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Vancomycin Toxicity in Neonates: A Review of the Evidence

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ABSTRACT

Purpose of review:

Vancomycin is a first-line agent in the treatment of serious Gram-positive infections in the neonatal population. The published evidence on vancomycin toxicity in neonates is limited. This review summarises pre-clinical studies and clinical trials describing vancomycin toxicity. We discuss proposed pathophysiology and summarise evidence supporting dose-response relationships, genetic and environmental determinants, and consider future research required to further define vancomycin toxicity.

Recent findings:

Current dosing regimens for vancomycin result in sub-therapeutic levels in a large proportion of patients. Higher daily doses have been proposed, which have led to concerns regarding increased toxicity. Nephrotoxicity occurs in 1-9% of neonates receiving currently recommended doses. The incidence is highest in those receiving concomitant nephrotoxic drugs. Vancomycin-associated ototoxicity is rare in patients of all ages. Exposure-toxicity relationships in relation to nephro- and ototoxicity have not been clearly defined in neonates receiving vancomycin.

Summary:

Current evidence supports the favourable safety profile of vancomycin in neonates. Further studies that address safety concerns relating to high-dose intermittent dosing regimens are needed. Such studies must include robust and standardised definitions of renal and hearing impairment, and include follow-up of sufficient length to establish the long-term implications of experimental findings.

KEYWORDS

Vancomycin, toxicity, neonates, renal impairment, hearing loss

INTRODUCTION

Vancomycin is a glycopeptide bactericidal antibiotic that disrupts cell wall synthesis in Gram-positive bacteria. (1) Impurities from early fermentation processes were associated with significant toxicity when the drug was first introduced in the early 1950s. The drug's poor safety profile, along with its thick brown appearance, led to the disparaging nickname 'Mississippi mud'. Refined purification methods improved the safety profile of vancomycin, and Food and Drug Administration approval was granted in 1958. Despite this, safety concerns lingered, leading to the drug's limited use. In recent decades clinical use has increased, however, owing to the rising incidence of infections caused by methicillin-resistant *Staphylococcus aureus* and other resistant Gram-positive pathogens that are susceptible to vancomycin. (2)

Vancomycin dosing strategies vary greatly and are generally based on a combination of post-menstrual age (PMA), post-natal age (PNA), weight and/or renal function (see table 1). Therapeutic drug monitoring (TDM) is widely advocated. Currently clinical guidelines recommend target trough concentrations of 10-15 μg/mL. (3, 4) However, recent studies suggest the need for target trough levels >15 μg/mL, based on the concern that lower trough concentrations may be selective for hetero-resistance. (5-7) In adults, higher daily doses of vancomycin (15 mg/kg 6 hourly) have yet to receive regulatory approval but have been proposed in recent consensus documents published by the Infectious Diseases Society of America, American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. (8-10) The use of higher vancomycin doses has raised concerns regarding the potentially increased risk

of toxicity. The significance of these concerns in paediatric populations is unclear. Here we summarise the current evidence relating to vancomycin toxicity including proposed pathophysiology, dose-toxicity relationships, genetic and environmental factors and future research needs. Studies pertaining to vancomycin-induced toxicity between March 1950 and March 2015 were identified from PubMed, Embase, Cochrane Controlled Trial Registry, and Medline databases. The following search terms were used “vancomycin”, “toxicity”, “adverse effects’, “nephrotoxicity”, “kidney disease”, “renal impairment”, “ototoxicity”, “hearing loss”, “neonate”, “infant”, “child”, “paediatrics”.

NEPHROTOXICITY

Quantification of Nephrotoxicity

Kidney function is difficult to define in the first month of life when renal physiology and fluid balance evolve rapidly. Serum creatinine (SCr) concentrations reflect maternal renal function in the first 48 hours after birth. (11, 12) In addition, preterm infants experience a rise in SCr due to tubular reabsorption, making this an imprecise proxy for glomerular filtration. (13) Clinical reports also often omit details of the laboratory methods used to quantify SCr (Jaffé colorimetry, enzymatic quantification, or isotope dilution mass spectroscopy), which can have an inter-test variability of up to 25% in neonates. (14, 15) Despite these limitations most studies define renal impairment as an increase in SCr. (16-19) Definitions for children and neonates have been reported based on several classifications systems, all of which were originally developed and validated in adults. (20, 21) Modified neonatal criteria exclude urine output or use a higher cut-off (< 1.0 mL/kg/h) in order to account for the non-oliguric

renal dysfunction that occurs in neonates due to fluid redistribution and impaired absorption in the immature renal tubule. (22, 23)

Pre-Clinical Studies

Murine models have demonstrated that vancomycin has an affinity for biological membranes and accumulates in renal tissue. (24, 25) The energy-dependent transport mechanisms within the tubular epithelium render the kidney highly susceptible to toxin-induced cellular injury. Vancomycin enhances cellular ATP concentrations and stimulate oxygen consumption, resulting in oxidative phosphorylation. (26-31) However, oxidative stress of sufficient magnitude to cause clinically detectable renal impairment has not been demonstrated in animals, even at supra-therapeutic doses. (32) Histopathological changes and biochemical evidence of nephrotoxicity have been observed in an uninfected murine model in which high-dose vancomycin was co-administered with tobramycin. (25)

Clinical Studies

The linear relationship between SCr and vancomycin exposure reflects the drugs primary route of elimination through renal excretion. As a result, a decrease in renal function from any cause will increase serum vancomycin concentrations, a fact that confounds the establishment of exposure-toxicity relationships. (33) Many studies that describe vancomycin-associated nephrotoxicity are conducted in patients otherwise at risk of renal impairment, such as those requiring intensive care and frequently include those receiving other potentially nephrotoxic drugs (e.g. NSAIDs, diuretics and aminoglycoside antibiotics) . However, irrespective of the difficulty in defining causal relationships, acute kidney injury from any cause is associated with a

significantly increased risk of mortality, hospital length of stay, and cost, even after adjustment for age, gender, chronic kidney disease, and co-morbidities at admission. (34)

Adult Studies

Nephrotoxicity in patients receiving vancomycin has been more systematically reported in adults than in neonates and children. The reported incidence of nephrotoxicity in adults receiving vancomycin is 10-15%. (35) In a recent meta-analysis, van Hal, *et al*. reviewed fifteen studies in which vancomycin was administered via intermittent infusion to adults >18 years of age. Randomised trials and observational studies in which data on renal function and trough vancomycin concentrations were available were included. The analysis found trough concentrations >15 μg/mL to be independently associated with an increased odds of nephrotoxicity (OR, 2.67; 95% CI, 1.95-3.65), and also suggested an incremental increase in nephrotoxicity risk with vancomycin administration beyond seven days. (36) The majority of reported cases were self resolving, with prolonged impairment requiring short-term dialysis occuring in 3% of cases. Similarly, a retrospective cohort study of 246 adults receiving intermittent-dosing of vancomycin for durations of >48 hours found toxicity to be correlated with exposure (based on dose). Patients receiving ≥4 g daily (n=26) had a significantly higher incidence of nephrotoxicity compared with those receiving <4 g daily (34.6% vs. 10.9%; $p = 0.001$). (18)

Concomitant aminoglycoside use has consistently been shown to increase the risk of nephrotoxicity in adults receiving vancomycin. In 2007, Fowler, *et al* reported a seminal open-label randomised trial of daptomycin versus either anti-staphylococcal

penicillin or vancomycin plus low-dose gentamicin in 236 patients with *S. aureus* bacteremia. The highest proportion of renal impairment occurred in patients receiving vancomycin plus gentamicin (20.4%), although this was not significantly higher than with penicillin plus gentamicin (18.6%).

Furthermore, the study found that the highest incidence of renal impairment in patients receiving vancomycin occurred later in treatment, peaking at 14-28 days. (37)

Paediatric & Neonatal Studies

Vancomycin administration with intermittent dosing and in accordance with published guidance has been shown to result in sub-therapeutic trough concentrations in up to half of treated neonates. (4) Furthermore, antimicrobial point prevalence surveys that describe prescribing practices have demonstrated that significant variation in prescribing of vancomycin in neonates exists in clinical practice, with a large proportion of neonates receiving daily doses of vancomycin that are significantly below even the most conservative current recommendations. (38) Table 2 outlines the clinical studies that have reported nephrotoxicity associated with vancomycin use in neonates and infants. The majority of studies identified are heterogeneous observational or opportunistic pharmacokinetic studies based on routine TDM and are insufficiently powered to detect toxicity.

As with adults, cases of renal impairment are more frequently reported in neonates and children receiving concomitant nephrotoxic drugs. (19, 35) Eight of ten studies describing concomitant nephrotoxic drugs alongside vancomycin therapy demonstrated evidence of renal impairment, which was mild and transient in all reported cases (see table 2). Other reports have not found vancomycin to be an

independent predictor of nephrotoxicity. Constance, *et al*, for example, found no significant difference in the proportion of neonates developing nephrotoxicity in those receiving vancomycin plus gentamicin (12/533, 2.2%) versus those receiving gentamicin alone (7/533, 1.3%). Logistic regression demonstrated that while positive blood culture, low birth weight, patent ductus arteriosus, concomitant non-steroidal anti-inflammatory drug (NSAID) use, and illness severity were all independent risk factors for nephrotoxicity, vancomycin in conjunction with gentamicin was not. (23) Six studies report rates of nephrotoxicity in neonates receiving vancomycin alone. A transient rise in SCr, microproteinuria, and elevated NAG were reported in only three, two and one patient, respectively (see table 2). (51, 54, 59-61)

Exposure-toxicity relationships have not been clearly defined for vancomycin in neonates. Two case reports have described clinical outcomes in four neonates receiving accidental overdoses of up to 10-fold the maximum recommended dose. (51, 59) All four patients developed transient renal impairment, though all had normal renal function at 6 months. It is noteworthy that these cases all involved single or brief exposures that were managed with immediate vancomycin withdrawal, and so these findings do not address the potential risk of cumulative exposure.

A number of recent studies have described the administration of vancomycin via continuous infusion in neonates. Continuous infusion has the theoretical advantage of maintaining constant plasma concentrations, meaning that overall drug exposure can be increased without a rise in peak concentrations. Studies investigating continuous vancomycin infusions in neonates have, to date, been based on studies defined toxicity differently and involved small patient cohorts that received varied dosing regimens. A loading dose of 7-15 mg/kg was given in three studies. Collectively, the

results of these studies suggest that continuous infusion may result in a higher proportion of patients achieving target concentrations between 15-20 μg/mL. Reported rates of nephrotoxicity do not differ significantly from those in patients receiving intermittent dosing, and there is currently no evidence to suggest the use of a loading dose increases the risk of nephrotoxicity. (3, 45, 47, 60) Continuous infusions may, however, be impractical in the neonatal population where venous access if limited, and may lead to periods without effective antibiotic cover if access is lost. There have, as yet, been no systematic studies comparing the safety and efficacy of continuous infusion with high-dose intermittent regimens that specifically target trough concentrations of >15 μg/mL.

OTOTOXICITY

Quantification of Ototoxicity in Neonates

The assessment of hearing in infants is challenging. Behavioural tests (e.g. visual reinforcement audiometry) are the gold standard, but cannot be performed reliably in children below ~8 months. (67) The methods currently employed to quantify auditory function in neonates are otoacoustic emissions (OAE) and auditory brainstem responses (ABR). Serial diagnostic OAE and ABR testing has been used to monitor ototoxicity in children receiving aminoglycosides. (68-71) There are no equivalent reports describing serial OAE or ABR following vancomycin use. Diagnostic OAE or ABR is labour-intensive and difficult to interpret in premature infants (PMA <34 weeks) due to immaturity of the cochlea and central auditory pathways (72-78).

Universal newborn hearing screening (UNHS) uses a combination of automated OAE and ABR, and is designed to identify severe permanent hearing impairment in term neonates. Standardised UNHS programmes are now being implemented in the USA

and Europe. (79, 80) UNHS is a single-point assessment and is not designed to detect and monitor subtle high-frequency hearing loss that typically occurs in drug-induced ototoxicity.

Pre-Clinical Studies

The association between vancomycin use and hearing impairment is controversial. As in the case of nephrotoxicity, the mechanism of vancomycin-induced ototoxicity is thought to involve dose-dependent intracellular oxidative damage, which leads to the loss of cochlear sensory hair cells resulting in high frequency hearing loss. (81) Ototoxicity has not been consistently demonstrated with vancomycin in animal models. (25, 82-84) Studies in guinea pigs found no evidence of vancomycin ototoxicity, but found that vancomycin increases the probability of ototoxicity, measured by OAE, when co-administered with gentamicin. (85)

Clinical Studies

The majority of vancomycin-associated ototoxicity was reported early in the drug's use in patients treated with indeterminate doses of an impure fermentation product who often received concomitant therapy with other severely ototoxic agents. (86, 87) Overall, the available recent literature on vancomycin-associated ototoxicity are heterogeneous and in many cases causation is uncertain.

Adult Studies

Observational studies have suggested the risk of ototoxicity may be increased with vancomycin doses ≥4 g daily in adults. In a retrospective study of 89 adults receiving > 14 days of high-dose vancomycin, Forouzesh, *et al* reported high-frequency hearing

loss identified by pure-tone audiometry in ten patients (12%), a rate significantly higher than reported at standard doses. (88) However, the study included patients receiving concomitant aminoglycosides and diuretics, and idenfitied no significant difference in mean trough vancomycin concentrations in patients with and without abnormal audiometry, suggesting the phenomenon was unlikely to be dose dependent.

Paediatric & Neonatal Studies

Ototoxicity is infrequently reported in neonates and children treated with vancomycin in general. (89) Buckingham, *et al*, however, reported a high incidence of hearing loss in children with pneumococcal meningitis treated with vancomycin. (90) Patients aged 5-20 years (n=109) received vancomycin alongside a third-generation cephalosporin. Over half of those surviving had significant permanent hearing loss (n=37, 55%). Of note, hearing loss was independently associated with vancomycin administration within two hours of presentation. Whether these findings apply to other populations or reflect the specific pathophysiology of pneumococcal meningitis is uncertain. The findings do, however, highlight the need to consider population and disease-specific factors when reporting drug toxicity.

In neonates, reporting of vancomycin-associated ototoxicity comes almost exclusively from routine UNHS. De Hoog, *et al* studied 625 neonates over two years from a single NICU in the Netherlands. Exposure to vancomycin (alone or in combination with tobramycin or furosemide) was not associated with a significant rise in screening failure rates. (91) Similarly, in a retrospective study of >7000 infants, Gopel, *et al* found no association between vancomycin exposure and UNHS failure rates. (92) Vella-Brincat*, et al* described UNHS outcomes over five years from a single centre in

New Zealand. The cohort included 41 neonates who received vancomycin, and found higher failure rates (n=6; 22%), compared with those not exposed to vancomycin (n = 85/1,233; 7%). The significance of these finding is uncertain given the lack of systematic follow-up and many potential confounding factors.

CONCLUSION

Despite historical concerns, a large body of evidence now exists to support the favourable safety profile of vancomycin in humans. In adults, nephrotoxicity is exposure-dependent, and more aggressive dosing may result in a significantly increased risk of toxicity. By comparison, current dosing regimens in neonates are conservative, and result in sub-therapeutic concentrations in a large proportion of patients. At present, insufficient evidence exists to inform conclusions about the safety of higher doses of vancomycin in neonates. Furthermore, the clinical difficulty in ascertaining a diagnosis of sepsis with certainty in neonates makes risk-benefit analyses challenging. The development and use of novel diagnostic biomarkers are likely to improve clinical decision-making and trial design in the years to come. (93) Dose modification based on trough vancomycin concentrations, which are, in turn, largely determined by renal function, adds complexity in determining exposure-toxicity relationships. These issues are probably best addressed with detailed prospective, observational data that define renal impairment according to standardised criteria and allow for a more clinically valid estimation of risk.

Ototoxicity appears rare in patients of all ages treated with vancomycin. Diagnostic OAE and ABR may detect subtle high-frequency hearing loss following vancomycin exposure. These tests can only reliably be carried out in babies >34 weeks before

which many preterm neonates will already have receive courses of vancomycin. UNHS at term is unlikely to detect subtle hearing impairment and identify exposure-toxicity relationships. Prospective studies that use robust and standardised definitions of hearing impairment based on diagnostic testing, such as with visual reinforcement audiometry at 8-12 months, are needed to further clarify the risk clinically significant ototoxicity.

Source	PMA (weeks)	PNA (days)	Creatinine (mg/dL)	Dose (mg/kg)	Interval (hourly)
British National Formulary for Children	<29			15	24
	29–35			15	12
Manual of Childhood Infections: The Blue Book	>35			15	8
Neofax®	≤29	0–14		10 (bactaeremia) 15 (meningitis)	18
		>14		10	12
The Harriet Lane Handbook	30–36	0–14		10	12
		>14		10	8
The Sanford guide	37–44	0–7		10	12
		>7		10	8
	≥45	Any PNA		10	6
			<0.7	15	12

Red Book® 2015 Report of the Committee on Infectious Disease			0.7–0.9	20	24
			1–1.2	15	24
			1.3–1.6	10	24
			>1.6	15	48

Table 1. Current dosing regimens for vancomycin in neonates

Table 2. Studies describing nephrotoxicity in neonates receiving vancomycin

Author (year) Design	Study population receiving vancomycin (mean ± SD unless otherwise stated)	Dosing regimen	Concomitant nephrotoxic agents	Timing/Target levels (μg/mL)	Nephrotoxicity Definition	Incidence of nephrotoxicity
Constance (2015) Propensity-matched cohort study (23)	n = 533 PMA <25 weeks n = 35, 25-28 weeks n = 73, 28-32 weeks n = 158, 32-27 weeks n = 152, >37 weeks n = 115 weight 1649 (1060-2504) g median (IQR)	Intermittent infusion: 12-40 mg/kg per day (not further described)	Gentamicin Ibuprofen	Timing and target concentrations not reported	SCr rise by ≥150% within 48 hours or SCr ≥1.5 mg/dL (132 μmol/L) persisting ≥48 h	Transient rise in SCr in 12/533 patients receiving vancomycin with gentamicin
Moffett (2015) Retrospective case-control study (39)	n= 83 neonates with critical cardiac disease	Not specified	Gentamicin Furosemide Amphotericin		Doubling of SCr	2 developed AKI. AKI more likely with concomitant nephrotoxic agents

Petrie (2015) Retrospective observational study (40)	n = 83 PMA 30+3 (23+6-52+4) weeks, weight 1.12 (0.56-4.7) g median (IQR)	Intermittent infusion: 15 mg/kg per dose 8-24 hourly according to PMA	Not reported	Timing not reported; trough 10–15	Rise in SCr not further defined	None detected
Vandendriessche (2014) Retrospective observational study (41)	n = 223 PMA 32 (24–41) weeks, median (range) 1650 (420–4680) g	Intermittent infusion: 10-15 mg/kg 6-24 hourly according to PMA, PNA and SCr	Not reported	Timing not reported; trough > 10	Difference in mean SCr	None detected
Frymoyer (2014)Prospective observational study (42)	n = 249 PMA 39 (32–42) weeks, weight 2900 (1600-3700) g median (IQR)	15-20 mg/kg per dose 12-24 hourly according to SCr and weight	Not reported	After 3rd dose; trough 7-10	Rise in SCr not further defined	None detected

Kim (2014) Retrospective observational study (43)	n=50 PMA 27.4 ± 2.5 weeks, weight 1020 ± 420 g	15-40 mg/kg per dose 6–12 hourly according to PMA	Not reported	Timing not reported; trough ≤ 40	SCr >25% above baseline or urine output <1 ml/kg/h	None detected
Linder (2013) Retrospective observational study (44)	n = 126 PMA 27.5 ± 2.6 weeks, weight 1026 ± 269 g	Intermittent infusion: 10 mg/kg per dose 8-18 hourly according to PMA and PNA	Not reported	1-2 days; Trough 10, peak 30-40	Not formally defined	None detected
Patel (2013) Retrospective observational study (3)	n = 32 (40 treatment courses) PMA 36 (26–62) weeks, weight 2200 (620-6900) g median (IQR)	n = 20 Intermittent infusion: 10-20 mg/kg per dose 8-12 hourly according to SCr n = 20	Not reported	Before 3rd dose; 15-25	Rise in mean ± SD in SCr not further defined	No significant rise in SCr (mean ± SD) in either intermittent dosing or continuous infusion.

		Continuous infusion: 20–60 mg/kg daily according to PMA and SCr				Two patients developed renal failure 2nd to a decline in overall clinical status.
Zhao (2013) Prospective observational study (45)	n = 116 PMA 33.8 ± 5.3 weeks, weight 1700 ± 964 g	Loading dose: 10-15 mg/kg Continuous infusion: 15-35 mg/kg daily according to PMA, PNA and SCr	Not reported	Timing not reported; 15-25	SCr > 70 or 90 µmol/L based on PNA	None detected
Irikura (2011)	n = 54 n = 21 (SCr-based dosing) PMA 29.65 ± 5.27 weeks Birthweight 1322 ± 951 g	n = 21 Intermittent infusion: 10-20 mg/kg per dose 12-48 hourly according to SCr	Not reported	Timing and target concentrations not reported	Rise in SCr not further defined	Transient rise in SCr in 3 patients (two receiving dose based on weight/PNA and one

Prospective observational study (46)	n = 33 (dosing based on weight & PNA) PMA 33.18 ± 5.94 weeks Birthweight 1839 ± 915 g	n = 33 Intermittent infusion: 10 mg/kg per dose 6-18 hourly according to weight and PNA				receiving dosing based on baseline SCr, respectively).
Oudin (2011) PK study (47)	n = 47 PMA 29.5 ± 27, weight 1500 ± 970 g	Loading dose: 7 mg/kg Continuous infusion: 30mg/kg daily	Not reported	Timing not reported; trough 10-30	Rise in SCr not further defined	Transient rise in SCr in 3 patients resolved by 3 weeks after exposure.
Plan (2008) Prospective observational study (48)	n = 145 PMA 28 (26–29) weeks, Weight 904 (780–1160) g median (IQR)	Intermittent infusion: 15-30 mg/kg per dose 24 hourly according to SCr	Diuretics, not further defined	Timing not reported; trough 10-25	Rise in SCr not further defined	No significant rise in SCr detected

Giapros (2007) Retrospective observational study (49)	n = 70 Weight <1000 g	Intermittent infusion every 12 – 48 h – not further defined	Gentamicin	Timing and target not reported	Increased urinary excretion of potassium, calcium and phosphate; raised SCr	5 patients with severe renal tubular disturbance (3 with raised SCr). All abnormalities returned to baseline within 2 weeks of the last antibiotic course
Frattarelli (2005) Retrospective observational study (50)	n = 153 SGA; PMA 48 ± 8 weeks, weight 641 ± 181 g Non-SGA; PMA 47 ± 8 weeks, weight 1158 ± 765 g	Intermittent infusion not further defined	Not reported	Timing not reported; trough, target not reported	Rise in SCr not further defined	None detected
Miner (2004)	n = 2	Intermittent infusion:	None	Timing not reported; peak	Rise in SCr not further defined	Transient rise SCr in one patient

Case series (51)	Case 1 – PMA 24 weeks at birth. Day 53 of life when vancomycin commenced Case 2 – PMA 28 weeks at birth. Vancomycin commenced day 9 of life	150 mg/kg (10x accidental overdose)		concentration, >300		
Deville (2003) Phase III, open label RCT (52)	n = 20 PMA 38.6 ± 7.3 weeks Population not further defined	Intermittent infusion: 10-15 mg/kg per dose 6-24 hourly according to PMA	Gentamicin	Timing not reported; trough, target not reported	SCr twice the upper limit of normal or double baseline	Transient rise in SCr in one patient not further described
Tan (2002)	n = 101 PMA 30 (23–45) weeks Median (range)	Intermittent infusion: 15 mg/kg per dose 12-18 hourly according to PNA	Not reported	Timing not reported; trough < 10	Difference in mean SCr	None detected

Retrospective observational study (53)	Population not further defined					
Feferbaum (2001) Prospective observational study (54)	n = 20 PMA 42 ± 3 weeks Population not further defined	Intermittent infusion: 30-60 mg/kg per day (not further described)	None	Timing not reported; trough 5-10, peak 30-40	Rise in SCr not further defined	None detected
Machado (2001) Prospective observational study (55)	n = 25 PMA 38 ± 1 weeks, 3130 ± 861.3 g	10-20 mg/kg per dose 6-24 hourly according to PMA	Gentamicin	Timing not reported; trough 5-10, peak 20-40	Rise in SCr and urea 5 days after treatment started not otherwise further defined	Significant transient rise in intra-individual SCr but not urea. Not further described.

De Hoog (2000) Retrospective observational study (56)	n = 108 PMA 28.9 (24 – 41) weeks Birthweight 1002 g (485 – 4625 g) Median (IQR)	Intermittent infusion: 30 mg/kg per dose 12 hourly	Not reported	Steady state (not further defined); Peak ≤40, trough 5-15	Increase in SCr or urea not further defined	None detected
Bhatt-Mehta (1999) Retrospective observational study (57)	n = 69 PMA 28.9 ± 3.0 weeks, weight 1219 ± 516 g	Intermittent infusion: 10-15 mg/kg per dose every 6-36 hourly according to PMA	Gentamicin	After 3rd dose; Peak ≤40	SCr double baseline or >0.6 mg/dL (53 µmol/L)	Transient rise in SCr in 6/61 patients with peak concentration ≤40 and none with peak concentrations >40
Goebel (1999) Case report (58)	n = 1 Term infant, PNA 6 d Solitary dysplastic kidney	100 mg/kg	Not reported	12 hours post dose; no target	Anuria. Not otherwise further defined	Commenced hemofiltration due to persistently elevated vancomycin level (240

						μg/mL). Normal renal function at PNA 3 weeks.
Müller (1999) Case series (59)	n = 2 PMA 35 weeks, weight 1985 and 2390 g	Intermittent infusion: Single dose 35 mg/kg and 38 mg/kg (accidental overdose)	None	9 hours post dose; no target reported	Reduced GFR or microproteinuria (urinary protein electrophoresis)	Transient microproteinuria in both patients but no change in GFR
Pawlotsky (1998) Non-randomised un-blinded trial (60)	n = 53 PMA 33.5 ± 3.7 weeks, weight 1500 ± 300 g (n = 29) PMA 33.9 ± 4.8 weeks, weight 1800 ± 800 g (n = 24)	n = 29 Loading dose: 7 mg/kg Continuous infusion: 10-40 mg/kg per over 24 hours according to PMA and weight n = 24 Continuous infusion:	None	Post loading dose; peak ≤40 Steady state (not further defined); 10-30	Rise in SCr and urea not further defined	Transient rise in SCr in one patient with klebsiella septicaemia

		10-30 mg/kg per over 24 hours according to PMA and weight				
Sakata (1996) Prospective observational study (61)	n = 20 PMA 26.3 ± 1.4 weeks Population not further defined	Intermittent infusion: 9-11 mg/kg per dose 12 hourly	None	Timing and target concentrations not reported	Rise in SCr, fractional excretion of sodium (FENa) and NAG index (NAG:creatinine ratio)	Transient rise in NAG index and FENa after treatment in one patient
McDougal (1995)	n = 44 PMA 29.4 ± 0.9 weeks, weight 972 ± 178 g (n = 16)	Intermittent infusion: 15-18 mg/kg per dose 12-36 hourly according to PMA	Not reported	Steady state (not further defined); peak	Increase in SCr or urea not further defined	None detected

Prospective observational study (62)	PMA 32.9 ± 1.8 weeks, weight 1379 ± 382 g (n = 15) PMA 39.2 ± 2 weeks, weight 2616 ± 753 g (n = 13)			25-35, trough 5-10		
Tissing (1993) Case report (63)	n = 1 PMA 29.3 weeks, weight 1520 g	Intermittent infusion: 15 mg/kg per dose every 12 hours	Tobramycin	Timing not reported; no target (reported level 63.3)	Rise in SCr and oliguria not further defined	Transient rise in SCr and persistently elevated vancomycin level. Resolution at 2 months of age.
Lisby-Sutch (1988) Prospective	n = 13 PMA 29.8 ± 3.4 weeks, weight 1350 ± 500 g	Intermittent infusion:	Not reported	Timing not reported; peak	Increase in SCr or urea not further defined	None detected

PK study (64)		10 mg/kg per dose 6-12 hourly according to PMA and weight		25–35, trough, 5–10		
Nahata (1987) Prospective observational study (65)	n = 61 < 1 year Further clinical information not available.	Intermittent infusion: 20-60 mg/kg/day (mean 35)	Gentamicin	Timing not reported; trough 2-18	Doubling of SCr concentration	None detected
James (1987) Prospective PK study (33)	n = 20 PMA 26.5 ± 2.6 weeks, weight 880 ± 340 g	Intermittent infusion: 9-18 mg/kg per dose 12 hourly	Not reported	Timing not reported; peak 30, trough 6	Not formally defined	None reported although positive linear correlation between vancomycin level and SCr identified

Dean (1985) Retrospective observational study (66)	n = 28 Population not further defined	Intermittent infusion: 11-55 mg/kg (mean 30 mg/kg) daily not further defined	Gentamicin	Timing not reported; peak 20-40, trough 5-10	Increase in SCr by >0.5 mg/dl (45 μmol/L)	Transient rise in SCr in 2/19 and 2/9 patients receiving vancomycin alone and with gentamicin, respectively.

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Table 1

Source	PMA (weeks)	PNA (days)	Creatinine (mg/dL)	Dose (mg/kg)	Interval (hourly)
British National Formulary for Children	<29			15	24
	29–35			15	12
Manual of Childhood Infections: The Blue Book	>35			15	8
Neofax®	≤29	0–14		10 (bactaeremia) 15 (meningitis)	18
		>14		10	12
The Harriet Lane Handbook	30–36	0–14		10	12
		>14		10	8
The Sanford guide	37–44	0–7		10	12
		>7		10	8
	≥45	Any PNA		10	6
Red Book® 2015 Report of the Committee on			<0.7	15	12
Infectious Disease			0.7–0.9	20	24

			1–1.2	15	24
			1.3–1.6	10	24
			>1.6	15	48

Table 1. Current dosing regimens for vancomycin in neonates

Table 2

Table 2. Studies describing nephrotoxicity in neonates receiving vancomycin

Author (year) Design	Study population receiving vancomycin (mean ± SD unless otherwise stated)	Dosing regimen	Concomitant nephrotoxic agents	Timing/Target levels (μg/mL)	Nephrotoxicity Definition	Incidence of nephrotoxicity
Constance (2015) Propensity-matched cohort study (23)	n = 533 PMA <25 weeks n = 35, 25-28 weeks n = 73, 28-32 weeks n = 158, 32-27 weeks n = 152, >37 weeks n = 115 weight 1649 (1060-2504) g median (IQR)	Intermittent infusion: 12-40 mg/kg per day (not further described)	Gentamicin Ibuprofen	Timing and target concentrations not reported	SCr rise by ≥150% within 48 hours or SCr ≥1.5 mg/dL (132 μmol/L) persisting ≥48 h	Transient rise in SCr in 12/533 patients receiving vancomycin with gentamicin
Moffett (2015) Retrospective case-control study (39)	n= 83 neonates with critical cardiac disease	Not specified	Gentamicin Furosemide Amphotericin		Doubling of SCr	2 developed AKI. AKI more likely with concomitant nephrotoxic agents

Petrie (2015) Retrospective observational study (40)	n = 83 PMA 30+3 (23+6-52+4) weeks, weight 1.12 (0.56-4.7) g median (IQR)	Intermittent infusion: 15 mg/kg per dose 8-24 hourly according to PMA	Not reported	Timing not reported; trough 10–15	Rise in SCr not further defined	None detected
Vandendriessche (2014) Retrospective observational study (41)	n = 223 PMA 32 (24–41) weeks, median (range) 1650 (420–4680) g	Intermittent infusion: 10-15 mg/kg 6-24 hourly according to PMA, PNA and SCr	Not reported	Timing not reported; trough > 10	Difference in mean SCr	None detected
Frymoyer (2014)Prospective observational study (42)	n = 249 PMA 39 (32–42) weeks, weight 2900 (1600-3700) g median (IQR)	15-20 mg/kg per dose 12-24 hourly according to SCr and weight	Not reported	After 3rd dose; trough 7-10	Rise in SCr not further defined	None detected

Kim (2014) Retrospective observational study (43)	n=50 PMA 27.4 ± 2.5 weeks, weight 1020 ± 420 g	15-40 mg/kg per dose 6–12 hourly according to PMA	Not reported	Timing not reported; trough ≤ 40	SCr >25% above baseline or urine output <1 ml/kg/h	None detected
Linder (2013) Retrospective observational study (44)	n = 126 PMA 27.5 ± 2.6 weeks, weight 1026 ± 269 g	Intermittent infusion: 10 mg/kg per dose 8-18 hourly according to PMA and PNA	Not reported	1-2 days; Trough 10, peak 30-40	Not formally defined	None detected
Patel (2013) Retrospective observational study (3)	n = 32 (40 treatment courses) PMA 36 (26–62) weeks, weight 2200 (620-6900) g median (IQR)	n = 20 Intermittent infusion: 10-20 mg/kg per dose 8-12 hourly according to SCr n = 20	Not reported	Before 3rd dose; 15-25	Rise in mean ± SD in SCr not further defined	No significant rise in SCr (mean ± SD) in either intermittent dosing or continuous infusion. Two patients developed renal failure 2nd to a

		Continuous infusion: 20–60 mg/kg daily according to PMA and SCr				decline in overall clinical status.
Zhao (2013) Prospective observational study (45)	n = 116 PMA 33.8 ± 5.3 weeks, weight 1700 ± 964 g	Loading dose: 10-15 mg/kg Continuous infusion: 15-35 mg/kg daily according to PMA, PNA and SCr	Not reported	Timing not reported; 15-25	SCr > 70 or 90 μmol/L based on PNA	None detected
Irikura (2011) Prospective observational study (46)	n = 54 n = 21 (SCr-based dosing) PMA 29.65 ± 5.27 weeks Birthweight 1322 ± 951 g n = 33 (dosing based on weight & PNA) PMA 33.18 ± 5.94 weeks	n = 21 Intermittent infusion: 10-20 mg/kg per dose 12-48 hourly according to SCr n = 33 Intermittent infusion: 10 mg/kg per dose 6-18 hourly	Not reported	Timing and target concentrations not reported	Rise in SCr not further defined	Transient rise in SCr in 3 patients (two receiving dose based on weight/PNA and one receiving dosing based on baseline SCr, respectively).

	Birthweight 1839 ± 915 g	according to weight and PNA				
Oudin (2011) PK study (47)	n = 47 PMA 29.5 ± 27, weight 1500 ± 970 g	Loading dose: 7 mg/kg Continuous infusion: 30mg/kg daily	Not reported	Timing not reported; trough 10-30	Rise in SCr not further defined	Transient rise in SCr in 3 patients resolved by 3 weeks after exposure.
Plan (2008) Prospective observational study (48)	n = 145 PMA 28 (26–29) weeks, Weight 904 (780–1160) g median (IQR)	Intermittent infusion: 15-30 mg/kg per dose 24 hourly according to SCr	Diuretics, not further defined	Timing not reported; trough 10-25	Rise in SCr not further defined	No significant rise in SCr detected
Giapros (2007) Retrospective observational study (49)	n = 70 Weight <1000 g	Intermittent infusion every 12 – 48 h – not further defined	Gentamicin	Timing and target not reported	Increased urinary excretion of potassium, calcium and phosphate; raised SCr	5 patients with severe renal tubular disturbance (3 with raised SCr). All abnormalities returned to baseline within 2 weeks

						of the last antibiotic course
Frattarelli (2005) Retrospective observational study (50)	n = 153 SGA; PMA 48 ± 8 weeks, weight 641 ± 181 g Non-SGA; PMA 47 ± 8 weeks, weight 1158 ± 765 g	Intermittent infusion not further defined	Not reported	Timing not reported; trough, target not reported	Rise in SCr not further defined	None detected
Miner (2004) Case series (51)	n = 2 Case 1 – PMA 24 weeks at birth. Day 53 of life when vancomycin commenced Case 2 – PMA 28 weeks at birth. Vancomycin commenced day 9 of life	Intermittent infusion: 150 mg/kg (10x accidental overdose)	None	Timing not reported; peak concentration, >300	Rise in SCr not further defined	Transient rise SCr in one patient

Deville (2003) Phase III, open label RCT (52)	n = 20 PMA 38.6 ± 7.3 weeks Population not further defined	Intermittent infusion: 10-15 mg/kg per dose 6-24 hourly according to PMA	Gentamicin	Timing not reported; trough, target not reported	SCr twice the upper limit of normal or double baseline	Transient rise in SCr in one patient not further described
Tan (2002) Retrospective observational study (53)	n = 101 PMA 30 (23–45) weeks Median (range) Population not further defined	Intermittent infusion: 15 mg/kg per dose 12-18 hourly according to PNA	Not reported	Timing not reported; trough < 10	Difference in mean SCr	None detected
Feferbaum (2001) Prospective observational study (54)	n = 20 PMA 42 ± 3 weeks Population not further defined	Intermittent infusion: 30-60 mg/kg per day (not further described)	None	Timing not reported; trough 5-10, peak 30-40	Rise in SCr not further defined	None detected
Machado (2001)	n = 25 PMA 38 ± 1 weeks,	10-20 mg/kg per dose 6-24 hourly according to PMA	Gentamicin	Timing not reported;	Rise in SCr and urea 5 days after	Significant transient rise in intra-individual SCr

Prospective observational study (55)	3130 ± 861.3 g			trough 5-10, peak 20-40	treatment started not otherwise further defined	but not urea. Not further described.
De Hoog (2000) Retrospective observational study (56)	n = 108 PMA 28.9 (24 – 41) weeks Birthweight 1002 g (485 – 4625 g) Median (IQR)	Intermittent infusion: 30 mg/kg per dose 12 hourly	Not reported	Steady state (not further defined); Peak ≤40, trough 5-15	Increase in SCr or urea not further defined	None detected
Bhatt-Mehta (1999) Retrospective observational study (57)	n = 69 PMA 28.9 ± 3.0 weeks, weight 1219 ± 516 g	Intermittent infusion: 10-15 mg/kg per dose every 6-36 hourly according to PMA	Gentamicin	After 3rd dose; Peak ≤40	SCr double baseline or >0.6 mg/dL (53 µmol/L)	Transient rise in SCr in 6/61 patients with peak concentration ≤40 and none with peak concentrations >40
Goebel (1999) Case report (58)	n = 1 Term infant, PNA 6 d Solitary dysplastic kidney	100 mg/kg	Not reported	12 hours post dose; no target	Anuria. Not otherwise further defined	Commenced hemofiltration due to persistently elevated

						vancomycin level (240 μg/mL). Normal renal function at PNA 3 weeks.
Müller (1999) Case series (59)	n = 2 PMA 35 weeks, weight 1985 and 2390 g	Intermittent infusion: Single dose 35 mg/kg and 38 mg/kg (accidental overdose)	None	9 hours post dose; no target reported	Reduced GFR or microproteinuria (urinary protein electrophoresis)	Transient microproteinuria in both patients but no change in GFR
Pawlotsky (1998) Non-randomised un-blinded trial (60)	n = 53 PMA 33.5 ± 3.7 weeks, weight 1500 ± 300 g (n = 29) PMA 33.9 ± 4.8 weeks, weight 1800 ± 800 g (n = 24)	n = 29 Loading dose: 7 mg/kg Continuous infusion: 10-40 mg/kg per over 24 hours according to PMA and weight n = 24 Continuous infusion:	None	Post loading dose; peak ≤40 Steady state (not further defined); 10-30	Rise in SCr and urea not further defined	Transient rise in SCr in one patient with klebsiella septicaemia

		10-30 mg/kg per over 24 hours according to PMA and weight				
Sakata (1996) Prospective observational study (61)	n = 20 PMA 26.3 ± 1.4 weeks Population not further defined	Intermittent infusion: 9-11 mg/kg per dose 12 hourly	None	Timing and target concentrations not reported	Rise in SCr, fractional excretion of sodium (FENa) and NAG index (NAG:creatinine ratio)	Transient rise in NAG index and FENa after treatment in one patient
McDougal (1995) Prospective observational study (62)	n = 44 PMA 29.4 ± 0.9 weeks, weight 972 ± 178 g (n = 16) PMA 32.9 ± 1.8 weeks, weight 1379 ± 382 g (n = 15)	Intermittent infusion: 15-18 mg/kg per dose 12-36 hourly according to PMA	Not reported	Steady state (not further defined); peak 25-35, trough 5-10	Increase in SCr or urea not further defined	None detected

	PMA 39.2 ± 2 weeks, weight 2616 ± 753 g (n = 13)					
Tissing (1993) Case report (63)	n = 1 PMA 29.3 weeks, weight 1520 g	Intermittent infusion: 15 mg/kg per dose every 12 hours	Tobramycin	Timing not reported; no target (reported level 63.3)	Rise in SCr and oliguria not further defined	Transient rise in SCr and persistently elevated vancomycin level. Resolution at 2 months of age.
Lisby-Sutch (1988) Prospective PK study (64)	n = 13 PMA 29.8 ± 3.4 weeks, weight 1350 ± 500 g	Intermittent infusion: 10 mg/kg per dose 6-12 hourly according to PMA and weight	Not reported	Timing not reported; peak 25–35, trough, 5–10	Increase in SCr or urea not further defined	None detected
Nahata (1987)	n = 61 < 1 year Further clinical information not available.	Intermittent infusion: 20-60 mg/kg/day (mean 35)	Gentamicin	Timing not reported; trough 2-18	Doubling of SCr concentration	None detected

Prospective observational study (65)						
James (1987) Prospective PK study (33)	n = 20 PMA 26.5 ± 2.6 weeks, weight 880 ± 340 g	Intermittent infusion: 9-18 mg/kg per dose 12 hourly	Not reported	Timing not reported; peak 30, trough 6	Not formally defined	None reported although positive linear correlation between vancomycin level and SCr identified
Dean (1985) Retrospective observational study (66)	n = 28 Population not further defined	Intermittent infusion: 11-55 mg/kg (mean 30 mg/kg) daily not further defined	Gentamicin	Timing not reported; peak 20-40, trough 5-10	Increase in SCr by >0.5 mg/dl (45 µmol/L)	Transient rise in SCr in 2/19 and 2/9 patients receiving vancomycin alone and with gentamicin, respectively.