 1264-g male who was delivered at 28 weeks of gestation, the case 2 subject was a 670-g male who was delivered at 31 weeks of gestation, and the case 3 subject was a 1150-g female who was delivered at 26 weeks of gestation. These three case subjects were treated with vancomycin at a daily dose of 20 mg/kg for 14 days. The article by Reiter and Doron (32) includes additional clinical details. In case 1, the vancomycin CSF concentration was 5.6 µg/ml at 17.25 h after infusion on day 8 of therapy, and the CSF penetration rate, which was measured by the CSF to serum vancomycin concentration ratio, was 32%. In case 2, the vancomycin CSF concentration was 2.2 µg/ml at 10.7 h after intravenous administration on day 2 of the vancomycin therapy, and the CSF penetration rate of vancomycin was 26%. Patient 3 had a vancomycin CSF concentration of 5.5 µg/ml at 23 h after infusion on day 9 of the vancomycin therapy, and the CSF penetration rate was 42%. Schaad et al. (27) (Table 4) administered 10-15 mg of vancomycin intravenously to three neonates whose gestational age and body weight were unreported. The vancomycin CSF concentration range was 1.2-4.8 µg/ml (mean = 3.1 µg/ml), and the CSF penetration rate of vancomycin ranged from 7-21% (mean = 14%). Finally, Pau et al. (33) reported the cases of two newborns who had received vancomycin intravenously and intra-ventricularly. The case 1 subject was a 1,280-g male who was born at 29 weeks of gestation and suffered from several diseases. This patient received the following vancomycin treatments: 50 mg/kg/day intravenously and 5-10 mg intra-ventricularly. The duration of vancomycin therapy was 26 days, and the vancomycin CSF concentration range was 12.7-92.1 µg/ml. Patient 2 was a female who was born at 31 weeks of gestation with multiple congenital anomalies. This neonate received the following vancomycin treatments: 60 mg/kg/day intravenously and

4 mg/day intraventricularly for 30 days. The vancomycin CSF concentration range was 9.5-55.3 µg/ml.

### DISCUSSION

Neonatal morbidity and mortality due to late-onset sepsis caused by coagulase-negative *staphylococci* or methicillin-resistant *staphylococci* has resulted in an increased necessity for the effective and safe administration of vancomycin in neonates. In the 1950s, *Staphylococcus* strains developed resistance to treatment with penicillin. Vancomycin arose as the treatment of choice for staphylococcal infections (34), and its use declined in the 1960s when methicillin was preferred because of its safer toxicity profile compared with vancomycin (35). In 1978, the use of vancomycin resurfaced as *Streptococcus* species developed further resistance to cephalosporins and other penicillins (35).

At present, vancomycin is the current treatment of choice for many neonatal staphylococcal infections. There are, however, no reports yet on the association between indices (i.e., peak, trough, and AUC<sub>0-24h</sub>) of vancomycin exposure and either bactericidal effects or nephro- or ototoxicity in neonates. Consequently, the target AUC<sub>0-24h</sub>/MIC index (≥400) of vancomycin, which is documented in adults, is used (36-39). Therefore, similar to a trough concentration of 10 µg/ml of vancomycin, the AUC<sub>0-24h</sub>/MIC target should be considered for any dosage recommendation to minimize treatment failure in neonates. Luster and Metsvaht (38) suggested that for mid-moderate neonatal infections, the AUC<sub>0-24h</sub>/MIC ratio should be ≥400, and for severe infections in immunocompromised hosts, such as cases of ventilator-associated pneumonia sustained by *Staphylococcus aureus*, this ratio should be ≥850. *Staphylococcus warneri* (40), which has reduced glycopeptide susceptibility (MIC > 2 µg/ml), also requires a higher vancomycin exposure.

Obviously, this target necessitates the integration of the most relevant vancomycin pharmacokinetic covariates in neonatal dosing strategies. Van den Anker (39) stated that the most important dosing strategies in neonates are based on a combination of postmenstrual and postnatal ages, which considers the known changes in body composition and renal function with a higher dose for the treatment of neonatal meningitis. Such strategies have been suggested or evaluated by different groups.

### Dosing guideline performance

Young and Mangum (8) suggested a vancomycin dosage of 15 mg/kg every 12 h in meningitis patients and 10 mg/kg every 12 h for the treatment of bacteremia. When the postmenstrual age is ≤29 weeks, the vancomycin dose should be administered every 12 or 18 h according to the postnatal age (>14 days postnatal age or younger). When the postmenstrual age range is 30-44 weeks, vancomycin should be administered every 8 or 12 h according to the postnatal age. When the postmenstrual age is ≥45 weeks, vancomycin should be administered every 6 h. This dosing guideline aims for a trough concentration between 5-10 µg/ml. However, Badran et al. (41) recently illustrated that 51% of the patients in their neonatal unit attained the desired therapeutic trough concentration, and the trough concentration was <5 µg/ml in 33% of the neonates when these guidelines were utilized.

To further illustrate the difficulties of effective dosing guideline implementation, we refer to the work of de Hoog

**Table 4** - Neonatal demographic data and pharmacokinetic parameters of vancomycin therapy. The results are presented as the mean ± standard deviation unless otherwise stated.

Comments	GA weeks	PNA days	Weight g	n	Dose mg/kg	Cl ml/min/kg	Vd l/kg	t <sub>1/2</sub> h	Peak µg/ml	Trough µg/ml	Reference
First dose	28.4	20.5	1069	15	12.6	1.22	0.53	6.0	31.2	9.5	13
	SD 2.6	SD 10.4	SD 435		q24 h	SD 0.7	SD 0.13	SD 2.0	SD 12	SD 3.5	
Steady state	<i>The values refer to the 26-case population</i>				+11	12.6	1.16	6.6	46.4	19.4	
					q24 h	SD 0.6	SD 0.10	SD 2.1	SD 15	SD 9.2	
Group 1	26.6	18	908	16	16	1.1	0.55	6.6	28.1	3.0	12
	SD 1.7	SD 8	SD 254		q24 h	SD 0.07	SD 0.02	SD 0.35	SD 1.2	SD 0.6	
Group 2	29.4	23	1194	15	18	1.19	0.56	5.6	27.9	3.9	
	SD 2.0	SD 14	SD 412		q18 h	SD 0.08	SD 0.02	SD 0.36	SD 1.2	SD 0.6	
Group 3	35.9	24	2405	13	15	1.36	0.57	4.9	26.1	5.5	
	SD 3.7	SD 18	SD 956		q12 h	SD 0.85	SD 0.02	SD 0.4	SD 1.3	SD 0.7	
Preterm	25.9	21 <sup>a</sup>	769	12	14.2	0.8 <sup>b</sup>	0.63	10 h <sup>b</sup>	32.6	5.7	14
	SD 1.3		SD 151		SD 3.2		SD 0.025		SD 9.3	SD 4.5	
Group 1	29.5	15.3	1232	13	Note A	0.98 <sup>a</sup>	0.85 <sup>a</sup>	11.3 <sup>a</sup>	23.6 <sup>a</sup>	10.5 <sup>a</sup>	15
	SD 1.1	SD 5.9	SD 263								16
Group 2	30.1	26.0	1289	12	Note A	0.89 <sup>a</sup>	0.56 <sup>a</sup>	8.7 <sup>a</sup>	2 0.6 <sup>a</sup>	9.9 <sup>a</sup>	
	SD 1.9	SD 14.2	SD 265								
Preterm	26.5	71 <sup>a</sup>	880	20	Note B	1.2 <sup>b</sup>	0.68	6.66 <sup>b</sup>	n.a.	n.a.	
	SD 2.6		SD 340				SD 0.15				
SGA	27.3	48	1140	20	n.a.	1.17 <sup>a</sup>	0.52	7.7	31.5	6.8	17
	SD 2.5	SD 38	SD 590				SD 0.26	SD 4.9	SD 8.3	SD 4.2	
AGA	26.5	38	1535	123	n.a.	1.84 <sup>a</sup>	0.72	8.	30.6	8.3	
	SD 1.9	SD 47	SD 986				SD 0.45	0SD 6.4	SD 10.7	SD 6.4	
GA 29 wks	29.3	29	1297	15	Note C	1.07	0.48	5.6	22.6	7.6	18
	SD 3.4	SD 20	SD 640			SD 0.34	SD 0.09	SD 1.6	SD 3.6	SD 2.0	
Population kinetics	30	>90%	1000	116	10	2.6 <sup>a</sup>	0.52 <sup>a</sup>	8.5 <sup>a</sup>	n.a.	n.a.	19
	SD 2.4	< 2 wks	SD 840								
Population kinetics	28.9 <sup>c</sup>	14 <sup>c</sup>	1045 <sup>c</sup>	108	15	3.4	0.43	6.0	34.3	8.2	20
					q12 h	SD 0.11	SD .013	SD 0.27	SD 7.7	SD 2.2	
Population kinetics	29.5	16.5	1492	192	Note G	3.5 <sup>a</sup>	0.76 <sup>a</sup>	13.4-33.7 (range)	n.a.	n.a.	21
	SD 5.1	SD 19.6	1053								
Population kinetics	32.2	16.9	1700	70	15	3.96 <sup>a</sup>	0.57 <sup>a</sup>	6.3 <sup>a</sup>	7.5 <sup>a</sup>	<20	22
	SD 5.0	SD 10.9	SD 800		q8-24						
Preterm and full-term	31.0	9.1	1620	11	Note F	0.74	0.51	7.2	28.0	4.9	23
	SD 7.3	SD 4.9	SD 550			SD 0.20	SD 0.03	SD 2.9	SD 5.4	SD 2.0	
ECMO	38.8	12.7	3100	15	10	0.65	0.45	8.3	27	13.7	24
	SD 2.2	SD 5.1	SD 600		q8 h	SD 0.28	SD 0.18	SD 2.2	SD 4.3	SD 2.7	
Controls	39.7	7.7	3400	15	10	0.79	0.39	6.5	23.0	13.2	
	SD 1.3	SD 2.3	SD 400		q8 h	SD 0.41	SD 0.12	SD 2.1	SD 5.4	SD 4.5	
ECMO	39	1.6	3300	12	15-20	0.78	1.1	16.9	30 <sup>a</sup>	5- 10	25
	SD 1.4	SD 1.7	SD 430			SD 0.19	SD 0.5	SD 9.5			
Controls	29.3	33.9	1780	19	Note D	1.22	0.52	5.6	27.8	7.5	26
	SD 4.2	SD 19.9	SD 1080			SD 0.54	SD 0.08	SD 1.2	SD 0.7	SD 1.2	
PDA (indo)	26.0	17.6	810	4	Note E	0.61	0.57	11.9	27.9	8.5	
	SD 1.2	SD 7.1	SD 160			SD 0.17	SD 0.06	SD 3.3	SD 0.4	SD 0.7	
Preterm	32 <sup>a</sup>	3.3 <sup>a</sup>	1530 <sup>a</sup>	7	10	15	0.74 <sup>a</sup>	9.8 <sup>a</sup>	16.8 <sup>a</sup>	5.7 <sup>a</sup>	27
					q24 h	ml/min/1.73 m <sup>2</sup>					
Preterm	34 <sup>a</sup>	4.7 <sup>a</sup>	1570 <sup>a</sup>	7	15	27	0.71 <sup>a</sup>	5.9 <sup>a</sup>	25.2 <sup>a</sup>	n.a.	
					q24 h	ml/min/1.73 m <sup>2</sup>					
Term	40 <sup>a</sup>	2.6 <sup>a</sup>	3070 <sup>a</sup>	7	15	30	0.69 <sup>a</sup>	6.7 <sup>a</sup>	29.8 <sup>a</sup>	n.a.	
					q24 h	ml/min/1.73 m <sup>2</sup>					

GA = gestational age; PNA = postnatal age; n = number of cases; SGA = small for gestational age; AGA = appropriate for gestational age; ECMO = extracorporeal membrane oxygenation; PDA = patent ductus arteriosus; n.a. = not available.

<sup>a</sup>Mean, SD is not available; <sup>b</sup>Extracted figure; <sup>c</sup>Median.

Note A: The vancomycin doses were 10, 15, or 20 mg/kg.

Note B: The vancomycin dose range was 9.2-18 mg/kg.

Note C: The loading dose was 15 ± 0.2 mg/kg, and the maintenance dose was 14.8 ± 4.3 mg/kg.

Note D: The loading dose was 15 ± 0.2 mg/kg, and the maintenance dose was 29.6 ± 13.1 mg/kg.

Note E: The loading dose was 15 mg/kg, and the maintenance dose was 14.8 ± 4. mg/kg.

Note F: The dose range was 12.1-13.8 mg/kg (12.6 ± 0.9 mg/kg), and the dosing interval range was 13-40 h (22.0 ± 7.5 h).

Note G: The dosing was initiated at 7.5, 10, 12, or 15 mg/kg, and the interval range was from q8 h to q24 h.

et al. (20). This group aimed to determine the best therapeutic dose for the treatment of vancomycin-sensitive bacterial infections in 108 neonates. The median gestational and

postnatal ages were 28.9 weeks and 14 days, respectively, and the median body weight was 1,045 g (Table 4). The vancomycin dose was 15 mg/kg every 12 h. Clearance was

$0.057 \pm 0.0018$  l/h/kg (variability = 31%); the distribution volume was  $0.43 \pm 0.013$  l/kg (variability = 25%), and  $t_{1/2}$  was  $6 \pm 0.27$  h (variability = 34%). Using this dosage (i.e., 15 mg/kg every 12 h), 95.5% of the initial trough concentration measurements were in the desired therapeutic range. Vancomycin trough concentrations before the second dose were  $8.2 \pm 2.2$  µg/ml. Trough concentrations before the fifth dose were  $12.3 \pm 4.1$  µg/ml. Only one trough concentration measurement was below 5 µg/ml. The vancomycin trough concentration range before the fifth dose was 15.3-20.6 µg/ml. Vancomycin accumulates in serum; accordingly, after the fifth dose, the peak concentration range was 16.6-34.5 µg/ml (mean =  $25.8 \pm 5.0$  µg/ml). The vancomycin trough concentration range was 5-15 µg/ml, and peak concentrations were <40 µg/ml (39) (Table 4). The authors suggested that a vancomycin dosage of  $3 \times 10$  mg/kg per day leads to a minimized high peak serum concentration and a trough serum concentration that is too low. However, this assertion was derived from a prospective validation study of 22 neonates in the same unit. However, these results are concomitant with the internal (same unit) prospective validation efforts of Seay et al. (n=20) and Marques-Minana et al. (n=41) (21,22).

#### Intermittent vs. continuous vancomycin administration

Because the AUC concept aims to maintain the vancomycin concentration above a given threshold, it has been suggested that vancomycin can be administered as a continuous infusion (42-45). Plan et al. (42) administered vancomycin as a continuous infusion of 15-25 mg/kg/day or 20-30 mg/kg/day to 145 neonates. The body weight range of the neonates was 500-1,160 g, and their gestational age range was 26-29 weeks. Using the abovementioned dosage, bactericidal efficacy was maintained, and most subjects had serum vancomycin concentrations within the therapeutic range. Pawlowsky et al. (43) administered vancomycin as a 24-h constant infusion to two neonatal groups. Group 1 (n=24) had a postmenstrual age range of 27-41 weeks and received 10-30 mg/kg/day according to the postmenstrual age. Group 2 (n=29) had a postmenstrual age range of 28-51.5 weeks and received a loading dose of 7 mg/kg, followed by a continuous infusion of 10-40 mg/kg/day according to the postmenstrual age. The mean vancomycin serum concentrations at steady state were  $11.0 \pm 3.1$  and  $15.4 \pm 6.2$  µg/ml in Groups 1 and 2, respectively. Both regimens were well tolerated. Oudin et al. (44) confirmed the feasibility of this approach (i.e., a 7-mg/kg loading dose and constant infusion of 30 mg/kg/day) but suggested increasing the initial loading dose to 20 mg/kg, which resulted in an exposure similar to that observed by Pawlowsky et al. (43).

#### The use and limitations of therapeutic drug monitoring

All pharmacokinetic studies demonstrate variability, which is only in part explained by weight, age, or creatinine level. This variability explains the use of therapeutic drug monitoring (TDM) of trough concentrations to ensure effectiveness and avoid nephrotoxicity. In contrast, the quantification of peak concentrations provides no additional monitoring value (4,8,39). Vancomycin-induced nephrotoxicity and ototoxicity were previously more common than is

currently observed. After eliminating impurities from the early preparations of vancomycin, the incidence of primary adverse effects, such as nephrotoxicity, ototoxicity and "red man syndrome", was reduced (46). The most important risk factors for developing nephrotoxicity are the following: trough concentrations >10 µg/ml, concomitant treatment with aminoglycosides and/or prolonged therapy (>21 days) (47,48). Other risk factors include high peak concentrations, high total dose, preexisting renal failure, and concurrent treatment with amphotericin and/or furosemide. However, the role of these factors in the neonatal population is not well-established (49). Proper vancomycin TDM minimized both glomerular and tubular nephrotoxicity in two studies in children and neonates (8,39,50,51). In most cases, nephrotoxicity is reversible, even after high doses (52). In contrast, there is no proven association between TDM and ototoxicity prevention (39).

#### Improving neonatal vancomycin effectiveness and tolerance

Despite the number of reported pharmacokinetic studies on vancomycin in neonates, there are still relevant issues that require further consideration. First, covariates differ between the different studies, and the prospective validation of dosing guidelines is limited but urgently required to improve the predictability and extrapolation of dosing guidelines. This may be partially related to analytical issues specific to quantifying vancomycin or creatinine concentrations. Immunoassays that are routinely used to quantify vancomycin may overestimate vancomycin concentrations because of the cross-reactivity with some of the vancomycin degradation products or endogenous compounds, such as bilirubin (53). The introduction of a more precise analytical method, such as liquid chromatography-tandem mass spectrometry, should be considered. Creatinine levels initially increase and are most pronounced in the most immature neonates (54). Postnatal observations also depend on techniques used to quantify creatinine levels (i.e., Jaffe colorimetry, compensated Jaffe quantification or enzymatic quantification). It is generally accepted that the Jaffe quantification method overestimates creatinine concentrations because of bilirubin and cephalosporin interference. This observation also indicates that the age- or weight-dependent creatinemia reference values will differ based on the quantification method used (55). Until recently, none of the studies in the literature explicitly discussed creatinine quantification methods.

Second, the external prospective validation of vancomycin dosing guidelines is only a first step to improving the efficacy and safety/tolerance of vancomycin. The  $AUC_{0-24h}/MIC$  ratio is derived from extrapolated data in adults and necessitates prospective validation in neonates that includes an analysis of the potential add-on value of continuous administration with or without a loading dose (39). Finally, data in specific settings, such as ECMO or meningitis, are limited and warrant a focused approach (56). Until these data emerge, there are no well-validated dosing guidelines that can be used routinely throughout the world. Therefore, we strongly recommend that neonatal units prospectively validate one of the dosing guidelines provided (Tables 1-4). Local validation efforts also enable caregivers to consider the local MIC values of the isolated pathogens.

In conclusion, neonatal vancomycin pharmacokinetic data were reviewed, which was followed by a critical analysis of

the literature. Renal function drives vancomycin pharmacokinetics. Consequently, age or weight are the most relevant covariates of vancomycin clearance and should be considered first in neonatal vancomycin dosing guidelines and further adjusted by indicators of renal dysfunction (e.g., ECMO and ibuprofen/indomethacin). In addition to the prospective validation of vancomycin dosing guidelines that includes an analysis of its effectiveness and tolerance, studies should focus on the relevance and the methods applied for therapeutic drug monitoring and on the value of continuous vancomycin administration in neonates, whereas specific settings (i.e., ECMO and ibuprofen/indomethacin) warrant focused studies.

**ACKNOWLEDGMENTS**

This work was supported by the Ministry of the University and Scientific and Technologic Research (Rome, Italy). Karel Allegaert is supported by the Fund for Scientific Research, Flanders (Belgium) (FWO Vlaanderen, Fundamental Clinical investigatorship 1800209N).

**AUTHOR CONTRIBUTIONS**

Pacifici GM performed the systematic review and is the principal and corresponding author of the paper. Allegaert K is the second reviewer and verified the results. Both authors wrote the paper and approved the final version.

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