FACTORS AFFECTING THE PHARMACOKINETICS OF VANCOMYCIN IN CHILDREN ADMITTED TO THE INTENSIVE CARE UNIT (ICU) OF THE RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL (RCWMCH).

By

Onyinye Onyeka Akunne

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Supervisor: Professor Pierre Mugabo

Co-supervisor: Professor Andrew Argent

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ABSTRACT

Vancomycin is a glycopeptide antibiotic that inhibits bacterial cell wall synthesis by binding to the D-alanyl-D-alanine terminal end of cell wall precursor units preventing the elongation and cross-linkage of the peptidoglycan. Vancomycin is used to treat infections with gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus (S. aureus), coagulase-negative staphylococci* and penicillin-resistant *Streptococcus pneumoniae (S. pneumoniae)*. It is a time-dependent drug, and its efficacy depends on the duration of pathogen exposure to vancomycin. Low plasma concentration may lead to treatment failure and the re-emergence of bacterial resistance. Vancomycin is known to cause adverse effects at high concentrations. Therefore, it is necessary to monitor plasma concentrations to maintain vancomycin concentration within the therapeutic window. Vancomycin is mainly administered as an intravenous (IV) infusion as it is poorly absorbed from the gastrointestinal system.

The effectiveness of vancomycin is hinged on its pharmacokinetics (PK). Previous studies have found wide variability in vancomycin PK parameters in critically ill children. Although some of the variability has been explained by factors such as age, weight, and renal function, there still exists large unexplained variability in vancomycin PK, especially in the volume of distribution (V_d). This study explores factors that may impact vancomycin pharmacokinetics in critically ill children.

Children aged (1 month – 16 years) admitted to the Paediatric Intensive Care Unit (PICU) of the Red Cross War Memorial Children's Hospital who received vancomycin for suspected or confirmed bacterial infections were included in the study. Patients were recruited according to the inclusion criteria after informed signed/ written consents were obtained from the parents/guardians and children. Vancomycin was administered under standard PICU practice. Six blood samples per patient were collected at optimal times (13hr 30mins, 19hrs and 21hrs, 29hr 22mins, 40hr 48mins

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and 55hr 21mins), were required for the vancomycin PK analysis and were submitted for plasma concentration analysis. Clinical data such as age, weight, the reason for admission, vital signs, biochemical (including protein concentrations) and haematological tests, disease profile, concomitant medication and fluid status were collected.

Population pharmacokinetics (popPK) analysis was performed using the pharmacokinetic modelling approach. Vancomycin PK was modelled using the one- and two-compartment models, and the model that best-described vancomycin PK in our patients was retained for analysis. The effects of variables (age, weight, renal function, liver function, fluid status, protein concentration, mean arterial blood pressure, concomitant medication, and severity of illness) on vancomycin PK were tested. Vancomycin PK was calculated over three time periods. Changes in vancomycin PK over the periods were evaluated, and possible contributory factors to the changes in vancomycin PK between periods were identified.

Consent and assent were provided for 39 out of 41 children, and their families were approached. Two of the 39 children had no arterial/venous lines from which blood samples could be drawn and were removed from the study. Blood samples were collected from 37 children for vancomycin PK analysis. The two-compartment model best described vancomycin PK in our patients and was used for vancomycin PK analysis. Adding weight and creatinine clearance on vancomycin CL and Vc improved the model's fit. External validation of the model using bootstraps of 1000 resampled datasets showed comparable estimates with the original dataset. Median (95% CI) for popPK CL, Vc, inter-compartmental distribution (Q) and volume of distribution in the central compartment (Vp) were 0.1 (0.09 – 0.11) L/kg/h, 0.35 (0.24 – 0.49) L/kg, 0.67 (0.35 – 1.29) L/kg/h and 0.17 (0.08 – 0.36) L/kg.

For the three periods studied, Vancomycin median (range) CL was 0.09 (0.02 – 0.27) L/h/kg, 0.11 (0.03 – 0.24) L/h/kg and 0.10 (0.03 – 0.22) L/h/kg. Vancomycin Q was 0.11 (0.02 – 0.38) L/kg/h, 0.53 (0.10 – 1.84) L/h/kg and 0.67 (0.12 – 2.49) L/kg/h. Vancomycin Vc was 0.67 (0.46 – 1.00) L/kg, 0.12 (0.03 – 1.60) L/kg and 0.35 (0.32 – 0.39) L/kg. Vancomycin Vp was 0.03 (0.001 – 60.06) L/kg, 0.47 (0.10 – 3.68) L/kg and 0.17 (0.06 – 5.6) L/kg. Vancomycin AUC was 150.85 (115.28 – 351.22) mg * h / L, 427.21 (58.10 – 1141.62) mg * h / L, and 455.26 (150.85 – 1762.47) mg * h / L. Vancomycin T½ was 2.50 (0.29 – 25.38) hr, 2.63 (1.26 – 8.79) h and 3.43 (0.49 – 16.80) hr. Vancomycin Ke was 0.17 (0.11 – 0.22) hr-1, 0.96 hr-1 (0.08 – 0.55) and 0.13 hr-1 (0.08 – 0.50). Vancomycin trough concentrations were 5.5 (2.0 – 13.90) µg/L, 7.7 (2.40 – 14.60) mcg/mL and 5.9 (2.50 – 19.70) mcg/mL. Vancomycin peak concentrations were 42.20 (18.60 – 83.80) mcg/mL, 49.30 (17.70 – 97.20) µg/L and 44.15 (32.90 – 69.30) µg/L. There was a significant increase in vancomycin V_d and AUC in the 48 – 72 h period ($p = 0.001$ and $p = 0.000$) compared to the 0 – 24 h and 24 – 48 h periods. Changes in vancomycin CL, T1/2, trough, and peak concentrations between periods were insignificant.

Age, weight, fluid status, renal function, mean arterial blood pressure, heart rate, concomitant diuretics use, and severity of illness were associated with vancomycin PK. Children < 2 years old had higher CL ($p=0.03$) and V_d ($p=0.00$) than children 2 – 16 years. Children that gained >5 % of their admission weight had higher CL ($p = 0.029$) and reduced Ke ($p = 0.024$), and trough concentration ($p = 0.025$). Fluid gain > 5 % was associated with high vancomycin V_d ($p=0.013$). A decrease in renal function was associated with decreased vancomycin CL ($p = 0.022$). Diuretics were associated with reduced vancomycin CL ($p = 0.028$) and longer vancomycin T½ ($P = 0.024$). Increased mean arterial blood pressure was associated with lower vancomycin AUC ($p = 0.041$). MABP correlated with vancomycin trough concentration ($p = 0.01$). Increased heart rate was associated with vancomycin peak concentration ($p = 0.05$). In children with higher severity of

illness scores, vancomycin T½ ($p = 0.032$) and trough concentration ($p = 0.026$) were high, and Ke was reduced ($p = 0.047$).

Wide variability in vancomycin PK exists in critically ill children. Studies in critically ill children are highly complex because of the heterogeneity of the population, the rapidly changing organ function during ICU admission and therapeutic interventions given to children. Factors associated with vancomycin pharmacokinetics include age, weight gain, fluid status, renal function, mean arterial blood pressure, heart rate, diuretics, and severity of illness. A relationship between protein concentrations and vancomycin PK was not observed, but this may be because of the small number of patients with protein concentration measurements in this study. While abnormal fluid collections (e.g., pleural effusions or ascites) were uncommon, they were associated with unexpectedly high vancomycin V_d. More research is needed in patient sub-groups, i.e. cardiac dysfunction, liver dysfunction, elevated protein concentration and patients in perioperative periods within the ICU.
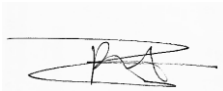
Declaration

I declare that: "*Factors Affecting the Pharmacokinetics of Vancomycin in Children Admitted to the RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL (RCWMCH)*" is my work, that it has not been submitted before for any degree or examination in any other university, and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

Onyinye Onyeka Akunne   Date: 29 September 2022

Signed:

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AIC	Akaike Information Criteria
AKI	Acute kidney injury
ALT	Alanine aminotransferase
ARC	Augmented renal clearance
AST	Aspartate transaminase
AUC	Area under the concentration time curve
AUC_{0-24}	Area under the concentration time curve over 24 hours
$AUC\infty$	Area under the concentration curve from time zero till infinity
BIC	Bayesian Information Criteria
CHF	Congestive heart failure
CL	Clearance
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CNS	Central nervous system
CRCL	Creatinine clearance
CT	Computerized tomography
CVP	Central venous pressure monitoring
CVVDH	Continuous veno-venous haemodialysis
CVVH	Continuous veno-venous hemofiltration
DBP	Diastolic blood pressure
DV	Observed concentration
ECS	Extracellular space
ESF	Extracellular fluid
ESRD	End-stage renal disease
FO	Fluid overload
ICS	Intracellular space
ICU	Intensive care unit
IPRED	Individual predicted concentration
ISS	Interstitial space
IV	Intravenous
IVS	Intravascular space
IWRES	Individual weighted residue
Ke	Elimination constant rate
MABP	Mean arterial blood pressure
MIC	Minimum inhibitory concentration
MRI	Magnetic resonance imaging
MRSA	Methicillin-resistant *Staphylococcus aureus*
NDPE	Normalized predictive distribution error
OFV	Objective function value
PELOD-2	Paediatric Logistic Organ Dysfunction-2
PICU	Paediatric intensive care unit
PK	Pharmacokinetic

PO	Pulmonary oedema
popPK	Population pharmacokinetics
PRED	Population predicted concentration
Q	Intercompartmental distribution
RCWMCH	Red Cross War Memorial Children Hospital
RSE	Residual standard error
SBP	Systolic blood pressure
SCr	Serum creatinine
$T^{1/2}$	Half-life
TBI	Traumatic brain injury
TBW	Total body water
TCS	Transcellular space
TDM	Therapeutic drug monitoring
TGA	Transposition of the great artery
T_{max}	Time to maximum concentration
T_{min}	Time to reach minimum concentration
Vc	Volume of distribution in the central compartment
V_d	Volume of distribution
V_p	Volume of distribution in the peripheral compartment
VSD	Ventricular septal defect
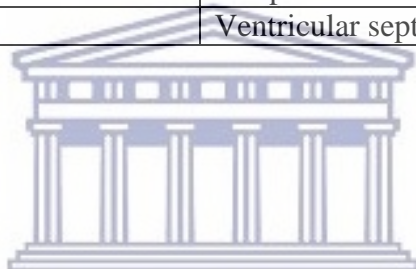
Chapter 1

Introduction

1.0 Background

Vancomycin, a glycopeptide antibiotic, is used to treat infections caused by gram-positive bacteria. It is essential in managing diseases with a high risk of resistant organisms or in patients where tissue penetrations may be required (Bauer, 2015). It is effective against methicillin-resistant *Staphylococcus aureus* (*MRSA*), *coagulase-negative staphylococci aureus* and penicillin-resistant *Streptococcus pneumoniae* (*S. pneumoniae*). Vancomycin is also used to treat hospital-acquired infections in the intensive care unit (ICU) since they are more likely to be resistant. Delaying the administration of effective agents until organisms have been identified may be risky in critically ill patients. Conditions treated with vancomycin include sepsis, pneumonia, empyema, endocarditis, osteomyelitis, and soft tissue abscesses (Bruniera et al., 2015).

1.0.1 Vancomycin use in paediatric critical illness

Children admitted to intensive care units are at high risk of dying because of the severity of their illness. Critically ill children are at risk of acquiring infections caused by drug-resistant pathogens, which is further increased in those in immunocompromised states (Vincent et al., 2016). While diseases can be transmitted via air, most infections in the ICU are transmitted through hands and contaminated equipment (catheters, ventilators, and other invasive equipment) and blood transfusion (not so common in high-quality blood transfusion services) (Pierce et al., 2017). Once established within the body, the bacterial population may increase without the restraint of the body's immune system and migrate to other organs (possibly through the blood), where they may elicit further harmful effects (Soares, Teixeira and Moita, 2017). Early recognition and rapid infection treatment are recommended and are associated with a decrease in morbidity and mortality

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rates in critically ill children (Patton and Young, 2017; Rybak et al., 2020). Rapid infection treatment can substantially impact the patient's clinical course and survival (Patton and Young, 2017). Vancomycin therapy is often initiated for the treatment of suspected or proven infections where gram-positive organisms (particularly those resistant to front-line antibiotics) are likely to be involved. In most cases, detailed information on the infective organisms and their antimicrobial sensitivity will only be available some days later. Occasionally vancomycin therapy is directly specifically at Gram-positive organisms known to be resistant to other agents and sensitive to vancomycin.

1.0.2 Red Cross War Memorial Children's Hospital recommendation for vancomycin use

In Red Cross War Memorial Children's Hospital (RCWMCH), vancomycin is recommended for the treatment of infective endocarditis caused by *MRSA*, prosthetic valve endocarditis caused by *MRSA*, hospital-acquired septicaemia from thrombophlebitis or indwelling central vascular line > 48hrs, suspected meningitis particularly in patients with a head injury, during and after placement of cerebrospinal fluid shunts and drains, other foci of suspected *staphylococcal* infection such as pneumonia with breakdown or empyema, and penicillin-resistant *enterococci, coagulase-negative staphylococci aureus* and S*treptococcus viridans* with penicillin MICs ≥ 4ug/ml (Red Cross War Memorial Children's Hospital (RCWMCH), 2012).

1.0.3 Pharmacokinetics of vancomycin

The pharmacokinetics of vancomycin in critically ill children is still a concern because of the wide variability in the PK parameters (Gomez et al., 2013; Villena et al., 2014; Avedissian et al., 2017; Zylbersztajn et al., 2018; Mali et al., 2019; Sridharan et al., 2019). Typically, the peak and trough vancomycin concentrations are measured in the ICU. Measuring the area under the concentration-

time curve over 24 hours (AUC0-24) is recommended and may be very useful in determining vancomycin concentrations over time in critically ill children (Rybak et al., 2020).

The goal trough levels have increased over time from 10 mcg/mL to 15 to 20 mcg/mL for *MRSA* isolates with minimum inhibitory concentration (MIC) < 2 mcg/mL. Increasing vancomycin trough concentration is necessary for body regions where penetration is a concern. Maintaining adequate vancomycin trough concentration will also prevent hetero resistance in *MRSA* (Dehority, 2010). There is an association between low vancomycin trough concentrations and treatment failure in adults (Forstner et al., 2013). Increasing vancomycin troughs levels in paediatrics may not improve treatment outcomes but increase the risk of nephrotoxicity (McNeil et al., 2016). Monitoring area under the concentration-time curve/minimum inhibitory concentration (AUC/MIC) has been observed in some studies to correlate with better clinical outcomes compared with monitoring trough concentrations (Dehority, 2010). This is because identical trough concentrations can be observed from a wide range of concentration-time profiles. Unlike the trough concentration that is obtained at the end of a dosing interval, the AUC is the integrated quantity of cumulative drug exposure (ie, the serum drug concentration-time curve over a defined interval) over a specified time, for instance, the AUC of a drug over 24 hours (AUC_{24}) represents the average concentration during 24 hours (AUC_{24} (mcg. h/mL) = average concentration (mcg/mL) x 24 (hours)) (Rybak et al., 2020). Results from a study showed similar trough concentrations from different dosing regimens; though the trough concentrations were similar, the AUC values ranged widely (Patel et al., 2011). Adult patients with AUC/MIC values ≥ 400 have significantly better results (clinician report of resolution of disease) and bacteriologic responses (sterilization of cultures) than those patients with an AUC/MIC < 400. In adult studies, trough concentrations of 15 to 20 mcg/mL correspond to an AUC/MIC ≥ 400 (Forstner et al., 2013). In some studies on critically ill children, a trough concentration of < 15 mcg/mL is required to reach an AUC/MIC ≥

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400 (Acuña et al., 2013, Gomez et al., 2013). There is no validation of the trough concentration to improve clinical outcomes or bacteriological response in critically ill children (Dehority, 2010). The recommended AUC0-24 of vancomycin in critically ill children is 400 – 600 μg * h / mL. (Rybak et al., 2020).

1.0.4 Effect of physiology differences and pathophysiology changes on vancomycin pharmacokinetics

Vancomycin pharmacokinetics in children differ from adults (Kearns et al., 2003). The variability relates to factors such as higher water content in younger infants, maturation of organ function and changes in relative sizes of organs and body compartments in children according to age (Roberts and Lipman, 2009).

The kidneys' glomerular filtration rate (GFR) positively correlates with gestational age in newborn infants (Gomez et al., 1999). The GFR continues to increase, reaching adult values by 1 – 2 years of age (Table 1.1). An increase in filtration surface area, glomerular permeability, arterial pressure and renal blood flow contribute to the maturational increase in GFR (Gomez et al., 1999).

Developmental changes in renal function can alter Vancomycin CL. These changes will warrant dosing regimens that are age-appropriate. Some studies show a correlation between the CL of renally eliminated drugs and normal maturational changes in GFR (James et al., 1998; van den Anker et al., 1995). Toxic serum levels of renally eliminated drugs can occur when ontogeny of renal function is not considered (Szefler et al., 1980). Therefore, age-appropriate individualised treatment regimens that account for maturational kidney function are necessary.

Table 1-1 Glomerular filtration rate (GFR) changes

Preterm (25-28 weeks)	
1 week	11.0±5.4
2-8 weeks	15.5± 6.2
Preterm (29-34 weeks)	
1 week	15.3±5.6
2-8 weeks	28.7±13.8
Term	
5-7 days	50.6±5.8
1-2 months	64.6±5.8
3-4 months	85.8±4.8
5-8 months	87.7±11.9
9-12 months	86.9±8.4
2-12 years	133±27

In the critically ill patient, there may be substantial fluid shifts (related to capillary functions), haemodynamic changes, renal function changes and other organ dysfunctions (Thakkar et al., 2017). Not only are there changes in function, but there may be substantial differences in the rate of change in function (the implications of poor renal function may differ from those of poor and deteriorating renal function) (Rodieux *et al.,* 2015). In addition, there may be a possibility of developing "new compartments" such as fluid collections in the chest (pleural effusions) or abdomen (ascites).
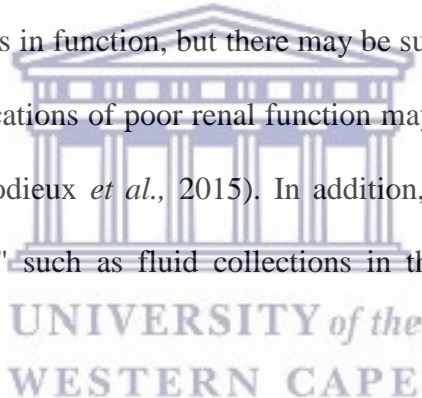
In addition, exposure of critically ill children to agents such as furosemide may dramatically alter the elimination rate of drugs (Medellín-Garibay et al., 2016). Multiple drugs given to critically ill children may interfere with the metabolism and distribution of vancomycin. Furthermore, the concomitant medication may have compounding effects on the toxicity of vancomycin (Thakkar et al., 2017).

According to Ronco et al. (2010), fluid overload with acute kidney injury (AKI) in critically ill patients, characterised by a rapid and sustained decline in glomerular filtration rate (GFR), is a

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complex interaction between fluid overload and renal function. Fluid overload is manifested clinically by increased weight and oedema with or without progressive reduction in urine output and fluid and electrolyte homeostasis interruption with reduced capacity for water and solute excretion (Claure-Del Granado and Mehta, 2016). Increased activation of the sympathetic nervous system (SNS), the renin-angiotensin-aldosterone system (RAAS), the stimulation of non-osmotic release of vasopressin and the effect of agents such as 0.9% saline on renal perfusion and urine output (with saline decreasing urine output) further complicates fluid overload (Claure-Del Granado and Mehta, 2016). In critical illness, shock and systemic inflammation contribute to reduced circulation, reduced oncotic pressure gradient (hypoalbuminemia) and alterations in capillary permeability. Capillary permeability interacts with high fluid intake (such as active resuscitation and intravenous medications) and may result in considerable leakage from the vascular compartment (Claure-Del Granado and Mehta, 2016). Critically ill children, especially those with acute kidney injury, are at the highest risk of developing fluid overload, capillary leakage syndrome and severe interstitial oedema. Fluid overload may also occur in critically ill children as a response to acute illness and injury or during the administration of resuscitation fluids and IV drugs (Claure-Del Granado and Mehta, 2016).
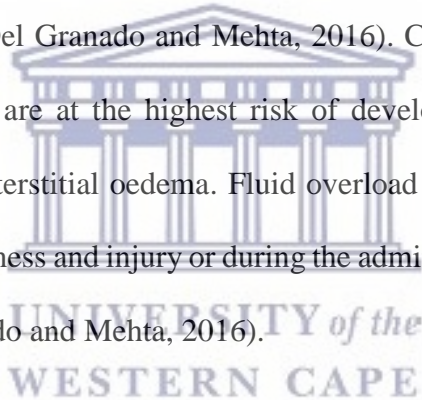
Fluid shifts may substantially affect vancomycin volume of distribution (V_d) because of its hydrophilic nature. The V_d may alter the maximum concentration of vancomycin and its pharmacodynamics (Thakkar et al., 2017).

Drug elimination may be affected by disease-related changes in organ function. The kidneys eliminate vancomycin from the body. The changes in renal function often seen in critical illness will affect vancomycin PK. Alterations in renal function affect many factors, such as renal clearance, pH, and total body water. These alterations are profound in conditions such as acute

kidney injury (AKI), chronic kidney disease (CKD) and end-stage renal disease (ESRD) (Thakkar et al., 2017). Disease states such as sepsis, traumatic brain injury and burns may be associated with delayed renal clearance. They can also be associated with augmented renal clearance (ARC). ARC leads to increased renal clearance of antibiotics such as vancomycin in critically ill children (De Cock et al., 2015).

In critically ill children, organ functions may change rapidly. The dilemma is how to adjust drug doses considering the constantly changing (with variable rates of change) organ function. Vancomycin clearance is affected by alterations in renal function. Patients' clinical presentation and renal function alterations should inform vancomycin dose adjustment (Eyler and Mueller, 2010; Chu et al., 2016).

Critical illness may be associated with rapid changes in serum protein concentration (both increases and decreases), and hypo-albuminaemia is common. Vancomycin is moderately (30 - 60%) bound to plasma protein (Oyaert et al., 2015), and factors such as age, serum albumin levels, and concomitant administration of drugs bound to the same proteins may affect unbound drug plasma levels. Critically ill children may present with hypoalbuminemia, and subsequent transfusions of protein (i.e. albumin and immunoglobulin) in these children will alter plasma protein levels and vancomycin binding. Hypoalbuminemia will likely contribute to a high Vd and CL of a hydrophilic drug (Ulldemolins, 2011) and dose adjustments according to the change in plasma protein concentration, particularly after protein transfusion, may be warranted. The effect of protein binding on vancomycin CL or Vd has not been evaluated. There is also no data showing the impact of protein binding on the bacterial killing rate. Only plasma concentrations are measured in studies on the effect of protein binding on vancomycin concentration in critically ill children. In the study by Oyaert et al., they found that the bound vancomycin concentration can be

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predicted by the albumin concentration (β = 1.826, SE = 0.271, P < 0.0011) in their paediatric cohort (Oyaert et al., 2015). Therapeutic vancomycin plasma concentrations were achieved when the vancomycin PK/PD indices were based on unbound vancomycin concentrations compared to total concentrations (De Cock et al., 2017). Although total protein (P<0.001) and albumin serum concentration were found to be significant covariates (P<0.001) that affected unbound vancomycin concentration, the effect of protein binding on bound vancomycin concentration was not evaluated in the study (De Cock et al., 2017). Unbound vancomycin is responsible for the pharmacological effects of vancomycin.

The therapeutic consequences of changes in vancomycin protein binding in children admitted to PICU should be evaluated. Life-saving medical interventions, such as renal dialysis, may also significantly alter physiologic balance (such as body water and electrolyte balance), further affecting vancomycin disposition (Thakkar et al., 2017). Even temperature changes can affect vancomycin concentration (Thakkar et al., 2017). A study showed that reduced vancomycin CL could increase the plasma concentration in clinically induced hypothermia (Zane et al., 2017).

It is necessary to study factors affecting vancomycin PK in critically ill children to improve vancomycin therapy.

1.1 Motivation

Although vancomycin has been in use for a long time, there are still concerns about its pharmacokinetics. A particular concern in critically ill children is the large variability in vancomycin PK. Several factors can affect vancomycin PK, including:

1. Patient-related factors.

2. Physiological factors, such as weight and age, explain some variability in vancomycin PK, while pathophysiological factors, such as changes in temperature, renal function and fluid balance, can affect vancomycin PK.

3. Medical interventions such as fluid resuscitation and dialysis.

4. Co-medications, particularly nephrotoxic medications

5. Prescriber-related factors such as the frequency and the dose of vancomycin.

6. Vancomycin administration-related factors. Patients receiving an amount sooner or later than indicated by the dosing frequency will affect vancomycin plasma concentration.

7. Timing of blood sample collection. This timing will affect decisions clinicians make concerning the patient. For example, trough and peak vancomycin blood samples collected too early or late during the dosing interval will lead to inaccurate peak and trough concentrations.

In studies including critically ill children, significant variations in vancomycin PK has been reported (Gomez et al., 2013; Villena et al., 2014; Seixas et al., 2016; Zane et al., 2017; Genuini et al., 2018; Zylbersztajn et al., 2018; Mali et al., 2019; Sridharan et al., 2019). Variations in vancomycin PK are related to the heterogeneity of the diseases in this population. In the study by Zylbersztajn et al., vancomycin PK in children with AKI and children with AKI on RRT had lower vancomycin CL than children with normal renal function (0.07 L/h/kg and 0.05 L/h/kg respectively compared to 0.10 L/h/kg). There is also a wide range of therapeutic interventions critically-ill children undergo, which may affect vancomycin PK. In the study by Zane et al., findings indicate that children with normal renal function subjected to therapeutic hypothermia had a 25% reduction in their vancomycin CL. Children with poor renal function placed on therapeutic hypothermia had an 85% reduction in vancomycin renal CL (Zane et al., 2017).

In summary, studies that evaluated vancomycin PK in critically ill children reported a wide range of values, especially for Vd and AUC though similar vancomycin doses were given to the children. A better understanding of vancomycin PK in our patient population and factors that may contribute to variations in vancomycin PK is needed to improve vancomycin therapy. This study aims to describe vancomycin PK in our local population and explore the possible factors that contribute to vancomycin PK variability in our population.

1.2 Statement of the problem

Pathophysiological changes occur in critical illness. In some cases, these changes occur rapidly over time. The goal of vancomycin therapy in critically ill children is to achieve therapeutic concentrations at the site of infection as soon as possible to eradicate bacteria and improve the clinical outcomes of patients. To optimise the therapeutic effects of vancomycin while minimising the adverse effects, it is necessary to 1) achieve therapeutic levels of vancomycin as soon as possible after initiation of therapy, 2) maintain levels in that range throughout therapy and 3) do so while minimising the amount of sampling required to ensure adequate therapeutic monitoring. The primary concern of clinicians with vancomycin therapy is to achieve these goals effectively and efficiently in the PICU setting. The problems that may present during vancomycin therapy in critically ill children are:

1. Children may show high individual variability in vancomycin pharmacokinetics. Children undergo physiological changes in growth and organ development. Some of the variability is associated with age, weight, and renal function.

2. Children admitted to the PICU have a wide range of ages, disease profiles and related organ function

3. Pharmacokinetics of antibiotics may change significantly during critical illness with marked inter-individual variability. Changes have different components.

3.1. The severity of illness will vary and change during the course of an illness. The changes may affect vancomycin PK.

3.2. Critically ill children often receive fluid resuscitation that affects their fluid balance. Since vancomycin is a hydrophilic drug, its PK (especially the volume of distribution) may be affected by fluid changes.

3.4. Significant changes in protein levels may occur in critical illness with effects on vancomycin volume of distribution because of moderate albumin binding.

3.5. Critically ill children receive multiple medications. Some may interact with vancomycin CL (i.e., nephrotoxic drugs) or V_d (i.e., highly protein-bound drugs).

4. Achievement and maintenance of vancomycin levels are critical to improving clinical outcomes and avoiding drug toxicity.

5. This leads to the need for interventions to improve therapeutic drug monitoring and dose change practices in the intensive care setting.

1.3 Research questions

I. Does vancomycin PK parameters (V_d, CL, T1/2, C_{max}, C_{min} K_e, AUC, T_{max}) substantially change during the treatment?

II. What trough concentration achieves an area under the concentration-time curve to the minimum inhibitory concentration (AUC/MIC) ratio > 400 as a predictor for vancomycin treatment outcome?

III. Does age influence vancomycin PK (V_d, CL, T1/2, C_{max}, C_{min} K_e, AUC, T_{max})?

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IV. Does body weight influence vancomycin PK (V_d, CL, T1/2, C_{max}, C_{min} K_e, AUC, T_{max})?

V. Does fluid balance affect vancomycin volume of distribution?

VI Does fluid resuscitation affect vancomycin volume of distribution?

VII. Do changes in renal function affect vancomycin pharmacokinetics?

VIII. Do changes in hepatic function affect vancomycin pharmacokinetics?

IX. Do changes in mean arterial pressure affect vancomycin pharmacokinetics?

X. Do changes and rate of change in heart rate affect vancomycin pharmacokinetics?

XI. How do concomitant medications frequently administer in the ICU affect vancomycin pharmacokinetics (V_d, CL, T1/2, C_{max}, C_{min} K_e, AUC, T_{max})?

XII. Are changes in albumin plasma concentration associated with changes in vancomycin pharmacokinetics (V_d, CL, T1/2, C_{max}, C_{min} K_e, AUC, T_{max})?

XIII. Are changes in the severity of illness associated with changes in vancomycin pharmacokinetics (V_d, CL, T1/2, C_{max}, C_{min} K_e, AUC, T_{max})?

XIV. Is frequent therapeutic drug monitoring (TDM) relevant in critically ill children?

1.4 Objectives of the study

This study will evaluate the following:

I. The pharmacokinetic model that best describes vancomycin pharmacokinetics profile (V_d, CL, T1/2, C_{max}, C_{min} K_e, AUC, MRT, T_{max}) in critically ill children

II. Vancomycin Pharmacokinetics (V_d, CL, T1/2, C_{max}, C_{min} K_e, AUC, MRT, T_{max}) in the following therapeutic phases: 0-24hrs, 24-48hrs and 48-72hrs after initiation of vancomycin treatment.

III. Vancomycin trough concentrations achieving an AUC/MIC ratio > 400 to predict vancomycin treatment outcome.

IV. The relationship between physiological changes in children (age, body weight) and vancomycin pharmacokinetics (V_d, CL, T1/2, C_{max}, C_{min} K_e, AUC, T_{max}) of vancomycin.

V. The relationships between fluid balance and vancomycin volume of distribution.

VI. The relationships between fluid resuscitation and vancomycin volume of distribution.

VII. The relationships between changes in renal function and vancomycin pharmacokinetics.

VIII. The relationships between changes in hepatic function and vancomycin pharmacokinetics.

IX. The relationships between changes in mean arterial blood pressure and vancomycin pharmacokinetics

X. The relationships between changes in the heart rate and vancomycin pharmacokinetics

XI. The relationships between concomitant medication and vancomycin pharmacokinetics

XII. The relationships between changes in serum albumin concentration and the pharmacokinetics of vancomycin.

XIII. The relationships between severity of illness and vancomycin pharmacokinetics.

XIV. The relevance of frequent therapeutic drug monitoring (TDM).

1.5 Null hypotheses

I. Changes in vancomycin pharmacokinetic parameters (V_d, CL, T1/2, C_{max}, C_{min} Ke, AUC, MRT, T_{max}) between phases: 0 - 24 hrs, 24-48hrs and 48-72hrs of treatment do not occur.

II. Vancomycin trough concentration of 15 - 20 mL is not a good predictor of AUC/MIC > 400, assuming a bacterial MIC of 1.

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III. Changes in children's age do not affect vancomycin pharmacokinetic parameters (V_d, CL, T1/2, C_{max}, C_{min} Ke, AUC, T_{max}).

IV. Changes in children's body weight do not affect vancomycin Pharmacokinetics (V_d, CL, T1/2, C_{max}, C_{min} Ke, AUC, T_{max}).

V. Fluid balance does not affect vancomycin volume of distribution.

VI. Fluid resuscitation does not affect vancomycin volume of distribution

VII. Changes in renal function do not affect vancomycin pharmacokinetics.

VIII. Changes in hepatic function do not affect vancomycin pharmacokinetics.

IX. Mean arterial blood pressure changes do not affect vancomycin pharmacokinetics.

X. Changes in heart rate do not affect vancomycin pharmacokinetics.

XI. Concomitant medications frequently prescribed in the ICU do not affect the vancomycin pharmacokinetics (V_d, CL, T1/2, C_{max}, C_{min} Ke, AUC, T_{max}).

XII. Albumin plasma concentration does not affect vancomycin pharmacokinetics (V_d, CL, T1/2, C_{max}, C_{min} Ke, AUC, T_{max}).

XIII. Severity of illness does not affect vancomycin pharmacokinetics (V_d, CL, T1/2, C_{max}, C_{min} Ke, AUC, T_{max}).

1.6 Alternative hypotheses

I. There are changes in vancomycin pharmacokinetic parameters (V_d, CL, T1/2, C_{max}, C_{min} Ke, AUC, MRT, T_{max}) between phases: 0 - 24 hrs, 24-48hrs and 48-72hrs of treatment.

II. Vancomycin trough concentration of 15 - 20 mL is a good predictor of AUC/MIC >400, assuming a bacterial MIC of 1.

III. Changes in children's age affect vancomycin pharmacokinetic parameters (V_d, CL, T1/2, C_{max}, C_{min} Ke, AUC, T_{max}).

IV. Changes in children's body weight affect vancomycin Pharmacokinetics (V_d, CL, T1/2, C_{max}, C_{min} Ke, AUC, T_{max}).

V. Fluid balance affects vancomycin volume of distribution.

VI. Fluid resuscitation affects vancomycin volume of distribution

VII. Changes in renal function affect vancomycin pharmacokinetics.

VIII. Changes in hepatic function affect vancomycin pharmacokinetics.

IX. Mean arterial blood pressure changes affect vancomycin pharmacokinetics.

X. Changes in heart rate affect vancomycin pharmacokinetics.

XI. Concomitant medications frequently prescribed in the ICU affect the vancomycin pharmacokinetics (V_d, CL, T1/2, C_{max}, C_{min} Ke, AUC, T_{max}).

XII. Albumin plasma concentration affects vancomycin pharmacokinetics (V_d, CL, T1/2, C_{max}, C_{min} Ke, AUC, T_{max}).

XIII. Severity of illness affects vancomycin pharmacokinetics (V_d, CL, T1/2, C_{max}, C_{min} Ke, AUC, T_{max}).

1.7 Hypotheses Testing

Hypotheses will be tested using statistical tests appropriate for each idea. Independent sample T-test will be used to compare the means of two groups, and analysis of variance (ANOVA) will be used to compare the mean of three or more groups when data is normally distributed. Non-parametric statistical test equivalents (Mann-Whitney U and Kruskal-Wallis tests) will be used

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when data is not normally distributed, and equal variances are not assumed. The decision to accept or reject the null hypothesis will be based on the *p*-value. The null hypothesis will be retained when the *p*-value is > 0.05; however, the alternative hypothesis will be accepted where the p-value is < 0.05.

Chapter 2
Literature Review

2.0 Introduction

This chapter provides a brief background of vancomycin and its therapeutic effect. The pathophysiological changes in critically ill children and their impact on vancomycin PK and PD are reviewed. Finally, a review of vancomycin PK in critically ill children is presented.

2.1 Therapeutic use of vancomycin

2.1.1 History of the clinical use of vancomycin

Vancomycin was isolated from *Streptomyces orientalis* in the 1950s by Eli Lily pharmaceuticals (Griffith, 1981). Though very promising and widely accepted for the treatment of penicillin-resistant *Staphylococcus aureus*, concerns about its ototoxicity and nephrotoxicity lead to it being dropped in favour of other less toxic and more efficacious antibiotics. The harmful effects were attributed to impurities contained in the formulation (Moellering, 2006). In the 1970s, with the emergence of methicillin-resistant *S. aureus*, vancomycin re-emerged as one of the drugs of choice for treating infections caused by this microbe.

Reformulation of vancomycin leads to a purer compound with less toxicity (Farber and Moellering, 1983; Levine, 2006). However, within the last few years, S. *aureus* resistance to vancomycin has been reported (CDC, 2002; Fridkin et al., 2003). Therefore, in the clinical setting, the onus is to keep optimal dose levels to mitigate bacterial resistance to vancomycin.

2.1.2 Recommended vancomycin dose

The recommended vancomycin dose in infants aged up to 3 months old ranges from 10 to 20 mg/kg every 8 to 48 hours, depending on postmenstrual age, weight, and SCr. The recommended vancomycin dose in children aged three months to less than 12 years is 60 to 80 mg/kg/day in

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equally divided doses given every 6 hours and 60 to 70 mg/kg/day in equally divided doses given every 6 to 8 hours in children ≥12 years old (Rybak et al., 2020). There is insufficient evidence to show that non-obese children benefit from a loading dose; obese children may be given a loading dose of 20 mg/kg based on their total body weight (Rybak et al., 2020).

According to Red Cross War Memorial Children's Hospital, 2012, the recommended vancomycin dose is 15 mg/kg/dose given six hours. Vancomycin must be delivered as a slow IV infusion over at least 1 hour. The slow IV infusion avoids hypersensitivity reactions such as vancomycin-flushing (the red man syndrome) when vancomycin is infused too quickly (Sivagnanam and Deleu, 2003). Vancomycin should only be given to children if there is evidence or strong suspicion of *staphylococcal* sepsis such as thrombophlebitis, indwelling central vascular line > 48hrs and other foci of suspected *staphylococcal* infection such as pneumonia with empyema.

2.3 Pharmacokinetics of vancomycin

2.3.1 Absorption

Vancomycin is poorly absorbed from the gastrointestinal tract. It is administered orally to treat colitis infection caused by *Clostridium difficile*. It is administered intravenously for systemic infections.

2.3.2 Distribution

Vancomycin is widely distributed in the body, including adipose tissue (Bauer, 2015). Vancomycin is poorly distributed in the central nervous system (CNS) when given intravenously except in case of meningeal inflammation, in which case vancomycin cerebrospinal fluid concentration of 7-30% of the serum concentration may be achieved (MacDougall and Chambers, 2011). Vancomycin penetrates poorly into lung tissues with an average serum-to-tissue ratio of 6:1 and an average plasma concentration to epithelial lining fluid ratio of 1:0.50 (Lodise et al.,

2011). The vancomycin pulmonary concentrations in patients are highly variable (Georges et al., 1997; Lodise et al., 2011). In paediatric patients, vancomycin has a V_d of 0.57 (0.26 to 1.05) L/kg (Marsot et al., 2012).

2.3.3 Protein binding

Vancomycin is a moderately (30 to 60%) protein-bound antibiotic. However, vancomycin protein binding shows considerable variability across studies (ranging from almost 0 to 90%) (Oyaert et al., 2015). Vancomycin binds primarily to both immunoglobulin A (IgA) and albumin. It does not attach to immunoglobulin M (IgM), immunoglobulin G (IgG) and α-1 acid glycoprotein (Sun, Maderazo and Krusell, 1993). Binding to IgA and albumin can explain most vancomycin serum protein binding. Vancomycin protein binding increases as the serum concentrations of IgA and albumin increase. At low IgA concentrations (< 0.05g/L), vancomycin has approximately 30% protein binding regardless of the vancomycin plasma concentration. IgA binding adversely affects vancomycin PK because trough vancomycin, plasma concentration may be high, and the free vancomycin concentration may not be above the bacterial MIC leading to poor clinical outcomes. (Sun, Maderazo, and Krusell, 1993). While a study evaluating the factors affecting unbound vancomycin concentration in children aged six months to 14 years old showed that serum albumin concentration significantly affected plasma unbound vancomycin concentration (Oyaert et al., 2015), another study describing vancomycin PK in children aged one month to 17 years showed no relationship between attaining AUC0-24 > 400 μg * h / mL and protein binding (Sridharan et al., 2019). The effect of protein binding on vancomycin CL, Vd and bacterial killing effects have not been evaluated. Most studies on vancomycin therapeutic drug monitoring use the total vancomycin serum concentrations and not the free vancomycin concentration to relate to AUC/MIC.

2.3.4 Metabolism

The liver does not metabolise vancomycin. It is mainly excreted unchanged in the urine (Cao et al., 2018).

2.3.5 Elimination /Excretion

About 90% of the administered vancomycin dose is eliminated by glomerular filtration. Vancomycin has a half-life of 2 – 6 hours in children with normal renal function (Broome and So, 2011).

At about three months, vancomycin clearance doubles (50 mL/min), resulting in a half-life of approximately 4 hours (Marqués-Miñana and Saadeddin, 2010). The increase in vancomycin clearance continues through 4-8 years of age when clearance equals 130-160 mL/min while the volume of distribution remains ~0.7 L/kg so that half-life is 3 hours (Lietman et al., 1980). In children 12 – 18 years, there is a decline in vancomycin clearance rate compared to normal adult rates of about 78 - 100 mL/min (Golper et al., 1988; Rybak et al., 2020). Le et al. (2014) found a significant difference ($p<0.001$) in vancomycin CL between children with normal renal function defined as SCr ≥ 0.9 mg/dL (CL = 0.10 ± 0.03 L/kg/hr) and children with impaired renal function defined as SCr < 0.9 mg/dL (CL = 0.10 ± 0.03 L/kg/hr). In functionally anephric children, vancomycin's half-life is 6–10 days. A significant amount of vancomycin is removed during standard haemodialysis runs using a high-flux membrane (Bauer, 2015).

2.4 Pharmacodynamics of vancomycin

2.4.1 Antibacterial activity

Vancomycin is active against methicillin-resistant gram-positive bacteria, majorly methicillin-resistant *S. aureus* and penicillin-resistant *S .pneumoniae* (Bruniera et al., 2015).

Vancomycin is time-dependent because its killing ability depends on the duration of the pathogen's exposure to an antibiotic. Vancomycin concentration must be above the minimum inhibitory concentration (MIC) for the bacteria to maintain its inhibitory effects throughout treatment (McKinnon and Davis, 2004). Experiments have shown that increasing its concentration does not influence vancomycin bactericidal activity (Ross et al., 2001). In one study that used incremental doses of vancomycin (from 5 – 40 mcg/mL), the effect of concentration on the bacterial activity of *S. aureus* showed that increasing the plasma concentrations of vancomycin does not yield any difference in the bactericidal effect of vancomycin (Larsson et al., 1996). A similar finding was reported by Lowdin et al., 1998. They concluded that peak plasma concentrations did not help determine the bactericidal effect of vancomycin. They also found that maintaining vancomycin plasma concentrations higher than the MIC at dosing intervals are necessary for vancomycin's efficacy. The most significant predictor of treatment outcome is said to be the AUC/MIC ratio. Assuming a MIC of 1 mcg/mL, an AUC/MIC ratio ≥ 400 leads to better clinical and bacteriological response to vancomycin (Moise-Broder et al., 2004). Clinical outcomes were seen to be at the apex when the AUC/MIC exceeded 500 (Lodise et al., 2014, 2020; Casapao et al., 2015).

2.4.2. Post-antibiotic effect (PAE) of vancomycin

A drug's post-antibiotic effect (PAE) is when no bacterial growth is observed after the termination of antibiotic therapy (Zhanel et al., 1991). The PAE of vancomycin increased from 0.2 to 2 hours for *S. aureus* and 4.3 to 6.5 h for *S. epidermidis* when vancomycin concentration exceeded the MIC by 2-4 fold (Löwdin et al., 1998). An AUC/MICratio of 400 hours or C_{min} >4 to 5 times the MIC is associated with effective bacterial killing (Löwdin et al., 1998; Moise-broder et al., 2004).

Maintaining vancomycin trough levels of 10-15mcg/mL in bacteria susceptible at a MIC of 1mcg/mL and 15-20mcg/mL in bacteria with MIC > 1mcg/mL was previously advocated as an appropriate surrogate marker for AUC/MICratio of 400 hours or higher (Liu et al., 2011).

However, other studies show that it may not be a correct indicator of optimal AUC (Mohr and Murray, 2007; Patel et al., 2011). Since the trough levels show a single concentration at the end of the dosing interval, it gives a specific concentration value as opposed to the AUC, which shows the average concentration over a specified time. The different concentrations over time mean that there may be considerable variability in the relationship between AUC (particularly in the upper limits) and trough concentration in patients, particularly children (Rybak et al., 2020). Some studies in critically ill children showed that children with trough levels below 15mcg/mL (11 – 13 mcg/mL) achieved AUCs ≥ 400 mg * h / L (Acuña et al., 2013; Gomez et al., 2013). Achieving high trough concentrations of 15 – 20 mcg/mL may not be necessary or appropriate in critically ill children.

Current guidelines recommend an AUC/MIC between 400 and 600 for bacteria with a MIC of 1 mcg/mL (Rybak et al., 2020).

Since vancomycin follows time-dependent pharmacodynamics, some clinicians advocate administering vancomycin as a continuous intravenous infusion to maintain vancomycin concentration in the body above the bacterial MIC. Continuous infusion will achieve target steady-state concentrations of 20 to 25 mg/L more rapidly than intermittent infusion (Schmelzer et al., 2013; Hutschala et al., 2009). A study in an outpatient parenteral antimicrobial therapy (OPAT) program comparing the rates of nephrotoxicity, time to nephrotoxicity onset, and clinical failure in patients receiving continuous vancomycin infusion or intermittent infusion showed that continuous vancomycin infusion was associated with a lower risk and slower onset of nephrotoxicity than intermittent vancomycin infusion (Shakeraneh et al., 2020). The study did not observe any statistically significant difference in clinical failure rates between the two groups (Shakeraneh et al., 2020). In another study in patients with osteomyelitis on vancomycin therapy for >4 weeks, patients achieved target concentrations quicker when receiving a continuous

infusion. Patients on continuous infusion did not show better clinical outcomes, but adverse drug effects were more frequent in patients receiving intermittent infusion than patients on continuous infusion (Vuagnat et al., 2004). Other studies agreed that patients on continuous infusion had less risk of nephrotoxicity than patients on continuous infusion (Akerset al., 2012; Hanrahan et al., 2014). However, there may be a cross-contamination risk and increased bacterial infection risk with prolonged catheter use (Pierce et al., 2017). An intravenous loading dose usually precedes continuous infusion; then, steady-state vancomycin concentration is titrated by changing the infusion rate of the drug (Jeurissen et al., 2011; Ampe et al., 2013). Although target concentration may be attained by continuous infusion, studies comparing continuous vancomycin administration and intermittent vancomycin administration have not found any significant difference in treatment outcomes (Wysocki et al., 2001) and adverse effects in the two groups (Akers et al., 2012).

2.4.3. Mechanism of action

Vancomycin is a glycopeptide antibiotic with a chemical structure shown in Figure 2.1.

Figure 2-1 Chemical structure of vancomycin (Vardanyan and Hruby, 2006).

It is hydrophilic and inhibits cell wall synthesis in susceptible bacteria by binding to the D-alanyl-D-alanine terminal end of nascent peptidoglycan pentapeptide (cell wall precursor units), preventing the elongation of the peptidoglycan and cross-linkage (Bauer, 2015). This binding directly blocks transglycosidase-mediated polymerization and the PBP-mediated cross-linking of bacterial cell wall units, sterically hindering bacterial cell wall formation (MacDougall, 2023). The peptidoglycan weakens, leading to cell lysis (Beauduy and Winston, 2021).

Vancomycin is bactericidal and exhibits a time-dependent (dependent on the duration of the pathogen exposure to an antibiotic) or concentration-independent bacterial killing pattern. The maximum bactericidal effect of time-dependent antibiotics occurs when the concentration-time above the bacterial MIC is extensive. Drug concentrations below the bacterial MIC during treatment will result in therapeutic failure (Shah et al., 2015). The bactericidal effect of vancomycin is independent of concentration; increasing vancomycin concentration may not affect its bactericidal ability, but low plasma concentration is significant because it reduces the bactericidal effects of vancomycin. However, maintaining optimal concentration throughout therapy improves the vancomycin therapeutic effect. Vancomycin may only demonstrate bacteriostatic properties in bacteria strains with MIC ≥2.

2.4.4. Mechanism of resistance

Bacterial resistance to vancomycin (especially in vancomycin-resistant *S. aureus* strains with MIC ≥ 16 mcg/mL) arises from the replacement of the terminal D-alanyl molecule with D-lactate or D-serine (Zeng et al., 2016; Beauduy and Winston, 2021). This modification causes a loss of the hydrogen bond that facilitates the high-affinity binding of vancomycin to its target leading to its loss of activity. The D-alanyl-D-lactate or D-alanyl D-serine terminal end poorly binds vancomycin, inhibiting its action (Beauduy and Winston, 2021). The mechanism for bacterial resistance in vancomycin-intermediate strains of *S. aureus* with MIC of 4–8 mcg/mL is unknown.

The cell wall metabolism in these strains is altered, leading to a thickened cell wall and increased numbers of D-Ala-D-Ala residues. These residues act as dead-end binding sites for vancomycin. Sequestration of vancomycin within the cell wall by the false targets prevents it from reaching its site of action (Beauduy and Winston, 2021).

2.4.5. Therapeutic use

Vancomycin is used to treat bloodstream infections, meningitis, *S. aureus* infections, and endocarditis (Pelletier-Dattu, 2017). Vancomycin IV injection is used for treatment because of its poor absorption from the gastrointestinal tract into the bloodstream. Vancomycin is given with aminoglycosides to treat enterococci endocarditis in patients allergic to penicillin. Vancomycin is also used to treat diphtheroid endocarditis in combination with rifampicin. Vancomycin treats endocarditis caused by *S. aureus*, *S. viridans*, or *S. bovis* as a monotherapy or in combination with aminoglycosides, cefotaxime, ceftriaxone, and rifampin. Vancomycin may be used to treat meningitis caused by penicillin-resistant pneumococcus. Vancomycin may treat severe infections such as bloodstream infections, bone infections, lower respiratory tract infections, and skin and skin structure infections caused by susceptible strains of methicillin-resistant *staphylococci*. It can also be used as an empiric therapy when methicillin-resistant *staphylococci* cause the disease (Beauduy and Winston, 2021).

Vancomycin is given orally to treat colitis caused by *Clostridioides difficile* and enterocolitis caused by *S. aureus* (Beauduy and Winston, 2021).

2.4.6. Side effects

Adverse reactions may occur with parenteral administration. Phlebitis at the site of injection may result from vancomycin tissue irritation. Chills and fever may also occur (Pelletier-Dattu, 2017).

Vancomycin-induced nephrotoxicity is rare, but nephrotoxicity may occur at high trough concentrations. Co-administrating other ototoxic or nephrotoxic drugs, such as aminoglycosides and furosemide, may increase the risk of ototoxicity and nephrotoxicity. A study in children aged ≥1 week old to ≤19 years with baseline serum creatinine values within the normal range and receiving vancomycin for ≥48 hours showed that nephrotoxicity (defined as a serum creatinine increase of ≥0.5 mg/dL or ≥50% baseline increase over two days) was more common in children with vancomycin trough concentrations ≥15 mg/L compared to children with vancomycin trough concentrations < 15 mg/L (McKamy et al., 2011). They also found that children receiving furosemide in the intensive care unit were more likely to have nephrotoxicity (McKamy et al., 2011). Avoiding high peak serum concentrations (above 60 mcg/mL) reduces the risk of ototoxicity and nephrotoxicity, especially in children (Beauduy and Winston, 2021). Another commonly reported adverse effect of vancomycin in children is the "red man" syndrome (also known as vancomycin flushing syndrome (VFS)), an erythematous rash affecting the face, neck, and upper torso (Sivagnanam and Deleu, 2003)caused by the activation of the immune system and subsequent histamine release. Prolonging the vancomycin infusion period to 1–2 hours or pre-treatment with an antihistamine prevents VFS (Beauduy and Winston, 2021).

2.5 Critical illness in children

2.5.1 Definition of critical illness

Critical care is treating a child with a life-threatening illness or injury in its broadest sense, without regard for the location, including prehospital, emergency and intensive care (Kissoon et al., 2009).

Critical illness is a state of ill health with vital organ dysfunction and a high risk of imminent death (Schell et al., 2021). Vital organs include the brain, heart, kidney, liver, GIT, and blood/blood-forming organs. In addition, there are problems with the airway, breathing or circulation, or acute deterioration of the conscious state. These issues include apnoea, upper airway obstruction,

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hypoxaemia, central cyanosis, severe respiratory distress, total inability to feed, shock, severe dehydration, active bleeding requiring blood transfusion, and unconsciousness or seizures (World Health Organization, 2016). Care for children with life-threatening illnesses or injuries or following major elective surgery requires invasive devices and aggressive treatment with close monitoring (Thakkar et al., 2017). In the ICU, patients are at higher risk of nosocomial infections, increasing the mortality rates.

2.5.2. Normal physiological changes with growth and development

Children undergo changes that affect their organ size and function. The normal growth and developmental changes children undergo are discussed below. These changes show how the expected PK parameters might change in critically ill children because of pathophysiological changes that affect this population's normal growth and development.

2.5.2.1. General growth

Normal growth (the quantitative increase in the physical development of the body) and maturation (the genetic, biological, and physical development of the child) take place from birth to adulthood (Marciniak, 2019). Significant changes in size from birth to adulthood occur, yet most organ function developments occur when a child is two years old (Marciniak, 2019).

Growth is observed by changes in weight. Weight changes as a child's muscle mass, adipose tissue, skeleton, body water change, and length changes; significant deviations from a child's past percentiles on a percentile chart may indicate the child's illness or nutrition state. Weight is commonly used and is easier to measure than the length or head circumference. In the first three months after birth, weight increases daily at an average of 30 g (210 g/week). Weight gain continues through childhood till adulthood when the average weight is 70 kg (Marciniak, 2019).

2.5.2.2. Total body water content

The total body water decreases significantly from the extracellular compartment during infancy. Children achieve adult values by approximately one year of age (Wells et al., 2005). Therefore, total body water distribution changes will affect an infant's drug dosing and distribution.

2.5.2.3. Cardiovascular system

The heart rate in infants at one month decreases from about 160 beats per minute to 75 beats per minute by adolescence (Southall et al., 1980). The change in mean systolic blood pressure increases is minimal between 6 weeks and six years. Systolic blood pressure gradually increases after the age of six years (Marciniak, 2019).

2.5.2.4. Renal function

Vancomycin is eliminated from the body through active tubular secretion and glomerular filtration. Tubular function reaches adult levels by two years of age (Gattineni and Baum, 2015), while the glomerular filtration rate (GFR) reaches adult rates at approximately two years (Rhodin et al., 2009). With rapid growth and increased muscular mass in infants, the serum creatinine values reach adult values at 2 – 3 years. Serum creatinine is higher in male children (Marciniak, 2019).

2.5.2.5. Liver function

Protein synthesis takes place in the liver. Albumin synthesis begins at 3 to 4 months of gestation and approaches adult values by one month of age (Marciniak, 2019; Batchelor and Marriott, 2015). There is a reduced ability to break down proteins such as albumin enzymatically at birth in the liver, and this ability reaches adult levels by adolescence (Marciniak, 2019).

2.5.3 Pathophysiological changes in critically ill children

In critical illness, multiple changes (such as fluid shifts, changes in protein concentration, and organ failure) related to the disease process (the infection or injury interacting with the patient system) and the therapies provided to the patients occur (Thakkar *et al.*, 2017).

2.5.3.1 Fluid balance

Fluid balance is essential in managing and maintaining normal body physiology in critically ill patients. Typically, total body water (TBW) accounts for approximately 70 - 80% of the body weight at birth and reduces to the adult value of approximately 60% at one year old. The higher Vd in infants due to higher TBW warrants higher doses per kg of hydrophilic drugs such as vancomycin to achieve adult plasma and tissue concentrations (Kearns et al., 2003; Batchelor and Marriott, 2015). TBW is distributed between the intracellular space (ICS) and the extracellular space (ECS). About 55% of the TBW is found in the ICS, while the remaining 45% lies within the ECS. Three compartments make up the ECS. These are (i) the intravascular space or plasma (IVS), which contains 15% of the total extracellular fluid (ECF), (ii) the interstitial space (ISS), which contains 45% of the total ECF, (iii) the transcellular space (TCS), which contains 40% of the total ECF (Ker and Gangadharan, 2019). The digestive, cerebrospinal, intraocular, pleural, peritoneal, and synovial fluids make up the TCS (Bianchetti et al., 2009). The movement of water between the three compartments of the ECS occurs through a semipermeable membrane dividing the compartments (Agrò and Vennari, 2013). The physical properties of fluids in each space or compartment and the properties of the semipermeable membrane separating each compartment play a vital role in maintaining the normal fluid balance in the body. The CNS, the endocrine, and the renal systems are responsible for efficiently regulating fluid movement in the body (Jain, 2015). In critically ill children, dysfunction of the CNS, endocrine or renal system may lead to fluid accumulation and retention in the body.

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2.5.3.2 Fluid changes in critically ill children

In critical illness, there is a range of fluid balance contexts depending on the child's fluid status. The normal balance of fluids in each compartment is often disturbed by systematic inflammation leading to capillary leaks and oedema (Shaffner and Nichols, 2015). Changes in the normal fluid distribution between the intracellular and extracellular compartments with or without renal dysfunction and aggressive fluid resuscitation will lead to fluid overload (hypervolemia), hypovolemia and dehydration in children. Fluid overload (FO) is a condition in which the patient has a positive fluid balance. Studies have shown that preventing>15–20% FO in critically ill children leads to better clinical outcomes (Arikan et al., 2012). Fluid imbalances and haemodynamic instability commonly occur in the PICU, as patients often receive fluid resuscitation to maintain adequate body water volume. FO is observed in disease states such as inflammation, infection, sepsis, and congestive heart failure (CHF) (Thakkar *et al.*, 2017).

Fluid overload can affect:

1. Heart function leading to CHF.

2. Respiratory function by causing pulmonary oedema (PO), leading to respiratory failure.

Fluid overload is observed in diseases such as inflammation, infection, sepsis, and CHF (Holte *et al.,* 2002).

Dehydration occurs when there is electrolyte and water loss leading to volume deficit in the extracellular compartment (and later in the intracellular compartments); this results in plasma loss affecting vancomycin Vd. When the patient is stabilized, after appropriate fluid administration, the vancomycin dose needs to be adjusted from the dose calculated using the weight at dehydration. In the absence of weight-based dose adjustments, hydration to the normal fluid status in the child will dilute plasma vancomycin concentration leading to low vancomycin

plasma concentrations. Dehydration is caused by water loss, mainly from the intracellular compartment (Asim et al., 2019). Although normovolemia (normal blood pressure and cardiac output) is re-established after appropriate fluid administration, blood flow to tissues may be prevented by factors such as low driving pressure, leukocyte/ platelet adhesion to endothelial cells and liberation of humoral/ cellular mediators (Kreimeier, 2000). This may lead to large vancomycin Vd intra-patient variations in patients undergoing and recovering from fluid imbalance.

2.5.3.3 Liver function

Changes in protein concentration, such as hypoalbuminaemia, occur in critical illness. Other causes of change in protein concentration may also be related to protein loss through membrane leaks and enzymatic breakdown of the proteins into smaller components (Yu and Lin, 2014). Increased protein concentration (hyperalbuminaemia) may occur after using products such as albumin and gamma globulins. Vancomycin has moderate to high protein binding. The change in protein concentration may affect its PK. An increase in the unbound drug occurs after administration, where the serum protein concentration is low and vice versa. Dilution of the free drug fraction and increased clearance result in inadequate drug concentration and treatment failure (Blot et al., 2014; Oyaert et al., 2015).

2.5.3.4 Cardiac function

There may be substantial changes in cardiovascular function in critically ill children. Hyperdynamic circulation (with high cardiac output) may occur, but it is more common to have a decrease in cardiac function in critically ill children. Poor cardiac function may be associated with damage to vital organs (particularly the kidneys), increasing vancomycin clearance and toxicity risks (Jefferson et al., 2010).

2.5.3.5 Renal function

Kidney function changes occur in critically ill children. A high proportion of children in the ICU have altered renal function. Acute kidney injury (AKI) resulting from sepsis, major surgery (especially open-heart surgery), and acute decompensated heart failure occurs in critical illness (Bellomo et al., 2012). AKI leads to higher-than-expected plasma concentration and half-life of renally eliminated drugs.

2.5.4 Clinical and laboratory characteristics of critical illness

Critical illness occurs with a change in vital signs (temperature, blood pressure, heart rate, respiratory rate), organ function (Liver, kidney, lung and cardiac), and tissue distribution (protein binding alterations, pH changes, and fluid shifts) (Thakkar *et al.*, 2017).

2.6 Studies on vancomycin pharmacokinetics in critically ill children

A systematic literature review on studies carried out in critically-ill children until September 2021 was carried out using all the appropriate methodologies (Akunne *et al.,* 2022). The literature search was performed using the keywords "Vancomycin" AND "Pharmacokinetics" AND "Children" AND "Paediatrics" AND "Critically-ill" AND "ICU", NOT "Adults" NOT "Neonates". Studies performed in children (>1 month of age and less than 19 years of age) admitted to the ICU and treated with vancomycin were selected, provided they presented results for Clearance (CL) and Volume of distribution (Vd). Out of 652 potential articles, 13 were selected for review.

2.6.1. Age of children in the studies

The age of children in studies evaluating vancomycin pharmacokinetics in critically ill children varied. Most studies comprised children of age 0.1–17 years (Gous et al., 1995; Giachetto et al., 2011; Acuña et al., 2013; Gomez et al., 2013; Villena et al., 2014; Seixas et al., 2016; Zane et al.,

2017; Genuini et al., 2018; Zylbersztajn et al., 2018; Mali et al., 2019; Sridharan et al., 2019). The

upper age limit in one study was 21 (Avedissian et al., 2017) (Table 2.1).

Table 2-1 Characteristics of Studies Included in the Review

Author, Year	Study design	Number of patients/ Samples	Age (range) Yrs	Weight (range) kg	Patient subgroup	AKI	Scr (range) µg/L	CrCl (range) mL/min/1.73m2	ALB (g/L)	Model*	Covariates
Mali et al., 2019	P	12/NS	1 – 10	15.58±4.5[a]	NS	N	NS	88±26 [a]	NS	0	NS
Zane et al, 2017	R	52/154	1 – 17	13 (7-88.3)	Cardiac Arrest	N	8.8–334.8	7.8 – 140	NS	2	Weight, Renal function, Temperature,
Sridharan et al, 2019[21]	R	63/182	1 – 17	12.5±10.2[a]	NS	N	23.9 ±15.0[a]	164.1 (130–679)	5.2±1.1[a]	1	NS
Villena et al, 2014[22]	R	45/65	0.1 – 10	11.7 (2.6-56)	NS	N	17.68 (8.8-35.4)	NS	NS	NS	NS
Avedissian et al, 2017[23]	R	250/658	1 – 21	30.0 (15–50)	NS	N	35.4 (27–47.7)	97.34 (76–115)		1	Weight, Concurrent nephrotoxic Medications, Sex, Age, SCr
Acuña et al, 2013[24]	R	84/NS	0 – 16	<2 years 6.5 (5-8) ≥2 years 26 (17-36)	NS	N	NS	NS	NS	1	NS
Genuini et al*, 2018[25]	R	28/NS	0.1 – 17	3-53	NS	N	21.2 (14–43.3)	159 (97–256)	NS	1	NS
Zylbersztajn et al, 2018[26]	R	29/NS	0.1 – 14		Extracorporeal Membrane Oxygenation Support	Y	Without AKI or RRT : 19.45 (9.7–26.5) With AKI and RRT: 65.42 (61–123) With AKI only: 26.52 (26–36)	Without AKI or RRT : 158 (144–288) With AKI and RRT: 48 (40–70) With AKI only: 153 (115–160)	NS	NS	NS

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	*										
Sexias et al, 2016[27]	R	94/256	4 – 11	22.34 (11.1-35.7)	Cancer	Y	46.85±42 a	157.45 ±69.11 a	3.91±0.49 a	NS	CRCL, urea, SCr, albumin, age and weight
Da Silva et al, 2012[28]	R	31/61	0. 2 – 13		Oncologic/Hematologic patients	N	38.9 ±15.9	136±44.8	2.44±0.3	NS	NS
Gomez et al, 2012[29]	P	13/30	0.1 – 11	25 (12-45)	Burns	N	NS	127.9 (113–138)		0	NS
Gous et al, 1995[30]	P	20/NS	0.1 – 0.8	6.4±2.37	NS	N	Day 2: 39.9±13.8 Day 8: 30.46±6.3	NS	NS	NS	NS
Giachetto et al, 2011[31]		22/NS	0.1 – 16		NS	N	NS	NS	NS	1	NS

*Number of compartments in model; P-Prospective study design; R-Retrospective study design; NS-Not Specified; N-No, Y-Yes; values given as median, range; ᵃmean, standard deviation

2.6.2. Vancomycin dose and mode of administration

Vancomycin is generally administered intravenously. Different studies reported a variation in the total daily dose administered to children with children receiving 20-60mg/kg/day of vancomycin over one hour (Gous *et al.*, 1995; da Silva *et al.*, 2012; Acuña *et al.*, 2013; Gomez *et al.*, 2013; Villena *et al.*, 2014; Genuini *et al.*, 2018) or 2 hours (Zylbersztajn *et al.*, 2018). These children received divided doses of either 10-15 mg/kg every 6 hours (Gous *et al.*, 1995; da Silva *et al.*, 2012; Acuña *et al.*, 2013; Villena *et al.*, 2014; Avedissian *et al.*, 2017; Zylbersztajn *et al.*, 2018), or 20mg/kg every 8 hours (Gomez *et al.*, 2013) (Table 2.2).

The dosing interval and the duration of dose administration also varied from 1 to 2 hours. However, some studies show that vancomycin was given continuously (usually after a single loading dose). For example, in a study of children aged 0.1 – 17 years, a 15 mg/kg loading vancomycin dose was infused over an hour, after which they received a continuous vancomycin infusion of 45mg/kg (Genuini et al., 2018).

Table 2-2 Vancomycin dosing regimen in critically ill children

Author, Year	Dose	Dosing Interval	Time of Infusion	Sampling times
Mali et al., 2019	60 mg/kg/day	Every 8 hours	1 hour	48 hours, 49 hours, 49.25 hours, 49.5 hours, 50 hours, 50.5 hours, 51 hours, 52 hours, 54 hours, 56 hours after treatment initiation
Zane et al, 2017	10 (5 – 20) mg/kg	Not provided	Not provided	Anytime within 10 days of cardiac arrest
Sridharan et al, 2019	13.7± (8.9) mg/Kg	Every 6,8 and 12 hours	Not provided	After the first dose and after the second or third dose
Villena et al, 2014	47.1 (36-75) mg/kg /day	Every 6 hours	1 hour	30 mins before fourth dose 30 mins after fourth infusion
Avedissian et al, 2017	45 (40–59) mg/kg /day	Not provided	Not provided	After 48 hours
Acuña et al, 2013	40 mg/kg /day	Every 6 hours	1 hour	49 hours after initiation 53.5 hours after initiation
Genuini et al, 2018	Loading dose 14.8 (12–16) mg/kg; continuous infusion 44 (35–61) mg/kg /day	Continuous infusion	Loading dose, then continuous infusion	According to physician's discretion
Zylbersztajn et al, 2018	Without AKI or RRT 40(34–60)mg/kg /day With AKI and RRT: 20(15–30)mg/kg /day With AKI only: 40 (30–45) mg/kg /day	Every 6 hours	2 hours	53.5 hours after initiation of treatment.
Sexias et al., 2016	60±50 mg/kg /day	6 to 48 hours	Not provided	One hour before the fifth dose
Da Silva et al., 2012	10–156 mg/kg/day	NS	NS	One hour before the 5th dose
Gomez et al., 2012	Initial dose 43.4 ± 9.0 mg/kg /day Adjusted dose 98.0±17.9 mg/kg /day	Every 6 hours	1 hour	30 hours after initiation of treatment
Gous et al., 1995	60 mg/kg/day	Every 6 hours	1 hour	Immediately before vancomycin infusion and 30, 60, 120 and 300 minutes after infusion on day 3 and day 9 after the first vancomycin infusion
Giachetto et al, 2011	40-60 mg/kg /day	Every 6 hours	1 hour	1 hr after the end of the third dose administration 15mins before the fourth dose

There have been several different approaches in the setting of AKI (with or without renal replacement therapy). The dose given to children with acute kidney injury (AKI) and renal replacement therapy (RRT) was 15–30 mg/kg/day with a dosing frequency ranging from 2-4 times daily in one study (Zylbersztajn et al., 2018). Some studies did not provide details on dose adjustment or the treating physician adjusted doses according to their preferences (Avedissian et al., 2017; Zane et al., 2017; Sridharan et al., 2019; da Silva *et al.*, 2012; Villena *et al.*, 2014; Genuini *et al.*, 2018; Zylbersztajn *et al.*, 2018).

2.6.3 Blood sampling strategies

The studies used various sampling strategies. Two studies collected the first blood sample after the third dose (Villena et al., 2014; Avedissian et al., 2017). Three studies collected it after the fourth vancomycin dose (da Silva et al., 2012; Gomez et al., 2013; Seixas et al., 2016). The study by Gomez et al. (2013) took the first blood sample after 30 hours. Three studies took the first blood sample after 48 hours (Villena et al., 2014; Zylbersztajn et al., 2018; Mali et al., 2019). One study took the first blood sample after the first or third dose (Sridharan et al., 2019).

In most studies that collected blood samples for peak concentration, sampling was typically done half an hour to one hour after vancomycin infusion (Gous et al., 1995; Acuña et al., 2013; Gomez et al., 2013; Villena et al., 2014). One study collected blood samples for peak concentrations two hours after vancomycin infusion (Avedissian et al., 2017). Blood samples collected for vancomycin trough concentration measurements were collected not more than 30 minutes before the next vancomycin dose in five studies (Gous et al., 1995; Acuña et al., 2013; Gomez et al., 2013; Villena et al., 2014; Zylbersztajn et al., 2018). In two studies, blood samples for vancomycin trough concentration measurement were obtained one hour before the next vancomycin administration (da Silva et al., 2012; Seixas et al., 2016). In one study, blood sample collection for

trough concentration measurement was up to two hours before the next vancomycin dose (Avedissian et al., 2017).

In studies of patients receiving about 60 mg/kg/day and with multiple sampling points, one study collected blood samples 1, 2, 3, and 4 hours after the fourth vancomycin dose or at 30hrs (Gomez et al., 2013). In addition, this study collected trough concentrations before the fifth vancomycin dose.

Another study collected blood samples at 48, 49, 49.25, 49.5, 50, 50.5, 51, 54, and 72 hours after the first dose of vancomycin (Mali et al., 2019).

One study collected blood samples on days three and seven after vancomycin infusion (Gous et al., 1995). On each of these days, vancomycin was collected immediately before the first infusion of the day and at 30, 60, 120, and 300 minutes after the first infusion on the specified days (days 3 and 9).

2.6.4 Number of blood samples collected

The number of blood samples collected in the studies varied. In six studies, 13 – 29 patients were recruited (Gous et al., 1995; Giachetto et al., 2011; Gomez et al., 2013; Genuini et al., 2018; Zylbersztajn et al., 2018; Mali et al., 2019), four of the studies did not specify the number of blood samples collected (Gous et al., 1995; Giachetto et al., 2011; Zylbersztajn et al., 2018; Mali et al., 2019). For example, one of the studies enrolling 13 patients collected 30 blood samples for vancomycin PK estimation (Gomez et al., 2013), and in the other study with 28 patients, 87 blood samples were collected for vancomycin concentration measurement (Genuini et al., 2018).

Six studies were conducted on 31 – 94 patients (da Silva et al., 2012; Acuña et al., 2013; Villena et al., 2014; Seixas et al., 2016; Zane et al., 2017; Sridharan et al., 2019). The study with 84 patients did not specify the number of blood samples collected (Acuña et al., 2013). One study comprising

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31 children collected 61 blood samples (da Silva et al., 2012); another that included 45 children collected 65 blood samples (Villena et al., 2014). The study comprised 52 (Zane et al., 2017), 63 (Sridharan et al., 2019), and 94 (Seixas et al., 2016) children, respectively, collected 154, 182, and 256 blood samples. One study collected 658 blood samples from 250 children (Avedissian et al., 2017).

Five studies reported limitations due to sample size and the number of blood specimens collected (Gomez et al., 2013; Zane et al., 2017; Genuini et al., 2018; Zylbersztajn et al., 2018; Mali et al., 2019). For example, in one study, the PK model could not assess significant covariates due to the small population size (Genuini et al., 2018). In another study, the model selected was less precise in estimating the volume of distribution and inter-compartmental distribution than CL because of the small sample size and the use of few trough-only samples (Zane et al., 2017). The limited number of samples resulted in a reduction in the ability of the model to predict vancomycin concentration. One study could not give dosing recommendations because of the small sample size (Zylbersztajn *et al.*, 2018).

2.6.5 Vancomycin pharmacokinetic in critically ill children

2.6.5.1 Vancomycin serum concentrations

Target vancomycin plasma concentration varied in studies (Table 2.3). In one study, vancomycin trough concentration of 5-15 µg / mL was deemed therapeutic (Acuña et al., 2013). Out of 84 children in this study, 41 had vancomycin plasma concentrations within the specified therapeutic range after receiving 40 mg/kg/day. Blood samples were collected 48 – 72 hours after the initiation of vancomycin treatment.

Table 2-3 Vancomycin Pharmacokinetic Parameters of Studies In Critically-ill Children

Author, Year	Trough (μg / mL)	Peak (μg /mL)	CL (L/h/Kg)	V or V_1 (L/Kg)	Q (L/h/Kg)	V_2 (L/kg)	$t_{1/2}$ (h)	AUC_{24} (mcg/mL/h)
Mali et al, 2019	48 hrs 10.56±8.5 72 hrs 10.1±6.7	NS	0.12 ±0.1	0.8±0.3	NS	NS	4.8±3	372.4±153.8
Zane et al, 2017	NS	NS	0.34 (0.3-0.4)	0.98 (0.6-1.3)	0.7 (0.5-0.8)	2.7 (2.2-3.2)	NS	NS
Sridharan et al, 2019	9±6.3	NS	0.38 (0.07–2.26)	0.1 (0.0–0.5)	NS	NS	7.2 (1–38)	375.5 (36.1–2029.2)
Villena et al, 2014	10.4 (1.4-25.5)	22.7	NS	0.7 (0.4-2.1)	NS	NS	3.1 (1.1-7.7)	NS
Avedissian et al, 2017	9 (4–14.03)	NS	0.118	0.62 (0.6–0.7)	NS	NS	3.62 (3.1–4.5)	229.1 (134.1–418.3)
Acuña et al, 2013	<2 years 11.04 (5.9-17.6) ≥2 years 11.43 (5.6-22.5)	<2 years 24.2 (15.7-32.3) ≥2 years 25.4 (17.3-36.7)	<2 years 0.10 (0.06-0.18) ≥2 years 0.10 (0.06-0.14)	<2 years 0.7 (0.4-1.2) ≥2 years 0.6 (0.4-1.0)	NS	NS	<2 years 3.6 (2.2-5.5) ≥2 years 3.8 (2.7-10.6)	<2 years 430.7 (242.2-612.7) ≥2 years 410.6 (261.5-689.1)
Genuini et al*, 2018	NS	NS	0.13 (0.1–0.2)	0.64 (0.6–0.7)	NS	NS	NS	355 (261–1,001)
Zylbersztajn* et al, 2018	NS	NS	Group 1 0.10 (0.06–0.10) Group 2 0.05 (0.02–0.06) Group 3 0.07 (0.04–0.09)	Group 1 0.73 0.7–0.9) Group 2 1.16 (0.7–1.6) Group 3 0.88 (0.7–0.9)	NS	NS	Group 1 6.2 (4.9-8.1) Group 2 23.6 (16.2-31) Group 3 8.69 (5.05-17.5)	Group 1 502.5 (444–569.1) Group 2 462.4 (279.65–538.5) Group 3 436.72 (381.7–463.36)
Sexias et al, 2016	15.6±12.4 (5.3-19.2)	25.26±5.41 (16.5-33.5)	0.16±0.098 (0.08-0.18)	1.04±0.1 (1.0-1.1)	NS	NS	NS	NS
Da Silva et al, 2012	16.11±11.3	29.33±11.6	0.18±0.11	1.03±0.1	NS	NS	NS	NS
Gomez et al, 2012	13.0±4.8	NS	0.10 (0.06–0.22)	0.41 (0.2–0.9)	NS	NS	2.4 (1.8–3.2)	552.8 (302.5–1008.2)
Gous et al, 1995	Day 3 12.0±5.9 Day 9 11.7±6.8	Day 3 29.1±12.1 Day 9 35.5±11.1	Day 3 0.09±0.03 Day 9 0.07±0.02	Day 3 0.81±0.6 Day 9 0.44±0.1	NS	NS	Day 3 5.3±3.2 Day 9 3.4±1.2	NS
Giachetto et al, 2011	Day 1 7.80 ±4.80 Day 3 9.36 ± 7.80	Day 1 21.8 ±13.6 Day 3 21.7 ±8.80	Day 1 0.12 ±0.07 Day 3 0.15± 0.06	Day1 0.51 ±0.2 Day 3 0.86 ±0.6	NS	NS	Day 1 3.1 ±0.8 Day 3 4.5±3.1	Day 1 364 ±218.9 Day 3 364 ± 212.8

*group 1 - Without AKI or RRT, group 2 - With AKI and group 3- With AKI only ; values given as median, range; a mean, standard deviation; AKI- acute kidney injury; RRT- renal replacement therapy; NS-Not Specified

In a second study, set therapeutic targets were trough concentrations of 5 - 10 μg /mL and peak concentrations of 25 - 40 μg /mL (Gous et al., 1995). Children received 60 mg/kg/ day in four divided doses. Blood sample collection was on day three and day nine of vancomycin treatment. Therapeutic trough levels were observed in 53% and 27% of children on days three and nine, respectively. About 53% and 60% of the children had therapeutic peak levels on days three and nine. Vancomycin trough concentrations at 72 hrs and 216 hrs were comparable.

In another study, the therapeutic range for the trough concentration was 10–20 mcg/mL in children receiving 20 mg/kg thrice a day (Mali et al., 2019); 31.43% of blood samples had vancomycin concentration within this range. However, trough concentration was below the recommended range in 65.71% of the samples evaluated. In addition, trough concentration was higher than the upper limit of the range in 2.86% of the samples. At 48 and 72 hrs, the vancomycin trough plasma concentrations were comparable.

In one study, children with varying renal functions were given 40 mg/kg/day vancomycin doses in three or four doses (Zylbersztajn et al., 2018). Vancomycin trough concentration of 10-20 mcg/mL was considered therapeutic. Blood samples were collected 48 – 72 hours after initiating vancomycin therapy. Therapeutic trough concentration was achieved in 8 (53%) of 15 children with normal renal function; four children (27%) had higher than normal trough concentration. Three children (20%) had sub-therapeutic concentrations. In 11 children with AKI, the trough concentration was within the therapeutic range in three (27%) children, seven children (64%) had higher than normal vancomycin concentration, and one child (9%) child had lower than normal vancomycin concentration. Adjusted vancomycin dose was given to 4 patients with high vancomycin trough concentration. Three of the four children did not reach therapeutic concentration as they either died or had their treatment terminated. Vancomycin therapy was discontinued in one patient with lower-than-normal vancomycin concentration before the dose

could be adjusted. Seven patients (63%) achieved therapeutic concentrations after one or 2-dose therapeutic modifications. Adjusted vancomycin doses were 20 mg/ kg/day in these children, with AKI given every 12 hours. This dose achieved a median trough of 15.95 (12.1–18.03) mcg/mL.

In another study, vancomycin plasma concentrations between 15 and 30 mcg/mL were considered therapeutic. Children in this study received a 15 mg/kg vancomycin infusion and a 45 mg/kg continuous infusion (Genuini et al., 2018). Blood samples were collected between 10 – 95 hours after initiation of treatment. Twelve (43%) of the 28 children enrolled in the study achieved therapeutic vancomycin concentration after the initial dose. Out of twenty patients with more than one vancomycin trough concentration, nine children (45%) had the second measured trough plasma concentration within the therapeutic range. After dose adjustment, the median vancomycin trough plasma concentration increased from 12.1 (9.8–17.3) mcg/mL to 15.5 (10–25.7) mcg/mL.

In a study, vancomycin trough concentrations of 5 - 20 mcg/mL and peak concentrations of 20–40 mcg/mL were considered therapeutic (Giachetto et al., 2011). Blood samples were collected on day one and day three of vancomycin treatment. On day one, 16 of the 22 children treated with a vancomycin dose of 10 mg/kg every six hours were given as a one-hour infusion, had therapeutic trough concentrations (5.02 – 20 mcg/mL), and seven had therapeutic peak concentrations (23.9 – 53.5 mcg/mL). On day three, 15 children had their doses adjusted to 44 mg/kg/day, therapeutic trough (6.65 – 29.2 mcg/mL) concentrations were achieved in 10 children, and therapeutic peak concentration of 20.56 – 45.4 mcg/mL in 7 children. Vancomycin trough concentrations at 24hrs were comparable to the concentration at 72 hours.

In another group of children (Villena et al., 2014), initial dosing of 47 mg/kg/day was given in four divided doses in 45 children. Blood sampling was done 30 mins before the fourth dose. Approximately two (4.4%) children attained therapeutic trough concentrations of 15 to 20 µg /

mL. Thirty-seven children (82.2%) had trough concentrations lower than the therapeutic range. Ten patients had trough concentrations of 10 - 14.9 µg /mL. Trough concentration was higher than the normal therapeutic range. Six children (13.3%) had vancomycin concentrations higher than the normal therapeutic range.

In another study (Seixas et al., 2016), children were given a mean vancomycin dose of 59.23±49.85mg/kg/day. Blood sampling was done 24 hours post-initiation of vancomycin therapy. The vancomycin trough concentrations in this study were 15 - 20 µg / mL in 35 (13.6%) blood samples. Vancomycin trough concentration > 20 µg / mL was observed in 73 (28.5%) blood samples.

2.6.5.2 Vancomycin Clearance

The average vancomycin CL in critically ill children ranged from 0.05 – 0.38 L/h/kg (Gous et al., 1995; Giachetto et al., 2011; da Silva et al., 2012; Acuña et al., 2013; Gomez et al., 2013; Avedissian et al., 2017; Zane et al., 2017; Genuini et al., 2018; Mali et al., 2019; Sridharan et al., 2019).

Using a reference vancomycin CL range of 0.08 – 0.13 L/h/kg, eight studies reported that vancomycin CL was within the normal range in critically ill children (Gous et al., 1995; Giachetto et al., 2011; Acuña et al., 2013; Gomez et al., 2013; Avedissian et al., 2017; Genuini et al., 2018; Zylbersztajn et al., 2018; Mali et al., 2019). In these studies, vancomycin doses of 40 mg were given six hourly or 8-hourly to patients. In one study reporting vancomycin CL of 0.13 mg/h/kg, children were given continuous vancomycin infusion of 45mg/kg after a loading dose of 15mg/kg. Four of these studies analysed different patient groups (Gous et al., 1995; Giachetto et al., 2011; Acuña et al., 2013; Zylbersztajn et al., 2018). Patients were divided into three groups in one study based on their renal function (Zylbersztajn et al., 2018). Patients with normal renal function

received 40mg/kg/day, their vancomycin CL was 0.10 L/h/kg, and their CrCl was 158 mL/min/1.73m^2. Those with AKI, either on or not on RRT, had vancomycin CL less than the normal range. Children with AKI, not on RRT, received 40mg/kg/day of vancomycin; their vancomycin CL was 0.07 L/h/kg, and their CrCl was 158 mL/min/1.73m^2. Children with AKI on RRT received 20mg/kg/day and had vancomycin CL of 0.05 L/h/kg and CrCl of 48 mL/min/1.73m^2. In another study that involved grouping children according to age (children < 2 years and > 2 years), similar vancomycin doses (40mg/kg/day in four divided doses) were given (Acuña et al., 2013). They had comparable vancomycin CL (0.10 L/h/kg, respectively). Two other studies analysed vancomycin CL according to the time blood samples were collected. In one of the studies, vancomycin CL on day 7 was lower than the lower limit of the normal range (0.07 L/h/kg) compared to day three when vancomycin CL was within the normal range (0.09 L/h/kg) (Gous et al., 1995). In the second study, vancomycin CL was higher than the normal range on day three (0.15 L/h/kg) and within the normal range on day one (0.12 L/h/kg). Patients received 40mg/kg/day and 44mg/kg/day of vancomycin on days one and three, respectively (Giachetto et al., 2011).
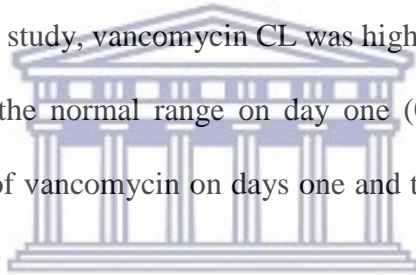
Patients in four studies had higher than normal vancomycin CL (0.16 – 0.38 L/h/kg). Two of these studies had very high vancomycin CL of 0.34 L/h/kg in patients on 10 mg/kg of vancomycin (dosing frequency or total daily dose were not indicated in the study) and 0.38 L/h/kg in children with vancomycin dose of 15mg/kg 6, 8 or 12 hourly. Two other studies with high vancomycin CL gave 40 – 60 mg/kg 6hrly to children with an average vancomycin CL of 0.16 L/h/kg and 10-156mg/kg/day to those with vancomycin CL of 0.18L/h/kg.

In four studies, inter-individual variability in vancomycin clearance in critically ill patients was between 38 – 90.5% (Gomez et al., 2013; Avedissian et al., 2017; Zane et al., 2017; Genuini et al., 2018). However, these studies did not explain the inter-individual variability.

2.6.5.3 Vancomycin Volume of distribution

The vancomycin V_d in critically ill children was reported to be between 0.1 and 1.16 L/kg [3, 20, 30, 21, 23–29]. Infants ($\leq$ 1-year-old) have significantly higher V_d compared to children in other age groups ($>$ 1-year-old) (Sridharan et al., 2019). Children with AKI who received RRT had a higher V_d (median [range]: 1.16 [0.68–1.6] L/kg) than children with AKI not receiving RRT (median [range]: 0.88 [0.68–0.92] L/kg) and children without AKI (median [range]: 0.73 [0.7–0.9] L/kg) (Zylbersztajn et al., 2018). High inter-individual variability in V_d was attributable to the difference in weight, serum creatinine, age, renal function, and temperature observed in critically ill children (Gomez et al., 2013; Avedissian et al., 2017; Genuini et al., 2018).

2.6.5.4. Vancomycin Half-Life

Vancomycin's half-life in critically ill children ranges from 2.4 to 23.6 h (Gous et al., 1995; Giachetto et al., 2011; Acuña et al., 2013; Gomez et al., 2013; Villena et al., 2014; Avedissian et al., 2017; Zylbersztajn et al., 2018; Mali et al., 2019; Sridharan et al., 2019). Higher vancomycin half-life has been observed in critically ill children with AKI and on RRT (23.6 [16.2–31] hours) compared to children with AKI and not on RRT (6.2 [4.9–8.06]) and children without AKI (8.69 [5.05–17.52] hours) (Zylbersztajn et al., 2018).

2.6.5.5. Vancomycin Area under the Concentration- Time Curve

Sridharan et al. (2019) found that trough vancomycin concentration was a good predictor of AUC0-24 [0.86; 95% CI 0.8–0.9; P = 0.0001]. Trough concentrations of 5-15 mcg/mL yielded AUC0-24 > 400 µg * h/mL in 97% of critically ill children (Acuña et al., 2013). Higher AUC0-24 in children without AKI (502.5 [444–569.1] µg * h/mL) compared to AUC0-24 in children with AKI with (462.4 [279.65–538.5] µg * h/mL) or without RRT (436.72 [381.7–463.36] µg * h/mL) (Zylbersztajn et al., 2018).

2.6.6 Effect of renal function on vancomycin pharmacokinetics

Critically ill children aged 1 – 17 years with high serum urea (9.7 – 412.2 µg/L) and creatinine (8.84 – 334.76 µg/L) concentrations had a high peak and trough concentrations and reduced vancomycin CL (Seixas et al., 2016; Zane et al., 2017). Vancomycin CL increased with increased creatinine CL (Seixas et al., 2016). Critically ill children (3.2–14.0 years) with augmented renal clearance (ARC) (8.7–13.8 years) received an equivalent dose per weight as critically ill children with normal renal clearance (NRC) (3.0–14.2 years). Renal clearance in children with ARC was 141.3 (132.7–148.9) mL/min/1.73 m^2 and 91.7 (74.8–106.6) mL/min/1.73 m^2 in children with NRC. There was no significant difference in their AUC0 - 24. About 79% of the children with ARC had trough levels < 10mcg/mL, while 53% of children with NRC had trough levels < 10mcg/mL (Avedissian et al., 2017). A study in children aged 1 – 17 years showed that 40% of children with ARC had significantly higher CL (8.1 [5.6–16.9] vs 3.7 [1.4–5.5] L/h), shorter half-life (4.3 [2–6.1] vs 9.2 [6.3–23.9] hrs) and lowered AUC24 (142.6 [61.1–363.9] vs 594.4 [114.1–1130.1] μg * h / mL) compared to children with NRC (Sridharan et al., 2019).

2.6.7 Effect of protein binding on vancomycin pharmacokinetics

A study reported that the free vancomycin concentration in critically ill children is 77.5% (Sridharan et al., 2019). Lower unbound (free) vancomycin concentrations (71.60% vs 80.88%) were observed in 28 older children (1 month to 5 years) compared and 55 younger children (6 – 17 years). Higher Vd (0.14 L/kg) was reported in infants (1 – 12 months) compared to older children (13 months – 17 years) (0.03 – 0.09 L/kg). There was no significant difference in protein-free vancomycin fraction (75.40%) in the children who achieved AUC 0-24 > 400 μg * h / mL and protein-free vancomycin fraction (80.18%) in those with AUC 0-24 < 400 μg * h / mL. The attainment of AUC 0-24 > 400 μg * h / mL was not influenced by protein binding in the study.

2.6.8 Effect of fluid balance on vancomycin pharmacokinetics

A study on 22 critically ill children aged 0.1 – 16 evaluated the effect of fluid balance on vancomycin PK parameters. They calculated the water balance during the 24 hours before initiation of vancomycin as the difference between patients' fluid incomes and outcomes. Those with negative water balance had a higher vancomycin peak (Day 1 = 30.07 mcg/mL and Day 3 = 37.55 mcg/mL) and trough concentrations (Day 1 = 10.87 mcg/mL and Day 3 = 25.10 mcg/mL) compared to peak (Day 1 = 6.4 mcg/mL and Day 3 = 6.5 mcg/mL) and trough (Day 1 = 17.2 mcg/mL and Day 3 = 19.21 mcg/mL) vancomycin concentrations in children with a positive fluid balance (Giachetto et al., 2011). In another study, 20 children aged 0.1 – 0.8 years received aggressive fluid resuscitation had larger vancomycin V_d (1.47 – 2.60 L/kg) and prolonged half-life (9.66 – 12.25 hrs) compared to other children (V_d (0.18 – 1.28 L/kg) and half-life (1.29 – 9.70 hrs)) on day three of vancomycin treatment. These parameters were similar to those in other children by day eight (Gous et al., 1995).

2.6.9 Effect of concomitant medication on vancomycin pharmacokinetics

A study reported the effects of nephrotoxic medications in children receiving vancomycin as a continuous infusion (Genuini et al., 2018). A total of three of the 20 critically ill children aged 0.1 – 17 years treated with nephrotoxic drugs- aminoglycosides, cyclosporin, tacrolimus, or diuretics - demonstrated renal dysfunction, defined as serum creatinine ≥ 2 times its upper limit for age or a 2-fold increase in baseline creatinine. However, these patients recovered their renal function without renal replacement therapy.

2.6.10 Vancomycin dose recommendation in critically ill children

Most vancomycin studies in critically ill children did not recommend vancomycin doses. Villena et al. (2014) suggested that higher doses of vancomycin should be given, especially in children

aged 1 – 12. This is understandable as children in the study were given doses of 40 mg/kg/day, which is lower than the current recommended dose of 60 mg/kg/day (Rybak et al., 2020).

Gomez et al. (2013) reported that 13 children aged 1 - 11 years received a vancomycin dose of 90–100 mg/kg/day for paediatric burn patients with sepsis and 80 mg/kg/day for critically ill children. Their suggestion on the dosage of vancomycin is because the initial mean (SD) vancomycin daily dose of 43.4 ± 9.0 mg/kg did not achieve the target plasma trough concentration of >10 mg/mL in most of the children (84.6%). However, increasing the dose to 98.0 ± 17.9 mg/kg significantly increased the trough concentration from 7.4 ± 6.0 mg/mL to 13.0 ± 4.8 mg/mL ($p =0.017$).

2.7 Conclusion

After a review of the literature on vancomycin usage in critically ill children, it is clear that there is substantial variation in the PK of vancomycin in this population. These variations are related to the wide range of disease profiles and therapeutic interventions and necessitate a better understanding of vancomycin PK in our patient population. There are substantial variations in prescription and therapeutic drug monitoring practices across the literature. Although preliminary data suggest that monitoring AUC is more predictive of outcome than monitoring trough levels, it has not been demonstrated clearly in children. There is still an inadequate understanding of what is required to optimise therapy with vancomycin.

Chapter 3
Methods

3.0 Introduction

This section presents the methods for patient recruitment, collection and storage, sample analysis, and data analysis.

3.1 Study design/site
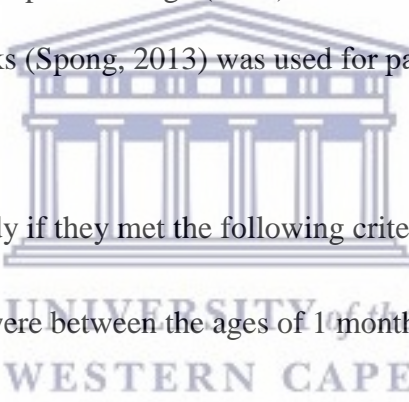
This study was a prospective open-label, non-randomized study of vancomycin pharmacokinetics in critically ill children admitted to the Red Cross War Memorial Hospital intensive care unit.

3.2 Study participants

Children aged 1 month-16 years old on vancomycin therapy for the treatment of suspected or confirmed bacterial infection. The postnatal age (PNA) of children that were not born as preterm babies (gestational age $\geq$ 37 weeks (Spong, 2013) was used for patients' selection.

3.3 Inclusion criteria

Patients were included in the study if they met the following criteria:

(a) Were not born pre-term and were between the ages of 1 month-16 years.

(b) On vancomycin treatment for infection (suspected or proven) of any origin.

(c) Had informed written/signed consent given by the parent or caregiver.

(d) Had intravenous lines (either central venous or arterial lines) through which blood specimens could be collected.

(e) Informed written and signed assent given by children $\geq$7 years participating in the study. Informed consent obtained from parent/guardian was sufficient to include the child in the study where a child could not give assent (i.e., critically ill).

(f) Where parents were unavailable to sign informed consent, blood samples were collected and stored for up to two days, within which parents were required to give consent. If parents were unable to give their consent, the samples were destroyed.

3.4 Exclusion criteria

a) Pre-term babies (including infants with chronological age ≥1 month but who have not reached ≥ 1 month using gestational age) and children <1 month.

b) Dissenting behaviour (refusals to participate noted by crying or body language) observed in a child by the researcher.

 (c) Withdrawal from the study by parent or caregiver.

(d) Withdrawal from the study by the child.

3.5 Sample size

This study describes vancomycin's PK and assesses factors that may influence vancomycin PK. Sample size calculation was done in two-part: (i). the sample size necessary to adequately describe vancomycin PK, and (ii) the sample size required to adequately assess the effect of physiological, pathophysiological and clinical factors on vancomycin PK.

The sample size for this study was the required number of children that adequately i) described the pharmacokinetics of vancomycin, ii) explained the pharmacodynamics effects of vancomycin and iii) evaluated the effect of the pathophysiological state of the children. Sample size calculations were performed according to the principles of Martínez-Mesa et al., 2014. A margin of error (confidence interval) of 5% was acceptable as the error in the estimate obtained in this study. The probability that the expected prevalence will be within the 5% error margin was 95%. To test for associations between two variables, the maximum probability of type I for this study was fixed at a value of 5% (0.05 or confidence level of 95%), and the maximum probability for type II errors

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was set at fixed at a value of 20% (or 0.20). Cluster selection was used to reduce the total estimated variance between groups. The design effect was estimated at 2. The Sample sizes comparing groups using combinations based on the study objectives ranged from 52 – 242 patients. Based on an accrual rate of 5 children monthly and the expected duration of the study, the sample size of 52 children was selected. The section below gives an in-depth analysis of the sample size calculation for this study.

3.5.1 Sampling size calculation for vancomycin PK analysis

Vancomycin PK parameters from each dataset were estimated using the Monolix package. The relative standard error (RSE) values (the measure of precision) for the PK parameters were plotted against sample size (central volume, central clearance, distribution clearance, and peripheral volume). The R package, ggplot2 R package ('ggPMX: "ggplot2" Based Tool to Facilitate Diagnostic Plots for NLME', 2020), was used to plot graphs of the sample size (number of patients included in the datasets) against relative standard error (RSE) values (the measure of precision) for each PK parameter (central volume, central clearance, distribution clearance, and peripheral volume).

The minimum sample size required was the smallest values, where the RSE for the PK parameters were the lowest (for example, Figure 3.1 for CL).
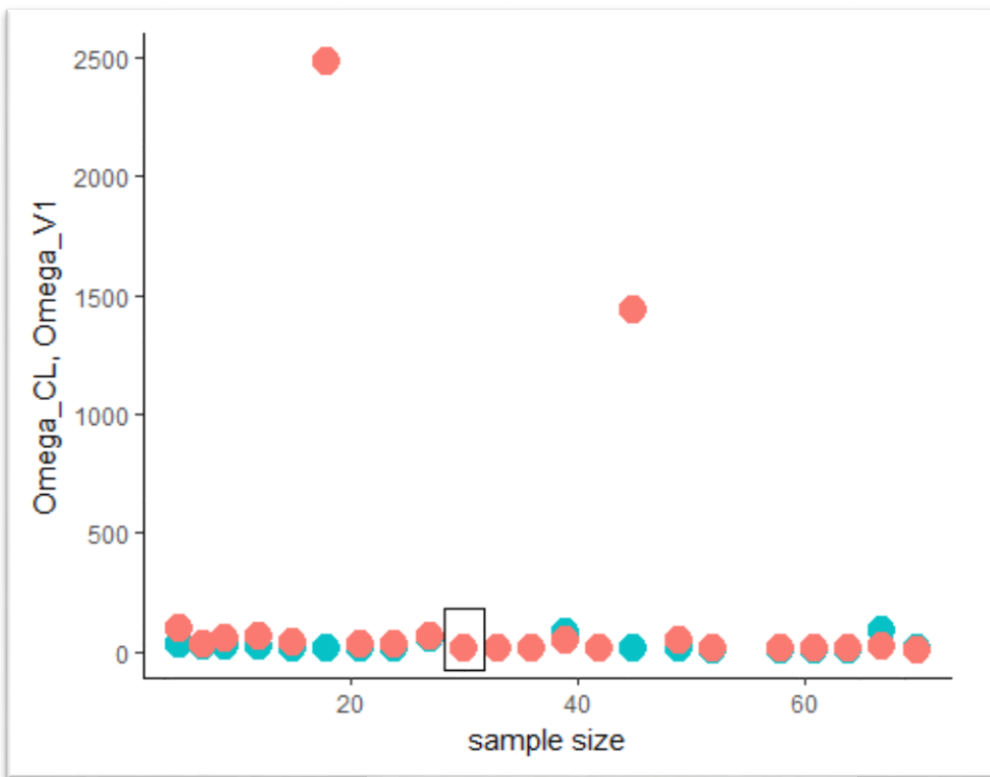
Omega_CL = RSE for CL in the central compartment ⬤ , Omega_V1 = RSE for Vd in the central compartment ⬤

Figure 3-1 Graph of RSE of inter-individual variation in vancomycin CL and Vd in the central compartment against sample size.

The sample size (N) for RSE against and Vc, CL, Q, Vp were:

1. Sample size against RSE for central clearance and central volume of distribution. *N*=18

2. Sample size against RSE of inter-compartmental clearance and volume of distribution. *N*=24

3. Sample size against RSE of inter-individual variation in central clearance and central volume of distribution. *N*=30

4. Sample size against RSE of inter-individual variation in distribution clearance and peripheral volume of distribution. *N*=21

A sample size of 30 for children < 2years old and children > 2 years old (15 children per group) was sufficient to estimate vancomycin PK (power= 0.8, effect size= 0.50, and p=0.01)..

3.5.2 Sampling size calculation to assess factors that affect vancomycin PK

This study evaluated a number of factors that may impact vancomycin PK, including age, weight, organ (renal, cardiac and hepatic) function, fluid status and severity of illness. Clinical outcomes and standard deviations from groups in the study by Le et al. (2015) were used to calculate the sample size required to assess the effect of physiological, pathophysiological and clinical factors on vancomycin PK. Sample size calculation was done using SAS version 9.4 (SAS Institute Inc).

The minimum number of patients required to test associations is 52 participants (power= 0.8, effect size= 0.50, and p=0.01). A power of 0.8 and a significance level of 0.01 were selected because of the large number of grouping variables to be assessed.

Calculation of the sample size to give a theoretical estimate of (i) the number of children required for the analysis and (ii) the accrual rate of study participants. In reality, practical issues such as patient availability may determine sample size.

3.6 Patient recruitment and enrolment

An investigator or the appointed nurse identified patients on vancomycin treatment and enlisted them to participate in the study. Informed consent was obtained from their caregiver and informed assent from the patients≥ 7 years old (where possible). Patients were recruited using a consecutive sampling method. In this method, all patients meeting the inclusion criteria are approached for recruitment into the study until the sample size is reached (Schuster and Powers, 2005).

3.7 Informed consent and assent

We sought Informed consent from parents/guardians of children and informed assent from children aged seven years and above. The parents of patients were fully informed regarding the nature of the research, and they provided signed consent. In cases where children could not give informed assent, parents/guardians gave informed consent on behalf of their child/ward. The researchers

verbally explained the content of the information leaflet to parents/guardians and children unable to read the information leaflet. In cases where parents/guardians and children did not fully understand study implications due to a language barrier, we used a language interpreter. Research team members did not place any pressure or influence on parents/guardians. Consent was voluntary and sought when caregivers were in the correct frame of mind to give it. The informed consent was obtained by one of the investigators or appointed nurses. The informed consent forms for parents/guardians and the informed assent for minors were available in English, Afrikaans, and Xhosa. Parents/guardians and children were at liberty to withdraw their consent/assent at any time without the treatment or welfare of the child adversely affected. Parents/guardians and children were given a copy of the signed informed consent/assent for reference.

3.8 Blood sampling procedure

Patients admitted to the RCWMCH paediatric ICU were attended to on arrival per RCWMCH protocol. Blood samples were collected to measure vancomycin plasma concentrations only. An appointed registered nurse noted each patient's time of treatment commencement and end. Sparse sampling utilizing a few blood samples per patient was used for sampling collection.

Blood samples were drawn at optimal sampling times. The optimal sampling time is the time that allows for robust PK parameter estimates with a minimal number of blood samples. According to the RCWMCH antimicrobial guidelines (RCWMCH, 2012), the first trough level should be measured 48 hours after starting vancomycin therapy. Routine sampling was done at the ICU. Vancomycin concentration results from blood samples collected within the study period was included in the PK analysis. We assessed the pharmacokinetics of vancomycin in three phases: the first phase was the first 24 hours, the second phase was between 24-48 hours, and the third phase was between 48-72 hours. In the event of an early transfer, patients were followed up in the transferred units.

3.8.1 Sampling times

Vancomycin sampling should typically follow the trend shown in Figure 3.1. The dots show arbitrary points of samples (i) just after vancomycin infusion for peak concentrations, (ii) at the mid-point of the dosing interval, showing concentrations at the distribution phase, and (iii) Just before the next vancomycin IV infusions, for trough concentrations. Vancomycin is expected to reach its steady state concentration after three doses of administration (Bauer, 2015). Sampling should typically be done 0 to 30 minutes after the third vancomycin infusion.
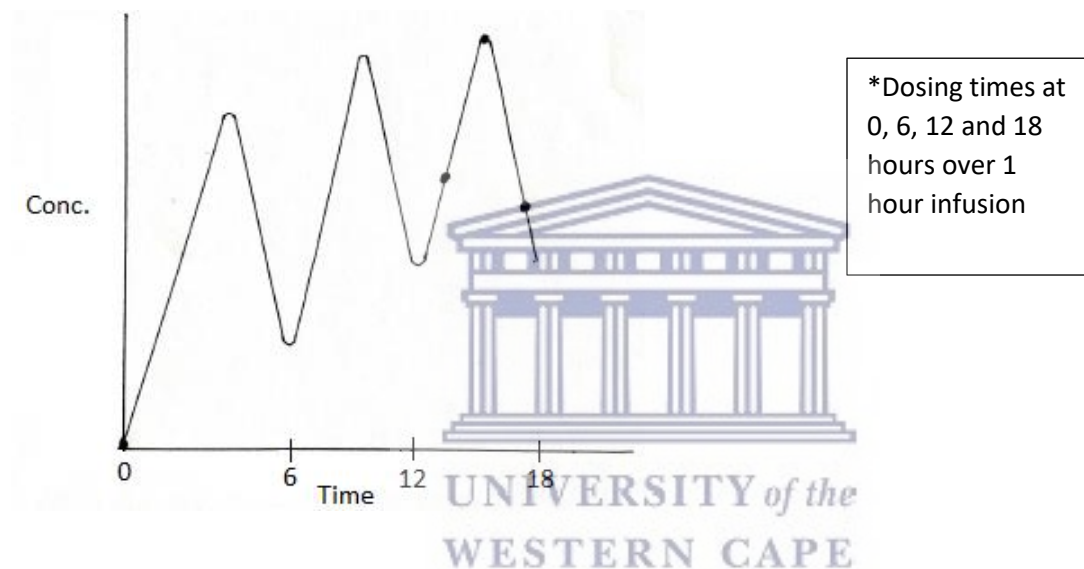
Figure 3-2Concentration-time graph of vancomycin showing the dosing time

We used PK parameter values from the study by Lamarre et al. (Lamarre, Lebel, and Ducharme, 2000) to calculate the sampling times for our study.

In their study, Vancomycin PK was modelled in 78 children with a typical weight of 30kg receiving standard vancomycin IV doses of 10mg/kg every 6 hours over a one-hour infusion. Vancomycin was described by a two-compartment model.

They generated the following PK parameters:

1. Vc =8.1L/kg

2. CL=3.0L/h/Kg

3. Vp =4.8L/Kg

4. Q = 4.8L/h/Kg

The volume of distribution in the central compartment (Vc) is the volume in which the drug distributes rapidly following availability in the circulatory system (i.e., blood and other highly perfused organs); Clearance in the central compartment is the ratio of the rate of drug elimination from the blood; Volume of distribution in the peripheral (Vp) is drug distribution to other tissues from the central compartment, i.e., fat, muscles; Inter-compartmental clearance (Q) is the ratio of drug distribution rate between the central and peripheral compartments (Bauer LA, 2015).

Other values included in our calculation were:

1. Measurement (Residual) error=6.5%

2. The coefficient of variation for PK parameters=30% (Average)

3. Limit of quantification= 4mcg/mL (estimated)

Measurement (residual) error is the difference between the observed and sample population data. The coefficient of variation is the ratio of the standard deviation to the mean of PK parameters. The limit of quantification is the lowest analyte concentration that can be quantitatively detected with a stated accuracy and precision.

We used these PK measurements to calculate the optimal sampling time for our study using the Population (and individual) optimal Experimental Design (PopEDlite) version 3.0 (GPLv3) software (Nyberg et al., 2012) for D-optimization. The optimal blood sampling times for vancomycin PK analysis were calculated from the time of vancomycin therapy initiation. Optimal sampling times were 13hr 30mins (30 mins after the 3rd vancomycin infusion (peak concentration)), 19hrs (just after the 4th vancomycin infusion (peak concentration)), 21hrs (Three

hours after the 4th vancomycin infusion (Concentration between peak and trough level)), 29hr 22mins (38 mins before the 6th vancomycin infusion (trough concentration)), 40hr 48mins (1 hr 12 mins before the 8th vancomycin infusion (Concentration between peak and trough level)), and 55hr 21mins (21 minutes after the 10th vancomycin infusion (peak concentration)).

When it was impossible to get samples at the stipulated optimum sampling times, samples were collected around the sampling times. A sampling window allowing up to 20% loss of efficiency was allowed if samples were collected in any of the three kinetic phases for a dosing interval- (i) after the start of vancomycin infusion when there is a rise in vancomycin concentration in the blood, (ii) at the mid-point of the dosing interval when vancomycin reaches its peak distributional concentration, (iii) just before the next vancomycin infusion when there is a decline of vancomycin plasma concentration following elimination over time.

3.8.2 Blood sample collection

Blood samples were only collected for vancomycin plasma concentration determination. We did not collect blood from the children for renal and liver function determination. Results from the test of the renal and liver function in children routinely carried out by the ICU team were collected from the patients' records. Patients had to have a baseline renal or liver function result (before vancomycin treatment commenced) and at least one result during any treatment period (0 – 24 hrs, 24 – 48 hrs, 48 -72 hrs). Patients who did not have these results were not included in the analysis to determine the effect of organ function on vancomycin PK. For the vancomycin plasma concentration analysis, we collected six blood samples of 0.5ml each in heparinized during the 72 hours at the optimal sampling times stipulated above. A day registered nurse and a night registered nurse oversaw drawing blood samples from children at the optimal sampling times. Alternatively, one of the co-researchers with medical qualifications collected the blood samples. Blood was drawn from the patient's IV lines (either central venous lines or arterial lines). The nurses or one

of the investigators monitored vancomycin infusion (start and stop) times and sampling times. We included left-over blood samples obtained after the third dose, and up to 72 hours were included, provided the ICU personnel in charge of blood collection indicated blood sampling times.

3.9 Blood sample handling

One of the research team members sent the blood samples to the National Health Laboratory Services (NHLS). The lab analysed the samples within 30 minutes after receipt. The person collecting blood samples flushed the venous or arterial line used for sampling with normal saline after each collection of blood samples to avoid any mixture of vancomycin from different sampling times. Before the subsequent blood sampling, a volume of 0.5 ml of blood was drawn just before the sample collection was used to determine vancomycin plasma levels.

3.10 Determination of vancomycin plasma concentrations

Vancomycin plasma concentrations were determined using the turbidimetric immunoassay method. The instrument used was the Beckman Coulter AU480 clinical chemistry system (Beckman Coulter Inc, Brea, CA, USA). The assay's linear range was between 2.5mcg/mL and 100mcg/mL. The lower limit of quantification was 2.0 mcg/mL. The Inter-assay precision rate was ≤ 20% CV, and the recovery rate was ≤ 15%.

3.11 Collection of patients' demographic data

Patients' ages and gender were collected and written in pre-designed templates by the attending nurse or one of the investigators at the time of patient enrolment. We used the National Institute of Child Health and Human Development guideline for the classification of age to classify patients' age (Job and Ward, 2009).

3.12 Collection of patients' clinical data

3.12.1 Patients' vital signs

The admission weight was obtained from patients' records. The convalescent weight was obtained for patients where mobilisation was permitted. One of the research team members collected the patients' temperature, respiratory rate, heart rate, and mean arterial blood pressure from the patient's chart before each blood sample was taken. The normal temperature limit was $36 - 37.5^{\circ}$C. Ranges from the paediatric advanced life support (PALS) guidelines (Ralston et al., 2006) were the normal limits of the vital signs (Table 3.1).

Table 3-1 Reference ranges for vital signs according to ages in children (Ralston et al., 2006)

Age (years)	Age	Heart Rate (beats/min)	Respiratory Rate (breaths/min)	Mean Arterial Blood Pressure (mmHg)
0.1 - <0.25	1 - < 3 months	110 – 160	35 – 55	52 – 65
0.25 – 0.5	3 – 6months	110 – 160	30 – 45	57 – 73
0.5 - 1	>6 months – 1 year	90 – 160	22 – 38	63 – 77
1 – 2.99	>1 year – 2.99 years	80 – 150	22 – 30	67 – 82
3 – 6.99	3 – 6.99 years	70 – 120	20 – 40	72 – 87
7 – 12	7 – 12 years	60 – 110	16 – 22	73 – 90
> 12	>12 years	60 – 100	12 – 20	80 – 102

3.12.2 Patients' renal function tests and liver function tests

We assessed the patient's renal and liver functions using results collected from medical records. Renal and liver function test values just before the commencement of vancomycin and daily during the study period were collected for children where used. Renal function was evaluated using serum creatinine tests. Liver function was assessed using alanine aminotransferase (ALT), aspartate aminotransferase (AST), and serum albumin tests. The limits of the normal ranges of laboratory parameters tested are listed in Table 3.2 according to gender and age.

Table 3-2 NHLS normal ranges for renal and liver function

Test / Age (years)	Males	Females
Creatinine (µmol/L)		
0.1	10 – 56	10 – 56
0.2 – 0.9	14 – 34	14 – 34
1.0 – 2.5	15 – 31	15 – 31
2.5 – 3.0	23 – 37	23 – 37
3.0 - 7.0	25 – 42	25 – 42
7.0 – 10.0	30 – 48	30 – 48
10 – 11	28 - 57	28 - 57
11 – 12	37 - 63	37 - 63
>12	36 - 96	39 – 85
CrCl (mL/min)		
0.1 – 0.2	41.0 – 90.6	41.0 – 90.6
0.2 – 2.0	74.0 – 117.4	74.0 – 117.4
2.0 – 12.0	106.0 – 160.0	106.0 – 160.0
13.0 – 16.0	110.0 – 170.0	104.0 – 148.0
Albumin (g/L)		
0.1 – 0.6	28 – 46	29 – 42
0.6 – 0.9	32 - 47	33 – 48
> 1.0	28 – 46	29 - 42
ALT (u/L)		
0.1 – 1.0	4 – 35	3 – 30
1.0 – 3.0	5 – 30	5 – 30
3.0 – 12.0	5 – 25	5 – 20
>12	5 – 30	5 – 20
AST (u/L)		
0.1 – 1.0	0 – 65	0 – 65
1.0 – 3.0	0 – 79	0 – 79
3.0 – 12.0	0 – 56	0 – 56
>12	0 – 56	0 – 69

3.12.3 Patients' disease (s) profile

Data collection forms were used to collect information on each patient's condition, including the acute/chronic state of illness, presence of sepsis, onset date, relevant symptoms, relevant investigation findings, and procedures, from their folders.

3.12.4 Severity of illness measurement

We used the Paediatric Logistic Organ Dysfunction-2 (Leteurtre et al., 2013) scoring system to classify infections according to severity.

3.12.5 Concomitant medication

The name, dose, frequency, and duration of administration of each drug co-administered with vancomycin during the study period were recorded for each enrolled child.

3.12.6 Patient Status/ Clinical outcome at the end of follow-up

At the end of the 72-hour study period, information on the duration of vancomycin treatment in days, discharge summary, patient condition just before discharge from the hospital (stable or otherwise), and treatment outcome were collected.

3.12.7 Fluid balance measurement

We obtained the total fluid intake and output of each patient from the fluid balance sheets of patients. Fluid balance was calculated as a percentage using the following formula (Goldstein, 2011):

$$\frac{(Total\ fluid\ in) - (Total\ fluid\ out)}{Admission\ body\ weight} * 100$$

3.13 Vancomycin dosage and administration

Each vial of 500mg vancomycin was reconstituted with 10 ml water for infusion (concentration = 50mg/1 ml). The RCWMCH antimicrobial guidelines (RCWMCH, 2012) stipulate that a vancomycin dose of 15 mg/kg/dose given six hourly (60mg/kg) over a one-hour IV infusion be given to children with evidence of possible infection by a gram-positive bacteria. However, vancomycin was administered as per the PICU practice. The study did not influence vancomycin dosing.

3.14 Vancomycin dose adjustment

The RCWMCH antimicrobial guidelines for care stipulate that routine trough concentration be carried out, with the first measurement done 48 hours after the commencement of treatment. For this study, vancomycin plasma concentration measurements were started in the first 24 hours of

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treatment. Current guidelines recommend that therapeutic monitoring of vancomycin begin within 24 to 48 hours of treatment initiation (Rybak et al., 2020). Target trough concentration of 10-15 mcg/mL for bacterial MIC < 1 mcg/mL and 15-20 mcg/mL for bacterial MIC of 1 to 2 mcg/mL should be maintained. Patients with renal failure had their vancomycin plasma levels measured before administering the next dose. The attending physician was informed when results showed vancomycin plasma concentration outside the recommended ranges (< 10 mcg/mL for trough concentrations and > 40 mcg/mL). The attending physician adjusted the vancomycin dose and dosing intervals following trough determination. Vancomycin dose increase or decrease, the time the dose was changed and changes in vancomycin dosing interval were noted and included in the vancomycin PK analysis.

3.15 Pharmacokinetic parameters

The pharmacokinetic profile assessed were CL, V_d, T1/2, Ke, AUC0-24, C_{min}, C_{max}, and T_{max}.

3.15.1 Pharmacokinetic data handling

Descriptive and continuous statistical analysis: descriptive and continuous variables were analysed using the SPSS software Psych in R (Revelle, 2020). Pharmacokinetic analysis: PK parameters were estimated using a non-linear mixed effect algorithm implemented in Monolix 2019R2 software (Lixoft SAS, 2019).

3.15.2 Structural model selection

Vancomycin plasma concentration was excluded if the % CV between the plasma concentration value and other plasma concentration values collected from the same patient was > 15% (US Food and Drug Administration, 2001). Data was fit to one- and two-compartment models. A first-order elimination model was used, and model selection was based on goodness-of-fit. We retained the model with a better visual predictive check (VPC) and significant reductions of the Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC).

A log-normal distribution of inter-individual variability was according to the exponential model below:

$$P_i = \theta_{pop} \times exp(\eta_i) \qquad Equation\ 1$$

P_i = the pharmacokinetic parameter of the ith individual, θ_{pop} = the typical value of the pharmacokinetic parameter and η_i = the normally distributed between-subject random effect with a mean of zero and a variance of ω^2.

The unexplained residual variability was evaluated using an additive model (Equation 2), a proportional model (Equation 3), and a combined additive and proportional (Equation 3):

$$Y_{ij} = \hat{Y}_{ij} + E_1 \qquad Equation\ 2$$

$$Y_{ij} = \hat{Y}_{ij} + E_2 \qquad Equation\ 3$$

$$Y_{ij} = \hat{Y}_{ij} + (E_1 + E_2) \qquad Equation\ 4$$
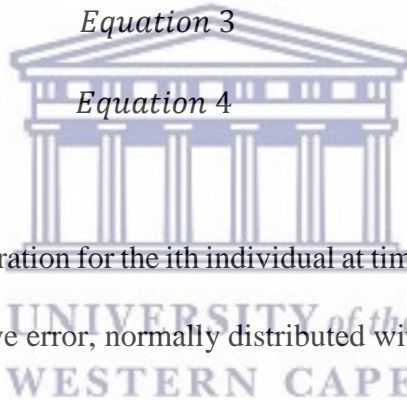
Where Y_{ij} = the observed concentration for the ith individual at time j, $\hat{Y}_{ij}$ = the individual predicted concentration, E = the additive error, normally distributed with a mean of zero and a variance of σ^2.

3.15.3 Statistical model selection

The effect of continuous covariate- age, body weight, serum creatinine, creatinine clearance (CrCl) (Shull et al., 1978), and categorical covariate- sex on CL and V were evaluated.

These effects were tested using equation 5 and equation 6, respectively:

$$P_i = \theta_{pop} * \left(\frac{COV_i}{COV_{median}}\right)^{\beta_{cov}} * exp(\eta_i) \qquad \textit{Equation 5}$$

$$P_i = \theta_{pop} * exp(\beta_{COV} * COV_i) * exp(\eta_i) \qquad \textit{Equation 6}$$

Where, P_i = the pharmacokinetic parameter estimates of subject i, θ_{pop} = the population typical value of CL and V the paramete, COV_i and COV_{median} = the individual covariate values and median covariate value for the population, β_{cov} = the covariate effect coefficient and η_i = between-subject variability.

The BSV, summarized by its variance, describes the distribution of the inter-individual variability of CL and V (Mould and Upton, 2012). Inter-individual variability is the difference between individual and population values. It is assumed to be normally or log-normally distributed across the population and is centred around zero.

Equation 7 calculates the predicted plasma concentration model, accounting for explainable inter-individual variability.

$$C_{PRED} = \frac{AMT}{V_{POP}} * exp\left(-1 * \frac{CL_{POP}}{V_{POP}} * TIME\right) \qquad \textit{Equation 7}$$

C_{PRED} = the population predicted concentration, AMT = the amount of drug in the body, CL_{POP} = the population clearance, V_{POP} = the population volume of distribution.

The unexplained inter-individual variability is calculated using equation 8.

$$C_{iPRED} = \frac{AMT}{V_i} * exp\left(-1 * \frac{CL_i}{V_i} * TIME\right) \qquad Equation\ 8$$

Where, C_{iPRED} = the individual predicted concentration, AMT = the amount of drug in the body, CL_i = the individual clearance, V_i = the individual volume of distribution.

The observed data were shown as the predicted model and the unexplained residual variability (RUV) using Equation 9. The RUV is the difference between an individual's observed data and the value predicted from the model. For each observation, the RUV value is different and is normally distributed with a variance or SD sigma and a mean of zero.

$$C_{DV} = C_{IPRED} + RUV \qquad Equation\ 9$$

C_{DV} = the observed concentration, C_{iPRED} = the individual predicted concentration, RUV = the residual unexplained variability.

Stepwise inclusion of covariates in the base model was performed. The effect of each covariate on the model's objective function value (OFV) was observed. A covariate significantly improved the model's fitness ($\chi2$, p<0.05) if there was an OFV decrease of more than 3.84. This fit was observed from the Akaike information criteria (AIC) and Bayesian information criteria (BIC). Significant covariates were retained. Retained covariates were added to the model by a stepwise forward inclusion, starting with the covariate that decreased the OFV to the most significant extent. Covariates were then removed from the model in a reverse elimination step, one at a time. The covariate effect on the model's goodness of fitness was considered significant when the OFV was increased by >6.63 ($\chi2$, p<0.01).

Creatinine clearance was evaluated using the Shull et al. (1978) equation:

CrCl (ml/min/1.72m^2) = ([0.035 × age] + 0.236) × 100/Scr \qquad $Equation\ 10$

This method was also used by Sridharan et al. (2019) to estimate creatinine clearance in critically ill children.

3.15.4 Model evaluation/validation

We evaluated the goodness of fit for the final model by using plots of (i) observed vs population-predicted concentrations, (ii) observed vs individual predicted concentrations, (iii) population-weighted residue (PWRES) vs time and concentration, (iv) individual weighted residue (IWRES) vs time and concentration (v) normalized prediction distribution error (NPDE) vs time and concentration generated from ggPMX version 1.0 (GPL-2). In addition, we used a visual predictive check (VPC) generated in Monolix to assess possible model misspecification.

The precision and stability of the final model at a 95% confidence interval were evaluated using a non-parametric bootstrap. Resampling of the dataset was performed with 1000 runs of the final model using the Rsmlx R package. We compared the estimated median values and SE of the popPK parameters from the bootstrap to the popPK values from the original dataset. The model was deemed reliable and stable if the results were significantly comparable.

3.15.5 Simulation and dose optimization

We simulated different vancomycin dosing regimens based on doses recommended for initial dosing in paediatric patients (Rybak et al., 2020). The effect of loading doses on vancomycin PK was also assessed. In addition, we performed a Monte Carlos simulation of 1000 patients using PK estimates generated from our study. Children's weight and creatinine clearance were included in the simulation (Appendix 3.1). The PK parameters assessed were AUC24, trough, and peak vancomycin concentration.

We simulated six dosing schedules. The treatment period was from 0-48 hours. The simulated route of administration for all dosing schedules was IV.

Simulation of intermittent infusion of 8 doses over an hour infusion and a dosing interval of 6 hours of the following schedules (i) a loading IV dose of 25mg/kg followed by an intermittent infusion of 15mg/kg, (ii) an intermittent infusion of 15mg/kg of vancomycin, (iii) an intermittent infusion of 20mg/kg was performed. Vancomycin concentrations were evaluated 24-48 hours post-initiation of treatment.

Simulation of continuous IV infusion with the following dosing schedules (i) loading dose of 25mg given over one hour followed by a continuous daily infusion of 60mg/kg/day, (ii) 60mg/kg/day, (iii) 80mg/kg/day were simulated. Vancomycin concentrations were evaluated 24-48 hours post-initiation of treatment.

An AUC ≥400 mg * h / L was considered therapeutic.

3.15.6 Pharmacokinetic parameter Calculations (Dhillon and Kostrzewski, 2006)

One and two-compartment models were assumed for the first-order kinetics of CL and V_d. Calculations were as follows:

1) $Vd = \frac{Amount\ of\ drug\ administered}{Plasma\ concentration}$

where: V_d=volume of distribution

2) $K_{el} = \frac{CL}{Vd}$

where: Kel= elimination constant; CL= clearance; V_d=volume of distribution

3) $CL = Vd.Ke = \frac{Dose}{AUC}$

where : CL= clearance; V_d=volume of distribution; Ke= elimination constant: AUC= area under the curve

4) $AUC_{ss} = \int_{t}^{t+r} C\ dt$

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where : AUCss= steady-state area under the plasma concentration-time curve; t= time; r= rate of infusion; C=plasma drug concentration; dt= difference in time

5) $T_{1/2} = \frac{0.693}{CL} \, X \, Vd$

where : $t_{1/2}$= elimination half-life ; CL= clearance; V_d=volume of distribution

6) Infusion rate= Css x CL

where: Css= plasma drug concentration at steady state; CL= clearance

7) C_{min}= measured directly as trough plasma concentration before the next IV administration

where: C_{min}= minimum plasma concentration of drug

Where samples were taken earlier than directly before the next dose, C_{min} was calculated as follows:

$$(C_p)_{TR} = (C_p)_{Lo} \left(e^{-K(t_{TRearly})} \right)$$

Where (Cp) Lo = trough concentration sampled too early; K = elimination rate constant; $t_{TRearly}$ = time at which sample $(C_p)_{Lo}$ was taken.

8) C_{max}= measured directly as peak plasma concentration after an IV administration

where: C_{max} = minimum plasma concentration of drug

Where peak concentrations were taken after C_{max}, the peak concentration was calculated as follows:

$$(C_p)_{peak} = \frac{(C_p)_{Hi}}{e^{-K(t_{Peaklate})}}$$

(Cp) Hi = peak concentration sampled too late; K is the elimination rate constant; $t_{Peaklate}$ = time at which sample $(C_p)_{Hi}$ was taken.

9) T_{max}= measured directly from the concentration-time curve

where: T_{max}= time to reach peak plasma concentration following administration

3.15.7 Steady state Pharmacokinetic parameter Calculations

Vancomycin PK after 24 hours was calculated in monolix using:

1. $Vd = \dfrac{Dose}{C_{ss\,peak} - C_{ss\,trough}} \times e^{-K_e\,t}$

2. $K_e = \dfrac{\ln\left(\dfrac{C_{ss}peak}{C_{ss}trough}\right)}{\Delta t}$

3. $CL = K_e \; X \; Vd$

Where **Dose** = the administered vancomycin dose; Δt = time interval (in hours) between measured peak and trough concentration; **T** = time in hours to the measured peak from the beginning of the infusion.

3.16 Ethics considerations

Ethical approval from the Ethics Committee of the University of Western Cape (Biomedical Research Ethics Committee Reference Number: BM17/8/25) and the University of Cape Town (Human Research Ethics Committee Reference Number: 216/2018) was obtained. Permission to conduct the study was obtained from the Red Cross War Memorial Hospital and the provincial health department. Informed consent was obtained from the parents or guardians of each study participant, and informed assent from children ≥ 7 years old (where possible). Ethics approval allowed no more than 0.5ml blood samples to be collected from children at each sampling point. Therefore, a total of 3 ml of blood was expected to be collected from each child for this study. Ethics approval also allowed blood samples to be stored for up to 2 days before obtaining informed consent and assent from parents and children. Samples were to be discarded in the absence of informed consent and assent.

The study was conducted according to the Declaration of Helsinki (World Medical Association., 2001) and the South African National Department of Health guidelines.

3.17 Database/Records

Patients' clinical test results were collected from the NHLS database at https://trakcarelabwebview.nhls.ac.za/trakcarelab/. Patients' vital signs were collected from bedside monitors. In addition, information on weight, fluid status, concomitant medication etc., were collected from patients' folders at their bedsides. All information was entered into preformed collection templates (Appendix I). The values were cross-checked for correctness at the end of patients' recruitment.

3.18 Protection of person information (POPI) act

Patients' data collected and processed were done following the POPI act.

Chapter 4
Demographics and Clinical Parameters of Patients

4.0 Introduction

This chapter presents information about patient enrolment, demographic and clinical parameters of the patients, variations in vancomycin administration, variations in sampling times, and withdrawal of vancomycin treatment.

4.1 Patient enrolment and recruitment

Patients were enrolled on the study from 18th September 2018 till 14th December 2019. Based on the sample size calculation, the expected number of children to include in this study was 52. However, only 41 patients were recruited. We could not reach the planned number of patients because the University suspended all hospital-related research during the COVID-19 pandemic. Four patients were excluded from the study. Two patients were excluded from the study because their parents did not consent to participate, and blood samples were not collected for these patients. The other two children were excluded because central and arterial lines from which blood was collected were absent. Thirty-seven patients were involved and completed the study (Fig. 4.1).
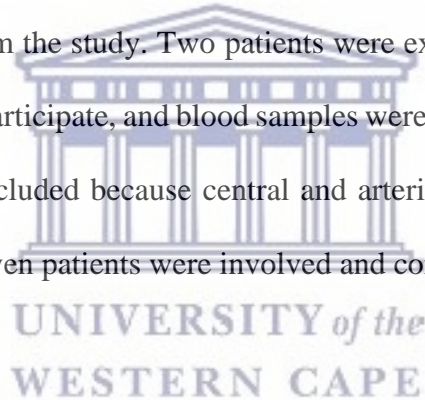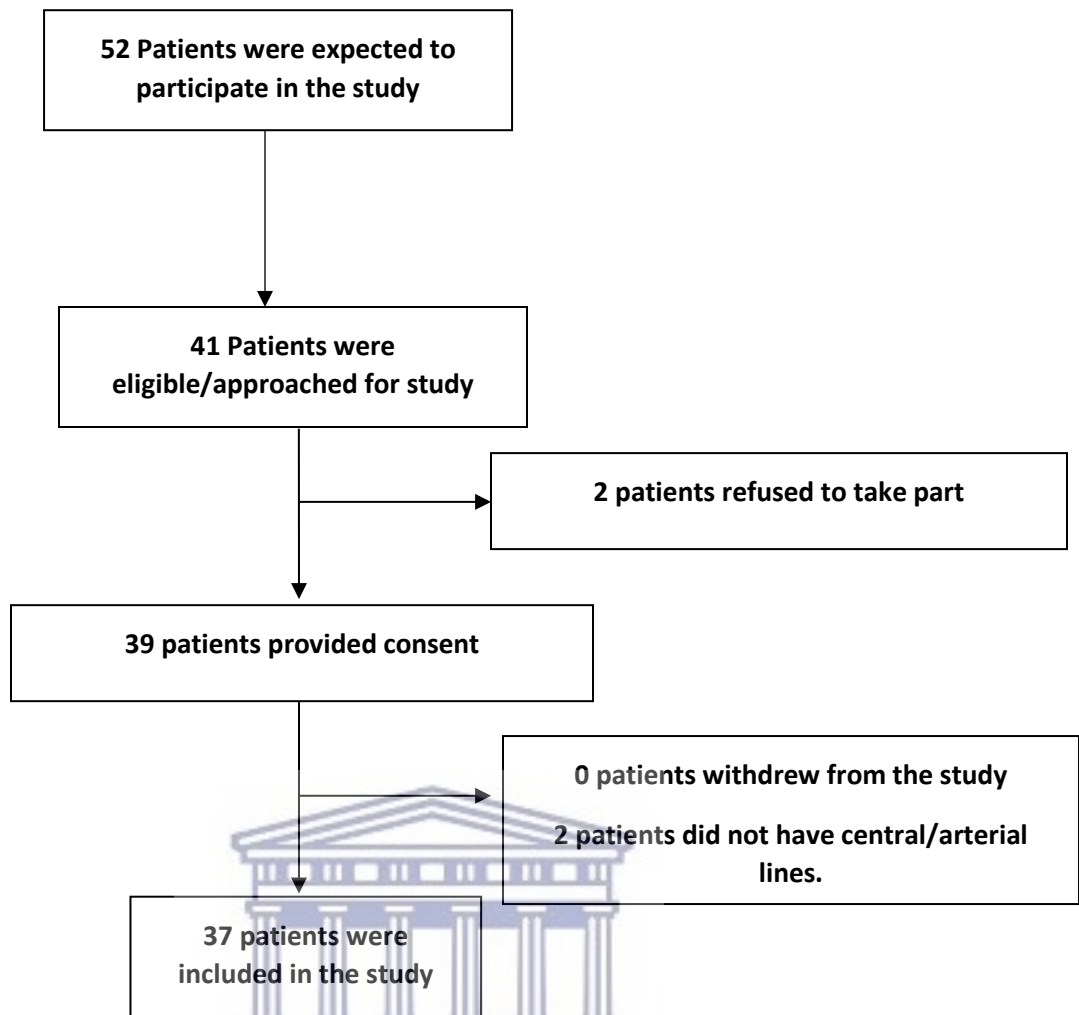
Figure 4-1 Flow diagram showing the selection/enrolment process of patients into the study

4.2 Patients' Demographics

There were 18 (48.6%) male and 19 (51.4%) female patients. The children's median (range) age was 2.2 (0.1- 15.2) years (Table 4.1). Fourteen patients were less than one year, ten children were between 1 and 6 years, and thirteen patients were older than six years. The median admission body weight was 10.6 (2.7 – 54.0) kg. Children < 1 year weighed between 2.7 – 9.3 kg. Children between 1 –2 years weighed 9 – 10.6 kg. The weight of children 2 – 6 years was between 10 – 20 kg. Children between 6 – 12 years weighed between 17.3 – 47 kg. Children aged 12 – 16 years weighed between 31.25 – 54.0 kg. Convalescent weight was collected from 13 (35.1%) patients. It was not

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measured in the remaining 24 (64.9%) patients because they were immobilized. In the 13 children, the median (range) convalescent weight of 9.3 (3 - 32) kg did not significantly differ from their median admission weight (9.3 (2.7 – 31.25) kg) (Z = - 0.051, *p* = .959).

Table 4-1 Demographics of children on vancomycin therapy

Variable	Number (Range)
Gender	
Male (%)	18 (48.6)
Female (%)	19 (51.4)
Median (range) Age (years)	2.2 (0.1 – 15.2)
Age Classification	
< 1 year (%)	14 (37.8)
1 – 4.99 years (%)	8 (21.6)
5 – 11.99 years (%)	12 (32.4)
≥12 years (%)	3 (8.1)
Median (range) Admission weight (kg) (N = 37)	10.6 (2.7 – 54.0)
Median (range) Convalescent weight (kg) (N = 13)	9.3 (3 - 32)

4.3 Patients' Clinical characteristics

4.3.1 Patients' clinical status during the study period

During the study period, eight of the 37 patients that participated in the study were unstable from an organ function perspective. Five patients were transferred to other units while still participating in the study. Unfortunately, three patients died; one was brain dead, one had multiple organ failures, and the third had life-supporting therapy terminated because the treatment was futile, according to the doctor in charge. At the end of the study, the remaining 21 patients were still receiving treatment in the ICU.

4.3.2 Vital signs

The median (range) vital signs were recorded just before the collection of blood samples for the vancomycin test and assessed using the PALS guidelines (Ralston et al., 2006). As indicated in Table 4.2, the temperature was within the normal range in 22 patients; 11 patients had pyrexia, while four had a temperature below the normal limits. Low respiratory rate was observed in 5 patients, while 11 patients had high respiratory rates. Nine patients were ventilated during the study period. Nine patients had tachycardia, and 24 had heart rates within the normal limits. The respiratory rate, heart rate and arterial mean blood pressure were not recorded in 2, 4, and 1 patient (s) at the time of sample collection.

Table 4-2 Vital signs of children on vancomycin therapy

Age (years)	Average Temperature (median(range)) ᵒC (N)	Average Respiratory rate (median(range)) breaths/min (N)	Average Heart rate (median(range)) breaths/min (N)	Average arterial blood Pressure (median(range)) mmHg (N)
< 1	36.6 (35.5 – 38.5) (11)	34.5 (22.3 – 43.5) (9)	135.5 (119.0 – 195.7) (10)	81.7 (63.0 – 113.0) (11)
1 – < 2	37.6 (36.9 – 38.0) (7)	33.9 (20.7 – 46.8) (7)	115.4 (146.0 – 164.8) (6)	102.1 (81.3 – 109.0) (7)
2 – < 6	37.4 (36.9 – 39.0) (6)	25.3 (24.2 – 36.0) (6)	114.7 (88.7 – 130.3) (6)	92.9 (84.8 – 128.6) (6)
6 – < 12	36.6 (35.1 – 38.4) (10)	22.7 (15.2 – 74.0) (10)	91.2 (64.0 – 138.3) (8)	108.0 (92.67 – 131.0) (9)
12 – < 16	38.5 (37.2 – 38.9) (3)	23.8 (16.33 – 26.75) (3)	111.0 (109.2 – 112.2) (3)	127.6 (107.0 – 132.0) (3)

4.3.3 Renal function

The median (range) creatinine clearance in children at the start of vancomycin therapy (on the day of therapy initiation and at most 24 hours before vancomycin initiation) was 62.28 (28.08 – 242.38) mL/min. Table 4.3 shows the distribution according to age. Median (range) SCr at 0 – 24 hrs, 24 – 48 hrs, and 48 -72 hrs were 30.0 (9.0 - 103.0) µmol/L, 30.0 (9.0 - 115.0) µmol/L and 30.0 (9.0 - 93.0) µmol/L respectively. Median (range) CrCl at 0 – 24 hrs, 24 – 48 hrs, and 48 -72 hrs were

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95.7 (25.6 - 242.4) mL/min, 92.2 (28.1 - 260.3) mL/min and 97.0 (28.1 - 242.4) mL/min respectively. Patients with CrCl values > 50% of the upper limit of the normal range according to age (Table 3.2) had severely increased CrCl, and children with < 50% of the lower limit of CrCl according to age (Table 3.2) had severely reduced CrCl (Soler et al., 2013). Three patients had severely decreased CrCl, and seven had mildly decreased CrCl. Fifteen patients had normal CrCl, five had mildly elevated CrCl, and three had severely elevated CrCl. Four patients did not have CrCl values because no SCr tests were done.

Table 4-3 Renal function (CrCl (mL/min)) test of children on vancomycin therapy

Age (years) (N)	Severely Reduced Creatinine clearance (median[range]) (N)	Mildly Reduced Creatinine clearance (median[range]) (N)	Normal creatinine clearance (median[range]) (N)	Mildly Increased creatinine clearance (median[range]) (N)	Severely Increased creatinine clearance (median[range]) (N)
< 1 (14)	31.46 (28.05 – 34.83) (2)	72.71 (1)	76.12 (67.20 – 107.60) (8)	109.33 (92.15 – 126.50) (2)	242.38 (1)
1 – < 2 (3)	-	61.52 (1)	89.85 (82.69 – 97.00) (2)	-	-
2 – < 6 (5)	70.18 (1)	-	153.88 (147.79 – 159.05) (3)	172.37 (1)	-
6 – < 12 (9)	-	63.63 (47.10 – 95.72) (4)	112.43 (109.26 –115.61) (2)	165.93 (1)	191.99 (183.97 – 200.00) (2)
12 – < 16 (2)	-	98.50 (1)	-	158.06 (1)	-

4.3.4 Liver function

The median (range) liver function test values (Alanine aminotransferase (ALT), aspartate transaminase (AST), total protein, and albumin test) are shown in Table 4.4.

Table 4-4 Liver function tests of children on vancomycin therapy

Liver function test	Age (years) (N)	Reduced (median[range]) (N)	Normal (median[range]) (N)	Mildly elevated (median[range]) (N)	Severely elevated (median[range]) (N)
ALT (median [range]) U/L (N)	< 1 (8)	-	16.5 (10.0 – 25.0) (4)	52.0 (1)	212.50 (165.0 – 351.0) (4)
	1 – < 2 (2)	-	20.00 (1)	-	101.1 (1)
	1 – < 6 (4)	-		32.0 (1)	81.0 (69.0 – 105.0) (3)
	6 – < 12 (5)	-	12.0 (1)	31.0 (27.0 – 58.0) (3)	451.0 (1)
	12 – < 16 (2)	-	21.5 (20.0 – 23.0) (2)	-	-
AST (median [range]) U/L (N)	< 1 (9)	-	48.50 (17.0 – 59.0) (6)	-	310.0 (143.0 – 1128.0) (3)
	1 – < 2 (2)	-	-	79.0 (1)	208.0 (1)
	1 – < 6 (4)	-	49.0 (48.0 – 50.0) (3)	76.0 (1)	-
	6 – < 12 (5)	-	37.0 (23.0 – 43.0) (3)	-	415.0 (113.0 – 717.0) (2)
	12 – < 16 (1)	-	19.0 (1)	-	-
Albumin (median [range]) g/L (N)	< 1 (7)	33.0 (21.0 – 33.0) (5)	36.5 (29.0 – 44.0) (2)	-	-
	1 – < 2 (1)	22.0 (1)	-	-	-
	1 – < 6 (3)	24.0 (1)	26.5 (25.0 – 28.0) (2)	-	-

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| | 6 – < 12 (5) | 25.5 (17.0 – 28.0) (4) | 33.0 (1) | - | - |
| | 12 – < 16 (2) | 25.0 (1) | 29.0 (1) | - | - |

The tests were performed at the start of vancomycin therapy (on the day of therapy initiation and at most one 24 hours before vancomycin initiation) and at 0 – 24 hrs, 24 – 48 hrs, and 48 -72 hrs.

Median (range) ALT values at 0 – 24 hrs, 24 – 48 hrs, and 48 -72 hrs were 38.5 (10.0 - 439.0) u/L, 42.0 (10.0 - 451.0) u/L and 42.0 (10.0 - 451.0) u/L respectively. Median (range) AST values at 0 – 24 hrs, 24 – 48 hrs, and 48 -72 hrs were 77.0 (16.0 - 1089.0) u/L, 56.0 (17.0 - 2882.0) u/L and 56.0 (17.0 - 1128.0) u/L respectively. Median (range) serum albumin values at 0 – 24 hrs, 24 – 48 hrs, and 48 -72 hrs were 27.5 (19.0 - 60.0) g/L, 28.0 (18.0 - 38.0) g/L and 28.0 (17.0 - 44.0) g/L respectively. Patients had reduced liver function when they had values less than 5 times the lower limit of the normal range of AST and ALT (Table 3.2). Patients with more than five times the upper limit of the normal range and more than 15 times the upper limit of the normal range of AST and ALT (Table 3.2) were classified as having a mildly and severely elevated liver function (Green and Flamm, 2002).
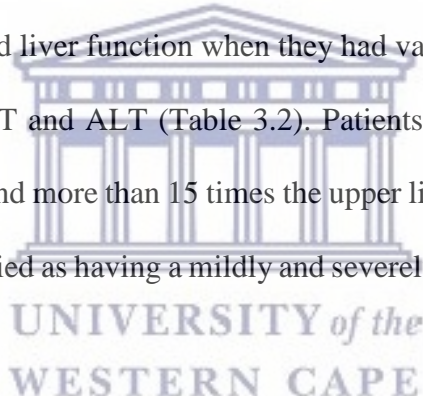
ALT was normal in 8 children, severely elevated in 9 patients, and slightly elevated in 5 children. Thirteen children had normal AST, while two and six children had slightly elevated and severely elevated AST, respectively. Six children had normal serum albumin concentrations, and 12 had low albumin levels. Total protein concentration was normal in 1 patient and low in 4 patients.

4.3.5 Concomitant medication

Children received concomitant medication during the vancomycin treatment period. Drugs that were either nephrotoxic or potentiate vancomycin distribution/ elimination (Mckamy et al., 2011; Beauduy and Winston, 2021) were selected from the list of medicines prescribed to the children

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during their vancomycin treatment period. Furosemide and spironolactone were prescribed in 19 children and 11 children, respectively (Table 4.5). These children had renal dysfunction. Two children on vancomycin received Nevirapine because they were HIV-exposed. One of the two children also received zidovudine. One child received carvedilol for heart failure. Two children were hypertensive, and each of them received amlodipine and captopril. One child received amikacin for bacterial infection

Table 4-5 Concomitant medication given to children on vancomycin therapy

Drug name	Number (%)
Amikacin	1 (2.7)
Amlodipine	1 (2.7)
Carvedilol	1 (2.7)
Captopril	1 (2.7)
Amphotericin B	1 (2.7)
Nevirapine	2 (5.4)
Zidovudine	1 (2.7)
Furosemide	19 (51.4)
Spironolactone	11 (29.7)

4.3.6 Blood transfusion

Six patients received a whole blood transfusion. Three patients received blood after blood loss due to surgical procedures. They started their vancomycin therapy one day (N = 1), two days (N = 1), and three days (N = 1) after the blood transfusion. One patient with burn wounds received vancomycin a day after a blood transfusion. In two patients with a head injury, one received vancomycin two days after a blood transfusion, and the other with a head injury received a blood transfusion on the day vancomycin therapy was initiated.

Blood transfusions may affect the vancomycin V_d as the volume into which the drug distributes increases with the blood transfusions.

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4.3.7 Fluid resuscitation

Patients that were haemodynamically unstable received fluid resuscitation. Fluid resuscitation may lead to fluid overload in critically ill children, affecting vancomycin's V_d. Seven of the 37 children included in the study received fluid IV infusions during their ICU stay. Two patients received IV fluids one day before the initiation of vancomycin therapy, while three patients were infused one day after treatment initiation. The other patients were infused at least two days before treatment initiation (range: 2 – 6 days before treatment). Five patients had bacterial infections, one had pancreatitis, and one had burns.

4.3.8 Disease profile

Ten patients (27.0%) were admitted to the ICU after surgical operation, eleven (29.73%) were admitted because of injuries sustained, and sixteen (43.24%) were admitted for paediatric illnesses. The reason for ICU admission and the primary diagnosis are shown in Table 4.6. Sepsis was diagnosed in twelve patients, and three of the children suffered from septic shock. The doctor in charge described the "sepsis" as associated with burns, gastro/neutropenia, nosocomial microorganisms, skin wounds, or stoma site sepsis. Fourteen children had pneumonia either as a primary diagnosis or as a secondary diagnosis. One child with dilated cardiomyopathy had an upper respiratory tract infection. One child with cardiac arrest had bacterial meningitis. Fourteen patients had a positive bacterial culture. Blood and tracheal aspirates were cultured in patients to determine the microorganism causing the infection. There was bacterial growth in 7 of the 37 blood samples and 7 of the tracheal samples. The organisms isolated from the samples were *Staphylococcus aureus*, *Streptococcus pneumoniae, Mycoplasma*, *Candida albicans*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Acinetobacter baumannii*, *Coagulase-negative staphylococcus*, *Staphylococcus hominis*, *Klebsiella pneumoniae*. There was no growth in the

samples from the remaining 23 patients, and they were treated for presumed infection based on high temperature, increased C-reactive protein, raised procalcitonin, and raised white cell count.

Two of the 37 patients had organ failure; one had heart failure, and the other had renal failure.

Table 4-6 Disease profile of children on vancomycin therapy

Reason for ICU Admission	Primary diagnosis	Number of children	Number of children with Pneumonia	Number with URTI	Number with positive bacterial culture
Accident	Burns	1	-	-	-
	Pneumothorax	1	-	-	-
	Traumatic Brain Injury*	8	4	-	5
	Traumatic Injury (others)	1	-	-	-
Paediatric illnesses	Abdominal mass*	1	-	-	1
	Acute lymphoblastic Leukaemia*	1	-	-	1
	Cardiac arrest*	1	1	-	-
	Dilated cardiomyopathy	2	1	1	-
	Hydrocephalus	1	1	-	-
	Pancytopenia*	1	1	-	-
	Pneumonia*	2	2	-	2
	Rhabdomyosarcoma*	1	1	-	1
	Status Epilepticus	1	-	-	-
	Toxic syndrome shock*	1	1	-	-
	Ventricular septal defect	2	-	-	-
	Wound dehiscence*	1	-	-	1

Reason for ICU Admission	Primary diagnosis	Number of children	Number of children with Pneumonia	Number with URTI	Number with positive bacterial culture
Post-surgery	Aortic insufficiency	1	-	-	1
	Hepatoblastoma	1	-	-	-
	Hiatal Hernia	1	-	-	-
	Lung Sepsis	1	-	-	-
	Scoliosis	1	-	-	-
	Tetralogy of Fallot*	1	1	-	1
	Transposition of the great artery	3	1	-	1
	Ulcerative Colitis	1	-	-	-
	Ventriculoperitoneal shunt blocked	1	-	-	-
Total		**37**	**14**	**1**	**14**

*Children may fall under multiple categories (presumed infection, pneumonia, UTI, +ve culture).

4.3.9 Severity of illness

The overall median severity of illness scores measured using the PELOD-2 at 0 - 24 h (0.87 [0.13 – 49.25]) was the same as the severity of illness score at 48 - 72 h (0.87 [0.13 – 49.25]). In 11 of the 37 children, the median predicted mortality reduced at 48 - 72 h by 55 (36 – 84) % compared to 0 - 24 h. In 3 of the 37 children, the median predicted mortality increased by 126 (61.76 – 136) % at 48 - 72 h compared to 0 - 24 h.

The PELOD-2 score assesses multiple organ dysfunction and comprises ten variables (Glasgow coma score, pupillary reaction, Lactatemia, Mean arterial pressure, Creatinine, PaO2/FiO2 ratio, PaCo2, Ventilation, WBC count, Platelets). The severity of illness score showed that the patient had varying degrees of multiple organ function. Most patients (87.5%) had a severity of illness score below 10%. Three patients had severity scores of 19.15%, 27.49%, and 49.25%, respectively.

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4.4 Variation of vancomycin dose and mode of administration

The thirty-seven children in this study received a median vancomycin dosage of 15.0 (9.7 – 19.5) mg/kg. The wide range of doses given to children was either because the vancomycin trough concentration was low or renal dysfunction. Vancomycin was given over an hour of infusion.

4.4.1 Dosing intervals

The dosing interval was the time between vancomycin doses. Typically, a 6-hour interval is allowed between two doses. However, the dosing interval in this study varied. Twenty-one children had a 6-hour dosing interval. In 8 children, the dosing interval was 8 hours, and two children had a 12-hour dosing interval. The attending physician adjusted the dose and frequency of administration based on vancomycin trough concentration obtained after the third or fourth vancomycin dose and kidney function (creatinine concentration).

The dosing interval was unclear in another six patients and ranged from 7.5 – 34h. Finally, the dosing interval in one patient was adjusted after the second dose to 12 hourly.

In the twenty-one children on a six-hourly interval, the dosing interval was changed to eight-hourly after three doses in 2 children and one dose in 1 child.

In the eight children on an eight-hourly dosing interval, two children had their dosing frequency increased to six-hourly after one dose. Likewise, two children on a 12-hourly interval had their dosing interval changed to six-hourly after two doses.

When vancomycin dosing time was changed for a child, the time dosing was missed, and the new dosing time was noted and included in the PK analysis. On the blood samples collection form, the dosing points at which optimal blood samples were to be collected (13hr 30mins, 19hrs, 21hrs, 29hr 22mins, 40hr 48mins, and 55hr 21mins) were transcribed into actual times on the dosing intervals (30 mins after the 3rd vancomycin infusion (peak concentration), just after the 4th

vancomycin infusion (peak concentration), Three hours after the 4th vancomycin infusion (Concentration between peak and trough level), 38 mins before the 6th vancomycin infusion (trough concentration), 1 hr 12 mins before the 8th vancomycin infusion (Concentration between peak and trough level), 21 minutes after the 10th vancomycin infusion (peak concentration)) (Appendix 1). Vancomycin plasma sampling times were adjusted according to the new dosing time.

4.4.2 Dosing schedules

The start times and end times of each vancomycin IV administration for each child were noted prospectively on a time sheet by either one of the researchers or a nurse. At the end of the vancomycin IV infusion, the IV line was flushed using a pump which infused normal saline at the same infusion rate as vancomycin. Blood sampling for vancomycin levels commenced one minute after flushing the IV line. Before blood sampling, the dead space (the internal volume of a catheter and tubing through which fluid must pass before reaching a patient's vascular space) in the port of the IV line was aspirated to avoid contamination of the vancomycin sample. Two mL of blood was pulled out of the catheter and set aside in a sterile condition, and slowly re-injected in the same line after drawing blood for vancomycin tests. Finally, the IV line was flushed with 1 mL of normal heparinized saline to keep the IV line patent. Dosing schedules (time for the next vancomycin IV infusion) for the patients were not always strictly followed. None of the patients had all their doses given at the scheduled time (Appendix 4.1). Most doses were between 0.01 – 2.08 hours later than the scheduled time (N = 101). One patient was given vancomycin 4.23 hours later than the scheduled time, forty-nine doses were given 0.02 – 1.75 hours earlier than the scheduled time, and forty-seven doses were given at the scheduled time. The difference between planned and actual vancomycin dosing times was due to the non-availability of the ICU nurse or delay in the

availability of the TDM results in cases where dose adjustments were required. In addition, some patients that had surgery around the dosing times missed their dose.

4.4.3 Vancomycin dose increase

Vancomycin dose increased in 11 patients because of low vancomycin trough concentration. Five patients had their dose increased after the 3rd dose, one of the five patients had a second dose increase after the 7th vancomycin dose, and four patients had an increased dose after the 4th vancomycin dose. One of the four patients had another dose increase after the 6th dose. Two patients had their vancomycin dose increased after the 6th dose.

4.4.4 Vancomycin dose reduction

Five patients had their dose reduced once during the study period. Vancomycin dose reduction was because of high trough levels in four patients and red man syndrome in one patient. In the patient with red man syndrome, vancomycin was reduced after the 1st dose. Vancomycin dose was reduced after the 2nd dose in 2 children, the 5th dose in one child, and the 6th dose in one child. Vancomycin doses were not changed in 21 patients.

4.5 Vancomycin treatment withdrawal

Three patients on vancomycin had their treatment stopped and was not restarted during the study period. Vancomycin was stopped in these patients because of high vancomycin plasma concentrations (97.2, 98.7, and 69.3 µg/L, respectively). They received a vancomycin dose of 15mg/kg.

The patient with a vancomycin plasma concentration of 97.2 µg/L had rapidly declining renal function. Therefore, the vancomycin dosing interval was reduced from 8 to 6 hours after the 2nd dose. The patient had a CrCl of 72.7 mL/min. Vancomycin therapy stopped after the 4th dose. The patient with a vancomycin plasma concentration of 98.7 µg/L was on a 6-hourly infusion. There

was no change in the dosing interval, and the patient stopped vancomycin treatment after the 3rd dose. The serum creatinine concentration in this patient was normal.

The patient with a vancomycin plasma concentration of 69.3 µg/L had a hypoxic brain injury that led to brain death. In addition, the patient had kidney failure. In one patient, vancomycin dosing was 12 hours, and this patient stopped treatment after the 4th dose.

4.6 Number of vancomycin samples taken and sampling times

4.6.1 Expected number of plasma samples

We expected to collect 222 blood samples from the 37 patients based on the predefined number of samples (six samples for each patient) and the scheduled sampling times.

4.6.2 Number of missing samples

Only 183 of the 222 expected blood samples were collected from the patients. The required number did not reach the expected because patients were discharged from the hospital before the end of the 72-hour observation window ($N = 9$), central/arterial lines were removed ($N = 3$), and difficulties in obtaining a sample where lines were present ($N = 11$).

4.6.3 Number of plasma samples excluded from the study

Three blood samples were excluded from the analysis. We did not include two samples from two patients in the data analysis because they had very high plasma concentrations (189.1 µg/L and 439 µg/L), indicative of cross-contamination during sampling. Comparing the levels with other plasma concentrations from the same patient showed a significant difference (189.1±178 and 439±420 µg/L) in vancomycin plasma concentration, indicating a possible error in blood sample collection.

4.6.4 Number of blood samples included in the PK analysis

A total of 180 vancomycin concentrations were used in the PK analysis. The number of blood samples collected from patients ranged from 2 to 6. Not all patients had the required samples ($N = 6$) taken. Six blood samples were collected from 8 patients. Twenty-three patients had less than six blood samples collected. Five patients had five blood specimens taken. Seven patients had four samples taken, seven patients had three samples taken, and four patients had two blood samples taken (Appendix 4.2).

In the first 24 hours, 75 (1-5 for each patient) samples were available and used for the pharmacokinetic analysis. For the pharmacokinetic profile of vancomycin in patients after 24 hours, 105 (1-5 for each patient) samples were available and analysed.

There were differences in the proposed blood sample collection time and the actual time blood samples for trough (Appendix 4.2) and peak concentrations (Appendix 4.3) were collected.

Overall, 26, 19, and 8 blood samples were collected earlier than scheduled in the 0 – 24, 24 – 48, and 48 – 72 hrs periods, respectively. A total of 29, 29, and 16 blood samples were collected later than the scheduled time in the 0 – 24, 24 – 48, and 48 – 72 hrs periods, respectively. Late collection of blood samples was because of difficulties in obtaining samples and patients undergoing procedures at the scheduled time for sample collection.

4.6.5 Left-over blood samples

Forty-six of the 183 blood samples collected from the patients were left-over samples from routine clinical tests. They were included in the analysis. The blood samples were collected in heparinised tubes/syringes for routine clinical tests (e.g., for blood gas tests and vancomycin TDM). There was no scheduled time for the collection of these samples. Twenty of these blood samples were collected in the first 24 hours, and twenty-six of the samples were collected after 24 hours.

4.7 Description of vancomycin plasma concentration

Plasma concentrations were grouped according to the closest times (± 30 mins from the specific hour) at which the blood samples were collected and according to the different dosing schedules.

4.7.1 Vancomycin plasma concentration in the first 24 hours

Seventy-nine vancomycin plasma concentrations were collected for analysis in the first 24 hours. Table 4.7 shows vancomycin plasma concentration according to the sampling times.

Table 4-7 Plasma concentration of vancomycin according to sampling times during 0 – 24 hours

Dosing Frequency	Number of samples	plasma concentrations (µg/L)
Six hourly (h)		
12^T	6	6.2 (2.0 – 9.9)
13^P	5	46.2 (18.6 – 76.7)
18^T	10	4.4 (2.4 – 13.9)
19^P	7	41.9 (14.9 – 82.2)
21^M	8	22.7 (14.9 – 51.0)
24^T	4	9.4 (5.7 – 13.0)
Eight hourly (h)		
8^T	5	6.2 (2.0 – 9.9)
10^P	5	46.3 (18.6 – 76.7)
16^T	10	4.4 (2.4 – 13.9)
19^M	7	41.9 (14.9 – 82.2)
21^M	8	22.6 (14.9 – 51.0)
24^T	4	9.4 (5.7 – 13.0)

P, peak vancomycin plasma concentration; M, vancomycin plasma concentration at points between the peak and trough concentrations; T, trough vancomycin plasma concentrations.

4.7.2 Vancomycin plasma concentration during 24 – 48 hours

Sixty-five plasma concentrations were collected for analysis between 24 – 48 hours. Table 4.8 shows vancomycin plasma concentration according to the sampling times.

Table 4-8 Plasma concentration of vancomycin according to sampling times during 24 – 48 hours

Dosing Frequency	Number of samples	plasma concentrations (µg/L)
Six hourly (h)		
25^P	6	39.7 (17.1 – 97.2)
27^M	1	23.9 µg/L
30^T	9	7.9 (3.3 – 14.6)
31^P	5	42.2 (17.7 – 49.3)
36^T	4	9.0 (7.7 – 10.9)
37^P	3	17.4 (12.5 – 24.1)
42^T	11	7.9 (2.4 – 22.8)
43^P	2	19.0 (16.1 – 21.9)
48^T	7	8.5 (3.6 – 12.5)
Eight hourly (h)		
25^P	3	24.9 µg/L
32^T	3	5.7 (5.5 – 6.1)
33^P	1	34.5 µg/L
41^P	5	36.3 (14.9 – 58.0)
48^T	5	5.5 (5.2 – 12.0)

P, peak vancomycin plasma concentration; M, vancomycin plasma concentration at points between the peak and trough concentrations; T, trough vancomycin plasma concentrations.

4.7.3 Vancomycin plasma concentration during 48 – 72 hours

The total number of vancomycin plasma concentrations collected 48 – 72 hours after the initiation of vancomycin therapy was 36. Table 4.9 shows vancomycin plasma concentration according to the sampling times.

Table 4-9 Plasma concentration of vancomycin according to sampling times during 48 – 72 hours

Dosing Frequency	Number of samples	plasma concentrations (µg/L)
Six hourly (h)		
49^P	4	21.8 (15.4 – 32.3)
54^T	6	8.5 (4.2 – 12.5)
55^P	5	23.2 (20.7 – 47.1)
60^T	6	9.0 (2.5 – 13.9)
65^M	4	10.4 (7.7 – 27.5)
72^T	3	8.8 (4.5 – 13.5)
Eight hourly (h)		
56^T	2	4.4 (3.6 – 5.2)
57^P	1	47
65^P	2	35.4 (21.9 – 48.8)
72^T	3	6.6 (4.2 – 9.0)

P, peak vancomycin plasma concentration; M, vancomycin plasma concentration at points between the peak and trough concentrations; T, trough vancomycin plasma concentrations.

4.8 Conclusion

The study population was heterogeneous, with different organ function levels and disease states. There were issues with vancomycin dosing times, as doses were not always given at the scheduled times. Earlier or later than scheduled dose intervals were observed. Blood samples for vancomycin peak and trough concentration measurements were not always taken at stipulated sampling times because of constraints. However, the time the samples were taken was always noted for the accurate modelling of vancomycin pharmacokinetics. Peak and trough plasma concentrations of samples taken at 0 – 24 hours, 24 – 48 hours, and 48 – 72 hours were within similar ranges. Vancomycin plasma concentrations from left-over blood samples were also within similar ranges.

Chapter 5
Vancomycin Pharmacokinetics in Critically-Ill Children

5.0 Introduction

This chapter presents the pharmacokinetic profile of vancomycin in critically ill children. Results from the model building and validation are given. Population pharmacokinetics use models to account for inter-individual variability in a population considering drug, disease, or environmental factors that may affect pharmacokinetics (Kiang et al., 2012). In population PK modelling, the body is divided into compartments (1-, 2-, or 3- compartments). Unlike the traditional PK methods, sparse samples can be used to make inferences about a population. Sparse sampling makes models very useful in PK studies in critically ill children. Traditional PK usually requires intense sampling (> 6 samples per patient) (Ette and Williams, 2004; US FDA, 2022). Population PK models are also helpful in generating results when there are heterogeneous factors to consider, for instance, patients receiving doses at different times, samples taken at different times, different disease conditions, etc. (US FDA, 2022). Where heterogeneity is profound, an adequate sample size is necessary to draw reliable conclusions (Kiang et al., 2012).

Vancomycin pharmacokinetics are presented at 0 - 24 h, 24- 48 h, and 48 - 72 h after initiation of vancomycin therapy. In addition, the simulation of optimized vancomycin dose using PK values generated from this study is also presented.

5.1 Pharmacokinetic model building

Vancomycin pharmacokinetics were modelled using one and two-compartment models as the structural model. The best-fit model was selected based on the objective function values (OFV) observed from the Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) values. Compared to the one-compartment model, the two-compartment model reduced the AIC and BIC values (Table 5.1). Hence, we selected the two-compartment model for the

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pharmacokinetic modelling. After comparison with other models, the error model selected was the proportional model with a log-normal distribution. The effect of variables - age, gender, weight, renal function (SCr and CrCl), liver function (AST, ALT and serum albumin), heart rate, mean arterial blood pressure, respiratory rate and temperature- on the model were tested. The variables that significantly improved the model (significantly reduced the OFV and improved the model fit) were weight and CrCl. Nonallometric and allometric weights were added to the model. Allometric weight, estimated at 0.75 for vancomycin clearance and 1 for the volume of distribution in the central compartment, improved the OFV of the model. CrCl improved the model fit when it was added to vancomycin CL.

The first step evaluated the compartmental model (one or two) that best-described vancomycin PK. The base model was then selected.

In the next step, each variable was added to the base model one at a time. The OFV was noted, and variables significantly improving the model (where the OFV decreased by more than 3.84) were identified (Mould and Upton, 2013).

In the next step, all the variables that significantly decreased the OFV were added to the base model and removed one at a time. The OFV was noted. Where a variable was removed, and the OFV increased by greater than 6.63, the variable significantly improved the model.

Weight and creatinine clearance was noted to improve the OFV of the model significantly and were included in the model in the stepwise manner indicated in Table 5.1. The effect of the two variables on the OFV of the model is also shown in Table 5.1.

Table 5-1 Model Building Procedure

Model	Model description	2xlog-likelihood OFV	AIC	BIC	BICc*
1	One compartment base	1296.50	1360.50	1314.55	1319.31
2	Two compartment base	1280.81	1298.81	1313.31	1321.24
3	Add wt (not fixed) to model 2	1227.59	1249.59	1267.31	1275.25
4	Add wt (fixed) to model 2	1230.92	1248.92	1263.42	1271.35
5	Remove the random effect on Q in model 4	1225.67	1241.67	1254.55	1262.49
6	Add CRCL to CL in model 5	1204.59	1222.59	1237.09	1245.03

Wt, Weight; CRCL, creatinine clearance, Q, inter-compartmental distribution
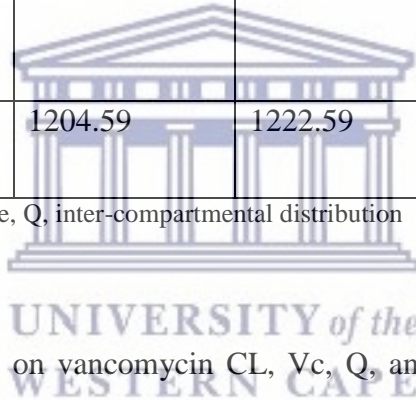
The random effects of variables on vancomycin CL, Vc, Q, and Vp were each assessed. The random effect on Q was removed to improve the model.

With the OFV, visual diagnostics were used to select the best-fit model. The goodness of fit plots of the final model are shown below:
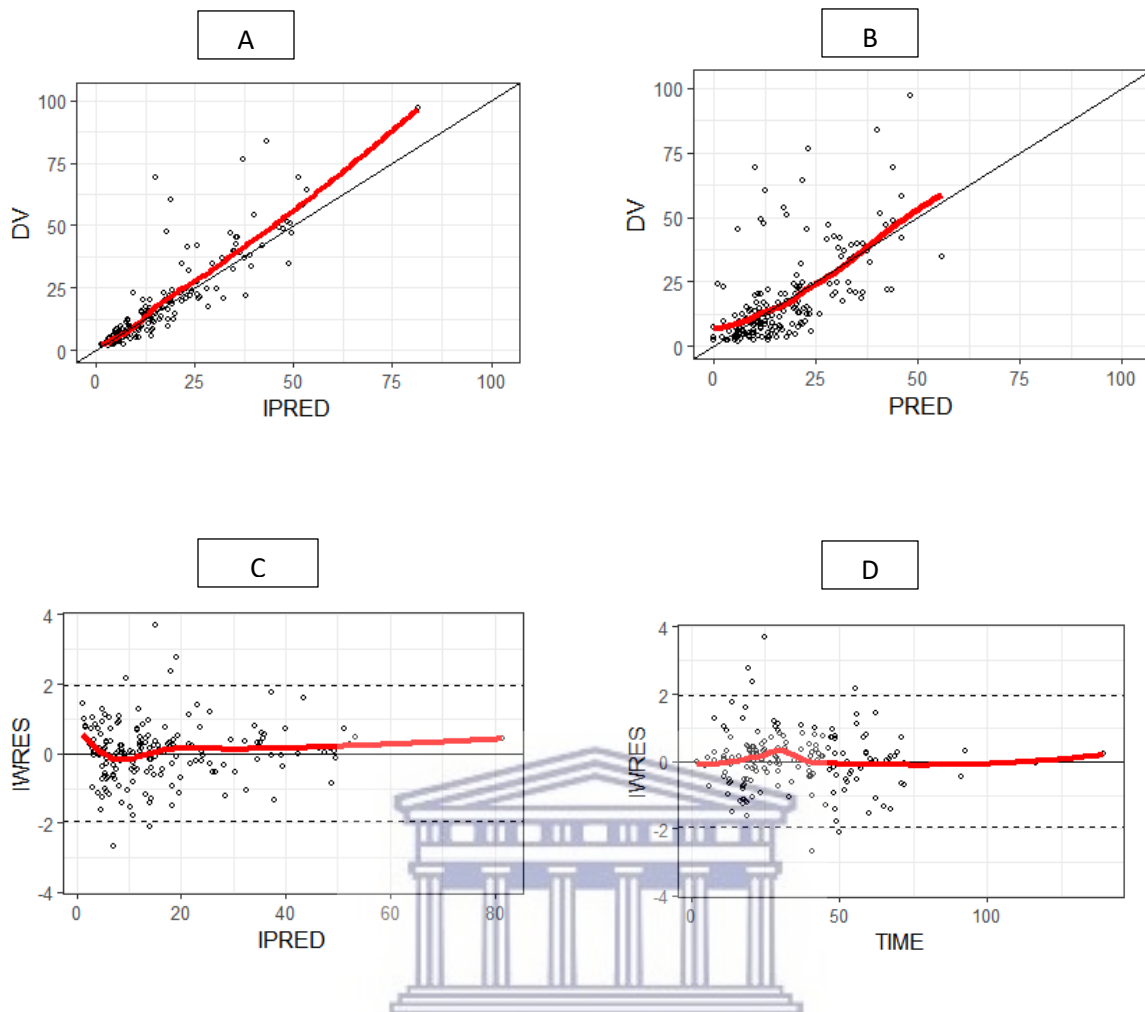
Figure 5-1 The goodness-of fit of the model (a measure of how well the model fits the set of observations) was observed from the following plots- (A) Observed concentration (DV) Vs individual predicted concentration (IPRED); (B) Observed concentration (DV) Vs population predicted concentration (PRED); (C) Individual weighted residue (IWRES) Vs Individual predicted concentration (IPRED); (D) Individual weighted residue (IWRES) Vs Time

The equation of the final model chosen was:

$$CL_i = 0.10 \times \left(\frac{Weight}{10.6}\right)^{0.75} \times \left(\frac{CRCL}{62.28}\right)^{0.08} \times exp(0.03)$$

$$V1_i = 0.42 \times \left(\frac{Weight}{10.6}\right)^{1} exp(0.18)$$

$$Q_i = 0.67$$

$$V2_i = 0.17 \times exp(0.20)$$

The quantile plots indicated normality in the NDPE as shown below:
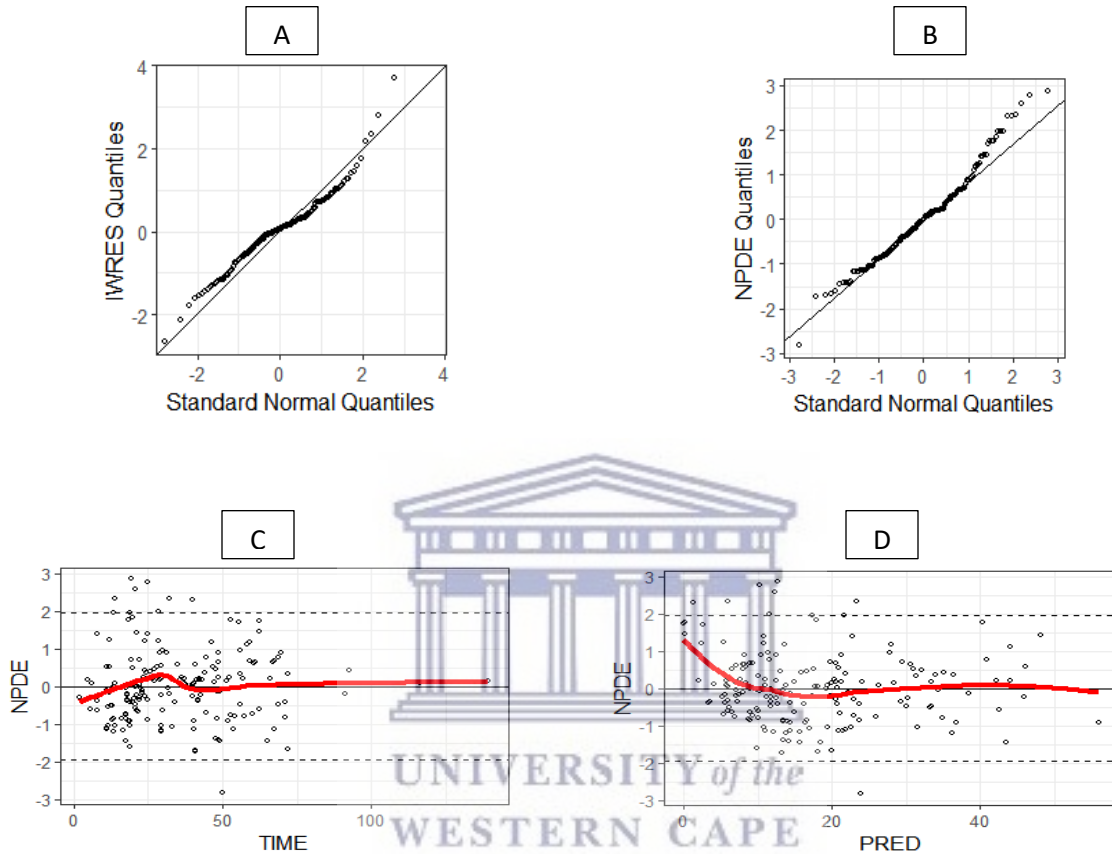
Figure 5-2 *Normalized predictive distribution error (NDPE) of the final model describing popPK. (A) Individual weighted residue (IWRES) Quantiles Vs Standard Normal Quantiles; (B) NDPE Quantile Vs Standard Normal Quantiles; (C) NDPE Vs Time; (D) NDPE Vs Population predicted concentration (PRED)*

5.2 Vancomycin pharmacokinetic parameters

The estimates from the base and final model are presented in Table 5.2. Inter-individual variability existed in pharmacokinetic parameters, but the inter-individual variability in the volume of distribution was high.

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Table 5-2 Population Pharmacokinetic Estimates of Vancomycin.

Parameter	Final model		Base model	
	Population Estimate	RSE (%)	Population Estimate	RSE (%)
θ_{CL}	1.06	7.32	0.91	16.2
θ_{Vc}	3.66	12.9	0.79	62.9
θ_Q	7.11	39.6	5.28	71.6
θ_{Vp}	1.80	62.4	5.99	32.5
θ_{CRCL} on CL	0.82	19.2	-	-
θ_{weight} on CL	0.75	-	-	-
θ_{weight} on Vc	1	-	-	-
ω_{CL}	0.36	17.2	0.84	14.7
ω_{Vc}	0.18	75.5	1.46	31.4
ω_Q	-	-	1.06	50.6
ω_{Vp}	2.15	22.6	1.5	18.8
Σ	0.41	7.17	0.4	8.67

θ_{CL}, population parameter of CL (L/h); θ_{Vc}, population parameter of the volume of distribution in the central compartment (L); θ_Q, population parameter of inter-compartment distribution (L/h); θ_{Vp}, population parameter of the volume of distribution in the peripheral compartment (L); θ_{CRCL}, Population parameter of creatinine clearance on CL; θ_{weight}, Population parameter of weight on CL; θ_{weight}, Population parameter of weight Vc; ω_{CL}, Inter-individual variation of CL; ω_{Vc}, Inter-individual variation of volume of distribution in the central compartment; ω_Q, Inter-individual variation of inter-compartment distribution; ω_{Vp}, Inter-individual variation of volume of distribution in the peripheral compartment; σ, proportional residual variation.

5.3 Vancomycin model validation

The final model was validated using 1000 dataset replicates generated by bootstrap (resampling the original population dataset). The bootstrap estimates were compared to the estimates from the model. Estimates generated from the bootstrap were comparable to the estimates generated by the model in Monolix (Table 5.3).

Table 5-3 Population pharmacokinetics parameters of vancomycin and bootstrap validation

Parameter	Final Model estimate		Bootstrap (n=1000)	
	Median	95% CI	Median	95% CI
θ_{CL}	0.10	(0.09, 0.11)	0.10	(0.08, 0.12)
θ_{Vc}	0.35	(0.24, 0.49)	0.35	(0.13, 0.72)
θ_{Q}	0.67	(0.35, 1.29)	0.67	(0.07, 1.09)
θ_{Vp}	0.17	(0.08, 0.36)	0.17	(0.00, 0.75)
θ_{CRCL} on CL	0.08	(0.05, 0.10)	0.08	(0.06, 0.10)
ω_{CL}	0.03	(0.03, 0.04)	0.03	(0.01, 0.05)
ω_{Vc}	0.02	(0.003, 0.10)	0.02	(0.00, 0.08)
ω_{Vp}	0.20	(0.16, 0.25)	0.20	(0.09, 0.73)
Σ	0.41	(0.37, 0.45)	0.41	(0.32, 0.52)

θ_{CL}, population parameter of CL (L/h/kg); θ_{Vc}, population parameter of volume of distribution in the central compartment (L/kg); θ_{Q}, population parameter of inter-compartment distribution (L/h/kg).; θ_{Vp}, population parameter of volume of distribution in the peripheral compartment (L/kg); θ_{CRCL}, Population parameter of creatinine clearance on CL; ω_{CL}, Inter-individual variation of CL; ω_{Vc}, Inter-individual variation of volume of distribution in the central compartment; ω_{Q}, Inter-individual variation of inter-compartment distribution; ω_{Vp}, Inter-individual variation of volume of distribution in the peripheral compartment; σ, constant residual variation.

5.4 Vancomycin pharmacokinetic parameters

Vancomycin PK parameters were assessed in three periods: 0 – 24 h, 24 – 48 h, and 48 – 72 h.

Blood samples were collected from all 37 children during the 48 – 72 period. A total of 26 of the

37 children had blood samples during 0 – 24 h, and 31 of the 37 children had blood samples

collected in the 24 – 48 h period.

5.4.1 Vancomycin pharmacokinetics in the first 24 hours of treatment

In the first 24 hours of treatment, the median (range) vancomycin clearance was 0.09 (0.02 – 0.27)

L/h/kg. The median (range) inter-compartmental distribution (Q) was 0.11 (0.02 – 0.38) L/kg/h.

The median (range) volume of distribution in the central (Vc) compartment was 0.67 (0.46 – 1.00)

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L/kg. The median (range) volume of distribution in the peripheral (Vp) compartment was 0.03 (0.001 – 60.06) L/kg. The median (range) AUC0-24 was 150.85 (115.28 – 351.22) mg * h / L.

The median (range) half-life (T1/2) of vancomycin was 2.50 (0.29 – 25.38) hr with a median (range) elimination rate constant (Ke) of 0.17 (0.11 – 0.22) hr-1. The median (range) vancomycin trough concentration was 5.5 (2.0 – 13.90 µg/L) in 21 children. The median (range) peak concentration was 42.20 (18.60 – 83.80) µg/L in 16 children. The number of children with vancomycin PK parameters within the normal reference range is shown in Table 5.4.

Table 5-4 Vancomycin PK parameters in the first 24 hours of treatment

PK Parameter (N = 26)*	Reference range	Lower than normal (%)	Within normal range (%)	Higher than normal (%)
CL (L/h/kg)	0.08 – 0.13	9 (34.6)	6 (23.1)	11 (42.3)
V_d (L/kg)	0.5 - 1	8 (30.8)	4 (15.4)	14 (53.8)
T½ (h)	2 - 6	14 (53.8)	6 (23.1)	6 (23.1)
AUC0-24 (µg · h/L)	400 - 600	26 (100)	0	0
Trough (µg/L)	10 – 15	18 (85.7)	3 (14.3)	0
Peak (µg/L)	20 – 40	3 (18.8)	5 (31.2)	8 (50.0)

Trough, N = 21; Peak, N = 16

5.4.2. Vancomycin pharmacokinetics during 24 – 48 hours of treatment

During 24 – 48 hours after vancomycin treatment initiation, the median (range) vancomycin clearance was 0.11 (0.03 – 0.24) L/h/kg and inter-compartmental distribution, Q, was 0.53 (0.10 – 1.84) L/h/kg. The median (range) volume of distribution in the central (Vc) compartment was 0.12 (0.03 – 1.60) L/kg, and the volume of distribution in the peripheral (Vp) compartment was 0.47 (0.10 – 3.68) L/kg. The median (range) vancomycin AUC0-48 was 427.21 (58.10 – 1141.62) mg

* h / L. The median (range) vancomycin half-life was 2.63 (1.26 – 8.79) h, and the elimination rate constant was 0.96 hr-1 (0.08 – 0.55).

The median (range) vancomycin trough concentration was 7.7 (2.40 – 14.60 µg/L) in 23 children. The median (range) peak concentration was 49.30 (17.70 – 97.20) µg/L in 11 children. The number of children with vancomycin PK parameters within the normal reference range is shown in Table 5.5.

Table 5-5 Vancomycin PK parameters during 24 – 48 hours of treatment

PK Parameter (N = 31)*	Reference range	Lower than normal (%)	Within normal range (%)	Higher than normal (%)
CL (L/h/kg)	0.08 – 0.13	8 (25.8)	12 (38.7)	11 (35.5)
V_d (L/kg)	0.5 - 1	4 (12.9)	17 (54.8)	10 (32.3)
T½ (h)	2 - 6	12 (38.7)	22 (71.0)	3 (9.7)
AUC0-24 (µg · h/L)	400 - 600	13 (41.9)	15 (48.4)	3 (9.7)
Trough (µg/L)	10 – 15	19 (82.6)	4 (17.4)	0
Peak (µg/L)	20 – 40	1 (9.1)	3 (27.3)	7 (63.6)

Trough, N = 23; Peak, N = 11

5.4.3 Vancomycin pharmacokinetics during 48 - 72 hours of treatment

During 48 – 72 hours after vancomycin treatment initiation, the median (range) vancomycin clearance was 0.10 (0.03 – 0.22) L/h/kg and inter-compartmental distribution, Q, was 0.67 (0.12 – 2.49) L/kg/h. The median (range) volume of distribution in the central (Vc) compartment was 0.35 (0.32 – 0.39) L/kg, and volume of distribution in the peripheral (Vp) compartment was 0.17 (0.06 – 5.6) L/kg. The median (range) vancomycin AUC0-72 was 455.26 (150.85 – 1762.47) mg

* h / L. The median (range) half-life and elimination rate constant was 3.43 (0.49 – 16.80) hr and 0.13 hr-1 (0.08 – 0.50), respectively.

The median (range) vancomycin trough concentration was 5.9 (2.50 – 19.70 µg/L) in 15 children. The median (range) peak concentration was 44.15 (32.90 – 69.30) µg/L in 6 children. The number of children with vancomycin PK parameters within the normal reference range is shown in Table 5.6.

Table 5-6 Vancomycin PK parameters during 48 – 72 hours of treatment

PK Parameter (N = 37)*	Reference range	Lower than normal (%)	Within normal range (%)	Higher than normal (%)
CL (L/h/kg)	0.08 – 0.13	15 (25.8)	10 (38.7)	12 (35.5)
V_d (L/kg)	0.5 - 1	10 (12.9)	16 (54.8)	11 (32.3)
T½ (h)	2 - 6	14 (38.7)	15 (71.0)	8 (9.7)
AUC0-24 (µg · h/L)	400 - 600	13 (41.9)	14 (48.4)	10 (9.7)
Trough (mcg/mL)	10 – 15	12 (80.0)	2 (13.3)	1 (6.7)
Peak (mcg/mL)	20 – 40	0	2 (33.3)	4 (66.7)

Trough, N = 15; Peak, N = 6

5.5 Changes in Vancomycin PK during the 0 – 24, 24 – 48, and 48 – 72 time periods

Changes were observed in the vancomycin PK in children. The changes in the CL, V_d, T1/2, AUC, peak, and trough concentrations are detailed below.

5.5.1 Changes in vancomycin clearance (CL)

Changes < or > 5% of the normal ranges of CL (0.08 – 0.13 L/h/kg) were used to make comparisons. Change in vancomycin CL ≥ 0.02 between periods was observed in 14 of the 37 patients. Vancomycin CL was lower than the lower limit of the normal range in 5 patients (0.05 – 0.07

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L/h/kg) during the 0 – 24 h period and increased to values within the normal range of vancomycin CL by the 24 – 48 h and the 48 – 72 h period (Figure 5.3). Vancomycin CL was higher than the upper limit of the normal range in 5 patients during the 0 – 24 h (0.17 – 0.24) and reduced to the normal range by the 24 – 48 h and the 48 – 72 h period in 2 children. In 3 of the five children, Vancomycin CL increased by 24 – 48 h and 48 – 72 h. One child had vancomycin CL within the normal range during 0 - 24 h that increased above the upper limit of the normal range by the 24 – 48 h (0.15 L/kg/h) and 48 – 72 h period (0.14 L/kg/h). In children, the Vancomycin CL values in the first 24 hours, 24 – 48 hours, and 48 – 72 hours of treatment were statistically insignificant ($P > 0.05$).

Changes in renal function and perfusion during treatment may be responsible for the differences in vancomycin CL observed in these children. Concomitant medication prescribed may also affect vancomycin CL.

Figure 5-3 Rate of change of vancomycin CL between 0 – 24 hrs, 24 – 48 hrs and 48 – 72 hrs of vancomycin treatment. The rate of change in vancomycin CL for each individual patients is observed from the values during 0 – 24 hrs, 24 – 48 hrs and 48 – 72 hrs (each period is denoted by a different colour in the figure) of treatment. The normal range of clearance is between 0.08 and 0.13 L/kg/h as denoted by the orange lines.

5.5.2 Changes in vancomycin volume of distribution (V_d)

Change in vancomycin $V_d \geq 0.02$ between periods was observed in 16 of the 37 patients. Vancomycin V_d was higher than the upper limit of the normal in all 16 children (1.34 – 4.75) L/kg during the 0 – 24 h period (Figure 5.4). Vancomycin V_d was reduced to values within the normal limit in 14 children. Vancomycin V_d increased during the 24 – 48 h and 48 – 72 h periods in 2 patients. Changes in fluid status and protein concentration during treatment may be responsible for the changes in vancomycin V_d observed in these children. Vancomycin V_d in the central compartment was significantly higher during the 48 – 72 h period (0.17 L/kg) compared to the 0 – 24 h period (0.03 L/kg) (Z= -4.37, p = 0.000).

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Figure 5-4 Rate of change of vancomycin Vd between 0 – 24 hrs, 24 – 48 hrs and 48 – 72 hrs of vancomycin treatment. The rate of change in vancomycin Vd for each individual patients is observed from the values during 0 – 24 hrs, 24 – 48 hrs and 48 – 72 hrs (each period denoted by a different colour in the figure) of treatment. The normal range of Vd is between 0.5 and 1 L/kg, as denoted by the orange lines.

5.5.3 Changes in vancomycin half-life (T1/2)

Change in vancomycin T½ ≥ 2 h (equal to the lower limit of the normal T½ range) between periods was observed in 11 of the 37 patients. Vancomycin T½ was within the normal range during the 24 – 48 h period in 7 children. Of the seven children, 3 and 5 had high T½ during the 0 – 24 h and 48 – 72 h periods, respectively. Two of the 11 children had higher vancomycin T½ during the 48 – 72 h period than the 24 – 48 h period. Two of the 11 children had high vancomycin T½ during the 24 – 48 h period compared to the 0 – 24 h and 48 – 72 h periods (Figure 5.5). Change in T½ may be affected by vancomycin CL. Renal function and perfusion may affect vancomycin T1/2.

 Changes in vancomycin T½ from 0 – 24 h to 24 – 48 h to 48 – 72 h were insignificant (P >0.05).
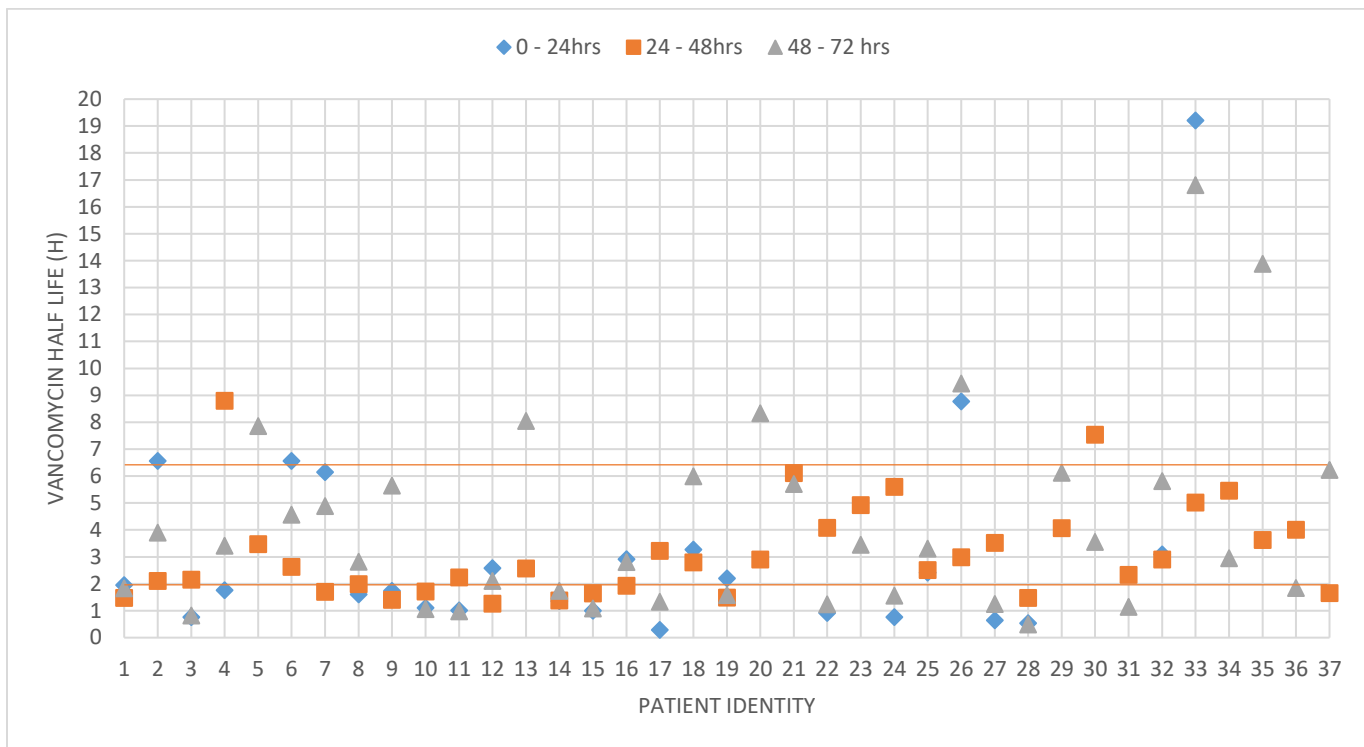
Figure 5-5 Rate of change of vancomycin T½ between 0 – 24 hrs, 24 – 48 hrs and 48 – 72 hrs of vancomycin treatment. The rate of change in vancomycin T½ for each patient is observed from the values during 0 – 24 hrs, 24 – 48 hrs and 48 – 72 hrs (a different colour denotes each period in the figure) of treatment. The normal range of clearance is between 2 and 6 h, as denoted by the orange lines.

5.5.4 Changes in vancomycin are under the concentration-time curve (AUC)

Vancomycin AUC was higher than the upper limit of the normal range (400 – 600 µg · h/L) in 7 of the 37 patients (0.05 – 0.07 L/h/kg) during the 48 – 72 h period (Figure 5.6). The AUC reduced to values within the normal limit during the 24 – 48 h and 0 – 24 h period in 6 children and values below the lower limit of the normal range during the 24 – 48 h and 0 – 24 h period in 1 child. In 5 of the 37 patients, AUC was lower than the lower limit of the normal range during the 0 – 24 h period and increased to values within the normal range during the 24 – 48 h and 48 – 72 h periods.

Vancomycin AUC significantly increased during the 48 – 72 h period compared to the AUC during the 24 – 48 h and 48 – 72 h periods (Z= -3.29, p = 0.001).
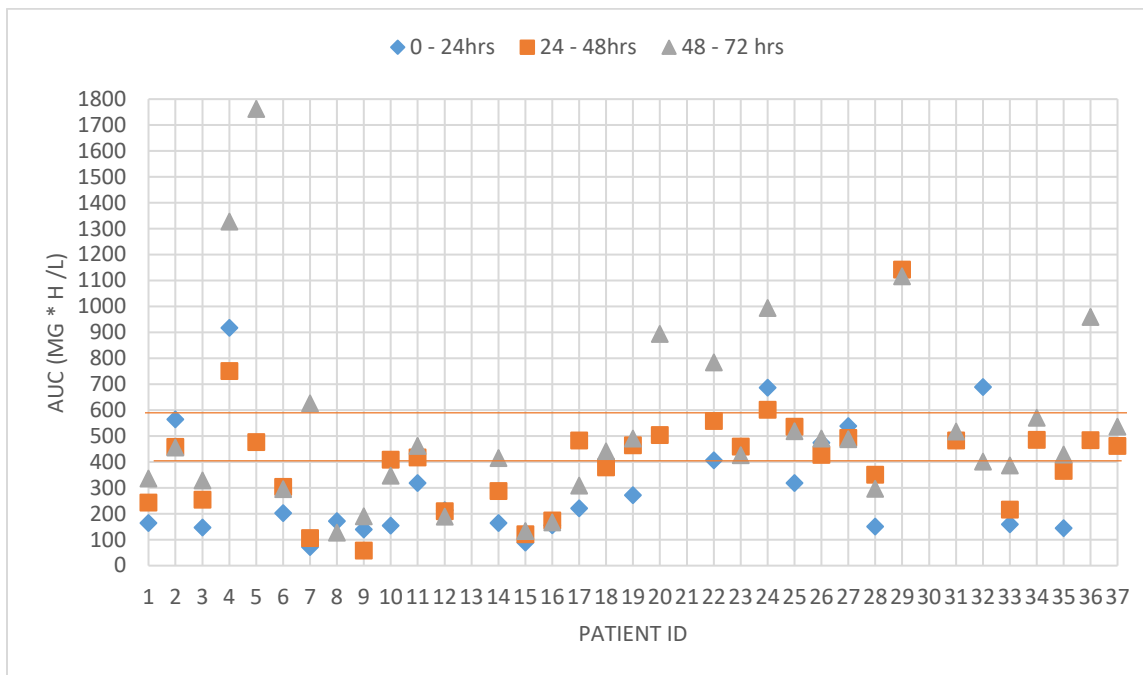
Figure 5-6 Rate of change of vancomycin AUC between 0 – 24 hrs, 24 – 48 hrs and 48 – 72 hrs of vancomycin treatment. The rate of change in vancomycin AUC for each patient is observed from the values during 0 – 24 hrs, 24 – 48 hrs and 48 – 72 hrs (a different colour denotes each period in the figure) of treatment. The normal range of AUC over 24 hrs is between 400 and 600 mg * h /L, as denoted by the orange lines.

5.5.5. Changes in vancomycin trough concentration

Trough concentrations were actually observed concentrations from blood samples collected just before the next vancomycin dose. Trough concentrations were calculated using the formula in section 3.14.3 for blood samples collected no more than 1 hour before the next vancomycin dose. Only 19 of the 37 patients had two (N = 10) or three (N = 9) trough concentrations. Vancomycin trough concentration was within the normal range (10 – 15 mcg/mL) in 3 patients (0.05 – 0.07 L/h/kg) during the 0 – 24 h period and reduced to values lower than the lower limit of the normal range (Figure 5.7). Vancomycin trough concentration was lower than the lower limit of the normal range in 4 children during the 0 – 24 h period and increased to normal during the 24 – 48 h and 48 – 72 h in 2 children. The trough concentration remained low in the other two children.

There was no significant change in vancomycin trough concentration during the 24 – 48 h compared to 0 – 24 h (Wilcoxon signed ranked Z= -0.942, p=0.346) and 48 – 72 h compared to 24 – 48 h in the children (Wilcoxon signed ranked Z= -0.663, p=0.507).
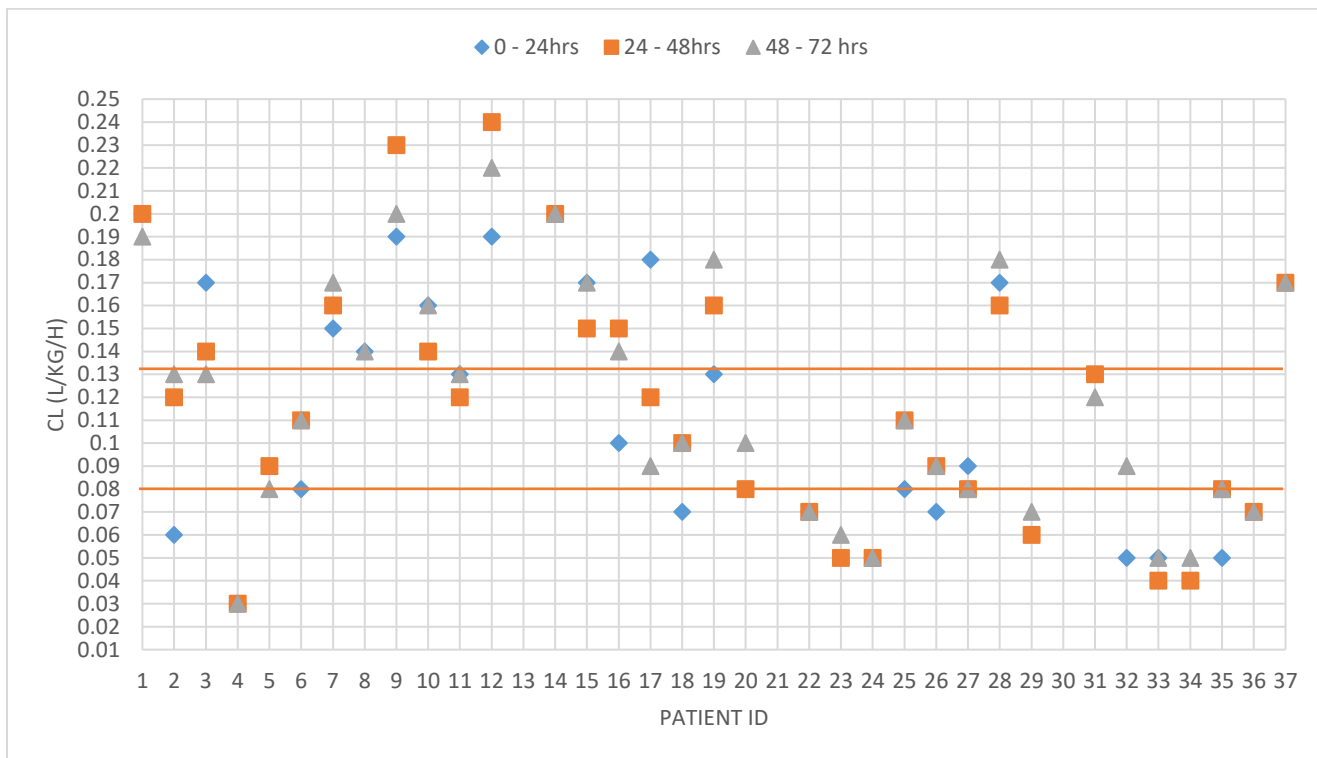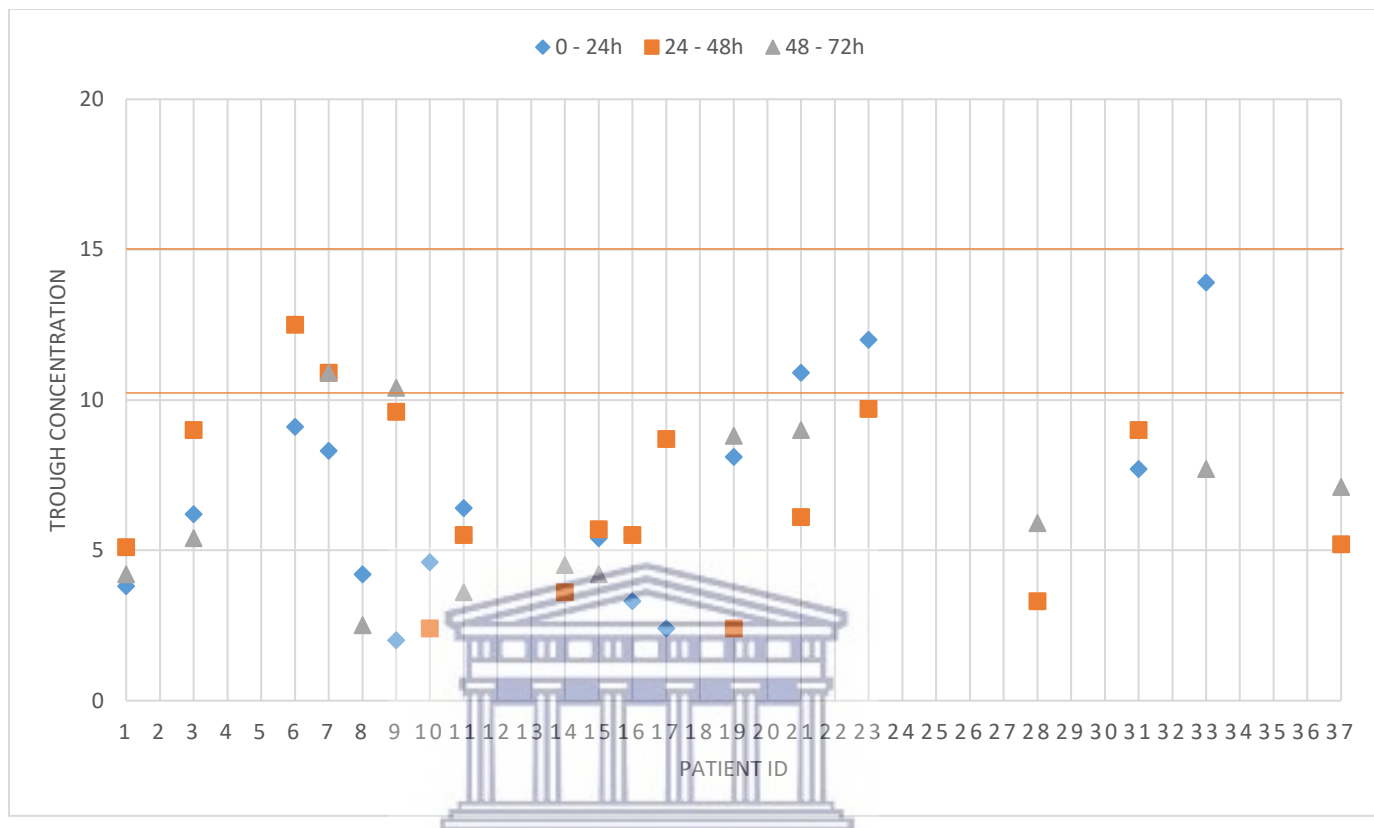

Figure 5-7 Rate of change of vancomycin trough concentration between 0 – 24 hrs, 24 – 48 hrs and 48 – 72 hrs of vancomycin treatment. The rate of change in vancomycin trough concentration for each patient is observed from the values during 0 – 24 hrs, 24 – 48 hrs and 48 – 72 hrs (a different colour denotes each period in the figure) of treatment. The normal range of trough concentration is between 10 and 15 µg/L as denoted by the orange lines.

5.5.6 Changes in vancomycin peak concentration

Peak concentrations were actually observed concentrations from blood samples collected just after the vancomycin IV infusion ended. Peak concentrations were calculated using the formula in section 3.14.3 for blood samples collected up to 1 hour after the end of the vancomycin IV infusion. Only 17 of the 37 patients had two (N = 15) or three (N = 2) peak concentrations. Vancomycin

peak concentration was higher than the upper limit of the normal range (20 – 40 mcg/mL) in 4 of the 37 patients (0.05 – 0.07 L/h/kg) during the 24 – 48 h period (Figure 5.8). The peak concentration reduced to values within the normal limit during the 24 – 48 h period in 2 children and remained high in 2 children. In 2 children, vancomycin trough concentration was within the normal range during the 0 – 24 h period and increased to higher values during the 24 – 48 h and 48 – 72 h periods.

There was no significant change in vancomycin peak concentration during the 24 – 48 h period compared to 0 – 24 h (Wilcoxon signed ranked Z= -0.365, p=0.715) and 48 – 72 h compared to 24 – 48 h in the children (Wilcoxon signed ranked Z= -1.342, p=0.180).
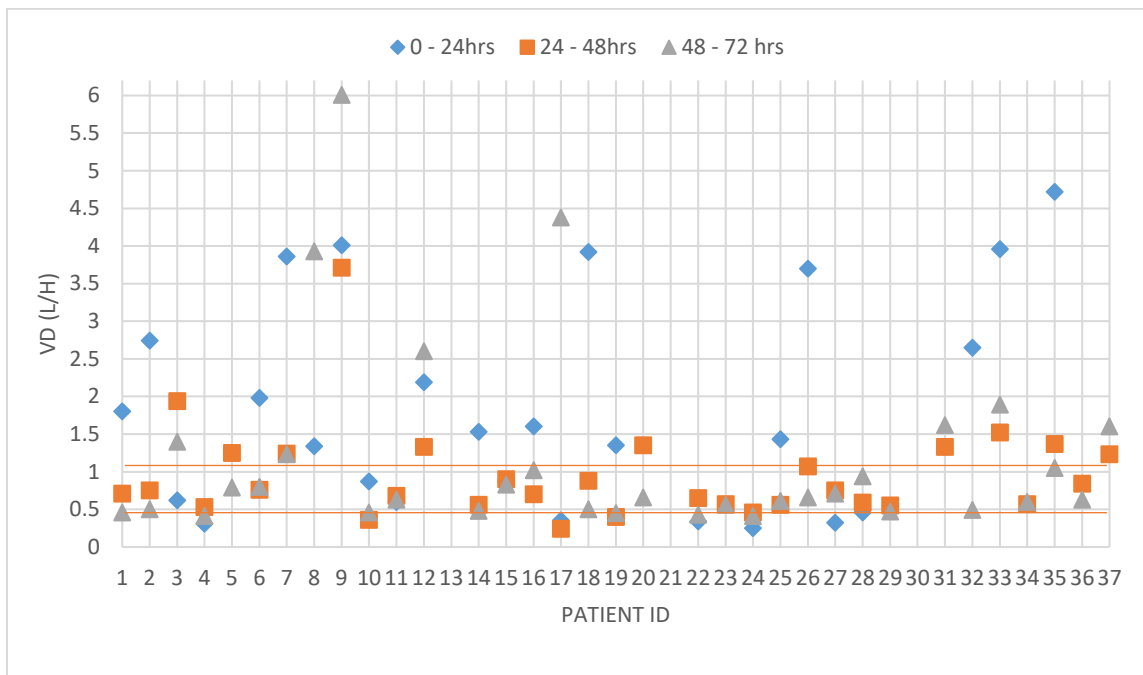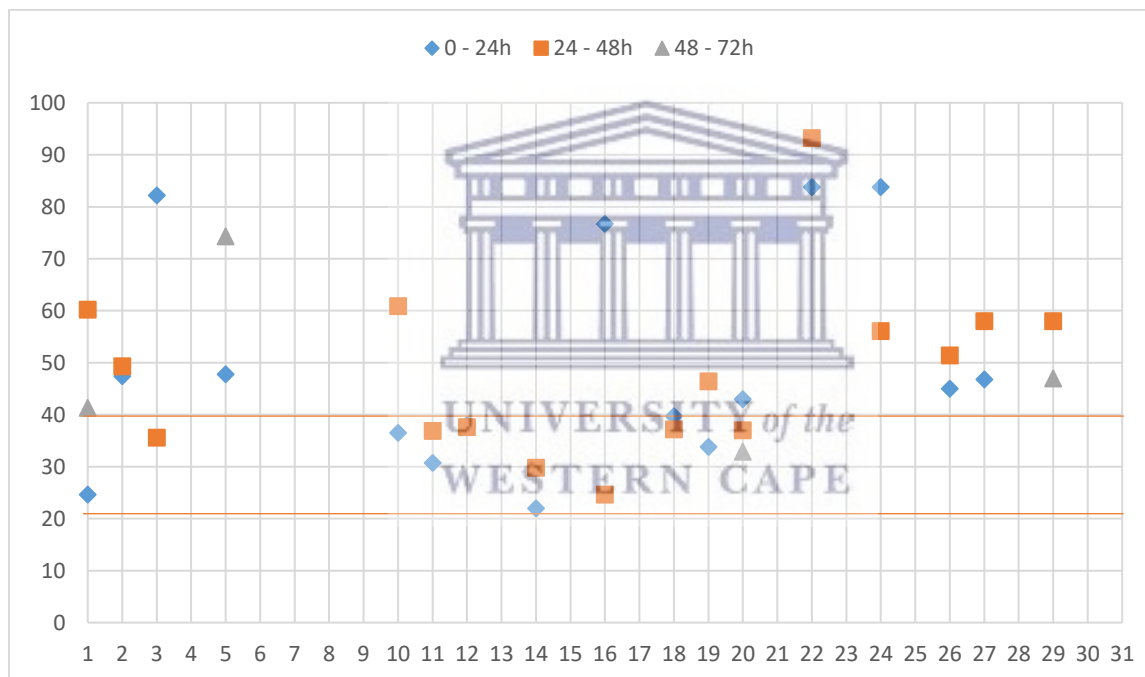

Figure 5-8 Rate of change of vancomycin peak concentration between 0 – 24 hrs, 24 – 48 hrs and 48 – 72 hrs of vancomycin treatment. The rate of change in vancomycin peak concentration for each patient is observed from the values during 0 – 24 hrs, 24 – 48 hrs and 48 – 72 hrs (a different colour denotes each period in the figure) of treatment. The normal range of peak concentration is between 20 and 40 µg/L, as denoted by the orange lines.

5.6 Vancomycin PK parameters variation during the three days of treatment

Vancomycin PK profiles in patients were assessed during the first 24 hours, 24-48 hours, and 48-72 hours. The coefficient of variation between the periods was lowest for CL (9%) and highest for Ke (82%). The CV was 50%, 50%, and 28% for the Vd, half-life, and AUC, respectively. Table 5.7 shows the number of patients with >30% coefficient of variation (the widely acceptable cuff-off for CV) in the vancomycin PK during the periods.

Table 5-7 Number of patients with CV within the acceptable limit (≤ 30%)

	Patients with CV ≤30%	Patients with CV >30%
CL	30	7
Vd	8	29
T1/2	11	26
Ke	3	34
AUC	17	20

5.7 Targeting trough concentration as a predictor of the area under the concentration-time curve over 0 – 72 hours/the minimum inhibitory concentration (AUC/MIC) of bacteria.

The bacterial MIC values were not measured in this study. A bacterial MIC of 1 µg/L was assumed for AUC/MIC determination. Thirty-one patients had vancomycin trough plasma concentration below 10mcg/mL. In five patients, the trough plasma concentration was 10 – 15 mcg/mL, and one had a plasma trough concentration between 15 -20 mcg/mL. Patients with higher vancomycin trough levels had significantly higher AUC 0-72 (r = 0.585, $N = 37$, $p = 0.000$). A vancomycin trough concentration of > 10 mcg/mL, AUC/MIC was adequate (400 – 600) in 12 of the 31 patients. Thirteen of the 31 patients had AUC/MIC < 400, and six of the 31 patients had AUC > 600.

In patients with vancomycin trough plasma concentration of 10 -15 mcg/mL, two patients had AUC/MIC of 400-600, and three had AUC/MIC > 600. The only patient with vancomycin plasma trough concentration between 15 -20 mcg/mL had an AUC/MIC of >600.

5.8 Optimization of vancomycin dose

Simulation of dose-response was theoretically performed using the PK values generated from this study. Monte Carlo's method generated theoretical concentrations in 1000 patients using a bootstrap method.

The AUC0-24 in the four groups receiving intermittent vancomycin infusion was 500 – 800 (μg * h / L). Vancomycin doses were selected based on the recommended guidelines (Rybak et al., 2020). They recommend a dose of 60 – 80 mg/kg/day in divided doses every 6 hours. The current recommended dose in RCWMCH is 60 mg/kg/day, given in divided doses every 6 hours (RCWMCH, 2012). Patients receiving a 60mg/kg/day dose with or without a loading dose attained an AUC >400 μg * h / L with a minimum plasma concentration below 15 mcg/mL (Table 5.8).

As expected, patients given 80mg/kg/day with or without a loading dose had higher AUC0-24 (738.4 and 720.5 μg * h / L, respectively). Trough levels were also higher in the two groups (16.6 and 17.7 mcg/mL).

Table 5-8 Simulation of 1000 patients receiving intermittent doses of vancomycin

Group	Mean				
	AUC_{0-24} (μg * h / L)	T_{max}(h)	C_{max}(mcg/mL)	T_{min}(h)	C_{min}(mcg/mL)
1	556.4	32.7	38.0	37.5	13.5
2	552.2	34.0	37.7	24.0	13.2
3	720.5	33.1	50.3	24.0	16.6
4	738.4	33.7	50.7	29.0	17.7

* Six hourly dosing of vancomycin over a 1 hr infusion with group 1: loading dose of 25mg/kg and daily maintenance dose of 60mg/kg; group 2: 60mg/kg/day; group 3: 80mg/kg; group 4: loading dose of 25mg/kg and daily maintenance of 80mg/kg

The AUC0-24 in patients receiving a continuous infusion of 60mg/kg/day after a loading dose of 25mg/kg was higher (613.6 μg * h / L) than in patients receiving 60mg/kg/day without a loading dose (553.4 μg * h / L) (Table 5.9). Patients on 80mg/kg/day with or without a loading dose had higher AUC_{0-24} values (792.4 μg * h / L and 721.9 μg * h / L, respectively). Trough concentration was above 20 mcg/mL in all groups.

Table 5-9 Simulation of 1000 patients receiving continuous infusion of vancomycin

Group	Mean				
	AUC_{0-24} (μg * h / L)	T_{max}(h)	C_{max}(mcg/mL)	T_{min}(h)	C_{min}(mcg/mL)
1	613.6	27.5	31.4	44.2	23.9
2	553.4	48.0	23.8	24.0	22.1
3	721.9	48.0	30.9	24.0	28.8
4	792.4	28.2	38.7	43.1	31.3

* Continuous vancomycin infusion with group 1: loading dose of 25mg/kg followed by a daily maintenance dose of 60mg/kg per day; group 2: 60mg/kg per day; group 3: 80mg/kg per day; group 4: loading dose of 25mg/kg followed by a daily maintenance dose of 80mg/kg

Time to reach maximum concentration was shorter in the children receiving either 60mg/kg/day (27.5 h) or 80 mg/kg/day (28 h) of vancomycin after a loading dose of 25mg/kg on the first day of treatment (27.5 h) compared to children in receiving 60mg/kg/day (48.0 h) or 80 mg/kg/day (48.0 h) of vancomycin without a loading dose.

5.9 Conclusion

A two-compartment model adequately describes vancomycin pharmacokinetics in critically ill children. In this group of children, wide variability exists in vancomycin PK, particularly in the volume of distribution. AUCs and vancomycin plasma concentrations are similar in patients receiving loading doses and patients not receiving loading doses. Changes in vancomycin CL and half-life from 0 – 24, 24 – 48, and 48 – 72 hours were insignificant. AUC changes from 0 - 24

hours was significantly lower than the AUC from 24 – 48 hours and 48 -72 hours (Z= -3.29, *p* = 0.001). The volume of distribution in the central compartment was higher on day 3 (48 – 72) hours compared to the other days (Z= -4.37, *p* = 0.000). Vancomycin trough and peak concentrations 24 – 48 hours and 48 – 72 hours did not significantly differ from the concentrations 0 – 24 hours of vancomycin therapy. Patients with higher vancomycin trough concentrations had significantly higher AUC 0-24 than children with lower trough concentrations (r = 0.585, *N* = 37, *p* = 0.000). More than half of the patients with trough levels < 10 mcg/mL attained AUC0-24 ≥400 6 μg * h / L for infections with bacterial MIC of 1 mcg/mL. Simulations of vancomycin doses show that patients on continuous infusions have a higher vancomycin plasma concentration than patients on intermittent infusions. Doses of 60mg/kg/day are adequate to maintain AUC0-24 of 400 – 600 mcg/mL. Patients may not benefit from higher doses and are a risk of vancomycin-related toxicities. Variability in vancomycin PK, especially the V_d, is high in critically ill children. The next chapter evaluated factors that may influence vancomycin PK.
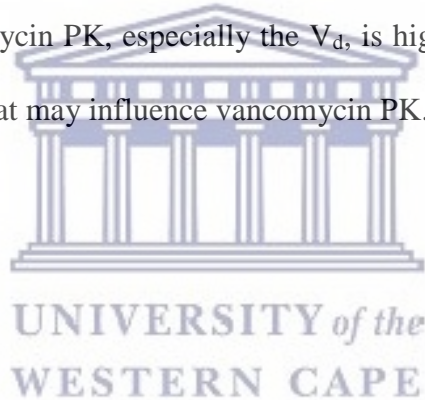
Chapter 6

Effect of Clinical and Pathophysiological Parameters on Vancomycin Pharmacokinetics in Critically Ill Children

6.0 Introduction

This chapter presents the effect of age, concomitant medication, organ function, fluid balance and fluid resuscitation, and severity of illness on vancomycin pharmacokinetics. The impact of changes in organ function, fluid balance, protein concentration, and severity of illness is also presented. The changes in PK parameters from 0 – 24 hours, 24 – 48 hours and 48 – 72 hours were assessed in individual patients. Vancomycin dose was increased in 3 patients during the 0 – 24 hour period and eight patients during the 24 – 48 period. Two patients had their vancomycin dose reduced in the 0 – 24 hour period and a patient during 24 – 48 hours. The increase or decrease in drug amount was included in the PK analysis.

6.1 Effect of age on vancomycin pharmacokinetics

Children younger than two years ($N = 18$) had higher vancomycin clearance (0.11 (0.05 – 0.22) L/h/kg) compared to children 2 -16 years old (0.09 (0.03 – 0.19) L/h/kg) (U=100.0, p=0.03). Vancomycin V_d in children < 2 years (0.73 (0.43 – 6.01) L/kg) was higher than the V_d in children 2 – 16 years old (0.63 (0.41 – 4.38) L/kg) (U=35.0, p=0.00) (Table 6.1). There was no significant difference in vancomycin T1/2, AUC, trough, and peak concentrations in children < 2 years and 2 – 16 years old. The half-life and AUC in children younger than two years was 2.6 (1.26 – 5.02) h and 434.68 (167.17 – 1762.47) mg * h / L compared to 3.22 (1.47 – 4.39) h (U= 129.0, p= 0.21) and 487.26 (127.39 – 1828.74) mg * h / L (U=153.0, p=0.60) in children 2 – 16 years old. Vancomycin peak and trough concentration in children younger than two years was 7.70 (4.50 – 10.92) µg/L and 47.0 (32.90 – 47.10) µg/L compared to 4.80 (2.50 – 19.70) µg/L (U=13.0, p=0.141) and 41.30 (34.50 – 69.30) µg/L (U= 4.0, p=0.827) in children 2 – 16 years old.

The age of children affected the CL and V_d of vancomycin. Younger children have a higher rate of vancomycin CL and higher vancomycin V_d.

Table 6-1 Vancomycin pharmacokinetics according to age in children.

Age (N)	CL* (L/h/kg)	Vd* (L/kg)	T½ (h)	Ke (h⁻¹)	AUC₀₋₂₄ (µg · h/L)	Trough (µg/L)	Peak (µg/L)
< 2 years (18)	0.11 (0.05 - 0.22)	0.73 (0.43 - 6.01)	2.60 (1.26 – 5.02)	0.27 (0.14 – 0.55)	434.68 (167.17 - 1762.47)	5.41 (0.01 - 13.70)	43.00 (21.90 - 90.70)
≥ 2 years (19)	0.09 (0.03 -0.19)	0.63 (0.41 - 4.38)	3.22 (1.47 - 8.79)	0.22 (0.08 - 0.47)	487.26 (127.39 - 1528.74)	5.41 (0.01 - 13.70)	43.00 (21.90 - 60.70)

CL*, $p = 0.03$; Vd*, $p = 0.00$; Results presented as median (range) values.

6.2 Effect of changes in body weight on vancomycin pharmacokinetics

Admission body weight and weight at 48 – 72 h of vancomycin treatment were available in 13 of the 37 children. Vancomycin PK was compared between children with weight loss > 5%, weight gain >5%, and no weight change (Table 6.2). Vancomycin CL and Ke were significantly lower in children with >5% loss of their admission body weight at 48 – 72 h (CL = 0.06 L/h/kg, U = 7.115, $p = 0.029$; Ke = 0.14 h-1, U = 7.438, $p = 0.024$) compared to children with no weight change (CL = 0.13 L/h/kg, Ke = 0.34 h-1) or increased body weight (CL = 0.18 L/h/kg, Ke = 0.46 h-1) (Table 6.2). In addition, Vancomycin half-life was significantly longer (T½= 4.92 h, U = 7.418, $p = 0.025$), and trough concentration (trough = 13.70 µg/L, U= 7.418, $p = 0.025$) was significantly higher in children with weight loss > 5% compared to children with no weight change (T½=2.05 h, trough = 3.41 µg/L) or weight gain > 5% (T½=1.55 h, trough = 1.90 µg/L) at 48 – 72 h compared to their admission weight. There was no significant difference in the vancomycin V_d, AUC, and peak concentration in children with weight loss > 5%, no weight change, and weight gain > 5% at 48 – 72 h compared to their admission weight.

Weight change affected vancomycin CL, T1/2, and trough concentration. Children with weight gain had a higher vancomycin CL. Fluid overload from resuscitation is a common reason for

weight increase in the ICU. These children are often given diuretics to reduce their total body water (TBW). TBW is a possible cause of increased vancomycin CL in these children, explaining the lower T½ and trough concentration.

Table 6-2 Vancomycin pharmacokinetics according to weight

PK Parameter	Weight loss > 5% (N = 3)	No weight change (N = 6)	Weight gain > 5% (N = 4)	Kruskal Wallis test*	df	P-value
CL (L/h/kg)	0.06 (0.04 - 0.08)	0.13 (0.11 - 0.19)	0.18 (0.10 - 0.20)	7.115	2	0.029
V_d (L/kg)	0.56 (0.51 - 1.05)	0.91 (0.46 - 3.93)	0.86 (0.43 - 6.01)	0.082	2	0.960
T½ (h)	4.92 (3.62 - 7.53)	2.05 (1.47 – 2.63)	1.55 (1.38 – 2.57)	7.418	2	0.025
Ke (h^{-1})	0.14 (0.09 - 0.19)	0.34 (0.26 - 0.47)	0.46 (0.27 - 0.50)	7.438	2	0.024
AUC0-24 (µg · h/L)	427.98 (426.55 – 1234.70)	311.55 (127.39 – 455.26)	369.31 (190.13 – 625.33)	3.989	2	0.136
Trough (µg/L)	13.70 (8.00 - 19.70)	3.41 (1.31 – 7.00)	1.90 (1.10 – 3.40)	7.418	2	0.025
Peak (µg/L)	50.65 (32.00 – 69.30)	44.35 (19.40 – 82.20)	45.15 (20.90 – 69.40)	0.001	2	1.000
CRCL (mL/min)	72.67 (71.11 – 89.11)	93.77 (49.28 – 145.00)	76.24 (61.42 – 80.82)	2.473	2	0.290

*Compares differences between the three groups; Results are presented as median (range) values.

6.3 Effect of changes in fluid balance on vancomycin pharmacokinetics

The children's fluid status changes during the 0 – 24 h, 24 – 48h, and 48 – 72 h periods are presented in sections 6.3.1, 6.3.2, and 6.3.3. The effect of the changes in their fluid balance on vancomycin PK is presented in section 6.3.4.

6.3.1 Fluid gain in critically-ill children

During 0 – 24 h of vancomycin treatment, 23 of the 37 children were fluid-positive with a 0.11 – 6.70 % increase in their body fluid. The fluid gain was < 1 (0.11 – 0.97) % in 3 patients, 1 – 2 (1.10 – 1.88) % in 6 patients, > 2 to 5 (2.25 – 4.88) % in 10 children and > 5 (6.19 – 6.70) % in 4 children. Five of the 23 children with fluid gain received a blood transfusion.

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By 24 – 48 h, 18 of the 23 children had 0.03 – 4.07% fluid loss. Four of the 23 children had fluid gain between 0.16 – 1.12 %. The fluid gain in one child was 63.64 %.

During the 48 – 72 h period, nine patients had 0.47 – 5.27 % fluid loss, and four had 0.83 – 3.11% fluid gain.

Fluid balance affects the V_d of vancomycin. Therefore, patients that are fluid-positive may have higher vancomycin V_d. The fluid status in children changed during the 0 – 24 h, 24 – 48 h, and 48 – 72 h of vancomycin treatment.

6.3.2 Fluid loss in critically ill children

During the 0 – 24 h of vancomycin treatment, 12 of the 37 children had a fluid-negative status with a 0.04 – 4.53 % decrease in their body fluid. The patients had presumed bacterial infections. They were admitted for toxic shock syndrome, pneumothorax, rhabdomyosarcoma, pancytopenia, traumatic brain injury, wound dehiscence, and cardiac arrest. The fluid gain was < 1 (0.04 – 0.47) % in 5 children, 1 – 2 (1.28 – 2.00) % in 4 children and > 2 to 5 (4.31 – 4.53) % in 3 children. Five of the 23 children with fluid gain received a blood transfusion. One patient received a blood transfusion just before vancomycin treatment commencement.

At 24 – 48 h, five children lost some of their body fluid. Three children lost 0.60 – 3.13% of their body fluid, and two had 12.47% and 16.70% fluid loss, respectively. Seven of the 12 children gained fluid. Four had fluid gain between 0.41 – 0.81 %, and three children had 3.60 %, 13.50% and 29.20 % each.

At 48 – 48 h, nine children had fluid loss. Four children had 0.25 – 0.83 % fluid loss, 2 had a fluid loss of 1.00% and 1.27 %, and three had 2.08 – 2.85 % fluid loss. Fluid loss may decrease the V_d of vancomycin.

6.3.3 Children with no net fluid change

No significant net fluid change was observed in the two patients with no net fluid change. One of the patients had an abdominal mass, severe acute malnutrition, and presumed bacterial infection. The other patient had a ventricular septal defect. The two patients had normal renal function and received no blood transfusion.

6.3.4 The effect of fluid change on vancomycin PK

Vancomycin V_d in children with no fluid change, fluid gain, and fluid loss was not significantly different during the $0 - 24$ h, $24 - 48$ h, and $48 - 72$h of vancomycin treatment ($p > 0.05$).

Three patients with pleural effusion, ascites, hydrocephalus, and subdural hematoma at either $0 - 24$ h or day $24 - 48$ h of treatment had vancomycin V_d of $1.02 - 4.38$ L/kg. Vancomycin V_d in 4 children with fluid accumulation around organs was lower ($0.67 - 4.03$ L/kg) than in children without fluid accumulation around or in any organ ($0.06 - 1.24$ L/kg) at $48 - 72$ h. However, this difference was not significant ($p > 0.05$).

Changes in fluid balance affected vancomycin Vd and AUC. In children with > 5 % fluid gain, vancomycin V_d was higher at $24 - 48$ h compared to $0 - 24$ h (Wilcoxon signed ranked Z= -2.476, p=0.013). There was no significant effect of change in fluid status on vancomycin Vd at $48 - 72$ h ($p > 0.05$). Vancomycin AUC was higher in children with fluid loss < 2 % at $24 - 48$ h (Wilcoxon signed ranked Z= -2.286, p=0.022) and $48 - 72$ h (Wilcoxon signed ranked Z= -2.567, p=0.010). Other PK parameters were not affected by a change in fluid status. Significant variations in vancomycin AUCs were observed within and between periods.

Table 6-3 Effect of fluid balance on vancomycin pharmacokinetics

	Fluid change (N)	CL (L/h/kg)	V_d (L/Kg)	T½ (h)	Ke (h^{-1})	AUC (µg · h/L)	Trough (µg/L)	Peak (µg/L)
0 - 24 hours	2-5% Negative (2)	0.04 (0.03-0.05)	2.36 (0.08 – 3.02)	13.57 (1.76 - 25.38)	0.21 (0.03-0.39)	531.1 (145.02 - 917.18)		64.3 (64.3-64.3)
	0.1- 2% Negative (5)	0.17 (0.08-0.20)	1.53 (0.31 - 1.48)	2.39 (1.36-6.56)	0.31 (0.11-0.91)	202.7 (147.31-271.92)	7.7 (3.0-10.9)	24.5 (20.9-82.2)
	0.1-2.0% Positive (7)	0.13 (0.07-0.18)	0.60 (0.32 – 1.60)	1.31 (1.00-2.91)	0.690 (0.24-2.40)	221.41 (89.48-538.68)	4.2 (2.4-6.4)	32.8 (18.6-46.2)
	2-5% Positive (6)	0.12 (0.05-0.19)	1.15 (0.05 – 4.01)	2.08 (1.11-19.21)	0.51 (0.04-1.31)	156.71 (139.57-686.31)	8.3 (2.0-13.9)	37.1 (21.7-83.8)
	> 5% Positive (4)	0.11 (0.06-0.20)	3.30 (1.80 – 3.92)	4.71 (1.95-6.56)	0.16 (0.11-0.36)	286.47 (72.07-564.62)	6.1 (3.8-8.3)	47.4 (19.1-76.7)
24 - 48 hours	2-5% Negative (%change)* (5)	0.17 (0.03-0.18) (0.76)	0.58 (0.24 – 1.94) (-3.07)	4.16 (1.76-6.56) (-2.26)	0.91 (0.11-2.40) (0.77)	202.65 (147.31-917.18) (-1.62)	9.1 (2.4-12.0)	64.3 (18.6-82.2) (0.00)
	1- 2% Negative (%change) (7)	0.08 (0.05-0.20) (-0.53)	0.56 (0.36 -1.52) (-0.63)	2.01 (1.11-19.21) (-0.16)	0.43 (0.04-0.91) (0.39)	171.43 (153.89-686'31) (-0.15)	4.6 (3.6-13.9) (-0.40)	37.1 (20.9-83.8) (0.51)
	No change (2)	0.06 (0.05-0.07)	1.12 (0.88 -1.37)	14.33 (3.27-25.38)	0.12 (0.03-0.21)	276.64 (145.02-408.26)		76.7 (76.7-76.7)
	0.1-2.0% Positive (%change) (6)	0.14 (0.09-0.19) (0.08)	0.90 (0.55 – 1.35) (0.50)	2.58 (1.00-6.15) (0.97)	0.48 (0.11-1.08) (-0.30)	184.85 (72.07 - 538.68) (-0.17)	5.9 (3.0- 8.3) (0.40)	44.1 (41.9-46.2) (0.34)
	2.0 - 5 Positive (%change) (3)	0.06 (0.05-0.13) (-0.50)	0.57 (0.40 - 0.75) (-0.50)	3.09 (2.20-6.56) (0.49)	0.22 (0.11-0.31) (-0.57)	564.62 (271.92 - 689.21) (2.60)	6.8 (5.5-8.1) (-0.18)	47.4 (24.5-60.1) (0.28)
	> 5% Positive (%change)* (3)	0.19 (0.07-0.20) (0.73)	0.71 (0.65 – 3.71) (-0.78)	1.84 (1.74 - 1.95) (-0.61)	0.40 (0.36-0.76) (1.50)	164.67 (139.57-406.85) (-0.43)	2.9 (2.0 - 3.8) (-0.52)	
48 - 72 hours	2-5% Negative (%change)** (2)	0.18 (0.17-0.19) (0.06)	0.47 (0.43 - 0.50) (-0.19)	1.79 (1.00 - 2.58) (-0.57)	0.48 (0.27-0.69) (-0.47)	151.73 (89.48-213.97) (-0.25)	4.2 (3.0 - 5.4) (-0.54)	
	1- 2% Negative (%change)** (4)	0.13 (0.08-0.17) (0.63)	0.63 (0.63 – 1.89) (0.13)	2.41 (2.41-2.41) (0.20)	0.99 (0.29-1.31) (1.30)	234.78 (147.31-538.68) (0.37)	8.6 (6.2-10.9) (0.87)	41.9 (37.1-82.2)
	No change (%change)** (11)	0.14 (0.03-0.20) (1.33)	0.56 (0.41 - 1.62) (-0.50)	2.08 (1.36 - 25.38) (-0.85)	0.36 (0.03-2.40) (2.00)	171.43 (72.07-917.18) (-0.38)	4.2 (2.0-12.0)	24.5 (18.6-76.7) (-0.68)
	0.1-2.0% Positive (%change)** (5)	0.07 (0.05-0.16) (-0.50)	0.73 (0.41 – 6.01) (-0.19)	3.00 (1.11 - 8.77) (0.16)	0.24 (0.08-0.91) (-0.50)	473.59 (153.89-689.21) (1.56)	5.5 (3.3-9.0) (-0.07)	60.1 (42.5-83.8) (0.36)

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	2.0 - 5 Positive (%change)** (1)	0.13 (0.13-0.13) (1.17)	0.71 (0.47 – 2.87) (0.25)	1.01 (1.01-1.01) (-0.67)	0.69 (0.69-0.69) (2.14)	319.05 (319.05-319.05) (-0.43)	6.40 (6.4-6.4) (-0.06)	
	> 5% Positive (%change)** (2)	0.06 (0.06-0.07) (-0.68)	1.72 (0.83 – 2.60) (1.42)	6.56 (6.56 - 6.56) (2.57)	0.44 (0.11-0.76) (0.10)	485.74 (406.85-564.62) (1.95)		35.5 (23.6-47.4)

*% change from period 0 – 24 h to 24 – 48 h; **% change from period 24 – 48 h to 48 – 72 h.

Vancomycin V_d and AUC were affected by a change in fluid balance in critically ill children. Increased body fluid will increase the space into which vancomycin distributes, leading to increased V_d. Results are presented in Table 6.3 as median (range) values.

6.4 The effect of blood or platelet transfusion on vancomycin pharmacokinetics

Children that received blood or platelet transfusion 1 – 3 days before the initiation of vancomycin therapy had similar vancomycin V_d to children that did not receive blood or platelet transfusion (0.80 (0.41 – 6.01) L/kg and 0.63 (0.41 – 2.87) L/kg) (U = 106.5, p = .335). Children that received fluid resuscitation during vancomycin treatment (N = 4) had V_d between 1.89 – 6.01 L/kg. The high V_d was most likely due to the positive fluid status of the children rather than the fluid resuscitation received.
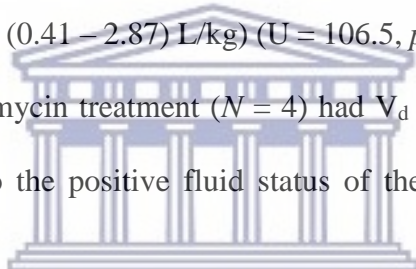
6.5 The effect of changes in renal function on vancomycin pharmacokinetics

Creatinine clearance was used as a marker for renal function. Vancomycin half-life, AUC, and trough concentrations were significantly higher (p < 0.05) in children with low creatinine clearance. Sixteen children had their vancomycin dose adjusted. However, there was no significant difference in the median dose given to patients in each group. Increased AUC that was not in keeping with the decrease in renal function was observed. Dose adjustments were included in the PK calculations.

The effect of renal function on vancomycin PK was evaluated in 35 children using the Paediatric Risk, Injury, Failure, Loss, End Stage Renal Disease (pRIFLE) criteria (Soler et al., 2013). Patients

were classified as having a severe decrease in CrCl (1.5-fold or > 50% decrease), moderate decrease (1.25 – 1.5 fold or 25-50% decrease), mild decrease (0.01 – 1.25 fold or > 25% decrease), normal (within the normal limit of range for age group), mild increase (0.01 – 1.25 fold or > 25% increase), moderate increase (1.25 – 1.5 fold or 25-50% increase) and severe increase (> 1.5 fold or > 50% increase).

Creatinine CL and vancomycin PK were available in 24 of the 37 patients at 0 – 24 h, 30 of the 37 children at 24 – 48 h, and 35 of the 37 children at 48 – 72 h. Vancomycin PK was not significantly different between the groups at 0 – 24 h (Table 6.4). At 24 – 48 h, vancomycin CL significantly decreased with reduced renal function (Kruskal-Wallis H = 12.05, df = 5, p = 0.035). At 48 – 72 h, vancomycin CL significantly decreased with reduced renal function (Kruskal-Wallis H = 13.15, df = 5, p = 0.022). There was no significant difference in the other vancomycin PK parameters at 0 – 24, 24 – 48 h, and 48 – 72 h.

Two children had a decrease in renal function at 24 – 48 h compared to 0 – 24 h. In one child, the renal function decreased by > 25%, and renal function in the second child decreased by > 50%. Conversely, renal function increased in three children. Two children had their renal function increase by >25 %, and one had a 50 % increase in renal function. The change in renal function at 24 – 48 h did not significantly affect vancomycin CL (Wilcoxon signed ranked Z= -1.486, p=0.137).

Table 6-4 The Effect of renal function on vancomycin PK on day 1, day 2 and day3 of vancomycin treatment

	CrCl (N)	CL (L/h/kg)	Vd (L/Kg)	T½ (h)	Ke (h-1)	AUC (µg · h/L)	Trough (µg/L)	Peak (µg/L)
0 - 24 hours	Severe increase (2)	0.13 (0.60-0.20)	2.27 (1.80 - 2.74)	4.26 (1.95-6.56)	0.24 (0.11-0.36)	364.65 (164.67 - 564.62)	3.80 (3.80 – 3.80)	33.3 (19.10 - 47.40)
	Mild increase (4)	0.16 (0.13-0.17)	0.67 (0.35 - 1.35)	1.66 (1.11-2.20)	0.97 (0.31-2.40)	192.70 (72.07 - 917.18)	4.6 (2.40 - 8.10)	21.56 (18.60 - 24.50)
	No change (16)	0.10 (0.03-0.20)	1.56 (0.25 - 4.72)	2.75 (1.00-25.4)	0.40 (0.03-1.08)	362.84 (139.57 - 917.18)	4.8 (2.00 - 9.00)	53.15 (20.90 - 83.80)
	Mild decrease (1)	0.10 (0.10-0.10)	1.60 (1.60 – 1.60)	2.91 (2.91-2.91)	0.24 (0.24-0.24)	155.73 (155.73 - 155.73)	3.30 (3.30 – 3.30)	
	Severe decrease (1)	0.05 (0.05-0.05)	3.96 (3.96 - 3.96)	19.21 (19.2-19.2)	0.04 (0.04-0.04)	159.52 (159.52 - 159.52)	10.90 (10.90 - 10.90)	21.70 (21.70 - 21.70)
24 - 48 hours	Severe increase (%change)* (2)	0.16 (0.12-0.20) (0.23)	0.73 (0.71 - 0.75) (-0.68)	1.79 (1.47-2.10) (-0.58)	1.70 (1.58-1.82) (6.08)	350.72 (243.52 - 457.91) (-0.04)	6.75 (5.10 - 8.40) (0.78)	49.3 (49.30 - 49.30)
	Mild increase (%change)* (4)	0.15 (0.12-0.16) (-0.06)	0.39 (0.24 - 0.59) (-0.42)	1.60 (1.48-3.22) (-0.04)	1.03 (0.50-1.88) (0.06)	463.21 (350.39 - 483.14) (1.40)	2.85 (2.40 - 8.70) (-0.38)	42.2 (42.2 - 42.2) (0.96)
	No change (%change)* (18)	0.09 (0.03-0.24) (-0.10)	0.97 (0.36 - 3.71) (-0.38)	2.9 (1.26-8.79) (0.05)	1.31 (0.08-7.30) (2.28)	451.91 (58.10 - 750.66) (0.25)	9 (2.40 - 14.60) (0.88)	51.4 (32.00 - 97.20) (-0.03)
	Mild decrease (%change)* (2)	0.09 (0.07-0.11) (-0.10)	0.70 (0.56 - 0.84) -(0.56)	3.26 (2.51-4.01) (0.12)	0.51 (0.10-0.92) (1.13)	509.71 (484.10 - 535.32) (2.27)	7.05 (6.40 - 7.70) 1.14	
	Moderate decrease (%change)* (2)	0.06 (0.05-0.06)	0.56 (0.55 - 0.57)	4.92 (4.06-6.11)	0.49 (0.23-0.76)	800.48 (459.33 - 1141.6)	9.7 (6.10 - 12.00)	58.0 (58.0 - 58.0)
	Severe decrease (%change)* (2)	0.04 (0.04 -0.04) (-0.20)	1.04 (0.57 - 1.52) (-0.74)	5.46 (5.02-7.53) (-0.72)	0.47 (0.14-0.80) (10.75)	350.73 (215.65 - 485.81) (1.20)	9.6 (9.6 - 9.6) (-0.12)	
48 - 72 hours	Severe increase (%change)** (1)	0.13 (0.13-0.13) (-0.19)	0.50 (0.50 - 0.50) (-0.32)	3.90 (3.9 – 3.90) (1.18)	0.18 (0.18-0.18) (-0.89)	416.00 (416.00 - 416.00) (0.19)		
	Moderate increase (%change)** (1)	0.19 (0.19-0.19)	0.46 (0.46 - 0.46)	1.83 (1.8 – 1.83)	0.38 (0.38-0.38)	272.94 (272.94 - 408.16)	4.20 (4.20 - 4.20)	41.3 (41.3 - 41.3)
	Mild increase (%change)** (4)	0.17 (0.09-0.18) (0.13)	0.7 (0.45 - 4.38) (0.79)	1.33 (1.06-1.58) (-0.17)	0.59 (0.44-1.42) (-0.43)	392.71 (356.75 - 408.16) (-0.15)	7.35 (5.90 - 8.80) (1.58)	

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No change (%change)** (22)	0.10 (0.03-0.22) (0.11)	0.75 (0.41 - 6.01) (-0.23)	3.41 (1.08-13.9) (0.18)	0.18 (0.05-0.84) (-0.86)	414.74 (158.50 -1528.6) (-0.08)	4.95 (2.50 - 10.90) (-0.45)	34.5 (32.90 - 47.10) (-0.33)
Mild decrease (%change)** (2)	0.08 (0.05-0.11) (-0.11)	0.63 (0.61 - 0.65) (-0.10)	4.50 (3.30-5.71) (0.38)	0.16 (0.12-0.21) (-0.69)	938.31 (467.44 - 1409.2) (0.84)	9 .00 (9.00 - 9.00)	
Moderate decrease (%change)** (2)	0.07 (0.06-0.07) (0.17)	0.52 (0.47 - 0.56) (-0.07)	4.79 (3.45-6.12) (-0.03)	0.16 (0.11-0.20) (-0.67)	632.35 (369.36 - 895.34) (-0.21)		47.0 (47.0 - 47.0) (-0.19)
Severe decrease (%change)** (3)	0.05 (0.04-0.05) (0.25)	0.60 (0.51 - 1.89) (-0.42)	3.55 (2.95-16.8) (-0.35)	0.20 (0.04-0.23) (-0.57)	560.82 (377.07 -1217.3) (0.60)	13.70 (7.7 - 19.70) (0.43)	69.30 (69.30 - 69.30)

*Results presented as median (range) values; No change, within the normal range according to age (Table 3.2); Mild increase or decrease, < 25% increase in the upper limit of the normal range (ULN) or decrease in the lower limit of the normal range (LLN); Moderate, 25 – 50% increase in ULN or decrease in LLN; Severe, >50% increase in ULN or decrease in LLN. *% change from period 0 – 24 h to 24 – 48 h; **% change from period 24 – 48 h to 48 – 72 h.*

Three children had decreased renal function at 48 – 72 h compared to 24 – 48 h. Renal function was reduced by > 25 % in 2 children and > 50% in one child. Conversely, renal function increased in 4 children; 3 children had a > 25 % increase in their renal function, and one child had > 50 % increase in their renal function. The change in renal function did not affect vancomycin CL (Wilcoxon signed ranked Z= -1.176, *p*=0.240).

Vancomycin CL reduced with decreased renal function. Although there were changes in renal function in children during vancomycin therapy, most changes in renal function were < 25%. Changes in renal function did not affect vancomycin CL because CrCl was consistently lower or higher than the lower limit or upper limit of the normal range during vancomycin treatment.

6.6 The effect of changes in the Liver function on vancomycin pharmacokinetics

Liver function was evaluated by plasma ALT and AST concentration in children.

6.6.1 Effect of changes in Alanine aminotransferase (ALT) concentration

The effect of ALT concentration was evaluated in 21 of the 37 patients. Vancomycin PK was assessed in 13 children at 0 – 24 h, 16 children at 24 – 48 h, and 21 children at 48 – 72 h. Vancomycin PK did not significantly differ between patients with mild, moderate, and severe increases in their ALT concentration at 0 – 24 h, 24 – 48 h, and 48 – 72 h ($P > 0.05$).

Four patients had ALT >5 – 10 –fold ULN at 0 – 24 h of vancomycin treatment. The ALT concentration remained the same in the patients at 24 – 48 h and 48 – 72 h. Vancomycin PK in the children at 0 – 24 h, 24 – 48 h, and 48 – 72 h did not change significantly ($P > 0.05$). Liver function measured by ALT did not affect vancomycin PK in critically ill children. Vancomycin PK was not affected by changes in ALT concentration during the study period. This may be because vancomycin is primarily eliminated renally.

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Table 6-5 Effect of Alanine aminotransferase on vancomycin pharmacokinetics

	ALT (N)	CL (L/h/kg)	V$_d$ (L/Kg)	T½ (h)	Ke (h-1)	AUC (µg · h/L)	Trough (µg/L)	Peak (µg/L)
0 - 24 hours	Normal (5)	0.17 (0.05-0.20)	1.80 (0.25 - 4.01)	3.09 (1.76 - 6.15)	0.31 (0.11 - 0.91)	687.76 (72.07 - 917.18)	8.30 (5.50 - 12.00)	64.30 (60.10 - 83.80)
	Mild Increase (4)	0.10 (0.07 - 0.15)	2.56 (0.32 - 3.85)	4.38 (2.20 - 6.56)	0.31 (0.11 - 1.08)	271.92 (202.65 - 538.68)	8.10 (7.70 - 9.10)	33.2 (24.50 - 41.90)
	Moderate Increase (2)	0.04 (0.03 - 0.05)	0.31 (0.28 - 3.96)	19.21 (19.2-19.2)	0.04 (0.04 - 0.04)	159.52 (159.52 - 159.52)	12.40 (10.90 - 13.90)	21.70 (21.70 - 21.70)
	Severe Increase (2)	0.12 (0.06 - 0.17)	1.68 (0.62 - 2.74)	2.41 (1.11 - 8.77)	0.29 (0.08 - 0.62)	213.97 (153.89 - 473.59)	4.20 (3.00 - 9.00)	39.80 (19.10 - 46.20)
24 - 48 hours	Normal (%change)* (5)	0.05 (0.03 - 0.15) (-0.71)	0.71 (0.46 - 3.71) (-0.61)	3.09 (1.76 - 6.15) (0.00)	0.31 (0.11 - 0.91) (0.00)	687.76 (72.07 - 917.18) (0.00)	8.30 (5.50 - 12.00) (0.00)	64.30 (60.10 - 83.80) (0.00)
	Mild increase (%change)* (7)	0.09 (0.08 - 0.13) (-0.10)	1.07 (0.57 - 1.33) (-0.58)	4.38 (2.20 - 6.56) (0.00)	0.31 (0.11 - 1.08) (0.00)	271.92 (202.65 - 538.68) (0.00)	8.10 (7.70 - 9.10) (0.00)	33.20 (24.50 - 41.90) (0.00)
	Moderate increase (%change)* (2)	0.16 (0.07 - 0.20) (3.00)	1.03 (0.53 - 1.52) (2.32)	1.95 (1.11 - 8.77) (-0.90)	0.36 (0.08 - 0.62) (8.00)	164.67 (153.89 - 473.59) (0.03)	6.80 (3.80 - 10.90) (-0.45)	30.80 (19.10 - 42.50) (0.42)
	Severe increase (%change)* (2)	0.08 (0.05 - 0.19) (-0.33)	1.34 (0.75 - 1.94) (-0.20)	2.58 (2.41-19.21) (0.07)	0.27 (0.04 - 0.29) (-0.07)	213.97 (159.52 - 318.84) (0.00)	8.45 (3.00 - 13.90) (1.01)	37.1 (21.70 - 46.20) (-0.07)
48 - 72 hours	Normal (%change)** (7)	0.05 (0.03 - 0.15) (0.00)	0.49 (0.41 - 1.23) (-0.31)	3.09 (1.76 – 6.15) (0.00)	0.30 (0.11-0.91) (-0.03)	687.76 (72.07 – 917.18) (0.00)	8.30 (5.50-12.00) (0.00)	64.30 (60.10-83.80) (0.00)
	Mild increase (%change)** (10)	0.11 (0.08 - 0.20) (0.22)	1.06 (0.45 - 1.62) (-0.01)	2.20 (1.95 - 6.56) (-0.50)	0.34 (0.11 - 1.08) (0.10)	237.29 (164.67-538.68) (-0.13)	7.90 (3.80 - 9.10) (-0.02)	24.50 (19.10 - 41.90) (-0.26)
	Moderate increase (%change)** (2)	0.08 (0.07 - 0.16) (-0.50)	2.25 (1.89 - 2.60) (1.18)	2.41 (1.11 - 8.77) (0.24)	0.29 (0.08 - 0.62) (-0.19)	318.84 (153.89-473.59) (0.94)	9.00 (4.60 - 10.90) (0.32)	39.80 (37.10 - 42.50) (0.29)

*Results presented as median (range) values; No change, within normal range according to age (Table 3.2); Mild increase, < 5 times increase in the upper limit of the normal range (ULN); Moderate, 5 – 15 times increase in ULN; Severe, > 15 times increase in ULN. . *% change from period 0 – 24 h to 24 – 48 h; **% change from period 24 – 48 h to 48 – 72 h.*

6.6.2 Changes in aspartate aminotransferase (AST) concentration

Twenty-one children had AST concentrations during the study period. Vancomycin PK did not differ significantly between children with normal AST concentration, with mild, moderate, and severe increases in their AST concentration at 0 – 24 h ($N = 11$), 24 – 48 h ($N = 15$), and 48 – 72 h ($N = 21$).

Changes in AST concentration at 24 – 48 h of vancomycin treatment were observed in 5 of the 11 children with AST concentrations at 0 – 24 h. Changes in AST concentration at 24 – 48 h were observed in 3 of these children at 48 – 72h. AST concentration increased by >1.2 –fold ULN in one child, >5 – 10 in 4 children at 24 – 48 h. The AST concentration remained the same in 3 patients and reduced by > 1.2 –fold ULN in one child at 48 – 72 h. The change in vancomycin PK at 0 – 24 h, 24 – 48 h, and 48 – 72 h was not significantly affected by a change in AST concentration.

Liver function measured by AST did not affect vancomycin PK in critically ill children. Vancomycin PK was not affected by changes in AST concentration during the study period. This may be because vancomycin is primarily eliminated renally.
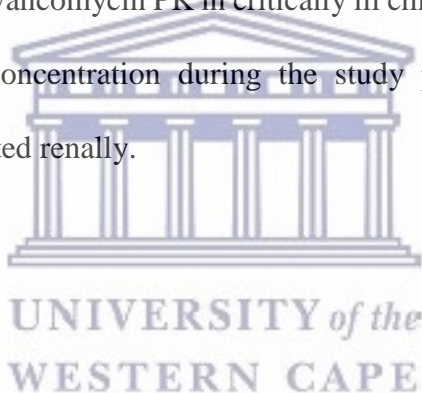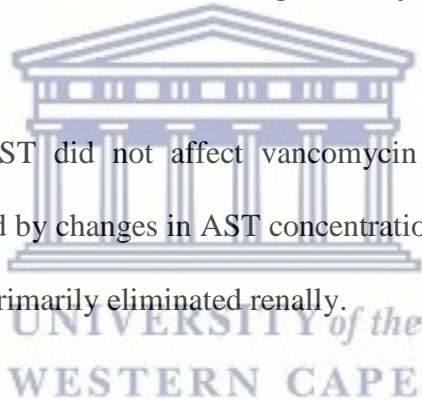
Table 6-6 Effect of aspartate aminotransferase on vancomycin pharmacokinetics

	AST (N)	CL (L/h/kg)	V$_d$ (L/Kg)	T½ (h)	Ke (h-1)	AUC (µg · h/L)	Trough (µg/L)	Peak (µg/L)
0 - 24 hours	Normal (6)	0.13 (0.05 - 0.17)	2.13 (0.32 - 4.01)	3.09 (1.76 - 6.56)	0.27 (0.11-1.08)	405.30 (72.07 - 917.18)	8.30 (5.50-12.0)	51.00 (24.50-64.30)
	Mild increase (2)	0.06 (0.05 - 0.07)	0.25 (0.25 - 3.70)	2.18 (1.11 - 25.38)	0.33 (0.03-0.62)	159.28 (145.02-318.84)	4.20 (3.80 - 4.6)	28.10 (19.10-37.10)
	Severe Increase (3)	0.11 (0.05 – 0.17)	2.74 (0.62 - 3.96)	13.99 (8.77 - 19.21)	0.06 (0.04-0.08)	316.56 (159.52-473.59)	11.45 (9.00 -13.9)	42.50 (21.70-46.20)
24 - 48 hours	Normal (%change)* (9)	0.09 (0.03 - 0.20) (-0.31)	0.84 (0.57 - 3.71) (-0.61)	2.65 (1.11 - 25.38) (-0.14)	0.31 (0.03-1.08) (0.15)	202.65 (72.07-917.18) (-0.50)	8.10 (3.80 - 12.0) (-0.02)	41.90 (19.10-64.30) (-0.18)
	Mild increase (%change)* (4)	0.08 (0.07 - 0.08) (0.33)	1.20 (0.46 - 1.94) (3.80)	5.59 (2.41 - 8.77) (1.56)	0.18 (0.08-0.29) (-0.45)	396.22 (318.84-473.59) (1.49)	9.00 (9.00 - 9.0) (1.14)	39.80 (37.10-42.50) (0.42)
	Severe Increase (%change)* (2)	0.05 (0.05 - 0.05) (-0.55)	1.13 (0.75 - 1.52) (-0.59)	19.21 (19.21-19.21) (0.37)	0.04 (0.04-0.04) (-0.33)	159.52 (159.52-159.52) (-0.50)	13.90 (13.9-13.9) (0.21)	33.95 (21.70-46.20) (-0.20)
48 - 72 hours	Normal (%change)** (7)	0.17 (0.05 - 0.20) (0.89)	0.66 (0.41 - 6.01) (-0.21)	5.64 (0.49 – 8.33) (1.13)	0.12 (0.08-1.42) (-0.61)	356.75 (254.95-1281.4) (0.76)	6.50 (4.20 -10.4) (-0.20)	58.20 (47.10-41.30) (0.39)
	Mild increase (%change)** (7)	0.08 (0.04 - 0.17) (0.00)	1.02 (0.51 - 1.89) (-0.15)	4.88 (1.14 – 16.8) (-0.13)	0.19 (0.04-0.14) (0.06)	604.51 (184.18-1528.6) (0.53)	9.90 (7.7 - 19.7) (0.10)	
	Moderate increase (5)	0.09 (0.03 - 0.13)	0.52 (0.41 - 4.10)	3.41 (0.82 - 9.44)	0.20 (0.07 -0.84)	442.86 (211.95-1438.0)	4.50 (3.60-5.4)	
	Severe Increase (%change)** (2)	0.11 (0.08 - 0.13) (1.20)	0.61 (0.50 - 0.71) (-0.46)	4.65 (1.25-8.05) (-0.76)	0.37 (0.18-0.55) (8.25)	476.67 (416.00-537.34) (1.99)		

*Results presented as median (range) values; No change, within the normal range according to age (Table 3.2); Mild increase, < 5 times increase in the upper limit of the normal range (ULN); Moderate, 5 – 15 times increase in ULN; Severe, > 15 times increase in ULN. *% change from period 0 – 24 h to 24 – 48 h; **% change from period 24 – 48 h to 48 – 72 h.*

6.7 Effect of changes in the mean arterial blood pressure on vancomycin pharmacokinetics

Vancomycin PK parameters and MABP values were available for 31 children during the study period. The mean arterial blood pressure (MABP) was normal in 10 of the 22 children with MABP values at 0 – 24 h. Eight of the 22 children had lower than the normal limit range, and 4 of the 22 children had MABP higher than the upper limit of the normal range at 0 – 24 h. Vancomycin

AUC0-24 was significantly lower in children with high MABP (median = 309.01 µg · h/L) compared to children with normal MABP (median = 517.91 µg · h/L) and children with low MABP (median = 386.96 µg · h/L) (Kruskal-Wallis H = 6.386, df = 2, p = 0.041). Other vancomycin PK was not significantly affected by MABP at 0 – 24 h. Vancomycin PK was unaffected by MABP at 24 – 48 h and 48 – 72 h.

At 24 – 48 h, there was no change in MABP in 9 of the ten children with normal MABP at 0 – 24 h, and one child had high MABP. Two patients with low MABP at 0 – 24 h had MABP within the normal range. One child with low MABP at 0 – 24 had high MABP.

At 48 – 72 h, two children with low MABP at 24 – 48 h had MABP within the normal range. One child with low MABP had high MABP. Increased mean arterial blood pressure was associated with lower vancomycin trough plasma concentration (r = -0.517, p = 0.01). There was no correlation between MABP and CrCl on treatment at 0 – 24 h (r = 0.247, p = 0.30), 24 – 48 h (r = 0.263, p = 0.18) and 48 – 72 h (r = 0.367, p = 0.11).

Patients with high MABP had reduced vancomycin AUC0-24 and reduced vancomycin trough concentration. High MABP may increase tissue perfusion reducing vancomycin plasma concentration.

Table 6-7 Changes in Mean arterial blood pressure from day 1 to day 3

	MABP (N)	CL (L/h/kg)	V_d (L/Kg)	T½ (h)	Ke (h-1)	AUC (µg · h/L)	Trough (µg/L)	Peak (µg/L)
0 - 24 hours	Moderate decrease (1)	0.05 (0.05-0.05)	4.72 (4.72-4.72)	25.38 (25.38-25.38)	0.03 (0.03-0.03)	145.02 (145.02-145.02)		
	Mild decrease (7)	0.16 (0.08-0.20)	1.15 (0.26-1.98)	2.41 (1.11-6.56)	0.36 (0.11-1.31)	155.73 (147.31-318.84)	5.40 (3.30-9.10)	37.10 (19.10-82.20).
	Normal (10)	0.079 (0.03-0.20)	1.44 (0.31-3.96)	2.42 (1.01-19.21)	0.41 (0.04-1.08)	362.95 (72.07-917.18)	7.35 (3.60-13.90)	42.20 (20.90-64.30)
	Mild increase (3)	0.17 (0.05-0.18)	0.35 (0.25-0.87)	1.00 (1.00-1.00)	0.91 (0.69-2,40)	221.41 (89.48-686.31)	3.90 (2.40-5.40)	51.20 (18.60-83.80)
	Moderate increase (1)	0.06 (0.06-0.06)	2.74 (2.74-2.74)	6.56 (6.56-6.56)	0.11 (0.11-0.11)	564.62 (564.62-564.62)		47.40 (47.40-47.40)
24 - 48 hours	Moderate decrease (%change)* (1)	0.08 (0.08-0.08) (0.60)	1.37 (1.37-1.37) (-0.71)	3.26 (2.90-3.62) (-0.87)	1.32 (1.32-1.32) (43.00)	365.77 (365.77-365.77) (1.52)	14.60 (14.6-14.6)	32.00 (32.00-32.00)
	Mild decrease (%change)* (8)	0.11 (0.06-0.20) (-0.31)	0.71 (0.36-1.25) (-0.38)	2.51 (1.47-4.06) (0.04)	1.19 (0.76-1.96) (2.31)	417.94 (174.58-1141.6) (1.68)	5.50 (2.40-12.50) (0.02)	54.70 (51.40-58.00) (0.47)
	Normal (%change)* (10)	0.10 (0.03-0.20) (0.27)	0.91 (0.46-1.94) (-0.37)	3.96 (1.38-8.79) (0.64)	0.32 (0.08-2.67) (-0.22)	416.69 (105.92-750.66) (0.15)	9.00 (3.30-10.90) (0.22)	42.20 (17.70-97.20) (0.00)
	Mild increase (%change)* (6)	0.12 (0.07-0.15) (-0.29)	0.75 (0.24-0.90) (1.14)	2.23 (1.64-4.01) (1.23)	0.38 (0.10-1.82) (-0.58)	470.53 (121.03-492.13) (1.13)	6.40 (5.50-8.70) (0.64)	41.90 (34.50-49.30) (-0.18)
	Moderate increase (%change)* (1)	0.07 (0.07-0.07) (0.17)	0.65 (0.65-0.65) (-0.76)	4.08 (4.08-4.08) (-0.38)	0.13 (0.13-0.13) (0.18)	558.36 (558.36-558.36) (-0.01)		
48 - 72 hours	Moderate decrease (%change)** (1)	0.08 (0.08-0.08) (0.00)	1.05 (1.05-1.05) (-0.23)	13.88 (13.88-13.88) (3.26)	0.05 (0.05-0.05) (-0.96)	375.66 (375.66-375.66) (0.03)		
	Mild decrease (%change)** (11)	0.12 (0.07-0.19) (0.09)	0.79 (0.46-2.87) (0.11)	3.93 (1.06-7.86) (0.57)	0.16 (0.09-0.84) (-0.87)	382.26 (184.18-1528.6) (-0.09)	5.40 (4.20-7.10) (-0.02)	47.00 (41.30-47.10) (-0.14)
	Normal (%change)** (11)	0.07 (0.03-0.18) (-0.30)	0.65 (0.41-1.89) (-0.29)	4.88 (1.84-16.80) (0.23)	0.20 (0.04-1.42) (-0.38)	604.51 (356.75-1438.0) (0.45)	7.70 (3.60-19.70) (-0.14)	34.50 (32.90-69.30) (0.18)
	Mild increase (%change)** (8)	0.11 (0.05-0.20) (-0.08)	0.61 (0.41-4.38) (-0.19)	1.45 (1.08-3.90) (-0.35)	0.48 (0.18-0.64) (0.26)	409.58 (158.50-1281.4) (-0.13)	4.20 (2.50-4.50) (-0.34)	

Results presented as median (range) values; No change, within the normal range according to age (Table 3.1); Mild increase or decrease, < 25% increase in the upper limit of the normal range (ULN) or

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decrease in the lower limit of the normal range (LLN); Moderate, 25 – 50% increase in ULN or decrease in LLN. *% change from period 0 – 24 h to 24 – 48 h; **% change from period 24 – 48 h to 48 – 72 h.

6.8 Effect of changes in the heart rate on vancomycin pharmacokinetics

Heart rate measurement during 0 - 24 h was collected in 21 of the 37 children and 26 of the 37 children at 24 – 48 h. Heart rate measurement was collected in 31 children at 48 – 72 h. Heart rate did not significantly affect vancomycin PK at 0 – 24 h and 24 – 48 h. At 48 – 72 h, vancomycin peak concentration was significantly lower in 4 children with moderately high heart rates compared to 19 children with normal heart rates and seven children with mildly increased heart rates (Kruskal-Wallis H = 3.857, df = 2, p = 0.05) (Table 6.8). There was no correlation between heart rate and CrCl on day 1 (r = -0.11, p = 0.72) and day 3 (r = -0.23, p = 0.47) of vancomycin treatment.

 Changes in heart rate were observed in 11 children with increased heart rate at 0 – 24 h. In 9 of the 11 children, the heart rate was lower than normal at 24 – 48 h and 48 – 72 h. In one of the 11 children, HR became normal at 24 – 48 h and 48 – 72 h. One of the 11 children was within the normal range at 24 – 48 h and higher than the normal values at 48 – 72 h. Changes in heart rate did not affect vancomycin PK in the children.
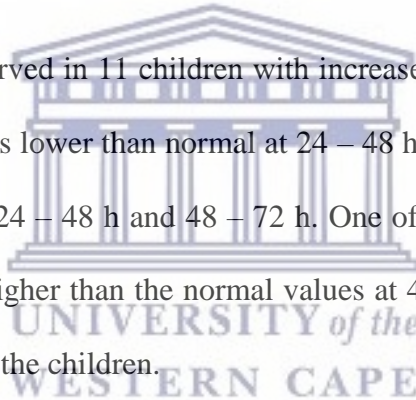
Table 6-8 Changes in Heart rate from day 1 to day 3

	Heart rate (N)	CL (L/h/kg)	Vd (L/Kg)	T½ (h)	Ke (h-1)	AUC (µg · h/L)	Trough (µg/L)	Peak (µg/L)
0 - 24 hours	Normal (9)	0.17 (0.08-0.20)	0.87 (0.51-2.19)	1.36 (1.00 - 6.56)	0.62 (0.11-2.40)	171.43 (89.48-319.05)	4.40 (2.40 - 12.00)	20.9 (18.60 - 46.20)
	Mild increase (7)	0.07 (0.03-0.17)	1.43 (0.31-3.96)	4.49 (1.76 - 19.21)	0.29 (0.04-0.91)	318.84 (147.31-917.2)	9.00 (6.20 - 13.90)	42.50 (21.70 - 82.20)
	Moderate increase (4)	0.11 (0.50-0.20)	2.83 (0.34-4.72)	6.15 (1.65 - 25.38)	0.24 (0.03-0.76)	154.85 (72.07-406.85)	6.05 (3.80 - 8.30)	21.35 (19.10 - 23.60)
	Severe increase (1)	0.045 (0.45-0.45)	0.25 (0.25-0.25)		0.91 (0.91-0.91)	686.31 (686.3-686.3)		83.8 (83.80 - 83.80)
24 - 48 hours	Normal (%change)* (15)	0.12 (0.04-0.24) (-0.29)	0.57 (0.24-1.94) (-0.34)	2.37 (1.26 -7.53) (0.74)	0.76 (0.08-2.67)	417.62 (121.0-1141.6) (1.44)	8.05 (2.40 - 12.50) (0.83)	45.75 (17.70 - 69.40) (1.19)
	Mild increase (%change)* (9)	0.08 (0.3 - 0.20) (0.14)	0.84 (0.40-1.52) (-0.41)	3.47 (1.47 - 8.79) (-0.23)	1.30 (0.08-1.90) (3.48)	476.61 (215.7-750.7) (0.49)	5.60 (2.40 - 6.40) (-0.38)	51.40 (39.70 - 97.20) (0.21)
	Moderate increase (%change)* (2)	0.12 (0.08-0.16) (0.09)	1.30 (1.24-1.37) (-0.54)	2.66 (1.70 - 3.62) (-0.57)	1.70 (1.32-2.09) (6.08)	235.85 (105.9-365.8) (0.52)	12.75 (10.90-14.60) (1.11)	58.50 (32.00 - 85.00) (1.74)
48 - 72 hours	Normal (%change)** (19)	0.13 (0.04-0.22) (0.08)	0.63 (0.41- 4.38) (0.11)	2.89 (1.06 - 8.05) (0.22)	0.33 (0.09-1.42)	386.61 (158.5-1281.4) (-0.07)	4.95 (2.5 - 19.70) (-0.39)	47.00 (34.50 - 69.30) (0.03)
	Mild increase (%change)** (7)	0.07 (0.03-0.18) (-0.13)	0.65 (0.41-1.89) (-0.23)	5.71 (1.24 - 16.80) (0.65)	0.12 (0.04-0.56) (-0.91)	953.61 (377.1-1528.6) (1.00)	8.25 (3.60 - 9.00) (0.47)	47.10 (47.10 - 47.10) (-0.08)
	Moderate increase (%change)** (4)	0.14 (0.10-0.19) (0.17)	0.64 (0.46-1.23) (-0.51)	4.09 (1.83 - 8.33) (0.54)	0.18 (0.08-0.38) (-0.89)	535.975 (273.0-822.8)	7.55 (4.20 - 10.90) (-0.41)	37.10 (32.90 - 41.30) (-0.37)
	Severe increase (1)	0.08 (0.08-0.08)	1.05 (1.05-1.05)	13.88 (13.88 - 13.88)	0.05 (0.05-0.05)	375.66 (375.7-375.7)		

*Results presented as median (range) values; No change, within the normal range according to age (Table 3.2); Mild increase, < 25% increase in the upper limit of the normal range (ULN); Moderate, 25 – 50% increase in ULN; Severe, >50% increase in ULN. *% change from period 0 – 24 h to 24 – 48 h; **% change from period 24 – 48 h to 48 – 72 h.*

Children with moderately high HR had low vancomycin peak concentration. Other vancomycin PK parameters were not affected by heart rate. Changes in HR did not affect vancomycin PK parameters.

6.9 Effect of concomitant medication on vancomycin pharmacokinetics

Nineteen of the 37 children received diuretics during the duration of vancomycin therapy. They had significantly lower median CL (0.08 (0.03 – 0.20) L/h/kg, U = 98.50, P = 0.028) and Ke (0.20 (0.08 - 0.50) h-1, U = 97. , P = 0.026) compared to children that did not receive diuretics (0.13 (0.05 - 0.22) L/h/kg and 0.32 (0.13 - 0.55) h-1), Vancomycin half-life was significantly longer in children on diuretics (3.47 (1.38 - 8.79) h, U = 96.0, P = 0.024) compared to children not receiving diuretics (2.19 (1.26 - 5.46) h). The AUC0-72 in children receiving diuretics (501.42 (167.17 - 1762.47) µg · h/L) was higher than in children not on diuretics (386.47 (127.39 - 784.08) µg · h/L) though this difference was not significant. Creatinine clearance was significantly lower in children receiving diuretics (73.75 (28.08 – 158.06) mL/min) compared to children not receiving diuretics (150.84 (47.10 – 242.38) mL/min). There was no significant difference in vancomycin dose for patients in the two groups (Table 7.8). Patients received diuretics because they had oedema caused by renal and congestive cardiac failure. Some patients received fluid resuscitation (N = 5) and had fluid overload requiring diuresis. These conditions may be responsible for the lower vancomycin CL, and higher vancomycin AUC observed in children on diuretics.

Table 6-9 Effect of diuretics on vancomycin pharmacokinetics

PK Parameter	No Diuretics (*N* = 17)	Diuretics (*N* = 20)	Man-Whitney U	*P*-value
CL (L/h/kg)	0.13 (0.05 - 0.22)	0.08 (0.03 - 0.20)	98.50	0.028
V_d (L/kg)	0.62 (0.43 - 4.38)	0.66 (0.41 - 6.01)	161.00	0.798
T½(h)	2.19 (1.26 - 5.46)	3.47 (1.38 - 8.79)	96.00	0.024
Ke (h^{-1})	0.32 (0.13 - 0.55)	0.20 (0.08 - 0.50)	97.00	0.026
AUC0-24 (µg · h/L)	386.47 (127.39 - 784.08)	501.42 (167.17 - 1762.47)	89.00	0.13
Trough (µg/L)	3.35 (1.00 - 9.60)	6.40 (0.01 - 19.70)	126.00	0.187
Peak (µg/L)	44.1 (22.20 - 60.90)	42.20 (21.90 - 98.00)	87.00	0.981
CRCL (mL/min)	150.84 (47.10 – 242.38)	73.75 (28.08 – 158.06)	59.00	0.006

Results are presented as median (range) values.

6.10 The effect of changes in serum albumin concentration on vancomycin pharmacokinetics

Patients were classified as having a severe decrease in serum albumin (> 1.5-fold decrease), moderate decrease (1.25 – 1.5 fold decrease), mild decrease (0.01 – 1.25 fold decrease), normal (within the normal limit of the range for age group), mild increase (0.01 – 1.25 fold increase), moderate increase (1.25 – 1.5 fold increase) and severe increase (> 1.5 fold increase). Vancomycin PK did not significantly differ between children with varying albumin concentrations at 0 – 24 h, 24 – 48 h, and 48 – 72 h (Table 6.10).

Albumin concentration changed in 9 children at 24 – 48 h and 48 – 72 h compared to 0 – 24 h. The change in serum albumin concentration at 24 – 48 h compared to 0 – 24 h and at 48 – 72 h compared to 24 – 48 h did not significantly affect vancomycin PK (p > 0.05). Vancomycin PK was not affected by serum albumin concentration.

Table 6-10 Effect of serum albumin concentration (g/L) on vancomycin pharmacokinetics

	Albumin (*N*)	CL (L/h/kg)	V_d (L/Kg)	T½ (h)	Ke (h-1)	AUC (µg · h/L)	Trough (µg/L)	Peak (µg/L)
0 - 24 hours	Severe decrease (2)	0.11 (0.05-0.17)	2.21 (0.46-3.96)	19.21 (19.21 - 19.21)	0.68 (0.04-1.31)	155.12 (150.7-159.5)	13.90 (13.90 - 13.90)	21.70 (21.70 - 21.70)
	Moderate decrease (1)	0.20 (0.20-0.20)	1.80 (1.80-1.80)	1.95 (1.95-1.95)	0.36 (0.36-0.36)	164.67 (164.7-164.7)	3.80 (3.80-3.80)	19.10 (19.10-19.10)
	Mild decrease (3)	0.05 (0.03- 0.07)	0.31 (0.25-3.70)	5.27 (1.76 - 8.77)	0.39 (0.08-0.91)	686.31 (473.6- 917.2)	9.00 (9.00 - 9.00)	64.30 (42.50 - 38.80)
	No change (6)	0.11 (0.05-0.19)	1.34 (0.87-4.72)	1.74 (1.11 - 25.38)	0.42 (0.03-1.08)	162.66 (139.6- 689.2)	4.60 (2.00 - 12.00)	51.00 (41.90 - 60.10)
24-48 hours	Severe decrease increase (%change)** (2)	0.10 (0.04-0.16) (-0.09)	1.05 (0.59-1.52) (-0.52)	3.25 (1.48 - 5.02) (-0.83)	0.65 (0.50-0.80) (-0.04)	283.02 (215.7 - 350.4) (0.82)	3.30 (3.30 - 3.30) (-0.76)	42.20 (42.20 - 42.20) (0.94)
	Moderate decrease increase (%change)** (1)	0.06 (0.06-0.06) (-0.70)	0.55 (0.55-0.55) (-0.69)	4.06 (4.06-4.06) (1.08)	0.76 (0.76-0.76) (1.11)	1141.62 (1141.6-1142) (5.93)	12.00 (12.00 - 12.00) (2.16)	58.00 (58.00 - 58.00) (2.04)
	Mild decrease increase (%change)** (3)	0.07 (0.03-0.20) (0.40)	0.71 (0.53-0.84) (1.29)	5.77 (1.47 - 8.97) (0.09)	0.10 (0.08-1.58) (-0.74)	484.10 (2.43.5-750.7) (-0.29)	5.75 (5.10 - 6.40) (-0.36)	97.20 (97.20 - 97.20) (0.51)
	No change increase (%change)** (3)	0.08 (0.05-0.23) (-0.27)	0.91 (0.36-3.71) (-0.32)	2.98 (1.40 - 5.60) (0.71)	1.19 (0.13-7.30) (1.83)	443.27 (58.10-601.26) (1.73)	9.60 (2.40 - 14.60) (1.09)	41.70 (32.00 - 51.40) (-0.18)
48 - 72 hours	Severe decrease increase (%change)** (2)	0.12 (0.05-0.18) (0.20)	1.42 (0.94-1.89) (0.35)	16.80 (16.80 - 16.80) (4.17)	0.73 (0.04-1.42) (0.12)	366.91 (356.8- 377.1) (0.30)	6.80 (5.90 - 7.70) (1.06)	
	Moderate decrease increase (%change)** (1)	0.07 (0.07-0.07) (0.17)	0.47 (0.47-0.47) (-0.15)	6.12 (6.12-6.12) (0.51)	0.11 (0.11-0.11) (-0.86)	895.34 (895.3- 895.3) (-0.22)		47.0 (47.0 - 47.0) (-0.19)
	Mild decrease increase (%change)** (5)	0.07 (0.03-0.19) (0.00)	0.46 (0.41-0.63) (-0.35)	1.84 (1.06 - 3.55) (-0.68)	0.38 (0.20-0.66) (2.80)	927.32 (272.9-1438.0) (0.92)	4.20 (3.60 - 19.70) (-0.27)	41.30 (34.50 - 69.30) (-0.58)
	No change increase (%change)** (10)	0.09 (0.05-0.20) (0.13)	0.75 (0.14-6.01) (-0.18)	5.72 (1.25 - 13.88) (0.92)	0.12 (0.05-0.55) (-0.90)	409.26 (255.0-1528.6) (-0.08)	7.10 (2.50 - 10.40) (-0.26)	47.10 (47.10 - 47.10) (0.13)

Results presented as median (range) values; No change, within normal range according to age (Table 3.2); Mild decrease, < 25% decrease in the lower limit of the normal range (LLN); Moderate, 25 – 50%

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decrease in LLN; Severe, >50% decrease in LLN. *% change from period 0 – 24 h to 24 – 48 h; **% change from period 24 – 48 h to 48 – 72 h.

6.11 Effect of severity of illness on vancomycin pharmacokinetics

There was no correlation between the severity of illness score/predicted death rate and vancomycin CL and V_d. (Table 6.11). The severity of the illness did not affect vancomycin AUC. Patients with higher severity of illness scores had longer vancomycin half-life. Half-life increased, and Ke reduced significantly ($p < 0.05$) as the severity of the illness increased. Trough concentration significantly increased ($p < 0.05$) as the severity of the illness increased.

Vancomycin T1/2, Ke, and trough concentration were affected by the severity of the illness.

Table 6-11 Correlation between severity of illness and vancomycin pharmacokinetic parameters

		PELOD-2 in the first 24 hours (score)	PELOD-2 after 24 hours (score)	PELOD-2 Predicted death rate (%)
CL (L/h/kg)	Pearson Correlation	-.315	-.271	-.204
	Sig. (2-tailed)	.058	.134	.262
	N	37	32	32
Vd (L/kg)	Pearson Correlation	-.114	-.123	-.173
	p-value	.502	.501	.344
	N	37	32	32
T½(h)	Pearson Correlation	.430**	.382*	.039
	p-value	.008	.031	.832
	N	37	32	32
Ke (h^{-1})	Pearson Correlation	-.329*	-.276	-.177
	p-value	.047	.126	.332
	N	37	32	32
AUC_{0-24} (µg · h/L)	Pearson Correlation	.244	.189	-.056
	p-value	.146	.300	.763
	N	37	32	32
Trough (mcg/uL)	Pearson Correlation	.429**	.392*	.102
	p-value	.008	.026	.577
	N	37	32	32
Peak (µg/L)	Pearson Correlation	.009	.046	-.253
	p-value	.963	.822	.232
	N	27	26	24

PELOD-2: Paediatric Logistic Organ Dysfunction-2; *p<0.05 and **p<0.01

6.12 Multivariate analysis of variables' effect on vancomycin PK in critically-ill children

Multivariate analysis showed some association between variables and vancomycin PK parameters. Association was found between vancomycin CL and furosemide co-administration (OR = 1.39, 95% CI = 1.12 – 1.71), Spironolactone co-administration (OR = 0.53, 95% CI = 0.43 – 0.66), normal heart rate (OR = 0.39, 95% CI = 0.03 – 0.52), low Scr (OR =3.81, 95% CI = 2.69 – 5.39), normal Scr (OR = 2.84, 95% CI = 2.20 – 3.65), > 5% weight loss (OR = 1.51, 95% CI = 1.11 – 2.05), > 5% weight gain (OR = 2.24, 95% CI = 1.71 – 2.92), the severity of illness (OR = 1.67, 95% CI = 1.31 – 2.92) and age (OR = 1.07, 95% CI = 0.82 – 1.41). Variables that predicted vancomycin Vd were normal heart rate (OR = 2.61, 95% CI = 2.09 – 3.27), > 5% weight loss (OR = .63, 95% CI = .48 - .85), > 5% weight gain (OR = 1.40, 95% CI = 1.04 – 1.87), positive fluid balance (OR = 2.68, 95% CI = 2.55 -4 .85) and age (OR = 7.04, 95% CI = 5.13 – 9.65). Predictors of vancomycin T1/2 were furosemide co-administration (OR = .74, 95% CI = .61 - .90), low MABP (OR = .43, 95% CI = .33 - .57), > 5% weight gain (OR = .45, 95% CI = .35 - .57). Predictors of vancomycin AUC were low MBP (OR = 2.38, 95% CI = 1.77 – 3.19), normal MABP (OR = 1.59, 95% CI = 1.27 – 1.98), severity of illness (OR = 1.72, 95% CI = 1.37 – 2.16) and age (OR = 1.14, 95% CI = .88 – 1.47). Predictors of vancomycin trough concentration were spironolactone co-administration (OR = 2.15, 95% CI = 1.71 -2.70), > 5% weight loss (OR = 0.70, 95% CI = 0.53-0.92), and severity of illness (OR = 0.53, 95% CI = 0.42-0.67). Compared to the individual analysis of the effect of variables on vancomycin PK, more variables included in the multivariate analysis influenced vancomycin PK.

Table 6-12 Multivariate analysis of variables' effect on vancomycin PK in critically-ill children

Parameter	CL (L/h)		Vd (L)		T$_{1/2}$ (h)		AUC		Trough	
	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
Furosemide	1.39 (1.12 – 1.71)	.002	1.74 (1.48 – 2.06)	0.994	.74 (.61 - .90)	.007	1.34 (1.01 – 1.62)	0.175	0.76 (0.64 -0.89)	.173
No Furosemide	1	-	1	-	1	-	1	-	1	-
Spironolactone	.53 (.43 - .66)	.000	.58 (.48 - .69)	0	1.93 (1.58- 2.36)	.716	.53 (.43 - .66)	0.607	2.15 (1.71 -2.70)	000
No Spironolactone	1	-	1	-	1	-	1	-	1	-
Normal Heart rate	.39 (0.30 – 0.52)	.000	2.61 (2.09 – 3.27)	0.045	2.61 (2.02- 3.39)	.402	.39 (.30 - .50)	0.073	2.86 (2.19-3.74)	.935
High Heart rate	1	-	1	-	1	-	1	-	1	-
Low MABP	2.37 (1.73 – 3.24)	.000	.44 (.34 - .57)	0.271	.43 (.33 - .57)	.031	2.38 (1.77 – 3.19)	0.014	0.32 (0.22-0.47)	.585
Normal MABP	1.54 (1.21 – 1.95)	.000	.36 (.28 - .46)	0.456	.63 (.51 - .78)	.406	1.59 (1.27 – 1.98)	0.015	0.51 (0.38 -0.67)	.854
High MABP	1	-	1	-	1	-	1	-	1	-
Low serum creatinine (umolL)	3.81 (2.69 – 5.39)	.029	1.27 (.10 – 1.61)	0.362	1.30 (1.02 -1.66)	.348	.78 (.61 - .10)	0.105	1.43 (1.12-1.83)	0.523
Normal serum creatinine (umolL)	2.84 (2.20 – 3.65)	.000	2.61 (2.09 – 3.27)	.	1.49 (1.22-1.82)	.045	.68 (.55 - .84)	0.115	1.63 (1.27-2.09)	.815
High serum creatinine (umolL)	1	-	1	-	1	-	1	-	1	-
Normal AST	1	-	1	-	1	-	1	-	-	.
Increased AST	2.84 (2.20 – 3.65)	.098	.98 (.78 – 1.24)	0.535	.34 (.27 - .44)	.186	2.91 (2.30 – 3.69)	0.305	0.30 (0.23-0.39)	.056
Normal ALT	1	-	1	-	1	-	1	-	1	-
Increased ALT	3.13 (2.22 – 4.41)	.125	0.515 (.36 - .66)	0.237	.36 (.26 -.49)	.192	3.00 (2.18 – 4.14)	0.203	0.30 (0.22-0.42)	.652
No weight gain	1	-	-	-	1	-	1	-	1	-
> 5% weight loss	1.51 (1.11 – 2.05)	.008	.63 (.48 - .85)	0.008	.70 (.53 - .92)	.049	1.52 (1.14 – 2.02)	0.231	0.70 (0.53-0.92)	000
> 5% weight gain	2.24 (1.71 – 2.92)	.000	1.40 (1.04 – 1.87)	0.028	.45 (.35 - .57)	.025	2.25 (1.75 – 2.89)	0.046	4.23 (2.38-7.53)	.959
Decreased albumin	.99 (.78 – 1.26)	.956	.59 (.46 - .76)	0.501	.99 (.79 – 1.23)	.549	1.04 (.83 – 1.30)	0.05	0.90 (0.68-1.17)	.071
Normal albumin	1	-	1	-	1	-	1	-	1	-
Fluid negative	.12 (.071 - .19)	0.846	.19 (.13 - .26)	.056	8.71 (5.5-13.75)	.068	.12 (.08 - .20)	0.562	8.90 (0.68-1.17)	0.231
Fluid positive	.40 (.27 - .59)	0.235	2.68 (2.55 -4 .85)	.023	2.55 (1.76-3.71)	.125	.38 (.26 - .56)	0.051	2.87 (1.95-4.22)	.422
No change in fluid balance	1	-	1	-	1	-	1	-	0.37 (0.28-0.50)	-
Severity of illness	1.67 (1.31 – 2.92)	.000	1.45 (1.24 – 1.70)	0.055	.60 (.48 - .75)	.855	1.72 (1.37 – 2.16)	0.031	0.53 (0.42-0.67)	.043
Age (yr)	1.07 (0.82 – 1.41)	.016	7.04 (5.13 – 9.65)	0.048	.84 (.66 – 1.06)	0.048	1.14 (.88 – 1.47)	0.023	0.91 (0.72-1.16)	0.524

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6.13 Conclusion

The effect of age, organ function, fluid balance, fluid resuscitation, and severity of illness on vancomycin PK was assessed. The impact of changes in the fluid balance, protein concentration, renal function, liver function, heart rate, and mean arterial blood pressure on vancomycin PK was also assessed. Vancomycin PK median estimates were compared between groups to test for significance in observed differences.

Younger children (< 2 years) had a higher V_d compared to older children (2 – 16 years). Patients with >5% decrease in body weight at 48 - 72 h compared to 0 - 24 h of vancomycin treatment had lower CL and Ke than children with no change in body weight or >5% increase in body weight. They also had a longer half-life and higher trough concentration.

Children with fluid gain > 5 % at 24 -4 48 h had higher vancomycin V_d (Wilcoxon signed ranked Z= -2.476, p=0.013). Vancomycin AUC was higher in children with fluid loss < 2 % (Wilcoxon signed ranked Z= -2.286, p=0.022). Children with reduced renal function had lower vancomycin CL than children with normal or increased renal function on day 2 (Kruskal-Wallis H = 12.05, df = 5, p = 0.035) and day 3 (Kruskal-Wallis H = 13.15, df = 5, p = 0.022). Patients with high mean arterial blood pressure had lower AUC0-24 than children with normal or low mean arterial blood pressure (Kruskal-Wallis H = 6.386, df = 2, p = 0.041). Increased MABP was also associated with reduced vancomycin trough concentration (r = -0.517, p = 0.01). Children with increased heart rate had lower vancomycin peak concentration (Kruskal-Wallis H = 3.857, df = 2, p = 0.05).

Children receiving diuretics (furosemide and Spironolactone) had low vancomycin CL and longer vancomycin half-life compared to patients not on diuretics. Children on diuretics had lower CrCl compared to children receiving no diuretics.

The PELOD score for severity of illness at 0- 24 hours and 24 – 72 hours correlated with vancomycin half-life (r = 0.430, p = 0.008, N = 37 and r = 0.382, p = 0.031 and N = 32), trough concentration (r = 0.429, p = 0.008, N = 37 and r = 0.392, p = 0.036 and N = 32) and reduced Ke during 0 – 24 hours (r = 0.329, p = 0.047, N = 37). This relationship may be due to organ failure, particularly the kidneys. Vancomycin PK was unaffected by fluid resuscitation, hepatic function, and protein concentration.

Chapter 7

Discussion

7.0 Introduction

This chapter discusses research findings and highlights the implication of the study. The limitations encountered during the study and suggestions for future studies are also detailed.

7.1 Vancomycin pharmacokinetics in critically-ill children

A two-compartment model best described the pharmacokinetics of vancomycin in our study population. Weight and creatinine clearance were significant predictors of vancomycin PK. Our model showed validity on external validation. Most studies use a one-compartment model to describe vancomycin pharmacokinetics (Santos Buelga et al., 2005; Safarnavadeh et al., 2009; Stockmann et al., 2013; Mahmoud et al., 2014; Zhao et al., 2014; Le et al., 2015; Abdel Hadi et al., 2016; Moffett et al., 2019; Sridharan et al., 2019). Some of the studies used sparse samples, at times including one trough sample per patient. Sparse sampling makes it challenging to model vancomycin pharmacokinetics using two-compartment models. Vancomycin typically follows a two-compartment model (the distribution and the elimination phases) when given as an IV infusion over 1 hour (Bauer LA, 2015); however, samples should be collected in both phases. In the study by (Maung et al. 2021), two-compartment modelling of trough-only data showed a significant deviation of 25.16% in AUC0-24 from the reference AUC (simulated using a robust model that included vancomycin concentration points set at 15 min intervals in 100 patients). They suggested that trough-only data should be used for one-compartment models. Using the one-compartment model is accurate in instances where there is a limited number of samples (Wu and Furlanut, 1998).

The pharmacokinetics of vancomycin from our study showed high variability among critically ill children. This variability is like that observed in other studies assessing vancomycin

pharmacokinetics in critically ill children (Acuña et al., 2013; Gomez et al., 2013; Villena et al., 2014; Zane et al., 2017; Genuini et al., 2018; Sridharan et al., 2019).

Renal function affected vancomycin clearance and improved the vancomycin model selected. This effect is expected as vancomycin is predominantly renally excreted (Bauer LA, 2015). Renal function assessed by the creatinine clearance rate has been shown to affect vancomycin pharmacokinetics in previous studies (Seixas et al., 2016; Zane et al., 2017). The renal function in a critically ill child should be considered throughout the vancomycin treatment period to avoid plasma concentrations outside the therapeutic range. Children's weight affected vancomycin clearance and the volume of distribution in the central compartment. Other studies have found weight to be a significant variable influencing vancomycin clearance and volume of distribution (Seixas et al., 2016; Avedissian et al., 2017). Patients' weight may change drastically in the PICU due to fluid loss or/ and fluid resuscitation. Vancomycin treatment therapy should be tailored to consider these weight changes.

Vancomycin CL in our study ranged from 0.1 – 0.13 L/h/kg. These values are like vancomycin CL reported by other studies carried out on critically-ill children (Giachetto et al., 2011; Acuña et al., 2013; Gomez et al., 2013; Avedissian et al., 2017; Zane et al., 2017; Genuini et al., 2018; Zylbersztajn et al., 2018; Mali et al., 2019). These studies, just like ours, showed high variability in vancomycin CL. The range of vancomycin clearance in the studies was 0.06 – 0.22 L/h/kg. Differences observed in vancomycin CL may result from varying renal function in the patient population.

The variability in the volume of distribution in the central compartment was low, and the variability in the volume of distribution in the peripheral compartment was large at 62.4%. Other studies also reported high variability of vancomycin volume of distribution (Gomez et al., 2013; Genuini et al.,

2018). The average volume of distribution in this study was similar to the average V_d in other studies carried out on critically-ill children (Giachetto et al., 2011; Acuña et al., 2013; Gomez et al., 2013; Villena et al., 2014; Genuini et al., 2018; Mali et al., 2019).

The average half-life of vancomycin in this study was similar to the average half-life reported by other studies carried out in critically-ill children and ranged from 2.4 – 4.5 h (Giachetto et al., 2011; Acuña et al., 2013; Gomez et al., 2013; Villena et al., 2014; Avedissian et al., 2017; Mali et al., 2019).

In this study, the peak vancomycin concentration was higher than those reported by other studies (Giachetto et al., 2011; Acuña et al., 2013; Villena et al., 2014; Seixas et al., 2016). The average peak concentration in these studies was between 21 – 25 mg/mL. The average vancomycin doses administered to our patients were higher than those reported by the studies. Trough vancomycin concentrations reported in these studies were higher than that reported in our study (Giachetto et al., 2011; Acuña et al., 2013; Gomez et al., 2013; Villena et al., 2014; Seixas et al., 2016; Avedissian et al., 2017; Mali et al., 2019; Sridharan et al., 2019). As observed in our study, the dosing and blood sample collection schedules were not always strictly followed. Care should be taken to interpret results from plasma concentration measurements to identify actual trough and peak concentrations of vancomycin. Our study tried to minimize the error by calculating backwards or forward when exact peak and trough concentrations should have been taken. The most appropriate method is to take trough samples just before the next dose and peak levels after vancomycin IV infusion following the specified dosing schedule. Appropriate sampling methods are not always feasible in the fast-paced environment of the PICU.

The AUC24 of vancomycin in this study was > 400 mg * h / L as per the recommendation for effective treatment of methicillin-resistant *Staphylococcus aureus* infections (Rybak et al., 2020).

While some studies carried out in the PICU reported similar findings (Acuña et al., 2013; Gomez et al., 2013), most studies reported AUC24 of less than 400 mg * h / L (Giachetto et al., 2011; Avedissian et al., 2017; Genuini et al., 2018; Mali et al., 2019; Sridharan et al., 2019).

Simulation of different dosing regimens showed that the current dosing regimen (60mg/kg/day) used in Red Cross War Memorial Hospital is adequate. The study by Gomez et al. (Gomez et al., 2013) calls for an increase in vancomycin doses, which may not be beneficial and lead to serious adverse effects. TDM of vancomycin remains very useful in critically ill children.

7.2 Vancomycin pharmacokinetic parameters 0-24hrs, 24-48hrs and 48-72hrs after treatment initiation

Vancomycin CL and half-life at 48 - 72 h were not significantly different from 0 - 24 h and 24 - 48 h. The V_d of vancomycin in the peripheral compartment was higher at 48 - 72h compared to 0 - 24 h, and Vancomycin V_d was higher in the central compartment at 0 - 24 h compared to 48 - 72 h. The AUC on day 3 was higher than the AUC at 0 - 24 h, and vancomycin AUC > 400 was not achieved at 0 - 24 h. Trough and peak concentrations in the first 24hrs did not differ from concentrations after 24 hours. Pathological changes in children did not affect vancomycin plasma concentration from day 1 to day 3. Increased mean arterial blood pressure was associated with lower trough plasma concentration, and high heart rate was associated with increased vancomycin peak concentration.

A study on critically ill children showed higher V_d on day 3 (0.86 ±0.58 L/kg) compared to day 1 (0.51 ±0.24 (L/kg)) (Giachetto et al., 2011). Vancomycin half-life was also longer on day 3 (4.5±3.07 h) compared to day 1 (3.1 ±0.78 h). The significance of this difference was not reported. Vancomycin CL in this study was comparable to Giachetto et al.'s (Giachetto et al., 2011) (0.12 ±0.07 L/h/kg Vs 0.15± 0.06 L/h/kg). The study also reported comparable AUC0-24 on Day 1 and Day 3, although the AUCs were not up to the recommended AUC (400) µg*L/h. In comparison,

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the AUC0-24 -reported by the study on day 1 was higher than the value reported in our study. In our study, Vancomycin AUC0-24 on day 3 was higher than the recommended 400 µg*L/h. The low AUC0-24 at 0 - 24 h could result from our patient population's rapidly changing clinical status during and after admission. By 48 - 72 h, most patients were clinically stable. Most patients had a better severity of illness score by 48-72 hrs. AUC and trough concentrations were higher at 48- 72 hrs than in other periods.

Trough concentration in the study by Giachetto (Giachetto et al., 2011) increased slightly on day three compared to day 1. The peak concentration on day one and day 3 was comparable. Another study reported comparable trough concentrations on days one and three (Mali et al., 2019). This result is similar to our study findings.

Overall, the volume of distribution decreased by 48 - 72 h compared to 0 - 24 h. Still, the volume of distribution in the peripheral compartment increased, and the volume of distribution in the central compartment decreased by 48 - 72 h compared to day 0- 24 h. The inter-compartmental distribution at 48 - 72 h in this study was similar to that of Zane et al. (2017). In our study, the AUC24 was lower at 0 - 24 h compared to 48 - 72 h.

7.3 Targeting trough concentration as a predictor of the area under the concentration–time curve over 72-hour /the minimum inhibitory concentration (AUC/MIC) of bacteria

Children with vancomycin trough concentrations of 10 – 15 µg/L had AUC0-72 > 400 µg*L/h. Studies in critically ill children reporting vancomycin trough concentration between 10 -15 µg/L achieved AUC0-24 > 400 µg*L/h (Acuña et al., 2013; Gomez et al., 2013). Vancomycin AUC0-24 was < 400 µg*L/h in other studies reporting vancomycin trough concentration of < 10 µg/L (Giachetto et al., 2011; Avedissian et al., 2017; Sridharan et al., 2019). Targeting vancomycin trough concentration of 10 – 15 µg/L may be more effective for treating bacteria with a MIC of 1

µg/L. This finding is in keeping with current guidelines suggesting that an AUC/MIC of 400 - 600 is adequate for killing bacteria with a MIC of 1 mcg/mL (Rybak et al., 2020).

7.4 Effect of age on vancomycin pharmacokinetics in critically-ill children

Younger children (< 2 years) had higher vancomycin CL and V_d compared to older children (2-16 years). In the study by Acuna et al. (Acuña et al., 2013), vancomycin CL of children younger than two years (0.10 (0.06-0.18) L/h/kg) was similar to that of children two years or older (0.10 (0.06-0.14) L/h/kg). The V_d was higher in children younger than two years old (0.67 (0.39-1.15) L/kg) compared to those two years or older (0.62 (0.41-1.04) L/kg). The total body water content reduces with age. Hydrophilic drugs such as vancomycin affect the plasma concentration when given according to weight-based doses (Kearns et al., 2003). In younger children, vancomycin volume of distribution tends to be much higher and the plasma concentration lower.

The study by Acuna et al. (2013) reported a longer half-life in children two years or older (3.8 (2.7-10.6) h) compared to children younger than two years (3.6 (2.2-5.5) h); the AUC was higher in children younger than two years (430.7 (242.2-612.7) µg*L/h) compared to children two years or older (410.6 (261.5-689.1) µg*L/h). As expected, organ maturation with age and reduced total body water content affect vancomycin CL and Vd. The half-life and AUC24 relate to vancomycin CL and may be affected.

7.5 Effect of changes in body weight on vancomycin pharmacokinetics in critically-ill children

Body weight affected vancomycin CL, Ke, T½ and trough concentration. Children that lost 5% of their body weight by day 3 had significantly lower CL and Ke than children without any weight difference and children with increased body weight. Longer vancomycin T½was also observed in children with body weight loss on day 3 of treatment. These children had significantly higher

vancomycin trough concentration. Vancomycin V_d, AUC0-24 and peak concentration were not affected by body weight.

Studies have shown the effect of body weight on CL and V_d in critically ill children (Seixas et al., 2016; Avedissian et al., 2017; Zane et al., 2017). Most studies show no difference in the trough concentration of children with normal weight and obese children (Miller et al., 2011; Moffett, Kim and Edwards, 2011; Eiland and Sonawane, 2014). There is a lack of the effect of weight loss on vancomycin PK. As observed in our study, body weight in critically ill children fluctuates, especially as they may receive aggressive fluid resuscitation, drugs that modify water loss or retention or undergo surgeries that influence their body weight. Modifications to doses must be regularly performed, considering the constant weight changes in these children.

7.6 Influence of fluid balance on vancomycin pharmacokinetics in critically-ill children

Children who were fluid-positive had a higher vancomycin V_d compared to those who were not fluid-positive. V_d was the only PK parameter significantly different when comparing the two groups. This finding is similar to another study on critically ill children (Giachetto et al., 2011). The study found higher vancomycin V_d in children that were fluid-positive compared to children that were not. Children who were fluid-positive also had lower trough and peak concentrations than those who were fluid-negative. Significant variations in vancomycin AUCs were observed within and between periods. The variation may be because of the rapidly changing fluid status in the children. The unexplained variability of vancomycin PK is why studies continue to show outliers in vancomycin PK. For example, in patients receiving the recommended vancomycin dose, some patients may have high trough concentrations (a risk factor for nephrotoxicity) (Slaughter, 2012). A study showed that 30% of patients given the standard vancomycin doses had trough concentrations above 15 mcg/mL (Bosso et al., 2011). Identifying additional factors that explain why patients have PK values with outliers continues to be a challenge with vancomycin therapy

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and remains one of the reasons for continuous TDM in children receiving vancomycin (Slaughter, 2012).

In this study, the volume of distribution was high in patients with extra fluid collection (pleural effusion, ascites, and hydrocephalus). The high V_d did not significantly differ from the V_d in other patients. This lack of association was likely due to relatively few patients with abnormal fluid collections. Abnormal fluid collection in regions of the body (pleura, abdomen, etc.) increases the V_d of vancomycin. Ascites have been shown to increase the V_d of vancomycin (Aldaz et al., 2000). Clinical outcomes may be compromised unless doses are increased in these patients. Patients who had their doses increased attained vancomycin AUC24 > 400 mg*L/h. Post-surgical drains and removal of pleura fluid have been shown to increase the V_d of hydrophilic drugs (Etzel, Nafziger and Bertino, 1992; Roberts and Lipman, 2009). TDM in patients with abnormal fluid collection may be necessary to maintain vancomycin plasma concentrations at therapeutic levels.

7.7 Effect of fluid resuscitation on vancomycin volume of distribution in critically-ill children
Vancomycin V_d in children receiving blood or platelet transfusion was not significantly different from that in children not receiving a transfusion. However, higher V_d was observed in children that received fluid resuscitation and were fluid-positive. In the study by Gous et al. (1995), critically ill children undergoing aggressive fluid resuscitation had large V_d and prolonged half-life. Fluid resuscitation occurs commonly in the ICU; the fluid balance in children may change during vancomycin treatment. Since vancomycin is hydrophilic, its V_d may be affected, changing vancomycin V_d and plasma concentrations. Changes in V_d are more pronounced in children receiving intravenous fluid (Blot, Pea and Lipman, 2014).

7.8 Effect of changes in renal function on vancomycin pharmacokinetics in critically-ill children

Vancomycin pharmacokinetics were significantly affected by renal function, and CrCl was used as a determinant of renal function. Children with low CrCl rates had lower vancomycin CL and Ke and higher vancomycin trough concentration and half-life. Increased AUC that was not in keeping with the decrease in renal function was observed. The increased AUC may be because of the large increase in Vd. In the study by Zylbersztain et al. (2018), critically ill children without AKI or RRT had higher vancomycin CL than children with AKI and RRT and children with AKI only. Since the primary route of vancomycin excretion is the kidneys, kidney function plays a central role in the amount of vancomycin in the body over time. TDM in rapidly changing renal function patients is essential to keep vancomycin plasma concentrations at therapeutic levels.

7.9 Effect of changes in hepatic function on vancomycin pharmacokinetics in critically-ill children

Vancomycin PK was not associated with liver function in children in our study. We did not have enough patients with liver dysfunction data to assess this issue adequately. One study found that patients with moderate to high liver dysfunction had a higher risk for high vancomycin plasma concentration (Brunetti et al., 2020). In these patients, liver dysfunction did not significantly increase the risk of AKI. In another study of patients with cancer, liver dysfunction did not affect vancomycin PK (Aldaz et al., 2000).

7.10 Effect of changes in the mean arterial blood pressure on vancomycin pharmacokinetics

Children with high MABP had lower vancomycin AUC0-24 than children with normal and low MABP. MABP determines the perfusion of blood to all organs. Reduced MABP will lead to reduced blood perfusion to organs and vice-versa (DeMers and Wachs, 2022). Children with higher MABP may have low vancomycin AUC because of increased blood flow to the kidney leading to increased vancomycin CL.

7.11 Effect of changes in the heart rate on vancomycin pharmacokinetics

Changes in heart rate from day 1 to days 2 and 3 were not associated with changes in vancomycin PK. The vancomycin PK in children with an average low heart rate did not differ from those with normal or high heart rates. Heart rate and stroke volume affect cardiac output. In our study, we could not measure cardiac output as data on the stroke volume was unavailable. Augmented renal clearance may result from higher cardiac output values in patients with normal renal function (Lipman, Udy and Roberts, 2011). Augmented renal CL may affect vancomycin clearance, necessitating dose adjustments to reach optimal plasma concentration.

7.12 Effect of concomitant medication on pharmacokinetics in critically-ill children

Diuretics significantly affected vancomycin CL in this study. Children on diuretics had lower vancomycin CL compared to children not receiving diuretics. This finding is similar to the result by Medellín-Garibay (Medellín-Garibay et al., 2016). They found that diuretics (Furosemide) reduced vancomycin CL by approximately 30%. Vancomycin half-life was higher and Ke lower in children receiving diuretics. AUC24 and trough concentration were associated with diuretics, but this difference was insignificant. Vancomycin dose was similar in the two groups. A study in critically ill patients that underwent cardiothoracic surgery showed sub-therapeutic plasma vancomycin concentration (<10µg/L) when furosemide was co-administered with vancomycin (Pea et al., 2000).

The CrCl rate in the children on diuretics was much lower than in those not. However, there may be a selection bias here, as children were potentially started on diuretics as a clinical response to poor renal function. Children on vancomycin receiving furosemide are at the highest risk of developing AKI (Bonazza et al., 2016). Furosemide is nephrotoxic and should be used cautiously in patients on vancomycin therapy. Medications that alter renal function should be used cautiously,

especially in critically ill children undergoing renal development (under two years) and rapidly changing renal functions related to disease progression.

7.13 Effect of changes in albumin concentration on the pharmacokinetics of vancomycin in critically-ill children

Albumin concentration was not associated with vancomycin pharmacokinetics in this study. This finding is similar to that of Sexias et al. (2016), where there was no correlation between vancomycin concentrations and serum albumin (P=0.38). A study reported associations between unbound vancomycin concentration and serum protein concentration; unbound vancomycin concentration significantly correlated with total protein and albumin concentration (P<0.001) (De Cock et al., 2017). In the study by Sridharan et al. (2019), protein-free vancomycin concentration did not affect patients' ability to attain AUC24 > 400. Our result should be interpreted cautiously since the number of patients with data on albumin concentrations was small. The effect of other proteins, such as IgA, on vancomycin PK, was not evaluated. It is also important to note that we did not assess the potential impact of altered free (available) vancomycin on bacterial killing and clinical outcomes. This remains an area that should potentially be studied.

7.14 Effect of severity of illness on vancomycin pharmacokinetics in critically-ill children

Vancomycin CL, Vd and AUC were associated with the severity of the illness., Children with higher severity of illness scores had longer vancomycin half-life, reduced Ke and higher trough concentrations. In the study by Hidayat et al. (2006), the severity of underlying illness was found to be an independent predictor of poor treatment response to vancomycin after controlling for potential confounders in a multivariate analysis, with risks of 3.14. They used the Acute Physiology and Chronic Health Evaluation II (APACHE II) score to evaluate patients' severity of illness at the time of admission. In the study by Hahn et al. (2015), they found no statistical association between markers of illness severity and vancomycin AUC24. They did not use a

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scoring system to assess patients' severity of illness but used the need for ICU support, shock or hypotension at presentation, renal insufficiency at presentation (CrCl < 75 ml/min/1.73m2), or the development of renal failure during the hospitalization (serum Cr increased by 50% from admission baseline for two occurrences) as markers of severity of illness. The severity of illness scores may be useful for assessing organ function (particularly multiple organ function) in critically ill children, both at admission and throughout the PICU stay. The degree of organ function, especially the kidneys, will affect vancomycin CL impacting vancomycin plasma concentration. The severity of illness and assessment of patients' organ function should be done throughout the ICU stay, and vancomycin doses should be adjusted according to organ function and TDM.

7.15 Implication of the study in clinical practice

1. This study has several implications for clinical practice. Effective vancomycin therapy aims to attain therapeutic plasma concentrations in the shortest possible time in critically ill children and maintain these concentrations throughout the treatment of infections with vancomycin. Sub-therapeutic vancomycin concentrations will lead to treatment failure and the emergence of vancomycin-resistant bacteria. Supra-therapeutic vancomycin concentrations may lead to adverse drug effects, including organ failure. When giving vancomycin doses, clinicians should be aware that:

2. The ICU comprises a heterogeneous population with different disease states and organ functions. The wide variation is at least partially responsible for the vast differences observed in vancomycin CL and, most importantly, vancomycin volume of distribution in the central compartment (Vc). The organ function, mainly the renal function, affects vancomycin pharmacokinetics and therapeutic vancomycin plasma concentration availability.

3. Patients in the ICU have changing organ functions, affecting vancomycin plasma concentration per time depending on the state of their current organ function. TDM is essential, especially in patients with rapidly evolving organ functions.

4. Changes in body fluid balance in patients affect the V_d of vancomycin. The total fluid content also changes in critically ill children depending on organ function and medications given to regulate fluid balance, often administered during vancomycin treatment. The fluid status also has implications in vancomycin dosing as vancomycin doses are given per kg, and the current weight (which increases or decreases based on total body water) should be used.

5. Abnormal collection of body fluids in regions of the body such as the abdomen, pleura and the brain may cause a change in the V_d of vancomycin, particularly in the peripheral compartment. Although a limited number of patients with these conditions were included in the study population, this pattern was noted.

6. In our model, children's weight and their renal function (CRCL) affected vancomycin CL and weight affected vancomycin Vc. Children's weight and renal function are primary considerations in vancomycin dosing.

7. The current 60mg/kg/day as four divided doses given as an intermittent infusion over one hour is sufficient to attain vancomycin AUC > 400 µg*L/h. Increasing the dose in critically ill children, as some studies advocate, may yield much higher AUC24 and trough concentrations that may be toxic to the patients. Although we did not study vancomycin PK in patients on continuous infusion, drug modelling using the data from this study suggests that continuous infusion may benefit patients.

8. Vancomycin doses are only sometimes given at the scheduled times, and trough concentrations are only sometimes collected just before the next dose. Therefore, caution should be taken when interpreting vancomycin plasma levels.

9. Diuretics are commonly used in the ICU; concomitant administration of diuretics in patients receiving vancomycin treatment may reduce vancomycin CL and increase its half-life. Renal function may be a contributory factor to reduced CL. Renal function will affect vancomycin plasma concentration and its therapeutic effect in patients.

7.16 Limitation of the study

The following limitations were observed:

1. Vancomycin doses were not always given to the children at the expected time.

2. Collection of blood samples at the specified times was not always possible because of several difficulties encountered, e.g., patients undergoing other procedures, non-availability of nurses, and difficulty withdrawing blood from IV lines.

3. The patient recruitment rate was low. Enrolment of children in the study was stopped because of the COVID-19 pandemic.

4. The sample size was not statistically powered to explain the variations in PK parameters in the different subgroups of the study.

5. The effect of unbound vancomycin plasma concentration on therapeutic attainment was not evaluated because of limited funds.

6. Vancomycin penetration and concentration in tissues poorly perfused, e.g., the lungs, were not evaluated.

Chapter 8
Conclusion and Recommendation

8.1 Conclusion

Children admitted to the ICU had a wide range of different clinical profiles and underlying conditions. Organ functions differed between patients, but notably, organ functions varied substantially over time throughout the study on multiple patients, meaning that in some cases, a "steady state" was never achieved. In addition, considerable variations in the vancomycin doses prescribed, the time and frequency of vancomycin administration, and the time of blood sampling occurred within the PICU. These variations contributed to the challenges of carrying out this study. However, this reflects the reality of PICU practice in this setting.

A two-compartment model was most appropriate for describing vancomycin PK in our study population. In keeping with previous studies, weight and CRCL were significant predictors of vancomycin CL, while vancomycin V_d in the central compartment was significantly predicted by weight.

There was high variability in all vancomycin PK parameters, particularly V_d, in the children. Significant changes in vancomycin V_d and AUC were observed between 0 – 24 hr, 24 – 48 h and 48 – 72 h. This is expected because of the constantly changing pathophysiology in critically ill children, but it highlights the need for the daily assessment of appropriate dosing strategies.

Simulations of different dosing scenarios using PK values generated from this study showed that continuous infusion potentially yields higher trough and AUC concentrations than intermittent infusions. This finding is not conclusive, and it will be worthwhile to do comparative studies between intermittent and continuous infusion in critically ill children. The studies would address issues such as the adequacy of AUC, associated side effects, clinical outcomes as well as practicalities of therapeutic drug monitoring

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This study did not conclusively determine the validity of targeting trough concentrations or AUCs. Targeting higher trough concentrations (10 – 15 mcg/mL) would lead to adequate AUC concentrations in children, though some children may attain adequate AUC concentrations at lower trough levels. The impact of targeting trough concentrations or AUCs on clinical outcomes, including toxicity, was not evaluated.

In the groups of patients studied, there was an association between certain vancomycin PK parameters (CL, Vd, $T_{1/2}$, AUC, trough and peak concentrations) and the variables- age, weight, fluid status, MABP, heart rate, diuretics and severity of illness. Individual changes in weight and fluid status during admission affected vancomycin PK. Large intra-individual variability was observed in the AST, ALT and albumin concentrations. Still, a good association could not be made because of the number of patients with these conditions.

Higher vancomycin Vd was observed in a small number of patients with abnormal fluid collections, such as ascites, pleural effusion, hydrocephalus, and subdural hematoma. However, the small number of children with an abnormal fluid collection made it difficult to evaluate this difference statistically.
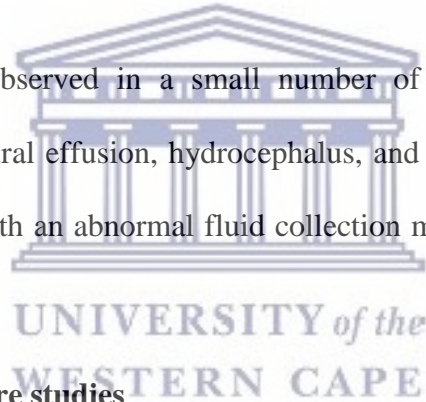
8.2 Recommendations for future studies

Given the complexities of issues in children admitted to the ICU, we recommend the following:

1. Include many more studies or focus on sub-groups of patients, such as patients receiving large amounts of fluids, those with abnormal fluid collections, patients with cardiac dysfunction, liver dysfunction and patients in perioperative periods.

2. Clinically, the priority is to achieve the best therapeutic outcomes. Therefore, studying the relationship between the PK/PD of vancomycin and patient outcomes is needed, and this is important because patients in the ICU have changing organ functions.

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3. Although we had limited data, it is clear that albumin levels (and probably binding) may vary substantially during the PICU stay. Further studies are required to elucidate the relationships between protein concentrations, changes in protein binding (and therefore drug availability both for therapeutic effect and excretion) and vancomycin effects.

4. The effect of the mode of administration of vancomycin (intermittent or continuous infusion) on its PK/ PD and clinical outcomes should be evaluated.

5. We measured only blood concentrations in this study. Since vancomycin is renally eliminated, it might be worthwhile to measure the urinary elimination of vancomycin. The relationship between vancomycin concentrations in the urine and blood should be evaluated.

6. The relationship between vancomycin concentration in fluids at target tissues (such as pleural fluids and cerebrospinal fluid) and vancomycin PK should be assessed.

7. A study on vancomycin therapeutic drug monitoring based on "fAUC/MIC ratio" (fAUC : area under vancomycin free plasma concentrations) should be conducted, and its advantages /disadvantages over therapeutic drug monitoring based on "AUC/MIC" (AUC= area under vancomycin total plasma concentrations) with a target of AUC/MIC 400 to 600.
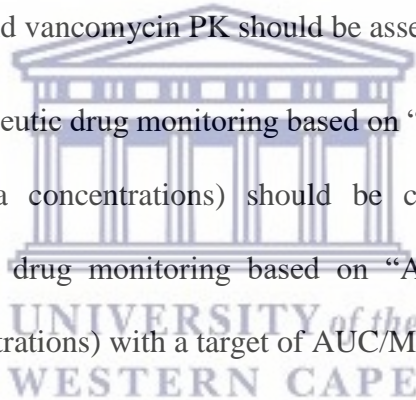
8.3 Recommendations for clinicians

Clinical status and vancomycin PK/PD may change substantially in critically ill children throughout their admission. Given the variability in clinical status, clinicians should consider changes in each patient's clinical status when considering the probable vancomycin PK in that patient. Therapeutic drug monitoring should be based on "vancomycin Trough concentrations" and "vancomycin AUC /MIC with a target of AUC/MIC 400 to 600.

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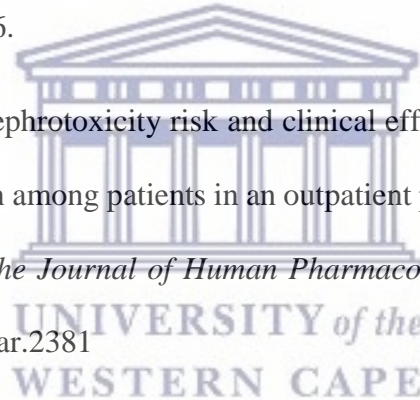
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Appendix I Data collection forms

PATIENT STICKER:

BLOOD COLLECTION SCHEDULE

	Scheduled Time	Current time	Plasma conc.	Temp	RR	HR	SBP	DBP	PaO_2	FiO_2	PCO_2
0 (Baseline)											
1 (Just after 3rd infusion)											
2 (4hrs after 3rd infusion)											
3 (Just before 4th infusion)											
4 (Just after 5th infusion)											
5 (4hrs after 6th infusion)											
6 (Just before 9th infusion)											

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VANCOMYCIN DOSING

S/N	Date of Infusion (DD/MMM/YYYY)	Loading Dose	Start time of infusion (24hr format)	Rate of Infusion prescribed	Stop time of infusion (24hr format)	Dose (including units)	Comment, only if drug delayed, interrupted, reduced or altered
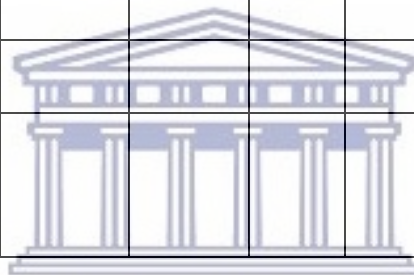
Demographic/Clinical Information

Date: **ID: VAN**

Date of Birth:

Gestational age:

Postnatal age:

Sex:

Weight: Day 1-   **Day 2-**   **Day 3-**

Height:

Elective Admission (YES/NO):

Primary diagnosis (Reason for ICU admission):

Other Diagnosis:

Sepsis Confirmed (YES/NO):

Procedures (Cardiac bypass, surgeries etc.)/Date

Recovered post-procedure (YES/NO):

Concomitant Medication   **Start**   **Stop**

Haematology

	Day 1 Date: Time:	Day 2 Date: Time:	Day 3 Date: Time:	Last Test Available Date: Time:
Procalcitonin				
White cell Count				
Red Cell Count				
Haemoglobin				
Heamatocrit				
MCV				
MCH				
MCHC				
Red Blood Cell Distribution Width				
Platelet count				
Neutrophils				
Lymphocytes				
Monocytes				
Eosinophils				
Basophils				
CRP				
Immature Cells				

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Biochemistry

	Day 1 Date: Time:	Day 2 Date: Time:	Day 3 Date: Time:	Last Test Available Date: Time:
Sodium				
Potassium				
Chloride				
BiCarbonate				
Albumin				
Ion gap				
Urea				
Creatinine				
Magnisium				
Inorganic Phosphate				
Total Protein				
Albumin				
ALT				
AST				
LD				
NH$_3$				
GGT				
ALP				
Total Bilirubin				
Conjugated Biliru				
cCA				
cAG				
pH				

Daily Collection Form

ID: VAN

	Day 1	Day 2	Day 3
MBP			
Lactatemia			
Pupillary Reaction			
Mechanical Ventilation			
Response to bright light			
Eyes			
Open spontaneously			
Open in response to verbal stimuli			
Open in response to pain only			
No response			
Verbal response			
Coos and babbles or Oriented/appropriate Irritable cries or confused			
Cries in response to pain or inappropriate word			
Moans in response to pain or incomprehensible word or nonspecific sounds			
No response			
Motor response			
Moves spontaneously and purposefully or obeys command			
Withdraws to touch or Localizes painful stimulus			
Withdraws in response to pain			
Responds to pain with decorticate posturing (abnormal flexion)			
Responds to pain with decerebrate posturing (abnormal extension)			
No response			
Fluid balance			
Fluid-in			
Fluid-out			

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End of Enrollment

ID: VAN

Duration of Vancomycin treatment (days):

Discharge Summary

Date of discharge:

Completed study (YES/NO):

Infection resolved (YES/NO):

Condition of patient (Stable/Not Stable):

Outcome (tick applicable)

- **Discharged**
- **Transferred to another unit**
- **Transferred to another hospital**
- **Dead**
- **Other (Specify):**

COMMENTS:

Appendix II Dosing times

ID	SD	AD	SD	AD	SD	AD	SD	AD	SD	AD	SD	AD	SD	AD	SD	AD	SD	AD	SD	AD	SD	AD	SD	AD
1	0	0	6	6	12	12	18	18	24	24	30	30	36	36	42	42	48	48	54	54				
2	0	0	6	5	12	12	18	18	24	23	30	29	36	35	42	41								
3	0	0	6	7	12	13	18	19	26	29	34	35	42	43			48	49	54	55				
4	0	0	8	8	14	14	20	20																
5	0	0	12	12	18	18	24	25	30	32	36	38	42	44	48	50	54	56	60	62				
6	0	0	6	6	12	14	18	19	24	26	30	32	36	38	42	44								
7	0	0	6	6	12	11	18	17	24	23	30	29	36	35	42	41	48	47	54	53				
8	0	0	6	6	12	11																		
9	0	0	6	6	12	13	18	18	24	24	30	30	36	36	42	42	48	49	54	54	60	61		
10	0	0	12	12	18	18	24	25	30	32														
11	0	0	6	6	14	14	22	22	30	30	38	38	46	47	54	54								
12	0	0	6	6	12	13	18	18	24	24														
13	0	0	8	8	16	20																		
14	0	0	6	6	12	12	18	18	24	24	30	30	36	36	42	41	48	49	54	56	60	61	66	67
15	0	0	8	8	16	16	24	24	32	32	40	39	48	48	56	57	64	64						
16	0	0	8	8	16	16	24	24																
17	0	0	6	6	12	12	18	19	24	25	30	31	36	36	42	42								
18	0	0	6	6	12	12	18	18																
19	0	0	6	6	12	12	18	19	24	24	30	30	36	36	42	45	48	50	54	54	60	60	66	66
20	0	0	6	5	12	11	18	16	24	23	30	29	36	35	42	41	48	47	54	53				
21	0	0		20		42		61																
22	0	0	6	6	12	12	18	18	24	24	30	30	36		42	42								
23	0	0		23		35																		
24	0	0	8	8	16	16	24	24	32	33	40	40	48	48	56	56	64	64						
25	0	0	6	6	12	12	18	18	24		30	30	36	36	42	43								
26	0	0	8	8	16	16	24	24	32	32	40	40	48	48										
27	0	0	6	6	12	12	18	20	24	26	30	30	36	36	42	42								
28	0	0	6	6	12	12	18	18	24	27	30	31	36	36	42	42	48	48						
29	0	0	8	8	16	16	24	24	32	33	40	40	48	49	56	56								
30	0	0		33		45		57																
31	0	0	6	7	14	14	22	23	30	31	36	37	42	43	48	49	54	54						
32	0	0	8	7	16	15																		
33	0	0		17		29	63																	
34	0	0		16	28	27	40	40	52	51	64	64												
35	0	0	6	6	12	12	18	18	24	24	30	30	36	36	42	42								
36	0	0		16		24	33		45		51													
37	0	0	6	5	12	14	18	20	29	30	37	38	45	46	53	54	61	62						

ID, Patients' ID; SD, Scheduled dosing time (h); AD, Actual dosing time (h)

Appendix III Sampling times of blood for vancomycin plasma concentration determination

Study ID	SS	AS	SS	AS	SS	AS	SS	AS	SS	AS	SS	AS
1	13.5	13	19	19.1	21	20.9	29.37	30	40.8	40.42	55.35	53.5
2	13.5	16.98	19	20.95	21	24.73	29.37	40.65	40.8	45.48	55.35	
3	13.5	19.42	19	21.48	21	28.63	29.37	35.75	40.8	40.07	55.35	60.12
4	13.5	13.48	19	19.03	21	19.83	29.37	20.95	40.8	40.07	55.35	52.63
5	13.5	13.63	19	17.98	21	29.42	29.37	43.67	40.8	58.95	55.35	67.17
6	13.5	13.87	19	21.95	21	37.18	29.37	48.03	40.8		55.35	
7	13.5	23.27	19	35.1	21		29.37		40.8	52.43	55.35	59.27
8	13.5	20.12	19	62.12	21		29.37		40.8		55.35	
9	13.5	12.72	19	48.58	21		29.37		40.8		55.35	66.83
10	13.5	13.93	19	18.08	21	20.98	29.37	36.97	40.8	41.58	55.35	
11	13.5	18.33	19	22.17	21	23.93	29.37	31.7	40.8	42.25	55.35	47.17
12	13.5	12.65	19	17.67	21	22.93	29.37	29.37	40.8		55.35	
13	13.5	18	19	24.67	21		29.37		40.8		55.35	
14	13.5	11.15	19	17.35	21	19	29.37	29.5	40.8	40.67	55.35	57.23
15	13.5	3.12	19	5.12	21	24	29.37	46	40.8	63.12	55.35	
16	13.5	13.45	19	15.95	21	19.13	29.37	21.07	40.8	29.37	55.35	40
17	13.5	13.55	19	19	21	24.75	29.37	29.28	40.8	40.52	55.35	55.43
18	13.5	13.67	19	17	21	25.82	29.37	41.51	40.8	44	55.35	
19	13.5	17.67	19	20.2	21	22.78	29.37	29.5	40.8	41.03	55.35	71.17
20	13.5	17.08	19	22.85	21	24.33	29.37	26.92	40.8	48.4	55.35	52.57
21	13.5	18.25	19	19.7	21	22.17	29.37	26.17	40.8	41.83	55.35	66.22
22	13.5	12	19	18.08	21	29.17	29.37	35.8	40.8	51.23	55.35	
23	13.5	11.88	19	46.88	21		29.37		40.8		55.35	
24	13.5	11.67	19	18.65	21	20.73	29.37	25.23	40.8	35	55.35	66.17
25	13.5	17.83	19	19.67	21	25.05	29.37	34	40.8	42.75	55.35	47.68
26	13.5	17.5	19	19.33	21	22.2	29.37	23.88	40.8	41.92	55.35	44.73
27	13.5	17.67	19	21.22	21	48.67	29.37		40.8		55.35	
28	13.5	12	19	26.58	21	27.9	29.37	42	40.8	50	55.35	
29	13.5	25.73	19	31.83	21	41	29.37	49	40.8		55.35	
30	13.5	58.08	19	60.92	21	68.92	29.37	69.75	40.8		55.35	
31	13.5	17.35	19	36.35	21	37.58	29.37	40.6	40.8	48.43	55.35	60.6
32	13.5	19.5	19	23.58	21		29.37		40.8		55.35	
33	13.5	10.22	19	19.63	21	20.87	29.37	26.38	40.8	43.22	55.35	59.72
34	13.5	10.83	19	15.98	21	22.87	29.37	27.33	40.8	40	55.35	65.13
35	13.5	18	19	23.17	21	24	29.37	25.08	40.8	40.5	55.35	
36	13.5	10.67	19	33.17	21	51.67	29.37	56.17	40.8		55.35	
37	13.5	22.25	19	49	21		29.37		40.8		55.35	

ID, Patients' ID; SS, Scheduled sampling time (h); AS, Actual sampling time (h)

Appendix IV Expected and actual collection times of blood samples for trough concentration determination

Patient ID	Expected trough blood collection time	Actual trough blood collection time	Difference in sampling time
1	19	16.73	-2.27
1	31	30	-1
1	43	40.42	-2.58
1	55	53.5	-1.5
2	46.87	45.48	-1.39
3	60.75	60.12	-0.63
3	12.75	12.87	0.12
6	14.9	13.87	-1.03
7	7	4.75	-2.25
9	13.83	12.72	-1.11
10	43.97	41.83	-2.14
12	19	17.67	-1.33
14	19.42	17.35	-2.07
16	17.3	15.95	-1.35
20	53.83	52.57	-1.26
21	92.2	91.08	-1.12
23	48.28	46.88	-1.4
26	27.08	23.88	-3.2
27	18	17.67	-0.33
31	20.1	17.35	-2.75
35	30.33	30	-0.33
37	51.75	49	-2.75

Indicates samples collected earlier than scheduled

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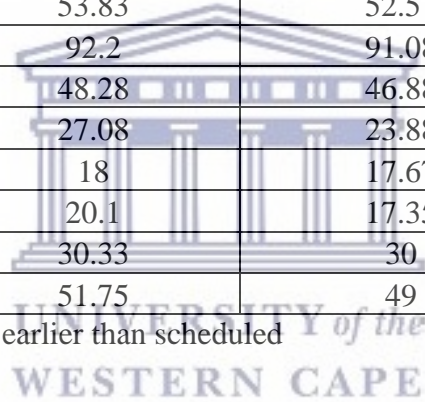
Appendix V Expected and actual collection times of blood samples for peak concentration determination

Patient ID	Expected peak blood collection time	Actual peak blood collection time	Difference in sampling time
1	13	13	0
1	55	55.8	0.8
2	18.5	20.95	2.45
2	24.27	24.73	0.46
3	19.75	21.48	1.73
3	35.57	37.75	2.18
4	9	13.48	4.48
4	15	19	4
4	21.3	21.4	0.1
5	25.67	29.42	3.75
5	56.67	58.95	2.28
6	20.12	21.95	1.83
10	19.1	20.98	1.88
10	32.83	36.79	3.96
11	23.25	23.93	0.68
11	31.48	31.7	0.22
14	21.2	24.67	3.47
14	18.9	19	0.1
14	56.5	57.23	0.73
16	17.15	19.13	1.98
17	12.75	13.55	0.8
18	13	13.67	0.67
19	19.5	20.2	0.7
20	24	24.33	0.33
20	47.83	48.4	0.57
20	54.08	56	1.92
21	92.2	92.53	0.33
21	115.67	116.12	0.45
24	17.13	18.65	1.52
24	65	66.17	1.17
25	19	19.62	0.62
26	19.08	19.33	0.25
26	41	41.25	0.25
26	44	44.73	0.73
27	20.67	21.22	0.55
28	27.7	27.9	0.2
29	40.84	40.84	
29	56.58	57	0.42

30	57.92	58.08	0.16
32	16.12	19.5	3.38
33	20.8	20.87	0.07
34	64.67	65.13	0.46
35	31.03	31.08	0.05
36	51.5	51.67	0.17
37	20.75	22.25	1.5

Appendix VI Monte Carlos simulation of vancomycin pharmacokinetics in critically-ill children

myModel <- inlineModel("

 [LONGITUDINAL]

input = {Cl, V1, Q, V2}

EQUATION:

; Parameter transformations:

V = V1

k = Cl/V1

k12 = Q/V1

k21 = Q/V2

; PK model definition:

Cc = pkmodel(V, k, k12, k21)

[INDIVIDUAL]

input={Cl_pop,omega_Cl,beta_Cl,Q_pop,omega_Q,V1_pop,omega_V1,beta_V1,

  V2_pop,omega_V2,Weight,Weight_pop,omega_Weight, CRCL, CRCL_pop, omega_CRCL}

EQUATION:

V1_pred = V1_pop*(Weight/Weight_pop)^beta_V1

Cl_pred = Cl_pop*(Weight/Weight_pop)^beta_Cl*(CRCL/CRCL_pop)^beta_Cl

DEFINITION:

Cl = {distribution=logNormal, prediction=Cl_pred, sd=omega_Cl}

Q = {distribution=logNormal, prediction=Q_pop, sd=omega_Q}

V1 = {distribution=logNormal, prediction=V1_pred, sd=omega_V1}

V2 = {distribution=logNormal, prediction=V2_pop, sd=omega_V2}

```
[COVARIATE]
input={Weight_pop,omega_Weight, CRCL_pop, omega_CRCL}


DEFINITION:
Weight={distribution=normal, mean=Weight_pop, sd=0}
CRCL={distribution=normal, mean=CRCL_pop, sd=0}
")
p <- c(Weight_pop=10,   omega_Weight = 0.5,
   Cl_pop=1.06,    omega_Cl=0.356,  beta_Cl=0.75,
   V1_pop=3.66,     omega_V1=0.18,  beta_V1=1,
   V2_pop=1.8,     omega_V2=2.15,
   Q_pop=7.11,    omega_Q=0,
   CRCL_pop = 0.3,  omega_CRCL=0.05)


N <- 1000
adm1 <- list(time=seq(0, 48, by=6), amount=150, tinf=1)
adm2 <- list(time=seq(0, 48, by=8), amount=200, tinf=1)
adm3 <- list(time=seq(0, 48, by=24), amount=600, tinf=1)
out <- list(name=c('Cc'), time=seq(24,48,length=100))

g1 <- list(treatment=adm1, size=N, level='covariate')
g2 <- list(treatment=adm2, size=N, level='covariate')
g3 <- list(treatment=adm3, size=N, level='covariate')
g4 <- list(treatment=adm4, size=N, level='covariate')


adm1 <- list(time=c(0, 6, 12, 18, 24,30, 36,42), amount=c(250, 150, 150, 150, 150, 150, 150,
150), tinf=1)
adm2 <- list(time=c(0, 6, 12, 18, 24,30, 36,42), amount=c(150, 150, 150, 150, 150, 150, 150,
150), tinf=1)
adm3 <- list(time=c(0, 6, 12, 18, 24,30, 36,42), amount=c(200, 200, 200, 200, 200, 200, 200,
200), tinf=1)
```

```
adm1 <- list(time=c(0, 24, 48), amount=c(850, 600, 600), tinf=24)
adm2 <- list(time=c(0, 24, 48), amount=c(600, 600, 600), tinf=24)
adm3 <- list(time=c(0, 24, 48), amount=c(800, 800, 800), tinf=24)


res <- exposure(model   = myModel,
     parameter = p,
     output  = out,
     group   = list(g1,g2,g3,g4))
citation("mlxR")
```


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