Clinical Pharmacology of Vancomycin in Infants and Children

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Abstract

Aim: The aim of this study is to review the clinical pharmacology of vancomycin in infants and children.

Methods: The literature search was performed electronically using PubMed as search engine.

Results: Vancomycin is active against gram-positive bacteria including methicillin-resistant Staphylococcus aureus, penicillin-resistant streptococci, and ampicillin-resistant enterococci. Vancomycin dosage consists in a loading dose followed by a maintenance dose in infants and ranges from 10 to 20 mg/kg 4 times-daily in children. Vancomycin elimination half-life is about 10 hours in preterm infants, 4.8 hours in children, and 2.6 hours in children with severe infections. Vancomycin concentrations ≥ 15 µg/ml is associated with nephrotoxicity and ototoxicity and the recommended trough concentration is 5 to 10 µg/ml. The prophylaxis and treatment with vancomycin have been studied in infants and children. Vancomycin administered intravenously and/or intraventricularly treats the meningitis caused by Elizabethkingia meningoseptica and by Staphylococcus aureus. Vancomycin poorly penetrates the human placenta and poorly migrates into the breast-milk.

Conclusion: This study reviews the published data of vancomycin dosing, efficacy and safety, adverse-effects, pharmacokinetics, drug interaction, prophylaxis, treatment, penetration into the cerebrospinal fluid and treatment of meningitis in infants and children and vancomycin transfer across the human placenta and migration into the breast-milk.

Keywords: vancomycin; dosing; adverse-effects; prophylaxis; treatment; cerebrospinal fluid; meningitis; placental; breast-milk

Abbreviations: CSF: Cerebrospinal Fluid.

Introduction

Vancomycin is a tricyclic glycopeptide antibiotic produced by Streptococcus orientalis [1].

Antimicrobial activity of vancomycin:

Vancomycin possesses activity against the vast majority of gram-positive bacteria including methicillin-resistant Staphylococcus aureus, penicillin-resistant streptococci, and ampicillin-resistant enterococci. The following gram-positive organisms: Lactobacillus, Leuconostoc, Pediococcus, and Erysipelothrix are intrinsically resistant to vancomycin. Essentially all species of gram-negative bacilli and mycobacteria are resistant [1].

Mechanism of action of vancomycin:

Vancomycin inhibits the synthesis of the cell wall in sensitive bacteria by binding with high affinity to the D-alanyl-D- alanine terminus of cell wall precursor units. Because of vancomycin large molecular size, it is unable to penetrate the outer membrane of gram-negative bacteria [1].
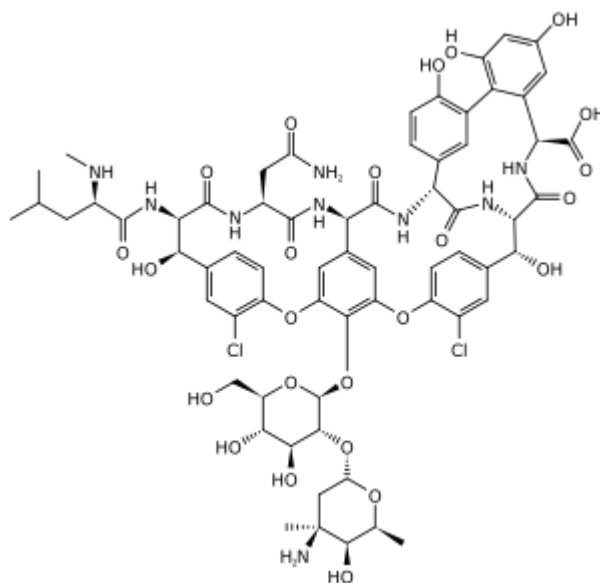
Figure 1: Vancomycin molecular structure (molecular weight = 1,449.3 grams/mole)

Literature search

The literature search was performed electronically using PubMed database as search engine and the following key words were used: "vancomycin dosing infants, children", vancomycin efficacy, safety infants, children", "vancomycin adverse-effects infants, children", "vancomycin pharmacokinetics infants, children", "drug-interactions", "vancomycin prophylaxis infants, children", "vancomycin treatment infants, children", "vancomycin penetration into the cerebrospinal fluid", "vancomycin meningitis infants, children", "vancomycin placental transfer" and "vancomycin migration into the breast-milk". In addition, the books: The Pharmacological Basis of Therapeutics [1], Neonatal Formulary [2], NEOFAX® by Young and magnum [3], and The British National Formulary for Children [4] were consulted.

Results and discussion

Administration schedules of vancomycin to infants and children

Intravenous administration to infants [2].

Infants aged < 7 days*

Infants with a postmenstrual age < 27 weeks. Give: a loading dose of 10 mg/kg followed by a maintenance dose of 20 mg/kg daily.

Infants with a postmenstrual age 27 to < 30 weeks. Give: a loading dose of 10 mg/kg followed by a maintenance dose of 25 mg/kg daily.

Infants with a postmenstrual age 30 to < 32 weeks. Give: a loading dose of 15 mg/kg followed by a maintenance dose of 25 mg/kg daily.

Infants with a postmenstrual age ≥ 32 weeks. Give: a loading dose of 15 mg/kg followed by a maintenance dose of 30 mg/kg daily.

Infants aged > one week*

Infants with a postmenstrual age < 27 weeks. Give: a loading dose of 10 mg/kg followed by a maintenance dose of 25 mg/kg daily.

Infants with a postmenstrual age 27 to < 30 weeks. Give: a loading dose of 10 mg/kg followed by a maintenance dose of 30 mg/kg daily.

Infants with a postmenstrual age 30 to < 32 weeks. Give: a loading dose of 15 mg/kg followed by a maintenance dose of 30 mg/kg daily.

*In infants with impaired renal function (creatinine > 90 µmol/L) the vancomycin dose should be reduced.

Vancomycin trough concentration should be followed in newborn infants because of changes in renal function related to maturation and severity of illness. Peak concentration has not been cleared demonstrated to correlate with efficacy, but monitoring has been recommended when treating meningitis. In meningitis the trough concentration should be 5 to 10 µg/ml but many experts recommend 10 to 20 µg/ml. The peak concentration should be 30 to 40 µg/ml. Vancomycin in incompatible with: cefazolin, cefepime, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, chloramphenicol, dexamethasone, heparin (concentration > 1 unit/ml), mezlocillin, nafcillin, pentobarbital, phenobarbital, piperacillin, piperacillin/tazobactam, ticarcillin, and ticarcillin/clavulanate [3].

Administration to children [4]

Oral treatment of Clostridium difficile infection (first episode)

Children aged 1 month to 11 years. Give:10 mg/kg 4 times-daily for 10 days, the treatment duration needs to be tailored to the clinical course of individual children (maximum dose = 2 grams).

Children aged 12 to 17 years. Give: 125 mg 4 times-daily for 10 days, increase the dose to 500 mg 4 times-daily for 10 days in severe or complicated infections.

Oral treatment of Clostridium difficile infection (multiple recurrences)

Children aged 12 to 17 years. Give: 125 mg 4 times-daily for 10 days, followed by either tapering the dose (gradually reducing until 125 mg daily) or a pulse regimen (125 to 500 mg every 2 to 3 days for at least 3 weeks.

Intravenous treatment of complicated **(1)** skin, **(2)** soft-tissue, **(3)** bone infections, **(4)** joint infections, **(5)** community-acquired-pneumonia, **(6)** hospital-acquired-pneumonia (including ventilator-associate-pneumonia), **(7)** infective endocarditis, **(8)** acute bacterial meningitis, and **(9)** bacteraemia.

Infants with a postmenstrual age ≥ 32 weeks. Give: a loading dose of 15 mg/kg followed by a maintenance dose of 35 mg/kg daily.

Children aged 1 month to 11 years. Give: 10 to 15 mg/kg 4 times-daily adjusted according to plasma concentration monitoring, the duration of the treatment should be tailored to type and severity of infection and the individual clinical response.

Children aged 12 to 17 years. Give: 15 to 20 mg/kg thrice-daily or twice-daily (maximum dose = 2 grams) adjusted according to plasma concentration, the duration of treatment should be tailored to type and severity of infection and the individual clinical response.

Intravenous treatment of perioperative prophylaxis of bacterial endocarditis in children at high risk of developing bacterial endocarditis when undergoing major surgical procedures

Children. Give: 15 mg/kg to be given prior to the induction of anaesthesia, a second dose may be required depending on the duration of surgery.

Intravenous treatment of central nervous system e.g., ventriculitis (administered on expert advice)

Children. Give: 10 mg once-daily, reduce the dose to 5 mg daily if ventricular size is reduced or increase the dose to 15 to 20 mg daily if the ventricular size is increased. Adjust the dose according to the cerebrospinal fluid concentration after 3 to 4 days. Aim for pre-dose through concentration < 10 µg/ml. If the cerebrospinal fluid is not draining free reduce the dose frequency to once every 2 to 3 days.

Intraperitoneal administration of peritonitis associated with peritoneal dialysis

Children. Add vancomycin to each bag of dialysis fluid to achieve a concentration of 20 to 25 µg/ml.

Inhalational or nebulisation treatment for the eradication of methicillin-resistant Staphylococcus aureus from the respiratory-tract in cystic fibrosis children

Children. Give: 4 mg/kg twice-daily (maximum dose = 250 mg) for 5 days, alternatively 4 mg/kg 4 times-daily (maximum dose = 250 mg) for 5 days.

This information reveals that vancomycin may be administered orally, intravenously, intraperitoneally, by

inhalation or by nebulisation. The length of treatment varies with the disease to be treated and the vancomycin blood concentration must be monitored in order to produce the desired effects and to prevent toxicity.

Efficacy and safety of vancomycin in infants and children

A vancomycin loading dose of 25 mg/kg followed by a maintenance dose of 15 mg/kg twice-daily or thrice-daily is found efficacy and safe to treat infants with an infection due to coagulase-negative staphylococci [5]. Vancomycin was intravenously infused at a dose of 25 mg/kg daily to 145 preterm infants infected by coagulase-negative staphylococci and this dosing-regimen is found efficacy and safe [6]. A dose of 60 mg/kg daily is found efficacy and safety to treat children with infections caused by gram-positive bacteria [7]. Seventy-hundred-ninety-five children, aged > 14 years, had an infection caused by methicillin-resistant Staphylococcus aureus and vancomycin is found effective and safe in treating the infection caused by this organism [8]. Vancomycin is an effective and safe agent for the treatment of staphylococcal infections in paediatric patients [9]. Thus, vancomycin is an effective and safe drug to treat the infection caused by coagulase-negative staphylococci, Staphylococcus aureus and different gram-positive organisms.

Adverse-effects caused by vancomycin in infants and children

Rapid intravenous infusion of vancomycin may cause erythematous or utricle reactions, flushing, tachycardia, and hypotension ("red man" or "red neck" syndrome). These reactions may be ameliorated administering vancomycin slowly. Other adverse-effects are nephrotoxicity and ototoxicity [1]. Following administration of vancomycin to 680 children, the vancomycin trough concentration was ≥ 15 µg/ml and AUC was ≥ 800 µg*h/ml. In these children the treatment with vancomycin is associated with a > 2.5-fold increased risk of nephrotoxicity and may provide justification for use of alternative antibiotics [10]. Renal toxicity appears in 72 of 265 children (27.2%) who had the trough concertation of vancomycin ≥ 10 µg/ml [11]. The renal function of children treated with vancomycin was impaired when the vancomycin trough concentration is ≥ 15 µg/ml [12]. Vancomycin exposure to very-low-birth-weight infants is associated with a dose-dependent risk of pathological hearing test which is observed at discharge and at 5 years of age [13]. Infants admitted to the neonatal intensive care unit were treated with vancomycin and developed ototoxicity when the trough concentration of vancomycin is ≥ 10 µg/ml [14]. Many children treated with vancomycin reached a peak serum concentration of vancomycin > 80 µg/ml and in 5 children the peak serum concentration of vancomycin was > 150 µg/ml. The estimated duration of exposure to toxic concentration of vancomycin was 15 to 43 hours and children developed nephrotoxicity and ototoxicity [15]. Thus the main adverse-effects caused by vancomycin are nephrotoxicity and ototoxicity and the blood concentration of vancomycin must be monitored in order to keep vancomycin trough concentration < 10 µg/ml to prevent toxicity.

Pharmacokinetics of vancomycin in infants

Machado et al. [16] studied the pharmacokinetics of vancomycin in two groups of preterm infants. Infants of group A (N = 13) had the mean postmenstrual, postnatal ages, and body-weight of 31.8 weeks (range, 31.2 to 32.3), 15.3 days (range, 12.0 to 18.5) and 1,184 grams (range, 1,030 to 1,338), respectively, and infants of group B (N = 12) had the mean postmenstrual, postnatal ages, and body-weight of 33.8 weeks (range, 33.5 to 34.1), 26.0 days (range, 18.0 to 34.0) and 1,175 grams (range, 1,000 to 1,350), respectively. The postmenstrual age and the postnatal age are significantly different in the two groups of infants. In infants of group A, vancomycin was administered at a dose of 15 mg/kg twice-daily (N = 9) and 20 mg/kg every 18 hours (N = 4). In infants of group B, vancomycin was administered at a dose of 10 mg/kg thrice-daily (N = 7), 15 mg/kg twice-daily (N = 3), and 20 mg/kg every 18 hours (N = 2).

Table 1. Trough and peak plasma concentrations of vancomycin which are obtained in two groups of infants. Figures are the percent of the through and peak concentrations of vancomycin, by Machado et al. [16].

Plasma concentration	Infants of group A	Infants of group B
Trough concentration of vancomycin (µg/ml)		
< 5	23% (3/13)	17% (2/12)
5 – 10	54% (7/13)	33% (4/12)
>5	23% (3/13)	50% (6/12)
Peak concentration of vancomycin (µg/ml)		
< 20	54% (7/13)	25% (3/12)
20 – 40	23% (3/13)	75% (9/12)
>40	23% (3/13)	0% (0/12)

Recommended range of doses: trough = 5 to 10 µg/ml, peak = 20 to 40 µg/ml.

Table 1 shows that the peak concentration of vancomycin is in the recommended range in 77% of infants of group A and in 50% in infants of group B. In addition, peak concentration < 20 µg/ml is obtained in 54% of infants of group A and in 25% of infants of group B. A peak concentration > 40 µg/ml is obtained in 23% of infants of group A and none in infants of group B. This peak concentration is a potential risk of ototoxicity. Regarding clinical efficacy, high percentages of peak concentration is obtained in 23% of infants of group A and in 75% of infants of group B.

Table 2. *Student t test for impaired data. Pharmacokinetic parameters of vancomycin which are obtained in two groups of preterm infants. Figures are the mean and (95% confidence interval), by Machado et al. **[16]**.

Parameter	Infants of group A	Infants of group B	*P-value
Peak concentration (µg/ml)	23.6 (16.0 – 31.2)	26.0 (20.6 – 31.4)	0.63
Trough concentration (µg/ml)	10.5 (5.4 – 15.7)	9.9 (8.1 – 11.8)	0.96
Elimination half-life (h)	11.3 (9.3 – 13.3)	8.7 (6.7 – 10.8)	0.50
Distribution volume (L/kg)	0.85 (0.63 – 1.06)	0.56 (0.45 – 0.66)	0.01
Total body clearance (ml/min/kg)	0.98 (0.70 – 1.20)	0.89 (0.70 – 1.07)	0.69

Table 2 shows that the distribution volume is different in the two groups of infants and it is lower than the water volume whereas the other pharmacokinetic parameters are similar in the two groups of infants.

Mali et al. **[17]** investigated the pharmacokinetics of vancomycin in 12 children, aged 5.3 years, and weighing 15.6 kg. Vancomycin was intravenously infused at a dose of 20 mg/kg thrice-daily.

Table 3. Pharmacokinetic parameters of vancomycin which are obtained in 12 children. Figures are the minimum, maximum, mean and standard deviation (SD), by Mali et al. **[17]**.

	Peak conc. (µg/ml)	Tss max (h)	*Half-life (h)	$AUCss_{0-8 h}$ (h*µg/ml)	DV (L)	TBC (ml/min)	$AUC_{0-24 h}$ (µg*h/ml)
Minimum	18.4	1	2.4	43.6	6.57	0.81	131
Maximum	52.4	1	11.9	208	20.7	3.5	625
Mean	40.9	1	4.8	124	12.5	2.1	372
±SD	15.1	1	2.7	51.3	4.4	0.89	154

Tss max = maximum time to achieve the peak concentration at steady-state. *Elimination half-life. $AUCss_{0-8 h}$ = AUC at steady-state from 0 to 8 hours. DV = distribution volume. TBC = total body clearance. $AUC_{0-24 h}$ = AUC from 0 to 24 hours.

Table 3 shows that vancomycin elimination half-life measured in children is shorter than that obtained in preterm infants, for comparison with preterm infants see the table 2. The distribution volume is greater than the water volume and there is a remarkable interindividual variability in the pharmacokinetic parameters. The comparison of the distribution volume between infants and children is difficult because it has been expressed in different units in the two studies. The longer elimination half-life of vancomycin observed in infants may be explained by the reduced renal function in infants as vancomycin is mainly eliminated by renal route and the renal function increases with infant maturation and child development.

Table 4. Trough concentrations of vancomycin which are obtained in 12 children on three sampling times. Figures are the minimum, maximum, mean and standard deviation (SD) by Mali et al. [17].

	48 hours	56 hours	72 hours
Minimum (µg/ml)	1.7	2.9	3.0
Maximum (µg/ml)	28.0	18.2	22.0
Mean (µg/ml)	10.5	7.6	10.0
±SD	8.5	5.6	6.7

Table 4 shows that the mean trough concentration of vancomycin is similar at the three sampling times and it falls within the recommended range of 5 to 10 µg/ml; however there is a remarkable difference in the trough concentration and in some cases the trough concentration is higher than the recommended values which may cause the toxicity.

Ayuthaya et al. [18] explored the pharmacokinetic of vancomycin in 14 children with severe infections who were aged 6.3 years (range, 3.3 to 10.8) and weighing 16.5 kg (range, 12.8 to 29.2). Vancomycin was intravenously infused at a dose of 15 mg/kg 4 times-daily for the treatment of invasive diseases and 20 mg/kg 4 times-daily for the infection caused by methicillin-resistant Staphylococcus aureus.

Table 5. Pharmacokinetic parameters of vancomycin which are obtained in 14 children with severe infections. Figures are the minimum, maximum, mean and standard deviation (SD), by Ayuthaya et al. [18].

	Dose mg/kg daily	Ke (h^{-1})	DV (L/kg)	DVss (L/kg)	*Half-life (h)	TBC (ml/kg/min)	Trough conc. (µg/ml)	$AUC_{0-24 h}$ (µg*h/ml)
Minimum	55.5	0.117	0.35	0.33	1.46	1.21	2.03	283
Maximum	83.3	0.476	0.68	0.61	5.94	363	12.67	925
Mean	64.3	0.293	0.55	0.49	2.65	2.63	5.69	450
±SD	7.7	0.090	0.10	0.09	1.12	0.69	3.00	184

Ke = elimination rate constant, DV = distribution volume. DVss = distribution volume at steady-state. *Elimination half-life. TBC = total body clearance. $AUC_{0-24 h}$ = Area under the serum concentration time from 0 to 24 hours.

Table 5 shows that the elimination half-life in children with severe infections is shorter and the $AUC_{0-24 h}$ is greater than those obtained in children without severe infections. For comparison of the values obtained in children without infections see the Table 3.

Table 6. Summary of simulation results of 10,000 children receiving vancomycin at doses of 40 mg/kg daily, 60 mg/kg daily, 80 mg/kg daily, and 100 mg/kg daily administered in 4 divided doses. Figures are the mean$\pm$SD and the median of interquartile range (IQR) of the trough concentration obtained at 6 and 24 hours after dosing in simulated children whom their $AUC_{0-24 h}$ values range from $\geq$ 400 to < 800 µg*h/ml, by Ayuthaya et al. [18].

	$AUC_{0-24 h} \geq 400$ and < 800 µg*h/ml			Trough concentration at 6 hours		Trough concentration at 24 hours	
Dose (mg/kg daily)	*Probability*	*Mean$\pm$SD*	*Median (IQR)*	*Mean$\pm$SD*	*Median (IQR)*	*Mean$\pm$SD*	*Median (IQR)*
40	0.258	536$\pm$103	510 (451 – 606)	7.04$\pm$2.17	6.95 (5.60 – 8.39)	11.75$\pm$4.22	11.18 (8.56 – 14.5)
60	0.406	561$\pm$111	543 (463 – 649)	6.81$\pm$2.54	6.67 (4.95 – 8.57)	10.10$\pm$4.36	9.50 (6.77 – 13.1)
80	0.434	580$\pm$112	570 (482 – 973)	6.20$\pm$2.81	5.98 (3.99 – 8.22)	8.51$\pm$4.20	7.91 (5.21 – 11.2)
100	0.401	595$\pm$114	591 (498 – 691)	5.49$\pm$2.78	5.20 (3.36 – 7.39)	7.18$\pm$3.68	6.55 (4.18 – 9.61)

Table 6 shows that the probability of target attainment ($AUC_{0-24 h} \geq 400$) for the MIC = 0.5 µg/ml in the group using vancomycin at a dose of 60 mg/kg daily (15 mg/kg 4 times-daily) is > 0.8 when the MIC value of the methicillin-resistant Staphylococcus aureus is 1 µg/ml. Thus a vancomycin dose of 100 mg/kg daily (25 mg/kg 4 times-daily) is required. The trough concentrations of vancomycin, measured at 6 and 24 hours after dosing, are generally < 10 µg/ml in the 4 simulated doses thus these doses produce appropriate vancomycin trough concentrations.

Interactions of vancomycin with drugs

The combination of vancomycin with trimethoprim and nitrofurantoin causes strong synergism in Escherichia coli [19]. The combination of vancomycin with piperacillin-tazobactam causes nephrotoxicity [20]. Vancomycin interacts with three hydrophobic cyclodextrins (triacetyl alpha-, beta-, or gamma cyclodextrin) and such interaction prolongs the delivery of vancomycin [21]. Ceftazidime precipitates vancomycin in-vitro [22]. Thus vancomycin may interact with drugs however the literature relative to the interaction of vancomycin with drugs is limited.

Prophylaxis with vancomycin in infants and children

The routine vancomycin prophylaxis is recommended in premature infants undergoing the removal of central catheter [23]. Prophylaxis with vancomycin is effective in preventing catheter-related sepsis in preterm neonates [24]. The prophylaxis with low-dose of vancomycin reduces the incidence of nosocomial sepsis in infants [25]. Prophylaxis with intermittent low-dose vancomycin may reduce the recurrent bacteraemia caused by coagulase-negative staphylococci in very-low-birth-weight infants [26]. Prophylactic oral vancomycin confers protection against necrotising enterocolitis in preterm and in very-low-birth-weight infants and is associated with a 50% reduction of the incidence [27]. Routine topical vancomycin administration during closure of non-instrumented spinal procedures is a safe and effective tool for reducing surgical site infections in the paediatric patients undergoing neurosurgery [28]. Prophylaxis with vancomycin is found efficacy in preventing bacterial infections in infants and children [29]. Prophylaxis with vancomycin prevents the infection caused by Clostridium difficile in children and adolescents with cancer [30]. These results are consistent with the view that the prophylaxis with vancomycin prevents the infections caused by different organisms and it is useful to prevent infection in paediatric patients undergoing surgery.

Treatment with vancomycin in infants and children

A loading vancomycin dose of 25 mg/kg followed by a

maintenance dose of 15 mg/kg twice-daily or thrice-daily is the appropriate dosing-regimen to treat infants with infections caused by susceptible gram-positive organisms [31]. Optimal treatment with vancomycin in infants must take into consideration the postmenstrual age, the postnatal age, and the serum creatinine concentration [32]. In infants, the vancomycin dosing-regimen of 10 to 20 mg/kg achieves therapeutic trough concentrations [33]. For infants aged < 1 year, the currently advised maintenance dose is 60 mg/kg daily for the treatment of infections caused by susceptible organisms [34]. In very-low-birth-weight infants with uncomplicated coagulase-negative Staphylococcus sepsis, the treatment with vancomycin for 5 days is satisfactory and does not cause adverse-effects [35]. Vancomycin trough concentration < 5 µg/ml is associated with compromised clinical outcomes and trough concentration up to 10 µg/ml should be used in paediatric patients with infections caused by sensitive gram-positive bacterial [36]. Initial empiric vancomycin dose of 60 mg/kg daily results in trough concentration $\geq$ 5 µg/ml in most infants and adolescents [37]. Vancomycin treatment is associated with acute kidney injury in 40% of critically ill adolescent and young adult patients [38]. Moderate to severe acute kidney injury due to vancomycin is infrequent in children but kidney injury may be caused by vancomycin overdose [39]. Acute kidney injury is common in children receiving high dose of vancomycin [40]. The administration of vancomycin with nephrotoxic drugs develops acute kidney injury in children [41]. Common vancomycin dosing-regimen of 40 mg/kg daily is not high enough to achieve trough concentration of 10 µg/ml in the majority of paediatric patients and a dose of 60 mg/kg daily should be used [42]. Vancomycin administered at a dose of 15 mg/kg thrice-daily did not provide therapeutic serum trough concentrations for any paediatric age groups and higher doses and/or more frequent dosing should be given to infants and children [43]. Optimal dosing-regimen of

vancomycin is needed in order to assure the desired pharmacological effect and to prevent toxicity.

Penetration of vancomycin into the cerebrospinal fluid (CSF) of infants, children, and adult patients

Eight preterm infants with the CSF infected by coagulase-negative Staphylococcus aureus received 15 mg of vancomycin intraventricularly. The maximum concentration of vancomycin in the CSF averaged to 24.9 µg/ml and the mean values of vancomycin clearance and distribution volume in the CSF are 0.002 L/h and 0.109 L, respectively [44]. Forty preterm infants had the CSF infected by staphylococci and received 15 mg of vancomycin intraventricularly and the maximum concentration in the CSF is 29.3 µg/ml [45]. Children had the CSF shunt infected by staphylococci or streptococci and were treated with vancomycin at a dose of 15 mg/kg 4 times-daily. The concentration of vancomycin in the CSF ranged from 5 to 20 µg/ml [46]. Seventeen infants and children had the CSF shunt infected by Staphylococcus epidermidis and received 10 mg of vancomycin intraventricularly. The mean concentration of vancomycin in the CSF varies widely and averages to 18.4 ± 21.8 µg/ml [47]. Twenty-two adult patients with postsurgical meningitis were treated with vancomycin at a dose of 500 mg 4 times-daily. The vancomycin trough concentration is 3.63 ± 1.64 µg/ml in the CSF and 13.38 ± 5.36 µg/ml in serum and the trough concentration in the CSF correlates with that in serum (P<0.003) [48]. Thirteen neurosurgical adult patients received 10 mg of vancomycin once-daily or twice-daily and the vancomycin in the CSF ranges from 10 to 30 µg/ml [49]. Vancomycin was administered at a dose of 50 to 60 mg/kg daily after a loading dose of 15 mg/kg to 13 mechanically ventilated adult patients with or without meningitis [50].

Table 7. Concentration of vancomycin which is measured in the cerebrospinal fluid and in the serum of adult patients with or without meningitis. Figures are the minimum, maximum, mean, and standard deviation (SD) of vancomycin, by Albanèse et al. [50].

Serum vancomycin conc. (μg/ml)		CSF vancomycin conc. (μg/ml)		CSF conc./serum conc. ratio	
Highest	*Lowest*	*Highest*	*Lowest*	*Highest*	*Lowest*
Patients with meningitis (N = 7)					
Minimum	21.2	11.6	6.3	0.21	0.11
Maximum	46.8	21.8	19.0	0.89	0.57
Mean	36.4	18.4	11.1	0.48	0.29
±SD	8.2	4.9	4.9	0.22	0.17
Patients without meningitis (N = 6)					
Minimum	24.2	15.0	2.4	0.07	0.10
Maximum	36.1	24.9	4.9	0.24	0.21
Mean	30.3	17.8	3.4	0.18	0.14
±SD	5.3	3.8	1.1	0.05	0.04
*P-value	0.1464	0.8153	0.0070	0.0100	0.0483

*Unpaired t test with Welch's correction.

Table 7 shows that the vancomycin concentration in the CSF to serum ratio is higher in patients with meningitis than in patients without meningitis suggesting that the inflamed meninges favour the penetration of vancomycin in the CSF. In addition, vancomycin administered systemically and/or ventricularly reaches appropriated concentrations in the CSF to treat cerebral sepsis caused by susceptible gram-positive bacteria.

Treatment of meningitis with vancomycin in infants and children

An infant with meningitis caused by Elizabethkingia meningoseptica is cured with intraventricular vancomycin and adverse-effects were not observed in the following 6 months of follow-up [51]. An infant with meningitis due to Elizabethkingia meningoseptica is cured with intraventricular vancomycin [52]. The bacterial meningitis was cured in children with vancomycin administered intraventricularly [53]. The bacterial meningitis is cured in children with vancomycin administered systemically and intraventricularly. Results of an investigation indicate that when the meningeal inflammation is present intravenously administered vancomycin penetrates into cerebrospinal fluid and therapeutically effective levels of drug therein are frequently attained [54]. The meningitis caused by Staphylococcus aureus is cured in children with vancomycin

administered systemically at a dose of 40 mg/kg daily and intraventricularly at a dose of 20 mg daily and the cerebrospinal fluid was sterilized after 48 hours of treatment [55]. These results suggest that vancomycin administered intravenously and/or intraventricularly cures the meningitis caused by Elizabethkingia meningoseptica and the meningitis caused by susceptible pathogens and by Staphylococcus aureus is cured with vancomycin administered systemically and intraventricularly.

Transfer of vancomycin across the human placenta

Vancomycin was administered to 10 pregnant women for the treatment of methicillin-resistant Staphylococcus aureus and vancomycin was detected in umbilical cord blood of only 2 newborn infants [56]. Transplacental transfer of vancomycin is minimal in the ex-vivo human placental perfusion model with no detectable accumulation [57]. Thus vancomycin poorly crosses the human placenta.

Migration of vancomycin into the breast-milk

Ten mothers were treated with vancomycin and vancomycin was detected in blood of only one breastfeeding infants [56]. Chung et al. [58] reviewed the migration of different antibiotics including vancomycin and observed that the migration of vancomycin into the breast-milk is minimal. These results indicate that vancomycin poorly migrates into

the breast-milk.

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This article is a review and drugs have not been administered to men or animals.

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