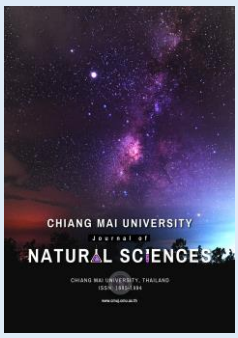

Editor:
Veerasak Punyapornwithaya,
Chiang Mai University, Thailand

Article history:
Received: December 5, 2021;
Revised: February 3, 2022;
Accepted: February 9, 2022;
https://doi.org/10.12982/CMUJNS.2022.031

Corresponding author:
Anutra Khangtragool,
E-mail: anutra.k@cmu.ac.th

Research article

Mortality and Factors Related in Pediatric Intensive Care Unit Patients Treated with Vancomycin

Anutra Khangtragool[1,*], Kanokkarn Sunkonkit[2], Aroonrut Lucksiri[3], and Sukanlaya Seetaboot[2]

1 Division of Pharmacy, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand
2 Department of Pediatrics, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand
3 Department of Pharmaceutical Care, Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand

Abstract There is limited information available regarding clinical outcome and rate of mortality in relation to invasive methicillin-resistant *Staphylococcus* aureus (MRSA) infection in pediatric intensive care unit (PICU) patients treated with vancomycin in this tertiary hospital in northern Thailand. Therapeutic drug monitoring (TDM) is recommended vancomycin prescription; however, it is important to investigate the outcome of this monitoring in PICU patients. This study aims to evaluate the mortality and factors related to these in PICU patients treated with vancomycin. A retrospective study was conducted in PICU patients given vancomycin from April 2018 to April 2019. The following variables were included: age, sex, underlying disease, diagnosis, length of stay (LOS) in PICU, Pediatric Index of Mortality 2 (PIM 2) score, mechanical ventilator use, renal replacement therapy (RRT), laboratory data, vancomycin dose, trough serum vancomycin concentration (C_{trough}) and mortality rate. One hundred and sixty pediatric patients were enrolled into the study (median age 12 months, range 2-180 months, 69.4% male). C_{trough} of vancomycin (10–20 mg/L) was recorded in 32.5% (n = 52) of cases. Septic shock was the most common diagnosis (49.3%) and the mortality rate was 39.4%. Results indicated that children who had a vancomycin C_{trough} outside the therapeutic range, mechanical ventilator use and RRT use were statistically significantly associated with higher mortality rate (adjusted OR 3.29, 95% CI, 1.41-7.69; P <0.05), (adjusted OR 6.22, 95% CI, 1.67-23.16; P < 0.05) and (adjusted OR 10.41, 95% CI, 2.62-41.37; P < 0.05). These factors were related to mortality and further studies are needed to determine if this outcome can be improved.

Keywords: Vancomycin, Vancomycin trough concentration, Pediatric patients, Intensive care, Mortality, Factors related to mortality

Citation: Khangtragool, A., Sunkonkit, K., Lucksiri, A., and Seetaboot, S. 2022. Mortality and factors related in pediatric intensive care unit patients treated with vancomycin. CMU J. Nat. Sci. 21(2): e2022031.

INTRODUCTION

A pediatric intensive care unit (PICU) is a unit specifically designed for the treatment of pediatric patients with severity of illness or other life-threatening conditions, required comprehensive and continuous intensive care by a medical team with specialist relevant skills (de la Oliva et al., 2018). Children admitted to the PICU represent a highly vulnerable patient population in which serious infection, both as a primary cause for admission and as a secondary healthcare-associated infection (HAI), is one of the most common problems (Renk et al., 2020). Across the world, infections in intensive care units (ICU) are associated with high morbidity and mortality rates (Vincent et al., 2009). Patients admitted to the ICU most commonly require antibiotic therapy to treat complicated infections (Abbas, et al., 2016). MRSA continues to be associated with significant morbidity and mortality, and vancomycin has become the gold standard for fighting this pathogen (Rodvold and McConeghy, 2014).

Vancomycin is an antibiotic isolated from the bacterium *Amycolatopsis orientalis* (Katzung, 2017). It has been available for clinical use for more than 50 years (Levine, 2006). It is a bactericidal drug, active primarily against gram-positive bacteria, and remains the most important drug for the treatment of MRSA (Holmes and Howden, 2014). In 2012, a review of the analyses of related population pharmacokinetics (Marsot et al., 2012) found that in adults dosing regimens for vancomycin should depend on creatinine clearance and body weight, whereas in children creatinine clearance, body weight and age were crucial factors. Early clinical studies suggest that in PICU patients with no renal impairment a vancomycin dosage regimen of 60 mg/kg/day, divided into 3 separate doses at 8 hourly intervals, is advisable (Glover et al., 2000).

The goal of therapeutic drug monitoring (TDM) is to use drug concentrations to manage the medication regimen of the patient and optimize the outcome (Gross, 2001). Vancomycin needs to be closely monitored to maximize clinical efficacy and limit toxicity. TDM is recommended and routinely used in many centers around the world (Monteiro, Hahn, Goncalves and Fresco, 2018; Ye et al., 2016) especially in neonate (Pokorna et al. 2019) and pediatric populations (Balch et al., 2015). The routine monitoring of vancomycin serum concentrations in clinical situations is typically carried out to ensure the steady state of trough concentration, independent of the estimation of the initial dose. The recommended doses for pediatric patients with mild/moderate infection and severe infections were found to be 15 mg/kg and 20 mg/kg, respectively (Ye et al., 2016). The target vancomycin trough concentration in pediatric patients with mild/moderate infection and severe infection were 10-15 mg/L and 15-20 mg/L, respectively (Ye et al., 2016).

The aim of this study was to evaluate the mortality and factors related in PICU patients treated with vancomycin.

MATERIAL AND METHODS

This retrospective study was conducted in the PICU in Maharaj Nakorn Chiang Mai Hospital from April 2018 to April 2019. The study was approved by the Institution Review Board of the Faculty of Medicine Chiang Mai University (STUDY CODE: D-PHA-2562-06588) with a waiver for the granting of informed consent. A chart review from electronic data records was conducted for all pediatric patients who were admitted to PICU between the ages of 1 month and 15 years, who fulfilled the inclusion criteria, were given intravenous vancomycin and had at least 1 trough concentration recorded. The recommended doses for pediatric patients with mild/moderate infection and severe infections were 15 mg/kg and 20 mg/kg respectively. Exclusion criteria were pediatric patients who were not given intravenous vancomycin. The patient data collected included age, sex, weight, underlying diseases, diagnosis, Pediatric Index of Mortality (PIM2) (Slater et al., 2003), length of PICU stay, mortality, serum creatinine and electrolyte levels,

vancomycin dosage, administration and blood sampling time, date of sampling time, mechanical ventilator use and renal replacement therapy (RRT). In accordance with the accepted protocol, vancomycin trough concentration was decided at a steady state within the 30 min prior to the fourth or subsequent dose. Serum vancomycin concentrations were analyzed using the Abbott Architect i1000SR Immunoassay system.

Data analysis was carried out using IBM SPSS 23.0. The demographic data were analyzed using descriptive statistics. Normally distributed continuous variables were compared using student t-tests and skewed continuous variables were compared using the Mann-Whitney U test. Categorical data were analyzed using a Chi-square or Fisher's exact test. The correlations between factors and mortality in PICU were assessed using univariable and multivariable logistic regression analysis. Variables with *P*-value <0.2 based on univariable logistic regression analysis were entered into a multivariable regression analysis. The -2 Log likelihood and the Hosmer–Lemeshow test have been used for the goodness of fit results of the logistic regression model. Multicollinearity was checked using Spearmans' rank correlation. A *P*-value less than 0.05 was used to indicate statistical significance.

RESULTS

A total of 160 patients (69.4% male) who received vancomycin treatment were enrolled into the study between April 2018 and April 2019. The demographic and clinical data of both the survival group (60.6%) and non-survival group (39.4%) are shown in table 1. In this study, the most common diagnosis found was septic shock (49.3%) and the mortality rate was 39.4%. There were no significant differences between survival and non-survival rates with regard to sex, blood urea nitrogen (BUN), serum creatinine and length of stay (LOS) in PICU. Significant differences were observed in the following criteria: patients aged over two years ($P < 0.05$), underlying disease ($P < 0.05$), diagnosis ($P < 0.05$), C_{trough} of vancomycin ($P < 0.05$), dose of vancomycin ($P < 0.05$), PIM 2 score > 10 ($P < 0.05$), mechanical ventilator use ($P < 0.05$) and RRT use ($P < 0.05$). The results of the univariable and multivariable regression analysis were used to indicate factors associated with higher mortality rate (see Table 2). According to univariable analysis, children aged less than 2 years old (unadjusted OR 3.80, 95% CI,1.93-7.49; $P < 0.05$), children with underlying disease (unadjusted OR 2.56, 95% CI, 1.11-5.86; $P < 0.05$), children who had a vancomycin C_{trough} outside the therapeutic range (unadjusted OR 2.69, 95% CI, 1.29-5.61; $P < 0.05$), mechanical ventilator use (unadjusted OR 4.58, 95% CI, 1.50-13.98; $P < 0.05$) and RRT use (unadjusted OR 12.48, 95% CI, 4.04-38.50; $P < 0.05$) were associated with mortality. Based on multivariable analysis, children who had a vancomycin C_{trough} outside the therapeutic range, mechanical ventilator use and RRT use were statistically significantly associated with higher mortality rate (adjusted OR 3.29, 95% CI, 1.41-7.69; $P < 0.05$), (adjusted OR 6.22, 95% CI, 1.67-23.16; $P < 0.05$) and (adjusted OR 10.41, 95% CI, 2.62-41.37; $P < 0.05$), respectively. However, there were no statistically significant differences in the different parameters in children aged over two years and children with underlying disease.

Table 1. Demographic and clinical characteristics of patients (N = 160)

Parameters	Survived (n=97)	Not-survived (n=63)	*P-value*
Age >2 years old, n (%)	24 (24.70)	35 (55.60)	*<0.05**
Male, n (%)	69 (71.10)	42 (66.70)	0.54
No underlying disease, n (%)	29 (29.90)	9 (14.30)	*<0.05**
Underlying disease			
Congenital heart disease, n (%)	59 (60.80)	20 (31.70)	
Gastrointestinal disease, n (%)	9 (9.30)	26 (41.30)	
Bronchopulmonary dysplasia, n (%)	0 (0.00)	4 (6.30)	
Hematologic disease, n (%)	0 (0.00)	4 (6.30)	
Diagnosis			*<0.05**
Pneumonia, n (%)	30 (30.90)	14 (22.20)	
Septic shock, n (%)	51 (52.60)	28 (44.40)	
Heart failure, n (%)	16 (16.50)	0 (0.00)	
Abdominal infection, n (%)	0 (0.00)	21 (33.30)	
C_{trough} of vancomycin			*0.05**
Within 10-20 µg/mL, n (%)	39 (40.20)	13 (20.60)	
Outside 10-20 µg/mL, n (%)	58 (59.80)	50 (79.40)	
Vancomycin dose (mg/kg/day)	50 (40, 60) [a]	40 (20, 60) [a]	*0.05**
BUN (mg/dl)	10 (8, 30) [a]	14 (9, 16) [a]	0.71
Creatinine (mg/dl)	0.3 (0.23, 0.59) [a]	0.23 (0.21, 0.49) [a]	0.10
PIM 2 > 10, n (%)	0 (0.00)	30 (47.60)	*<0.05**
LOS in PICU > 14 days, n (%)	87 (89.70)	57 (90.50)	0.87
Mechanical ventilation, n (%)	74 (76.30)	59 (93.70)	*0.05**
Renal replacement therapy, n (%)	4 (4.10)	22 (34.90)	*<0.05**

Note: [a] median (interquartile range); Abbreviations: µg = microgram; mL = milliliter; dL = deciliter; LOS=length of stay; mg = milligram; *= statistically significant at $P < 0.05$, Ctrough = trough concentration

Table 2. Factors associated with higher mortality rate (N=160).

Parameters	Survived (n=97)	Not-survived (n=63)	Unadjusted Odds Ratio (95% CI)	*P-value*	Adjusted Odds Ratio (95% CI)	*P-value*
Age >2 years old, n (%)	24 (24.70)	35 (55.60)	3.80 (1.93-7.49)	<0.05*	-	0.10
Underlying disease, n (%)	68 (70.10)	54 (85.70)	2.56 (1.11-5.86)	<0.05*	-	0.28
C_{trough} of vancomycin outside the therapeutic range, n (%)	58 (59.80)	50 (79.40)	2.69 (1.29-5.61)	0.05*	3.29	0.05*
Mechanical ventilation, n (%)	74 (76.30)	59 (93.70)	4.58 (1.50-13.98)	0.05*	(1.41-7.69)	0.05*
Renal replacement therapy, n (%)	4 (4.10)	22 (34.90)	12.48 (4.04-38.50)	<0.05*	6.22	0.00*

Note: *= statistically significant at $P < 0.05$; Abbreviation: Ctrough = trough concentration

DISCUSSION

Vancomycin is a glycopeptide antimicrobial agent with an important therapeutic role in the treatment of invasive MRSA infection in pediatric patients (Liu et al., 2011; Fiorito et al., 2018; Maloni et al., 2019). However, to date, the mortality and factors related in PICU patients treated with vancomycin have not been analyzed. Our aims were to identify the factors having influence on the mortality pediatric patients treated with vancomycin in PICU. There is a significant burden of MRSA infection in hospitals and the community, therefore it is crucial that vancomycin is used appropriately to its efficacy in the long term and also to ensure optimal drug use in PICU patients.

In this retrospective study of 160 pediatric patients treated with vancomycin, only one-third of the patients (32.5%, n = 52/160) had a recorded trough concentration of vancomycin within the target concentrations (10–20 mg/L). The results of our study showed that a C_{trough} of vancomycin outside the therapeutic range, being on a mechanical ventilator and undergoing RRT were all associated with higher mortality rate.

Therapeutic drug monitoring (TDM) of vancomycin has been used to maximize therapeutic impact while minimizing adverse effects (Rybak et al., 2009). It is routinely recommended that the vancomycin serum trough concentration is ascertained after the fourth dose to optimize the vancomycin dosage regimen (Suryadevara et al., 2012). Most guidelines (Miloslavsky et al., 2017) suggest a vancomycin dose of 15 mg/kg every 6 hours for a mild to moderate infection and recommend the target trough is between 10 to 15 µg/mL. In the case of severe infections, including those caused by MRSA, guidelines suggest a dose of 20 mg/kg every 6 hours with a target trough concentration between 15 to 20 µg/mL (Ye et al., 2016). However, the dosage of vancomycin in pediatric patients with acute kidney injury or underlying kidney diseases need to be extremely closely monitored and adjusted in relation to creatinine clearance ability.

In our study, there was an association between pediatric patients who had a vancomycin trough concentration outside the therapeutic range and a higher mortality rate. A retrospective review found that the mean vancomycin trough concentration in pediatric patients with complicated infections who received 60 mg/kg per day (15 mg/kg per dose every 6 hours) was 10.7 mg/L and only 16.7% of patients between the ages of 2 and 5 years had a therapeutic trough within the guidelines (10 to 20 mg/L) (Madigan et al., 2013). A vancomycin regimen of 15 mg/kg per dose every 6 hours is not likely to achieve a trough concentration of 15 to 20 mg/L in pediatric patients with complicated infections whereas an initial regimen of 80 mg/kg per day for these patients is more likely to result in the recommended therapeutic steady-state concentrations of vancomycin (Durham et al., 2015). Relevant studies show that children who were younger than 6 years had lower repeat-adjusted trough concentrations of serum vancomycin when compared with children aged more than 6 years (Gordon et al., 2012). The half-life of vancomycin ranges from 2 to 10 hours depending on age. For example, in children from 3 months to 4 years old there is an approximate twofold difference in the half-life of vancomycin when compared to those older than 4 years. This knowledge can be used to adjust the vancomycin dose (Broome and So, 2011).

In critically ill children the mean volume of distribution (VD) ranged from 0.44 to 0.81 L/kg, the mean (± SD) clearance (CL) was 1.95 (± 1.1) mL/kg/min, and the mean half-life ranged from 3.1 to 5.3 hours (Giachetto et al., 2011; Gous et al., 1995). Pharmacokinetics (PK) values for vancomycin, especially the VD, are highly variable in critically ill children and more cautionary vancomycin drug monitoring may be necessary in this population (Thakkar et al., 2017).Thus, the TDM is vital for individual adjustment of the dose maximizing its efficacy and safety.

This study found that being on a mechanical ventilator was a factor which was directly related to mortality in PICU patients treated with vancomycin. Ventilator-associated pneumonia (VAP) is still one of the major causes of mortality in PICUs (Amanati et al., 2017). Sanderson KR, et al. (Sanderson and Harshman, 2020) have shown that mortality rates for children on dialysis remain high, although outcomes are improving with the support of a multidisciplinary team and advances in dialysis technology. Our study found that RRT associated factors were a cause of mortality in PICU patients treated with vancomycin. Goals for the future, therefore, need to be healthcare development and technology which reduce mortality in cases of RRT.

In this study, it was found that septic shock was the most common diagnosis associated with mortality. Sepsis and pneumonia, congestive heart failure, and hepatic encephalopathy with underlying diseases including malignancy, heart and liver disease are the most common causes of death (Fallahzadeh et al., 2015). Sepsis is defined as a systemic inflammatory response syndrome (Angus and van der Poll, 2013) in response to infection and is associated with high mortality and

morbidity (Chuma et al., 2016). This study by Chuma et al. (2016), who found that there were significant deviations in vancomycin concentrations both above and below the predicted values in patients with sepsis and it is therefore reasonable to conclude that the duration of systemic inflammatory response syndrome influenced vancomycin concentration in these patients. Our results confirm that the monitoring of vancomycin is vital for the effective management of a vancomycin dosage regimen for pediatric patients in PICU.

There are three main limitations of our study. Firstly, this study is a single-center retrospective study; therefore, these results cannot be directly applied to other populations. Secondly, there are a range of factors impacting on the mortality of PICU patients. Finally, there were more non-survived children undergoing RRT as children who underwent RRT were usually at risk for renal failure as well as multi-organ failure resulting in a wide range of confidence interval for this group. Therefore, the clinical application for other children in PICU should be considered. Future prospective multicenter PICU studies are needed in order to clarify the factors or other conditions which impact on vancomycin concentration in critically ill pediatric patients and to determine if these interventions can reduce the mortality in the study population.

CONCLUSION

PICU patients who were treated with vancomycin and had been on mechanical ventilators and RRT showed a correlation with mortality and need to be monitored closely. We also strongly suggest the use of TDM in all pediatric patients in PICU for the management of a vancomycin dosage regimen to maximize a positive outcome.

AUTHOR CONTRIBUTIONS

All authors read and approved the final manuscript.

ETHICAL APPROVAL

Ethical Approval was given by the Institution Review Board of the Faculty of Medicine Chiang Mai University (STUDY CODE: D-PHA-2562-06588)

REFERENCES

Abbas, Q., Ul Haq, A., Kumar, R., Ali SA, Hussain, K., and Shakoor, S. 2016. Evaluation of antibiotic use in Pediatric Intensive Care Unit of a developing country. Indian journal of critical care medicine: peer-reviewed, official publication of Indian Society of Critical Care Medicine, 20: 291-294.

Amanati, A., Karimi, A., Fahimzad, A., Shamshiri, A.R., Fallah, F., Mahdavi, A., et al. 2017. Incidence of Ventilator-Associated Pneumonia in Critically Ill Children Undergoing Mechanical Ventilation in Pediatric Intensive Care Unit. Children (Basel, Switzerland) 4.

Angus, D.C. and van der Poll, T. 2013. Severe sepsis and septic shock. The New England Journal of Medicine, 369: 840-851.

Balch, A.H., Constance, J.E., Thorell, E.A., Stockmann, C., Korgenski, E.K., Campbell, S.C., et al. 2015. Pediatric vancomycin dosing: Trends over time and the impact of therapeutic drug monitoring. The Journal of Clinical Pharmacology, 55: 212-220.

Broome, L. and So, T.Y. 2011. An evaluation of initial vancomycin dosing in infants, children, and adolescents. International Journal of Pediatrics, 2011: 470364.

Chuma, M., Makishima, M., Imai, T., Tochikura, N., Sakaue, T., Kikuchi, N., et al. 2016. Duration of systemic inflammatory response syndrome influences serum vancomycin concentration in patients with sepsis. Clinical Therapeutics, 38: 2598-2609.

de la Oliva, P., Cambra-Lasaosa, F.J., Quintana-Díaz, M., Rey-Galán, C., Sánchez-Díaz, J.I., Martín-Delgado, M.C., et al. 2018. Admission, discharge and triage guidelines for paediatric intensive care units in Spain. Medicina Intensiva, 42: 235-246.

Durham, S.H., Simmons, M.L., Mulherin, D.W., and Foland, J.A. 2015. An evaluation of vancomycin dosing for complicated infections in pediatric patients. Hospital Pediatrics, 5: 276-281.

Fallahzadeh, M.A., Abdehou, S.T., Hassanzadeh, J., Fallhzadeh, F., Fallahzadeh, M.H., and Malekmakan, L. 2015. Pattern of in-hospital pediatric mortality over a 3-year period at University teaching hospitals in Iran. Indian journal of critical care medicine: peer-reviewed, official publication of Indian Society of Critical Care Medicine, 19: 311-315.

Fiorito, T.M., Luther, M.K., Dennehy, P.H., LaPlante, K.L., and Matson, K.L. 2018. Nephrotoxicity with vancomycin in the pediatric population: a systematic review and meta-analysis. The Pediatric Infectious Disease Journal, 37: 654-661.

Giachetto, G.A., Telechea, H.M., Speranza, N., Oyarzun, M., Nanni, L., and Menchaca, A. 2011. Vancomycin pharmacokinetic-pharmacodynamic parameters to optimize dosage administration in critically ill children. Pediatric critical care medicine: a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies, 12: e250-254.

Glover, M.L., Cole, E., and Wolfsdorf, J. 2000. Vancomycin dosage requirements among pediatric intensive care unit patients with normal renal function. Journal of Critical Care, 15: 1-4.

Gordon, C.L., Thompson, C., Carapetis, J.R., Turnidge, J., Kilburn, C., and Currie, B.J. 2012. Trough concentrations of vancomycin: adult therapeutic targets are not appropriate for children. The Pediatric Infectious Disease Journal, 31: 1269-1271.

Gous, A.G., Dance, M.D., Lipman, J., Luyt, D.K., Mathivha, R., and Scribante, J. 1995. Changes in vancomycin pharmacokinetics in critically ill infants. Anaesthesia and intensive care 23: 678-682.

Gross, A.S. 2001. Best practice in therapeutic drug monitoring. British Journal of Clinical Pharmacology, 52 Suppl 1: 5s-10s.

Holmes, N.E. and Howden, B.P. 2014. What's new in the treatment of serious MRSA infection? Current opinion in infectious diseases, 27: 471-478.

Katzung, B.G. 2017. Basic and Clinical Pharmacology 14th edn. McGraw-Hill Education.

Levine, D.P. 2006. Vancomycin: a history. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America, 42 Suppl 1: S5-12.

Liu, C., Bayer, A., Cosgrove, S.E., Daum, R.S., Fridkin, S.K., Gorwitz, R.J., et al. 2011. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America, 52: e18-55.

Madigan, T., Sieve, R.M., Graner, K.K., and Banerjee, R. 2013. The effect of age and weight on vancomycin serum trough concentrations in pediatric patients. Pharmacotherapy, 33: 1264-1272.

Maloni, T.M., Belucci, T.R., Malagutti, S.R., and Furtado, G.H.C. 2019. Describing vancomycin serum levels in pediatric intensive care unit (ICU) patients: are expected goals being met. BMC Pediatrics, 19: 240.

Marsot, A., Boulamery, A., Bruguerolle, B., and Simon, N. 2012. Vancomycin: a review of population pharmacokinetic analyses. Clinical Pharmacokinetics, 51: 1-13.

Miloslavsky, M., Galler, M.F., Moawad, I., Actis, J., Cummings, B.M., and El Saleeby, C.M. 2017. The Impact of Pediatric-Specific Vancomycin Dosing Guidelines: A Quality Improvement Initiative. Pediatrics, 139.

Monteiro, J.F., Hahn, S.R., Goncalves, J., and Fresco, P. 2018. Vancomycin therapeutic drug monitoring and population pharmacokinetic models in special patient subpopulations. Pharmacology Research & Perspectives, 6: e00420.

Pokorna, P., Sima, M., Cerna, O., Allegaert, K., Tibboel, D., and Slanar, O. 2019. Actual body weight-based vancomycin dosing in neonates. Journal of Chemotherapy, 31: 307-312.

Renk, H., Sarmisak, E., Spott, C., Kumpf, M., Hofbeck, M., and Hölzl, F. 2020. Antibiotic stewardship in the PICU: Impact of ward rounds led by paediatric infectious diseases specialists on antibiotic consumption. Scientific reports, 10: 8826.

Rodvold, K.A. and McConeghy, K.W. 2014. Methicillin-resistant Staphylococcus aureus therapy: past, present, and future. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 58 Supplement, 1: S20-27.

Rybak, M., Lomaestro, B., Rotschafer, J.C., Moellering, R., Jr., Craig, W., Billeter, M., et al. 2009. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. American Journal of Health-System Pharmacy, 66: 82-98.

Sanderson, K.R. and Harshman, L.A. 2020. Renal replacement therapies for infants and children in the ICU. Current opinion in pediatrics, 32: 360-366.

Slater, A., Shann, F., and Pearson, G. 2003. PIM2: a revised version of the Paediatric Index of Mortality. Intensive Care Medicine, 29: 278-285.

Suryadevara, M., Steidl, K.E., Probst, L.A., and Shaw, J. 2012. Inappropriate vancomycin therapeutic drug monitoring in hospitalized pediatric patients increases pediatric trauma and hospital costs. Journal of Pediatric Pharmacology and Therapeutics, 17: 159-165.

Thakkar, N., Salerno, S., Hornik, C.P., and Gonzalez, D. 2017. Clinical Pharmacology Studies in Critically Ill Children. Pharmaceutical research, 34: 7-24.

Vincent, J.L., Rello, J., Marshall, J., Silva, E., Anzueto, A., Martin, C.D., et al. 2009. International study of the prevalence and outcomes of infection in intensive care units. Jama, 302: 2323-2329.

Ye, Z.K., Chen, Y.L., Chen, K., Zhang, X.L., Du, G.H., He, B., et al. 2016. Therapeutic drug monitoring of vancomycin: a guideline of the Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society. Journal of Antimicrobial Chemotherapy, 71: 3020-3025.

OPEN access freely available online
Chiang Mai University Journal of Natural Sciences [ISSN 16851994]
Chiang Mai University, Thailand
https://cmuj.cmu.ac.th