Attainment of Therapeutic Vancomycin Trough Serum Concentrations with Initial Dosing in Neonatal Intensive Care Unit Patients

Lee Choy Ee[1], Suhaida Shukor[1], Seah Yin Kuan[1]

[1]Pharmacy Department, Hospital Kajang, Selangor, Ministry of Health Malaysia

Abstract

Introduction: Vancomycin is commonly used to treat neonatal late-onset sepsis. It is the first-line antibiotic for treatment of infections caused by coagulase-negative staphylococci (CoNS) and methicillin-resistant *Staphylococcus aureus* (MRSA). However, data for dosing and monitoring of vancomycin in the local neonatal population is lacking.

Objective: This study aimed to assess the percentage of neonates achieving a vancomycin serum trough concentration between 10 to 20 mcg/mL with initial vancomycin dosing.

Methods: A retrospective cross-sectional study was conducted to review the therapeutic drug monitoring serum trough levels in Hospital Kajang Neonatal Intensive Care Unit (NICU) patients who received at least 48 hours of intravenous vancomycin therapy from January 2013 to December 2018. The percentage of neonates achieving sub-therapeutic (<10mcg/mL), therapeutic (10-20mcg/mL), and supra-therapeutic (>20mcg/mL) vancomycin trough levels were compared.

Results: Of the 51 patients included, the mean gestational age was 31.8 ± 4.7 weeks whereas mean postmenstrual age was 35.3 ± 5.2 weeks. Majority of them were preterm neonates (82.4%). On average, vancomycin therapy was initiated at a mean postnatal age of 24.1 ± 20.3 days and mean weight of 1,922.5 ± 1,012.8 grams. These neonates received vancomycin for an average of 6.7 ± 2.8 days. Overall, 41.2% achieved the target vancomycin trough level, while 21.6% of trough concentrations were sub-therapeutic and 37.3% were supra-therapeutic. Supra-therapeutic trough concentrations were more often observed in the preterm group compared to term neonates (45.2% vs 0%, $p < 0.05$). Only one neonate experienced nephrotoxicity (defined as double increment of serum creatinine from baseline).

Conclusion: The current vancomycin dosing regimens used in NICU patients yielded 41.2% of therapeutic trough concentrations. Preterm neonates experienced higher occurrence of supra-therapeutic trough levels. Further studies are required to assess the optimal dosing regimen to attain therapeutic trough concentrations in this neonatal population.

Keywords: Vancomycin, trough, neonates, initial dosing, empiric dosing

NMRR ID: NMRR-17-3080-39364

Correspondence author: Lee Choy Ee
Department of Pharmacy, Hospital Kajang, Jalan Semenyih, 43000 Kajang, Selangor.
Email: leechoyee@moh.gov.my

Introduction

Vancomycin is a glycopeptide antibiotic that is commonly used for empiric treatment of late-onset sepsis in the neonatal intensive care unit (NICU) (1). The most frequent pathogens responsible for late-onset sepsis in NICU patients were Coagulase negative *Staphylococcus* (CoNS) and *Staphylococcus aureus (S. aureus)* (2). The area under the curve (AUC) and minimum inhibitory concentration (MIC) of vancomycin were evaluated by multiple pharmacokinetic/ and pharmacodynamic studies in neonates. The studies demonstrated that serum vancomycin troughs of around 10 mcg/mL (range, 7 to 15 mcg/mL) for MICs of 1 mcg/mL or less may be sufficient for the treatment of the most common neonatal gram-positive infections, predominantly CoNS (3,4).

In the setting of Hospital Kajang, the initial vancomycin dosing commonly prescribed by the clinicians was based on Micromedex NeoFax Reference with the target trough level of 10 to 20 mcg/mL. Micromedex NeoFax Reference is a neonatal drug information intended for full-term babies up to 28 days of postnatal age (PNA) and preterm babies up to 44 weeks postmenstrual age (PMA). The dosing

recommendation from NeoFax suggested intravenous vancomycin 10 to 15 mg/kg every 12 or 18 hours for PMA 29 weeks or less and 10 to 15 mg/kg every 8 or 12 hours for PMA more than 30 weeks, depending on PNA (5). The subsequent dosing of vancomycin will be guided by the therapeutic drug monitoring (TDM) of serum vancomycin trough level (6).

In 2009, the consensus guidelines by the Infectious Diseases Society of America (IDSA) increased the lower limit of trough concentration from 5 to 10 mcg/mL due to the findings that exposure of *Staphylococcus aureus* to trough level of less than 10 mcg/mL can yield strains with vancomycin-intermediate *Staphylococcus aureus* (VISA). In 2011, the IDSA Methicillin-resistant *Staphylococcus aureus* (MRSA) guidelines suggested a higher trough level of 15 to 20 mcg/mL to improve vancomycin bacterial killing when treating serious MRSA infections in adults (7). Although a higher trough level was implemented, the approach of initial vancomycin dosing was not addressed (8). Given the lack of data for vancomycin efficacy and monitoring in the paediatric and neonatal population, the information was often based on data extrapolated from the adult population (9). Moreover, the current dosing practices in Malaysia were derived from literature data of Caucasian infants. The pharmacokinetic variability among these populations should be considered (10).

This study aimed to evaluate the attainment of trough vancomycin concentration between 10 to 20 mcg/mL in NICU patients with the current initial vancomycin dosing. The finding of this study will help the optimisation of vancomycin therapy in this patient group. Besides prevention of toxicity, achieving the therapeutic serum level of vancomycin is crucial in ensuring the efficacy and to avoid the development of resistance (11).

Methods

A retrospective cross-sectional study was conducted to review the therapeutic drug monitoring (TDM) records of vancomycin serum trough levels in Hospital Kajang Neonatal Intensive Care Unit (NICU) patients. The ethical approval was obtained from the Medical Research Ethics Committee (MREC), Ministry of Health Malaysia (MOH). The study was registered with the National Medical Research Register (NMRR-17-3080-39364).

All neonates who received intravenous vancomycin for at least 48 hours and had steady-state vancomycin trough concentrations records between January 2013 and December 2018 were included in this study. In the ward, vancomycin was infused at a constant rate over 60 minutes via an infusion pump. Blood samples were usually collected 30 minutes prior to the fourth or a subsequent dose of vancomycin to assess the vancomycin trough concentrations, ensuring the evaluation of steady-state concentrations as recommended by Clinical Pharmacokinetics Pharmacy Handbook (6). A minimum vancomycin therapy duration of 48 hours was required as one of the inclusion criteria to achieve steady-state serum concentration. Moreover, TDM was deemed impractical for therapy durations under 48 hours, as dose adjustments cannot be carried out unless toxicity was suspected. Repeated serum measurement such as TDM after dosing adjustment and follow-up TDM after toxic concentrations were excluded in this study. In addition, patients who had renal impairment before the initiation of vancomycin therapy were excluded. Renal impairment was defined as a serum creatinine (SCr) greater than 1.5 mg/dL (133 µmol/L) or urine output less than 1 mL/kg/hour (12). Other exclusion criteria were medical records with missing data, trough levels not drawn at steady state and inappropriate sampling time.

The TDM requests during the study period were retrieved from the TDM database while the detailed information was further retrieved from patients' records at the Medical Record Department. Data collected included demographic characteristics, vancomycin doses and administration intervals, the resultant serum trough concentrations, duration of vancomycin therapy and serum creatinine levels.

The primary study outcome was the percentage of NICU patients achieving therapeutic trough concentrations between 10 to 20 mcg/mL with initial vancomycin dosing. Trough concentrations below 10 mcg/mL were classified as sub-therapeutic while trough concentrations more than 20 mcg/mL were classified as supra-therapeutic. Additional outcome included the incidence of nephrotoxicity. Nephrotoxicity was defined as double increment of the serum creatinine from baseline.

Descriptive statistics were used to illustrate the demographic data and outcomes. Proportions were compared using Chi–Square Test of Independence. Fisher's Exact Test was used when assumptions for the Chi–Square Test of Independence cannot be met. SPSS version 21 was used for the data analysis with p–value of less than 0.05 was considered as statistically significant.

Results

A total of 132 TDM observations were obtained. Forty-eight repeated TDM results were excluded. Another 33 observations were excluded based on criteria summarised in Figure 1, leaving 51 vancomycin TDM records for analysis.

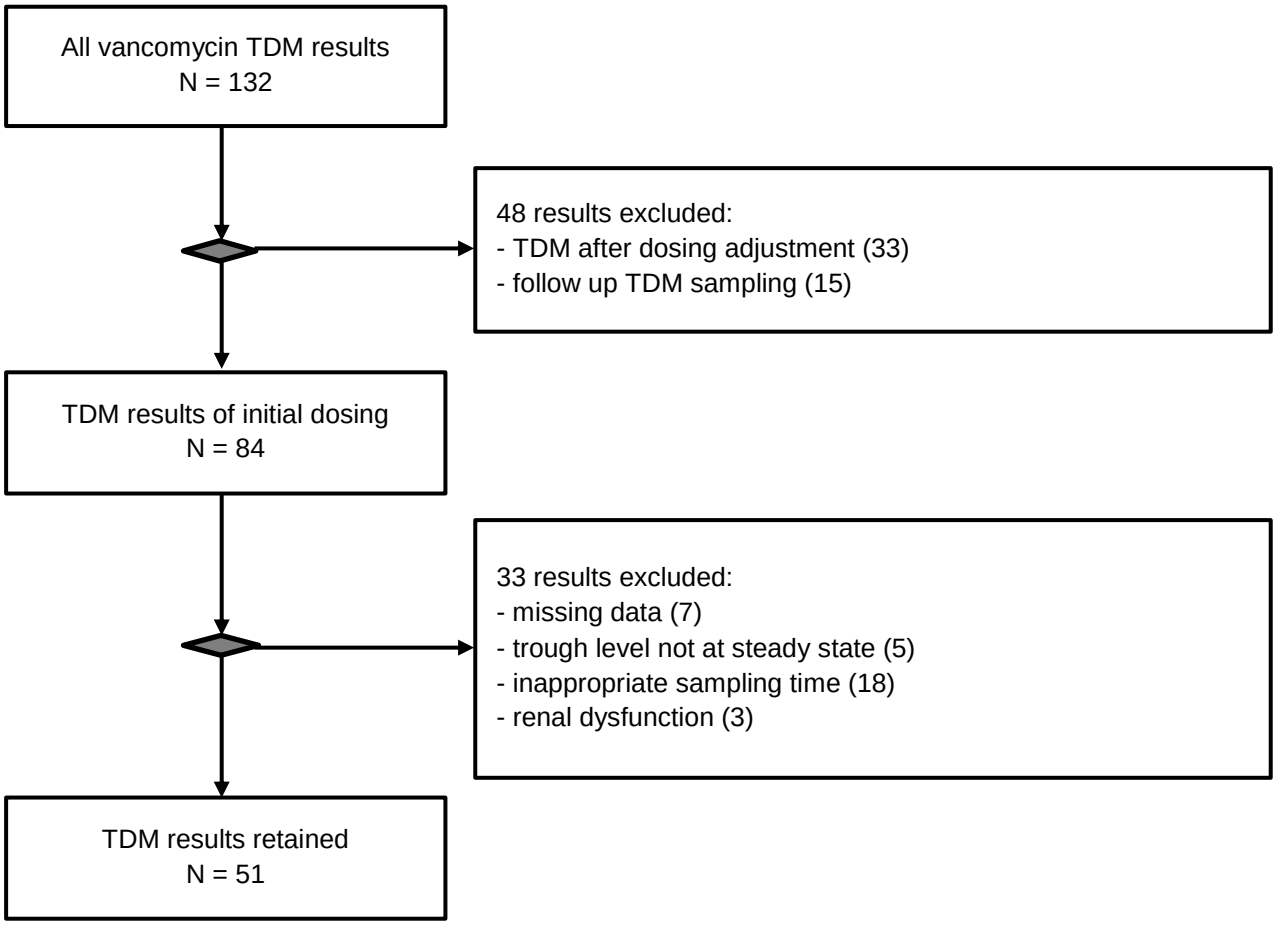

Figure 1: Flowchart of included vancomycin therapeutic drug monitoring (TDM) observations

The demographic characteristics of included patients were presented in Table 1. The mean gestational age (GA) was 31.8 ± 4.7 weeks. Preterm neonates comprised the majority of patients (82.4%), with 10 (19.6%) patients at less than 28 weeks GA, 20 (39.2%) patients were born at a GA of 28 to 32 weeks and 12 (23.5%) at a GA of 32 to 37 weeks. The mean postmenstrual age (PMA) was 35.3 ± 5.2 weeks. Majority of the neonates (76.5%) had a birth weight of less than 2500 grams, and 21.6% of neonates were small for gestational age (SGA). Small for gestational age (SGA) is defined as a birth weight of less than 10th percentile for gestational age. On average, vancomycin therapy was initiated at a postnatal age (PNA) of 24.1 ± 20.3 days with weight of 1,922.5 ± 1,012.8 grams. These neonates received vancomycin for an average of 6.7 ± 2.8 days.

The primary clinical indication of vancomycin therapy was sepsis (43.1%) as shown in Table 1. Most (76.5%) of the patients were covered with vancomycin empirically. Among twelve patients who had positive cultures, seven cultures grew MRSA (13.7% from total samples). Other cultures included *Staphylococcus aureus*, CoNS and other gram-positive bacteria.

Table 1: Demographic characteristics of patients (n=51)

Characteristics	n (%) or Mean ± SD
Gender	
Male	27 (52.9)
Female	24 (47.1)
Ethnicity	
Malay	30 (58.8)
Chinese	6 (11.8)
Indian	7 (13.7)
Foreigner	8 (15.7)
Mean gestational age (weeks)	31.8 ± 4.7
Gestational age categories	
<28 weeks	10 (19.6)
28 weeks - 31 weeks 6 days	20 (39.2)
32 weeks - 36 weeks 6 days	12 (23.5)
>37 weeks	9 (17.6)
Mean postnatal age (days)	24.1 ± 20.3
Mean postmenstrual age (weeks)	35.3 ± 5.2
Postmenstrual age categories	
≤29 weeks	8 (15.7)
30-36 weeks	24 (47.1)
≥37 weeks	19 (37.3)
Mean birth weight (g)	1,659.7 ± 936.3
Birth weight categories	
ELBW (<1,000g)	13 (25.5)
VLBW (<1,500g)	20 (39.2)
LBW (<2,500g)	6 (11.8)
≥2,500g	12 (23.5)
Mean weight at vancomycin initiation (g)	1,922.5 ± 1,012.8
SGA/AGA status	
SGA	11 (21.6)
AGA	40 (78.4)
Mean SCr at vancomycin initiation (µmol/L)	50.6 ± 17.4
Mean WBC at vancomycin initiation ($x10^3$/µl)	14.8 ± 6.3
Mean duration of antibiotic (days)	6.7 ± 2.8
Clinical indications for vancomycin therapy	
Sepsis	22 (43.1)
Pneumonia	14 (27.5)
Catheter related infection	10 (19.6)
Meningitis	2 (3.9)
Conjunctivitis	2 (3.9)
Urinary tract infection	1 (2.0)
Infection type	
MRSA	7 (13.7)
Staphylococcus aureus	1 (2.0)
CoNS	1 (2.0)
Other gram-positive bacteria (enterococcus, cellulomonas, bacillus species)	3 (5.9)
Negative blood culture	39 (76.5)

Abbreviation: ELBW = Extremely low birth weight; VLBW = Very low birth weight; LBW = Low birth weight; SGA = Small for gestational age; AGA = Appropriate for gestational age; SCr = Serum creatinine; WBC = White blood cell

With initial vancomycin dosing, only 21 (41.2%) patients achieved the target vancomycin trough concentration of 10 to 20 mcg/mL. Eleven (21.5%) patients had sub-therapeutic (less than 10 mcg/mL) trough concentrations and 19 (37.3%) were supra-therapeutic (more than 20 mcg/mL). Comparing preterm and term neonates (Table 2), 45.2% of preterm neonates had supra-therapeutic trough concentrations whereas none of the trough values from term neonates were supra-therapeutic. The percentage of sub-

therapeutic troughs were 16.7% and 44.4% for preterm and term neonates respectively. These differences were statistically significant with a p-value less than 0.05. Among neonates with PMA <37 weeks, 80% who received total daily dose (TDD) of more than 30 mg/kg/day had supratherapeutic levels compared with 31.8% who received 30 mg/kg/day or less (p <0.05).

Table 2: Achievement of vancomycin trough concentrations between preterm and term neonates and overall achievement of vancomycin trough concentrations (n=51)

Parameters	Trough levels, N (%)			p-value [a]
	<10 mg/L	10-20 mg/L	>20 mg/L	
Preterm	7 (16.7)	16 (38.1)	19 (45.2)	0.014
Term	4 (44.4)	5 (55.6)	0 (0)	
Overall	11 (21.5)	21 (41.2)	19 (37.3)	

[a] Fisher's exact tests

Table 3: Distribution of vancomycin trough concentrations with different total daily dose in neonates with PMA <37 weeks (n=32)

Total daily dose	Trough levels, N (%)			p-value [b]
	<10 mg/L	10-20 mg/L	>20 mg/L	
≤30 mg/kg/day	5 (22.7)	10 (45.5)	7 (31.8)	0.043
>30 mg/kg/day	0 (0)	2 (20.0)	8 (80.0)	

[b] Fisher's exact tests

In our study, there was one patient who was on concomitant nephrotoxin, furosemide experienced nephrotoxicity. Nephrotoxicity is defined as double increment of serum creatinine from baseline. This patient's serum creatinine increased from 52 µmol/L before initiation of vancomycin therapy to 152 µmol/L after two days of vancomycin therapy. Vancomycin was withheld due to supratherapeutic vancomycin trough concentration.

Discussion

In the neonatal population, the key factors influencing vancomycin pharmacokinetics are body weight, maturation and serum creatinine (1). Maturation of neonates is reflected by postmenstrual age (PMA), gestational age (GA) and postnatal age (PNA). Micromedex NeoFax Reference recommends vancomycin dosing based on a combination of PMA and PNA. The initial dose suggested is 10 to 15 mg/kg intravenously every 6 to 18 hours, depending on the PMA and PNA (5).

Based on the dosing recommendation from Micromedex NeoFax Reference, we found that 41.2% of patients achieved the target trough vancomycin concentration of 10 to 20 mcg/mL. A higher percentage of trough concentrations were supra-therapeutic (37.3%) compared to sub-therapeutic concentrations (21.5%). This was in contrast to several studies which reported a higher proportion of sub-therapeutic trough concentrations. Studies conducted by Ringenberg et al. and Vandendriessche et al. recorded 71.9% and 76.2% of sub-therapeutic trough concentrations, respectively. The attainment of therapeutic levels was low, 25.1% and 23.8%, respectively. Both the studies were using Micromedex NeoFax Reference as dosing regimen in their settings. It was proposed that the current dosing regimen was insufficient to yield trough levels of 10 to 20 mcg/mL (1, 13).

Our findings showed that supra-therapeutic trough concentrations were more often observed in the preterm group compared to term neonates. On the other hand, sub-therapeutic troughs were more often observed in the term neonates compared to the preterm group. This could be explained by the glomerular filtration (GFR) development in neonates. Nephrogenesis begins at the fifth week of gestation and continues until 34 to 36 weeks. In neonates born at 34 weeks of gestation or later, the development of GFR is linear. For premature neonates, the GFR development is slower (14). As vancomycin is eliminated primarily through glomerular filtration, the vancomycin elimination capacity in early days of life in premature neonates is lower, resulting in significant reduction of drug clearance (15,16).

Further analysing the distribution of vancomycin trough concentrations among neonates with PMA less than 37 weeks, the incidence of supratherapeutic levels were significantly higher in patients who received total daily dose (TDD) of more than 30 mg/kg/day compared with those who received 30 mg/kg/day

or less (80% vs 31.8%, p <0.05). The dosing recommendation from Micromedex NeoFax Reference suggested 10 to 15 mg/kg of vancomycin every 12 or 18 hours for PMA 29 weeks or less and 10 to 15 mg/kg every 8 or 12 hours for PMA 30 to 36 weeks, depending on PNA. For neonates with PMA 37 weeks and above, the dose recommended is 10 to 15 mg/kg every 6 to 12 hours, depending on PNA. The results of our study suggested that our premature neonatal population required lower dosages than the current recommendation. This could be explained by a local study conducted by Lo et al. which demonstrated that the clearance of vancomycin was lower than that estimated in the Caucasian patients. Current dosing practice was derived from literature data of Caucasian infants. Hence, it is important to consider the pharmacokinetic variability among these populations (10).

A retrospective population pharmacokinetic analysis conducted by Mehrotra et al. in 2012 assessed four different dosing regimens: based on standard weight, postmenstrual age (PMA), both postmenstrual and postnatal age (PMA/PNA), and based on serum creatinine (SCr). The study found that SCr-based dosing resulted in the least variability in predicted trough concentrations for both premature and full-term neonates. Furthermore, SCr-based dosing was the most effective in achieving trough levels of 5 to 15 mcg/mL in 63% of cases, followed by PMA/PNA-based dosing (52%), PMA-based dosing (42%), and weight-based dosing (34%) (17).

Currently, there is no consensus among the experts on the optimal dosing regimen for neonatal vancomycin (15). Developing an appropriate dosing strategy remains challenging due to the influence of multiple covariates (1), and the complex relationship between these factors and vancomycin clearance in premature neonates (10). Recently, revised consensus guidelines and reviews have recommended AUC-guided therapeutic dosing and monitoring, ideally using Bayesian estimation, to achieve the target vancomycin exposure needed for effective treatment of MRSA infections in all neonates. Monte Carlo simulations with Bayesian estimation indicated that trough concentrations between 7 and 11 mg/L are highly predictive of an AUC24 >400 mg·h/L in at least 90% of neonates. Assuming a minimum inhibitory concentration (MIC) of 1 mg/L, the guidelines suggest dosing between 10 to 20 mg/kg every 8 to 48 hours in neonates and infants up to 3 months old, depending on PMA, weight, and SCr, to achieve an AUC of 400 mg·h/L (18). Thus, an AUC24/MIC target should be considered alongside traditional trough concentration targets to minimise the risk of treatment failure and prevent vancomycin overexposure (19).

In our study, there was one (2%) incidence of nephrotoxicity from vancomycin therapy. The patient was concomitantly on furosemide. This was in accordance with a review by Lestner et al. which reported 1% to 9% occurrence of nephrotoxicity in neonates, supporting the favourable safety profile of vancomycin in neonates (20). Despite higher vancomycin trough concentrations were positively correlated with an increased risk of acute kidney injury (AKI), it was proposed that vancomycin was associated with AKI when administered concomitantly with other nephrotoxins or in other nephrotoxic disease states (21, 22).

The present study has several limitations. Because of its retrospective design, medical records that were not originally intended for research purposes were used for data collection. Also, confounders affecting vancomycin trough concentrations such as concurrent nephrotoxins and renal dysfunction were unable to be controlled. As dosing recommendations were stated in a range, different clinicians may prescribe vancomycin doses differently based on their own clinical judgement while some may be more conservative with initial dosing. Nonetheless, the study's findings may provide valuable insights for future research on optimal vancomycin dosing in neonates.

Conclusion

The current vancomycin dosing regimens used in NICU patients (10 to 15 mg/kg intravenously every 6 to 18 hours, depending on PMA and PNA) yielded 41.2% of therapeutic trough concentrations. Preterm neonates experienced higher occurrence of supra-therapeutic trough levels. Further studies are needed to determine the optimal vancomycin dosing regimen to attain therapeutic trough concentrations in this neonatal population.

Acknowledgement

The authors would like to thank the Director General of Health Malaysia for the permission to publish this paper. We would like to express our sincere gratitude for everyone who has been involved directly or indirectly in helping us to complete this study.

Conflict of interest statement

The authors declare that there is no conflict of interest.

References

1. Ringenberg T, Robinson C, Meyers R, Degnan L, Shah P, Siu A, et al. Achievement of therapeutic vancomycin trough serum concentrations with empiric dosing in neonatal intensive care unit patients. Pediatr Infect Dis J [Internet]. 2015 Jul;34(7):742–7. Available from: https://doi.org/10.1097/INF.0000000000000664.
2. Lessa FC, Edwards JR, Fridkin SK, Tenover FC, Horan TC, Gorwitz RJ. Trends in incidence of late-onset methicillin-resistant Staphylococcus aureus infection in neonatal intensive care units: data from the National Nosocomial Infections Surveillance System, 1995-2004. Pediatr Infect Dis J [Internet]. 2009 Jul;28(7):577—581. Available from: https://doi.org/10.1097/INF.0b013e31819988bf
3. Janssen EJ, Valitalo PA, Allegaert K et al: Towards rational dosing algorithms for vancomycin in neonates and infants based on population pharmacokinetic modelling. Antimicrob Agents Chemother [Internet]. 2015; 60(2): 1013-1021. Available from: https://doi.org/10.1128/AAC.01968-15.
4. Madigan T, Teng CB, Koshaish J et al: Optimization of vancomycin dosing in very low-birth-weight preterm neonates. Am J Perinatol Jan [Internet]. 2015; 32(1): 83-86. Available from: https://doi.org/10.1055/s-0034-1376183.
5. Micromedex NeoFax Reference. Merative US L.P.2013, 2022. Version 3.0.5(201).
6. Clinical Pharmacokinetics Pharmacy Handbook. 2nd ed. Selangor: Pharmacy Practice and Development Division, Ministry of Health Malaysia; 2019. p. 255-269.
7. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis [Internet]. 2011 Feb;52(3):e18-55. Available from: https://doi.org/10.1093/cid/ciq146.
8. Legal M, Wan M. Influence of age on frequency of vancomycin dosing. Can J Hosp Pharm [Internet]. 2010 Jan;63(1):13–9. Available from: https://doi.org/10.4212/cjhp.v63i1.863.
9. Hoang J, Dersch-Mills D, Bresee L, Kraft T, Vanderkooi OG. Achieving therapeutic vancomycin levels in pediatric patients. Can J Hosp Pharm [Internet]. 2014;67(6):416–22. Available from: https://doi.org/10.4212/cjhp.v67i6.1403.
10. Lo YL, Van Hasselt JGC, Heng SC, Lim CT, Lee TC, Charles BG. Population pharmacokinetics of vancomycin in premature Malaysian neonates: Identification of predictors for dosing determination. Antimicrob Agents Chemother [Internet]. 2010;54(6):2626–32. Available from: https://doi.org/10.1128/AAC.01370-09.
11. Gordon CL, Thompson C, Carapetis JR, Turnidge J, Kilburn C, Currie BJ. Trough concentrations of vancomycin: adult therapeutic targets are not appropriate for children. Pediatr Infect Dis J [Internet]. 2012 Dec;31(12):1269–71. Available from: https://doi.org/10.1097/INF.0b013e31826a3eaf
12. Karlowicz MG, Adelman RD. Nonoliguric and oliguric acute renal failure in asphyxiated term neonates. Pediatr Nephrol [Internet]. 1995 Dec;9(6):718–22. Available from: https://doi.org/10.1007/BF00868721.
13. Vandendriessche A, Allegaert K, Cossey V, Naulaers G, Saegeman V, Smits A. Prospective validation of neonatal vancomycin dosing regimens is urgently needed. Curr Ther Res - Clin Exp [Internet]. 2014;76:51–7. Available from: https://doi.org/10.1016/j.curtheres.2014.06.001
14. Arant BS. Postnatal development of renal function during the first year of life. Pediatr Nephrol [Internet]. 1987;1:308-13. Available from: https://doi.org/10.1007/BF00849229.
15. Zhao W, Lopez E, Biran V, Durrmeyer X, Fakhoury M, Jacqz-Aigrain E. Vancomycin continuous infusion in neonates: dosing optimisation and therapeutic drug monitoring. Arch Dis Child [Internet]. 2013 Jun;98(6):449–53. Available from: https://doi.org/10.1136/archdischild-2012-302765.
16. Robinson D, Weiner CP, Nakamura KT, Robillard JE. Effect of Intrauterine Growth Retardation on Renal Function on Day One of Life. Am J Perinatol [Internet]. 1990;7(04):343–6. Available from: https://doi.org/10.1055/s-2007-999519.
17. Mehrotra N, Tang L, Phelps SJ, Meibohm B. Evaluation of vancomycin dosing regimens in preterm and term neonates using Monte Carlo simulations. Pharmacotherapy [Internet]. 2012 May;32(5):408–19. Available from: https://doi.org/10.1002/j.1875-9114.2012.01029.x.
18. Rybak MJ, Le J, Lodise TP, Levine DP, Bradley JS, Liu C, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: A revised consensus guideline and

review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatr. Am J Heal Pharm [Internet]. 2020;77(11):835–63. Available from: https://doi.org/10.1093/ajhp/zxaa036.

19. Dersch-Mills D, Bengry T, Akierman A, Alshaikh B, Yusuf K. Assessment of initial vancomycin dosing in neonates. Paediatr Child Health [Internet]. 2014;19(6):291–291. Available from: https://doi.org/10.1093/pch/19.6.e30.
20. Lestner JM, Hill LF, Heath PT, Sharland M. Vancomycin toxicity in neonates: a review of the evidence. Curr Opin Infect Dis [Internet]. 2016;29(3). Available from: https://doi.org/10.1097/QCO.0000000000000263.
21. Bhargava V, Malloy M, Fonseca R. The association between vancomycin trough concentrations and acute kidney injury in the neonatal intensive care unit. BMC Pediatr [Internet]. 2017;17(1):1–6. Available from: https://doi.org/10.1186/s12887-017-0777-0.
22. Glanzmann C, Frey B, Vonbach P, et al. Drugs as risk factors of acute kidney injury in critically ill children. Pediatr Nephrol [Internet]. 2016;31:145-51. Available from: https://doi.org/10.1007/s00467-015-3180-9.