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THE
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**Exploring population pharmacokinetic models in patients
treated with vancomycin during continuous venovenous
hemodiafiltration on different anticoagulant modalities.**

A thesis submitted for the degree of

Master in science

By

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Declaration

I hereby declare that this is entirely my own work, except where otherwise acknowledged, and it is entirely original and has not been submitted to any other purpose.

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Dedication

This dissertation is dedicated with a special feeling of gratitude and thanks for all the inspiration and support to my lovely mother **Asia Bahar** and to the soul of **Rami Munshi** (may God have mercy on him) who was the best brother.

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First of all, I would like to thank **God** who helped and inspired me to finish this thesis. I owe my deepest gratitude to my **mother**, the best mother in the world, without her continuous support and encouragement I have never been able to achieve my goals. She planted the seed of education since my childhood. She always supports me with her love, and there is no word that can explain my thanks for her.

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"go raibh maith agat"

Abstract

Uncertainty remains concerning pharmacokinetics (PK) of antimicrobials in critically ill patients due to the scarcity of data and the variable physiology of the patient cohort. This project incorporates two distinct aims. The first aim was to describe the population PK estimates and the influence of patient covariates on PK of vancomycin following intermittent infusion in critically ill patients receiving continuous venovenous hemodiafiltration (CVVHDF), and on different anticoagulant modalities. Whereas, the second aim was to explore the potential for automatic data extraction from the electronic health record (EHR) for population PK analysis.

Vancomycin dose and concentration data (peak, trough) were collected retrospectively from 31 critically ill patients (n= 280 levels). A one-compartment model was used to describe the vancomycin concentration-time profiles, using Pmetrics software. A base structural model was developed and covariates assessed for inclusion in PK models were as follows: Dialysis status was categorised as 1) dialysis with regional citrate anticoagulation (RCA) (60 levels) 2) dialysis not using RCA (non-citrate) (120 levels) or 3) no dialysis (44 levels). Continuous covariates were: cumulative fluid balance (FB), effluent flow rate (EFR), blood flow rate, body weight, albumin concentration (Alb) and age.

Considering the high inherent variability in this patient cohort, the structural base models were reasonable using both clearance (CL) with volume of distribution (V) and elimination rate constant (Ke) with V, even without addition of covariates, with observed vs. predicted (o-p) R^2 values of 0.51 and 0.81 for population and posterior individual predicted models respectively. The mean $\pm$ SD of total vancomycin PK estimates were: CL: 2.16 ± 0.57 L/h, V: 80.65 ± 22.65 L, and Ke: 0.03 ± 0.01 h. The best population predicted models (o-p $R^2 = 0.59$) included FB as a continuous covariate applied to the V parameter and Alb applied to the Ke parameter (using the inverse approach). Interestingly, there was a suggested improvement in the population model of the RCA modality group over the non-dialysis cohort, with o-p R^2 of 0.86 and 0.28, respectively (o-p R^2 non-citrate dialysis = 0.58). The less variable PK estimates in the RCA group model suggests that initial vancomycin dosing in this type of patient might be more straightforward than in the other anticoagulant categories,

due to the homogeneity of patients in the citrate group. No single covariate model using all patients provided a notable improvement simultaneously in both population predictions and posterior individual predictions. Inclusion of an intercept in the PK parameter-covariate relationship was necessary to detect significant covariate relationships with PK parameters. Furthermore, investigated automated data extraction method was potentially valuable for use in PK analysis, after further development to achieve a reliable automated extraction system.

Ultimately, FB, Alb data and RCA status are suggested as covariates for further analysis with richer data, to optimise covariate PK modelling of vancomycin in these patients, and support dose optimisation.

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List of abbreviations

%	Percent
1-Citrate	Dosing intervals not on RCA
1-DIAL	Dosing intervals on non-dialysis status
2*LL	-2*Log-likelihood value
4h	Data taken from 4 hours closest to dose
ACCP	American College of Chest Physicians
ACT	Activated Clotting Time
AIC	Akaike's Information Criterion value
AIDS	Acquired Immune Deficiency Syndrome
AKI	Acute Kidney Injury
Alb	Albumin level
APACHE II	Acute Physiology and Chronic Health Evaluation
aPTT	activated Partial Thromboplastin Time
AUC	Area Under the Curve
AUC ₂₄	24-hour period of Area Under the Curve
BFR	Blood flow rate
BIC	Bayesian or Schwartz Information Criterion value
BMI	Body mass index
CAVH	Continuous Arteriovenous Hemofiltration
CCD	Categorical Covariate Dialysis
CCD-AP	Categorical Covariate Dialysis-All Patients
CCD-G	Categorical Covariate Dialysis-Groups
CL	Plasma Clearance
CRRT	Continuous Renal Replacement Therapy
CV%	Coefficient of Variation value
CVVH	Continuous Venovenous Hemofiltration
CVVHD	Continuous Venovenous Hemodialysis
CVVHDF	Continuous Venovenous Hemodiafiltration
DIAL	Dosing intervals on dialysis
e.g.	For example
EFR	Effluent flow rate
EHR	Electronic Health Records
EMR	Electronic Medical Record
EPR	Electronic Patients Records
ESCCM	European Society of Critical Care Medicine
FB	Fluid balance
FIO ₂	Fraction of Inspired Oxygen
h	hour (s)
i.e.	That is
IC	Initial Condition
ICIP	Intellivue Clinical Information Port- folio
ICU	Intensive Care Unit

ID	Study number
IHD	Intermittent Hemodialysis
Imp	Imprecision
IQR	Interquartile Range
IT2B	Iterative 2-stage Bayesian
IUF	Intermittent Isolated Ultrafiltration
IV	Intravenous administration
KA	Absorption rate constant
Ke	Elimination rate constant
Kei	Elimination rate constant using inverse approach
Ket	Elimination rate constant using total volume approach
Key	Laboratory information system
kg	kilogram (s)
L	Liter
LMWH	Low Molecular Weight Heparin
MAP	Mean Arterial Pressure.
mg	Milligram (s)
mg/dl	Milligrams per deciliter
MIC	Minimum Inhibitory Concentration
min	minute (s)
ml	Milliliter
mm ³	Cubic millimeter
mmol/l	Millimoles per liter
MODS	Multiple Organ Dysfunction Syndrome
MRSA	Methicillin-resistant Staphylococcus Aureus
MRSE	Multi-Resistant Staphylococcus Epidermidis
MTC	Minimum Toxic Concentration
NP	Nonparametric Approaches
NPAG	Nonparametric Adaptive Grid
NPB	Nonparametric Bayesian
NPDE	Normalized prediction distribution errors
oC	Degree Celsius
PaO ₂	Partial Pressure of Oxygen
PD	Pharmacodynamics
PK	Pharmacokinetics
PK/PD	Pharmacokinetics/Pharmacodynamics principles
R ²	The observed vs. predicted concentration value
RCA	Regional Citrate Anticoagulation
REDCap	Research Electronic Data Capture
RRT	Renal Replacement Therapy
SCCM	Society of Critical Care Medicine
SCUF	Slow Continuous Ultrafiltration
SD	Standard deviation
SIRS	Systemic inflammatory response syndrome
SOFA	Sequential Organ Failure Assessment
t _{1/2}	Elimination Half-life

TDM	Therapeutic Drug Monitoring
UFH	Unfractionated Heparin
US	United States of America
V	Volume of distribution
V _i	Volume of distribution using inverse approach
VPC	Visual Predictive Checks
VRE	Vancomycin Resistant Enterococci
vs.	Versus
V _t	Volume of distribution using total volume approach
WD	Data from the whole dosing interval
W _t	Body weight
μg	Microgram (s)

1.Introduction and literature review

1.1 Intensive Care Unit (ICU)

Intensive care units (ICU) have a high rate of nosocomial infections that can affect admitted patients. Those patients are highly susceptible to certain types of microorganisms such as *Enterococci* and gram-positive strains of *Staphylococcus aureus*, which are the most common pathogens in ICU (1).

According to evidence, critically ill patients are associated with severe or complex medical conditions (2) such as sepsis, acute kidney injury (AKI), or multiple organ failures (3). Those clinical conditions can affect the body's physiology and significantly alter the pharmacokinetic behaviour of antibiotics (4). In individual patients, changes in the PK parameters can occur due to the alteration of disease severity, as the dose that was appropriate on one day may be inadequate a few days later (5). Therefore, management of antibacterial doses in this population remains challenging (6).

Changes in the body's physiology during critical conditions might cause an alteration in the main PK parameters (7), such as the volume of distribution (V) and plasma clearance (CL) (4, 8). The V represents the relationship between concentration and mass of drug in the body. Alteration of V can be associated with critical illnesses such as sepsis, burn injury, and pancreatitis (5), as changing of extracellular fluid as a result of oedema, hypoalbuminemia or ascites could change V (4). Additionally, acute renal/hepatic dysfunction (8) and fluid resuscitation, which is required in critically ill patients, would cause an increase in V for some antibiotics (5). Alterations of protein bound drug could increase free fraction of drug and thereby increase drug distribution (i.e. increase in V) and drug elimination (i.e. increase in elimination rate constant (Ke)). This increase in either or both Ke or V will lead to an increase in CL parameters of high protein binding drugs in critically ill patients (4, 5). Furthermore, alteration of Plasma Clearance may occur from changes in renal/hepatic impairment and cardiac output (4, 9) as shown in Figure 1. Alternatively, the physicochemical properties of drugs can play roles in the changing PK of drugs, as hydrophilic antibiotics that are strongly protein bound are often associated with high risk of sub-

therapeutic drug concentrations and the need to increase the loading doses in critical illness compared to non-critical illness (4, 5).

Some studies recommend increasing loading doses in order to obtain therapeutic drug concentrations in critically ill patients (4, 10). Thus, sufficient drug concentration is necessary for killing or suppressing the growth of bacteria at the site of infection (6). Therefore, optimisation of antibiotic regimen can be considered for achieving therapeutic drug concentrations. Application of pharmacokinetic/pharmacodynamic principles (PK/PD) can improve clinical outcomes and suppress bacterial resistance (11, 12).

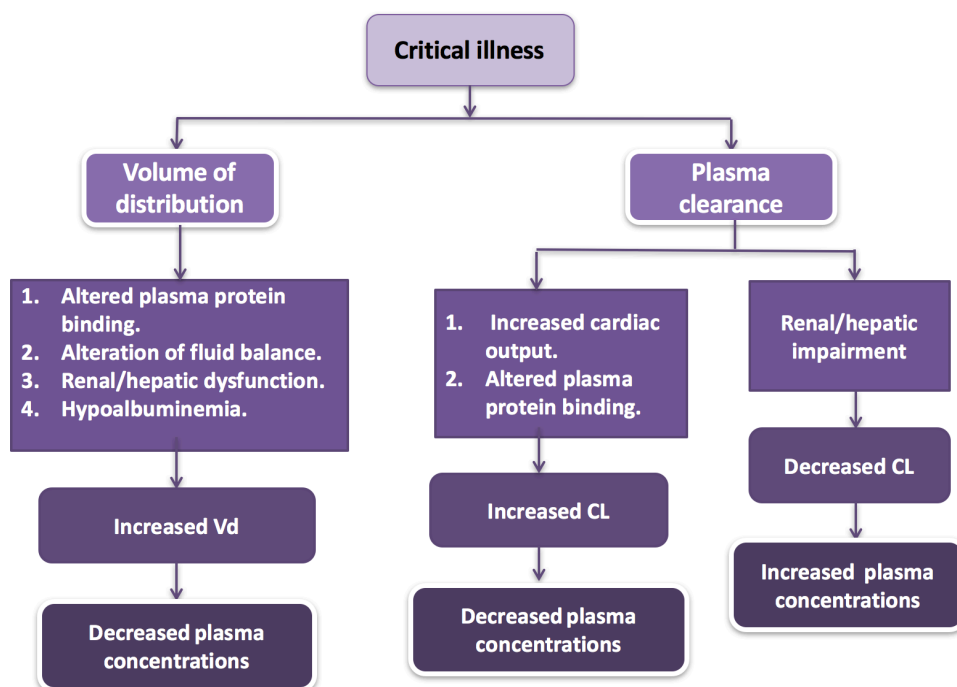


Figure 1: Pathophysiological changes in critical illness.

1.2 Vancomycin

1.2.1 History

In 1952, an organism was isolated from a soil sample named "*Streptomyces orientalis*", which produced a substance "compound 05865". This substance was later called vancomycin and the name derived from the word "vanquish". In 1958, Food and Drug Administration in the United States (US) was approved vancomycin for the

treatment of drug-resistant *Staphylococcus aureus* due to the absence of an adequate alternative (13-15).

1.2.2 Mechanism of Action and Resistance

Vancomycin is a a class of glycopeptide antibiotic with bactericidal activity (16). It binds to the D-alanyl-D-alanine protein of peptide chain of the precursor peptidoglycan subunits and inhibits peptidoglycan cross-linking into the cell wall by preventing them from binding to penicillin-binding proteins, and so inhibits cell wall syntheses and kills the bacteria as summarised in Figure 2 (16, 17). However, some *enterococcus species* have the ability to modify their wall structures by changing the D-alanyl-D-alanine to D-alanyl-D-lactate. By doing so, vancomycin would not be effective against them, thus the peptidoglycan subunits are inserted into the cell wall and generate resistance (17). The first strains of these *enterococci* called vancomycin-resistant enterococci (VRE) were reported in Europe by 1986 and in the United States by 1987 (18).

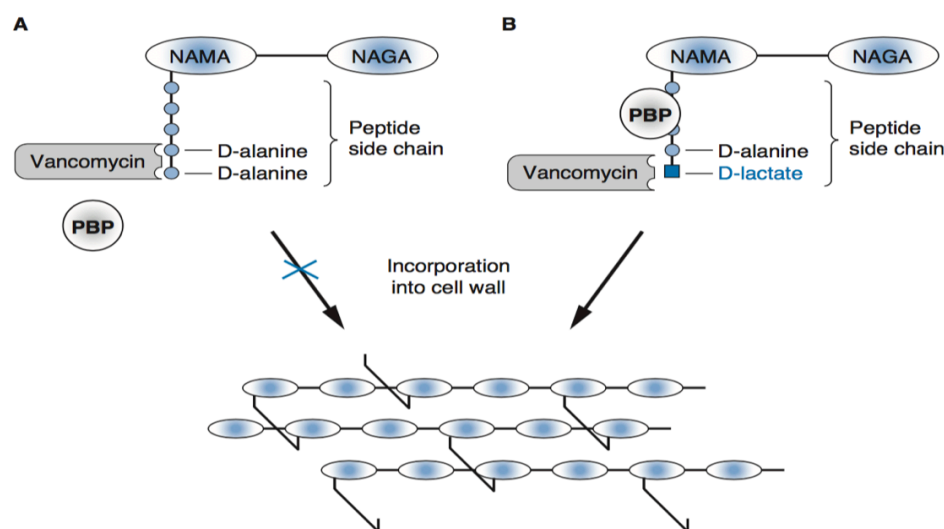


Figure 2: The interaction between vancomycin and bacteria. A) Vancomycin mechanism kills the bacteria and B) mechanism of bacterial resistance. Adapted from Hauser (17).

Moreover, methicillin-resistant *Staphylococcus aureus* (MRSA) developed resistant strains called heteroresistant to vancomycin, which was isolated in Japan. It is still susceptible to vancomycin with minimum inhibitory concentration (MIC) ≤ 4 mg/l, but some of these strains develop resistance to vancomycin (19, 20). Wong *et al.* (21)

reported that vancomycin alone failed to cure four patients with bacteraemia due to *Staphylococcus aureus* with heteroresistance to vancomycin (21).

One of the most important reasons for treatment failure is the development of *Staphylococcal resistance*, which is correlated to long exposure to low serum concentrations of the drug (22). So, application of PK/PD criteria helps to overcome this problem and increase clinical cure especially in ICUs (23). However, there is a limitation in the data available due to high pharmacokinetic variations in clinically ill patients (24, 25).

The ratio of the area under the serum concentration-time curve over a 24-hour period of area under the curve (AUC_{24}) and the MIC are the best PK/PD parameters used to achieve a significant outcome in the vancomycin (22). Some investigators considered that optimal vancomycin efficacy could be achieved with AUC_{24}/MIC ratio ≥ 400 in lower respiratory tract infections caused by *Staphylococcus aureus* (26, 27). *Moise-Broder et al.* (28) measured vancomycin AUC_{24}/MIC in 108 patients and confirmed that (AUC_{24}/MIC ratio of ≥ 400) was correlated to successful clinical effectiveness ($p = 0.0046$) (28).

1.2.3 Clinical Pharmacology of Vancomycin

The vancomycin pharmacokinetic profile is complex and characterised by one-, two- and three-compartment pharmacokinetic patterns (22). In patients with normal kidney function, vancomycin follows α -distribution phase that ranges from 30 min to 1 h, and β -elimination half-life of 6-12h as shown in Figure 3. Vancomycin V ranges from 0.4-1 L/kg (29, 30), and protein binding in range of 10-50% (22, 31). Vancomycin is eliminated completely unchanged in the urine primarily by glomerular filtration (16, 32).

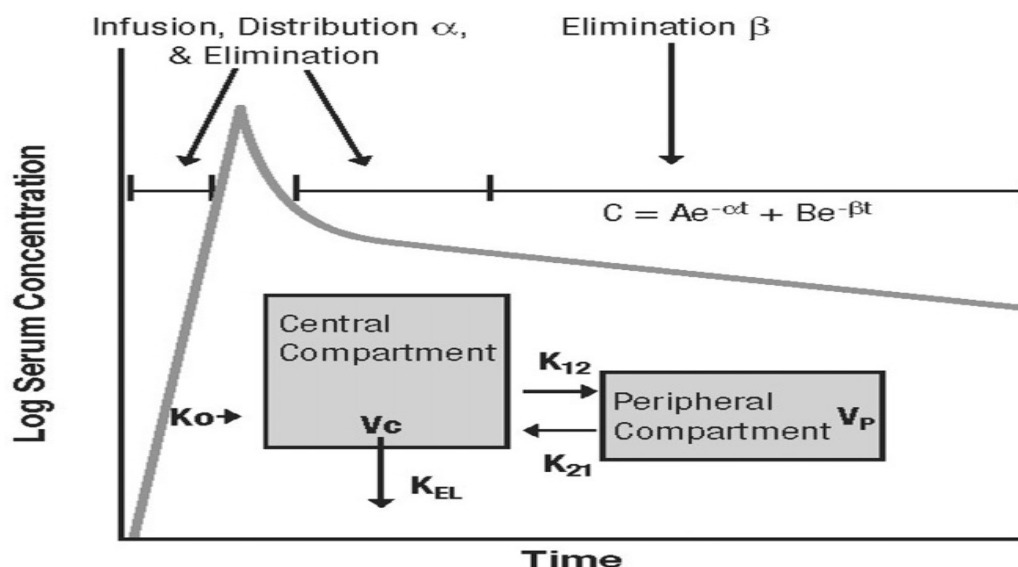


Figure 3: Two-compartment pharmacokinetics diagram. Where C is the concentration, α and β are the rate constants for the distribution and elimination phases respectively, e is the base of the natural logarithm, t is time, A and B are the respective zero time intercepts for α and β , K_o is the infusion rate constant, V_C is the volume of the central compartment, V_P is the volume of the peripheral compartment, K_{12} and K_{21} are inter-compartmental rate constants, and K_{EL} is the elimination rate constant from the central compartment. Taken from Rybak (22).

Vancomycin has low bioavailability (< 10%) and not recommended for oral use. So, intravenous administration (IV) is preferred for systemic infections because some potential toxicity has been observed after oral vancomycin doses in the treatment of pseudomembranous colitis patients (16, 33).

Vancomycin is active and used (i) against most gram-positive organisms including MRSA and multi-resistant *Staphylococcus Epidermidis* (MRSE), as shown in Figure 4, (ii) in treatment of *Clostridium-difficile* that causes diarrhea or other inflammation of the colon and small intestines by using oral vancomycin because its work is limited only for the treatment of intestinal infection, (iii) in patients who are allergic to beta-lactam antimicrobials, (iv) as a surgical prophylaxis for major procedures including implantation of prostheses and patients with prosthetic heart valves undergoing genitourinary or gastrointestinal surgery, (v) in treatment of *Enterococcal* endocarditis when using a combination of vancomycin and aminoglycosides to produce a synergistic effect (13, 34).

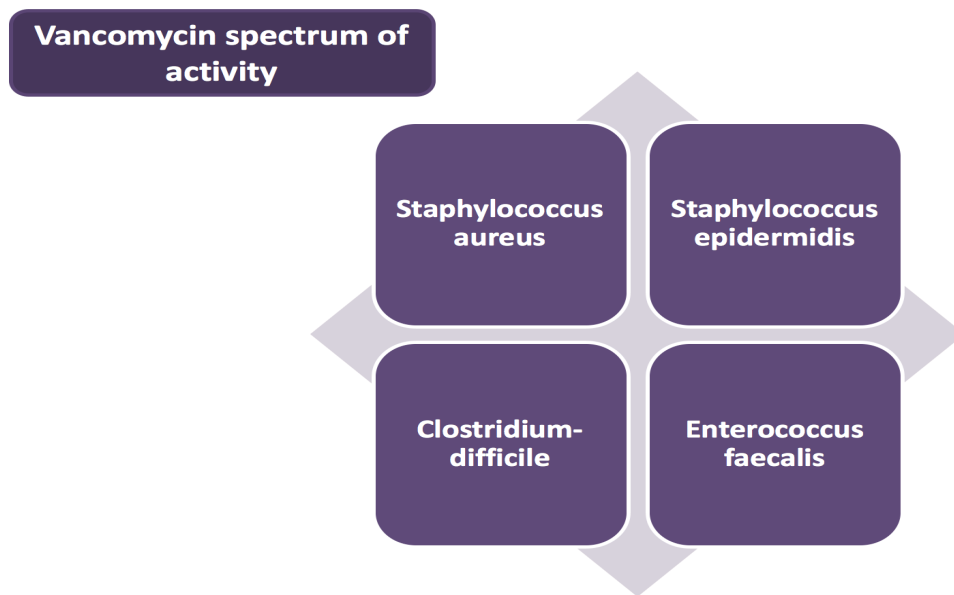


Figure 4: Antimicrobial activity of vancomycin.

The consensus guidelines of American Society of Health-System Pharmacists, the Infectious Diseases Society of America and the Society of Infectious Diseases Pharmacists regarding vancomycin-dosing strategies in adults (35, 36) recommend that:

- In patients with normal renal function the vancomycin IV dose of 15-20 mg/kg (actual body weight) every 8-12 h, not greater than 2 g per dose, is considered to obtain the recommended concentration in the vancomycin MIC of ≤ 1 mg/l.
- In patients with severe illness due to MRSA infection (e.g., sepsis, pneumonia, endocarditis, or meningitis); the considered loading dose is 25-30 mg/kg (actual body weight). The large vancomycin doses can lead to increased risk of red man syndrome and anaphylaxis. Therefore, delaying the infusion time up to 2 h and use of antihistamine is recommended in this case.
- In patients with MRSA infection, the recommended vancomycin trough concentration is 15-20 $\mu\text{g/ml}$.
- Vancomycin trough concentration of 10 $\mu\text{g/ml}$ should be attained to prevent the development of resistance, and it should be at least 15 $\mu\text{g/ml}$ to achieve the target AUC/MIC of 400 for a pathogen with a MIC of 1 mg/l (35-37).

In patients with continuous renal replacement therapy (CRRT), the recommended vancomycin loading dose is 25-30 mg/kg/day followed by maintenance dose of 15-20 mg/kg /day (38).

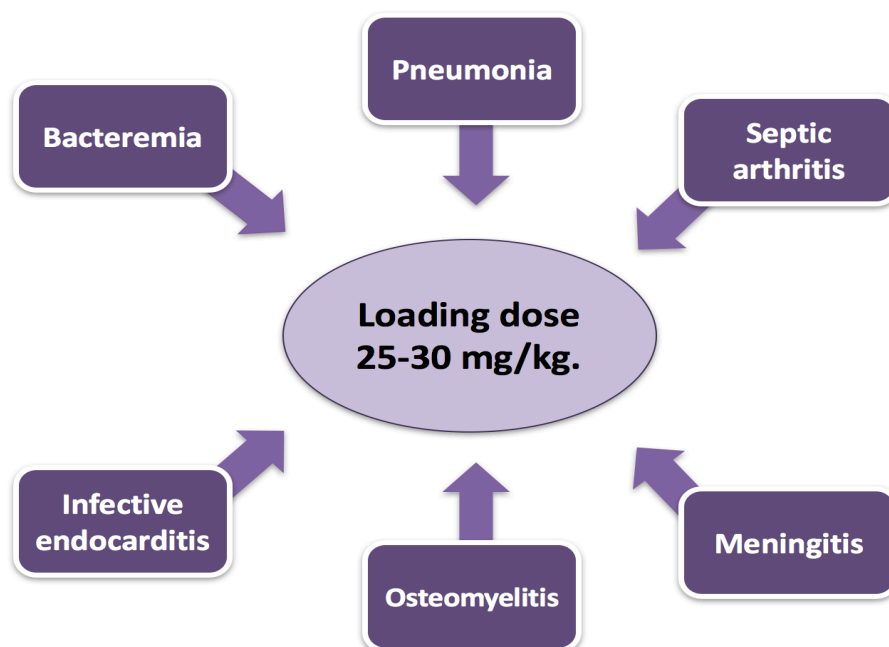


Figure 5: The recommended vancomycin doses for treatment of MRSA infection.

The toxicity associated with vancomycin treatment results from an impurity in the manufacturing process. The most common adverse effects include fever, chills, and phlebitis, which are related to a rapid infusion. Additionally, the rapid infusion of a large dose (>500 mg over ≤30 min) can cause red man syndrome, which is a histamine release phenomenon, described by tingling and flushing of the face and neck (13, 39).

There is some ototoxicity observed in patients with renal failure due to high serum concentration (13). *Farber and Moellering*. (40) reported that no signs of auditory toxicity were observed/detected. However, fever and rash were detected in 1%-3% of patients, phlebitis was noticed in 13% of patients but only 2% of patients needed to discontinue the therapy.

Moreover, the nephrotoxicity due to vancomycin monotherapy was uncommon (5% of patients) and can be reversed (40). Nevertheless, the frequency of nephrotoxicity increased in patients who received the combination of vancomycin and

aminoglycoside (22), 35% of these patients have a noticeable increase in serum creatinine (40).

1.3 Sepsis

Sepsis is a syndrome caused by an infection that changes the body's physiology. It influences the antibiotic pharmacokinetics in critically ill patients. Sepsis is a life-threatening disease costing US hospitals more than \$20 billion in 2011 (41).

In the US alone, the rate of infected patients is up to 750,000 septic patients annually, which costs \$US 17 billion, resulting in 210,000 cases of death (42).

Harrison et al. (43) found that the incidence of admissions with severe sepsis increased to 5.2% and the total number of deaths increased from an estimated 9,000 to 14,000 from 1996 to 2004 in general critical care units in England, Wales and Northern Ireland (43). The incidence of sepsis has increased due to rising population age, number of immunocompromised patients, and antibiotic resistance (12). Sepsis became one of the main causes of mortality around the world (44). It outstrips other diseases such as colon cancer, breast cancer and acquired immune deficiency syndrome (AIDS). The mortality ranges from 30% for mild to moderate sepsis and more than 82% for severe sepsis and septic shock (12, 45).

The Consensus of American College of Chest Physicians (ACCP) Conference and the Society of Critical Care Medicine (SCCM) in 1991 (46) considered the general definition of sepsis as “a systemic inflammatory response to infection”. In 1992, the ACCP/ SCCM Consensus Conference inserted the term “systemic inflammatory response syndrome (SIRS)”, which can be triggered by infection, thermal injury, or trauma. SIRS is identified by the presence of two or more of the clinical criteria in Table 1 (46).

Bone et al. (46) defined sepsis as SIRS triggered by an infection, and severe sepsis can arise in sepsis with failure or dysfunction of one or more organ, hypoperfusion, or hypotension, while septic shock is defined as “sepsis with arterial hypotension despite adequate fluid resuscitation” (46).

Recently, the definition of sepsis has been updated as “life-threatening organ dysfunction caused by a dysregulated host response to infection”, and septic shock as “a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality” (41).

Table 1: Clinical criteria associated with SIRS.

SIRS criteria:
1) Temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$
2) Heart rate $>90/\text{min}$
3) Respiratory rate $>20/\text{min}$
4) White blood cell count $>12000/\text{mm}^3$ or $<4000/\text{mm}^3$

* Adapted from Bone et al. (46)

In sepsis, infection triggers an inflammatory reaction that produces clinical symptoms which include fever or hypothermia, hypoxia, leukocytosis, tachycardia or tachypnea (47). Further changes in blood flow and capillary permeability (48), as well as depression of myocardial function, might lead to end-organ failure. Progression of disease in severe sepsis or septic shock results in multiple organ dysfunction syndromes (MODS) (12). These pathophysiological changes can affect PK parameters which lead to failure to achieve the therapeutic drug concentrations (49).

In renal or hepatic dysfunction patients, accumulation of antibiotic concentration may occur due to a decrease in CL and prolonged elimination half-life ($t_{1/2}$) (12). The progress of organ dysfunction in severe sepsis is determined by various scoring systems that assess the patient's outcome. The most common score used to measure ICU septic patients is the Sequential Organ Failure Assessment (SOFA) which was generated by European Society of Critical Care Medicine (ESCCM) (50).

The SOFA score is a simple score, which evaluates six organ systems (respiratory, coagulatory, liver, cardiovascular, renal and neurological) to describe both the number and the severity of organ failures as described in Table 2. The score varies from 0-4, increasing score numbers are associated with increased organ dysfunction and mortality rate (50). *Acharya et al.* (51) attempted to find the utility of SOFA scoring system in ICU patients with SIRS. It was found that the SOFA score was able to

facilitate clinical course monitoring, patients transferring out of ICU, estimation of organ dysfunction and predict the mortality (51).

Table 2: The Sequential Organ Failure Assessment (SOFA) score*.

system	0	1	2	3	4
Respiration					
Pao ₂ /Fio ₂ , mmHg	>400	≤400	≤300	≤200	≤100
Coagulation					
Platelets x10 ³ μL	>150	≤150	≤100	≤50	≤20
Liver					
Bilirubin,mg/dl	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular	MAP≥ 70 mmHg	MAP< 70 mmHg	Dopamine <5 or dobutamine (any dose) ^b	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1 ^b	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1 ^b
Central-nervous system					
Glasgow Coma Score Scale ^c	15	13-14	10-12	6-9	<6
Renal					
Creatinine,mg/dl	<1.2	1.2-1.9	2.0-3.4	3.5-4.9	>5.0
or urine output,ml/dl				<500	<200

*Adapted from Vincent et al. (50). Abbreviations: PaO₂, partial pressure of oxygen; Fio₂, fraction of inspired oxygen; MAP, mean arterial pressure. ^b Catecholamine doses are given as μg/kg/min for at least 1 hour.

^cGlasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

1.4 AKI and Renal Replacement Therapy (RRT)

AKI is defined as a sudden and continued decrease in kidney function (52). The high variation in the mortality rate of between 28% and 83% in these patients might be due to differences in patient population. In ICU patients, about 5%-25% of these patients have AKI (53). Sepsis is a complex disease in critically ill patients and is often associated with an increase in the risk of AKI development. Consequently, 35% to 50% of AKI in ICU patients can occur due to sepsis disease (53-55).

AKI was found to affect 16.2% of patients, 70.0% of whom required organ support with renal replacement therapy (RRT) (53). RRT is a supportive treatment for the management of AKI, the available RRT modalities include (56, 57):

- Intermittent hemodialysis (IHD).
- CRRT in the form of: slow continuous ultrafiltration (SCUF), continuous venovenous hemodialysis (CVVHD), continuous arteriovenous hemofiltration (CAVH), continuous venovenous hemofiltration (CVVH) and continuous venovenous hemodiafiltration (CVVHDF).
- Peritoneal dialysis.

Despite the difference of the technique used in RRT, the semipermeable membrane is the major principle for unwanted water and solutes removal. The process of water removal through the semi-permeable membrane called ultrafiltration, while solute, can be cleared through either convection or diffusion process (56).

Peritoneal dialysis depends on the diffusion process through peritoneal membrane inside the peritoneal cavity for solutes clearance. It does not need a hospital setting and can be used at home after surgical insertion of a peritoneal catheter, with a high risk of catheter leakage complication (58). Peritoneal dialysis takes around 2 to 4 hours for infusion of 1.5-3L of the solution into peritoneal cavity (56).

In ICU, treatment of AKI can involve both IHD and CRRT (59). IHD is set for removing a large amount of unwanted solutes and water using diffusion process in short periods of time. However, the large volume that is cleaned over the short period

causes hypotension which leads to ischemia of the nephrons and could prevent renal recovery if repeated (56, 59).

CRRT, on the other hand, provides solute clearance in a slow rate through 24 hours per day in ICU as presented in Table 3 (58). It maintains hemodynamic stability with better control of fluid, electrolyte balance, acid-base status and a higher level of biocompatibility; all these features make CRRT preferable to IHD in critically ill patients and hence, it is the best choice in ICU patients suffering from AKI (60, 61). CRRT indicated to support renal function and improve survival in patients with insufficient kidney function as listed in Table 4. Also, it used in patients with unstable conditions such as severe hyperphosphatemia and metabolic acidosis to achieve the therapeutic goal as shown in Table 5 (61, 62). The main technique for solutes transport in CVVH is convection, while in CVVHD is diffusion. The CVVHDF uses both CVVH and CVVHD principles, allowing small solutes to be removed as well as large solutes (60).

Table 3: The differences between intermittent vs. continuous dialysis techniques.

	CRRT	IHD
Time	24 hours	4-6 hours
Dialysis flow rate	0-2 L/h	500-7500 ml/min
Pump speed	100-180 ml/min	200-500 ml/min
Fluid removal	+100ml/h to -500 ml/h	500-1000 ml/h

* Adapted from Pannu and Gibney (58).

Table 4: Indications for initiation of CRRT in ICU patients*.

CRRT indications:
• Nonobstructive oliguria (urine output <200 ml/12 h) or anuria.
• Severe acidemia (pH <7.1) due to metabolic acidosis.
• Azotaemia ([urea] >30 mmol/l).
• Hyperkalaemia ([K+] >6.5 mmol/l or rapidly rising values).
• Suspected uremic organ involvement (pericarditis/encephalopathy/ neuropathy/myopathy).
• Progressive severe dysnatraemia ([Na+] >160 or <115 mmol/l).
• Hyperthermia (temperature >39.5°C).
• Clinically significant organ oedema (especially lung).
• Drug overdose with the dialyzable intoxication.

*Adapted from Bellomo and Ronco (61).

Table 5: Specific renal replacement for therapeutic goals. *

Therapeutic Goal	Hemodynamic Condition	Preferred Renal Replacement Therapy
Fluid removal	Stable	Intermittent Isolated Ultrafiltration (IUF)
	Unstable	SCUF Peritoneal dialysis
Urea clearance	Stable	Intermittent hemodialysis
	Unstable	CRRT: Convection—CAVH, CVVH. Diffusion—CAVHD, CVVHD. Both—CAVHDF, CVVHDF.
Severe hyperkalemia	Stable/unstable	Intermittent hemodialysis
Severe Metabolic Acidosis	Stable	Intermittent hemodialysis
	Unstable	CRRT
Severe Hyperphosphatemia	Stable/unstable	CRRT

*Adapted from Murray and Hall (62). Abbreviation: CAVH, continuous arteriovenous hemofiltration; CVVH, continuous venovenous hemofiltration; CAVHD, continuous arteriovenous hemodialysis; CVVHD, continuous venovenous hemodialysis; CAVHDF, continuous arteriovenous hemodiafiltration; CVVHDF, continuous venovenous hemodiafiltration; CRRT, continuous renal replacement therapy; SCUF, Slow Continuous Ultrafiltration.

During the flow of blood into the CRRT circuit and in contact with tubing and filters, there is a possibility for clotting to occur. Anticoagulation is considered to prevent clotting of filters and membranes and optimises circuit life (63, 64). However, a higher risk of endothelial disruption and coagulopathy in critically ill patients may cause bleeding with excessive anticoagulation (65). The most widely used systemic anticoagulation in CRRT are heparins (66), other options include regional citrate, protease inhibitors and thrombin inhibitors are listed in Table 6. In contrast, CRRT can be performed without any anticoagulation in patients who have a high risk of bleeding (coagulation disorders, thrombocytopenia and recent surgery) (65, 67).

Table 6: Anticoagulation strategies for clotting prevention in CRRT.

Anticoagulation options:
• Systemic Anticoagulation: Heparins and heparinoids.
• Minimal Systemic Anticoagulation: Prostacyclin and prostaglandin E₁ and protease inhibitors.
• Regional Anticoagulation: Citrate and unfractionated heparin-protamine.

1.4.1 Heparins

Heparins consist of unfractionated heparin (UFH) and low molecular weight heparin (LMWH) (65). UFH is inexpensive and is one of the main anticoagulants applied in CRRT. The anticoagulation effect is illustrated by enhancing the response of antithrombin, inhibiting factors Xa, and thrombin IIa (65). Use of heparin anticoagulant requires monitoring to determine the anticoagulant effect and prevent haemorrhagic complications. Various techniques are used to measure heparin therapy: activated partial thromboplastin time (aPTT) and activated clotting time (ACT). There are several studies recommending aPTT as a gold standard for unfractionated heparin therapy monitoring (68). The most evident complications linked with heparin are systemic bleeding and heparin-induced thrombocytopenia (69).

1.4.2 Regional Citrate Anticoagulation (RCA)

Clotting occurs through a specific coagulation cascade and calcium plays an important role in this clotting cascade. Citrate has been used as an anticoagulant agent during CRRT because it chelates ionized calcium and decreases its concentration in blood. Citrate is metabolised by liver, kidney and muscle cell after being transformed into citric acid. In the case where the metabolism of citrate was not reduced, citrate accumulation will occur leading to metabolic complications. This problem can be avoided by metabolic monitoring (65). *Kutsogiannis et al.* (70) studied the effectiveness of regional citrate anticoagulation (RCA) vs. systemic heparin

anticoagulation for CRRT and found that RCA has an advantage of prolonged dialysis “circuit life” and less bleeding over systemic heparin in critically ill patients with AKI. Therefore, it was advised to be the best anticoagulant choice in patients at both high risk and non-high risk for haemorrhage during CRRT (70).

1.5 Pharmacokinetics (PK)

Understanding a drug’s behaviour inside the body is very important to estimate the efficacy of drugs. This occurs by studying the pharmacokinetics (PK), which are defined as a measurement drug process (absorption, distribution, metabolism and elimination) that describes the movement of the drug inside the body. On the other hand, pharmacodynamics (PD) describes the pharmacological effect through certain interaction between drug and body at the site of action (7, 71).

Studying a drug’s behaviour requires the simplification of body processes, which are carried out by the application of mathematical principles that are represented using a model (72, 73). There are different types of models, where PK models can be used to describe and estimate plasma drug concentrations over time after drug administration (74). Moreover, PK/PD models integrate the PK and PD models in order to enhance therapeutic effects of dose regimens and decrease adverse effects as well as reducing resistance to antimicrobials (75) and understanding the dose-response-exposure correlation (76). While the compartmental model approach is a relatively simple approach and can be used to study drug’s behaviour (72, 73).

Theoretically, the body is divided into multiple compartments models (one-compartment, two-compartment and multi-compartment) that can be used to estimate and describe the drug concentration-time curve. It assumes (i.e. as a mathematical not physiological model) that each compartment represents a group of tissues or organs that have identical blood flow and drug properties. In the mathematical model, distribution to/from these groups of tissues can be represented by one-compartment for each group of tissues. The highly perfused organs that include the heart, kidneys, blood, liver and lungs are represented in one compartment called the central compartment. The muscle tissue, cerebrospinal fluid and fat tissue, which have lower blood perfusion, are known as the peripheral compartment (72).

The one-compartment model is a simple model as shown in **Figure 6**, in which all tissues are represented by one compartment; this assumes drug distribution occurs straight away after dose administration. On the other hand, the drug distribution in a two-compartment model has rapid distribution into highly perfused tissues in the central compartment. The drug also distributes at a slower rate into the peripheral compartment until equilibration is achieved between the two compartments. Initially, drug concentration declines rapidly due to the fast transfer from central to the peripheral compartment; this is known as the distribution phase. The drug concentration then declines more slowly after equilibrium, and this is known as the elimination phase (73).

Pharmacokinetic parameters such as CL, V, and bioavailability (75) can be estimated from either individual pharmacokinetics or population pharmacokinetics. The individual pharmacokinetics study drug concentration in an individual while ignoring any associated inter-individual variability. Whereas, the population pharmacokinetics characterise the drug's kinetics in a population, where inter-individual variability is included in the total variability (77).

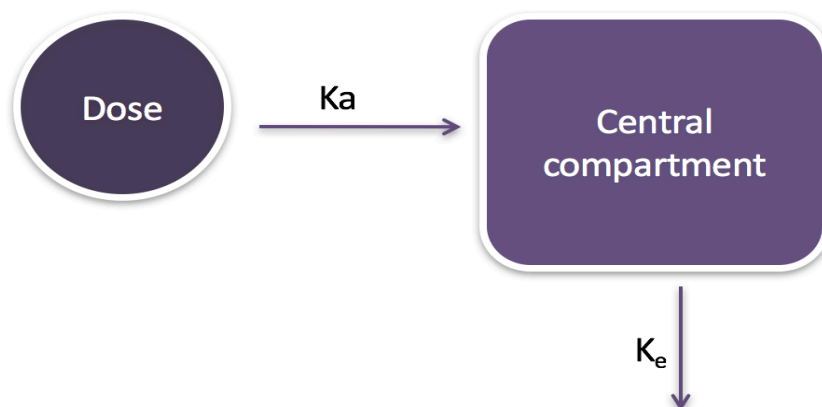


Figure 6: One-compartment pharmacokinetic model. Abbreviation: K_a , absorption rate constant; K_e , elimination rate constant.

1.5.1 Population Pharmacokinetics

Population pharmacokinetics can be defined as the study of the variability in plasma concentrations and kinetic drug behaviour in a target population. This approach of pharmacokinetics concentrates on different kinds of features that vary between individuals: certain demographical and pathophysiological features, which are responsible for some changes in the drug concentrations. Application of population PK facilitates the use of sparse data and also dense data, or even a combination of dense/sparse data to gain integrated information on pharmacokinetics. This gives population PK a great advantage for analysing the data from a variety of unbalanced design studies or even from those that have been excluded because they do not lend themselves to regular forms of pharmacokinetic analysis (78). Different statistical methods applied to analyse population PK models are explained in the following sections.

1.5.1.1 Naïve Pooled Data analysis

The Naïve Pooled Data (NPD) approach fits the data of all individuals together and is considered as coming from a single individual. It is a general and easy approach that can be applied to routine pharmacokinetic data, experimental data and nonstandard data. However, the disadvantages of this approach including (i) poor parameter estimation, and (ii) variability sources are distracted or not available (79).

1.5.1.2 The Two-Stage approach

The two-stage approach is known as the traditional pharmacokinetic analysis. Population PK parameters are performed over two stages. The first stage utilises non-linear regression of individual rich data then uses these individual parameters as input data for statistical calculation such as covariance and variance of parameter estimates and mean parameter of these parameters is estimated in the second stage (78, 79).

1.5.1.3 Non-linear Mixed Effects approach

The non-linear mixed effects approach is a mathematical/statistical model which obtains the data from all individuals for the estimation of population parameters, as well as the variability within and between individuals (inter-individual and intra-individual) and residual (80). It uses the population instead of individuals for estimates of population parameters and their covariates. The non-linear mixed effects model is convenient to use in observation data (fragmentary, sparse and unbalanced data) and in dense data (78). This approach consists of structural, covariate and statistical model (81).

Population PK is able to estimate the unknown population distribution using data collected from nonlinear models. It can be performed by applying either parametric or nonparametric (NP) approaches. Each approach can be divided into Bayesian or maximum likelihood methods as summarised in Figure 7 (82). The NP approach advantages properties over the parametric approach, including superiority for detection of PK/PD and outliers within a study population. Additionally, the discrete nature of the NP approach enables it to achieve target concentration with maximum precision in individual patients (83).

Nonparametric approach (NP):

This approach includes two general NP algorithms: (i) NP Adaptive Grid (NPAG), (ii) NP Bayesian (NPB) both used for estimation of unknown population distribution as a discrete distribution in PK dataset. NPAG discovers unexpected sub-group and outliers and allows calculation of the maximum likelihood estimate rather than approximate likelihoods. NPB gives a Bayesian estimate of unknown population distribution with rigorous credibility intervals around all parameter estimates (82).

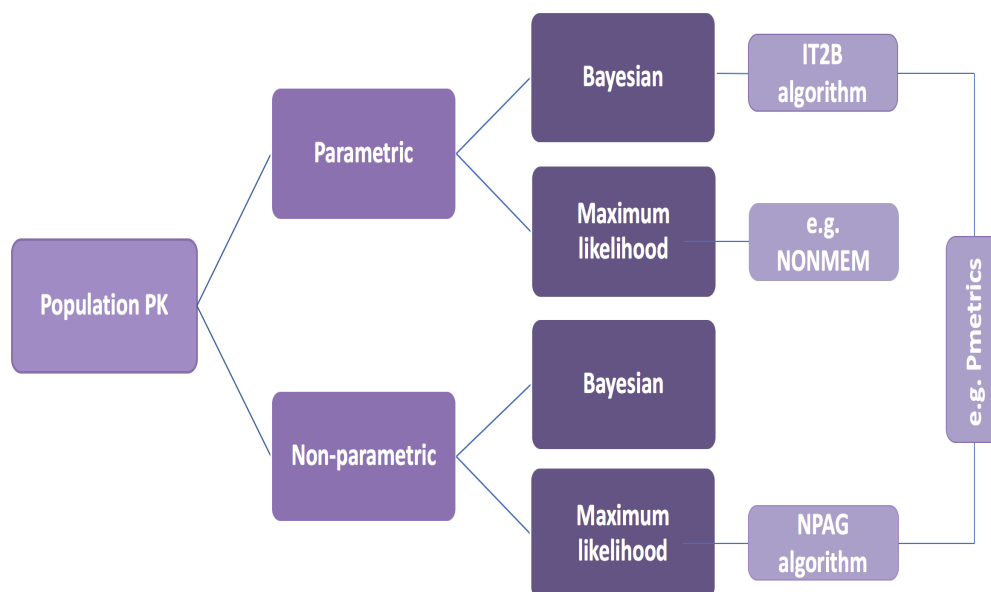


Figure 7: Population PK classification.

1.5.2 Pmetrics Modelling and Simulation

Pmetrics is a short term for pharmacometrics. It is software freely available for download from LAPK website at <http://www.lapk.org>. This software is used in PK research for obtaining parametric and non-parametric population and individual modelling and simulation. It is composed of various programs: Iterative 2-stage Bayesian (IT2B) as a parametric method, Non-Parametric Adaptive Grid (NPAG) algorithms as a non-parametric method and a simulator program (83, 84), as summarised in Figure 7. Running the model in Pmetrics needs model and data files as shown in Figure 8, which illustrates how Pmetrics is processed using the R package. The structure of the model files used in the current study is described in section 3.2.2. After completing a successful running, the NPAG output report is generated which includes: the predicted observed plots for the population and the individual posterior estimates, convergence plots, marginal plots, parameter values, and the summary of the main information from run (see appendix 8.1 for more details).

The PK parameters variability can be estimated in the form of inter-individual, intra-individual, and residual in the parametric population-PK analysis (e.g. NONMEM), but Pmetrics, using the NP approach, estimates the PK variability in general (i.e. population variability). It is helpful to apply the population predicted model from

Pmetrics on new patients to estimate the PK. However, The posterior estimate for a new patient outside the model-building cohort needs a special software, e.g. Best Dose, which is freely available at the laboratory of applied pharmacokinetics and bioinformatics website (www.lapk.org).

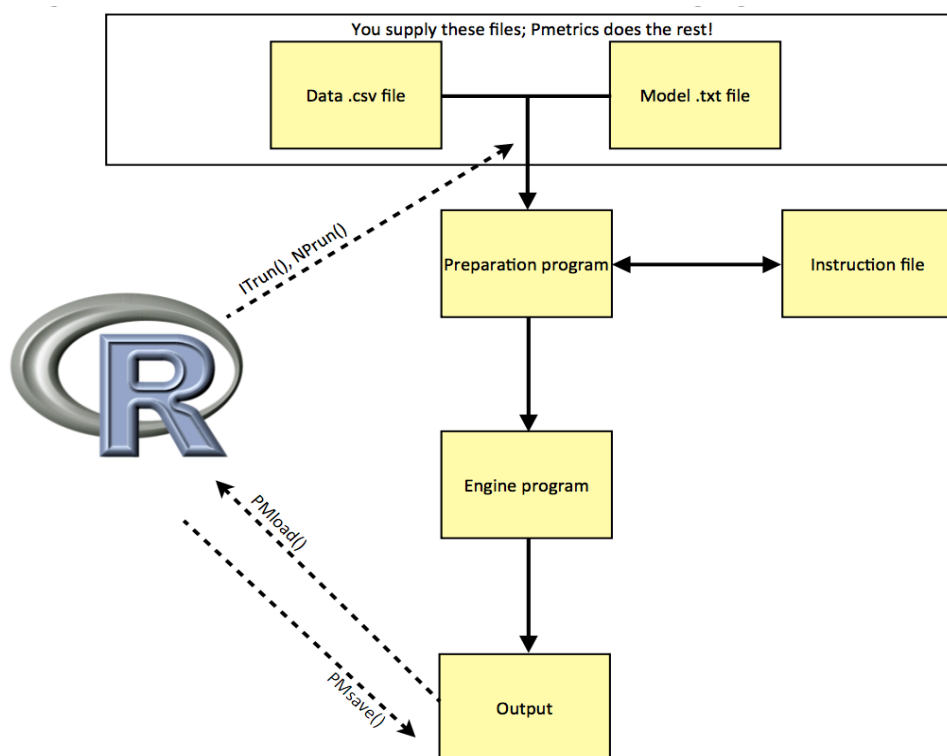


Figure 8: General Pmetrics diagram for IT2B and NPAG workflow. Adapted from Pmetrics manual (85).

1.6 PK of Vancomycin during CRRT Dialysis

Critically ill patients with severe sepsis receiving RRT can be exposed to suboptimal antibiotic concentrations during standard dosing as a result of alterations in antibiotic pharmacokinetics. This change represents the complex interactions between the patient, the mode of CRRT used and the drug. The drug properties that allow it to be cleared efficiently include: a small V , molecular weight < 5000 Da, and low plasma protein binding (86).

DelDot et al. (86) found that the drug clearance during continuous CVVHD or CVVHDF is significantly higher than other forms of CRRT used. Up to 60% of vancomycin was removed over a 12 h period, therefore around three-quarters of vancomycin

clearance was eliminated by CVVHDF. In extracorporeal clearance, if it outstrips 25-30% of total body elimination, it is considered clinically significant. CVVHDF clearance was 1.8 (0.4) L/h and represented 76% of total body clearance. Therefore, elimination of vancomycin by CVVHDF is clinically significant (86). Similar findings have been shown in other studies, *Roberts et al.* (55), reported that there is a positive relationship between effluent flow rate and extracorporeal CL of vancomycin (55).

Furthermore, *Muhl et al.* (87) studied six patients treated with vancomycin infusion during CVVH or CVVHDF and reported that extracorporeal vancomycin CL was significantly higher during CVVHDF than during CVVH (87). The effectiveness of CVVHDF to eliminate drugs could be affected by the severity of sickness, the severity of hypoalbuminemia, and the degree of residual renal function; all these parameters affecting the therapeutic concentration of vancomycin (88, 89).

Besides, *Beumier et al.* (90) found that the intensity of CRRT(CVVHDF, CVVH) could possibly impact on vancomycin CL (90). *Covajes et al.* (91) have shown that using continuous vancomycin infusion with standard doses of 16-35 mg/kg/day are adequate in most critically ill patients receiving CRRT to achieve therapeutic drug concentration. This study found a relationship between CRRT intensity and vancomycin doses and should take into account that higher vancomycin doses are needed with greater CRRT intensity to obtain adequate drug concentrations. They reported that the drug clearance could be changed by RRT parameters which include: blood flow rate (BFR), ultrafiltration rate and dialysis rate that might increase drug requirements. Also, the elimination of vancomycin can be considerably influenced by non-renal clearance during CRRT (91). Other study suggested that there was some non-renal elimination between 30% and 50% of total body CL which can affect vancomycin pharmacokinetics (32).

Udy et al. (32) used the data presented in the study by *Covajes et al.* (91) for studying vancomycin PK in critically ill patients receiving a continuous infusion of CVVHDF or CVVH. Whereas *Covajes et al.* (91) found a correlation between CRRT and vancomycin dose (it was a statistical correlation) (91), no correlation was discovered in this large retrospective analysis between PK parameters and CRRT parameters (32).

One study found that the pharmacokinetics of vancomycin may be affected by the age of critically ill patients. *Mo et al.* (88) studied pharmacokinetic parameters of vancomycin in elderly critically ill patients aged ≥ 72 years. The result found that the elderly critically ill patients had V and $t_{1/2}$ greater than non-elderly patients and CL was higher in these elderly patients compared with non-elderly critically ill patients. These findings suggest the need to monitor vancomycin concentrations to avoid the risk of adverse effects. Dose adjustments are also required to maintain therapeutic drug concentrations (88).

1.7 Therapeutic Drug Monitoring (TDM)

Therapeutic drug monitoring (TDM) is a clinical technique used to measure the drug concentration, maintain the therapeutic level in the blood and therefore improve the dosage regimens. It is necessary for drugs with a narrow range therapeutic index to maintain the drug within therapeutic ranges (i.e. above MIC and below the Minimum Toxic Concentration (MTC)), thereby avoid adverse effect or toxicity and used to achieve a target concentration as shown in **Figure 9**. It can also be used for drugs with high variable PK estimates, drugs that are associated with a notable adverse effect and that are difficult to monitor their target concentration (92).

It was found that the TDM of vancomycin can reduce the rate of nephrotoxicity and raises the efficacy rate in patients who have Gram-positive organism infections, which suggest the routine monitoring of serum vancomycin concentrations, especially in patients with a risk of changing vancomycin pharmacokinetics (93).

The accurate method used for monitoring vancomycin efficacy is the trough serum concentration, and trough samples should be taken just prior the next dose (i.e. when the steady state is attained) (35-37), while peak serum concentration should be taken 1–2 h after the end of infusion. In serum vancomycin monitoring, consideration of trough level should be taken for patients: (i) receiving a high dose or prolonged courses of ≥ 5 days, (ii) with MRSA infection, (iii) on dialysis or with unstable renal function, (iv) using a combination of vancomycin with nephrotoxic agents. It is considered appropriate once per week in patients with stable renal function and frequently in patients with unstable renal function (38).

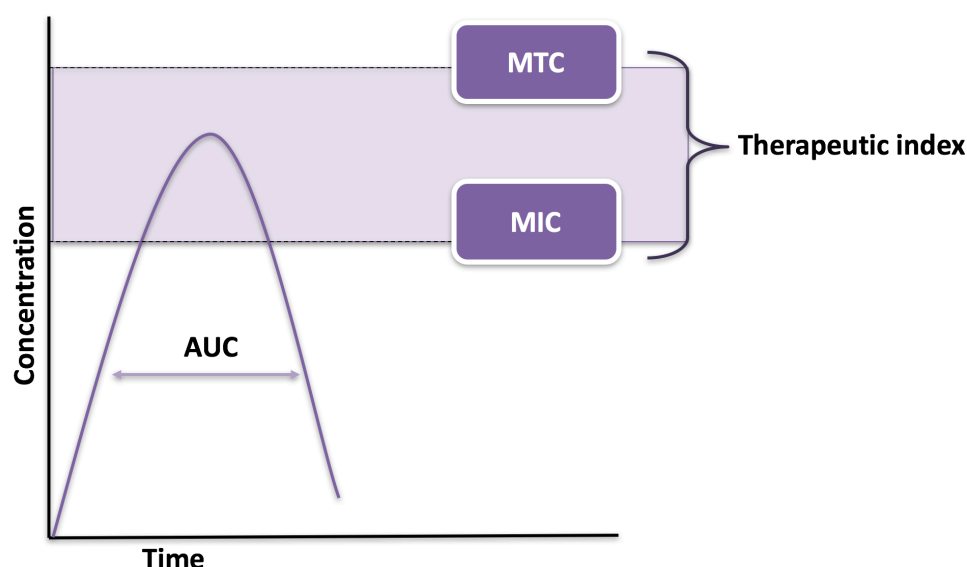


Figure 9: Therapeutic drug range after drug administration diagram. Abbreviation: MTC, minimum toxic concentration; MIC, minimum inhibitory concentration; AUC, Area Under the Curve.

1.8 Electronic Health Records (EHR) and their Optimal Use for PK Analysis

As PK analysis requires numerical and categorical quantitative data, and benefits from large amounts of data, the automated extraction of PK-relevant data from an electronic health record (EHR) holds potential for conducting more frequent and more rapid PK analyses for patient cohorts of interest.

Often clinical research data is collected manually from patient files or manually from the EHR unless there is a method available to extract the relevant data automatically. EHR can be defined as a computerised system able to collect patient's clinical information in electronic form. The digital format allows the recording of a wide range of data including: demographics, medications, laboratory test results, medical history, diagnosis, vital signs and other clinically relevant information in the hospital. It provides clear, effective and quick clinical information and is easy to access using the network by health care providers from different health care organisations and facilitates changing the clinical data electronically better than the paper records. The term electronic medical record (EMR), is a kind of EHR, and refers to patient's medical history in only one health care organisation (94). The other kind is the

electronic patient's records (EPR) defined as "all patients clinical information from a particular hospital" (95). It should be considered the various types of EHR and not confuse them in data collection of clinical research.

1.8.1 Intellivue Clinical Information Portfolio (ICIP)

Intellivue Clinical Information Portfolio (ICIP) is the EHR system used in the ICU. ICIP allows clinicians to access clinical information that is needed to enable them to decide on specific clinical support for patients' care anywhere. It connects all patient data. A patient's flow sheet consists of vital signs, lab results, patient observations, pathology reports, electronic record of medication orders, planned interventions and other information that helps to eliminate transcription errors and time lost recording data by hand (96), as presented in Figure 10.

Admission Discharge Flowsheets Medication Orders Work Folder Medical Notes Investigations Nursing Notes Wounds Microbiology Lab Data Dietetics Physiotherapy	24hr Flowsheet	02/09/2016	01:00	02:00	03:00	04:00	05:00	06:00	07:00
VS Graph	Vas cath site check			blood color		blood color		blood color	
Cardiovascular/Vital Signs	Hepatitis Screen								
Respiratory	Dialysate Hemosol BO 5000...	0	0	0	0	0	0	0	(0)
Neurology	Rate	2000	2000	2000	2000	2000	2000	2000	1500
Gastrointestinal	0								
Medications	Action								
Intake/Drug Infusions	Bag changed		Changed		Changed		Changed		
Output	Cosign		✓		✓				
Totals & Balance	Electrolytes to Dialysate Bag		KCL 20m...						
Nutritional Calcs	Replacement Hemosol BO 5...	0	0	0	0	0	0	0	(0)
Dialysis Therapies	Rate	200	200	200	200	200	200	200	200
Daily Checks/Lines	0								
Patient Care	Action								
Scores	Bag changed								
Weaning	Cosign								
Labs	PBP Solution Hemosol BO 5...	0	0	0	0	0	0	0	(0)
	Electrolytes added to PBP B...		KCL 20m...						
	Effluent rate	4000	4000	4000	4000	4000	4000	4000	3000
	Calcium ratio								
	Ionised Calcium								
	HCO3 Actual	25		25		24		24	
	HCO3 STD	25		24		24		25	
	Deaeration Chamber Check:	Fluid Leve...	Fluid Leve...	Fluid Leve...	Fluid Leve...	Fluid Leve...	Fluid Leve...	Fluid Leve...	
	Access Pressure	-132	-122	-121	-115	-114	-121	-118	
	Filter Pressure	223	225	220	222	228	232	230	

Figure 10: ICIP flow sheet contains all the patient data that helps clinicians to improve patient care.

1.9 Automated Data Extraction Systems

The data from EHR can be collected manually or can be automatically extracted. However, an automated data extraction process requires stringent validation procedures to ensure that the extracted database is complete and accurate and is usually established by using statistical methods. Thus, it is important that validation

occurs before doing any analysis to ensure there are no mistakes when collecting the data, and to ensure the quality of data in terms of consistency of location (97, 98).

1.9.1 Research Electronic Data Capture (REDCap)

Research Electronic Data Capture (REDCap) is a web-based application designed securely for building and managing online survey of coded-anonymised databases quickly and securely to support clinical research and other data types for different purposes. It can also be used for extraction and amalgamation of large and detailed datasets. REDCap was generated at Vanderbilt University in 2004 and is now supported by a global consortium of a non-profit organisation. It allows the user to access the data collaboratively from multiple sites on the same data, validate the data in real time, central storage of data and backups, export data to statistical packages (SAS, R, and SPSS) and facilitate bulk import of data from other systems (99, 100), as shown in Figure 11.

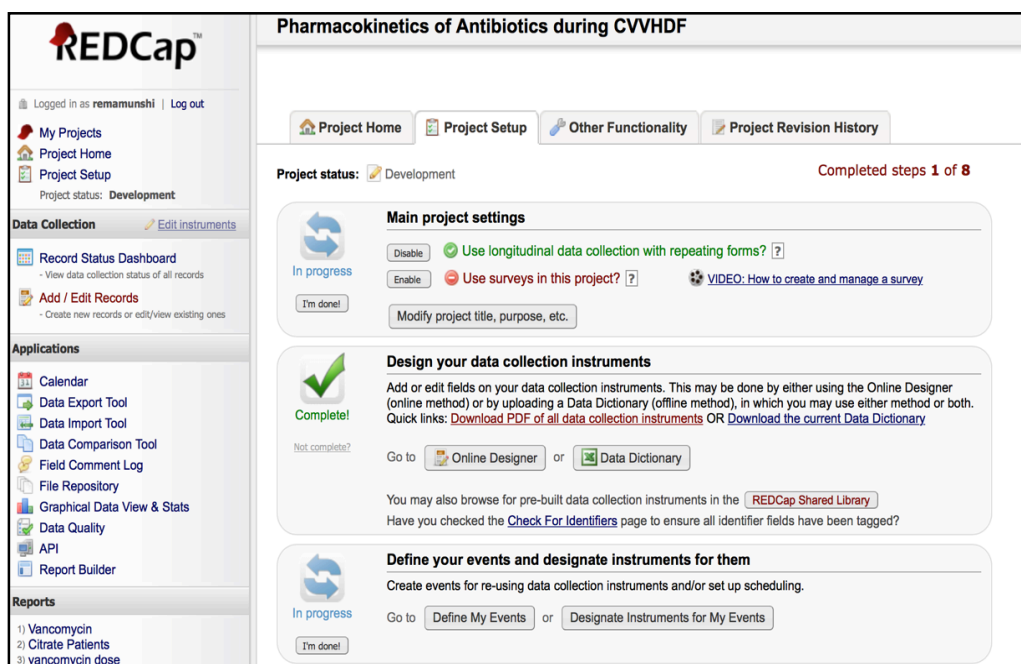


Figure 11: REDCap website provides access for building and managing the data.

The validation of automated data extraction can be assessed by the application of the following concepts:

- ***Completeness:*** demonstrates the availability and accuracy of data; investigates the presence or absence of data, and the agreement between different sources of data.
- ***Correctness:*** refers to the proportion of the data to be correct; shows if the data from the EHR is correct or not, comparing the data by using gold standard and identifying errors.
- ***Concordance:*** describes the compatibility, consistency and display agreement of data within various EHR sources.

These concepts estimated by methods include:

- Gold standard.
- Data element agreement.
- Element presence.
- Data source agreement: comparing data from different sources to define the agreement.
- Cross validity (98).

2.Aims and objectives

2.1 Study aims

This study aims to:

- Describe the population pharmacokinetics of vancomycin administered by intermittent infusion in critically ill patients receiving CVVHDF through different anticoagulant modalities, along with identified covariates. The population PK analysis aims to support vancomycin dosing regimen design.
- To explore the potential of automatic data extraction from EHR for population PK analysis.

2.2 Current objectives

Specifically, the objectives of this project were to:

- Generate a structural base model to describe the PK parameter estimates and the performance of the model.
- Build covariate models with allowing an intercept for detection of significant relationships between relevant covariates and parameter estimates.
- Explore continuous covariates associated with CVVHDF, clinical and demographic characteristics to identify those associated with a PK model.
- Explore categorical covariates of dialysis anticoagulant modalities used to identify those associated with a PK model.
- Suggest covariates for consideration for a) initial dosing/dose adjustment, b) for design of prospective PK studies.
- Perform the validation of automated data extraction method.

3. Methodology

3.1 Study design of retrospective PK analysis

This retrospective study was performed in the ICU Department of Tallaght Hospital (Dublin, Ireland) between 22nd January 2015 and July 2016. This study protocol was approved by the SJH/AMNCH research ethics committee. All data in this study was coded-anonymised to ensure data protection and confidentiality policy and legislation and was recorded manually from the ICIP EHR system on the ICU.

3.1.1 Patient section

Critically ill adult patients who were treated with vancomycin and requiring CVVHDF were eligible for inclusion in this study.

Inclusion criteria:

- Aged > 18 years.
- Non-pregnant and non-lactating females.
- Received vancomycin for one or more dose interval.
- Experienced at least one peak and trough level through the treatment course.
- One course per patient was included.

Patients with no dialysis data or those who had dialysis data and vancomycin doses that did not overlap for at least one vancomycin-dosing interval were excluded.

3.1.2 Vancomycin treatment

All patients received vancomycin via intermittent IV infusion using an infusion pump. The vancomycin was administered through an infusion rate of 10mg/min where it is in the drug library of the pump. Vancomycin is available in the form of 500 mg and 1g dry powder vial, diluted with either sodium chloride 0.9% or glucose 5%, by adding 10ml or 20 ml, respectively for reconstitution of the powder. Then the intermittent IV infusion is prepared by adding the reconstituted doses to an appropriate volume according to the hospital vancomycin monograph.

Infusion start times were considered as the time of first sign off/co-sign (which gives the exact time of the dose administration). Also, peak levels were recorded and peak times based on 60 minutes after the end of the infusion. The end of infusion was calculated as the dose multiplied by the infusion rate from the recorded start time, and times of trough levels were assumed to 5 minutes before the next dose. The hospital ICU protocol considers 60 minutes after the end of infusion as a time for the peak sample and just before the next dose for trough sample (the hospital protocol is in the appendix 8.2).

3.1.3 RRT

CRRT was received by insertion of a catheter into the subclavian, femoral or jugular vein through double-lumen. The modality of CRRT was CVVHDF through intermittent infusion using a prismaflex® machine, with a polyacrylonitrile hemofilter. The BFR used was approximately 120-220 ml/min, and the effluent flow rate (EFR) was calculated by the formula: (dialysate rate + replacement rate + ultrafiltration rate), and the rate was approximately 2000-4771 ml/kg/h. Most patients commenced dialysis on the same day of vancomycin therapy. However, some of them commenced dialysis before or after a few days of vancomycin treatment. When the anticoagulant was used, systemic heparin or RCA was used as an anticoagulant to minimise clotting into the circuit.

3.1.4 Data collection

The clinical data for all patients enrolled were collected for the PK study. This data included: demographics, hospital and ICU length of stay, hospital diagnosis, date of ICU admission, mortality outcome, and fluid data in the form of cumulative fluid balance were documented. Additionally, all vancomycin doses and times, time of admission, and microbiological data in the form of peak and trough levels were recorded, along with times of levels as described in section 3.1.2. The Acute Physiology and Chronic Health Evaluation (APACHE) II score was recorded on admission for measuring patients' severity of illness. Also, the SOFA score was recorded on the first day of ICU admission.

3.2 PK analysis

3.2.1 Compartmental PK

The PK analysis was conducted using a one-compartment model to illustrate the concentration-time course of vancomycin by using the population PK software program Pmetrics (version 1.4.1; University of Southern California, Los Angeles, CA, USA [<http://www.lapk.org/Pmetrics.php>]) (83). Essentially, Pmetrics needs to embed R program (version 3.2.2, Institution for Statistics and Mathematics, Vienna, Austria [<http://www.R-project.org/>]) (84) and Fortran software programs in order to run.

3.2.2 Model building

In Pmetrics workflow, the structure of model files must have at least three important blocks: (i) primary block, (ii) outputs block and (iii) error block, as shown in Figure 12.

Primary block:

Primary block details the variable parameters with a defined range designed for parameter estimation, for example, K_e and V as presented in Figure 12.

Output block:

This contains the output equations in the form of $Y(\text{output equation number}) = \text{expression}$. The expression can contain covariates and primary or secondary variables, e.g.:

$$Y(1) = X(1)/V \quad (85)$$

Error block:

The Error block is used to describe the structure of the error model in the model file. The lambda error term in our study is explained as:

$$\text{Error} = (SD^2 + \lambda^2)^{0.5} \quad (85)$$

where lambda is the error term used to capture extra process noise associated with the observation and SD is the standard deviation (SD) of each observation [obs]. The four terms C_0 , C_1 , C_2 , and C_3 were used with a polynomial equation using:

$$C_0 + C_1[\text{obs}] + C_2[\text{obs}]^2 + C_3[\text{obs}]^3 \quad (85)$$

The recommended starting value for C_0 can be set using a generic coefficient, which is set as half of the lowest concentration in the data, C_1 can be 0.15, C_2 and C_3 set as 0. Also, an initial lambda value can be calculated using $3 \times C_0$ for good quality data and $5-10 \times C_0$ for poor quality.

```
#Primary
Ke,0.001,0.12
V,43,139

#Out
Y(1) = X(1)/V

#Err
L=0.1
0.1,0.15,0,0
```

Figure 12: Model file structure with the main blocks. Abbreviation, L= lambda.

3.2.3 Model development

Development of vancomycin PK models requires at first a base structural model including a set of parameter estimates. Particular covariates can then be added after initial structural model fitting.

3.2.3.1 Base structural models

As only peak and trough data were available in this study, PK modelling was limited to a one-compartment model. This model was used to analyse PK parameters in terms of V, CL and Ke. Therefore, we used two structural models. The first was the Ke and V model and the second was the CL and V model. We will use “CL model” for “CL

and V model” as an abbreviation. The CL model was applied by using the following equation:

$$K_e = CL / V \quad (1)$$

3.2.3.2 Covariate models

Changes in vancomycin PK can occur due to high individual variation. This variation can be described by using a set of related covariates. Thus, covariate analysis processes help to detect the relationship between PK parameters and covariates of interest. So, we classified our covariates into categorical and continuous covariates.

3.2.3.2.1 Categorical Covariate Dialysis (CCD) models

Categorical Covariate Dialysis (CCD) models consist of three different categories of anticoagulation mode and dialysis status: citrate anticoagulation, non-citrate anticoagulation, and no dialysis. Then, according to the method used we divide the CCD data into subgroups: CCD All Patients (CCD-AP) and CCD Groups (CCD-G) as presented in Figure 13.

CCD-AP is a model used to describe the 3 different dialysis modes (citrate, non-citrate, and no dialysis) for all patients in one model file and applied to K_e , V , both K_e and V together, and to CL parameters according to the following equations:

- **For K_e parameter estimate:**

$$k_e = K_{e1} * ((\text{Citrate}) * (\text{DIAL})) + K_{e2} * ((1 - \text{CITRATE}) * (\text{DIAL})) + K_{e3} * (1 - \text{DIAL}) \quad (2)$$

- **For V parameter estimate:**

$$V = V_1 * ((\text{Citrate}) * (\text{DIAL})) + V_2 * ((1 - \text{CITRATE}) * (\text{DIAL})) + V_3 * (1 - \text{DIAL}) \quad (3)$$

- **For both K_e and V parameter estimates:**

Both equations (2) and (3) were used.

- **For CL parameter estimates:**

$$K_e = CL / V \quad (1)$$

$$CL = CL_1 * ((\text{Citrate}) * (\text{DIAL})) + CL_2 * ((1 - \text{CITRATE}) * (\text{DIAL})) + CL_3 * (1 - \text{DIAL}) \quad (4)$$

where:

All dosing intervals assigned 0 or 1 for each of the following:

Citrate = dosing intervals on citrate anticoagulant modality.

DIAL= dosing intervals on dialysis.

whereas, other CCD dosing intervals can be interpreted as:

1-DIAL = dosing intervals on non-dialysis status.

1-Citrate = dosing intervals not on RCA.

CCD-G are models used to illustrate the 3 different groups (citrate, non-citrate, and no dialysis). Dosing intervals have been assigned to groups according to the anticoagulant modalities and dialysis status during those dosing intervals. Then one model file was used for each group, which estimated K_e and V parameters without using any categorical covariate equation because each patient in each group has similar characteristics (same anticoagulant modality and same dialysis status).

An initial condition equation was used to designate the CCD-G models for intervals which were not the first dose. In the initial condition (IC), we used the measured trough concentration "TROUGH" prior to an observed dose by application of the following equation under "IC" block in the model file:

$$X(1) = \text{TROUGH} * V.$$

where "X" is a mass of drug in the compartment.

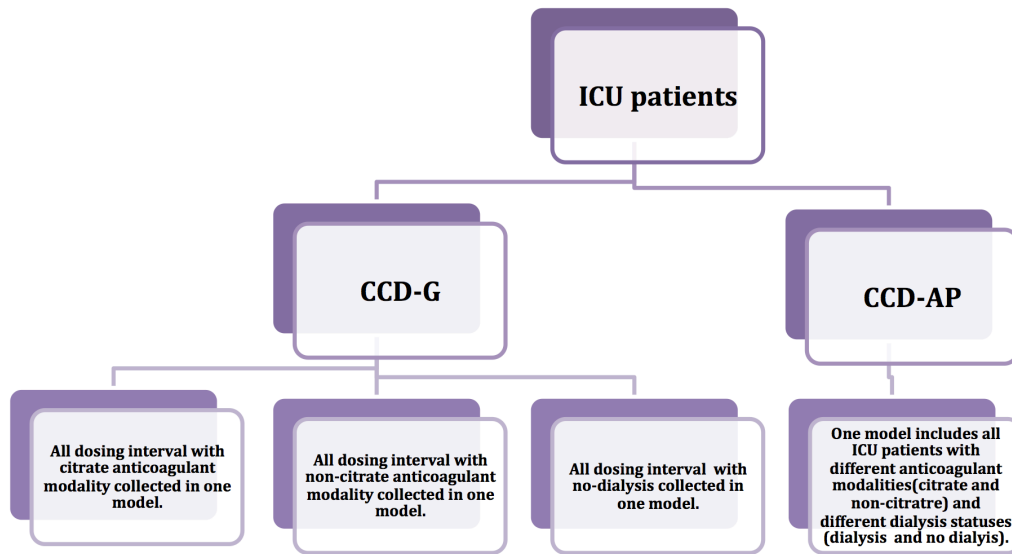


Figure 13: CCD model groups in ICU patients.

3.2.3.2.2 Continuous covariate models

Continuous covariates included: BFR, Fluid balance (FB), EFR, Albumin level (Alb), age and body weight (Wt). Then, we classified all of the BFR, FB, and EFR data into two different classes: data taken from 4 hours closest to dose “4h” and data from the whole dosing interval “WD”. The inverse method models were used to reflect the negative correlation between the covariate and the PK parameters estimate.

3.2.3.2.2.1 BFR models

BFR 4h and WD data were applied to Ke, V, both Ke and V together and to CL parameters using the *non-inverse, including an intercept* approach according to the following equations:

- **For Ke parameter estimate:**

$$Ke = Ke_1 + Ke_2 * (BFR / \text{average BFR}) \quad (5)$$

- **For V parameter estimate:**

$$V = V_1 + V_2 * (BFR / \text{average BFR}) \quad (6)$$

- **For both Ke and V parameter estimates:**

Both equations (5) and (6) were used.

- **For CL parameter estimate:**

$$K_e = CL/V \quad (1)$$

$$CL = CL_1 + CL_2 * (BFR / \text{average BFR}) \quad (7)$$

Then, we used the *inverse, including an intercept method* with covariate data for 4h and WD applied to K_e and V parameters according to the following equations:

- **For K_e parameter estimate:**

$$K_{ei} = K_{e1} + K_{e2} * (\text{average BFR} / BFR) \quad (8)$$

- **For V parameter estimate:**

$$V_i = V_1 + V_2 * (\text{average BFR} / BFR) \quad (9)$$

where:

Identical equations were used with appropriate covariate data for either 4h or WD models.

3.2.3.2.2.2 FB models

FB 4h and WD data were applied to K_e , V , both K_e and V together and to CL parameters using the *non-inverse, including an intercept* approach according to the following equations:

- **For K_e parameter estimate:**

$$K_e = K_{e1} + K_{e2} * (FB / \text{average FB}) \quad (10)$$

- **For V parameter estimate:**

$$V = V_1 + V_2 * (FB / \text{average FB}) \quad (11)$$

- **For both K_e and V parameter estimates:**

Both equations (10) and (11) were used.

- **For CL parameter estimate:**

$$K_e = CL/V \quad (1)$$

$$CL = CL_1 + CL_2 * (FB / \text{average FB}) \quad (12)$$

Then, we used the *inverse, including an intercept method* with covariate data for 4h and WD applied to Ke and V parameters according to the following equations:

- **For Ke parameter estimate:**

$$Ke_i = Ke_1 + Ke_2 * (\text{average FB} / \text{FB}) \quad (13)$$

- **For V parameter estimate:**

$$V_i = V_1 + V_2 * (\text{average FB} / \text{FB}) \quad (14)$$

Also, FB 4h and WD data were applied to the V parameter estimate using the *total volume* (no intercept) approach according to the following equations:

- **For V parameter estimate:**

$$V_t = V_1 * (\text{FB} / \text{average FB}). \quad (15)$$

where:

Identical equations were used with appropriate covariate data for either 4h or WD models.

3.2.3.2.2.3 EFR models

EFR 4h and WD data were applied to Ke, V, both Ke and V together and to CL parameters using the *non-inverse, including an intercept* approach according to the following equations:

- **For Ke parameter estimate:**

$$Ke = Ke_1 + Ke_2 * (\text{EFR} / \text{average EFR}) \quad (16)$$

- **For V parameter estimate:**

$$V = V_1 + V_2 * (\text{EFR} / \text{average EFR}) \quad (17)$$

- **For both Ke and V parameter estimates:**

Both equations (16) and (17) were used.

- **For CL parameter estimate:**

$$Ke = CL / V \quad (1)$$

$$CL = CL_1 + CL_2 * (\text{EFR} / \text{average EFR}) \quad (18)$$

Then, we used the *inverse, including an intercept method* with covariate data for 4h and WD applied to Ke and V parameters according to the following equations:

- **For Ke parameter estimate:**

$$Ke_i = Ke_1 + Ke_2 * (\text{average EFR} / \text{EFR}) \quad (19)$$

- **For V parameter estimate:**

$$V_i = V_1 + V_2 * (\text{average EFR} / \text{EFR}) \quad (20)$$

where:

Identical equations were used with appropriate covariate data for either 4h or WD models.

3.2.3.2.2.4 Alb models

Alb was applied to Ke, V and to CL parameters using the *non-inverse, including an intercept* approach according to the following equations:

- **For Ke parameter estimate:**

$$Ke = Ke_1 + Ke_2 * (\text{Alb} / \text{average Alb}) \quad (21)$$

- **For V parameter estimate:**

$$V = V_1 + V_2 * (\text{Alb} / \text{average Alb}) \quad (22)$$

Also, Alb was applied to the Ke and V parameter estimates using the *total volume approach* according to the following equations:

- **For Ke parameter estimate:**

$$Ke_t = Ke_1 * (\text{Alb} / \text{average Alb}) \quad (23)$$

- **For V parameter estimate:**

$$V_t = V_1 * (\text{Alb} / \text{average Alb}) \quad [24]$$

- **For CL parameter estimate:**

$$Ke = CL / V \quad (1)$$

$$CL_t = CL_1 * (\text{Alb} / \text{average Alb}) \quad (25)$$

Then, we used the *inverse, including an intercept method* with Alb data for 4h and WD applied to K and V parameters according to the following equations:

- **For Ke parameter estimate:**

$$Ke_i = Ke_1 + Ke_2 * (\text{average Alb} / \text{Alb}) \quad (26)$$

- **For V parameter estimate:**

$$V_i = V_1 + V_2 * (\text{average Alb} / \text{Alb}) \quad (27)$$

- **For both Ke and V parameter estimates:**

Both equations (26) and (27) were used.

3.2.3.2.2.5 Age covariate models

Age was applied to Ke, V and to CL parameters using the *non-inverse, including an intercept* approach according to the following equations:

- **For Ke parameter estimate:**

$$Ke = Ke_1 + Ke_2 * (\text{AGE} / \text{average AGE}) \quad (28)$$

- **For V parameter estimate:**

$$V = V_1 + V_2 * (\text{AGE} / \text{average AGE}) \quad (29)$$

- **For CL parameter estimate:**

$$Ke = CL / V \quad (1)$$

$$CL = CL_1 + CL_2 * (\text{AGE} / \text{average AGE}) \quad (30)$$

Also, age was applied to the Ke and V parameters estimates using the *total volume approach* according to the following equations:

- **For V parameter estimate:**

$$V_t = V_1 * (\text{AGE} / \text{average AGE}). \quad (31)$$

- **For Ke parameter estimate:**

$$K_{et} = Ke_1 * (\text{AGE} / \text{average AGE}). \quad (32)$$

3.2.3.2.2.6 Wt models

Wt was applied to V and CL parameters using the *non-inverse, including an intercept* approach according to the following equations:

- **For V parameter estimate:**

$$V=V1+V2*(Wt/ \text{average } Wt) \quad (33)$$

- **For CL parameter estimate:**

$$Ke=CL/V \quad (1)$$

$$CL=CL1+CL2*(Wt / \text{average } Wt) \quad (34)$$

Then, Wt was applied to V parameter estimate using the *total volume approach* according to the following equation:

- **For V parameter estimate:**

$$Vt=V1 *(Wt / \text{average } Wt) \quad (35)$$

3.2.3.3 Model selection

Identification of an improved or deteriorated model depended on comparing the values of $-2*\log\text{-likelihood}$ value ($-2*LL$), Akaike's Information Criterion value (AIC), Bayesian or Schwartz Information Criterion (BIC) as well as the evaluation of the visual diagnostic scattered plots of Goodness-of-fit that detects the observed vs. predicted concentration based on (the observed vs. predicted concentration value (R^2), bias, and Imprecision) and residual plots. The observed vs. predicted plots are generated for both the population model and also the posterior individual model. Bias and imprecision statistics were calculated based on the following equations:

Bias = Σ weighted prediction error / N.

Imprecision= Σ weighted squared prediction error / N – mean weighted prediction error² (85)

To identify an improved model the observed vs. predicted plots were considered, and those with a higher R^2 for predicted vs. observed data were considered first for models including covariates, then the lowest $-2*LL$, AIC and BIC were considered for statistical improvement over the base model.

3.2.3.4 Model evaluation

Assessing and checking the effectiveness of covariate model was carried out by applying internal validity techniques.

3.2.3.4.1 Internal validation

The internal validation methods are used to assist the model selection through several internal approaches:

- **Observed vs. predicted plotting and associated residuals outputs:**

An approach used is to plot the observed against the predicted data to compare the dataset along with exploration of the residuals plots for model assessment. The residuals output includes three panels (85):

- a) weighted residuals(predicted – observed) vs. time.
- b) weighted residual vs. predicted concentration.
- c) a histogram of residuals with a normal curve, which assesses by using normality tests.

- **Normalized prediction distribution errors (NPDE) and visual predictive checks (VPC)**

This is an option available in Pmetrics which is useful for assessing the internal model validation based on simulation. Each subject data is a basis for generating e.g. 1000 simulation profiles, the plot is presented in quantiles (5%, 25%, 50%, 75% and 95%) and the observed data can be compared to the distribution of simulated data. VPC plots can be more cumbersome after including covariates in the model (85).

3.3 Statistical analysis

Statistical analyses for numeric, clinical and demographic data is represented as the mean $\pm$ SD, median, interquartile range (IQR) and range. The structural and covariate models comparison was made statistically by performing the likelihood ratio test, the reduction of $-2*LL$ against X^2 distribution with consideration of the appropriate degrees of freedom.

Furthermore, univariate and multivariate regression analyses were performed to give us some suggested information about the relationship between the PK parameter estimates and covariates. More specifically, the univariate regression analysis was undertaken using SPSS statistical program (version 24, IMP SPSS), whereas multivariate regression analysis was carried out using (PM-step) in Pmetrics program.

PM-step is a function used in the Pmetrics program to estimate the linear regression of multivariate p-values for each covariate vs. posterior parameter values. Using PM-step is suggested to be useful for detection of the covariates to retain in the final model (85). In the current study, a P-value of (<0.05) is considered statistically significant and (<0.005) is a highly statistical significance.

3.4 Validation of automated data extraction from ICIP

The validation study was conducted on 22 patients treated with vancomycin using CVVHDF in 2014. This data set was separate to that for the PK analysis described in the previous sections. The relevant data had been previously automatically extracted by the nephrology team. The nephrology team generated an in-house method for automated data extraction intended for population PK analysis of vancomycin data in patients on CVVHDF using PERL and MySQL open source technologies. These methods were based on an identification of appropriate patient and data fields within ICIP, which were then targeted for automated data extraction. The selected anonymised data was automatically extracted to REDCap (101). Consequently, the corresponding data was manually retrieved from ICIP, in order to validate the automated data extraction method.

In this study, the completeness, correctness, and concordance validation techniques were used to compare the data uploaded to the REDCap system with clinical data that was collected from the following hospital electronic sources:

- ICIP system.
- Laboratory information system (Key).

The Key system is the internal hospital intranet portal for accessing patients' laboratory data. The data is recorded first in this system, and then the relevant data is taken from Key to be uploaded in ICIP. This uploaded data was previously validated prior to installation of ICIP for use on the ICU.

3.4.1 Cross Systems Validation

The two systems (ICIP and REDCap) have been compared with regard to three concepts. Firstly, the completeness concept was applied to all data to check the availability and the accuracy of the vancomycin data.

This helped to investigate the presence or absence of any data by using the element present method for all data that had been retrieved from ICIP. The second concept is the correctness that was used to check if the data on REDCap was correct and there were no errors relating to data on ICIP by using ICIP as gold standard. The third concept is assessing the concordance using compatibility and consistency between ICIP and REDCap data using data source agreement method. This was achieved by subtracting ICIP value from REDCap and the results should be zero (at accuracy of least precise metric) as shown in Figure 14.

V	W	X	Y	Z	AA	AB	AC	AD	AE	AF	AG
Dose-vanco-ICIP	Dose-vanco-redCap	Round	ICIP-redCap	% difference	Acceptable	Time-start-ICIP	Time-start-redCap	Round	(redCap-ICIP)	difference-in min	Acceptable
1500	1500		0			15:00	15:00		0.00		
1500	1500		0			16:00	18:30		02:30		
1500	1500		0			16:00	16:00		00:00		
1500	1500		0			16:00	16:00		00:00		
1500	1500		0			17:00	16:00		01:00		
1500	1500		0			05:00	05:02		0.00		
1500	NA					04:00					
1500	NA					16:00					
1500	1500		0			06:00					
						16:00					
						04:00					
1500	1500		0			17:30	17:30		00:00		
1500	1500		0			17:30	17:00		00:30		
1250	1250		0			18:47	17:00		01:47		
						17:00					
750	750					10:00	10:00		00:00		
1500						15:59					
750	750		0			16:00	16:00		00:00		
750	750		0			04:00	04:00		00:00		
750	750		0			16:00	16:00		00:00		
750	750		0			04:00	04:00		00:00		
1250	1250		0			18:00	18:00		00:00		

Figure 14: Example of validation excel sheet comparing vancomycin doses between ICIP and REDCap.

For concordance, the three systems (ICIP, REDCap, and Key) were compared using the vancomycin level reported by microbiology (peak and trough levels), by subtraction of the REDCap value from the ICIP value and subtraction of the REDCap value from the Key value; the results should be zero (at accuracy of the least precise metric) as presented in Figure 15.

AZ	BA	BB	BC	BD	BE	BF	BG	BH	BI	BJ
Peak-Level-ICIP	Peak-level-Key	Peak-Level-redCap	Round	Round	(redCap-ICIP)	%difference	Acceptable	(redCap-Key)	%difference	Acceptable
N/a										
21.2mg	21.2	21.2								
21.7mg	21.7	21.7			0			0		
N/a										
30.7mg	30.7	30.7			0			0		
N/A	N/A	N/A								
19.8mg	19.8	19.8			0			0		
24.9mg	24.9	24.9			0			0		
28.1mg	28.1	28.1			0			0		
25.0mg	25	25			0			0		
N/A	N/A	N/A								
37.7mg	37.7	37.7			0			0		
20.4mg	20.4	20.4			0			0		

Figure 15: Example of validation sheet comparing peak levels between different systems.

4. Results

4.1 Clinical PK analysis

4.1.1 Patient demographics and clinical characteristics

During the study period, 35 patients were treated with vancomycin who also received CVVHDF therapy, three patients of whom were excluded because their effluent flow rate data was not available in the ICIP system and a further patient was excluded as an outlier (patient number 32). A final total of 31 patients were included in this analysis. The total of vancomycin doses was 234 doses with 140 peak levels and 140 trough levels. The mean $\pm$ SD of the dose was 1131.4 ± 286.3 , the mean $\pm$ SD of peak level was 31 ± 7.8 , and the mean $\pm$ SD of trough level was 16.4 ± 6.17 . Table 7 shows the main demographic and clinical characteristics and Figure 16 provides the mortality data in the hospital and the ICU department.

Table 7: Patient demographic and clinical characteristics.

Characteristics of patients *	Mean	Standard deviation	Median
Age (years)	64.1	13.46	67.0
Sex (Male/Female)	21/10	-	-
Weight (kg)	80.1	21.59	76.9
BMI (n=28), 10 of those 28 patients had BMI > 30	28.6	7.37	27.0
Hospital length of stay (days)	54.0	57.0	36.0
ICU length of stay (days)	20.0	22.0	12.0
SOFA-score at admission (day)	11.6	3.39	11.0
APACHE II score at admission day (n=29)	22.3	5.45	23.0
Vancomycin dose (mg)	1131.4	286.3	1000.0
Peak levels (mg/L)	31.0	7.8	29.4
Trough levels (mg/L)	16.4	6.17	15.6

* total patient number =31. Abbreviations: BMI is the Body mass index, SOFA-score is the Sequential Organ Failure Assessment score, APACHE II score is the Acute Physiology and Chronic Health Evaluation.

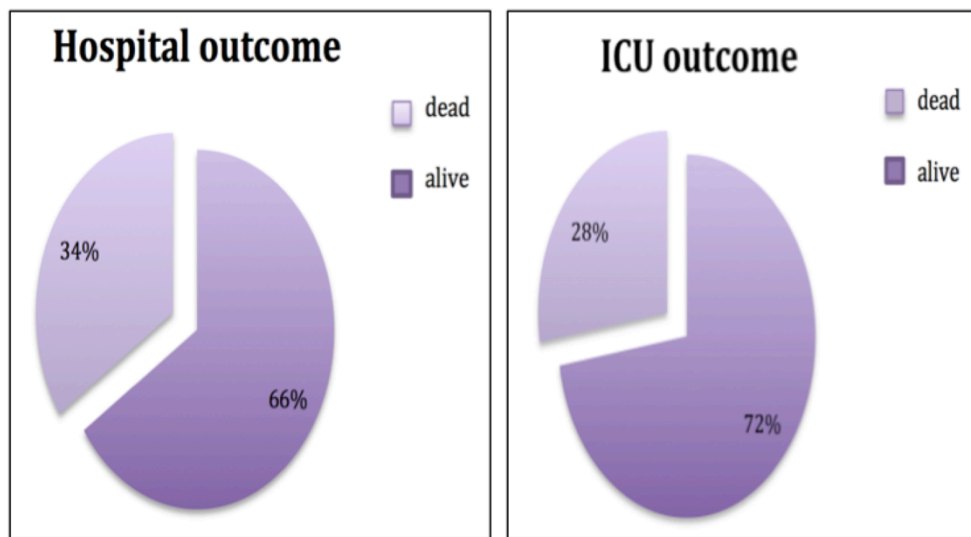


Figure 16: ICU and hospital mortality outcome(n=29).

- **Data Refining:**

Patient number 32 was excluded from the population analysis as an outlier because he had high K_e and CL estimate values, which were not observed in other patients as shown in Figure 17 and Figure 18. We found that he had the lowest trough level over all patients and was admitted post cardiac arrest and was receiving vancomycin before ICU admission. So the low trough level suggests that this patient possibly could not get the whole dose immediately prior to admission to ICU, as he deteriorated from sepsis at around the time that the vancomycin infusion being administered. This reason could explain the low trough level and the high PK estimates in this patient because his condition worsened further and he was then started on the CVVHDF in ICU.

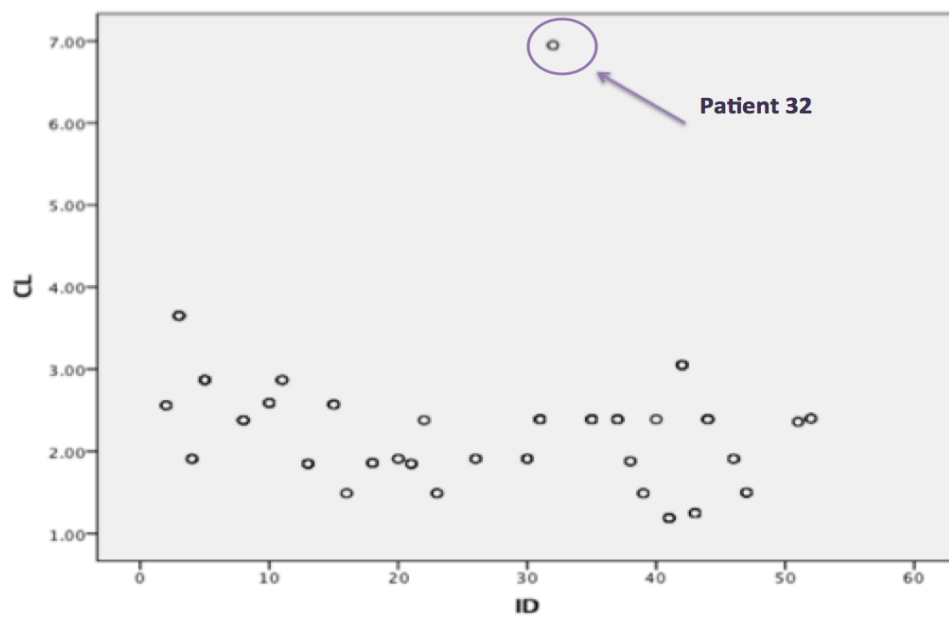


Figure 17: Scatter plot of CL parameter estimate with patients study number (ID).

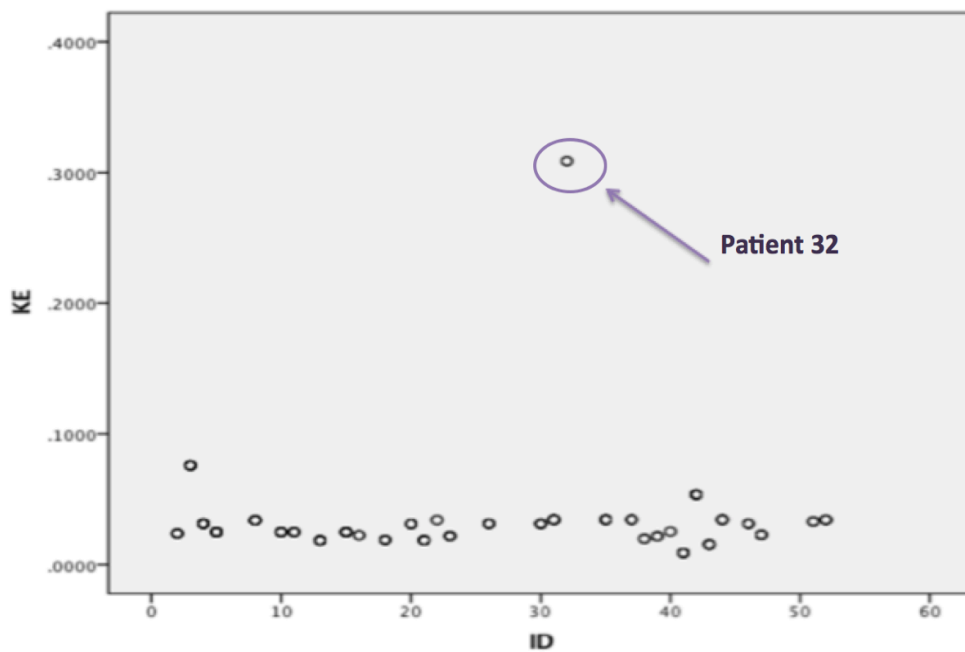


Figure 18: Scatter plot for Ke parameter estimate with patients study number (ID).

4.1.2 Base structural model

Building the base model was implemented (one-compartment model) in order to fit the structural model. This structural model can consist of CL, V and Ke parameters. These parameters were used in 2 base models: (i) CL, V (referred to as the CL model) and (ii) Ke, V. Pharmacokinetic parameter estimates from those base models are provided in Table 8.

Table 8: PK parameter estimates of vancomycin base models.

Model	parameter	Mean	SD	Coefficient of variation	Median
a)	Ke (h)	0.03	0.01	44.3	0.03
	V (L)	80.65	22.65	28.08	70.17
b)	CL (L/h)	2.16	0.57	26.78	2.15
	V (L)	80.7	22.74	28.18	70.16

4.1.3 Population PK analysis of the base model

It can be seen from the data in Table 9 that the base models using either Ke and V or CL and V were similar in terms of $-2*LL$, AIC, BIC, bias and imprecision. The V parameter was almost identical in the two structural models as set out in Table 8. The goodness-of-fit plots carried out from diagnostic plots as shown in Figure 19 and Figure 20, illustrate the observed vancomycin concentration versus the predicted concentration of both population and individual posterior data for Ke and CL respectively.

Table 9: Statistical comparison of pharmacokinetic base models.

				Population				Individual			
Parameter	-2*LL	AIC	BIC	R ²	Bias	Imp	Slope	R ²	Bias	Imp	Slope
Ke,V base model	1678	1684	1694	0.51	0.47	1.77	0.70	0.81	-0.1	0.51	1.05
CL,V base model	1678	1684	1694	0.51	0.48	1.77	0.70	0.81	-0.09	0.50	1.05

Abbreviations: -2*LL, -2*Log-likelihood value; AIC, Akaike's Information Criterion value; BIC, Bayesian or Schwartz Information Criterion value; R², the observed vs. predicted concentration value; Imp, imprecision.

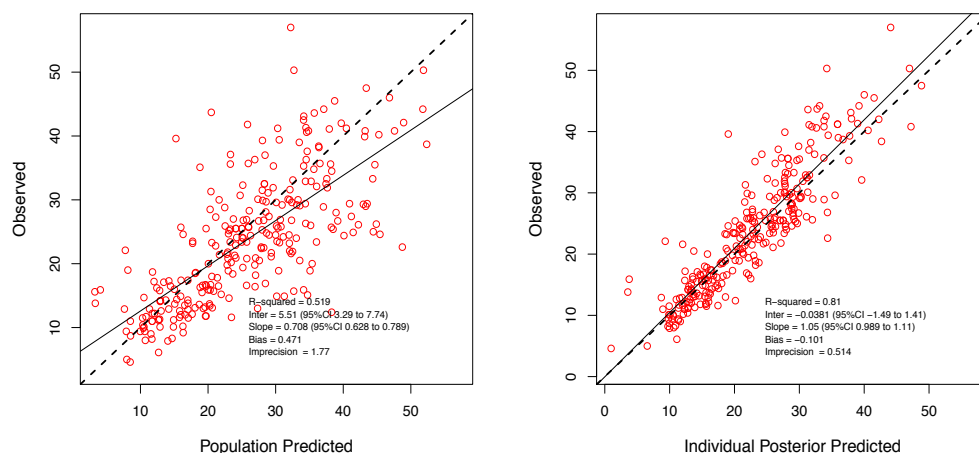


Figure 19: Diagnostic observed vs. predicted concentration plots of Ke and V structural model. The left panel describes the population predicted plot. The right panel describes the posterior individual predicted plot.

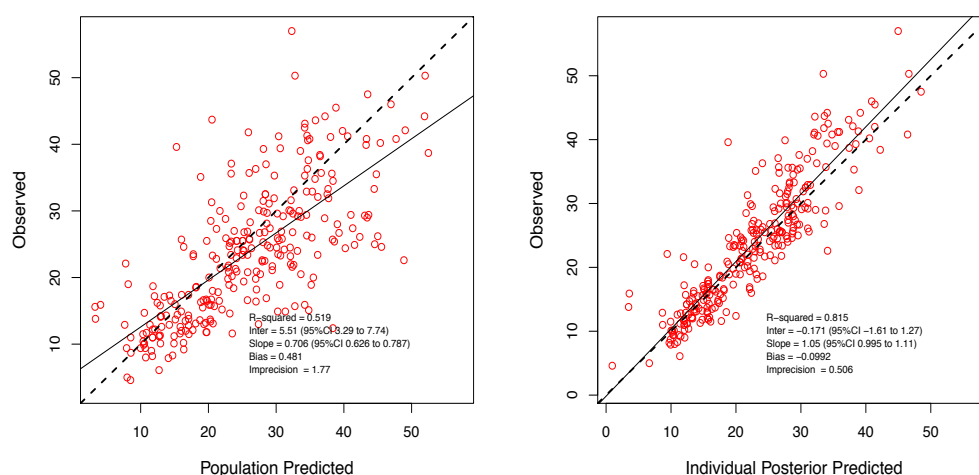


Figure 20: Diagnostic observed vs. predicted concentration plots of the CL structural model. The left panel describes the population predicted plot. The right panel describes the posterior individual predicted plot.

The following section presents our results of PK analysis including the influence of categorical CCD models as well as the covariates from the 4h and the WD for the following continuous covariates: BFR, FB, EFR, Alb levels, age and Wt. The covariates for consideration in the PK analysis are presented in Table 10. The univariate and multivariate regression analysis from the base model PK estimates and the covariates are then described, followed by description of covariate models.

Table 10: Descriptive statistics of covariates.

	Mean *	SD *	Median *	Minimum	Maximum	IQR	Range
BFR WD (ml/min)	182.3	33.44	180.0	120	220	160	100
EFR WD (ml/kg/h)	3021.2	655.43	3035.3	2039	4269	2426	2230
FB WD (ml)	4048.3	3188.12	2465.7	516	11103	1447	10588
Alb (mg/dl)	24.3	5.19	25.0	13	38	21	25
BFR 4h (ml/min)	183.7	37.8	200.0	120	220	140	100
EFR 4h (ml/kg/h)	2996.7	741.29	2863.0	2000	4771	2338	2771
FB 4h (ml)	4568.3	4036.65	3266.0	22	19121	1579	19099

* The dosing intervals during non-dialysis in BFR, EFR and FB were zero, where zero-data is excluded from this descriptive statistical analysis. IQR, Interquartile Range.

4.1.4 Univariate and multivariate (PM-step) regression analysis

The relationship between the covariates: BFR, FB, EFR, Alb levels, age and Wt and PK parameters was discovered by using univariate linear regression analysis, to show how much patients' PK parameter estimates changed when the other covariates were varied. From Table 11 we can see that PK parameters have statistically significant correlations with some of the corresponding covariates. The CL was statistically significant with FB WD, while V was significant with Alb and Ke was significant with age. Furthermore, Ke was highly significant with albumin, CL was highly significant with FB 4h and Alb, also V was highly significant with EFR 4h. The relationship of PK parameters with other covariates, however, was negligible.

Table 11: The univariate regression analysis between PK parameters and different covariates.

PK parameter	Covariates	P-value
CL	FB 4h	0.000**
CL	Alb	0.003**
Ke	Alb	0.000**
Ke	Age	0.04*
V	EFR 4h	0.001**
V	Alb	0.007*
CL	FB WD	0.01*

*(Statistically significant was considered as $P < 0.05$) and **($p < 0.005$ for highly significant).

Moreover, applying the PM-step (multivariate regression analysis) run in Pmetrics helps to predict which covariates could improve the model vs. those that are not retrieved as summarised in Table 12. There was a high correlation detected between FB covariate for both 4h and WD with CL parameter as well as for BFR 4h covariate with Ke parameter. Also, there was a correlation for age covariate with Ke parameter and for albumin with all PK parameters.

Table 12: Suggested correlation between PK parameters and covariates from PM-step.

Covariates	Ke	V	CL
Age	0.03*	0.11	NA
Weight	NA	0.11	NA
BFR 4h	0.05*	0.06	NA
FB 4h	NA	NA	0.01*
EFR 4h	NA	0.15	NA
Albumin	0.01*	0.05*	0.03*
BFR WD	NA	NA	NA
EFR WD	NA	0.1	0.13
FB WD	0.16	NA	0.03*

*($P < 0.05$). Abbreviation: NA, there is no significant correlation.

The CL parameter was statistically significant with the FB 4h, Alb, and FB WD in both univariate regression analysis and PM-step, while Ke was significant with age and albumin, also V was with albumin, as described in Table 11 and Table 12. Before proceeding to examine covariate PK analysis, it is important to mention that the regression analyses suggestions were not taken into account in the current study. This analysis was carried out to determine whether the regression analysis methods suggested any identified covariate and parameter estimate relationships as was identified from the PK covariate modelling. As will be discussed in section 5, the PK covariate models allow for intra-individual variation as the covariates are estimated per dosing interval and not per patient, whereas the regression analysis uses patient estimates.

4.1.5 Covariate PK analysis

4.1.6 CL –PK covariate analysis

The results of using vancomycin CL with relevant covariates are summarised in Table 13. It was attempted to decrease the tolerance for run convergence to 0.001 lower than the default (0.01) to force the model to find a more improved fit and further

improve the model. However, tolerance was not advantageous in covariate model over higher tolerance.

Surprisingly, it was found that both categorical and continuous covariate models by application of equations (1,4,7,12,18,25,30,34) did not provide any improvement in modelling over the base model. Indeed, it was very strange that all covariates have identical results with CL regarding $-2*LL$, AIC, and BIC and the reason for the similarity in these results was unknown. Besides, all covariates were almost the same for R^2 values ($R^2= 0.058$, and $R^2= 0.21$) for population and posterior individual prediction respectively (see appendix 8.3 for more details). Additionally, the goodness of fit plots of both categorical and continuous covariates was worse than the base model and not distinguishable, as shown in Figure 21 and Figure 22.

Table 13: Analysis of CL- structural model with covariates.

				Population				Individual			
parameter	-2*LL	AIC	BIC	R ²	Bias	Imp	Slope	R ²	Bias	Imp	Slope
CL base model	1678	1684	1694	0.51	0.48	1.77	0.70	0.81	-0.09	0.50	1.05
EFR 4h	2155	2163	2178	0.06	0.55	1.99	0.14	0.24	-0.19	0.55	0.51
EFR WD	2155	2163	2178	0.06	0.57	2.01	0.14	0.24	-0.17	0.56	0.51
BFR 4h	2155	2163	2178	0.06	0.56	2.01	0.14	0.24	-0.17	0.56	0.51
BFR WD	2155	2163	2178	0.06	0.56	2.01	0.14	0.24	-0.17	0.56	0.51
FB 4h	2155	2163	2178	0.06	0.56	2.01	0.14	0.24	-0.17	0.56	0.51
FB WD	2155	2163	2178	0.06	0.56	2.01	0.14	0.24	-0.17	0.56	0.51
CCD-AP	2155	2165	2183	0.06	0.54	1.98	0.14	0.24	-0.18	0.56	0.51
Alb.	2155	2161	2172	0.06	0.56	2.01	0.14	0.24	-0.17	0.56	0.51
Age	2155	2163	2178	0.06	0.56	1.99	0.14	0.24	-0.17	0.55	0.51
Wt	2155	2163	2178	0.06	0.56	2.01	0.14	0.24	-0.17	0.56	0.51

Abbreviations: EFR, Effluent flow rate; BFR, Blood flow rate; FB, Fluid balance; 4h, Data taken from 4 hours closest to dose; WD, Data from the whole dosing interval; -2*LL, -2*Log-likelihood value; AIC, Akaike's Information Criterion value; BIC, Bayesian or Schwartz Information Criterion value; R², the observed vs. predicted concentration value; Imp, imprecision.

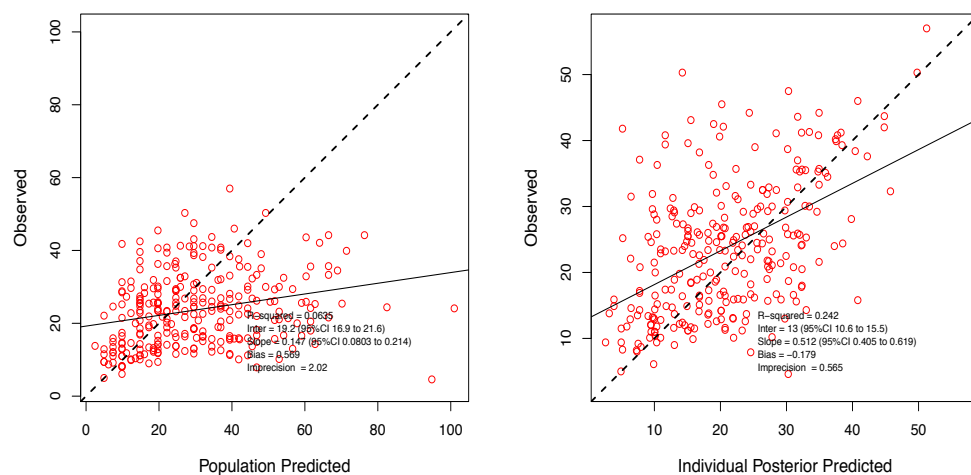


Figure 21: Diagnostic observed vs. predicted concentration plots of CL with FB 4h. The left panel describes the population predicted plot. The right panel describes the posterior individual predicted plot.

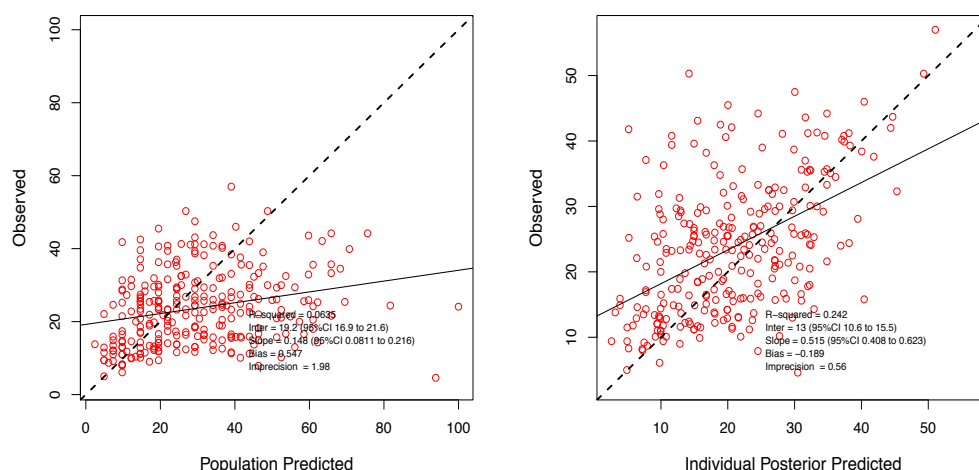


Figure 22: Diagnostic observed vs. predicted concentration plots of CL with CCD-AP. The left panel describes the population predicted plot. The right panel describes the posterior individual predicted plot.

4.1.7 Ke and V –PK covariate analysis

4.1.7.1 CCD models

- **CCD-AP:**

The CCD-AP model was carried out by using equation (2,3) as described in the method section 3.2.3.2.1. Table 14 compares an overview of vancomycin dosing intervals and levels with patient numbers in each anticoagulant modality and dialysis status category for CCD-AP group.

Table 14: Dialysis characteristics for CCD-AP with vancomycin dosing intervals, levels and patient numbers in each category.

	Citrate anticoagulant	Non-citrate anticoagulant	Non-dialysis
Number of (peak/trough) levels	34/34	75/76	31/30
Number of dosing intervals	47	115	72
Number of patients	11/31	26/31	23/31
	5 of those 11 patients on citrate only- of whom 4 also had dosing intervals with no dialysis.	20 of those 26 patients on non-citrate only- of whom 16 also had dosing interval with no dialysis.	8 patients had no dosing intervals with no dialysis (i.e. all dosing intervals on citrate or non-citrate modalities.
	6 of those 11 patients also had non-citrate dosing intervals -3 of whom also had dosing intervals with no dialysis.	6 of those 26 patients also had citrate dosing intervals -3 of whom also had dosing intervals with no dialysis.	

The results obtained from the CCD-AP models are summarised in Table 15. From this table, the most interesting aspect of these results was the posterior individual prediction for CCD-AP applied to both Ke and V parameters. It was the best posterior individual model compared to other covariates models and also over the base model in terms of $-2*LL$, AIC and BIC. This posterior individual model has an improvement, with $R^2 = 0.89$, over the base model. It was statistically significant ($P < 0.001$) with a drop in 175 points from the base model (the P-value for 3 degrees of freedom in chi-square test table at a value of 0.05 is 7.82), as shown in Figure 19 and Figure 23. The

population prediction model, however, was slightly better than the base model with $R^2 = 0.54$ and low bias value.

Additionally, the population prediction model of CCD-AP covariate applied to the V parameter estimate was improved slightly with $R^2 = 0.55$ over the base model. It was statistically significant ($P < 0.001$) with a drop in 41 points from the base model (the P-value for 2 degrees of freedom in chi-square test table at a value of 0.05 is 5.99), with better R^2 and lower bias but not imprecision. However, the posterior individual prediction was similar to the base model. Although the population prediction model of CCD-AP covariate that applied to V and to both Ke and V estimates have an advantage over the base model, it is still not good as the FB WD applied to V or Alb applied to Kei (inverse approach) parameters that will be detailed later in section 4.1.7.2.

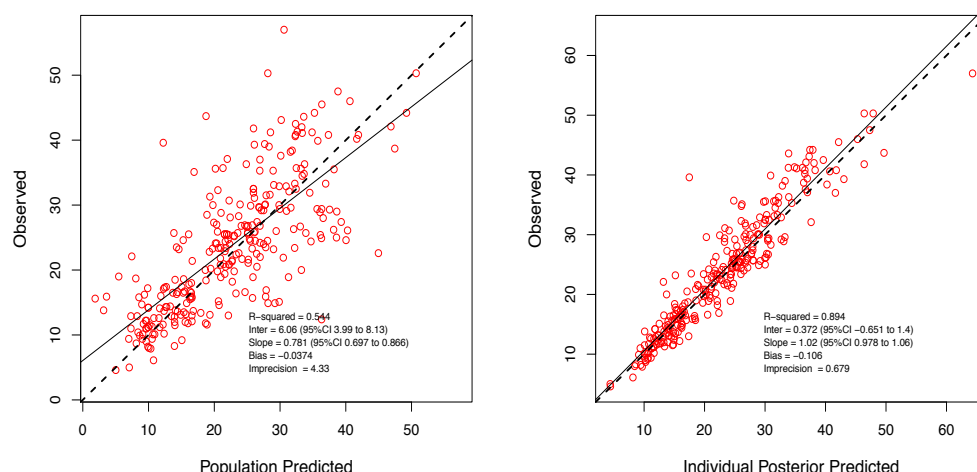


Figure 23: Diagnostic observed vs. predicted concentration plots of CCD-AP applied to both Ke and V. The left panel describes the population predicted plot. The right panel describes the posterior individual predicted plot.

Table 15: PK statistics for CCD-AP models and base model.

Parameter	Population							Individual			
	-2*ll	AIC	BIC	R2	Bias	Imp	Slope	R2	Bias	Imp	Slope
Base model	1678	1684	1694	0.51	0.47	1.77	0.7	0.81	-0.1	0.51	1.05
CCD-AP with Ke	1546	1556	1574	0.45	0.33	5.73	0.62	0.86	-0.12	0.69	1.05
CCD-AP with V	1637	1647	1665	0.55	-0.02	1.89	0.79	0.83	-0.12	0.55	1.03
CCD-AP with both	1503	1517	1542	0.54	-0.03	4.32	0.78	0.89	-0.1	0.67	1.02

Abbreviations: -2*ll, -2*Log-likelihood value; AIC, Akaike's Information Criterion value; BIC, Bayesian or Schwartz Information Criterion value; R², the observed vs. predicted concentration value; Imp, imprecision; CCD-AP, Categorical Covariate Dialysis-All Patients.

The following table illustrates the PK parameter estimates from CCD-AP applied to both Ke and V parameter estimates were only slightly different when compared with the base model. The coefficient of variation (CV%) was higher in Ke1-3 and V1, while the mean of V1-3 was slightly lower, and the median was a little bit higher only in V1 and V2 than the base model as shown in Table 16.

Table 16: PK statistics for CCD-AP applied to both Ke and V parameter estimates, along with the base model estimates.

	parameter	Mean	SD	Coefficient of variation	Median
CCD-AP model	Ke1	0.04	0.05	107.66	0.03
	Ke2	0.03	0.02	60.02	0.03
	Ke3	0.03	0.02	96.49	0.02
	V1	72.9	31.89	43.75	76.13
	V2	75.9	15.27	20.11	73.82
	V3	69.8	19.24	27.55	63.96
Base model	Ke	0.03	0.01	44.3	0.03
	V	80.65	22.65	28.08	70.17

Abbreviations: ke1 and V1 for citrate dosing intervals; Ke2 and V2 for non-citrate dosing intervals; Ke3 and V3 for no-dialysis dosing intervals; CCD-AP for Categorical Covariate Dialysis-All Patients.

- **CCD-G:**

CCD-G was performed on groups of dosing intervals with different anticoagulant modalities and dialysis characteristics as presented in Table 17. The results from this table show that the demographic data in all groups (citrate, non-citrate and no dialysis) appear to be similar. Importantly, the model applied to dosing intervals with citrate anticoagulant modality provided a notable improvement over its application to the dataset with non-citrate anticoagulant modality with $R^2 = 0.90$, $R^2 = 0.81$ in individual posterior, and $R^2 = 0.86$, $R^2 = 0.58$ in population predicted model for citrate and non-citrate groups, respectively, as shown in Figure 24 and Figure 25. The population predicted model for dosing interval applied to the non-dialysis group was unacceptable with $R^2 = 0.28$, with a slight improvement in the posterior individual predicted concentration with $R^2 = 0.84$ as shown in Figure 26.

Additionally, there were only three patients with data for comparison from both citrate and non-citrate groups. Therefore, the number was too small to draw judgments about intra-patients data (see appendix 8.4 for more details).

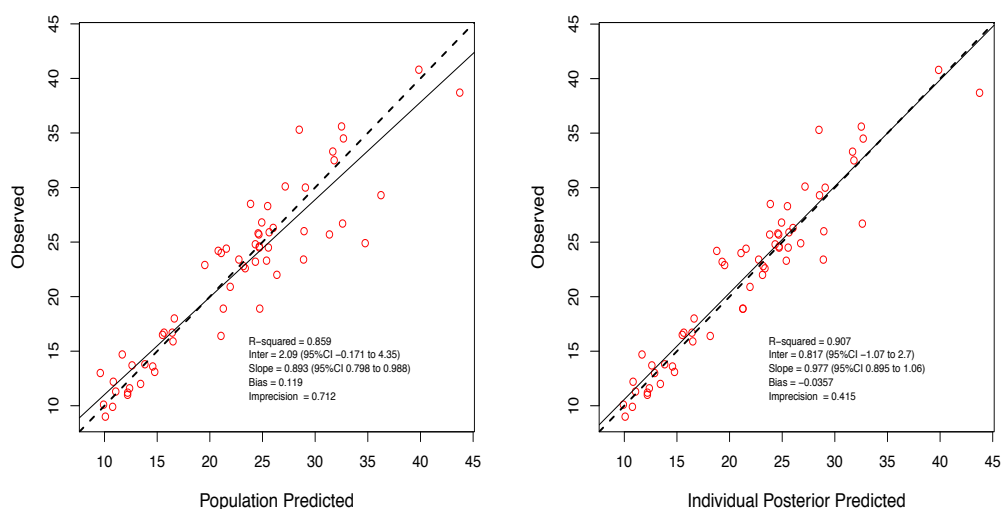
Table 17: Dialysis characteristics, number of dosing intervals, vancomycin levels, and some demographic data for CCD-G models.

	Citrate anticoagulant	Non-citrate anticoagulant	Non-dialysis
Patient number	10	18	10
Number of dosing intervals (mg)	40	89	34
Number of peak levels ($\mu\text{g/ml}$)	34	68	25
Number of trough levels($\mu\text{g/ml}$)	26	52	19
Age (mean)	67	63.4	58.6
Weight (mean)	83.5	83.5	84.2
ICU length (mean)	22.2	18	23
APACHE II score(mean/median)	21.2/21	22.2/23	22.1/26
SOFA score(mean/median)	11/11	11.5/11	10.2/10
Albumin (mean)	24	25.1	23.3

Furthermore, the model applied to dosing intervals with citrate data compared with dosing intervals applied to non-citrate and non-dialysis data, along with the base model is summarised in Table 18. It should be noted that all CCD-G groups have different combinations of patients (i.e. various patient numbers and types), whereas it is possible to compare the PK estimates between them (while being cognizant of the differences between the groups), we cannot compare the -2LL*, AIC, and BIC.

Table 18: PK parameter estimates from citrate, non-citrate, and non-dialysis dosing interval data, along with the base model estimates.

Model	Parameter	Mean	SD	Coefficient of variation	Median
Citrate model	Ke	0.03	0.004	13.46	0.03
	V	87.5	21.86	25	79.602
Non-citrate model	Ke	0.03	0.01	37	0.03
	V	88.5	34.1	38.5	75.82
Non-dialysis model	Ke	0.03	0.03	115.38	0.01
	V	83.53	38.33	46	82.7
Base model	Ke	0.03	0.01	44.3	0.03
	V	80.65	22.65	28.08	70.17

**Figure 24: Diagnostic observed vs. predicted concentration plots of CCD-G citrate anticoagulant modality model.** The left panel describes the population predicted plot. The right panel describes the posterior individual predicted plot.

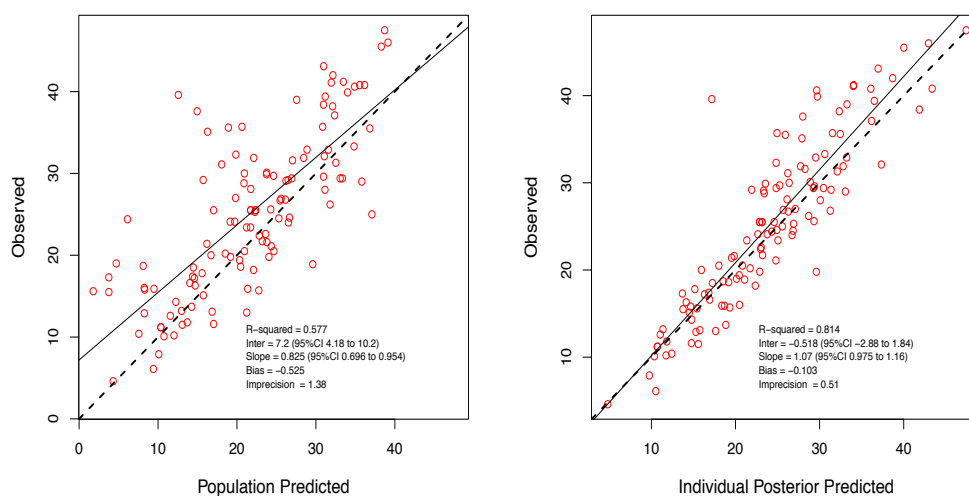


Figure 25: Diagnostic observed vs. predicted concentration plots for CCD-G non-citrate anticoagulant modality model. The left panel describes the population predicted plot. The right panel describes the posterior individual predicted plot.

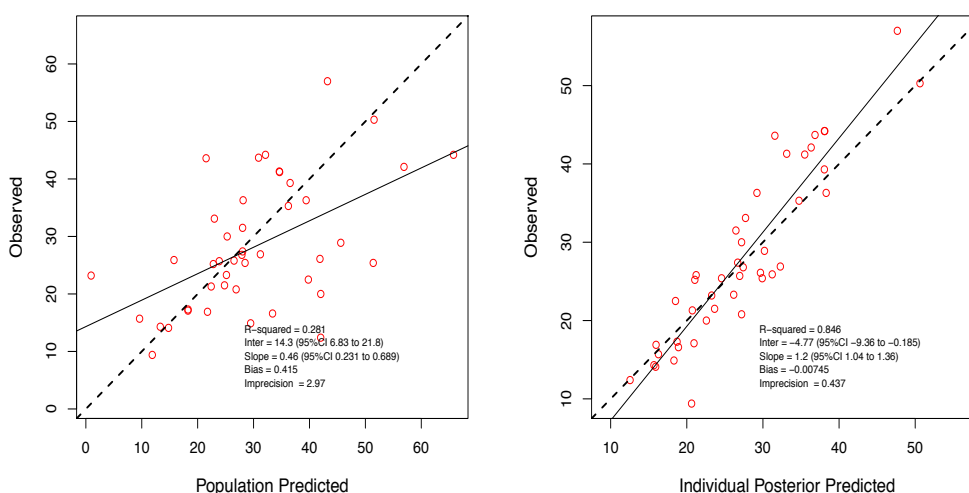


Figure 26: Diagnostic observed vs. predicted concentration plots for CCD-G no dialysis model. The left panel describes the population predicted plot. The right panel describes the posterior individual predicted plot.

4.1.7.2 Continuous covariate models

4.1.7.2.1 BFR covariate models

The BFR PK analysis was implemented by using equations (5,6,7,8,9) as described in method section 3.2.3.2.2. The population prediction model for BFR 4h applied to V

parameter using the original (non-inverse, including an intercept) was slightly better than other blood flow models with slight improvement in R^2 (0.54) over the base model. It was statistically significant ($P < 0.001$) in terms of $-2 \cdot LL$, AIC and BIC, with a drop in 34 points from the base mode (the P-value for 2 degrees of freedom in chi-square test table at a value of 0.05 is 5.99). However, the posterior individual models for BFR 4h applied to both K_e and V have slight improvement with $R^2 = 0.84$ over the base model as presented in Table 19, but not as much as CCD-AP model applied to both K_e and V parameters. On the other hand, BFR and K_e using the inverse approach, was higher in R^2 but there was no statistically significant improvement in $-2 \cdot LL$, AIC and BIC. So, the predicted concentrations were improved over the base model, whereas no improvement in the model structural fit was obtained.

Table 19: PK statistics for blood flow covariates models and base model.

Parameter	Population							Individual			
	-2*LL	AIC	BIC	R ²	Bias	Imp	Slope	R ²	Bias	Imp	Slope
Base model	1678	1684	1694	0.51	0.47	1.77	0.7	0.81	-0.1	0.51	1.05
BFR 4h Ke	1611	1620	1634	0.43	1.63	4.26	0.54	0.84	-0.11	0.54	1.06
BFR 4h V	1644	1653	1667	0.54	0.11	1.89	0.75	0.83	-0.09	0.54	1.02
BFR 4h both	1606	1617	1635	0.42	1.64	4.42	0.55	0.84	-0.08	0.56	1.04
BFR WD Ke	1674	1683	1697	0.43	1.72	3.16	0.53	0.81	-0.06	0.52	1.04
BFR WD V	1674	1683	1697	0.50	1.16	2.36	0.6	0.81	-0.08	0.51	1.06
BFR WD both	1672	1682	1700	0.46	1.11	2.47	0.61	0.81	-0.1	0.51	1.05
BFR WD Kei	1674	1683	1697	0.56	-0.33	1.26	0.83	0.78	-0.06	0.61	1.03
BFR WD Vi	1673	1681	1695	0.53	0.27	1.65	0.74	0.81	-0.10	0.51	1.06

Abbreviations: BFR, Blood flow rate; 4h, Data taken from 4 hours closest to dose; WD, Data from the whole dosing interval; -2*LL, -2*Log-likelihood value; AIC, Akaike's Information Criterion value; BIC, Bayesian or Schwartz Information Criterion value; R², the observed vs. predicted concentration value; Imp, imprecision; V and Ke, model applied using non-inverse approach; Vi and Kei, model applied by using the inverse approach.

4.1.7.2.2 FB covariate models

FB was a highly variable covariate for both inter and intra-patient data. The FB covariate analysis was obtained by using equations (10,11,12,13,14,15) as described in the method section 3.2.3.2.2. The most obvious result in fluid balance was the higher improvement in FB WD covariate applied to V parameter using the original (non-inverse partial volume) approach. It was the best population prediction model with $R^2 = 0.59$ over the base model as described in Figure 27. Also, this model was statistically significant ($P < 0.01$) in terms of $-2 \cdot LL$, AIC and BIC, with a drop in 12 points from the base mode (the P-value for 2 degrees of freedom in chi-square test table at a value of 0.05 is 5.99). Meanwhile, the FB WD applied to both Ke and V offers no advantage over an application to V alone, as shown in Table 20.

Concerning the FB 4h, FB 4h applied to both Ke and V (non-inverse, including an intercept) was a marginally better posterior individual prediction model and population prediction over the base model. Using the original inverse approach for FB WD applied to Ke and V parameter estimates there was no improvement in R^2 value compared with the original non-inverse approach over the base model, and also the model structures are not better. On the other hand, using the total volume approach for FB applied to V parameter for both 4h and WD provided unacceptable population predicted and posterior individual predicted models, which led to results worse than the original approach as presented in Table 20.

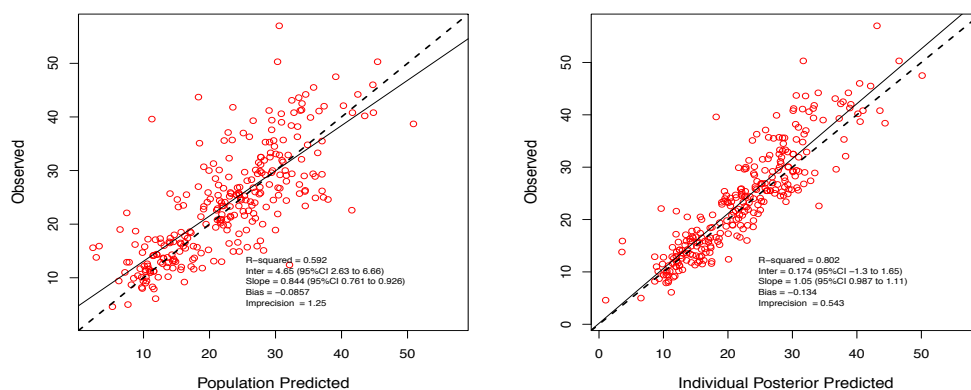


Figure 27: Diagnostic observed vs. predicted concentration plots for FB WD applied to V. The left panel describes the population predicted plot. The right panel describes the posterior individual predicted plot.

Table 20: PK statistics for fluid balance covariate models and base model.

Parameter	Population							Individual			
	-2*LL	AIC	BIC	R ²	Bias	Imp	Slope	R ²	Bias	Imp	Slope
Base model	1678	1684	1694	0.51	0.47	1.77	0.7	0.81	-0.1	0.51	1.05
FB 4h with Ke	1649	1657	1672	0.55	0.56	1.99	0.7	0.82	-0.21	0.56	1.03
FB 4h with V	1645	1653	1667	0.54	0.59	2.00	0.7	0.83	-0.09	0.50	1.06
FB 4h with both	1634	1645	1663	0.55	0.63	1.99	0.71	0.84	-0.14	0.51	1.04
FB 4h with Vt	2418	2424	2435	0.01	-0.06	9.26	0.02	0.11	-0.50	0.41	0.28
FB WD with Ke	1663	1671	1685	0.54	1.06	1.95	0.69	0.81	-0.14	0.50	1.05
FB WD with V	1666	1674	1688	0.59	-0.08	1.24	0.84	0.80	-0.13	0.54	1.05
FB WD with both	1662	1672	1690	0.59	-0.09	1.26	0.81	0.79	-0.008	0.58	1.01
FB WD with Vt	1796	1802	1813	0.19	-0.009	6.55	0.21	0.77	-0.09	0.48	0.93
FB WD with Kei	1677	1685	1700	0.51	0.39	1.77	0.71	0.81	-0.14	0.51	1.07
FB WD with Vi	1678	1686	1700	0.51	0.54	1.84	0.69	0.81	0.11	0.50	1.06

Abbreviations: FB, Fluid balance; 4h, Data taken from 4 hours closest to dose; WD, Data from the whole dosing interval; -2*LL, -2*Log-likelihood value; AIC, Akaike's Information Criterion value; BIC, Bayesian or Schwartz Information Criterion value; R², the observed vs. predicted concentration value; Imp, imprecision; V and Ke, for the non-inverse (including an intercept) approach; Vt, for the total volume(no intercept) approach; Vi and Kei for the inverse approach.

In addition, PK estimates for FB WD applied to V parameter estimate compared to the base model were not much different in total mean and median V (i.e. V1+V2), while V2, the proportion of V that varies with relative changes in FB covariate, is small and highly variable as presented in Table 21.

Table 21: PK parameter estimates for FB WD applied to V parameter model using the non-inverse approach and Alb applied to Kei parameter using the inverse approach along with the base model estimates

Model	Parameter	Mean	SD	Coefficient of variation	Median
FB model using non-inverse approach (include an intercept)	Ke	0.03	0.013	42.66	0.031
	V1	69.9	22.32	31.92	66.39
	V2	10.07	10.05	99.83	6.67
Base model	Ke	0.03	0.01	44.3	0.03
	V	80.65	22.65	28.08	70.17
Alb model using inverse approach (include an intercept)	Ke1	0.02	0.01	66.00	0.02
	Ke2	0.01	0.01	115.70	0.02
	V	80.1	22.53	28.13	72.48

4.1.7.2.3 EFR covariate models

The EFR covariate analysis was performed by using equations (16,17,18,19,20) as described in method section 3.2.3.2.2. Overall, the population models for EFR WD were marginally better than EFR 4h in term of R^2 of observed vs. predicted data. The population model for EFR 4h applied to the V parameter using the non-inverse (including an intercept) approach, was better than the other EFR models in terms of $-2*LL$, AIC and BIC, with $R^2 = 0.55$ as set out in Table 22. The posterior individual prediction for EFR 4h applied to Ke parameter with $R^2 = 0.85$ was the best continuous covariate model. It was statistically significant ($P < 0.001$) with 2 degrees of freedom, and a drop in 69 points from the base model. Also, the posterior individual prediction for EFR 4h applied to both Ke and V parameter was better with $R^2 = 0.86$ but it was more complex than EFR 4h applied to Ke parameter. On the other hand, using the inverse approach for EFR WD applied to Ke or V parameters models did not show any

improvement over either the non-inverse approach or the base model.

Table 22: PK statistics for effluent flow covariate models and base model.

Parameter	Population							Individual			
	-2*LL	AIC	BIC	R ²	Bias	Imp	Slope	R ²	Bias	Imp	Slope
Base model	1678	1684	1694	0.51	0.47	1.77	0.7	0.81	-0.1	0.51	1.05
EFR 4h with Ke	1609	1617	1631	0.45	0.75	3.78	0.57	0.85	-0.08	0.54	1.04
EFR 4h with V	1639	1647	1661	0.55	0.55	2.27	0.7	0.82	-0.08	0.60	1.02
EFR 4h with both	1600	1611	1629	0.46	1.30	4.64	0.55	0.86	-0.12	0.55	1.03
EFR WD with Ke	1667	1675	1690	0.53	0.57	1.85	0.68	0.75	0.01	0.67	0.92
EFR WD with V	1667	1675	1690	0.55	-0.47	1.23	0.86	0.80	-0.12	0.53	1.06
EFR WD with both	1665	1675	1693	0.54	1.34	2.32	0.59	0.80	-0.06	0.52	1.06
EFR WD with Kei	1672	1680	1694	0.52	0.01	1.52	0.76	0.81	-0.11	0.51	1.05
EFR WD with Vi	1674	1682	1696	0.5	0.39	1.83	0.70	0.81	-0.12	0.51	1.05

Abbreviations: EFR, Effluent flow rate; 4h, Data taken from 4 hours closest to dose; WD, Data from the whole dosing interval; -2*LL, -2*Log-likelihood value; AIC, Akaike's Information Criterion value; BIC, Bayesian or Schwartz Information Criterion value; R², the observed vs. predicted concentration value; Imp, imprecision; V and Ke, for the non-inverse (including an intercept) approach; Vi and Kei, for the inverse approach.

4.1.7.2.4 Alb covariate models

The albumin covariate analysis was achieved by using equation (21,22,23,24,25,26,27) as described in the method section 3.2.3.2.2. None of the albumin models, using total volume approach, applied to Ke and V parameters, provided any advantage over the base model in terms of $-2*LL$, AIC, BIC and R^2 as shown in Table 23. However, Alb applied to V using the original (non-inverse partial volume) approach was statistically significant with a drop in 14 points from the base model, and 2 degrees of freedom ($P<0.001$), but did not provide an advantage in population model over the base model in terms of R^2 .

On the other hand, Alb applied to V_i parameter using the inverse approach improved the population model and was statistically significant with a drop in 18 points from the base model, and 2 degrees of freedom ($P<0.001$)), with a high bias value. Surprisingly, Alb applied to Kei parameter provided notable improvement in the population predicted model in terms of $-2*LL$, AIC, BIC with $R^2= 0.59$ over the base model as presented in Figure 28 and Table 23. This result was similar to FB WD covariate applied to V parameter. The PK estimates for Alb applied to Ke parameter compared to the base model were similar in mean and median Ke1-2 and V, however the variability (i.e. CV%) was high in Ke1-2 as shown in Table 21.

Table 23: PK statistic for albumin covariates models and base model.

Parameter	Population							Individual			
	-2*LL	AIC	BIC	R ²	Bias	Imp	Slope	R ²	Bias	Imp	Slope
Base model	1678	1684	1694	0.51	0.47	1.77	0.7	0.81	-0.1	0.51	1.05
Alb.with Ket	1701	1707	1718	0.33	0.81	3.74	0.42	0.8	-0.08	0.51	1.04
Alb. with Vt	1742	1748	1759	0.29	0.04	3.25	0.42	0.77	-0.13	0.54	1.01
Alb.with Ke	1672	1680	1695	0.49	-0.04	1.76	0.69	0.81	-0.1	0.51	1.06
Alb. with V	1664	1672	1686	0.45	0.03	1.92	0.69	0.8	-0.1	0.54	1
Alb. with Vi	1660	1668	1683	0.55	0.92	1.97	0.66	0.81	-0.2	0.55	1.04
Alb. with Kei	1664	1672	1686	0.59	-0.19	1.16	0.86	0.79	-0.05	0.6	0.99
Alb. With both Kei and Vi	1652	1662	1680	0.58	0.06	1.4	0.81	0.76	0.05	0.72	0.91

Abbreviations: -2*LL, -2*Log-likelihood value; AIC, Akaike's Information Criterion value; BIC, Bayesian or Schwartz Information Criterion value; R², the observed vs. predicted concentration value; Imp, imprecision; V and Ke, for the non-inverse (including an intercept) approach; Ket and Vt, applied using total (no intercept) approach, Vi and Kei, applied using inverse approach.

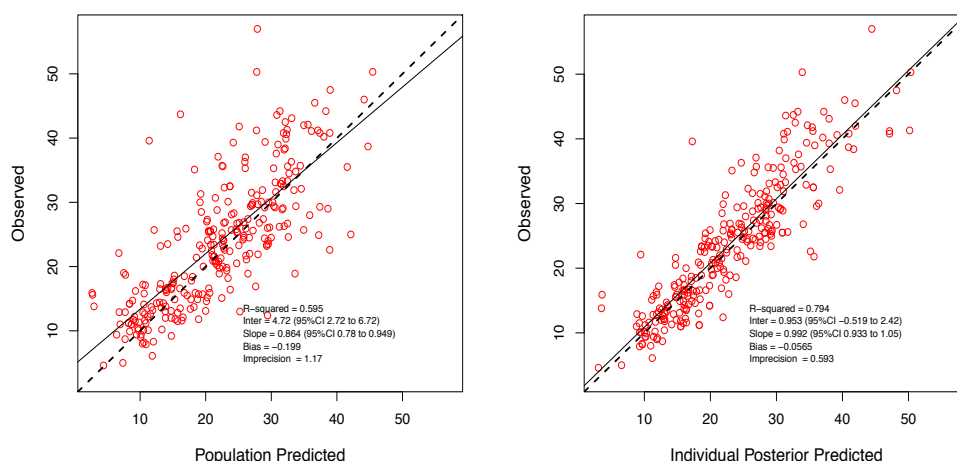


Figure 28: Diagnostic observed vs. predicted concentration plots for Alb applied to Kei (inverse approach). The left panel describes the population predicted plot. The right panel describes the posterior individual predicted plot.

4.1.7.2.5 *Wt covariate models*

The weight covariate analysis was carried out by using equation (33,34,35) as described in the method section 3.2.3.2.2. As can be seen from Table 24 the population prediction model applied to V parameter offers little improvement in terms of $-2*LL$, AIC, and BIC over the base model using the original (non-inverse partial volume) approach. The model structure was better with a drop in 7 points from the base model, and 2 degrees of freedom ($P < 0.05$), with higher R^2 (0.55) over the base model. However, using the total volume approach instead of partial by using equation (27) as described in the method section (3.2.3.2.2) made the model much worse than the base model.

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Table 24: PK statistics for weight covariate models and base model.

	Population							Individual			
Parameter	-2*LL	AIC	BIC	R ²	Bias	Imp	Slope	R ²	Bias	Imp	Slope
Base model	1678	1684	1694	0.51	0.47	1.77	0.7	0.81	-0.1	0.51	1.05
Wt with V	1671	1679	1694	0.55	0.05	1.38	0.78	0.79	-0.15	0.56	1.05
Wt with Vt	1688	1694	1705	0.46	-0.85	1.2	0.84	0.80	-0.13	0.51	1.07

Abbreviations: -2*LL, -2*Log-likelihood value; AIC, Akaike's Information Criterion value; BIC, Bayesian or Schwartz Information Criterion value; R², the observed vs. predicted concentration value; Imp, imprecision; V, for the non-inverse (including an intercept) approach; Vt, applied using total (no intercept) approach.

4.1.7.2.6 Age covariate models

The age covariate analysis was performed by using equations (28,29,30) as described in the method section 3.2.3.2.2. The results from **Table 25** show that age applied to K_e or V parameter did not provide any advantage over the base model. The model structure was better in terms of $-2*LL$, AIC and BIC, with a drop in 9 points from the base model, and 2 degrees of freedom ($p < 0.05$), but the R^2 was worse. Furthermore, application of the total volume approach using equations (31,34) as described in the method section 3.2.3.2.2, resulted in population predicted models worse than the base model.

Table 25: PK statistic for age covariant models and base model.

Parameter	Population						Individual				
	-2*ll	AIC	BIC	R2	Bias	Imp	Slope	R2	Bias	Imp	Slope
Base model	1678	1684	1694	0.51	0.47	1.77	0.7	0.81	-0.1	0.51	1.05
Age with V	1669	1677	1691	0.48	-0.02	1.88	0.67	0.77	-0.16	0.56	1.04
Age with Ke	1669	1677	1691	0.36	1.17	3.51	0.48	0.80	-0.09	0.51	1.05
Age with Vt	1679	1685	1695	0.32	-0.16	3.22	0.46	0.80	-0.1	0.51	1.06
Age with Ket	1677	1683	1694	0.33	0.09	3.27	0.48	0.80	-0.08	0.52	1.05

Abbreviations: -2*LL, -2*Log-likelihood value; AIC, Akaike's Information Criterion value; BIC, Bayesian or Schwartz Information Criterion value; R², the observed vs. predicted concentration value; Imp, imprecision; V and Ke, for the non-inverse (including an intercept) approach; Ket and Vt, applied using total (no intercept) approach.

4.1.8 Model diagnostics of selected PK models

In order to select the best model, we compared the relevant covariate models and considered the best model is the model that has the significant reduction in terms of $-2*LL$, AIC and BIC, with little changes in bias and imprecision and an increase in R^2 values over the base model. The model providing the best posterior individual estimates was considered to be the CCD-AP model applied to both Ke and V parameters (CCD-AP Ke and V). The posterior individual plots from the CCD-AP Ke and V model were compared to the posterior individual plots from the base model for individual patients, as presented for 2 patients in Figure 29. This figure illustrates an improvement in the individual plot of some patients over the base model, such as patient 8 and 18. However, some of these were better in the base model such as patient 21 and 47 as shown in Figure 30. Patient 21 is an example of unrealistic estimates (i.e. Ke of 0.18 h and V of 0.77 L) generated in the covariate model for dosing intervals where there was no observed data for the vancomycin concentrations, so parameter estimates could not be fitted to that observed data as shown in Figure 30. As the CCD-AP Ke and V model allowed 6 covariates the potential for overfitting should be borne in mind, and thus the final model would require rigorous external validation. Whereas the CCD-G models can not be compared to the CCD-AP models or base model for statistical improvement due to different groups of data included in each model, the result from the CCD-G citrate model, in particular, is also of interest.

The best population models were considered to be the continuous covariate models of FB WD V model and Alb applied to Kei model. The FB WD applied to V parameter (FB WD V model), used the non-inverse approach including an intercept, whereas the Alb applied to Kei parameter (Alb Kei model) used the inverse approach, also including an intercept. The individual plot from the population prediction FB WD V model was compared with the equivalent plot from the base model. There was an improvement in the prediction of the population FB individual model in some patients, which can explain better individual observation for clinical purpose in many patients, such as in patients 44 and 10 in Figure 31. Nevertheless, the population observed the plot of the base model did not seem inferior to the covariate model for

other patients as in patients 39 and 23 summarised in Figure 32. Furthermore, the population prediction of Alb Kei model was identical to FB WD V model with the same R^2 value. The population individual plot from the population of Alb Kei model was compared with the comparable plot from the base model in two examples of patients. It can be seen from the individual plot in Figure 33 that there was an improvement in individual observation of some patients when compared with the base model, as shown in patients 10 and 15. Though, some of these individual plots revealed marginal improvement in the base model over the covariate model for other patients as in patients 26 and 46, which was presented in Figure 34.

As we can see from these individual plots, there is a high variation among critically ill patients. However, the base model plot remained adequate for some patients and not worse than the predicted data from the covariate model. Therefore, considering covariates in practice might not improve dosing predictions for all patients. While we consider the FB WD V model and Alb Kei model to be an improvement over the base model for the population data, it is only a marginal improvement. An R^2 of 0.59 means that approximately 40% of the variability in the observed vs. predicted data is not explained by this model.

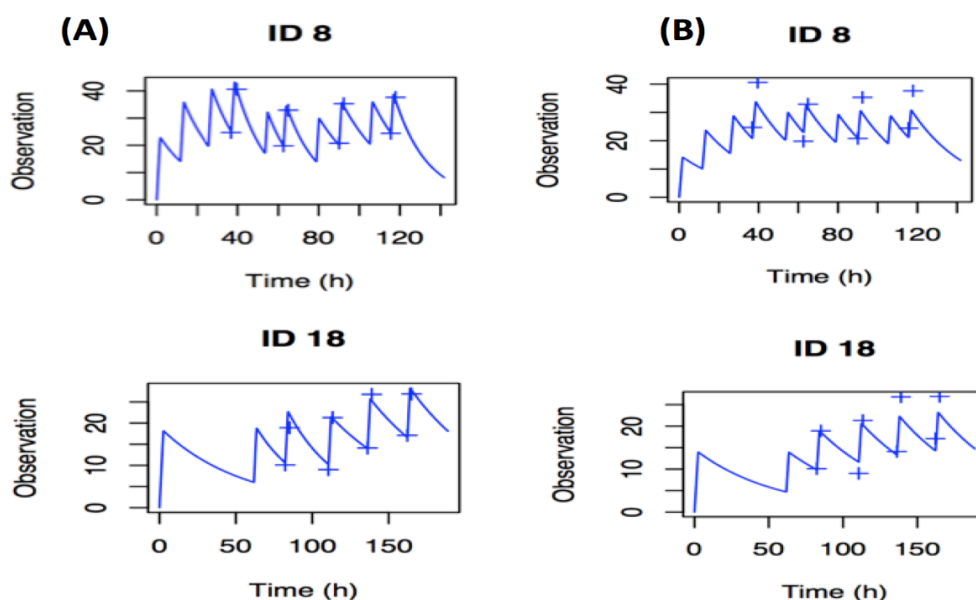


Figure 29: Posterior individual predicted and observed concentration vs. time plots for 2 sample patients. (A) describes the data from CCD-AP Ke and V model, while (B) describes the data from the base model.

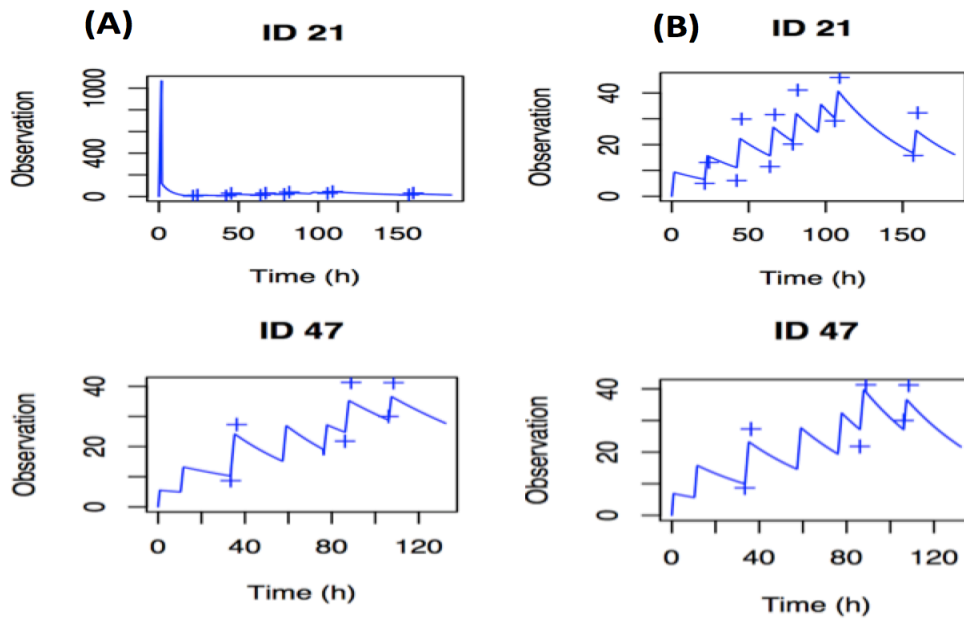


Figure 30: Posterior individual predicted and observed concentration vs. time plots for 2 sample patients. (A) describes the data from the CCD-AP Ke and V model, while (B) describes the data from the base model.

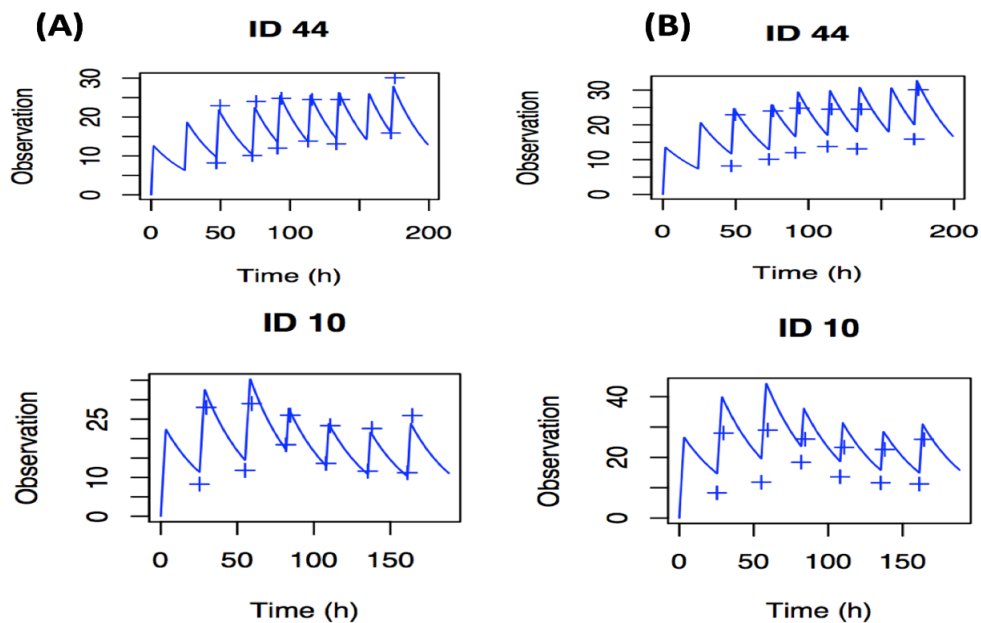


Figure 31: Population predicted and observed concentration vs. time plots for 2 sample patients. (A) describes the data from the FB WD V model, while (B) describes the data from the base model.

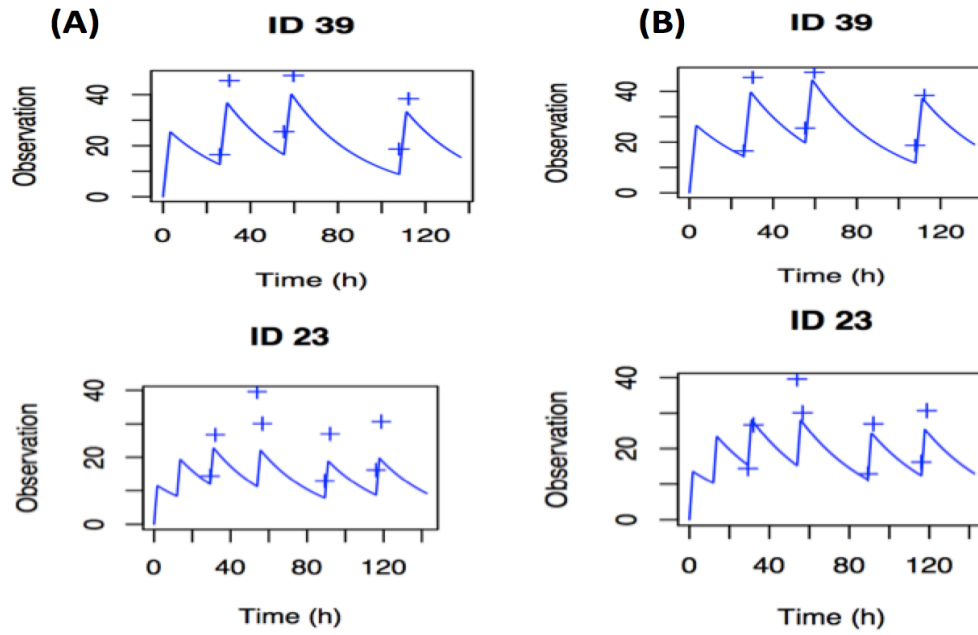


Figure 32: Population predicted and observed concentration vs. time plots for 2 sample patients. (A) describes the data from the FB WD V model, while (B) describes the data from the base model.

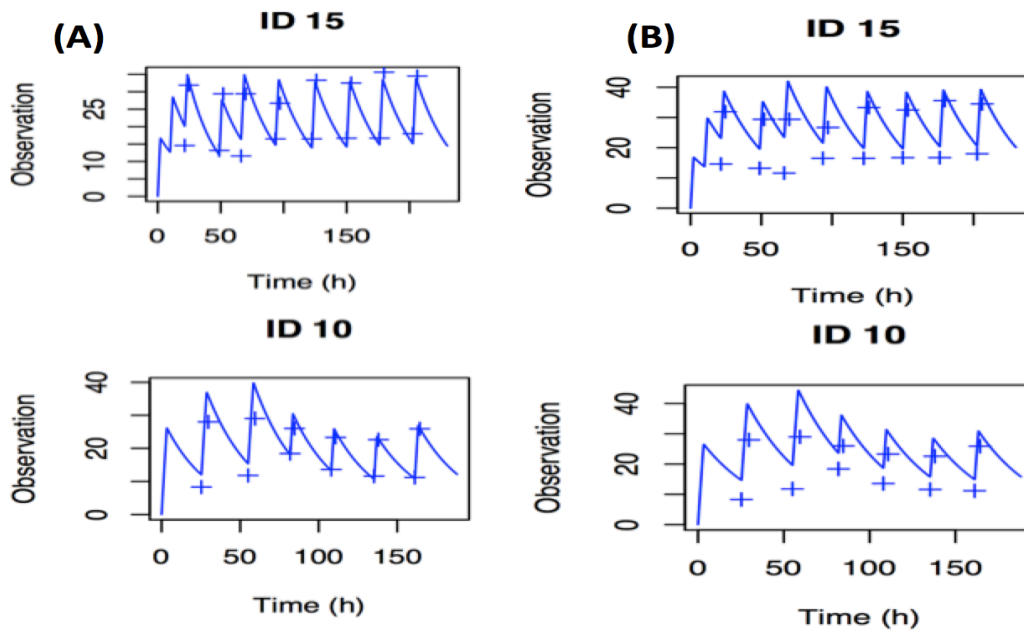


Figure 33: Population predicted and observed concentration vs. time plots for 2 sample patients. (A) describes the data from the Alb Kei model, while (B) describes the data from the base model.

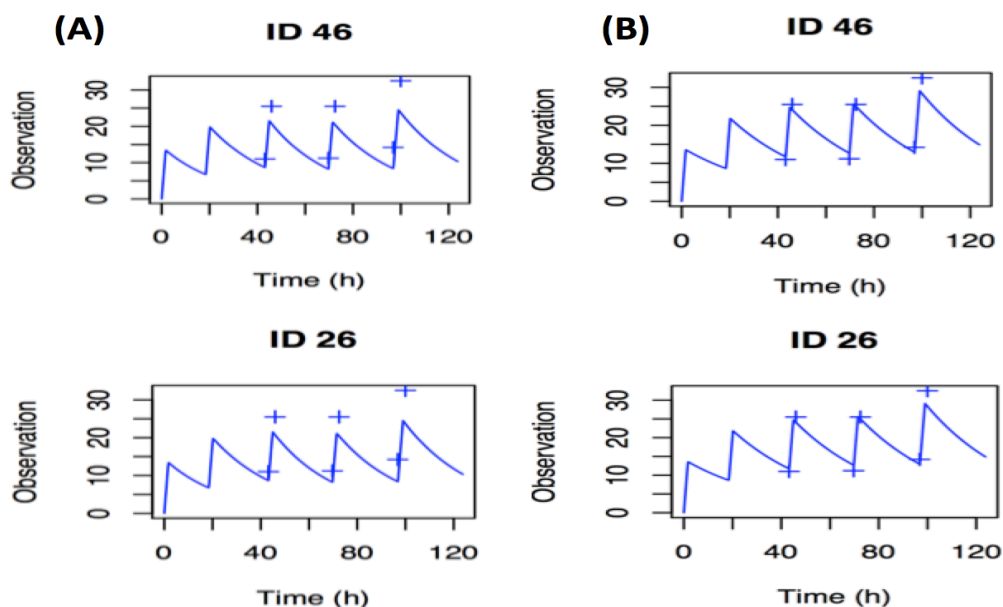


Figure 34: Population predicted and observed concentration vs. time plots for 2 sample patients. (A) describes the data from the Alb Kei model, while (B) describes the data from the base model.

4.1.8.1 Internal validation for selected models

- **VPC:**

A complex VPC tool is used to distribute the performance of the PK model by comparing the observed data with multiple simulations from the predicted data from PK parameter estimates, ranging from 5% to 95% percentiles of predicted data. It is based on simulation using model parameter predictions. The VPC plot for the FB WD V and in Alb Kei population models help to evaluate all the observed data with the predicted estimates as shown in Figure 35 and Figure 36. The observed values were almost all within 5%-95% percentiles and resulted in realistically predicted estimates. However, although the VPC plot for CCD-AP Ke and V model included the observed data within the predicted estimates, the VPC provided an unrealistically wide predicted range which does not mean the data is wrong, but this tool is inappropriate for use with this model in particular, as presented in Figure 37.

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Meanwhile, the observed data in VPC plot for CCD-G dosing intervals applied to citrate group was mostly distributed within the predicted intervals for a small homogeneous group of patients. There is probably a tendency for the observed data to lie towards the lower end of the predicted range, suggesting some caution around low levels. A model based on increased observations would facilitate optimising the predicted VPC range, as shown in Figure 38. The VPC for the base model is presented in Figure 39, and the range is quite realistic, and the observed data fall mostly within the 5-95% quantiles.

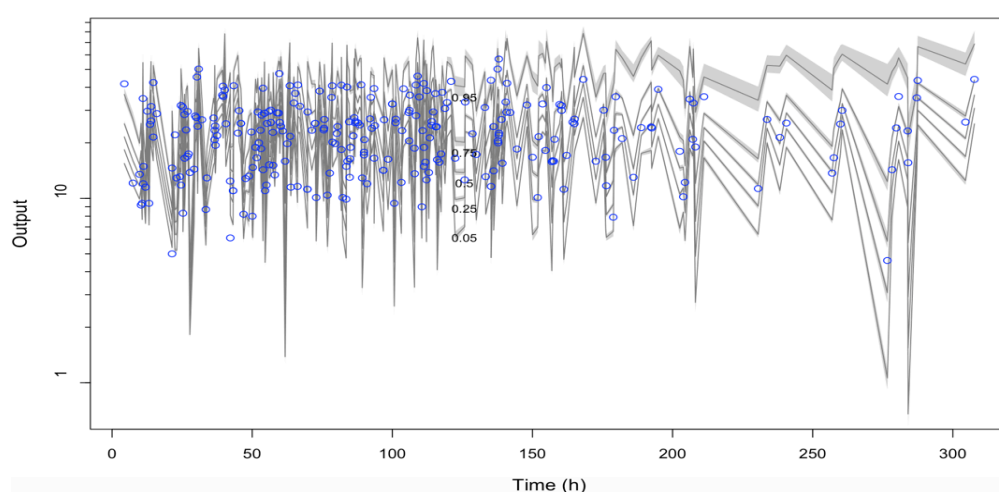


Figure 35: VPC for FB WD population model.

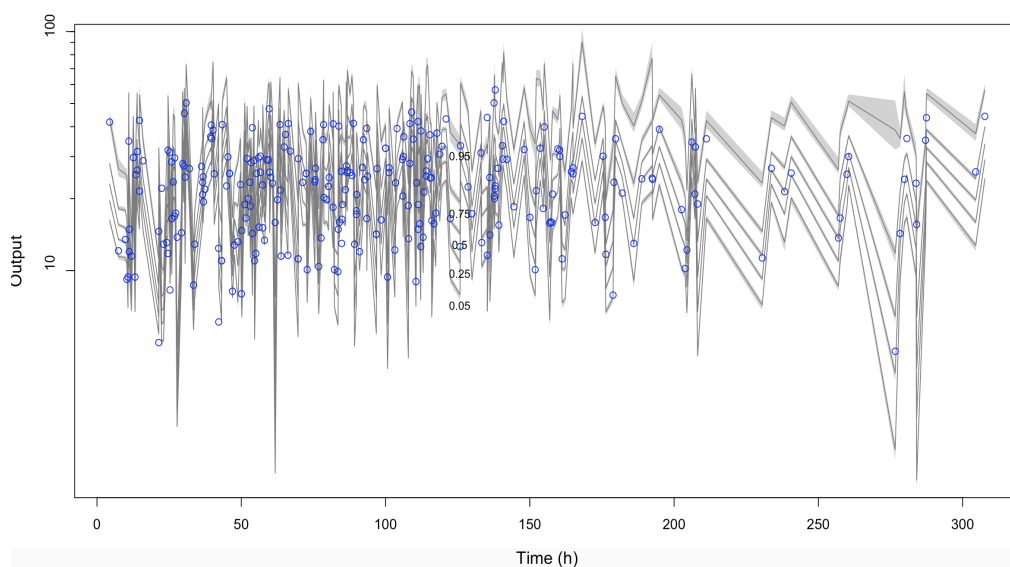


Figure 36: VPC for Alb Kei population model.

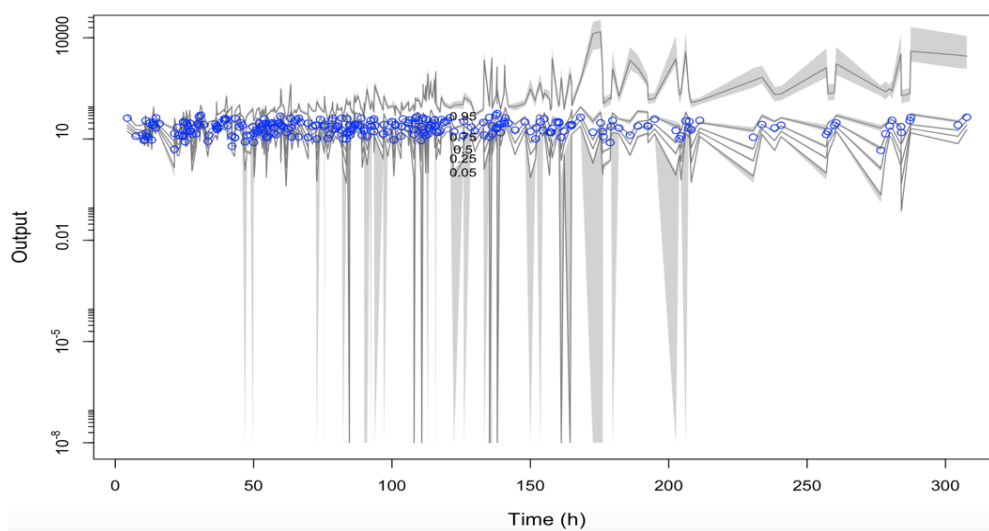


Figure 37: VPC for CCD-AP posterior individual model.

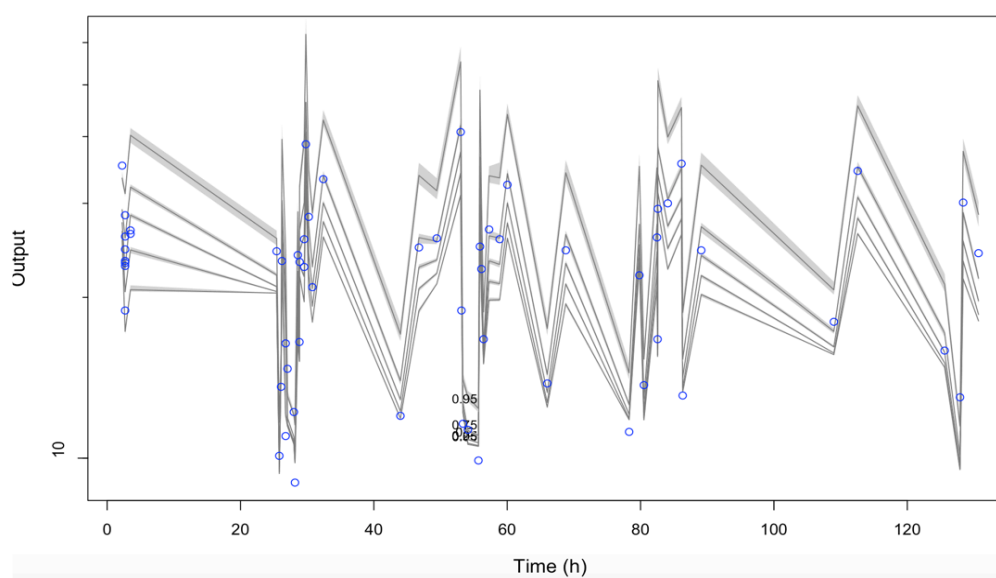


Figure 38: VPC for the CCD-G citrate dosing interval group data.

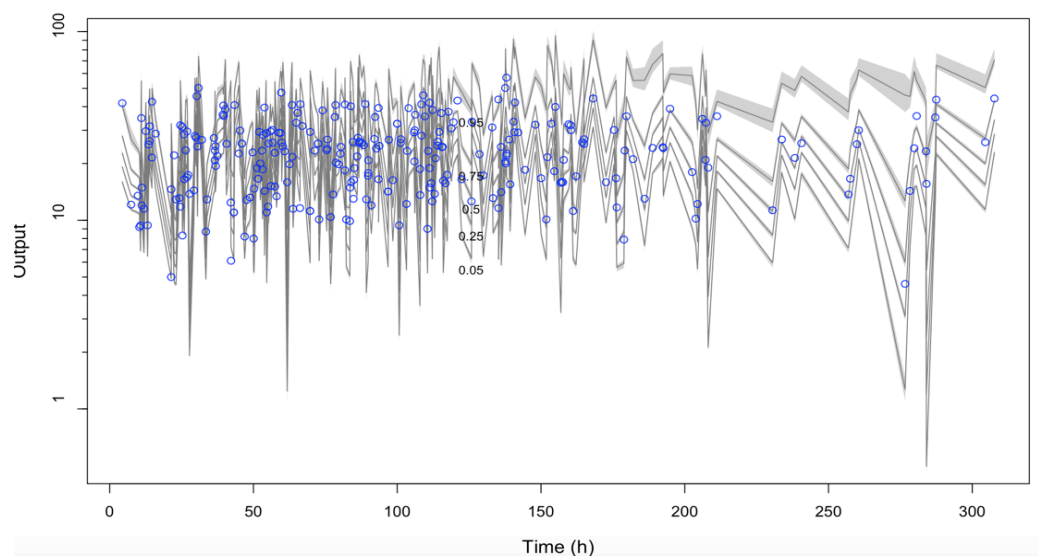


Figure 39: VPC for the base model.

- **Residual plots:**

Residual plots show the dispersion of the observed residual values for the parameter estimates with concentration and time. The residual plots for CDD-AP Ke and V, FB WD V, Alb Kei and CCD-G citrate group, and the base model are randomly dispersed, which indicate to a good fitting of data in a linear regression model and normal distribution of data in the left panel of the figures, with no obvious bias or trend as shown from Figure 40 to Figure 44.

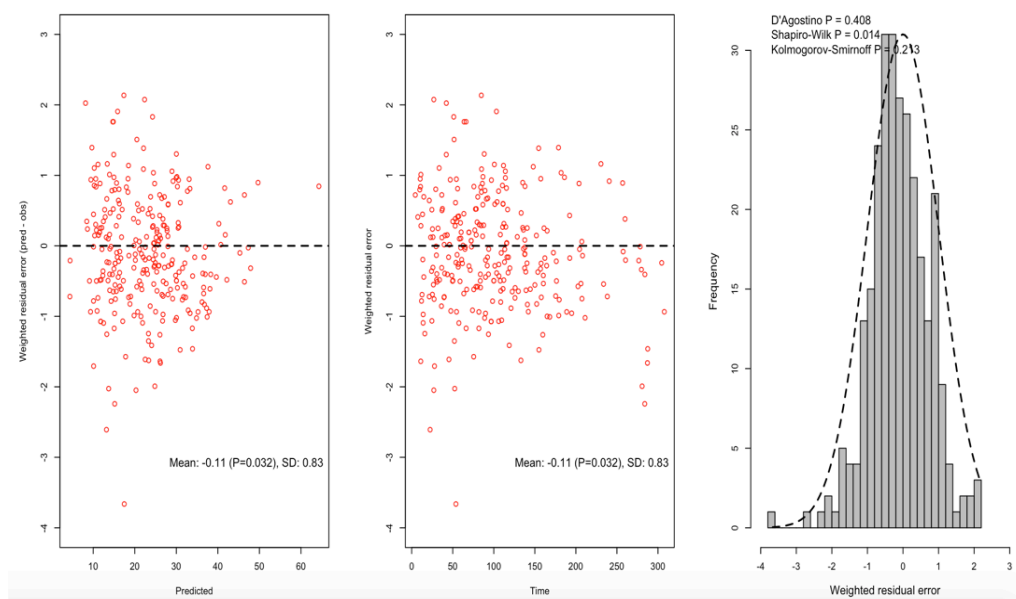


Figure 40: Residual plot for the CDD-AP Ke and V posterior individual model.

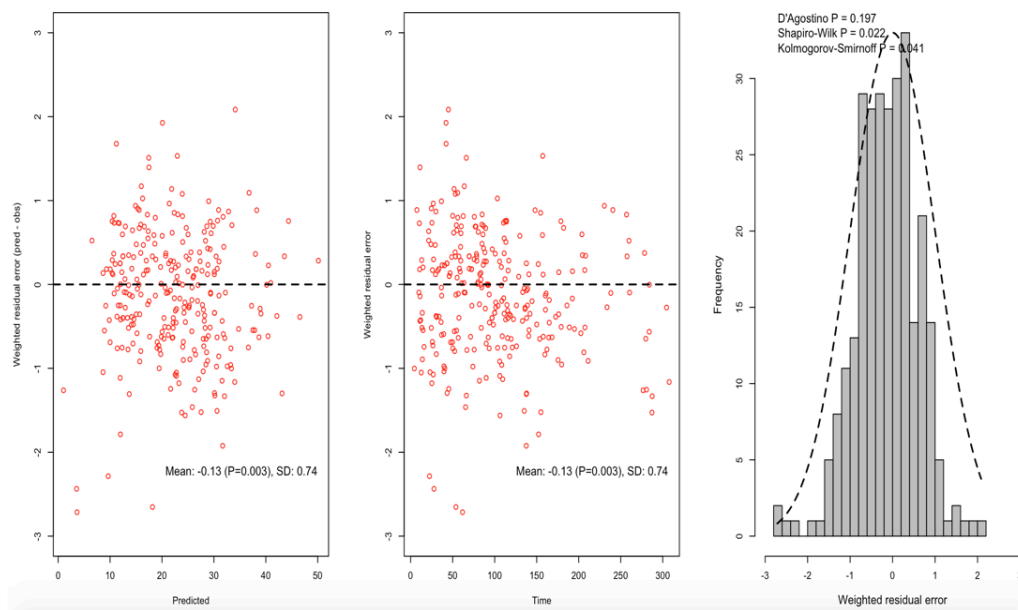


Figure 41: Residual plot for the FB WD V population model.

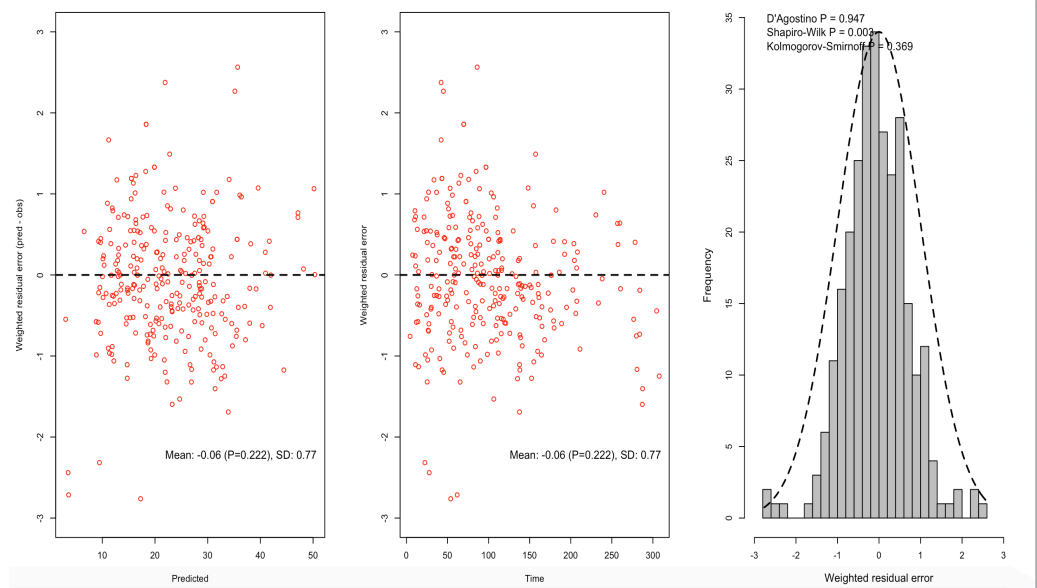


Figure 42: Residual plot for the Alb Kei population model.

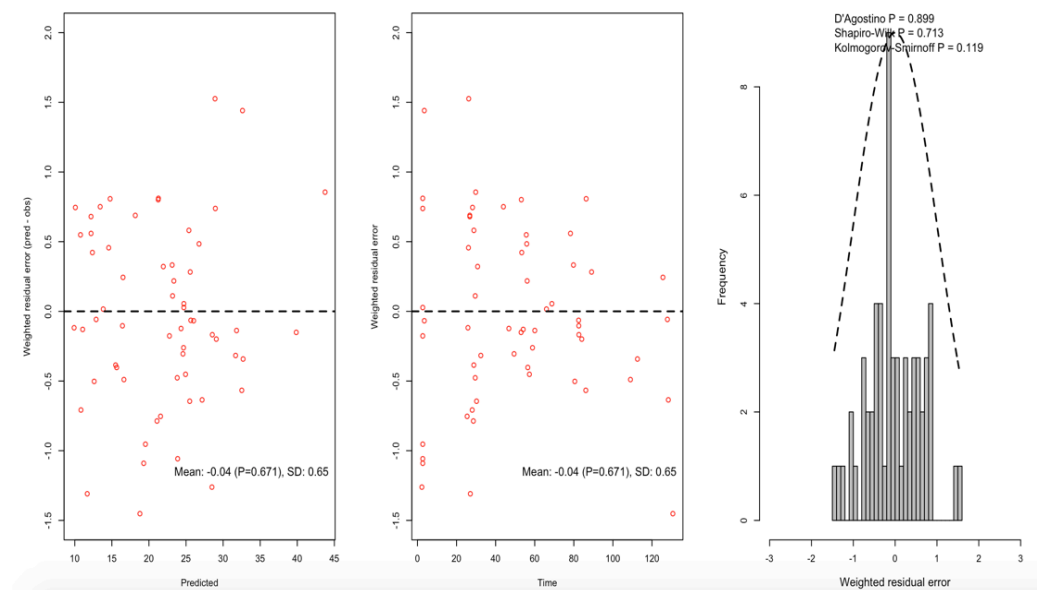


Figure 43: Residual plot for the CDD-G citrate intervals group.

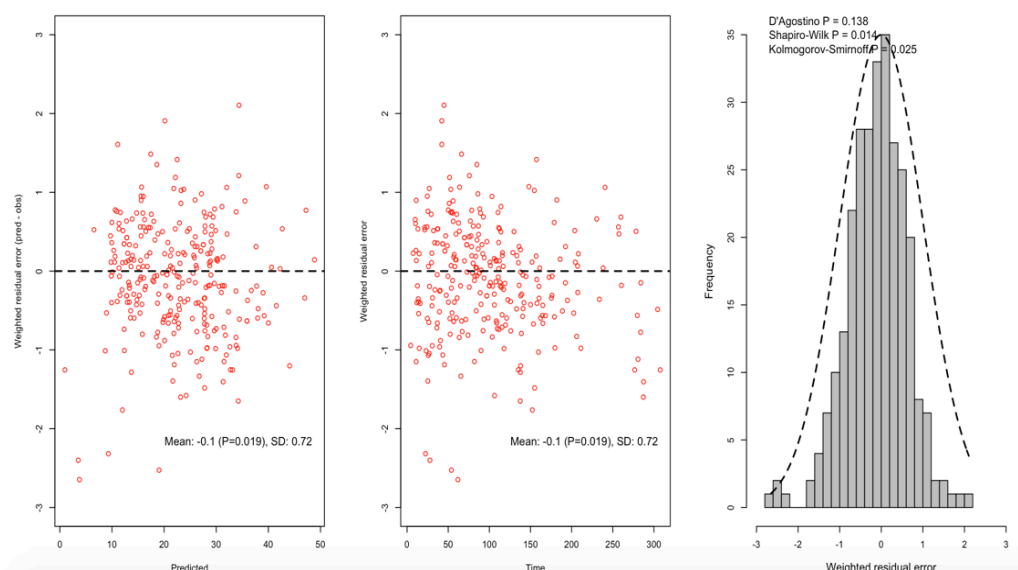


Figure 44: Residual plot for the base model.

From our results, there were a lot of plots used to describe and present the relation between the observed data within the predicted estimates. *Firstly*, the observed vs. predicted plot which was quite good with the population model of FB applied to V-continuous covariate model, the population model of Alb Kei and the posterior model for CDD-AP Ke and V categorical covariate model compared with the base model. Also of interest, the results from the CCD-G categorical models, suggesting more homogeneous data in the citrate group. Actually, there was no population model gave an R^2 for observed vs. predicted of >0.59 , therefore, no single outstanding population covariate model.

Secondly, the predicted individual plot applied for CDD-AP Ke and V, Alb Kei and FB WD V model when compared with the base model, was not always better, it differed from patient to patient as in patient 21, shown in Figure 30. *Thirdly*, the residual plot was acceptable for covariates and base models and normally distributed. *Finally*, the VPC plots were supportive of the covariate models adequately describing the observed data, but not appropriate for use with the CCD-AP covariate model. The unrealistic VPC CCD-AP plot was possibly due to the difference in the prediction parameter estimates e.g. the unrealistically low V and unrealistically high Ke as mentioned in patient 21.

4.2 Validation of automated data extraction from ICIP

Clinical Patient's data was automatically extracted from EHR sources and uploaded to RedCap system, and then the data was compared with the relevant data from hospital electronic sources (i.e. ICIP and Key) for use in PK analysis.

4.2.1 Completeness:

Based on the data that have been collected from ICIP, the total vancomycin doses are represented as 151 doses in ICIP. However, 7.9% of all these doses have not been found in the REDCap. Furthermore, the total peak levels are represented as 99 levels; around 96% of these levels have been in ICIP while 94% had been in REDCap, and 98% in Key, whereas 2% of the total levels have been found only in ICIP and 2% have been missed from REDCap. Additionally, the total trough levels are calculated as 98 levels; up to 96% of these levels have been in ICIP, 97% in Key, and 93% in REDCap. However, 2% of the total levels have been found only in ICIP, 3% have been found in Key only, and 2% levels have been missed from REDCap.

All details are summarised in **Table 26**, which shows there was some differences between the data in ICIP and the data that were extracted from the REDCap possibly due to the automated extraction method not capturing everything from ICIP. Also, there was no difference at all is expected between ICIP and Key system (i.e. clinical data recorded in Key (original source) then it is uploaded to ICIP system). There are also levels found in Key and not found in the other databases, might be because these levels are saved in another field in ICIP or Key and were not detected during the manual data collection.

Further investigation is required to determine the sources of the discrepancies in data collection between Key and ICIP, and also between ICIP and REDcap, to determine if there are any systematic causes for the discrepancies which could be accounted for in future data extraction method design.

Table 26: Variability between ICIP, REDCap, Key systems in vancomycin doses, peak, and trough levels.

	Vancomycin doses	Peak level	Trough level
ICIP	- 151 vancomycin doses for all 22 patients. -12 doses have been found in ICIP only.	- 95 peak levels for all 22 patients. -2 levels have been found in ICIP only. -2 levels have been missed from ICIP but found in other systems.	- 94 trough levels for all 22 patients. -2 levels have been found in ICIP only. -One level has been missed from ICIP but found in other systems.
REDCap	- 139 vancomycin doses for all 22 patients.	- 93 peak levels for all 22 patients. -2 levels have been missed from REDCap but found in other systems.	- 91 trough levels for all 22 patients. -2 levels have been missed from REDCap but found in other systems.
Key	No data was compared in this system.	- 97 peak levels for all 22 patients. -2 levels have been found in Key only.	- 95 trough levels for all 22 patients. -3 levels have been found in Key only. -One level has been missed from Key but found in other systems.

Abbreviation: ICIP, Intellivue Clinical Information Port- folio; REDCap, Research Electronic Data Capture.

4.2.2 Correctness

According to the above table, all vancomycin doses and levels in REDCap that compared with ICIP were correct, and there was no error in the compared data.

4.2.3 Concordance

In the context of compatibility, when we subtracted the dose values between the REDCap and ICIP systems, and the level between the different systems, we found that the results were zero in all data, which confirm that the results were in agreement and consistent.

5. Discussion

5.1 Patient demographics of retrospective PK analysis

5.1.1 Data cleaning

Patient 32 was excluded from our PK analysis. This patient was only in ICU for a day and vancomycin CL occurred prior to the ICU admission as the vancomycin dose was possibly not fully administered in this patient. We also excluded this patient to avoid any bias that might come from high K_e or CL parameter estimates, which could influence the PK estimates. Nevertheless, we should be aware in practice that such a patient can be found in the ICU.

5.2 Univariate and PM-step (multivariate) regression analysis

From the statistical point of view, the results from PM-step and univariate regression analysis were almost the same. However, PM-step indicated the presence of a correlation between the K_e parameter and BFR 4h ($p < 0.05$) that was not statistically significant in univariate analysis, while the univariate analysis suggested a relationship between V parameter and EFR 4h ($p < 0.005$), which was not significant in PM-step.

The difference in analysis techniques could be assumed as a reason for the variation in these results between univariate and PM-step. Conceptually, univariate regression assumes that the PK parameter is influenced by only one covariate to find a considered relationship each time; whereas multi-regression considers more than one variable together with the PK parameters each time, possibly not suggesting the EFR due to the presence of another covariate being related to V more than EFR. The results from regression analysis are not always indicative of model performance and just help to give suggestions for covariate addition. Importantly, both univariate and PM-step regression analyses were helpful in suggesting a correlation between PK parameter and Alb, which has less intra-individual variation, where also the covariate PK modelling found a significant correlation in Alb applied to K_{ei} (the non-inverse, partial approach). The regression analyses found the same result as the PK modelling in the case of Alb only. Whereas, EFR 4h applied to V parameter was suggested for inclusion by regression analyses. It resulted in only a minor

improvement and not as relevant as FB WD or Alb Kei models in term of R^2 , but was lower than those models in terms of $-2*LL$, AIC and BIC. Therefore the regression analyses did not suggest the most predictive covariates in terms of observed vs. predicted concentrations. Both Alb and EFR could be considered physiologically to be relevant covariates, and it is interesting that both regression analyses and our covariate modelling investigation identify these parameters for further investigation. However, FB can also be considered to be physiologically relevant to V, and it is of interest that it was not detected as a relevant covariate by the regression analyses.

These regression analyses use patient estimates from the base model with patient covariates, whereas the covariate PK modelling allows intra-individual variation for PK parameter estimates with dosing intervals. Both PM-step and univariate regression analysis can help to suggest the relationship between the continuous covariates that varies inter-individually, rather than that which varies intra-individually.

Therefore, neither PM-step nor univariate regression was recommended for covariate selection. Since ICU patients have high intra-individual variation, such regression analysis is less helpful for their covariate modelling. Also, p-values based on inter-patient relationships are difficult to interpret when there is intra-patient variability, such as the variability in critically ill patients. So, the search for related covariates could be complicated, especially in the presence of large numbers of relevant covariates and highly variable patients. In summary, using PK modelling is superior to regression analysis using inter-patient data in this patient cohort to identify relevant covariates and relate covariates and parameter estimates.

5.3 PK structural models

In the current study, we have developed structural PK models to explain the variation in vancomycin CL, V, and Ke parameter estimates. Several studies have been conducted on the pharmacokinetics of vancomycin; these used CL and V as parameter estimates (86, 90, 102). In our study, we used both CL and Ke with V parameters to build the base model, and these results were identical in both models.

DelDot et al. (86) found that the mean $\pm$ SD of total vancomycin CL was 2.5 ± 0.7 L/h in ten prospective patients treated with CVVHDF (86). The study by *Santre et al.* (103) reported that the mean of total CL was 2.3 L/h (38.9 ± 4.3 ml/min), while the mean V was 47.4 ± 6.4 L in three patients receiving CVVHD (103). *Roberts et al.* (55) studied the effect of CVVDHF on the different antibiotics, of which vancomycin was one, using one-compartment model. They discovered that the mean of total vancomycin CL was 1.5 L/h (25 (16-33) ml/min) with a mean V of 39.7 L (0.32-0.74 L/kg) (55).

Additionally, *Okada et al.* (104) examined the vancomycin PK in five patients with multiple organ failure who received CVVHDF and found that the mean $\pm$ SD of total vancomycin CL was 1.7 L/h (29 ± 1.8 ml/min) and the mean V was 54.4 ± 10.2 L (1.21 ± 0.26 L/kg). Another study reported that the median of total vancomycin CL was 2.9 L/h (IQR 2.4-3.4 L/h) and the median of V was 0.8 L/kg (IQR 0.6-1.1 L/kg) in a large retrospective study of patients receiving either CVVH or CVVHDF using a one-compartment model (32). Whereas the current study observed that the mean $\pm$ SD of total vancomycin CL was 2.2 ± 0.6 L/h and the mean $\pm$ SD of V was 80.7 ± 22.7 L (1 L/kg (based on mean body weight of our study cohort)) in patients receiving CVVHDF.

Ultimately, our results are similar to the CL values found in other studies, however the findings from other studies in which CL ranges from 1.5 to 2.9 L/h illustrate the variability in critically ill patients during CRRT modes and possibly reflect differences in the PK models used. The slightly higher V (1 L/kg) found in our study compared with the other CVVHDF studies, may be related to limitation of using a one-compartment model, and also as a result of obesity, as obese patients can have an increase in V.

Grace (105) reports that obesity is associated with an increase in both muscle mass and adipose tissue. This increase allows vancomycin to penetrate and distribute in adipose tissue. An increase in the distribution is related to increasing V in obese over non-obese patients. Also, obesity could cause an alteration in vancomycin CL (105). 10 of our 28 patients had BMI > 30, as presented in Table 7, which could explain the high V observed in our study.

Moreover, it is important to note that in this study we considered the Ke and V model as a final structural base model. The mean $\pm$ SD of Ke was 0.03 ± 0.01 h, and mean $\pm$ SD of V was 80.7 ± 22.7 L. Importantly, this result has not been previously described. To our knowledge, there are no published studies that have presented Ke with V parameter estimates instead of CL-based model during intermittent vancomycin treatment in ICU patients receiving CVVHDF.

Indeed, we found that the base model resulted in quite reasonable population and posterior individual predictions, given that ICU patients are recognised as being physiologically highly variable. In other words, the base model was able to explain 50% of the observed individual variability among the predicted population and observed PK estimates. Consequently, it was hard to improve on with covariates, especially on the posterior individual model which is largely independent of the covariates unless one or more can explain some of the inpatient variability. In our case, R^2 was truly high ($R^2 = 0.81$) for the posterior model, and displays a good relation between predicted and observed data even without adding a covariate. This result illustrates the ability of the base model and Pmetrics Bayesian methods to add to individual patient data. Thus, we can recommend that the base model can be used practically as a simple model to describe the PK variability and support broad dosing estimates in highly variable ICU patients.

5.4 Covariate models

Covariate models utilise the individual-specific data to identify and explain the relationship between model parameter estimates and relevant covariates, and also to describe the variability of PK estimates among the individuals examined. Therefore, a selection of good covariate models depended on: physiological plausibility and the clinical relevance of covariates to explain the variability in PK parameter estimates.

In the previous studies, covariate models have been described using the CL and V parameter estimates. As studied by *Roberts et al.* (55), they found a relationship between extracorporeal CL and CRRT intensity, but CRRT intensity as a covariate did not significantly affect the systemic CL estimate (55). Similarly, we found that adding the covariates to the CL model did not provide an advantage over the base model. A

possible explanation might be that CL was a composite measure calculated by multiplying V by Ke, and only allows a covariate to explain the combined variation in Ke and V. Also, the flexibility of the CL model seemed to be reduced by including covariates, in comparison to the Ke and V model, and did not enable the explanation of variation in the observed data. Thus, performing further investigation could help to develop a better CL with covariate model. Our finding does not mean that a CL model with covariates would not be good for estimating the PK, but that it is more difficult to develop a covariate model than the approach using Ke and V parameters.

5.5 Ke and V with covariate models

The covariates that applied specifically to the Ke and V parameters provided a significant improvement with some covariates over the base model. V and Ke would not always vary together to the same extent with each patient, with this approach allowing them to vary independently with covariates. However, regardless of the ease of the investigation of the covariate models for the Ke and V base model, it remains unclear why this approach, as opposed to the CL structural model, is not used more frequently in PK estimation in highly-variable critically ill patients.

5.5.1 Categorical Covariate Models

In the categorical covariate, there is a high variation in the PK parameter estimates in different patient types/dosing intervals. For instance, one patient can transfer from one category to another from one dosing interval to another. Therefore, the same patient could be a different patient type among the various dosing intervals.

From our study findings, we discovered that application of the CCD-AP covariate to PK parameters gave a significant improvement over the base model with chi-square test ($p < 0.001$). What is interesting is that the model of CCD-AP applied to both Ke and V together was the best individual posterior over the base model. It allows the PK estimates to vary and has more flexibility over the base model. Upon comparison, the models show a high variability (i.e. CV%) in Ke1, Ke2, Ke3, and V1 parameters in the CCD-AP than the base model, with no improvement over the base model for the population estimates. Using both Ke and V together, with a high number of

parameters (i.e. Ke 1-3 and V 1-3) improves the flexibility of PK parameter estimates and improves model performance when fitting the posterior individual data. However, the drawbacks of this model were: the unsatisfactory VPC plots, as well as the unclear individual prediction plots. Therefore, we should be very careful of over-fitting when using this model.

From a clinical point of view, CCD-G with citrate anticoagulant modality provides an excellent fit to the data compared to the non-dialysis group, despite the similarity in the number of patients data. Moreover, no difference in demographic data was noted between these groups as listed in Table 21. The citrate group was apparently more homogeneous, possibly resulting from prolonged dialysis “circuit life” and less bleeding when using citrate anticoagulant (70) or also possibly due to inherent bias (i.e. this group only included patient types suitable for citrate group). Non-dialysis intervals have extremely variable patients who have begun/just finished dialysis or have renal function recovering/ deteriorating. For that reason, the PK estimates in the citrate model were less variable than the non-dialysis cohort when compared with the base model. In addition, the Ke estimates (i.e. mean and median) were similar to the base model but V estimates (i.e. mean and median) were slightly higher for both citrate and non-dialysis groups as listed in Table 18. As a result, the population predicted model from the citrate anticoagulant modality group could be more reliable for suggesting the initial doses in these more homogeneous patients, followed by TDM, whereas the population predicted model of non-dialysis was not reliable and cannot be used practically.

On the other hand, data from the non-citrate anticoagulant modality dosing interval group did not provide a population prediction as good as that from the citrate group, possibly because of differences in patient numbers, types and observed data (i.e. less homogeneous patients). These differences prevented PK estimates predicting profiles which fit as well to the data as those generated from the citrate group. The PK estimates were less variable in the citrate group than the non-citrate group, as presented in Table 18. It should be noted that the difference in citrate and non-citrate groups was the difference in dialysis set-up (i.e. the comparison was not between anticoagulant choice because non-citrate could include patients on heparin or with

no-anticoagulant). Also, it must be recalled when comparing PK estimates and variability between these CCD-G models, that different numbers and types of patients were in each group, and therefore further studies are needed to quantify the differences in variability between the groups with more confidence.

5.5.2 Continuous Covariate Models

5.5.2.1 *FB models*

Changing volume of distribution is likely to occur in critically ill patients due to complex physiology such as increasing capillary permeability with endothelial damage in septic patients receiving vancomycin (106).

The volume of distribution of various drugs increases in patients with severe kidney disease compared to healthy people could be considered clinically significant if increased by more than 25%. However, the volume of distribution of vancomycin in healthy volunteers was 0.64 L/kg, while it was 0.85 L/kg in patients with end-stage kidney disease (i.e glomerular filtration rate less than 15 ml/min), an increase of 33% (107). However, *Petejova et al.* (106) observed that the volume of distribution of vancomycin in patients receiving CVVH was actually similar to healthy volunteers (106), this illustrates the effect of dialysis on volume of distribution. Our patients have some dosing intervals, not on dialysis, which could, therefore, contribute to variability in V also. However, it would be difficult to separate the effect of dialysis from the other physiological effects on V .

Changing fluid balance can significantly influence the vancomycin volume of distribution. It seems that changing the fluid balance can be considered a significant covariate. *Wang et al.* (108) studied the effect of fluid balance on mortality outcome in patients with AKI. They found that patients who suffer from AKI have high fluid balance; in particular, the cumulative fluid balance which had a considerable impact on the mortality of such patients more than on the non-AKI ones (108). These findings can help to suggest the use of FB as a covariate to estimate the PK parameters in critically ill patients during CRRT. Also, the cumulative fluid balance

can reflect a combination of other variables: fluid removal from dialysis and fluid input from large volume drug infusions, for example.

In our results, the FB WD applied to the V parameter model and applied to both Ke and V together model were identical in $R^2 = 0.59$, and both were statistically significant with chi-square test ($p < 0.01$). However, we selected the simpler FB covariate with less parameter estimate numbers as the best population prediction model, because the complex covariate models that improve the population predictions can tend to constrain individual predictions.

Additionally, ICU patients receiving CRRT are at risk of not only drug underdose but also overdose; both of which are considered to be life threatening conditions and require dose adjustment. Dose adjustment is a challenging issue in critically ill patients, and the estimation of the initial dose is consequently dependent on the volume of distribution parameter. So, using the FB applied to V parameter population model can help in guiding the initial dosing in critically ill patients. While it is frequently suggested that fluid balance may affect V for some drugs in critically ill patients (4, 5, 109), we are not aware of population PK studies which have explored the use of cumulative fluid balance as a covariate for vancomycin volume of distribution following intermittent infusion administration in patients on CVVHDF.

5.5.2.2 EFR and BFR models

In the present dataset, all of the 4h and WD EFR covariate models applied to PK parameters resulted in a statistically significant improvement ($p < 0.01$) over the base model, using the original methods (i.e. non-inverse methods and allowing an intercept). Since the potential overfitting with the posterior individual model for CCD-AP Ke and V, the next best posterior individual predicted model was the EFR 4h applied to Ke with statistically significant improvement ($p < 0.001$) and $R^2 = 0.85$ over the base model.

Udy et al. (32) and *Roberts et al.* (55) found that there is no significant correlation between CL via CRRT or V parameters and EFR (55) or other CRRT settings (dialysate rate, BFR, and ultrafiltration rate) (32), similar to what was obtained in our study with Ke and V parameters model and BFR covariate, where there was no obvious

improvement over the base model. However, EFR applied to the V parameter resulted in a small improvement in the population prediction model over the base model. The improvement obtained from EFR covariates was not as good as the FB or Alb covariates, perhaps because the FB is the patient's property related to patient's condition and severity of illness that allowing it to vary differently with PK estimates, unlike EFR which is a dialysis property. Besides that, FB can reflect changes in EFR, including ultrafiltration in combination with the changes in other fluids, making it a possible better metric for V estimate than EFR. The effect of inclusion of EFR as a covariate on the population prediction is in contrast to that from *Udy et al.* (32) who found no correlation between effluent rate and CL, and our findings of a lack of improvement in covariate CL models over the base model.

Furthermore, there is a correlation between vancomycin CL and ultrafiltration rate where an increased ultrafiltration rate was associated with higher vancomycin CL in different CRRT modes (89, 110). *Chaijamorn et al.* (110) reported that the ultrafiltration rate of 800-1200 ml/h in seven patients receiving CVVH afford a drug CL_{CVVH} of 0.73 ± 0.21 L/h (110). In another study, the drug CL by CVVHDF was 1.8 L/h during ultrafiltration rate of 3000 ml/h (86). This result suggests further work with more data using the ultrafiltration rate and CL via CVVHDF might result in a better covariate model, since EFR was calculated from the ultrafiltration rate.

5.5.2.3 Wt models

Changes in the muscle mass and connective tissue are often associated with an increase in body weight, as described in section 5.3 This change could affect the PK estimates. Therefore, this study tried to assess the effects of actual body weight on V parameter in critically ill patients treated with vancomycin. Consequently, we found a slight advantage from using weight as a covariate over the base model whereas, *Udy et al.* (32) found no positive correlation was observed between the body weight and V (32).

5.5.2.4 Alb models

The relationship between the albumin level and drug pharmacokinetics frequently changes in critically ill patients. Low serum protein concentration often decreases

protein binding which in turn increases the free fraction in plasma, leading to an elevation in the volume of distribution in critically ill patients. Also, decreasing the renal function in these patients can cause alterations in protein binding. Thus, hypoalbuminemia is associated with a higher drug CL and the V of hydrophilic drugs during critical illness (4). These physiological changes suggest a correlation between the albumin level and V and/or Ke. Alb was one of the suggested covariates in regression analyses with PK parameter estimates in our study. The effect of this physiological alteration was detected by using the inverse approach (i.e. it was found a good correlation between Alb and Ke), as presented in Table 23, which will be explained later in section 5.7.

5.5.2.5 Age covariate

With respect to the elimination rate constant, a significant correlation was observed with age covariate in the linear regression analysis. However, modelling the age covariate with PK parameters did not offer an advantage over the base model greater than other covariates in the current study, using the non-inverse, including an intercept method. However, the unexpected correlation was found in a study by *Mo et al.* (88) who studied the PK parameters of vancomycin in nine elderly patients undergoing CVVHDF. They found that the V was higher in elderly critically ill patients when compared with non-elderly critically ill patients (88). The difference between our finding and this may be due to the strategy of data collection (i.e. retrospective vs. prospective). The prospective nature resulting in richer intra-patient data (i.e. more blood samples were taken) but in a smaller cohort (n=9), and all patients included were aged ≥ 72 years vs. our study that aged between 67 ± 47 (median $\pm$ range).

5.6 The partial volume vs. total volume in the covariate analysis

The PK analyses were undertaken to describe the relationship between PK parameters and covariates. In the current study, the partial approach (including inverse and non-inverse methods) was used for all covariates. In addition to that, the total approach was used for FB, Alb, Wt, and Age covariates. In the partial approach method, the V and the Ke are divided into V 1-2 and Ke 1-2. This approach allows for an intercept (V1 or Ke1) in the relationship between the PK parameter estimate and

the covariate. That allows the V_2 and Ke_2 to vary quite well with the covariate and improve the performance of the population prediction model over the base model. Therefore, this approach provides more flexible parameter estimates to adapt with the covariate. In comparison, the total approach used whole Ke and V values to vary with the covariate, making unrealistic population prediction models with R^2 values much worse than not only the partial, but also from the base model. Thus, this approach failed to detect a good relationship between the PK parameter estimates and the covariate.

In this study, PK estimates are approximated through use of a one-compartment model with only V and Ke estimates calculated; what was detected in this study was achieved using the partial approach, allowing an intercept, which was more appropriate to explain the population prediction in a one-compartment model.

Therefore, an intercept should be considered because we would not have detected some of the significant relationships if we had not allowed for an intercept. Some PK studies have not detected a relationship where an intercept is not present in their covariate model (32, 55). The study by *Beumier et al.* (90) found that inclusion of CRRT intensity to PK model, specifically CL , provided significant improvement; this is an example of a study finding a relationship where an intercept is present (90).

5.7 The inverse approach vs. the non-inverse approach in covariate analysis

It was attempted to use an inverse approach to explain the variability of Alb , EFR , BFR and FB with PK estimates and compare it with the opposite approach to find which was an acceptable approach and clarify the nature of the physiological variation with the PK variation, where a relationship was found. The non-inverse approach reflects that the model will assume the PK parameter estimate will vary positively with the covariate, while the inverse approach reflects that it will vary negatively with the covariate.

Alb covariate

In critically ill patients, changing the protein binding and hypoalbuminemia can result in changes in PK estimates (8). So, an increase in Alb is more likely to decrease V. In the non-inverse approach using equations (21,22), this might be reflected in a lower V1 to compensate for a high V2 in a patient with increased Alb, while V2 will decrease as Alb increased in the inverse approach using equations (26,27). Therefore, the inverse approach is more meaningful and leads to a statistically better population predicted model than the base model with $R^2 = 0.55$, and also was better than non-inverse approach as shown in Table 23. Using the inverse approach allows the detection of significant correlation between Alb and Kei. This was interesting because vancomycin has moderate protein binding, and Alb is often associated with changing in V more than Ke. However, Alb with Kei revealed a notable improvement in the population predicted model with $R^2 = 0.59$ over the base model.

BFR covariate

In general, BFR changes very little in heparin patients. However, it is low in citrate patients, and the prolonged dialysis circuit life could lead to slight increase in Ke. Thus, the suggestion of decreasing BFR associated with increased Ke could reflect the lower BFR used in citrate patients. In the inverse approach, a decrease BFR reflected an increase in Ke2. This reflection allowed to increase R^2 value of the population predicted model but did not provide statistically significant improvement in $-2*LL$, AIC, and BIC over the base model, as presented in Table 19.

EFR covariate

It might be expected that Ke would increase as EFR increases (a positive association), using the non-inverse approach (equation 16). However, increased EFR could be used for various reasons, e.g. if there is a change in ionised calcium levels with RCA, to achieve a negative fluid balance relative to the previous day or to compensate for a high fluid load from infused drugs. Therefore, it could happen that for other reasons a higher EFR is used in patients with a lower Ke1 (a negative correlation) by using the inverse approach (equation 19). The relationship between EFR and Ke is unclear, this could be investigated further by investigating the relationship between EFR and CVVHDF CL (as opposed to total CL), along with the effect of EFR on V. On the other

hand, alteration of EFR can affect V , the component that varies to affect V is the ultrafiltration. Therefore, this expectation was reflected in the non-inverse approach for EFR applied to V and improved the population prediction model over the base model as shown in Table 22. However, as discussed, cumulative fluid balance reflects the combination of these changes along with fluid input, and had a better relationship with V than EFR in terms of model performance.

Furthermore, the inverse approach did not detect any improvement over the base model for the covariates with 4h applied to K_e or V . The reason for this was that the data showed a lot of predicted concentrations with zero values during the dosing interval, which will, therefore, result in an infinite value estimate for K_{e2} and V_2 estimates. That did not happen to the covariates in WD dosing intervals, which contained only non-zero values. Therefore, if a zero covariate value is present, the intercept value is the relevant parameter estimate, thereby this inverse method cannot be used.

5.8 Validation of automated data extraction from ICIP

The second aim of this study was carried out to demonstrate the ability of the automated data extraction method, used by the nephrology team, from the EHR source for application in PK analysis.

Indeed, using an EHR for data retrieval should save time and effort compared to manual files/charts, however, automated data extraction from an EHR could save more time. Recording the data manually from the EHR consumed up to 64 hours while the automated extraction from EHR took a few minutes and was able to extract huge numbers of data.

The point here was to test the automated extraction method vs. manual extraction of data from EHR, by comparing the vancomycin data extracted and uploaded to REDCap with the data that was recorded manually for the same patients. It was confirmed that the data uploaded to REDCap is correct compared to ICIP and Key. While the data present in REDCap was correct, there was some data missing from REDCap when compared to that manually extracted ICIP. These differences are

possible because the automated extraction does not catch everything from ICIP (i.e. some data may have been in the different field and could not be targetted for extraction).

As a result, the automated data extraction method was reasonable and ensured that all data present was correct, but there were some instances of missing data. Amounts of missing data were small, but the effect of the missing data on the results of a PK analysis has not been determined. Therefore the extraction method would be very useful for PK analysis in term of time saving, but first requires further validation and investigation for development into a reliable system to ensure clinical data accuracy and completeness.

6. Conclusion

6.1 Conclusion

The purpose of the current retrospective study was to describe the population PK estimates and the influence of patient covariates following intermittent infusion of vancomycin in critically ill patients receiving CVVHDF.

This thesis was able to detect the basic and relevant covariate models through an application of the pharmacokinetic principles. Also, it supports using the reliable EHR methods of automated data extraction for future work on the PK analysis in a more efficient manner.

The following conclusions can be drawn from the present thesis:

- A reasonable structural model was achieved using either CL or K and V parameter estimates. The base model was quite useful, the population prediction model explained approximately 50%, while the posterior individual model explained approximately 80% of the variability of the response covariate around the estimates. Therefore, it was challenging to identify covariate models providing practical improvement over the base model.
- The regression analyses were not helpful for identifying covariates with the exception of albumin. FB would not have been identified for inclusion in a covariate model if regression analyses data alone had been used for considering covariate inclusion.
- It was found that using the Ke and V instead of CL base model were able to explore a meaningful improvement with some covariates over the base model. Also, allowing Ke and V parameters to vary independently were beneficial for detection covariates association.
- No single covariate model using all patients provided a notable improvement simultaneously in both population predictions and posterior individual predictions.
- Allowing an intercept for both the inverse and non-inverse approaches help to detect significant covariate correlation, whereas using the total volume

approach (no intercept) did not adequately predict an advantage on the population model over the base model.

- This study used covariates from both 4h and WD for the initial dose and dose adjustment. The models using 4h covariate data were not as good as the WD data for the selected (best) models.
- With respect to categorical covariates: the CCD-AP covariate model has a good R^2 value, for the posterior individual predicted model of both Ke and V parameter estimates, and has been shown to be the best posterior model over the base model. This is probably because increased parameters allowed for the capture of more inter- and intra-individual variability and improved model fitting. Regardless of this outcome, we should be careful to avoid model overfitting when a complex covariate model is used. On the other hand, in the CCD-G covariate model, the citrate anticoagulant group has a better population predicted model and suggests it might be easier to manage dosing within this homogeneous group of patients, rather than a non-dialysis group.
- With respect to continuous covariates: the best population predicted model in this study were the FB WD applied to V parameter (non-inverse partial approach) and Alb applied to Ke (inverse partial approach). Obviously, these population predicted models improved the model in terms of $-2*LL$, AIC and BIC, with V $R^2 = 0.59$ in both FB V and Alb with Ke models over the base model. One should be cognizant that selection of 2 different models e.g. adjust V for FB and Kei for Alb from 2 different models is not ideal in dose estimations, we should use parameters from the same model.
- Collection of clinical data manually using EHR instead of the traditional data collection manually from the patient files/charts was adequate to access complete and accurate patients' information in a short time. Also, one advantage is the possibility of automated data extraction from it.
- The results found that the automated data extraction method was quite good, along with notable time-saving. However, it needs more investigation to ensure all data are present and to develop a reliable system for automated extraction.

6.2 Future work

This research will serve as a base for future studies using the K_e and V estimates. Also, further work on the CL model could help to identify a better covariate model in highly variable ICU patients.

It is recommended that further research be undertaken in the following areas:

Firstly, it points to using the two-compartment model instead of one-compartment, which requires extra data to be applied (more peak and trough levels, and more blood samples in between these levels, especially at earlier time points to capture distribution phase). As vancomycin has multi-compartment PK, utilising a two-compartment model could lead to better improvement in parameter estimates and an improved correlation with the covariates, when using the partial parameter approach.

Secondly, carrying out a prospective research study could help to detect more covariate affecting the K_e and V pharmacokinetic estimates. It would also help in the collection of specific data, such as effluent concentration data, to calculate CVVHDF clearance.

Thirdly, the population predicted model for the citrate anticoagulant group was reasonable, suggesting homogeneous patient characteristics compared with non-dialysis and non-citrate cohort. Therefore, further work with a large patient sample could achieve an improved covariate model. We found an improvement in the population prediction of the citrate anticoagulant group compared with the non-citrate cohort in an extremely small patient sample, which did not allow us to conclude on the intra-patient data in these patients. Also, the effects of continuous covariates, e.g. Alb and FB, could be explored within the different categories of the CCD-G groups. Therefore, further work is suggested in this area.

Fourthly, we recommend studying the effect of Alb on K_{ei} (inverse approach) and FB on V (non-inverse approach) together in one model for exploration of the general interplay between Alb and FB trends in patients.

Finally, we recommend further investigation to detect the effect of using vasopressors on the variation of V during CVVHDF; this was previously studied with different CRRT.

6.3 Limitation

The most important limitation discovered in this study was the retrospective nature of the small group in a single centre which limited the data available for analysis. The available samples for collection were only peak and trough levels that restrict the study of the population PK variability in critically ill patients to a one-compartment model only. Additionally, no data on the non-renal clearance of CVVHDF were collected, further studies are needed to describe the CRRT characteristics and drug clearance. Finally, the unbounded or free vancomycin concentration can cause alteration in CL and V parameters (4), the free fraction was not measured as a part of the scope of this study because it was not available. Also, despite the fact that albumin levels were available and were the best population predictive model with Kei (inverse, partial approach), albumin might correlate better with the free fraction.

Although it was a retrospective study, its advantages were identified as: the data collected has been gathered from patients who received vancomycin when infusion pumps with vancomycin administration rates in the drug library were used, therefore, there was more certainty about infusion rates and thus, infusion duration. Also, using the EHR-dose sign off time with the dose itself to confirm when the drug was given added to the confidence of the time data. In addition to the strict protocols in the ICU for the timing of vancomycin levels, these factors were considered to improve accuracy and minimise the bias in the data collection period.

7. References

1. Grüneberg R, Wilson A. Anti-infective treatment in intensive care: the role of glycopeptides. *Intensive Care Medicine*. 1994;20(4):S17-S22.
2. Chow A, Azar R. Glycopeptides and nephrotoxicity. *Intensive Care Medicine*. 1994;20(4):S23-S9.
3. Bagshaw SM, Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, et al. Septic acute kidney injury in critically ill patients: clinical characteristics and outcomes. *Clinical Journal of the American Society of Nephrology*. 2007;2(3):431-9.
4. Fernández de Gatta MadM, Martin-Suarez A, Lanao JM. Approaches for dosage individualisation in critically ill patients. *Expert opinion on Drug Metabolism & Toxicology*. 2013;9(11):1481-93.
5. Blot SI, Pea F, Lipman J. The effect of pathophysiology on pharmacokinetics in the critically ill patient—concepts appraised by the example of antimicrobial agents. *Advanced Drug Delivery Reviews*. 2014;77:3-11.
6. Udy AA, Roberts JA, Lipman J. Clinical implications of antibiotic pharmacokinetic principles in the critically ill. *Intensive Care Medicine*. 2013;39(12):2070-82.
7. Smith BS, Yogaratnam D, Levasseur-Franklin KE, Forni A, Fong J. Introduction to drug pharmacokinetics in the critically ill patient. *CHEST Journal*. 2012;141(5):1327-36.
8. Roberts JA. Using PK/PD to optimize antibiotic dosing for critically ill patients. *Current Pharmaceutical Biotechnology*. 2011;12(12):2070-9.
9. Roberts JA, Abdul-Aziz MH, Lipman J, Mouton JW, Vinks AA, Felton TW, et al. Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. *The Lancet Infectious Diseases*. 2014;14(6):498-509.
10. McKenzie C. Antibiotic dosing in critical illness. *Journal of Antimicrobial Chemotherapy*. 2011;66(suppl 2):ii25-ii31.
11. Nicolau DP. Optimizing outcomes with antimicrobial therapy through pharmacodynamic profiling. *Journal of Infection and Chemotherapy*. 2003;9(4):292-6.
12. Roberts JA, Lipman J. Antibacterial dosing in intensive care. *Clinical Pharmacokinetics*. 2006;45(8):755-73.
13. Levine DP. Vancomycin: a history. *Clinical Infectious Diseases*. 2006;42(Supplement 1):S5-S12.
14. Moellering RC. Vancomycin: a 50-year reassessment. *Clinical Infectious Diseases*. 2006;42(Supplement 1):S3-S4.
15. Anderson R, Higgins Jr H, Pettinga C. Symposium: how a drug is born. *Cincinnati J Med*. 1961;42:49-60.
16. Bauer L. The aminoglycoside antibiotics. *Applied Clinical Pharmacokinetics*, 2nd ed, McGraw Hill, New York. 2008:97-206.
17. Hauser AR. Antibiotic basics for clinicians: The ABCs of choosing the right antibacterial agent: Lippincott Williams & Wilkins; 2012. 45-8 p.
18. Murray BE. Vancomycin-resistant enterococcal infections. *New England Journal of Medicine*. 2000;342(10):710-21.

19. Schwaber MJ, Venkataraman L, DeGirolami PC, Gramatikova A, Perl TM, Sakoulas G, et al. Clinical Significance of Varying Degrees of Vancomycin Susceptibility in Methicillin-Resistant *Staphylococcus aureus* Bacteremia. 2003.
20. Hiramatsu K, Aritaka N, Hanaki H, Kawasaki S, Hosoda Y, Hori S, et al. Dissemination in Japanese hospitals of strains of *Staphylococcus aureus* heterogeneously resistant to vancomycin. *The Lancet*. 1997;350(9092):1670-3.
21. Wong SS-Y, Ng T-K, Yam W-C, Tsang DN-C, Woo PC-Y, Fung SK-S, et al. Bacteremia due to *Staphylococcus aureus* with reduced susceptibility to vancomycin. *Diagnostic Microbiology and Infectious Disease*. 2000;36(4):261-8.
22. Rybak MJ. The pharmacokinetic and pharmacodynamic properties of vancomycin. *Clinical Infectious Diseases*. 2006;42(Supplement 1):S35-S9.
23. Sánchez-Navarro A, Recio MMS. Basis of Anti-Infective Therapy. *Clinical Pharmacokinetics*. 1999;37(4):289-304.
24. Power BM, Forbes AM, van Heerden PV. Pharmacokinetics of drugs used in critically ill adults. *Clinical Pharmacokinetics*. 1998;34(1):25-56.
25. de Gatta MdMF, Revilla N, Calvo MV, Domínguez-Gil A, Navarro AS. Pharmacokinetic/pharmacodynamic analysis of vancomycin in ICU patients. *Intensive Care Medicine*. 2007;33(2):279-85.
26. Holmes NE, Turnidge JD, Munckhof WJ, Robinson JO, Korman TM, O'Sullivan MV, et al. Vancomycin AUC/MIC ratio and 30-day mortality in patients with *Staphylococcus aureus* bacteremia. *Int J Antimicrobial Agents and Chemotherapy*. 2013;57(4):1654-63.
27. Kullar R, Davis SL, Levine DP, Rybak MJ. Impact of vancomycin exposure on outcomes in patients with methicillin-resistant *Staphylococcus aureus* bacteremia: support for consensus guidelines suggested targets. *Clinical Infectious Diseases*. 2011;52(8):975-81.
28. Moise-Broder PA, Forrest A, Birmingham MC, Schentag JJ. Pharmacodynamics of vancomycin and other antimicrobials in patients with *Staphylococcus aureus* lower respiratory tract infections. *Clinical Pharmacokinetics*. 2004;43(13):925-42.
29. Blouin RA, Bauer LA, Miller DD, Record KE, Griffen WO. Vancomycin pharmacokinetics in normal and morbidly obese subjects. *Antimicrobial Agents and Chemotherapy*. 1982;21(4):575-80.
30. Rotschafer J, Crossley K, Zaske D, Mead K, Sawchuk R, Solem L. Pharmacokinetics of vancomycin: observations in 28 patients and dosage recommendations. *Antimicrobial Agents and Chemotherapy*. 1982;22(3):391-4.
31. Ackerman B, Taylor E, Olsen K, Abdel-Malak W, Pappas A. Vancomycin serum protein binding determination by ultrafiltration. *Drug Intelligence & Clinical Pharmacy*. 1988;22(4):300-3.
32. Udy AA, Covajes C, Taccone FS, Jacobs F, Vincent J-L, Lipman J, et al. Can population pharmacokinetic modelling guide vancomycin dosing during continuous renal replacement therapy in critically ill patients? *International Journal of Antimicrobial Agents*. 2013;41(6):564-8.
33. Matzke G, Zhanel G, Guay D. Clinical pharmacokinetics of vancomycin. *Clinical Pharmacokinetics*. 1986;11(4):257-82.

34. Harvey RA, Clark M, Finkel R, Rey J, Whalen K. Lippincott's illustrated reviews: Pharmacology: Baltimore, MD: Lippincott Williams & Wilkins; 2012.
35. Rybak M, Lomaestro B, Rotschafer JC, Moellering R, Craig W, Billeter M, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *American Journal of Health-System Pharmacy*. 2009;66(1):82-98.
36. Rybak MJ, Lomaestro BM, Rotschafer JC, Moellering RC, Craig WA, Billeter M, et al. Vancomycin therapeutic guidelines: a summary of consensus recommendations from the infectious diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. *Clinical Infectious Diseases*. 2009;49(3):325-7.
37. Martin JH, Norris R, Barras M, Roberts J, Morris R, Doogue M, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Clin Biochem Rev*. 2010;31(1):21-4.
38. Cosgrove S, Avdic E, Dzintars K, Smith J. Antibiotic guidelines 2015-2016.
39. Darko W, Medicis JJ, Smith A, Guharoy R, Lehmann DF. Mississippi mud no more: cost-effectiveness of pharmacokinetic dosage adjustment of vancomycin to prevent nephrotoxicity. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*. 2003;23(5):643-50.
40. Farber BF, Moellering RC. Retrospective study of the toxicity of preparations of vancomycin from 1974 to 1981. *Antimicrobial Agents and Chemotherapy*. 1983;23(1):138-41.
41. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus definitions for sepsis and septic shock (Sepsis-3). *Jama*. 2016;315(8):801-10.
42. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Critical Care Medicine-Baltimore*. 2001;29(7):1303-10.
43. Harrison DA, Welch CA, Eddleston JM. The epidemiology of severe sepsis in England, Wales and Northern Ireland, 1996 to 2004: secondary analysis of a high quality clinical database, the ICNARC Case Mix Programme Database. *Critical care*. 2006;10(2):R42.
44. Vincent J-L, Marshall JC, Namendys-Silva SA, François B, Martin-Loeches I, Lipman J, et al. Assessment of the worldwide burden of critical illness: the Intensive Care Over Nations (ICON) audit. *The lancet Respiratory Medicine*. 2014;2(5):380-6.
45. Marshall JC. Inflammation, coagulopathy, and the pathogenesis of multiple organ dysfunction syndrome. *Critical Care Medicine*. 2001;29(7):S99-S106.
46. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest Journal*. 1992;101(6):1644-55.
47. DiPiro J, Schwinghammer T, DiPiro C. *Pharmacotherapy handbook*: McGraw-Hill Companies, Incorporated; 2009

48. Jacobi J. Pathophysiology of sepsis. *American Journal of Health-system Pharmacy*. 2002;59.
49. Varghese JM, Roberts JA, Lipman J. Antimicrobial pharmacokinetic and pharmacodynamic issues in the critically ill with severe sepsis and septic shock. *Critical Care Clinics*. 2011;27(1):19-34.
50. Vincent J-L, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Medicine*. 1996;22(7):707-10.
51. Acharya S, Pradhan B, Marhatta M. Application of" the Sequential Organ Failure Assessment (SOFA) score" in predicting outcome in ICU patients with SIRS. 2007.
52. Hoste EA, Clermont G, Kersten A, Venkataraman R, Angus DC, De Bacquer D, et al. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. *Critical Care*. 2006;10(3):1.
53. Hoste EA, Lameire NH, Vanholder RC, Benoit DD, Decruyenaere JM, Colardyn FA. Acute renal failure in patients with sepsis in a surgical ICU: predictive factors, incidence, comorbidity, and outcome. *Journal of the American Society of Nephrology*. 2003;14(4):1022-30.
54. Huh JW, Lim C-M, Koh Y, Hong S-B, Kim WY. A comparison of acute kidney injury classifications in patients with severe sepsis and septic shock. *The American Journal of The Medical Sciences*. 2012;344(5):350-6.
55. Roberts DM, Liu X, Roberts JA, Nair P, Cole L, Roberts MS, et al. A multicenter study on the effect of continuous hemodiafiltration intensity on antibiotic pharmacokinetics. *Critical Care*. 2015;19(1):1.
56. Deepa C, Muralidhar K. Renal replacement therapy in ICU. *Journal of Anaesthesiology Clinical Pharmacology*. 2012;28(3):386.
57. Trotman RL, Williamson JC, Shoemaker DM, Salzer WL. Antibiotic dosing in critically ill adult patients receiving continuous renal replacement therapy. *Clinical Infectious Diseases*. 2005;41(8):1159-66.
58. Pannu N, Gibney R. Renal replacement therapy in the intensive care unit. *Ther Clin Risk Manag*. 2005;1(2):141-50.
59. Kellum JA, Angus DC, Johnson JP, Leblanc M, Griffin M, Ramakrishnan N, et al. Continuous versus intermittent renal replacement therapy: a meta-analysis. *Intensive Care Medicine*. 2002;28(1):29-37.
60. Bugge J. Pharmacokinetics and drug dosing adjustments during continuous venovenous hemofiltration or hemodiafiltration in critically ill patients. *Acta Anaesthesiologica Scandinavica*. 2001;45(8):929-34.
61. Bellomo R, Ronco C. Continuous haemofiltration in the intensive care unit. *Critical Care*. 2000;4(6):1.
62. Murray P, Hall J. Renal replacement therapy for acute renal failure. *American Journal of Respiratory and Critical Care Medicine*. 2000;162(3):777-81.
63. Dirkes S, Hodge K. Continuous renal replacement therapy in the adult intensive care unit: history and current trends. *Critical Care Nurse*. 2007;27(2):61-80.

64. Mehta RL. Anticoagulation for continuous renal replacement therapies. *Critical Care Nephrology*: Springer; 1998. p. 1199-211.
65. Oudemans-van Straaten H, Wester J, De Pont A, Schetz M. Anticoagulation strategies in continuous renal replacement therapy: can the choice be evidence based? *Intensive Care Medicine*. 2006;32(2):188-202.
66. Van de Wetering J, Westendorp R, Van der Hoeven J, Stolk B, Feuth J, Chang P. Heparin use in continuous renal replacement procedures: the struggle between filter coagulation and patient hemorrhage. *Journal of The American Society of Nephrology*. 1996;7(1):145-50.
67. Morabito S, Guzzo I, Solazzo A, Muzi L, Luciani R, Pierucci A. Continuous renal replacement therapies: anticoagulation in the critically ill at high risk of bleeding. *Journal of Nephrology*. 2003;16(4):566-71.
68. De Waele JJ, Van Cauwenberghe S, Hoste E, Benoit D, Colardyn F. The use of the activated clotting time for monitoring heparin therapy in critically ill patients. *Intensive Care Medicine*. 2003;29(2):325-8.
69. Palsson R, Niles JL. Regional citrate anticoagulation in continuous venovenous hemofiltration in critically ill patients with a high risk of bleeding. *Kidney International*. 1999;55(5):1991-7.
70. Kutsogiannis DJ, Gibney RN, Stollery D, Gao J. Regional citrate versus systemic heparin anticoagulation for continuous renal replacement in critically ill patients. *Kidney International*. 2005;67(6):2361-7.
71. Meibohm B, Derendorf H. Basic concepts of pharmacokinetic/pharmacodynamic (PK/PD) modelling. *Evolution*. 1997;130:009.
72. DiPiro JT, Spruill WJ, Wade WE, Blouin RA, Pruemer JM. Concepts in clinical pharmacokinetics. 5th ed: American Society of Health -System Pharmacists, US; 2010.
73. Shargel L, Dunzo E. Comprehensive pharmacy review for NAPLEX: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2013. 103-10 p.
74. Mould D, Upton R. Basic concepts in population modeling, simulation, and model-based drug development. *CPT: Pharmacometrics & Systems Pharmacology*. 2012;1(9):1-14.
75. Asín-Prieto E, Rodríguez-Gascón A, Isla A. Applications of the pharmacokinetic/pharmacodynamic (PK/PD) analysis of antimicrobial agents. *Journal of Infection and Chemotherapy*. 2015;21(5):319-29.
76. Williams PJ, Ette EI. Pharmacometrics: impacting drug development and pharmacotherapy. *Pharmacometrics: The Science of Quantitative Pharmacology*. 2007:1-21.
77. Sheiner LB, Beal SL. Evaluation of methods for estimating population pharmacokinetic parameters II. Biexponential model and experimental pharmacokinetic data. *Journal of Pharmacokinetics and Biopharmaceutics*. 1981;9(5):635-51.
78. Rockville M. Guidance for Industry. Dissolution Testing of Immediate Release Solid Oral Dosage Forms. 1997.
79. Ette EI, Williams PJ. Population pharmacokinetics II: estimation methods. *Annals of Pharmacotherapy*. 2004;38(11):1907-15.

80. Wright P. Population based pharmacokinetic analysis: why do we need it; what is it; and what has it told us about anaesthetics? *British Journal of Anaesthesia*. 1998;80(4):488-501.
81. Bonate PL. The Art of Modeling. *Pharmacokinetic-Pharmacodynamic Modeling and Simulation*: Springer; 2011. p. 1-60.
82. Tatarinova T, Neely M, Bartroff J, van Guilder M, Yamada W, Bayard D, et al. Two general methods for population pharmacokinetic modeling: non-parametric adaptive grid and non-parametric Bayesian. *Journal of Pharmacokinetics and Pharmacodynamics*. 2013;40(2):189-99.
83. Neely M, van Guilder M, Yamada W, Schumitzky A, Jelliffe R. Accurate detection of outliers and subpopulations with Pmetrics, a non-parametric and parametric pharmacometric modeling and simulation package for R. *Therapeutic Drug Monitoring*. 2012;34(4):467-76.
84. R Development CoreTEAM. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Online: <http://www.R-project.org>. 2013.
85. Neely M. Pmetrics User's Manual. University of Southern California Laboratory of Applied Pharmacokinetics. available at: www.lap.korg/pmetrics.php. 2015:3-53.
86. DelDot ME, Lipman J, Tett SE. Vancomycin pharmacokinetics in critically ill patients receiving continuous venovenous haemodiafiltration. *British Journal of Clinical Pharmacology*. 2004;58(3):259-68.
87. Muhl E, Bundesen J, Iven H, Bruch HP. Measurement and calculation of the extracorporeal elimination of vancomycin during continuous venovenous hemodiafiltration and continuous venovenous hemofiltration in critically ill patients. *Journal of Intensive Care Medicine*. 2001;16(5):222-30.
88. Mo Z, Sun J, Chen R, Xiao F, Xiong R, Dong J, et al. Serum vancomycin levels in critically ill elderly patients undergoing continuous renal replacement therapy. *Int J Clin Exp Med*. 2016;9(6):9286-93.
89. Joy MS, Matzke GR, Armstrong DK, Marx MA, Zarowitz BJ. A primer on continuous renal replacement therapy for critically ill patients. *Annals of Pharmacotherapy*. 1998;32(3):362-75.
90. Beumier M, Roberts JA, Kabtouri H, Hites M, Cotton F, Wolff F, et al. A new regimen for continuous infusion of vancomycin during continuous renal replacement therapy. *Journal of Antimicrobial Chemotherapy*. 2013;68(12):2859-65.
91. Covajes C, Scolletta S, Penaccini L, Ocampos-Martinez E, Abdelhadii A, Beumier M, et al. Continuous infusion of vancomycin in septic patients receiving continuous renal replacement therapy. *International Journal of Antimicrobial Agents*. 2013;41(3):261-6.
92. Kang J-S, Lee M-H. Overview of therapeutic drug monitoring. *The Korean Journal of Internal Medicine*. 2009;24(1):1-10.
93. Ye Z-K, Tang H-L, Zhai S-D. Benefits of therapeutic drug monitoring of vancomycin: a systematic review and meta-analysis. *PloS One*. 2013;8(10):e77169.
94. Kierkegaard P. Electronic health record: Wiring Europe's healthcare. *Computer Law & Security Review*. 2011;27(5):503-15.

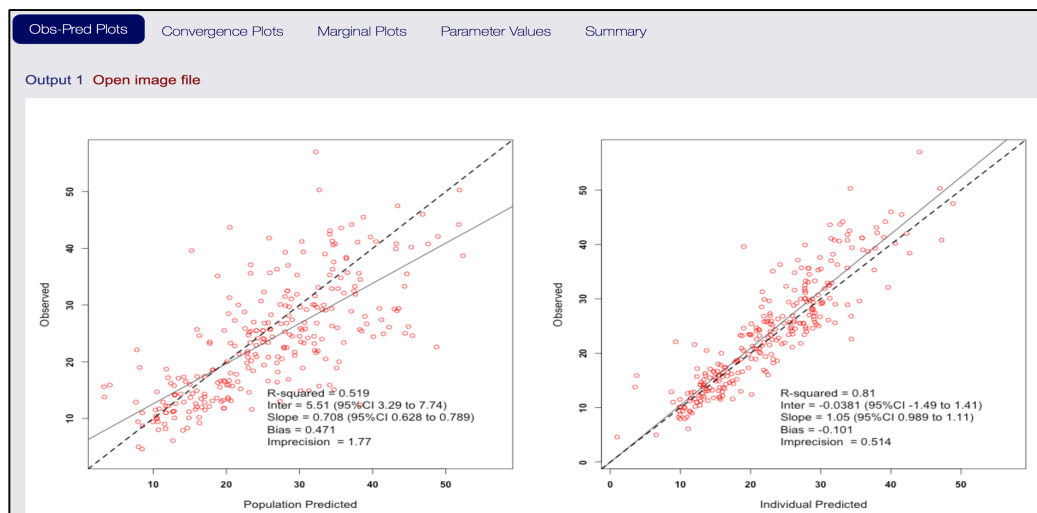
95. Häyrynen K, Saranto K, Nykänen P. Definition, structure, content, use and impacts of electronic health records: a review of the research literature. *International Journal of Medical Informatics*. 2008;77(5):291-304.
96. Warrick C, Naik H, Avis S, Fletcher P, Franklin BD, Inwald D. A clinical information system reduces medication errors in paediatric intensive care. *Intensive Care Medicine*. 2011;37(4):691-4.
97. Heale R, Twycross A. Validity and reliability in quantitative studies. *Evidence Based Nursing*. 2015;18(3):66-7.
98. Weiskopf NG, Weng C. Methods and dimensions of electronic health record data quality assessment: enabling reuse for clinical research. *Journal of the American Medical Informatics Association*. 2013;20(1):144-51.
99. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics*. 2009;42(2):377-81.
100. Obeid JS, McGraw CA, Minor BL, Conde JG, Pawluk R, Lin M, et al. Procurement of shared data instruments for Research Electronic Data Capture (REDCap). *Journal of Biomedical Informatics*. 2013;46(2):259-65.
101. Judge C, Drew T, Misran H, Munshi R, McGovern L, Coyle M, et al. Development of an automated data extraction process for use in retrospective pharmacokinetic analyses: initial application to vancomycin dose and concentration data in patients using citrate and heparin CVVHDF anticoagulation modalities. *European Society of Intensive Care Medicine Annual Congress; 1st-5th October 2016; Milan, Italy: Intensive Care Medicine Experimental 2016*. p. ppA632-.
102. Escobar Oregón LD, Andresen M, Downey P, Gai Hernández MN, Regueira T, Bórquez T, et al. Population pharmacokinetics and dose simulation of vancomycin in critically ill patients during high-volume haemofiltration. 2014.
103. Santre C, Leroy O, Simon M, Georges H, Guery B, Beuscart C, et al. Pharmacokinetics of vancomycin during continuous hemodiafiltration. *Intensive Care Medicine*. 1993;19(6):347-50.
104. Okada H, Konishi K, Matsuda S, Saruta T, Suzuki H. Pharmacokinetics of vancomycin in patients with multiple organ failure during continuous hemodiafiltration. *Clinical and Experimental Nephrology*. 1999;3(4):296-9.
105. Grace E. Altered vancomycin pharmacokinetics in obese and morbidly obese patients: what we have learned over the past 30 years. *Journal of Antimicrobial Chemotherapy*. 2012;67(6):1305-10.
106. Petejova N, Martinek A, Zahalkova J, Duricova J, Brozmannova H, Urbanek K, et al. Vancomycin pharmacokinetics during high-volume continuous venovenous hemofiltration in critically ill septic patients. *Biomedical Papers*. 2014;158(1):065-72.
107. Burton ME. *Applied pharmacokinetics & pharmacodynamics: principles of therapeutic drug monitoring*: Lippincott Williams & Wilkins; 2006. 285-353 p.
108. Wang N, Jiang L, Zhu B, Wen Y, Xi X-M. Fluid balance and mortality in critically ill patients with acute kidney injury: a multicenter prospective epidemiological study. *Critical Care*. 2015;19(1):371.

109. Gonzalez D, J Conrado D, Theuretzbacher U, Derendorf H. The effect of critical illness on drug distribution. *Current Pharmaceutical Biotechnology*. 2011;12(12):2030-6.
110. Chaijamorn W, Jitsurong A, Wiwattanawongsa K, Wanakamanee U, Dandecha P. Vancomycin clearance during continuous venovenous haemofiltration in critically ill patients. *International Journal of Antimicrobial Agents*. 2011;38(2):152-6.

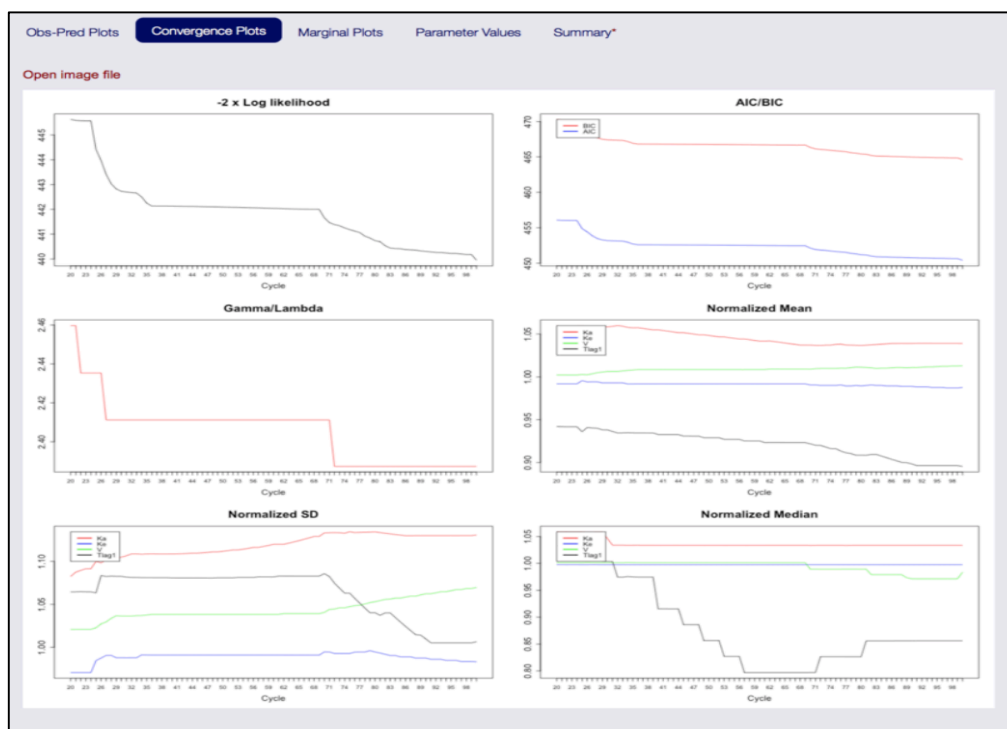
8. Appendix

8.1 Sample of general output report from Pmetrics NPAG run

- The predicted-observed plots for the population and the individual posterior estimates:



- The convergence:



- **The marginals:**



- **Parameter values:**

Obs-Pred Plots Convergence Plots Marginal Plots **Parameter Values** Summary

Support Points

	Ke	V	prob
1	0.032	60.025	0.046
2	0.021	72.287	0.107
3	0.032	60.044	0.144
4	0.035	68.059	0.216
5	0.026	111.747	0.087
6	0.026	98.031	0.098
7	0.075	48.728	0.038
8	0.054	55.947	0.043
9	0.018	104.650	0.128
10	0.018	104.631	0.005
11	0.016	75.888	0.044
12	0.009	136.234	0.043

Population Parameter Value Summaries

	mean	sd	CV	var	median
Ke	0.029	0.013	44.290	0.000	0.029
V	80.654	22.649	28.081	512.960	70.173

- **Run summary:**

Obs-Pred Plots
Convergence Plots
Marginal Plots
Parameter Values
Summary

Engine: NPAG
Computation mode: Serial
Output file: /Users/reemamunshi/Desktop/pmetrics /drug/Runs/76/outputs/NP_RF0001.TXT
Random parameters: Ke, V
There were no fixed parameters.
Number of analyzed subjects: 31
Number of output equations: 1
Number of cycles: 166 - The run converged.
Additional covariates: NA
Prior density: Uniform
Assay error model: SD, lambda
Elapsed time for this run was 8 secs

- **Example of some appropriate commands from the Pmetrics library in R script used for model run**

```

1 library(Pmetrics)
2
3 setwd("~/Desktop/pmetrics /analysis/Runs")
4
5 setwd("~/Desktop/pmetrics /drug/Runs")
6
7 NPrun(model="1c_amb.txt",data= "proj-1.csv",cycles = 1000)
8
9 plot(op.1,pred.type ="pop")
10
11 plot(op.1)
12
13 plot(final.1)
14
15 plot(cycle.1)
16
17 PMcompare(1,2,3, icen="median", plot=T)
18
19 PMload(1)
20

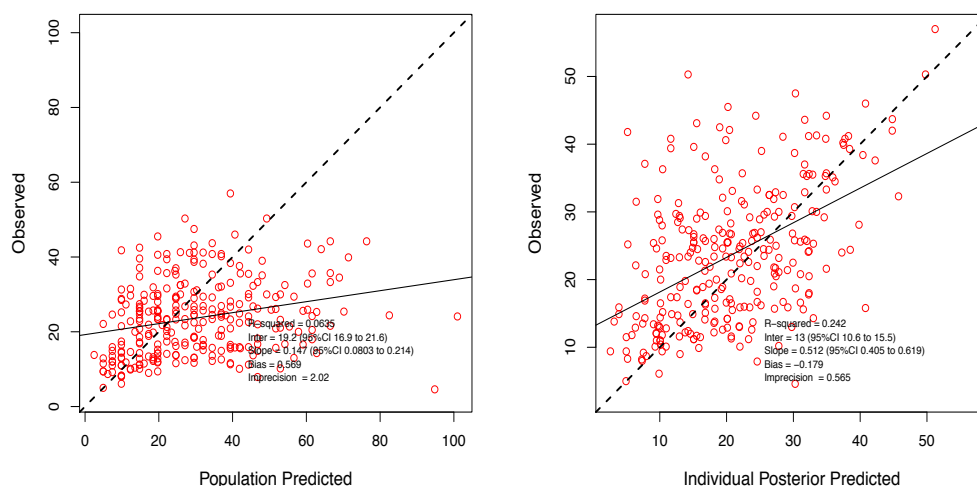
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8.2 The hospital protocol for vancomycin TDM

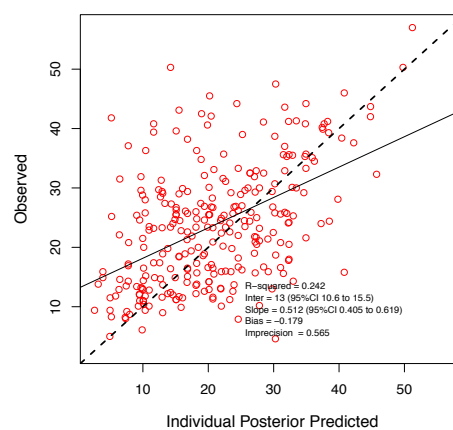
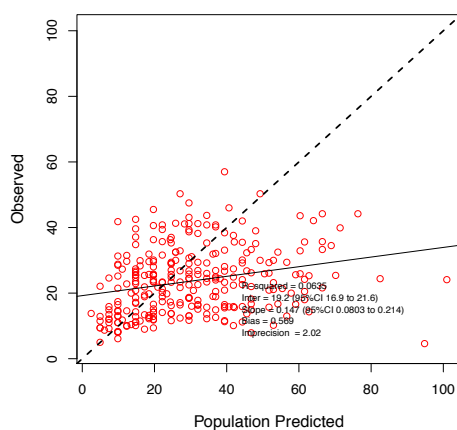
[illegible]

8.3 Examples of some observed vs. predicted concentrations from the covariate CL models

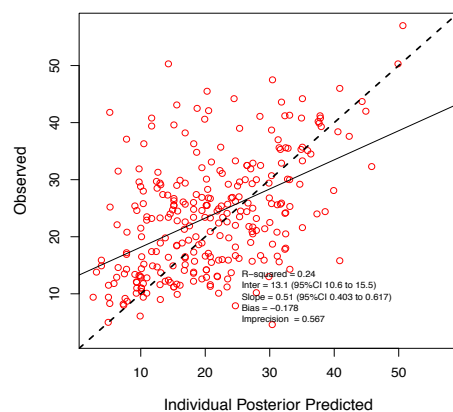
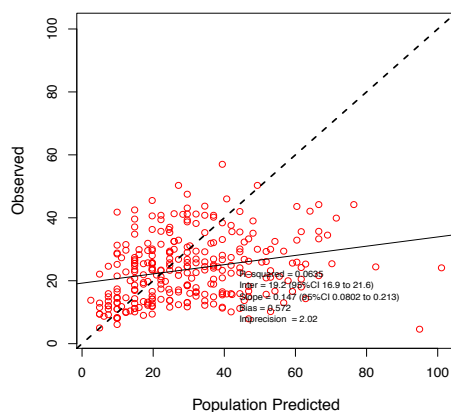
- **Wt applied to CL**



- **Alb applied to CL:**

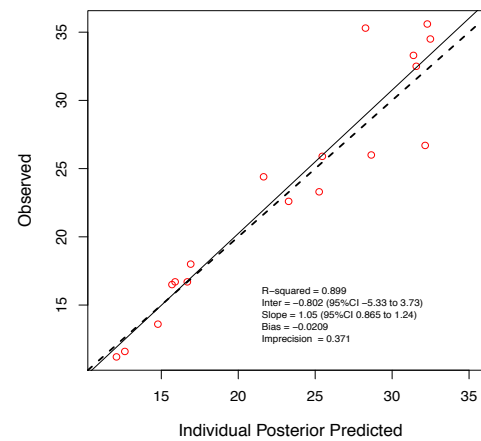
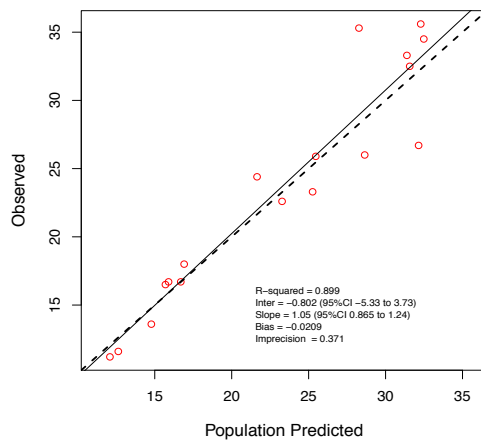
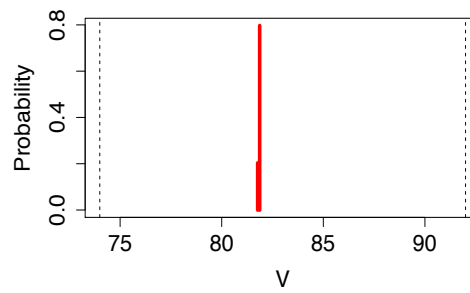
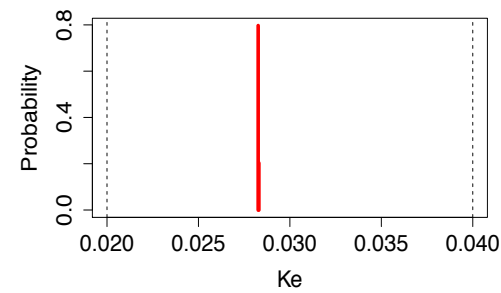


- **EFR WD applied to CL:**



8.4 The observed vs. predicted concentrations for intra-patients data from citrate and non-citrate groups

- **Intra-patients data for citrate anticoagulant group**



Support Points

	Ke	V	prob
1	0.028	81.868	0.797
2	0.028	81.770	0.203

Population Parameter Value Summaries

	mean	sd	CV	var	median
Ke	0.028	0.000	0.056	0.000	0.028
V	81.848	0.040	0.048	0.002	81.868

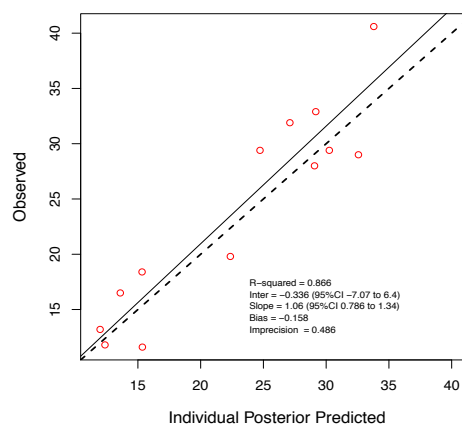
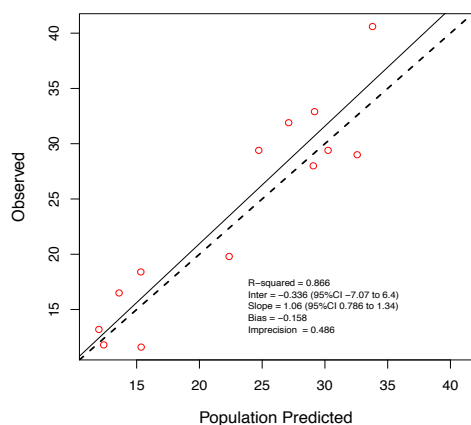
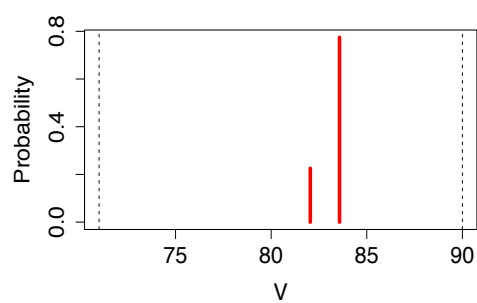
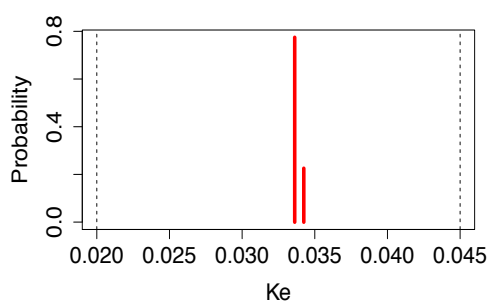
Population Parameter Value Covariance Matrix

	Ke	V
Ke	0.000	-0.000
V	-0.000	0.002

Population Parameter Value Correlation Matrix

	Ke	V
Ke	1.000	-1.000
V	-1.000	1.000

- Intra-patients data for non-citrate anticoagulant group



Support Points

	K_e	V	prob
1	0.034	83.576	0.775
2	0.034	82.047	0.225

Population Parameter Value Summaries

	mean	sd	CV	var	median
K_e	0.034	0.000	0.774	0.000	0.034
V	83.232	0.639	0.768	0.408	83.576

Population Parameter Value Covariance Matrix

	K_e	V
K_e	0.000	-0.000
V	-0.000	0.408

Population Parameter Value Correlation Matrix

	K_e	V
K_e	1.000	-1.000
V	-1.000	1.000