THE UNIVERSITY OF QUEENSLAND

AUSTRALIA

Improving antibiotic dosing in critically ill Australian Indigenous patients with severe sepsis

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BPharm (Hons) GDipClinPharm

A thesis submitted for the degree of Doctor of Philosophy at

The University of Queensland in 2017

School of Medicine

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Abstract

Sepsis is a major health issue in the Australian Indigenous population. Unfortunately, the high rates of mortality and morbidity caused by sepsis or severe sepsis in this population have not significantly reduced over recent decades. Research into the role of optimisation of antibiotic therapy for improving patient outcomes is certainly an important area of need. In other patient populations, there is increasing evidence of an improvement of clinical cure rates and survival in patients with severe sepsis when antibiotic dosing results in therapeutic concentrations, that is, achieves pharmacokinetic/pharmacodynamic (PK/PD) targets. However, numerous PK changes caused by the altered physiology associated with critical illness may reduce the likelihood of such effective dosing.

Previous studies have identified a number of physiological characteristics in the Australian Indigenous population which suggest that interethnic PK differences are likely in comparison with the non-Indigenous. As most PK data of antibiotics were obtained from healthy Caucasian volunteers, whether these data can be extrapolated to the critically ill Indigenous patients requires investigation.

The aims of this thesis are to describe the PK of meropenem, ceftriaxone, vancomycin and piperacillin in severely septic Indigenous patients; compare the PK with existing data from non-Indigenous patients; design optimised dosing regimens for each of the study antibiotics; and quantify the variation in renal function of critically ill Indigenous patients.

This thesis consists of nine Chapters:

Chapter one provides an overview of the current clinical challenges encountered in antibiotic dosing in critically ill patients. It also discusses specific physiological characteristics of Australian Indigenous patients which may lead to different PK compared with non-Indigenous comparators.

Chapter two comprises of a narrative review which discusses the PK/PD factors that should be considered when prescribing antibiotics to critically ill patients. This Chapter summarises data which describe an improvement in clinical outcome when antibiotics achieve PK/PD targets. This Chapter concludes to support an individualised approach to dosing antibiotics as opposed to the ‘one dose fits all’ approach that is common to clinical practice.

Chapter three incorporates a systematic review which investigates the published data describing differences in antibiotic PK between different ethnic groups. No reports on PK in Indigenous Australians were found. The predominant data described differences in PK between the Asian and Caucasian ethnicities. Typically, Asian subjects manifested higher antibiotic concentrations for antibiotics that have significant hepatic metabolism, are substrates to p-glycoprotein or other forms of active transport and/or have high alpha-1-acid glycoprotein binding.

Chapter four incorporates a study which described the renal function of critically ill Australian Indigenous patients. This study found a numerically higher incidence of augmented renal clearance (ARC) in the Indigenous patients and a similar rate of acute kidney injury (AKI) when compared with the non-Indigenous patients. The study also found that major surgery, male sex and younger age were each associated with the presence of ARC.

Chapter five includes a population PK study aiming to optimise meropenem dosing in critically ill Australian Indigenous patients. No significant interethnic differences in meropenem PK between the Indigenous (n=6) and Caucasian (n=5) patients were observed and CrCL was found to be the strongest determinant of dosing requirements.

Chapter six includes a population PK study aiming to optimise piperacillin dosing in critically ill Australian Indigenous patients. CrCL was found to be the most important determinant of appropriate dosing regimens. When compared with other published data, a slightly lower mean piperacillin CL was observed.

Chapter seven includes a PK study aiming to optimise ceftriaxone dosing in critically ill Australian Indigenous patients. The unbound trough concentration for the first and second dosing intervals exceeds the minimum inhibitory concentration (MIC) of all typical target pathogens, supporting the empiric dosing regimen of 1 g 12-hourly. Ceftriaxone CL and V_d in this study were generally lower than previously published data in critically ill non-Indigenous patients.

Chapter eight includes a population PK study aiming to optimise vancomycin dosing in critically ill Australian Indigenous patients. Loading dose requirements were found to be heavily dependent on weight and CrCL. Maintenance doses were highly dependent on CrCL. These results provide a framework for effective dosing of vancomycin in these patients.

Chapter nine provides a summary of all findings obtained from the five research projects conducted and recommendations for the implementation of these findings in the clinical setting. The Chapter also includes a discussion of potential future research directions.

The overall results of this thesis do not support any significant interethnic PK differences for meropenem or vancomycin between the Indigenous compared with the non-Indigenous comparators. However, a slightly lower drug CL was observed for ceftriaxone and piperacillin in the Indigenous patients, and lower of V_d in the ceftriaxone. These differences observed are unlikely to affect the dosing of these antibiotics. Nonetheless, it is concluded that dose individualisation is necessary to maximise PK/PD target attainment in the patients that are critically ill.

Declaration by author

This thesis is composed of my original work, and contains no material previously published or written by another person except where due reference has been made in the text. I have clearly stated the contribution by others to jointly-authored works that I have included in my thesis.

I have clearly stated the contribution of others to my thesis as a whole, including statistical assistance, survey design, data analysis, significant technical procedures, professional editorial advice, and any other original research work used or reported in my thesis. The content of my thesis is the result of work I have carried out since the commencement of my research higher degree candidature and does not include a substantial part of work that has been submitted to qualify for the award of any other degree or diploma in any university or other tertiary institution. I have clearly stated which parts of my thesis, if any, have been submitted to qualify for another award.

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Publications during candidature

Published articles

Tsai D, Jamal JA, Davis J, Lipman J, Roberts JA. Interethnic differences in pharmacokinetics of antibacterials. *Clin Pharmacokinet* 2015; 54:243-260.

Tsai D, Lipman J, Roberts JA. Pharmacokinetic/pharmacodynamic considerations for the optimisation of antimicrobial delivery in the critically ill. *Curr Opin Crit Care* 2015; 21(5):412-20.

Tsai D, Stewart P, Gourley S, Goud R, Hewagama S, Krishnaswamy S, Wallis S, Lipman J, Roberts JA. Optimising meropenem dosing in critically ill Australian Indigenous patients with severe sepsis. *Int J Antimicrob Agents* 2016; 48:542-46.

Tsai D, Stewart P, Gourley S, Goud R, Hewagama S, Krishnaswamy S, Wallis S, Lipman J, Roberts JA. Piperacillin pharmacokinetics in critically ill Australian Indigenous patients with severe sepsis. *Antimicrob Agents Chemother* 2016; 60(12):7402-6.

Tsai D, Stewart P, Gourley S, Goud R, Hewagama S, Krishnaswamy S, Wallis S, Lipman J, Roberts JA. Pharmacokinetics of total and unbound ceftriaxone in critically ill Australian Indigenous patients with severe sepsis. *Int J Antimicrob Agents* 2016; 48:748-52.

Oral presentations

Tsai D, Stewart P, Goud R, Gourley S, Hewagama S, Krishnaswamy S, Wallis S, Lipman J, Roberts JA. Optimising Meropenem dosing in critically ill Australian Indigenous patients with severe sepsis. European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) 25th International Conference, Amsterdam, 8-12 April 2016.

Tsai D, Stewart P, Goud R, Gourley S, Hewagama S, Krishnaswamy S, Wallis S, Lipman J, Roberts JA. Optimising Meropenem dosing in critically ill Australian Indigenous patients with severe sepsis. Society of Hospital Pharmacists of Australia (SHPA) Critical Care Medicine seminar, Brisbane, 21-22 May 2016.

Tsai D, Udy A, Stewart P, Goud R, Gourley S, Hewagama S, Krishnaswamy S, Wallis S, Lipman J, Roberts JA. Optimising antibiotic dosing in critically ill Australian Indigenous patients with severe sepsis. Centres of Research of Excellence – Redefining Antibiotic Doses Launch, Brisbane, 29 July 2016.

Tsai D, Udy A, Stewart P, Goud R, Gourley S, Hewagama S, Krishnaswamy S, Wallis S, Lipman J, Roberts JA. Optimising antibiotic dosing in critically ill Australian Indigenous patients with severe sepsis. Alice Springs Hospital grand round, 3 November 2016.

Poster presentation

Tsai D, Jamal JA, Davis J, Lipman J, Roberts JA. Interethnic differences in pharmacokinetics of antibacterial. Medicines Management 40th Society of Hospital Pharmacist of Australia (SHPA) National Conference, 11-14 September 2014.

Publications included in this thesis

Tsai D, Lipman J, Roberts JA. Pharmacokinetic/pharmacodynamic considerations for the optimisation of antimicrobial delivery in the critically ill. *Curr Opin Crit Care* 2015; 21(5):412-20. Incorporated as Chapter 2.

Contributor	**Statement of contribution**
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Lipman J	Critical review (30%)
Roberts JA	Wrote the paper (20%) Critical review (70%)

Tsai D, Jamal JA, Davis J, Lipman J, Roberts JA. Interethnic differences in pharmacokinetics of antibacterial. *Clin Pharmacokinet* 2015; 54:243-260. Incorporated as Chapter 3.

Contributor	**Statement of contribution**
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Jamal JA	Literature review (10%) Wrote the paper (10%)
Davies J	Critical review (30%)
Lipman J	Critical review (10%)
Roberts JA	Literature review (10%) Wrote the paper (20%) Critical review (60%)

Tsai D, Stewart P, Gourley S, Goud R, Hewagama S, Krishnaswamy S, Lipman J, Roberts JA. Optimising meropenem dosing in critically ill Australian Indigenous patients with severe sepsis *Int J Antimicrob Agents* 2016; 48:542-46. Incorporated as Chapter 5.

Contributor	Statement of contribution
Tsai D (Candidate)	Wrote the paper (70%) Data collection (100%) Drug assay (70%) Data analysis (20%)
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Gourley S	Critical review (5%)
Goud R	Critical review (5%)
Hewagama S	Critical review (10%)
Krishnaswamy S	Critical review (10%)
Wallis S	Wrote the paper (10%) Drug assay (30%) Critical review (5%)
Lipman J	Critical review (10%)
Roberts JA	Wrote paper (20%) Data analysis (80%) Critical review (50%)

Tsai D, Stewart P, Gourley S, Goud R, Hewagama S, Krishnaswamy S, Wallis S, Lipman J, Roberts JA. Pharmacokinetics of piperacillin in critically ill Australian Indigenous patients. *Antimicrob Agents Chemother* 2016; 60(12):7402-6. Incorporated as Chapter 6.

Contributor	Statement of contribution
Tsai D (Candidate)	Wrote the paper (70%) Data collection (100%) Data analysis (70%)
Stewart P	Critical review (5%)
Gourley S	Critical review (5%)
Goud R	Critical review (5%)
Hewagama S	Critical review (10%)
Krishnaswamy S	Critical review (10%)
Wallis S	Wrote the paper (10%) Drug assay (100%) Critical review (5%)
Lipman J	Critical review (10%)

Roberts JA	Wrote paper (20%) Data analysis (30%) Critical review (50%)

Tsai D, Stewart P, Gourley S, Goud R, Hewagama S, Krishnaswamy S, Wallis S, Lipman J, Roberts JA. Pharmacokinetics of total and unbound ceftriaxone in critically ill Australian Indigenous patients with severe sepsis. *Int J Antimicrob Agents* 48:748-52. Incorporated as Chapter 7.

Contributor	**Statement of contribution**
Tsai D (Candidate)	Wrote the paper (70%) Data collection (100%) Data analysis (70%)
Stewart P	Critical review (5%)
Gourley S	Critical review (5%)
Goud R	Critical review (5%)
Hewagama S	Critical review (5%)
Krishnaswamy S	Critical review (10%)
Wallis S	Wrote the paper (10%) Drug assay (100%) Critical review (5%)
Lipman J	Critical review (10%)
Roberts JA	Wrote paper (20%) Data analysis (30%) Critical review (50%)

Contributions by others to the thesis

I would like to acknowledge the significant contribution made to this thesis by Professor Jason A. Roberts. Professor Roberts played the central role in developing the fundamental concept and structure of this thesis. Professor Roberts also consistently provided guidance in all steps of the conducting of the projects included in this thesis, including PK modelling, data analysis and write-ups.

I would like to acknowledge the significant contribution made by Professor Jeffrey Lipman which include his advice and guidance throughout the conducting of projects in this thesis as well as critically reviewing all manuscripts and Chapters in the thesis.

I would also like to acknowledge the important contribution made by Dr Steven C. Wallis for managing and conducting the bioanalysis component of this thesis.

I would also like to acknowledge all co-authors including A/Prof Andrew Udy, Dr Joshua Davis, Dr Penelope Stewart, Dr Rajendra Goud, Dr Saliya Hewagama and Dr Sushena Krishnaswamy for their critical reviews of the manuscripts incorporated in this thesis.

Statement of parts of the thesis submitted to qualify for the award of another degree

None

Acknowledgements

I would like to acknowledge the postgraduate scholarship offered by the National Health and Medical Research Council of Australia; the Douglas and Lola Douglas scholarship offered by the Australian Academy of Science; support provided by the Alice Springs Specialists' Private Practice Trust Fund; and travel allowance and drug assay fundings provided by Centres of Research of Excellence – Redefining Antibiotic Doses.

I would like to express my sincere gratitude to my principal advisor, Professor Jason A. Roberts, without whom the publication of this thesis would not have been possible. Professor Roberts provided me with extensive support, guidance, advice and training even though I am a remote student conducting these research projects in a very isolated area. Professor Roberts facilitated my participation in publication and collaborations with other leading researchers and provided me with many opportunities for oral presentations in major public settings. He always guided with immense patience and with great humour.

I would also like to thank Professor Jeffrey Lipman, Director of Department of Intensive Care Medicine at the Royal Brisbane and Women's Hospital (RBWH) and Dr Steven C. Wallis, Laboratory Manager, Burns, Trauma and Critical Care Research Centre (BTCCRC), The University of Queensland (UQ) for their guidance and encouragement throughout this journey.

I would like to thank the reviewers and chairpersons of the three Milestones, A/Prof Rob Boots Deputy Director, Department of Intensive Care Medicine, RBWH, Dr Adrian Kark, Nephrology Specialist, Department of Nephrology, RBWH, Dr Steven Wallis, Laboratory Manager, BTCCRC, UQ, and Dr Sia Athanasas, Research Manager, BTCCRC, UQ.

I would also like to thank all co-authors involved in the published manuscripts of this thesis; their contribution is invaluable for the submission and acceptance of the manuscripts for publication.

I would also like to thank the laboratory team at BTCCRC, for their assistance with drug assays as well as both the ICU/ED doctors and nursing teams at the Alice Springs Hospital for their constant support and assistance with the conducting of the projects published in this thesis.

I would also like to thank my close friends Richard, Hamed and Adel for their encouragement throughout this journey.

I would especially like to thank my dearest family - father Peter, mother Mary, sister Sarah, brother-in-law Opat, niece Ayla, for their support, care and patience with me while I selfishly took on this research journey and put the rest of my life on hold.

Lastly, I would like to thank my beautiful and caring wife, Linda, for her constant support, care and patience. This thesis is not the work of a single person or a research group, and would not be accomplished without all my loved ones around me.

Keywords

Antibacterial, antibiotic, pharmacokinetics, pharmacodynamics, Indigenous health, interethnic difference, severe sepsis, intensive care, critically ill

Australian and New Zealand Standard Research Classifications (ANZSRC)

ANZSRC code: 111502, Clinical Pharmacology and Therapeutics, 50%

ANZSRC code: 110309, Infectious Disease, 25%

ANZSRC code: 110310, Intensive Care, 25%

Fields of Research (FoR) Classification

FoR code: 1103, Clinical Sciences, 80%

FoR code: 1115, Pharmacology and Pharmaceutical Sciences, 20%

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List of Abbreviations

β-lactams	Beta-lactam antibiotics
ARC	Augmented renal clearance
ABW	Adjusted body weight
AGP	Alpha-1-acid glycoprotein
AKI	Acute kidney injury
ALT	Alanine transferase
APACHE II	Acute Physiology Assessment and Chronic Health Evaluation II
ARC	Augmented renal clearance
ARF	Acute renal failure
AUC	Area under the concentration-time curve
$AUC_{0\text{-}24}$	Area under the concentration-time curve from time zero to 24 hours
$AUC_{0\text{-}\infty}$	Area under the concentration-time curve from time zero to infinity
BLING-II study	Beta-Lactam Infusion Group II study
CKD-EPI	Chronic Kidney Diseases – Epidemiology Collaboration
C_{720}	Concentration at time 720minutes
CI	Continuous infusion
CKD	Chronic kidney disease
CL	Drug clearance
C_{max}	Maximum (peak) concentration
C_{min}	Minimum (trough) concentration
CrCL	Creatinine clearance
$CrCL_m$	Measured urinary creatinine clearance
$CrCL_{CG}$	Creatinine clearance calculated with the Cockcroft-Gault equation
CRRT	Continuous renal replacement therapy
CV	Coefficient of variance
CYP	Cytochrome P450
DALI study	Defining Antibiotic Levels in Intensive care unit patients study
DI	Drug dosing interval
DIHS	Drug-induced hypersensitivity syndrome
DRESS syndrome	Drug reaction with eosinophilia and systemic symptoms syndrome
ECMO	Extracorporeal membrane oxygenation
eGFR	Estimated glomerular filtration rate

$eGFR_{CKD-EPI}$	Estimated glomerular filtration rate calculated from Chronic Kidney Disease – Epidemiology Collaboration formula
$eGFR_{MDRD}$	Estimated glomerular filtration rate calculated from Modification of Diet in Renal Disease formula
EUCAST	European Committee on Antimicrobial Susceptibility Testing
F	Bioavailability
f	Unbound drug concentration
$fAUC_{0-24}$:MIC	Free drug exposure within 24 hours relative to the minimum inhibitory concentration
$fCmax_{>8xMIC}$	Maximum free drug concentration is greater than 8x the minimum inhibitory concentration
$fT_{>MIC}$	Time of the free drug concentration remains above the minimum inhibitory concentration during the dosing interval
$fT_{>4xMIC}$	Time of the free drug concentration remains above 4x minimum inhibitory concentration during the dosing interval
GFR	Glomerular filtration rate
HILIC	Hydrophilic interaction liquid chromatography
HPLC	High-pressure liquid-chromatography
HPLC-MS/MS	high pressure liquid chromatography-mass spectroscopy/mass spectroscopy
HPLC-UV	High-pressure liquid-chromatography-ultra violet
ICU	Intensive care unit
IV	Intravenous
k_e	Elimination rate constant
k_{cp}	Distribution rate constant from central to peripheral compartment
k_{pc}	Distribution rate constant from peripheral to central compartment
LBW	Lean body weight
LBW_B	Lean body weight calculated with the Boer equation
LBW_H	Lean body weight calculated with the Hume equation
LBW_J	Lean body weight calculated with the James equation
LD	Loading dose
MD	Maintenance dose
MDRD	Modified diet in renal diseases
MRSA	Methicillin-resistance *Staphylococcus aureus*
MIC	Minimum inhibitory concentration

NA	Data not available
NHMRC	National Health and Medical Research Council of Australia
NPAG	Nonparametric adaptive grid
OATP	Active transporters such as organic anionic transporters
PD	Pharmacodynamics
PI	Prolonged infusion
PK	Pharmacokinetics
PO	Oral
PTA	Probability of target attainment
rAKI	Risk of acute kidney injury
r_s	Spearman's rank correlation coefficient
RRT	Renal replacement therapy
SMARRT study	SaMpling Antibiotics in Renal Replacement Therapy study
SIRS	Systemic inflammatory response syndrome
SOFA	Sequential Organ Failure Assessment
$T_{½}$	Elimination half-life
TBW	Total body weight
TDM	Therapeutic drug monitoring
$T_{>4xMIC}$	Time for which drug concentration is maintained above four times of the minimum inhibitory concentration
$T_{>MIC}$	Time for which drug concentration is maintained above the minimum inhibitory concentration
T_{max}	Time to maximum concentration
TVCL	Typical value of antibiotic clearance
TVV_c	Typical value of V_c
UHPLC	Ultra-high pressure liquid chromatography
U_{Cr}	Creatinine concentration in urine
V_c	Volume of distribution of central compartment
V_d	Volume of distribution
V_{dss}	Volume of distribution at steady state
VPC	Visual predictive check plots
V_{Ur}	Volume of urine

Chapter 1 Introduction

1.1 Overview

Severe sepsis is a major disease burden and is associated with a mortality rate 3-times greater than the Australian road toll(1). It is an even greater health concern for the Indigenous population in the Central Australian regions and is associated with higher morbidity and similar mortality rates (2-5).

Growing evidence suggests that optimised antibiotic dosing in severely septic patients can increase clinical cure rates and reduce mortality (6-8). To develop such dosing regimens, detailed knowledge of the antibiotic's PK is required. A number of physiological differences have been identified between ethnic groups that can significantly affect the PK of drugs, such as body size, body fat percentage, hepatic metabolism, biliary excretion, renal secretion and alpha1-acid glycoprotein (AGP) concentration (9-16). Unfortunately, despite optimisation of antibiotic administration in accordance with its PK/PD properties being an important clinical determinant (8, 17), there are currently no antibiotic PK data available for the Indigenous population to guide treatment therapies, let alone for severely septic patients that can anticipate drastic PK alterations (18, 19). The current practice of treating this patient cohort is with dosing guidelines obtained mainly from healthy Caucasian patients, and with an assumption that interethnic differences do not exist.

1.2 Treatment of Sepsis

1.2.1 Sepsis

Severe sepsis is a life-threatening condition commonly seen in critically ill patients and has a mortality rate of 20-50% around the world (20-23). A multi-centre epidemiological study published in 2004 looking at patients with severe sepsis in an intensive care unit (ICU) setting in 23 Australian and New Zealand hospitals found that 11.8% of ICU admissions were diagnosed with severe sepsis, which had a 26.5% mortality rate in ICU, and 37.5% overall in-hospital mortality rate (24). This mortality rate is further supported by another study conducted in Victoria published in 2005, which described a hospital mortality of 28.9% for septic patients needing intensive care (21, 25).

1.2.2 Sepsis in the Australian Indigenous population

A study conducted at Alice Springs Hospital (ASH) has found that 60% of all hospital deaths were related to infection compared to 25% in non-Indigenous patients. Furthermore, 56% of these deaths in the Indigenous patients were due to bacterial sepsis (26). Indigenous patients were found have four times higher hospital admission rates due to sepsis when compared with their non-Indigenous counterparts, and three times higher ICU admission rate due to severe sepsis (27). Although critically ill Indigenous patients were found to be generally younger, they also have more co-morbidities and greater disease severity, leading to similar mortality rates as observed in the non-Indigenous critically ill patients (2, 28-30).

1.2.3 Antibiotic PK/PD

Early antibiotic therapy is the cornerstone of treatment of sepsis and is associated with increased survival (14, 31-33). Moreover, there is growing evidence which demonstrates the optimisation of antibiotic dosing in accordance with its PK/PD profile increases clinical cure rates and reduces mortality, especially in severely septic patients (6, 7, 34-37).

Every antibiotic has a defined PK/PD index associated with optimal efficacy. PK describes a drug's changing concentrations in the body after administration of a dose. In this respect, it is affected by absorption, distribution, metabolism and excretion. Whereas PD describes the pharmacological effect (i.e. bacteria killing) of the antibiotic relative to concentration. The PK/PD profile describes the relationship between the PK and PD. In other words, by administering an antibiotic in a way that follows its bacterial kill characteristics, the optimal bacterial killing can be anticipated (18, 38).

There are three categorisations of PK/PD and each antibiotic would fall under one or two of the following categories (as only the unbound antibiotic molecules are of any clinical value for most antibiotics, these PK/PD categorisations only apply to unbound antibiotic concentrations):

- **Time dependent** ($fT_{>MIC}$) – the length of time the unbound drug concentration remains above the MIC for the duration of the dosing interval. Examples: β-lactams, carbapenems, linezolid,

lincosamides and erythromycin (18, 38).

Optimisation of bacterial killing for this type of antibiotics can be achieved by modulating dosing regimens or infusion time to increase the duration where the unbound drug concentration remains above the maximum bacterial killing concentration (6, 36, 39).

- **Concentration-dependent** (fC_{max}:MIC) – the ratio of the maximum unbound drug concentration during a dosing interval relative to the MIC. Examples: Aminoglycosides, metronidazole, fluoroquinolones and daptomycin (18, 38).

  Optimisation of bacterial killing for this type of antibiotics can be achieved by increasing the dose to achieve a maximum unbound concentration (fC_{max}) that is 8-10 x MIC of the pathogen (40).

- **Time-dependent with concentration dependence** ($fAUC_{0-24}$:MIC) – the ratio of the area under the drug concentration-time curve during the 24 hour time period to the MIC (18, 38).

  Optimisation of bacterial killing for these antibiotics can be achieved by modulating the dosing regimen to increase the $fAUC_{0-24}$:MIC ratio to the recommended indices for the respective antibiotic and bacteria. Examples: Glycopeptides, fluoroquinolones, aminoglycosides, and azithromycin (41, 42).

1.3 PK changes in critical illnesses

Optimisation of antibiotic dosing can improve clinical cure rates especially in severely septic patients (6-8). Nonetheless, there are many factors that can affect the PK parameters of antibiotics in the setting of severe sepsis, and subsequently alter the probability of toxicity and clinical outcome (18, 38, 43). The two main PK parameters affecting drug exposure are the volume of distribution (V_d) and drug clearance (CL) (18).

An increase in V_d and CL are commonly seen in critically ill patients, leading to decreased antibiotic concentrations in the patient's body. Factors that drive these PK changes include vasodilation, presence of extracorporeal circuits, third spacing due to leaky capillaries, high fluid

resuscitation volumes and presence of ARC. Antibiotic CL can also decrease due to end-organ failure (renal and/or hepatic failure), increasing the likelihood of antibiotic accumulation (18, 38). Antibiotics with a hydrophilic physicochemical property are especially affected by the PK changes, and hence need particular consideration when devising a dosing plan for the severely septic.

1.4 Physiology of the Australian Indigenous

Numerous physiological characteristics of the Australian Indigenous population differ to the Caucasian populations, which may provide the basis for interethnic PK differences for commonly used antibiotics.

Young and healthy Australian Indigenous are reported to have approximately 30% fewer nephrons yet 27% greater kidney mass compared with non-Indigenous comparators (44). This is thought be one of the main explanations for the dramatically high rates of chronic kidney disease in this population, but the effect of this physiology has not been well explored in acute settings. Pharmacogenetic polymorphisms of metabolic enzymes are known to cause interethnic PK differences for numerous drugs, and it has been identified that the Australian Indigenous population share similar allele frequencies with South Asians for cytochrome P450 (CYP) 2C19 and 2D6 enzymes, although other enzymes with more prominent effect on drugs were not tested (such as P450 3A4) (45). It has been reported that 25.6% of Indigenous Australians are poor CYP2C19 metabolisers compared to 3-5% of the Caucasian population (45). Furthermore, from an anthropometric point of view, the Indigenous people are more likely to have smaller body mass, a higher level of central fat and slimmer limbs (46). Finally, significantly higher rates of some severe and rare adverse drug effects are seen in this population (47). Recent case reports have suggested the presence of human leucocyte antigen-B*56:02 allele (HLA-B*56:02) correlates with an increased risk of phenytoin-related drug-induced hypersensitivity syndrome (DIHS, formally known as drug reaction with eosinophilia and systemic symptoms syndrome – DRESS syndrome), especially in the Australian Indigenous population (48). The central Australian Indigenous population appear to carry an extra-ordinary high prevalence of this allele when compared with the general Australian population on the Australian Bone Marrow Donor Registry (>10% vs. 0.6%), however the population prevalence in the Indigenous Australians living in Western Australian and Arnhem Land are likely to be <2% (49).

Aims

The global aim of this thesis is to improve antibiotic dosing in critically ill Australian Indigenous patients.

The specific aims are:

1. To systematically review the interethnic differences in the PK of antibiotics which also discusses their probable mechanisms and any clinical implications.
2. Describe the incidence of ARC in critically ill Indigenous and non-Indigenous patients, and to identify the likely determinants of ARC in the Indigenous patient group. Assess the accuracy of available CrCL equations, using measured urinary CrCL as the reference.
3. Describe the population PK of meropenem in Australian Indigenous patients with severe sepsis and compare with critically ill Caucasian patients with sepsis, and define optimal meropenem dosing regimens for this population.
4. Describe the population PK of piperacillin in critically ill Australian Indigenous with severe sepsis, and define optimal piperacillin dosing regimens for this population.
5. Describe the PK of total and unbound ceftriaxone in critically ill Australian Indigenous patients with severe sepsis.
6. Describe the population PK of vancomycin in critically ill Australian Indigenous with severe sepsis, and define optimal loading and maintenance doses for vancomycin in this population.

Chapter 2 Pharmacokinetic/pharmacodynamic considerations for the optimisation of antimicrobial delivery in the critically ill

2.1 Synopsis

Antibiotics and antifungals are commonly used in the intensive care setting. This Chapter discusses the recently published data around the PK and PD of these antimicrobials. This Chapter also describes the data correlating an improvement in clinical outcome with the optimisation of dosing regimens and associated PK/PD target attainment. Nonetheless, changes in PK observed in critical illness may complicate the attainment of these targets, especially for antibiotics/antifungals that are hydrophilic and extensively renally eliminated. In such situations, individualised dosing regimens and therapeutic drug monitoring is advised.

2.2 Published review article entitled "Pharmacokinetic/pharmacodynamic considerations for the optimisation of antimicrobial delivery in the critically ill"

The manuscript entitled "Pharmacokinetic/pharmacodynamic considerations for the optimisation of antimicrobial delivery in the critically ill" was published by *Current Opinion in Critical Care* (2015; 21(5):412-20.)

The co-authors contributed to the manuscript as follows: The literature review was performed by the PhD Candidate, Danny Tsai under the supervision of Prof. Jason A. Roberts. Data extraction from cited articles and analysis of data was performed by the PhD Candidate, Danny Tsai, under the guidance of Prof. Jason A Roberts and Prof. Jeffrey Lipman. The PhD Candidate, Danny Tsai, took the leading role in manuscript preparation and writing, Prof. Jason A. Roberts took the leading role in critical review and revision of the manuscript, and Prof. Jeffrey Lipman critically reviewed the manuscript.

The manuscript is presented as per the accepted manuscript. The figures and tables have been inserted into the text in locations close to where they were referred. The abbreviations and numberings of pages, figures and tables have been adjusted to comply with the format of this thesis. The references can be found in the references section of the thesis.

Pharmacokinetic/pharmacodynamic considerations for the optimisation of antimicrobial delivery in the critically ill

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2.2.1 Abstract

Purpose of review Antimicrobials are very commonly used drugs in the intensive care setting. Extensive research has been conducted in recent years to describe their PK/PD in order to maximise the pharmacological benefit and patient outcome. Translating these new findings into clinical practice is encouraged.

Recent findings This paper will discuss mechanistic data on factors causing changes in antimicrobial PK in critically ill patients, such as the phenomena of ARC as well as the effects of hypoalbuminaemia, renal replacement therapy and extracorporeal membrane oxygenation. Failure to achieve clinical cure has been correlated with PK/PD target non-attainment, and a recent meta-analysis suggests an association between dosing strategies aimed at optimising antimicrobial PK/PD with improvement in clinical cure and survival. Novel dosing strategies including therapeutic drug monitoring (TDM) are also now being tested to address challenges in the optimisation of antimicrobial PK/PD.

Summary Optimisation of antimicrobial dosing in accordance with PK/PD targets can improve survival and clinical cure. Dosing regimens for critically ill patients should aim for PK/PD target attainment by utilising altered dosing strategies including adaptive feedback using TDM.

2.2.2 Introduction

Despite the advancement in the management of critically ill patients over the past few decades, severe sepsis and septic shock still remain responsible for persisting high mortality rates for patients in the ICU. The cornerstone of infection treatment is initiation of early antimicrobial therapy and source control of the infection, both of which have a high likelihood of improving clinical cure and survival rates (50, 51). There is increasing evidence that optimisation of antimicrobial dosing regimens can lead to further patient outcome benefits. The aim of these dosing regimens is to maximise pathogen killing through application of PK/PD principles that account for the significant changes in PK and pathogen susceptibility that are common to the critically ill patient. This review will explore the recent evidence on dose optimisation of antimicrobials in critically ill patients as well as provide dosing recommendations based on this data.

2.2.3 Main text

Critically ill patients experience drastic derangements in their physiological parameters, subsequently impacting on the PK of antimicrobials. Unfortunately, treatment success for these drugs is heavily dependent on the drug concentration achieved at the site of infection and thus extensive research has been committed to further our understanding of the physiological processes that cause PK changes, as well as investigating treatment strategies that can address and overcome the aforementioned obstacles.

2.2.3.1 PK/PD of antimicrobials

In the context of PK/PD, antimicrobials can be categorised by either their physicochemical properties (Figure 2.1) or pathogenic kill characteristics (Figure 2.2 and Table 2.1). Understanding these characteristics can aid us in formulating an optimal antimicrobial treatment regimen for an individual patient.

Time-dependent – pathogenic kill is dependent on the time the free drug concentration (*f*) remains above the MIC during the dosing interval ($fT_{>MIC}$).

Concentration-dependent – pathogenic kill is dependent on the ratio of the maximum free drug concentration (fC_{max}) to the MIC of the pathogen (fC_{max}/MIC).

Concentration-dependent with time-dependence – pathogenic kill is dependent on the free drug exposure within 24 hours relative to the MIC of the pathogen, and is represented by area under the concentration-time curve ($fAUC_{0-24}$:MIC).

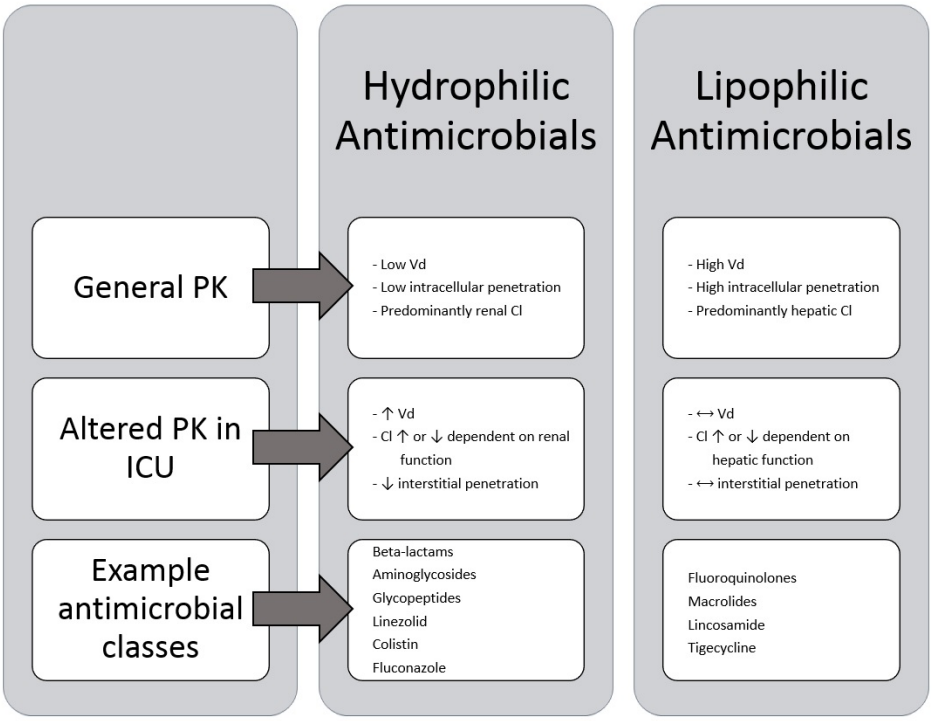

Figure 2.1 Physiochemical properties of antimicrobials, PK of general patients, PK in the critically ill and sample antimicrobials

Abbreviation: PK, pharmacokinetics; ICU, intensive care unit; V_d, volume of distribution; CL, drug clearance.

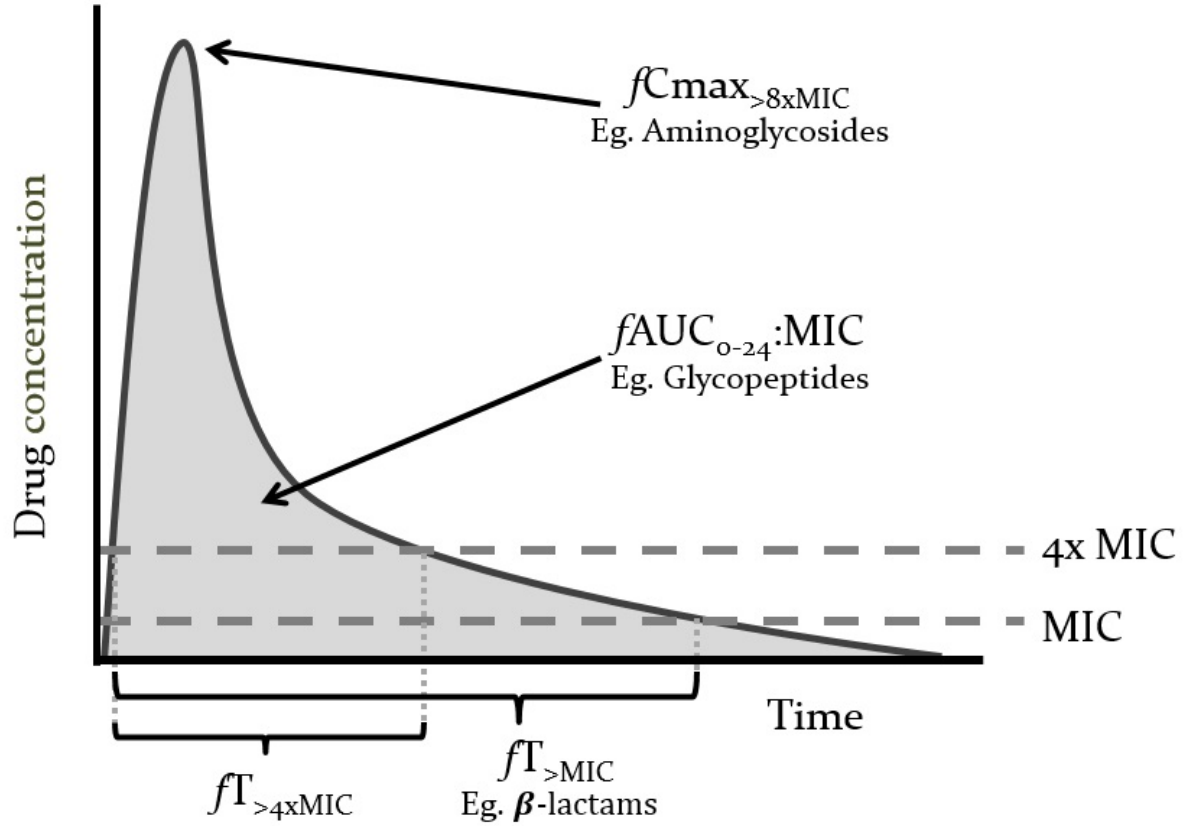

Figure 2.2 PK/PD of antimicrobials

Abbreviation: $fC_{max>8xMIC}$, maximum free drug concentration is greater than 8x the minimum inhibitory concentration; $fAUC_{0-24}$:MIC, free drug exposure within 24 hours relative to the minimum inhibitory concentration; MIC, minimum inhibitory concentration; $fT_{>MIC}$, time of the free drug concentration remains above the minimum inhibitory concentration during the dosing interval; $fT_{>4xMIC}$, time of the free drug concentration remains above 4x minimum inhibitory concentration during the dosing interval.

Table 2.1. PK/PD of antimicrobials, optimal PD of antimicrobials, sample antimicrobials and pathogenic kill targets

Pathogenic kill characteristics	Time-dependent	Concentration-dependent	Concentration-dependent with time-dependence
Optimal PD parameter	$fT_{>MIC}$	fCmax/MIC	fAUC$_{0-24}$:MIC
Antimicrobials	β-lactams Lincosamide Erythromycin Clarithromycin Linezolid Flucytosine	Aminoglycosides Metronidazole Fluoroquinolones Daptomycin Echinocandins Polyenes	Fluoroquinolones Aminoglycosides Azithromycin Glycopeptides Tigecycline Linezolid Echinocandins Triazoles
Pathogenic kill target	*>40%* $fT_{>MIC}$ for carbapenems *>50%* $fT_{>MIC}$ for penicillin *>70%* $fT_{>MIC}$ for cephalosporins (Maximal pathogenic kill activity seen at 4-5xMIC for some agents)	fCmax$_{>8-10xMIC}$ (Maximal pathogenic activity is often seen when fCmax$_{>8-10xMIC}$)	Each antimicrobial is individualized (Dose is the main determinant of achieving maximal pharmacological efficacy.)

Abbreviation: PD, pharmacodynamics; $fT_{>MIC}$, time of the free drug concentration remains above the minimum inhibitory concentration during the dosing interval; fC$_{max}$/MIC, ratio of the maximum free drug concentration to the minimum inhibitory concentration; fAUC$_{0-24}$:MIC, free drug exposure within 24 hours relative to the minimum inhibitory concentration; fC$_{max>8-10xMIC}$, maximum free drug concentration is greater than 8-10x the minimum inhibitory concentration

2.2.3.2 Factors impacting PK/PD of antimicrobials and their clinical consequences

Numerous factors alter the PK of antimicrobials in the critically ill by changing either or both of the two main PK parameters – V_d and CL.

2.2.3.2.1 V_d and CL in the critically ill

V_d significantly increases in critically ill patients mainly due to volume expansion from rigorous fluid resuscitation and the presence of systemic inflammatory response syndrome (SIRS), whereby the phenomenon of third spacing precipitates from capillary leakage. In this circumstance, hydrophilic antimicrobials will be diluted and the PK significantly altered. On the other hand, PK of lipophilic drugs are relatively unaffected due to more extensive intracellular and adipose tissue penetration (52). The extent of volume expansion is described by changes in disease severity, with

increasing Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores associated with increased V_d for hydrophilic antimicrobials (53). V_d is also affected by hypoalbuminaemia, which may have profound effects on highly albumin bound antimicrobials (54, 55), such as ceftriaxone, cefazolin, flucloxacillin, ertapenem, teicoplanin and daptomycin, with protein binding percentage approximating 90, 80, 93, 90, 90 and 92% respectively. In this scenario, a transient increase in free drug concentration will be observed, followed by an increase in V_d and drug CL. Furthermore, high variability of protein binding and free drug concentration is reported in the critically ill even for lower binding antimicrobials such as linezolid and vancomycin (31 and 55% respectively) (56, 57). Obesity is also a major contributing factor to sub-therapeutic dosing (58-60).

A decline in CL is usually caused by end organ dysfunction (renal and/or hepatic) (61). Renal impairment significantly alters the PK of renally clear antimicrobials, in particular those with higher hydrophilicity and most of the commonly used antimicrobials in the ICU fall into this category. On the other hand, reduction for dose or dosing frequency for hepatically cleared antimicrobials is only recommended in the presence of liver decompensation (62). Nonetheless, should altered renal function coexist, revision of dosing regimens based on the CL mechanisms of the prescribed antimicrobial is especially necessary (61, 62).

A recent multicentre observational study found that 65% of critically ill patients without history of renal impairment will experience ARC, (defined as 'enhanced renal elimination of circulating solute' (63)), and factors correlate with its prevalence include male gender, younger age, multiple-trauma and ventilation (64). Furthermore, many studies have demonstrated higher antimicrobial CL in presence of burns, SIRS, multiple trauma, severe medical illnesses, use of inotropes and increase in cardiac output, which increases the risk of sub-therapeutic drug concentration and thus, treatment failure (59, 65-68). Udy *et al.* have found high CrCL in the critically ill the greatest predictor of PK/PD target non-attainment for β-lactams (69).

Renal replacement therapy (RRT) also increases antimicrobial CL (especially β-lactams and other small molecule, hydrophilic and low protein bound antimicrobials) relative to patients with renal dysfunction. The extent of this extracorporeal CL varies with different settings of the RRT, RRT dose and haemofilters used. A recent meta-analysis by Jamal *et al*. has found effluent flow rate the strongest predictor of the extent of drug removal by RRT, which includes vancomycin ($r_s = 0.90$; $p = 0.08$), meropenem ($r_s = 0.43$; $p = 0.12$) and piperacillin ($r_s = 0.77$; $p = 0.10$) (70). The large multicentre SMARRT (SaMpling Antibiotics in Renal Replacement Therapy) study is under

progress, which examines antimicrobial dosing and PK in patients on RRT (Australian New Zealand Clinical Trials Registry ACTRN12613000241730). Its result hopes to provide further information to guide antimicrobial dosing in patients receiving any form of RRT.

Studies investigating antimicrobial PK for patients on extracorporeal membrane oxygenation (ECMO) have been mostly performed on paediatric patients and animals. Though these data show large variability between studies, higher V_d and lower CL were generally observed in the ECMO arms. Notwithstanding these findings, small PK studies have found no significant PK differences for vancomycin, piperacillin/tazobactam and meropenem in adult cohorts (71, 72). Currently, a multinational study investigating the effect of ECMO on conventional antimicrobial regimens is being conducted (73).

2.2.3.2.2 Evidence of failure of PK/PD target attainment and its clinical relevance

Changes in CL and/or V_d can lead to a significant decrease in the plasma drug concentration leading to non-attainment of PK/PD targets and thus a higher treatment failure rate (74-76). Recent studies have correlated ARC with failure of PK/PD target attainment for a number of β-lactams, subsequently requiring dose escalation (77, 78). The DALI-(Defining Antibiotic Levels in ICU patients) study, a multinational, observational study involving 68 hospitals, assessed β-lactam PK/PD target attainment in a large cohort of critically ill patients and found that 16% of the 361 enrolled patients failed to achieve 50%$fT_{>MIC}$ with conventional therapy, and were 32% less likely to achieve a positive clinical outcome (79).

2.2.3.3 PK/PD target attainment of antimicrobial classes

Despite confirmation of relationship between unsuccessful PK/PD target attainment and treatment failure, the association of PK/PD target attainment and treatment success is still a subject of ongoing debate.

2.2.3.3.1 β-lactam

β-lactams are the commonest and most extensively studied antibacterials in ICU. Maximised $fT_{>MIC}$ can be achieved by extending the infusion time, although a number of previous studies and meta-analyses failed to show superior clinical outcome. Many of the studies used lower doses in the prolonged infusion (PI, includes extended and continuous infusion) arm and had small sample sizes. It has been shown that $T_{>MIC}$ for a thrice daily meropenem regimen is similar between 1 g infused over 30 minutes and 0.5 g over 3 hours (80). Similar results are found between a regimen of thrice daily imipenem 1g infused over 30 minutes compared with a four times daily regimen of 0.5 g over 3 hours (81), and thus a superior outcome would not be anticipated. Nonetheless, a number of recently published larger single-centre studies have shown superior clinical outcome with PI (82-85). A meta-analysis by Teo *et al.* (86) has also demonstrated improvement in clinical cure with a significant reduction in mortality (relative risk = 0.66, 95% confidence interval 0.53-0.83) based on a total of 19 studies encompassing 1620 hospitalised patients. This important finding based on the most recent and robust data challenges some of the previously conducted systematic reviews (87, 88). Furthermore, BLING-II (Beta-Lactam Infusion Group) study, the largest international multicentre randomised controlled trial studying the correlation between PI and clinical outcome for β-lactams will report its results soon (89), to provide further clarification on this intervention.

2.2.3.3.2 Glycopeptides

Recent studies suggest that vancomycin-induced nephrotoxicity is reduced via administration by continuous infusion (Tafelski *et al.* 26 vs 35%; Hanrahan *et al*. intermittent infusion with higher risk of nephrotoxicity odds ratio = 8.204, $p \leq 0.001$) (90, 91). Continuous infusion is also associated with earlier PK/PD target attainment and a lower incidence of sub-therapeutic concentrations (91). However, the low AUC achieved in the first 24 hours of administration is an independent risk factor for treatment failure for MRSA bacteraemia (adjusted odds ratio = 4.39, 95%, confidence interval 1.26-15.35 by Etest), and as such a loading dose (LD) is recommended prior to initiation of continuous infusion (76).

Teicoplanin is slightly different. In a retrospective PK study, Matsumoto *et al.* recommended 3 LDs of 11-15mg/kg 12 hours apart for teicoplanin with a target trough concentration (C_{min}) of 15-30mg/L (92). The 11mg/kg and 15mg/kg regimens each achieved a respective C_{min} of 17.5 and 27.8mg/L after 3 LDs. Due to teicoplanin's prolonged terminal half-life ($T_{½}$) of 90-157 hours, TDM

is still recommended thereafter. Furthermore, teicoplanin's high protein binding complicates its PK/PD because of the increased free drug concentrations that have been described in hypoalbuminaemia (55). Studying the teicoplanin dataset of the DALI-study, Roberts *et al*. have found albumin bound percentages varying between 71-97% and free drug C_{min} between 0.1-4.5mg/L (target 1.5-3mg/L), and the free drug concentration inversely increases in proportion to the severity of hypoalbuminaemia (55).

2.2.3.3.3 Aminoglycosides

Two studies investigating the PK of 25mg/kg dosing regimen of amikacin in critically ill patients have found 25-33% of participants failed to achieve the defined PK/PD target, which was a C_{max} >60-64mg/L (53, 93). The 25mg/kg dosing regimen was calculated according to total body weight (TBW). Neither study had an upper limit to the C_{max}, and toxicity was not assessed. In the De Montmollin *et al.* study, PK/PD target non-attainment with positive 24-hour fluid balance and body mass index (BMI) lower than 25kg/m^2 (93). This highlights the importance of using adjusted body weight (ABW) or lean body weight (LBW) especially in patients with lower BMI.

2.2.3.3.4 Echinocandins

The antifungal dataset from the DALI-study revealed a significantly lower AUC_{0-24} for a 100mg daily regimen of anidulafungin when compared with the study by Liu *et al.* (55 vs 93mg.h/L) (94, 95). Plasma sampling was obtained for Liu *et al.*'s study after 3-7 days (included a 200mg LD) with the DALI-study having sampling on various days of therapy. Anidulafungin has a mean $T_{½}$ of 26.5 hours, hence the AUC_{0-24} may differ significantly on different dosing days before steady state is reached. Patients recruited from the Liu's study were older and had lesser weight than the DALI study (mean age and weight 51 vs 60 years, 82 vs 65kg respectively), and only patients with an APACHE II score of <25 were recruited whereas the median score for DALI is 18 (range 15-32).

The DALI-study also found a mean AUC_{0-24} of 52mg.h/L for a 70mg LD of caspofungin compared to 89mg.h/L reported by Muilwijk *et al.* on day 3 after a LD of 70mg followed by 50mg daily regimen (94, 96). For both Muilwijk and Liu's studies, the PK findings are comparable to general

patients, and therefore further studies are warranted to guide dosing regimens in the critically ill (95, 96).

2.2.3.3.5 Triazoles

The DALI-study found that of the 15 ICU patients receiving fluconazole regimens (mean daily dose 4.9mg/kg), 33% did not reach the PK/PD index of AUC_{0-24}/MIC >100 for an MIC of 2mg/L (breakpoint for most *Candida species*) (94). Fluconazole was observed to be given commonly as a standard 400mg daily dose and hence have produced significantly varied PK in the DALI study. Weight based dosing may need to be considered.

Hypoalbuminaemia is also correlated to an increase in free drug concentration for voriconazole, and this relationship is more pronounced in the presence of hyperbilirubinaemia (97). Voriconazole is ~56% protein bound and is subject to saturable hepatic metabolism, monitoring of free drug concentration may prove to be a useful intervention in later studies.

2.2.3.4 Application of PKPD in clinical setting

Both sub-therapeutic and toxic drug concentrations may eventuate in unwanted outcomes. Unfortunately the unpredictability of PK in this patient group complicates PD target attainment, leading to the predicament where a consistent dosing regimen does not produce consistent concentrations (98, 99). Various strategies can be implemented to address these challenges.

2.2.3.4.1 Dose individualisation without TDM availability

Many ICUs do not have immediate access to a pathology service with drug assay capability for antimicrobials other than vancomycin and gentamicin although there is an increasing number of such centres (100).

2.2.3.4.1.1 Loading dose

Timely administration of appropriate antimicrobial is imperative to ensure early achievement of therapeutic concentration (101). This is commonly referred to as the bucket theory, where the bucket needs to be filled (antimicrobial distribution) before water leak (CL) needs to be considered, and hence the presence of end organ dysfunction should not discourage the administration of a LD (Figure 2.3). Usually a single conventional dose is sufficient, exceptions are glycopeptides where the change in V_d can be quite high relative to standard doses. An LD up to twice the conventional dose (vancomycin) or multiple LDs (teicoplanin) may be needed.

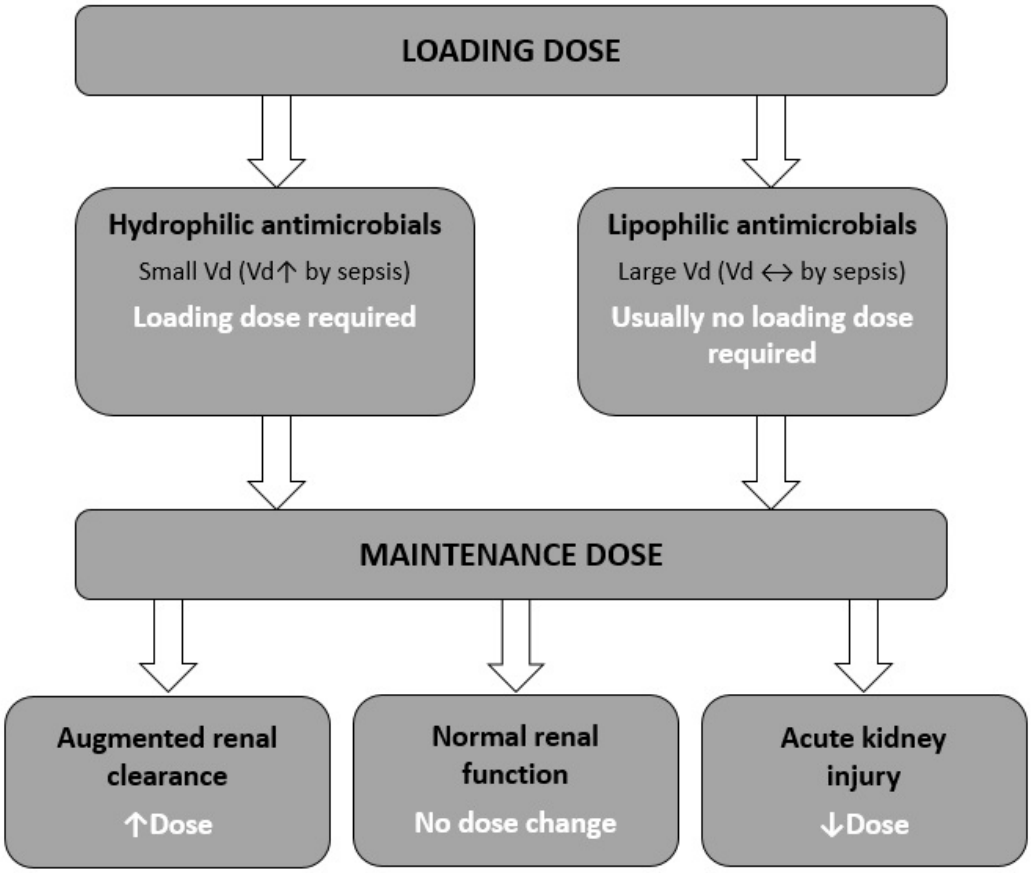

Figure 2.3. A proposed process for optimising the dose for a renally cleared antimicrobial in a critically ill patient.

Abbreviation: V_d, volume of distribution

2.2.3.4.1.2 Maintenance dose

Accurate estimation of glomerular filtration rate (GFR) is imperative for renally-cleared antimicrobials. CrCL calculated from 8-12 hours urine collection remains the gold standard for clinical practice. Where this is not achievable in a timely manner, estimated GFR (eGFR) calculated from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula has been shown to be superior to the Modified Diet in Renal Diseases (MDRD) and eGFR of the Cockroft Gault CrCL in the critically ill, albeit the CKD-EPI eGFR has a tendency to underestimate the likely value in the presence of ARC (67, 102). TBW can generally be used for weight based dosing for patients with average body weight, with LBW or ABW recommended in either extremes of body weight (exception is vancomycin where TBW should be used).

2.2.3.4.1.3 Administration

The administration method of an antimicrobial should be in accordance with its pathogenic kill characteristic, maximising the chance of PK/PD target attainment.

Time-dependent antimicrobials – Maximising $fT_{>MIC}$ is the aim of dosing, especially when the suspected pathogen is likely to have a high MIC such as Pseudomonas aeruginosa (83). This can be achieved by extending the infusion time to ≥3 hours.

Concentration dependent antimicrobials – Achieving a high Cmax is the aim of dosing and is mainly achieved by choosing an adequate dose.

Concentration dependent with time-dependence antimicrobials – Administration method is individualised for each antimicrobial.

2.2.3.4.1.4 Regimen reassessment

Signs of antimicrobial toxicity should be monitored. Antimicrobial doses should be adjusted in accordance with the MIC of the pathogen cultured. ARC, third spacing and other inflammatory related complications are likely to subside as the patient clinically improves (99), and hence review of antimicrobial regimen is advised daily.

2.2.3.4.2 Therapeutic drug monitoring

Various methods of TDM show improvement in PK/PD target attainment (though their clinical relevance still needs to be ascertained), for example one PK study suggests an 100% attainment of 100%$fT_{>MIC}$ if daily TDM is performed for 2 studied β-lactams (99).

Time dependent antimicrobials – after administration of a LD, subsequent maintenance doses should be guided by the PK/PD indices in concert with the MIC. Attaining a target of 100%$fT_{>MIC}$ is generally encouraged, where the C_{min} can guide subsequent doses. For continuous infusions, a random concentration at least 4x MIC is suggested. Drug assays usually describe the total drug concentration, but only the unbound concentration is of clinical value (calculated by multiplying the total concentration by 1 less than the binding fraction). For deep tissue infection, the concentration ratio between serum and target site should also be addressed as serum concentrations may in fact not be sufficiently representative (103).

Concentration dependent antimicrobials – achieving a C_{max} (obtained 30 minutes after end of infusion) >8-10xMIC of suspected pathogen is the aim of therapy unless if in toxicity. Eg. C_{max} of >64mg/L is aimed for MIC of 8mg/L. Doses can be adjusted in proportion to the change in concentration needed.

Concentration dependent with time-dependence antimicrobials – TDM for each antimicrobial (e.g. ciprofloxacin, linezolid and colistin) is different and individualised.

2.2.5 Conclusion

Optimisation of antimicrobial dosing in accordance with PK/PD indices can improve survival and clinical cure rates for critically ill patients. Hence, dosing regimens should aim to maximise PK/PD target attainment by utilising techniques such as TDM. Further studies may be needed to assess the clinical relevance of target site free drug concentration, antimicrobial PK/PD in patients on ECMO and RRT.

2.2.6 Financial support and sponsorship

Danny Tsai is funded by a PhD scholarship provided by the National Health and Medical Research Council of Australia (NHMRC); Australian Academy of Science's Douglas and Lola Douglas Scholarship; and receives support from the Alice Springs Specialists' Private Practice Trust Fund. Jason Roberts is funded in part by an Australian National Health and Medical Research Council Fellowship (APP1048652).

2.3 Conclusion

This Chapter has reviewed the recently published PK/PD data for different classes of antibiotics and antifungals in critical illness. There is increasing evidence demonstrating improved clinical outcomes when antibiotic PK/PD targets are achieved. Furthermore, TDM can facilitate attainment of PK/PD targets in scenarios where drastic PK changes are anticipated yet are difficult-to-predict.

Chapter 3 Interethnic differences in pharmacokinetics of antibacterials

3.1 Synopsis

Significant differences in PK of drugs between different ethnic groups have been reported for many drugs. Subsequent dose adjustment is often advised when these PK differences are identified. However, the effect of ethnicity on antibacterial PK is less certain. This Chapter consists of a systematic review which aims to describe possible PK differences in antibiotics between ethnicities, discuss their probable mechanisms as well as any clinical implications.

3.2 Published review article entitled "Interethnic differences in pharmacokinetics of antibacterials"

The manuscript entitled "Interethnic differences in the pharmacokinetics of antibacterials" is published in *Clinical Pharmacokinetics* (2015; 54:243-260.)

The co-authors contributed to the manuscript as follows: The literature review and data extraction from cited articles were performed by the PhD Candidate, Danny Tsai under the supervision of Prof. Jason A. Roberts. Analysis of data was performed by the PhD Candidate, Danny Tsai and Dr Janattul-Ain Jamal, under the guidance of Prof. Jason A Roberts. The PhD Candidate, Danny Tsai, took the leading role in manuscript preparation and writing. Prof. Jason A. Roberts took the leading role in critical review and revision of the manuscript. Critical review was performed by Dr Joshua Davis, Prof. Jeffrey Lipman and Prof. Jason A. Roberts.

The manuscript is presented as per the accepted manuscript. The figures and tables have been inserted into the text in locations close to where they were referred to. The abbreviations and numberings of pages, figures and tables have been adjusted to comply with the format of this thesis. The references can be found in the references section of the thesis.

Interethnic differences in pharmacokinetics of antibacterials

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3.2.1 Abstract

Background Optimal antibacterial dosing is imperative for maximising clinical outcome. Many factors can contribute to changes in the PK of antibacterials to the extent where dose adjustment may be needed. In acute illness, substantial changes in important PK parameters for certain antibacterials such as V_d and CL can occur. The possibility of interethnic PK differences can further complicate attempts to design an appropriate dosing regimen. Factors of ethnicity, such as genetics, body size and fat distribution contribute to differences in absorption, distribution, metabolism and elimination of drugs. Despite extensive previous work on the altered PK of antibacterials in some patient groups such as the critically ill, knowledge of interethnic PK differences for antibacterials is limited.

Objectives This review aims to describe any PK differences in antibacterials between different ethnic groups, discuss their probable mechanisms as well as any clinical implications.

Methods We performed a structured literature review to identify and describe available data of the interethnic differences in the PK of antibacterials.

Results We found 50 articles that met our inclusion criteria and only 6 of these compared antibacterial PK between different ethnicities within the same study. Overall there was limited evidence available. We found that interethnic PK differences are negligible for carbapenems, most β-lactams, aminoglycosides, glycopeptides, most fluoroquinolones, linezolid and daptomycin, whereas significant difference is likely for ciprofloxacin, macrolides, clindamycin, tinidazole and some cephalosporins. In general, subjects of Asian ethnicity achieve drug exposures up to 2-3 fold greater than Caucasian counterparts for these antibacterials. This difference is caused by a comparatively lower V_d and/or drug CL.

Conclusion Interethnic PK difference is likely; however, the clinical relevance of these differences is unknown and warrants further research.

3.2.2 Introduction

Clinically significant interethnic PK differences requiring adjusted dosing regimens have been identified for numerous commonly used drugs (16, 104-110). However, there are few published data describing interethnic differences in the PK of antibacterials. Titration of doses to therapeutic response for antibacterials is not appropriate because resolution of symptoms and signs may take days to weeks to occur and therefore accuracy of dosing at the commencement of treatment should be considered essential (111). Sub-optimal dosing of antibacterials may directly lead to undesired outcomes such as treatment failure, toxicity or indirectly adversely affect the microbial ecology of an individual, ICU or hospital by selecting for antibacterial resistant organisms. Whilst most PK differences can be estimated by adjusting the V_d and CL in accordance to the ethnic group's average body size, renal function and other basic physiological characteristics, there are still many factors which may affect the PK that cannot not be accounted for in such simple dose adaptations.

Extensive research has identified a number of PK processes which may contribute to interethnic PK differences (15, 106, 112-116). These processes include the physiological mechanisms involved in the absorption, distribution, metabolism and elimination of a drug. Active drug transport serves as a mechanism for absorption differences observed between ethnic groups. Alpha-1-acid glycoprotein (AGP) concentrations, body size and body fat percentage may affect the distribution of a drug. Metabolic enzyme activities (including cytochrome P450 [CYP450], p-glycoprotein and phase II metabolism) contribute to differences seen in metabolic drug CL between ethnicities; whereas active transport mechanisms that result in drug secretion in the renal distal tubules may contribute to disparities in renal drug CL. While PD differences of antimicrobials between ethnic groups can also be an important determinant of treatment success and/or hypersensitivity (117), this article is only focused on the interethnic PK differences.

Currently, most antibacterial dosing regimens are based on PK and PD data collected from studies performed on the healthy Caucasian population. Whether it is appropriate to extrapolate these dosing recommendations to other ethnic groups remains uncertain. The aim of this review is to describe the antibacterial PK differences between ethnic groups and discuss the clinical implication of these findings.

3.2.3 Methods

3.2.3.1 Search strategy and selection criteria

Data were identified through keyword searches on PubMed (from 1960 to July 2014). The keywords included ethnic, interethnic, ethnicity, race, racial, interracial, Asian, Caucasian, African, African American, European, Chinese, Japanese, Korean, Indonesian, Indian, Jordanian, Thai, Iranian, Taiwanese, Nigerian, pharmacokinetic(s), pharmacodynamics(s), antibiotic, antibacterial, aminoglycoside, carbapenem, cephalosporin, glycopeptide, clindamycin, lincomycin, macrolide, penicillin, quinolone, colistin, daptomycin, linezolid and tigecycline. Searches were limited to English and Chinese languages. The reference lists of identified articles were then hand-searched to identify further relevant articles. All non-duplicate articles reporting original research or literature reviews related to interethnic PK differences only on antibacterial drugs were included in this review. Relevant articles that demonstrated possible interethnic PK differences were investigated in detail. Studies which did not demonstrate interethnic difference for a specific drug, unless the results were contrary to other studies, were not included further. Only studies that recruited healthy subjects are included, with the exception of clinical PK studies with comparable illnesses between different ethnicities, in which the condition would be specified.

3.2.4 Results – Studies identified

Studies comparing the PK of antibacterials in different ethnicities are limited. The article selection process is shown in Figure 3.1. The initial number of studies identified with the keywords was 13,767 with only 82 studies deemed suitable for full review. Upon reviewing references of the identified articles, 17 further studies became eligible for inclusion. A total of 50 studies have demonstrated significant interethnic PK difference and were included for a comparative review (See Table 3.1). This includes 32 studies on non-Caucasian subjects and 18 studies from Caucasian subjects. Overall, six studies were particularly robust in their design because they have recruited ethnicities within the same study (13, 118-122). The article selection process was undertaken by DT and JR.

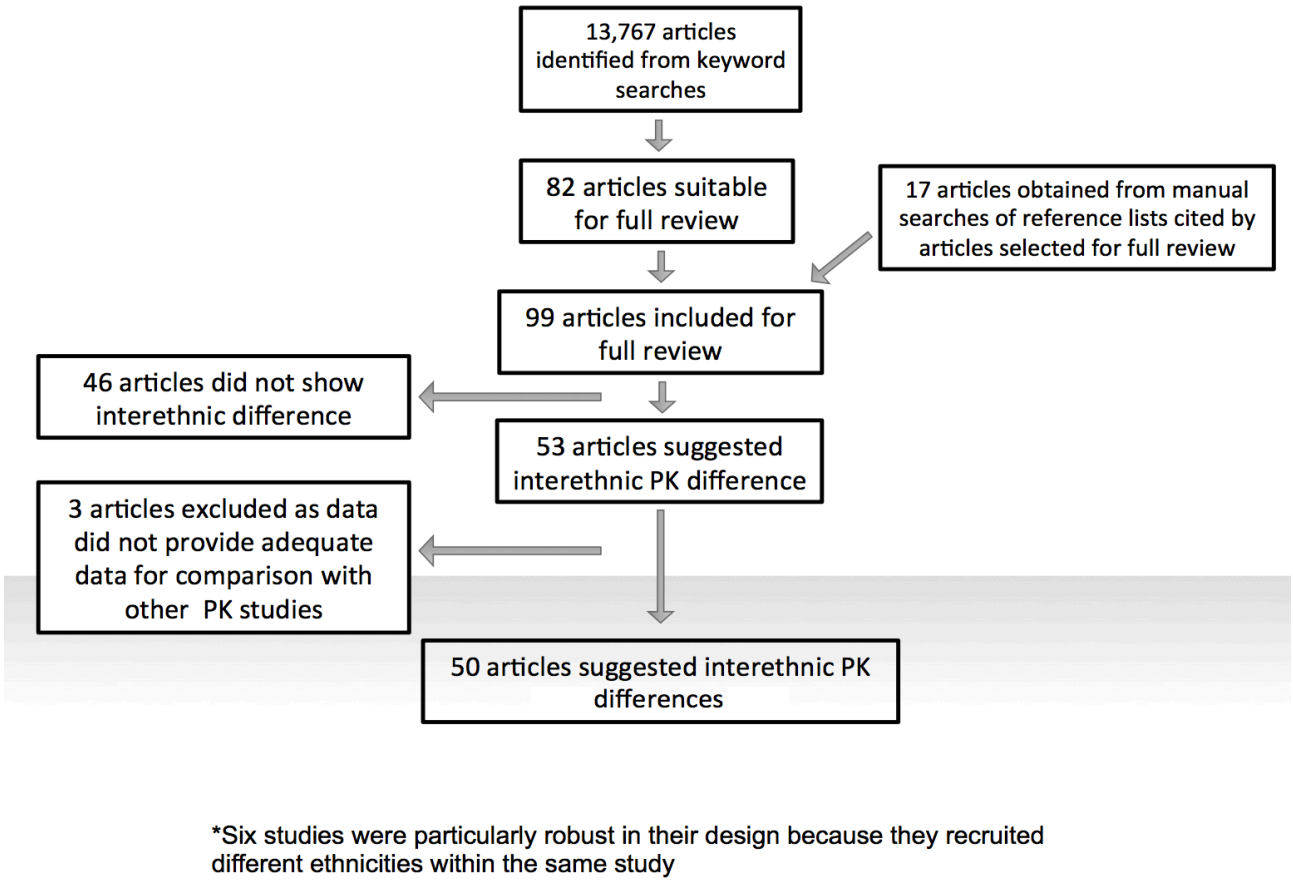

Figure 3.1 Flowchart illustrating the selection of studies included in this review

Abbreviation: PK, pharmacokinetic.

Table 3.1 PK of antimicrobials showing interethnic differences in healthy volunteers[a]

Antimicrobial	Population	No. of females	Age (y)	TBW (kg)	PK parameters						
					C_{max} (μg/mL)	V_d (L/kg)	$k_e \times 10^2$ (h^{-1})	$AUC_{0-\infty}$ (μg*h/mL)	CL (mL/min/kg)	T_{max} (h)	$T_{½}$ (h)
Aminoglycosides											
Gentamicin/Tobramycin (IV) (123)	Alaskan native[b] (n=101)	44/101	45 ± 21	67 ± 19	5.36	0.3 ± 0.1	26 ± 8	NA	1.2 ± 0.5	NA	3.5 ± 2.0
Gentamicin (IV) (124)	US American[b] (n=1369)	842/1369	41 ± 23	65 ± 18	NA	0.2 ± 0.1	46 ± 23	NA	1.3 ± 0.6	NA	2.2 ± 2.1
Cephalosporins											
Cefdinir 100mg (PO) (125)	Chinese (n=12)	0/12	23 ± 2	65 ± 4	0.8 ± 0.2	0.4 ± 0.3[c]	NA	5.4 ± 1.2	0.61 ± 0.38[c]	2.5 ± 0.5	1.7 ± 0.3
Cefdinir 100mg (PO) (126)	Chinese (n=20)	0/20	26 ± 2	64 ± 6	0.9 ±0.2	NA	40.5 ± 8.0	4.5 ± 0.8	NA	3.7 ± 1.0	1.8 ± 0.4
Cefdinir 200mg (PO) (127)	Chinese (n=12)	0/12	28 ± 2	67 ± 4	1.5 ± 0.3	NA	NA	7.2 ± 1.6	NA	4.0	1.9 ± 0.3
Cefdinir 200mg (PO) (128)	Canadian (n=16)	0/16	23 ± 4	70 ± 6	1.0 ± 0.3	0.4 ± 0.1	NA	4.1 ± 1.1	0.69 ± 0.15	3.3 ± 0.6	1.4 ± 0.2
Cephradine 250mg (PO) (129)	Pakistani (n=12)	0/12	22	64	11.5 ± 1.7	NA	42 ± 4	17.6 ± 0.4	3.7 ± 0.05	0.8 ± 0.1	1.7 ± 0.2
Cephradine 250mg (PO) (130)	US American (n=20)	0/20	24 ± 2	64-94	NA	0.29	NA	12.10	3.1	1.0	0.85
Cefroxadine 500mg (PO) (131)	Korean (n=9)	NA	24 ± 2	71 ± 7	17.6 ± 4.9	NA	73 ± 18	48.4 ± 7.2	NA	1.4 ± 0.4	1.0 ± 0.3
Cefroxadine 500mg (PO) (132)	Japanese (n=5)	NA	20-24	55-66	10.7 ± 1.1	0.36	76.8 ± 10	29.8 ± 2.1	NA	1.5 ± 0.2	1.0 ± 0.1
Cefroxadine 500mg (PO) (133)	Caucasian (n=10)	3/10	26	68	12.3 ± 4.2	NA	86.4 ± 19.8	23.6 ± 2.9	5.1 ± 0.6	0.8	0.9 ± 0.2

Antimicrobial	Population	No. of females	Age (y)	TBW (kg)	PK parameters						
					C_{max} (μg/mL)	V_d (L/kg)	$k_e \times 10^2$ (h^{-1})	$AUC_{0-\infty}$ (μg*h/mL)	CL (mL/min/kg)	T_{max} (h)	$T_{½}$ (h)
Cefroxadine 424mg (PO) (134)	French (n=6)	0/6	23-30	73	7.6 ± 2.5	NA	NA	21.3 ± 2.3	4.6 ± 0.8	0.8	1.0 ± 0.2
Fluoroquinolones											
Ciprofloxacin 500mg (PO) (135)	Chinese (n=6)	3/6	20 ± 1	52 ± 10	4.2 ± 1.1	3.7 ± 0.8	30 ± 3	18.1 ± 2.7	9.0 ± 1.2	1.8 ± 0.4	2.3 ± 0.8
Ciprofloxacin 500mg (PO) (136)	Indonesian (n=24)	both	26 ± 5	57 ± 7	2.9	NA	NA	16.4	NA	1.3 ± 0.9	5.6
Ciprofloxacin 500mg (PO) (137)	Brazilian (n=8)	3/8	28 ± 2	63 ± 3	1.3 ± 0.2	2.1 ± 0.2[g]	23 ± 4	5.5 ± 0.8	8.5 ± 0.7[g]	1.2 ± 0.3	3.0 ± 0.6
Ciprofloxacin 500mg (PO) (138)	Caucasian (n=11)	both	27 ± 4	70 ± 11	2.1 ± 0.6	NA	NA	8.8 ± 2.5	NA	1.1 ± 0.6	4.7 ± 1.1
Ciprofloxacin 500mg (PO) (139)	German (n=10)	5/10	28	66	1.5 ± 0.4	4.7 ± 2.7	NA	6.8 ± 1.3	NA	1.2 ± 0.3	5.4 ± 2.9
Ciprofloxacin 500mg (PO) (140)	US American (n=6)	0/6	30	70	2.6 ± 0.9	1.4 ± 1.8	26 ± 3	11.1 ± 3.3	5.5 ± 2.4[d]	1.3 ± 0.4	4.2 ± 0.6
Ciprofloxacin 200mg (IV) (141)	Nigerian (n=12)	0/12	23 ± 2	68 ± 8	2.7 ± 1.1	0.4 ± 0.3[h]	NA	8.8 ± 3.2	6.4 ± 2.7	0.8 ± 0.2	7.3 ± 4.7
Ciprofloxacin 200mg (IV) (142)	Chinese (n=8)	0/8	21	59	NA	0.8 ± 0.2[h]	NA	7.1 ± 1.2	4.8 ± 1.3[d]	NA	3.9 ± 0.7
Ciprofloxacin 200mg (IV) (139)	German (n=10)	5/10	28	66	NA	3.0 ± 0.5	NA	5.3 ± 1.1	9.9 ± 2.0	NA	NA
Lincosamides											
Clindamycin 150mg (PO) (143)	Jordanian (n=24)	0/24	29 ± 8	76 ± 11	4.5 ± 1.3	NA	27 ± 17	22.2 ± 9.9	NA	0.9 ± 0.4	4.1 ± 2.8
Clindamycin 300mg (PO) (144)	Chinese (n=24)	0/24	24 ± 2	64 ± 5	3.0 ± 1.2	NA	NA	11.3 ± 5.0	NA	1.0 ± 0.6	2.6 ± 0.7
Clindamycin 300mg (PO) (145)	Indian (n=32)	8/32	27 ± 9	62 ± 15	4.1 ± 1.2	NA	26.9	15.5 ± 7.2	NA	1.0 ± 0.5	3.5 ± 3.3

Antimicrobial	Population	No. of females	Age (y)	TBW (kg)	PK parameters						
					C_{max} (μg/mL)	V_d (L/kg)	$k_e \times 10^2$ (h^{-1})	$AUC_{0-\infty}$ (μg*h/mL)	CL (mL/min/kg)	T_{max} (h)	$T_{½}$ (h)
Clindamycin 600mg (PO) (146)	Korean (n=8)	4/4	22	60 ± 6	6.7 ± 2.1	NA	20.2 ± 6.8	20.4 ± 6.1	NA	1.1 ± 0.3	3.8 ± 1.2
Clindamycin 600mg (PO) (147)	US American (n=16)	0/16	27 ± 4	73 ± 13	5.3 ± 1.0	NA	NA	16.9 ± 6.1	NA	0.8 ± 0.4	2.4 ± 0.8
Clindamycin 600mg (PO) (148)	German (n=20)	0/20	29	80	3.4	NA	NA	13.1 ± 4.6	NA	0.9 ± 0.3	2.3± 0.6
Macrolides											
Azithromycin 500mg (PO) (149)	Thai (n=14)	0/14	21 ± 1	63 ± 8	0.43 ±0.2	NA	3.0 ± 1.4	4.5 ± 2.2	NA	1.5 ± 0.4	28.1 ± 13.1
Azithromycin 500mg (PO) (150)	Jordanian (n=24)	0/24	24 ± 6	73 ± 11	0.33 ± 0.09	NA	2 ± 0.5	4.1 ± 1.1	NA	2.8 ± 1.1	45.0 ± 12.3
Azithromycin 500mg (PO) (151)	Mexican (n=27)	13/27	22	54-77	0.51 ± 0.24	NA	NA	4.4 ± 1.4	NA	2.0 ± 0.8	43.4 ± 17.3
Azithromycin 500mg (PO) (152)	US American (n=12)	0/12	29	NA	0.41	NA	NA	3.39	NA	NA	11-14
Azithromycin 500mg (PO) (153)	Chinese (=20)	0/20	NA	NA	0.57 ± 0.21	NA	NA	5.2 ± 1.3	NA	1.9 ± 0.6	50.1 ± 5.0
Azithromycin 500mg (PO) (154)	Chinese (n=20)	0/20	20-26	57-75	0.41 ± 0.17	NA	NA	5.5 ± 1.7	NA	2.5 ± 1.0	38.3 ± 6.0
Erythromycin 250mg (PO) (155)	Australian (n=12)	0/12	21 ± 3	70 ± 5	1.7 ± 0.9	NA	NA	4.7 ± 2.0	NA	2.8 ± 0.5	1.5 ± 0.4
Erythromycin 500mg (PO) (156)	Swedish (n=23)	Mostly females	34	61	2.0 ± 0.8	NA	NA	6.1 ± 2.4	NA	NA	NA
Erythromycin 500mg (PO) (119)	Koreans (n=10)	0/10	24	63 ± 4	3.3 ± 1.5	NA	NA	13.6 ± 5.0	3.3 ± 1.1[i]	4.00	1.8 ± 0.5
Erythromycin 500mg (PO) (119)	Caucasian (n=10)	0/10	25	77 ± 9	2.3 ± 0.5	NA	NA	8.2 ± 2.1	4.3 ± 1.4[i]	3.00	1.5 ± 0.5
Clarithromycin 200mg (PO) (157)	Caucasian (n=8)	0/8	NA	NA	0.6 ± 0.4	5.4 ± 4.6	NA	3.0 ± 2.0	1645 ± 1039[j]	1.6 ± 0.5	2.3

Antimicrobial	Population	No. of females	Age (y)	TBW (kg)	PK parameters						
					C_{max} (μg/mL)	V_d (L/kg)	$k_e \times 10^2$ (h^{-1})	$AUC_{0-\infty}$ (μg*h/mL)	CL (mL/min/kg)	T_{max} (h)	$T_{½}$ (h)
Clarithromycin 250mg (PO) (158)	Iranian (n=14)	NA	NA	NA	1.1 ± 0.2	NA	NA	6.3 ± 1.6	NA	1.6 ± 0.5	4.3 ± 0.9
Clarithromycin 250mg (PO) (159)	Korean (n=24)	0/24	30 ± 5	65 ± 5	1.3	NA	NA	7.0	NA	1.9 ± 0.4	NA
Clarithromycin 250mg (PO) (160)	Turkish (n=24)	0/24	28	67.4	1.2 ± 0.4	NA	NA	8.2 ± 3.3	NA	1.6 ± 1.3	4.9 ± 3.0
Clarithromycin 400mg (PO) (157)	Caucasian (n=8)	0/8	NA	NA	1.1 ± 0.2	3.7 ± 0.7	NA	8.6 ± 2.4	829 ± 209[j]	1.9 ± 0.7	3.6
Clarithromycin 500mg (PO) (161)	Caucasian (n=12)	0/12	29 ± 5	82 ± 8	1.8 ± 0.5	NA	NA	12.6 ± 3.3	NA	3.4 ± 1.3	3.7
Clarithromycin 500mg (PO) (162)	Iranian (n=12)	0/12	29 ± 3	69 ± 6	3.2 ± 0.5	NA	NA	31.1 ± 1.0	NA	2.7 ± 1.1	6.9 ± 2.6
Clarithromycin 500mg (PO) (163)	Norwegian (n=16)	0/16	32 ± 5	NA	2.25 ± 0.6	NA	NA	19.7 ± 7.9	NA	2.5 ± 1.6	3.8 ± 1.3
Clarithromycin 500mg (PO) (164)	Pakistani (n=14)	0/14	22	66	3.3 ± 0.4	NA	NA	20.2 ± 2.4	6.3 ± 1.0	1.5 ± 0.2	3.1 ± 0.6
Clarithromycin 500mg (PO) (165)	Thai (n=24)	0/24	21 ± 2	21 ± 2[k]	3.0 ± 0.8	NA	NA	23.1 ± 7.4	NA	2.0 ± 0.9	5.1 ± 4.5
Clarithromycin 500mg (PO) (166)	Thai (n=24)	0/24	21 ± 1	21 ± 2[k]	2.5± 0.7	NA	NA	15.8 ± 6.1	NA	2.1 ± 0.7	3.1 ± 0.8
Clarithromycin 500mg (PO) (167)	Thai (n=24)	0/24	21 ± 4	20 ± 1[k]	2.8 ± 1.3	NA	NA	17.9 ± 7.4	NA	2.0 ± 0.8	3.6 ± 1.8
Clarithromycin 500mg (PO) (168)	Thai (n=24)	0/24	21 ± 1	21 ± 2[k]	2.4 ± 1.1	NA	NA	16.9 ± 8.0	NA	2.2 ± 0.9	3.9 ± 1.1
Nitroimidazoles											
Tinidazole 1g (PO) (13)	Han (n=10)	5/10	23 ± 1	56 ± 5	19.0 ± 2.4	0.9 ± 0.2	4.2 ± 0.6	486 ± 66	0.011 ± 0.002	2.2 ± 0.5	16.9 ± 2.4
Tinidazole 1g (PO) (13)	Mongolian (n=10)	5/10	21 ± 1	56 ± 8	19.2 ± 4.9	0.9 ± 0.2	4.3 ± 0.5	480 ± 100	0.013 ± 0.002	2.2 ± 0.6	16.4 ± 1.8

Antimicrobial	Population	No. of females	Age (y)	TBW (kg)	PK parameters						
					C_{max} (μg/mL)	V_d (L/kg)	$k_e \times 10^2$ (h^{-1})	$AUC_{0-\infty}$ (μg*h/mL)	CL (mL/min/kg)	T_{max} (h)	$T_{½}$ (h)
Tinidazole 1g (PO) (13)	Korean (n=10)	5/10	23 ± 1	57 ± 8	20.8 ± 3.3	0.8 ± 0.1	4.2 ± 0.5	511 ± 54	0.011± 0.002	2.3 ± 0.6	16.6 ± 1.8
Tinidazole 1g (PO) (13)	Hui (n=10)	5/10	21 ± 2	59 ± 7	20.3 ± 4.1	0.8 ± 0.2	4.2 ± 0.4	514 ± 131	0.010 ± 0.002	2.1 ± 0.7	16.8 ± 1.6
Tinidazole 1g (PO) (13)	Uighur (n=10)	5/10	21 ± 1	57 ± 6	18.8 ± 3.1	0.9 ± 0.2	4.9 ± 0.7	389 ± 37	0.014 ± 0.002	2.3 ± 0.5	14.3 ± 1.9
Penicillins											
Flucloxacillin 250mg (PO) (169)	Chinese (n=20)	0/20	NA	NA	13.9 ± 1.6	NA	NA	28.8 ± 1.3	NA	0.8 ± 0.4	1.7 ± 0.4
Flucloxacillin 250mg (PO) (170)	New Zealander (n=8)	2/8	20-21	NA	7.4 ± 1.4	NA	NA	15.9 ± 2.0	NA	0.9 ± 0.1	1.4 ± 0.2

Abbreviations: C_{max}, maximum concentration; V_d, volume of distribution; k_e, elimination rate constant; $AUC_{0-\infty}$, area under concentration-over-time curve from time 0 to ∞; CL, clearance; T_{max}, time to achieve maximum concentration; $T_{½}$, half-life; PO, oral; IV, intravenous; NA, data not available.
Data is presented as mean ± standard deviation, unless otherwise stated. Where bioequivalence studies are used, data obtained from the reference arm is included into this review. For papers that have performed both compartmental analysis and non-compartmental analysis, data obtained from the non-compartmental analysis are used.

[a] Subject ethnicity shown unless if not specified, of which the nationality will be recorded
[b] Hospitalised patients with infection. Multiple dose administered.
[c] Calculated with an oral bioavailability of 0.23 (128)
[d] Serum clearance
[e] Area under the curve from time 0 to 8 hours ($AUC_{0-\infty}$)
[f] Median
[g] Calculated with an oral bioavailability of 0.69 (171)
[h] Volume of distribution of central compartment (V_c)
[i] Calculated with an oral bioavailability of 0.30 from Mather's study (172)
[j] mL/min.
[k] Body mass index (in kg/m^2)

Table 3.2: Potential determinants of interethnic PK differences

PK phases	Interethnic difference unlikely		Ref	Interethnic difference possible		Ref
	Mechanism	Example		Mechanism	Example	
Absorption	Passive diffusion	*Sparfloxacin, norfloxacin*[a]	(15, 173, 174)	Active transport (also include p-glycoprotein efflux/secretion)	*β-lactams, macrolides, ciprofloxacin*	(114, 175-183)
Distribution	No/low AGP binding Albumin binding	*Aminoglycosides, carbapenems, linezolid ceftriaxone*	(16, 23, 184-187)	AGP binding	*Macrolides*[b]*, lincosamides*	(11, 16, 23, 119, 188-191)
				Different body size	*Most antibacterials*	(119, 192, 193)
Metabolism	-	-		CYP enzyme metabolism, acetylation and glucuronidation	*Macrolides, ciprofloxacin, tinidazole, isoniazid*	(13, 112, 114, 119, 182, 194, 195)
Elimination	Glomerular filtration	*Glycopeptides and aminoglycosides*	(15, 196, 197)	Biliary secretion, Active intestinal secretion, Active tubular secretion	*Tigecycline, fluoroquinolones, macrolides, cephalosporins, penicillins*	(122, 182, 198-200)

Abbreviations: PK, pharmacokinetics; Ref, references; AGP, alpha-1-acid glycoprotein; CYP, cytochrome P450.

[a] Sparfloxacin and norfloxacin are predominantly absorbed via passive diffusion, however the absorption mechanism of passive diffusion for antibiotics is not extensively studied, hence this is more of a theoretical determinant.

[b] Erythromycin, azithromycin and clarithromycin.

3.2.5 Overview of interethnic physiological differences and physicochemical properties of antibacterials

A number of physiological mechanisms have been identified as potential causes of interethnic PK differences when compared with other processes (Table 3.2).

3.2.5.1 Body size & fat distribution

People from different ethnic backgrounds may have physiological differences due to genetic, dietary, lifestyle or environmental factors (201). In particular, body composition, including fat percentage, fat distribution, organ size, total body weight (TBW) and height may vary (9, 10, 202-204). According to the World Health Organization, North American adults (predominantly Caucasian) have the highest average TBW of 80.7 kg, with 73.9% of this population defined as at least 'overweight'. In comparison, Asian adults have the lowest average TBW of 57.7 kg (28.5% less than North Americans), with only 24.4% of the population considered at least overweight. Compared to North American adults – African, European and Oceanic adults weigh 24.8%, 12.3% and 8.2% less respectively (204).

Differences in fat composition between ethnic groups have been widely investigated (202, 203, 205, 206). Body mass index (BMI) is the most commonly used surrogate measure (207, 208) but it does not account for differences in body proportion and fat distribution. In general, Asian adults are of smaller stature, smaller BMI but have higher body fat percentage compared with Caucasian adults. Chinese, Thai and Indonesian adults have a body fat percentage that is 96, 118 and 108% of Caucasians, but is only 92, 95 and 93% of their BMI. African adults have higher BMI but less body fat percentage. Polynesian adults have 23% higher BMI and a body fat percentage only 4% greater than Caucasians (208). Australian Indigenous adults also display significantly different body composition when compared with their non-Indigenous counterparts. Though they have, in general, smaller body mass, they have a higher proportion of central fat as well as longer extremities (46, 209).

3.2.5.2 Mechanisms of altered antibacterial PK in different ethnicities

3.2.5.2.1 Absorption – Interethnic differences for drug absorption by passive diffusion in the absorption phase are considered unlikely (15). On the other hand, differences related to active transporters are considered likely and are discussed in detail in section 3.3.

3.2.5.2.2 Metabolism – Most hepatically metabolised drugs will undergo phase I and/or II metabolism. Different ethnicities are associated with different levels of enzymatic metabolism and may be subject to polymorphism, dividing a population into fast, moderate or slow metabolisers (19, 114, 210, 211). CYP3A4 is the CYP450 enzyme which metabolises the most hepatically cleared antibacterials and Asians generally exhibit less CYP3A4 activity compared to Caucasians (212). CYP3A4 is also expressed in the intestinal epithelium (213), where decreased activity may increase the absorption of its substrates (214). Acetylation is a phase II metabolic process which displays interethnic differences in a number of antituberculosis drugs (33, 215, 216).

3.2.5.2.3 Renal Excretion – For drugs predominantly cleared renally, the subject's renal function and the unbound drug fraction remain the most important determinants of CL (15, 217). Interethnic differences are thus considered unlikely for passive processes like glomerular filtration (15). On the other hand, drug secretion in renal tubules involves active transport is a possible source for interethnic differences as demonstrated for ciprofloxacin and cephalosporins (15, 17, 182, 200, 218, 219).

3.2.5.2.4 Environmental factors that can influence PK – Different types of food ingested (220-222), cigarette smoking (223, 224) and living in higher altitudes (225, 226) may alter PK parameters of drugs and antibacterials. It is also recognised that diseases like diabetes that are widespread in a patient group, may affect the results of an interethnic PK study. For example, for groups like the Australian Indigenous where high burden of diabetes exists, comorbidities like gastroparesis may affect drug absorption, peripheral vascular disease may cause reduced drug distribution into tissues and we would expect that reduced drug CL of renally cleared drugs may be associated with nephropathy (227-233).

3.2.5.3 Active transport and relevance to antibacterial PK

Active transporters such as organic anionic transporters (OATP) and p-glycoproteins in the gut epithelium are subject to polymorphisms which may influence the rate and extent of drug

absorption (15, 175, 234-237). P-glycoprotein is more likely to transport positively charged or neutral drugs that are hydrophobic (238). *In vitro* and animal studies have suggested that fluoroquinolones, trimethoprim, cephalosporins and amoxycillin are subject to active transport, especially in the small intestine (177, 179, 239, 240), and hence are likely to be subject to interethnic PK differences because of genetic polymorphisms. These genetic differences are considered to be independent of environmental effects on PK and support the importance of pharmacogenomics in characterising and predicting interethnic PK differences (175, 182, 241-243).

Active transporters reside in various organ tissues, their influx/efflux mechanisms influence antibacterial penetration into tissues such as pulmonary epithelial cells and brain capillary endothelial cells (179, 219, 244, 245). This may also influence a drug's PD, but unfortunately antibacterial PD studies comparing ethnic groups are rarely carried out.

Lastly, active transporters can also be found in epithelial cell membranes of renal cells and hepatocytes (clarithromycin and erythromycin are substrates) and can influence the drug CL/reabsorption of these organs (200, 234, 246, 247). A number of haplotypes of PEPT2 (a carrier mediated protein responsible for renal reabsorption) have been described in three different Asian ethnic groups, although these appear of academic interest only with no PK differences evident for the PEPT2 substrate cephalexin (118).

3.2.5.4 Antibacterial physicochemical characteristics – hydrophilicity and AGP binding

Antibacterials with higher lipophilicity (eg. macrolides, fluoroquinolones and lincosamides) are considered to exhibit more extensive tissue penetration (248). Upon dosing a lipophilic antibacterial in an obese patient, it has been postulated that patient's TBW can be used to calculate the dose regardless of the body fat percentage (248). Whilst this is likely to be an oversimplification, this general approach can be logically applied to interethnic differences in body weight. On the other hand, hydrophilic antibacterials (eg. aminoglycosides, glycopeptides and β-lactams) are thought to only penetrate into extracellular fluid. It may mean that giving a conventional dose to a smaller patient that has a higher body fat percentage will increase drug exposure (determined by area under the concentration-over-time curve [AUC]) due to the smaller V_d. In those cases, dosing according to patient's lean body weight would seem more appropriate for such hydrophilic drugs. However, due to the small interethnic body fat percentage differences observed, the literature does not report

significant PK differences between ethnicities for V_d at this time. Hydrophilic agents still exhibit at least some level of adipose penetration (approximately 30% of adipose tissues are water) (249) and studies have shown that antibacterial concentrations in subcutaneous tissues are comparable to those measured in deeper tissues in many cases where tissue perfusion is not compromised (250).

AGP is the second most important drug-binding plasma protein after albumin and has high affinity for basic and neutral drugs (251-253). Antibacterials such as clindamycin, erythromycin and rifampicin have approximately 70-80% AGP binding, whereas vancomycin and daptomycin have 20-40% (188, 189, 251, 254-257). Asian, Iranian and African people have approximately 10-20% less AGP than Caucasians, whereas no interethnic differences have been reported in these subjects for albumin (14, 16, 23, 115, 258). For AGP-bound drugs, an increased unbound drug fraction is observed in populations with lower AGP concentration and this increase in unbound drug available for distribution around the body leads to an overall increase in V_d and CL (14, 23, 115, 253).

3.2.6 Antibacterial PK/PD

Antibacterials can generally be considered as having one (or more) of the three PK/PD bacterial kill characteristics: time dependent, concentration dependent and concentration dependent with time-dependence (18). Bacterial killing is maximised when an antibacterial is administered in accordance with these characteristics (6, 259, 260). As such, changes in PK due to a patient's ethnicity will affect the killing of the targeted pathogen and may also influence clinical outcome in selected instances. For example, a reduced CL can lead to drug accumulation and toxicity, whereas increased CL and V_d can cause sub-therapeutic drug concentrations, subsequently leading to treatment failure.

Given that most antibacterials have a wide therapeutic range and are generally used with a 'one-size-fits-all' or weight-based dosing regimen, should profound interethnic PK differences be present, such a simplified approach to dosing would risk failure.

3.2.7 Pharmacokinetic studies of different classes of antibacterials in different ethnicity

Table 3.1 describes the comparative PK parameters of single dose antibacterials in different ethnic groups. Unless stated otherwise in the table, study participants included in these PK studies are healthy subjects that have fasted overnight with the age, sex, weight and ethnicity (nationality is used if ethnicity is not revealed) specified in the table.

3.2.7.1 Aminoglycosides – These antibacterials are hydrophilic and are mainly eliminated renally, hence the patient's glomerular filtration rate, age and body size remain the predominant determinants of their PK (124). To date, no studies have identified any PK differences between African-American, Caucasian, Asian and Hispanic hospitalised patients for aminoglycosides (120, 196, 261) with renal function and body weight the most important determinants. However, a population PK study performed on hospitalised Alaskan natives has identified a longer $T_{½}$ and larger V_d compared with the American data after being adjusted for age and weight (123, 124). In summary, with the possible exception of Alaskan natives, there appear to be no important interethnic PK differences for aminoglycosides.

3.2.7.2 Glycopeptides – These antibacterials share similar physicochemical and PK properties with the aminoglycosides, although have a larger molecular size and a larger V_d (197, 262). The PK of teicoplanin is similar between hospitalised Japanese, Caucasian and African-American subjects (263), and vancomycin between hospitalised Japanese, Chinese and Caucasian subjects (264, 265).

3.2.7.3 β-lactams – This class of antibacterials are eliminated by glomerular filtration, renal tubular secretion and, to a lesser extent, hepatic metabolism. A higher AUC from zero to infinity ($AUC_{0-\infty}$) and slightly longer $T_{½}$ have been observed in a number of Asian and Hispanic subjects when compared with Caucasian data for cefdinir, cephradine, cefroxadine and flucloxacillin (125-134, 169, 170). A population PK study observed a 16% higher CL of doripenem in Hispanic/Latino study subjects compared with Caucasians (121), another study found no difference between Japanese and Caucasians (266). No significant PK differences have been identified for cephalexin, cefotetan, cefpodoxime, cefaclor, ampicillin, piperacillin/tazobactam and meropenem between various ethnicities after adjusted for weight (118, 125, 184, 192, 193, 267-281). In summary, there is little evidence for clinically significant interethnic differences in the PK of most β-lactams.

3.2.7.4 Fluoroquinolones – Ciprofloxacin is moderately lipophilic and undergoes hepatic metabolism, glomerular filtration and tubular secretion. It is a p-glycoprotein and active transport substrate in various drug disposition pathways (173, 175, 178, 282). After an administration of a single oral dose (500mg), the $AUC_{0-\infty}$ observed in Brazilian subjects was 1.5 to 4-fold smaller than that observed in German, Caucasian, US American, Indonesian and Chinese subjects (135-140). A significantly higher ciprofloxacin $AUC_{0-\infty}$ has been observed in Nigerian and Chinese compared with German subjects as well when administered intravenously (139, 141, 142). Interethnic PK differences have not been described for levofloxacin, gatifloxacin and moxifloxacin (161, 283-287).

3.2.7.5 Lincosamides – Clindamycin binds extensively to AGP and is predominantly metabolised in the liver (188, 288, 289). When given orally, Jordanians achieve a 3-4 fold greater $AUC_{0-\infty}$ than Chinese, Indians and Koreans, and 5-6 fold greater than US American and German volunteers after adjusted for dose (143-148).

3.2.7.6 Macrolides – Erythromycin and clarithromycin are both extensively metabolised by CYP3A4 and are highly AGP bound (189, 191, 290). They are substrates for various active carrier proteins such as OATP and p-glycoprotein (234). Yu *et al.* (119) compared the PK parameters of Korean and Caucasian healthy subjects for a single oral dose of erythromycin and found a 65% higher $AUC_{0-\infty}$ in Koreans. Interethnic PK differences have also been described for oral clarithromycin across a number of ethnicities including Caucasian, Iranian, Korean, Turkish, Norwegian, Pakistani and Thai (157-168, 291, 292). Azithromycin has been shown to have a greater $AUC_{0-\infty}$ and longer $T_{½}$ in Mexican, Thai, Chinese, Japanese and Jordanian subjects compared to equivalent Caucasians and US Americans (11, 149-154).

3.2.7.7 Nitroimidazoles – Tinidazole undergoes extensive liver metabolism, about 77% of the drug is cleared by the CYP3A4 enzyme (13). An oral dose of 1g showed higher CL, shorter $T_{½}$ and lower $AUC_{0-\infty}$ in Uighur people when compared with four other Asian groups – Han, Mongolian, Korean and Hui (13). Uighur people have closer genetic characteristics to Caucasians (293), which also has higher CYP3A4 metabolic activity.

3.2.7.8 Anti-mycobacterials – Isoniazid, dapsone and pyrazinamide undergo acetylation. Acetylation polymorphisms lead to significant interethnic PK differences and chances of toxicity for these anti-mycobacterials (195, 294, 295). Rifampicin undergoes extensive hepatic metabolism

and has been shown to have a significantly higher maximum concentration (C_{max}) and greater $AUC_{0-\infty}$ in Indonesians compared with British, Italian, Japanese, Indian and Mexican subjects (296-298).

3.2.7.9 Other antibacterials – Tigecycline is cleared predominantly by biliary excretion and glucuronidation (12). A meta-analysis has revealed that healthy and young black subjects have 33% higher CL than their Caucasian counterparts (122). A lower V_d at steady state and shorter $T_{½}$ was also reported in this study (122). However no significant PK differences were found between Japanese and Caucasians in another study (299). Daptomycin is cleared predominantly by glomerular filtration and exhibits no PK differences when compared between Taiwanese and Caucasian subjects (300). Renal excretion is the main route of elimination for colistin methanesulfonate sodium and linezolid, with no PK differences identified between Japanese and Caucasian subjects (301-303).

3.2.8 Clinical implications of interethnic PK differences

Most antibacterial dosing recommendations are based on studies performed in Caucasian healthy volunteers and do not account for interethnic differences in PK. However, due to the wide therapeutic range of most commonly used antibacterials, adverse drug effects are probably unlikely in short term treatment courses within recommended doses, provided the differences in patient weight have been taken into account. Exceptions may be for antibacterials with a narrow therapeutic range, dose-dependent adverse effects, or in specific patient groups that are more vulnerable to excessive drug exposure (eg. the elderly, renal failure) or those that are experiencing physiological changes that may already have increased drug exposure (eg. hypoalbuminaemia).

Our review has found that most of the antibacterial PK data has been described across Caucasian and Asian populations. However, other ethnic groups under these generalised categories may also display different PK. Examples of this include the 40% reduced $AUC_{0-\infty}$ of cefroxadine in Japanese compared with Korean subjects. Nonetheless, Caucasian subjects appear to generally have a lower $AUC_{0-\infty}$. This phenomenon is likely to a higher V_d resulting from higher concentrations of AGP and a larger TBW as well as a higher CL from higher levels of metabolism and/or renal excretion. These differences appear to be more prominent in lipophilic antibacterials.

On the other hand, ethnic groups of Asian origin achieve higher drug exposures. For time-dependent β-lactams, this effect is advantageous as can result in a higher percentage of time above MIC (Table 3.3) thereby increasing the likelihood of optimal antibacterial effects. However, this PK characteristic also means that these Asian ethnic groups are at greater risk of drug accumulation and potentially concentration-related adverse drug effects. Such adverse effects are unlikely in short-term antibacterial courses.

For antibacterials used over a long-term course, the clinical relevance of interethnic PK differences becomes more significant. Ethnicity-related prolonged and elevated drug exposures have been described for some antituberculosis agents (195, 241, 295).

Table 3.3 Percentage of time above MIC in a dosing interval for selected time-dependent antibacterials

Antibiotic	Population	Weight (kg)	DI (h)	V_d (L/kg)	$T_{½}$ (h)	F	$\%T_{>MIC}$[a]		
							MIC 0.25mg/L	MIC 0.5mg/L	MIC 1.0mg/L
Cephalosporins									
Cephradine 250mg (PO) (129)	Pakistani (n=12)	64	6	*33.80*	1.66	1[b]	100	100	80
Cephradine 250mg (PO) (130)	US American (n=20)	64-94	6	22.53	0.85	1[b]	77	63	49
Cefroxadine 500mg (PO) (132)	Japanese (n=5)	55-66	6	20.99	0.97	1[c]	100	90	74
Cefroxadine 500mg (PO) (133)	Caucasian (n=10)	68	6	*23.86*	0.9	1[c]	96	81	66
Macrolides									
Erythromycin 500mg (PO) (119)	Koreans (n=10)	63	6	*31.28*	1.75	0.3[d]	100	95	66
Erythromycin 500mg (PO) (119)	Caucasian (n=10)	77	6	*42.19*	1.48	0.3[d]	94	70	45

Abbreviations: DI, dose interval; V_d, volume of distribution; $T_{½}$, half-life; F, bioavailability; $T_{>MIC}$, duration of time above the minimum inhibitory concentration.

[a] $\%T_{>MIC}$ is worked out by the equation – $\ln\left(\frac{\text{Dose} \times \text{F}}{\text{Vd} \times \text{MIC}}\right) \times \frac{\text{T½}}{\ln(2)} \times \frac{100}{\text{DI}}$, modified from Turnidge's publication, 1998 (304)

[b] Rattie 1976 (130)

[c] Bergan. 1980 (133)

[d] Mather 1981 (172)

AGP concentrations can increase up to 5-fold in acute and chronic inflammatory diseases (305). Whether the interethnic difference in AGP concentration is diminished or amplified is unknown in such cases and remains largely unexplored.

Most of the differences identified in this review are from studies of orally administered drugs and highlight the importance of gastrointestinal absorption and first-pass metabolism in interethnic differences. Where oral administration of flucloxacillin was compared between Chinese and Caucasian subjects, the Chinese demonstrated a 33% longer $T_{½}$ (169, 170). However, this difference was not replicated when flucloxacillin was administered intravenously highlighting that the interethnic altered PK is driven by absorption and first pass metabolism differences (275, 306). Similar findings have been observed for ciprofloxacin (135, 139, 142), with these differences likely explained by transporter and metabolising enzyme polymorphisms (307).

Furthermore, many of the antibacterials that have exhibited interethnic PK differences have relatively low bioavailability. Ciprofloxacin, clindamycin, erythromycin, azithromycin, flucloxacillin and clarithromycin have bioavailabilities of 0.69, 0.53, 0.25, 0.37, 0.54 and 0.55 (147, 171, 191, 308, 309) respectively, comparing to amoxycillin, linezolid, levofloxacin and moxifloxacin of 0.77, 1.0, ≥0.99 and >0.91 (310-313), respectively. This supports the hypothesis that the presence of significant first pass metabolism and active transport mechanisms predominate in interethnic differences. Unfortunately, we could not find any research that specifically examined interethnic differences in antibacterial bioavailability to test this hypothesis.

There are still many questions that need to be answered for the identified PK differences – whether these differences will persist, increase or decrease as the dose escalates, duration of treatment lengthens, AGP concentrations increase or based on the severity of the patient's infection.

3.2.9 Limitations of data

Given that this area is not well recognised, there are a number of limitations with the available literature that has been used for this review. Many studies did not specify the ethnicity for individual subjects and in such cases the nationality was used. The results are further complicated by gender related PK differences. Furthermore, most of the studies are based on Asian and

Caucasian subjects and there is a lack of study performed in other common ethnic groups such as African, African/American, Hispanic and Australian Indigenous subjects.

The majority of studies included in this review are performed on healthy volunteers, and the clinical relevance of the interethnic difference identified in cases of severe pathology is unknown.

Most interethnic PK differences of antibacterials identified in this review are based on small PK and bioequivalence studies conducted in different ethnic groups. Differences in study methods, apparatus used, assaying techniques, methods and drug formulations may form a source of error, and because of the small sample size, none of the studies are sufficiently powered to advise on dose adjustment.

3.2.10 Conclusion

Interethnic PK differences exist for many antibacterials. Although there are limited direct comparative PK studies between ethnic groups, we found that upon comparing between different studies on healthy volunteers, significant differences in antibacterial exposure are likely for ciprofloxacin, macrolides, various cephalosporins, clindamycin and tinidazole. Body mass, active transport in the gut, metabolism, AGP binding and active processes for renal secretion appear to be the sources of these interethnic PK differences. On the other hand, other antibacterials including the carbapenems, most β-lactams, aminoglycosides, glycopeptides, most fluoroquinolones, linezolid and daptomycin, have little or no interethnic PK differences.

Until the clinical relevance of any antibacterial PK differences can be described, optimised antibacterial dosing should be considered imperative for the treatment of infections. PK studies of antibacterials in specific ethnic populations are suggested to procure doses that will maximise patient outcome, especially in the clinically vulnerable groups.

3.2.11 Funding information

Danny Tsai is funded by a PhD scholarship provided by the National Health and Medical Research Council of Australia (NHMRC); Australian Academy of Science's Douglas and Lola Douglas Scholarship; and receives support from the Alice Springs Specialists' Private Practice Trust Fund. Jason Roberts is funded in part by an Australian National Health and Medical Research Council Fellowship (APP1048652). Joshua Davis is funded by a Hepatitis B virus infection research grant provided by Gilead Sciences. All other authors declare no conflict of interest.

3.3 Conclusion

The systematic review performed in this Chapter has found that significant interethnic PK differences are likely for antibiotics with higher hepatic CL such as ciprofloxacin, macrolides, clindamycin, tinidazole and some cephalosporins. Interethnic PK differences are negligible for carbapenems, most β-lactams, aminoglycosides, glycopeptides, most fluoroquinolones, linezolid and daptomycin. Where interethnic differences were identified, subjects of Asian ethnicity generally manifested higher drug exposures when compared with the Caucasian counterparts. This difference is caused by a comparatively lower V_d and/or drug CL. The clinical relevance of these differences is unknown and warrants further research.

Chapter 4 Creatinine clearance of critically Ill Australian Indigenous patients

4.1 Synopsis

Drastic fluctuations observed in critical illnesses can lead to undesired pharmacological outcomes for antibiotics that are predominantly eliminated via the renal route. ARC can lead to sub-therapeutic antibiotic concentrations in the plasma, whereas AKI increases the risk of toxicity from higher concentrations. This Chapter investigates the prevalence of ARC in the critically ill Australian Indigenous compared against non-Indigenous patients, and assesses the accuracy of various CrCL equations. Factors which correlate with ARC in the critically ill Australian Indigenous patients are also described.

4.2 Submitted manuscript entitled "Augmented renal clearance is common in Australian Indigenous patients requiring ICU admission"

The manuscript entitled "Augmented renal clearance in Australian Indigenous patients requiring ICU admission" has been submitted for publication.

The co-authors contributed to the manuscript as follows: The conducting of this observational study was performed by the PhD Candidate, Danny Tsai under the supervision of Prof. Jason A. Roberts and A/Prof. Andrew Udy. Data collection was performed by the PhD Candidate, Danny Tsai under the guidance of Prof. Jason A Roberts and A/Prof. Andrew Udy. Data analysis and statistical analysis were predominantly performed by A/Prof. Andrew Udy. The PhD Candidate, Danny Tsai, took the leading role in manuscript preparation and writing. Prof. Jason A. Roberts and A/Prof. Andrew Udy took the leading role in critical review and revision of the manuscript. Critical review was performed by A/Prof. Andrew Udy, Dr Penelope Stewart, Dr Stephen Gourley, Ms Naomi Morick, Prof. Jeffrey Lipman and Prof. Jason A. Roberts.

The manuscript is presented as per the submitted manuscript. The figures and tables have been inserted into the text in locations close to where they were referred to in the text. The abbreviations and numberings of pages, figures and tables have been adjusted to comply with the format of this thesis. The references can be found in the references section of the thesis.

Augmented renal clearance in Australian Indigenous patients requiring ICU admission

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4.2.1 Abstract

Objectives ARC refers to the enhanced renal excretion of circulating solute commonly demonstrated in numerous critically ill sub-groups. This study aimed to describe the prevalence of ARC in critically ill Australian Indigenous patients and explore the accuracy of commonly employed mathematical estimates of glomerular filtration.

Design Single-centre, prospective, observational study.

Setting ICU, Alice Springs Hospital, Central Australia.

Participants Critically ill adult Australian Indigenous and non-Indigenous patients with a urinary catheter *in situ*. Exclusion– anuria, pregnancy or the requirement for renal replacement therapy.

Main outcome measures Daily eight-hour $CrCL_m$ were collected throughout the ICU stay. ARC was defined by a $CrCL_m$ ≥130mL/min/1.73m^2. The Cockcroft-Gault and Chronic Kidney Disease Epidemiology Collaboration equations were also used to calculate mathematical estimates for comparison.

Results A total of 131 patients were recruited (97 Indigenous, 34 non-Indigenous) and 445 samples were collected. The median (range) $CrCL_m$ was 93.0 (5.14-205.2) and 90.4 (18.7-206.8) mL/min/1.73m^2 in Indigenous and non-Indigenous patients, respectively. Thirty-one of 97 (32.0%) Indigenous patients manifested ARC, compared to 7 of 34 (20.6%) non-Indigenous patients (p=0.21). Throughout the ICU stay, ARC was detected more frequently in Indigenous patients (24.7% vs 12.8% of samples, p<0.01). Younger age, major surgery, higher baseline renal function and an absence of diabetes were all associated with ARC. Both mathematical estimates manifest poor accuracy.

Conclusions ARC was highly prevalent in critically ill Indigenous patients, which places them at significant risk of underdosing with renally excreted drugs. $CrCL_m$ should be obtained wherever possible to ensure accurate dosing.

4.2.2 Introduction

Fluctuation in renal function is commonly observed in critically ill patients (64, 314), and can lead to detrimental clinical outcomes. An acute reduction in renal function, commonly referred to as AKI, is a form of end-organ dysfunction which is associated with a worse prognosis (315). From a pharmacological perspective, it leads to accumulation of renally eliminated drugs and increased risk of toxicity. On the other hand, compelling data over the past decade describes a phenomenon in critical illness termed ARC, which is characterised by an increase in renal solute excretion (64).

The prevalence of ARC is reported between 30-65% in those with normal SCr (102). ARC is of particular interest, as it is associated with low serum concentrations for renally eliminated drugs (69, 77, 316, 317). Commonly used antibiotics in the ICU such as beta-lactams and glycopeptides are susceptible to such an effect, resulting in sub-therapeutic drug concentrations (317-319) and potentially worse clinical outcomes (320).

Critically ill Australian Indigenous patients with sepsis are a major health concern, with high morbidity and mortality rates (29). They are generally younger and have greater sickness severity (321). However, the prevalence of ARC has not been described in this population, although Indigenous Australians are reported to have 30% fewer nephrons as compared with their non-Indigenous counterparts (44). This is theorised to be a leading cause of the high prevalence of chronic kidney disease (CKD) in this population, and may impact the development of ARC.

In addition, numerous methods to determine the glomerular filtration rate (GFR) are available. Over the last decade various mathematical equations to estimate GFR (eGFR) have been widely implemented, despite concerns about their application in specific populations (322, 323). Indeed, a recent study has suggested the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation manifests the greatest accuracy in non-critically ill Australian Indigenous patients (324), although no data are availble for this group in the ICU.

Therefore the aims of this study were to (1) describe the prevalence of ARC in critically ill Australian Indigenous patients, (2) identify risk factors for ARC in this group and (3) study the accuracy of various existing eGFR equations.

4.2.3 Participants and methods

This was a prospective, observational cohort study of critically ill Australian Indigenous and non-Indigenous patients admitted to a general 10-bed ICU in Alice Springs Hospital, Australia. Approximately 85-90% of patients admitted to this hospital are Indigenous. Common characteristics of patients admitted to this ICU include sepsis, major trauma, exacerbation of heart failure, multiple medical complications (eg. cardiovascular, renal, hepatic, pancreatic and respiratory), alcohol related illnesses, and major surgery. Patients who are not routinely admitted include those requiring specialised surgery (eg. complex neurosurgery, cardiothoracic, head and neck, complex vascular surgery and organ transplantation), specialised medical services (eg. extra-corporeal membrane oxygenation, plasmapheresis and induction of chemotherapy) and those with spinal, head or pelvic injuries requiring specialised interventions. Ethical approval was granted by the local (Central Australian Human Research Ethics Committee, approval code HREC-15-309) and university (the University of Queensland Human Research Ethics Committee, approval code 2015000820) ethics committees.

4.2.3.1 Study population

The inclusion criteria were: (1) ≥18 years of age; (2) admitted to ICU; (3) an indwelling urinary catheter *in situ;* and (4) expected ICU stay for ≥24 hours. The exclusion criteria were (1) anuria; (2) requiring haemodialysis or continuous renal replacement therapy (CRRT); (3) pregnancy; (4) treating clinician considered the patient unsuitable for enrolment; and (5) participant chooses to opt out.

4.2.3.2 Study protocol

All patients were screened upon ICU admission. In those meeting the inclusion criteria, and none of the exclusion criteria, the total amount of urine excreted between 3 am and 11 am everyday was collected via the urinary catheter and sent to the local hospital pathology laboratory. The volume of urine and exact duration of urine collection were recorded. The creatinine concentration in the urine sample was assayed using the VITROS® CREA slide method with the Vitros fusion 5.1 analyser.

Demographic and clinical data collected include age, ethnicity, gender, height, weight, diabetes status, baseline SCr, baseline glomerular filtration rate according to the CKD-EPI equation ($eGFR_{CKD-EPI}$), 24-hour fluid balance, inotrope usage, APACHE II score, SOFA score, length of ICU and hospital stay, and admission diagnosis.

4.2.3.3 Calculation of $CrCL_m$ and eGFR/CrCL

CrCL was both measured ($CrCL_m$) and calculated using the Cockcroft-Gault equation ($CrCL_{CG}$). eGFR was also calculated using the CKD-EPI equation. Table 1 describes each method in detail. The SCr used in these calculations was extracted from the routine laboratory test performed between 5 am and 6 am on each sampling day. All values were normalised to a body surface area of $1.73m^2$.

4.2.3.4 Data analysis

ARC was defined as a $CrCL_m \geq 130mL/min/1.73m^2$ as it is correlated with sub-therapeutic antibiotic concentrations when conventional doses are used (64, 69). Different levels of renal dysfunction were categorised in accordance with the RIFLE criteria (325). Risk of AKI (rAKI) was defined as a 1.5 to <2 x increase from baseline SCr; AKI was defined as 2 to <3 x increase from baseline SCr; and acute renal failure (ARF) was defined as ≥3 x increase from baseline SCr or SCr >354 μmol/L with an acute rise of >44 μmol/L. Where a baseline SCr was not available, this was 'back-calculated' using the CKD-EPI equation. The prevalence (based on the number of patients who met these criteria on at least one occasion during the ICU stay) and frequency (based on the number of samples where these criteria were met) of ARC, rAKI, AKI and ARF were compared between Indigenous and non-Indigenous patients. Demographic and clinical data associated with ARC in Indigenous patients were also assessed.

Table 4.1. Mathematical equations used to calculate eGFR/CrCL

Name of equation	Mathematical formula	Notes
$CrCL_m$	(UCr/SCr) x (V_{Ur}/T x 60) x 1.73 / BSA	UCr is urine creatinine, (μmol/L) SCr is serum creatinine (μmol /L) V_{Ur} is urine volume (L) T is time (h) BSA is body surface area (m^2)
$CrCL_{CG}$	(140- age) x (TBW or LBW) [x 0.85 for females] / (SCr x 0.813) x 1.73/BSA	Age (yr) TBW is total body weight (kg) LBW is lean body weight (kg)
$eGFR_{CKD-EPI}$	141 x minimum(SCr x 0.0113/k, 1)$^{\alpha}$ x maximum(SCr x 0.0113/k, 1)$^{-1.209}$ x 0.993^{Age} [x 1.018 for female]	k is 0.7 for female, 0.9 for male $^{\alpha}$ is -0.329 for female, -0.411 for male

Abbreviation: $CrCL_m$, measured creatinine clearance; $CrCL_{CG}$, creatinine clearance calculated by the Cockcroft-Gault equation; $eGFR_{CKD-EPI}$, estimated glomerular filtration rate calculated by the Chronic Kidney Disease-Epidemiology collaboration equation.

All creatinine clearance/estimated glomerular filtration are represented in mL/min/1.73m^2

4.2.3.5 Statistical analysis

Data were analysed using SPSS 23.0 for Windows (SPSS, Chicago, IL). Continuous data are presented as the median (interquartile range) or mean (standard deviation), and categorical data presented as counts (%), as appropriate. Between patient differences were assessed using a Student's T-test, Mann-Whitney U-test, or Chi-squared test. Bland-Altman plots were used to assess the precision and bias of different mathematical equations using $CrCL_m$ as the reference. These mathematical equations include $eGFR_{CKD-EPI}$ and $CrCL_{CG}$ calculated using total body weight (TBW) and lean body weight using the James, Boer and Hume formulae (LBW_J, LBW_B and LBW_H, respectively) (326-328). A *p*-value of <0.05 was considered as statistically significant.

4.2.4 Results

Study recruitment was conducted over the 5-month period 1st June to 31st October 2015. The process for patient enrolment is presented in Figure 4.1. A total of 131 patients (97 Indigenous and 34 non-Indigenous) were included, providing 445 urine samples. Demographic and clinical data are presented in Table 4.2. Indigenous and non-Indigenous patients provided a similar number of urinary collections (median of 2 (1-4) per Indigenous patient, and 2 (1-5) per non-Indigenous patient). The Indigenous patient group had more males, was significantly younger and had a higher prevalence of sepsis and diabetes.

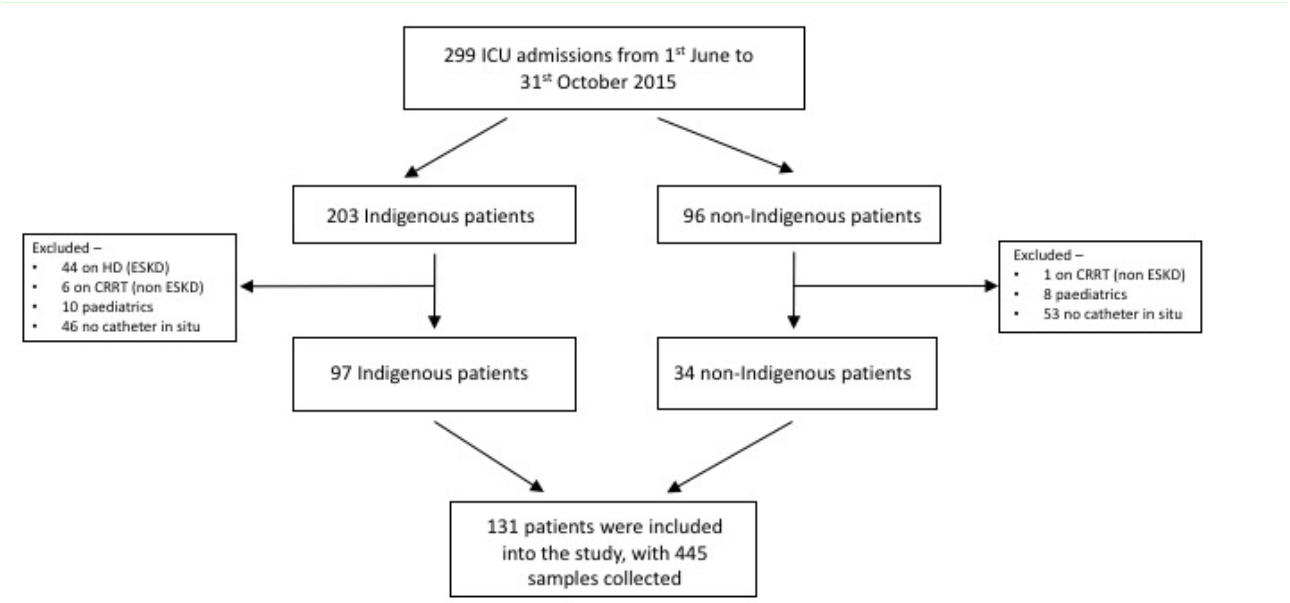

Figure 4.1 Participant inclusion processes

Abbreviation: ICU, intensive care unit; HD, haemodialysis; CRRT, continuous renal replacement therapy; ESKD, end stage kidney disease

4.2.4.1 Prevalence and frequency of ARC rAKI, AKI and ARF

The prevalence of ARC, rAKI, AKI and ARF are presented in Table 4.3. A higher rate of ARC was observed in the Indigenous group, although this was not statistically significant (p=0.21). The frequency (per urinary sample) of ARC, rAKI, AKI and ARF are presented in Table 4.4. There were significantly more occasions of ARC in the Indigenous patient group (p<0.01). Twenty-nine of the 66 (43.9%) Indigenous patients admitted with baseline $eGFR_{CKD\text{-}EPI}$ >90mL/min/1.73m^2 manifested ARC during their ICU stay.

4.2.4.2 Determinants of ARC in Indigenous patients and assessment of accuracy of eGFR equations

A comparison of demographic and clinical characteristics between Indigenous patients with and without ARC is presented in Table 4.5. Indigenous patients who developed ARC were significantly younger, had a higher baseline $eGFR_{CKD\text{-}EPI}$, were more likely to have had major surgery and less likely to have diabetes.

Statistical comparison of various mathematical equations versus $CrCL_m$ for the first sampling occasions is presented in Table 4.6. All tested equations show poor agreement with $CrCL_m$. Figure 4.2 presents the Bland-Altman plots which compare the $CrCL_m$ against $eGFR_{CKD\text{-}EPI}$ and $CrCL_{CG}$ calculated from TBW, LBW_J, LBW_B and LBW_H. Overall, $CrCL_{CG}$ calculated with TBW showed the lowest bias and highest precision. However, $eGFR_{CKD\text{-}EPI}$ has the narrowest 95% confidence interval for limits of agreement in the Bland-Altman analysis.

Table 4.2 Demographic and clinical information

Variable	All (n=131)	Indigenous (n=97)	Non-Indigenous (n=34)	*p*-value
Age, years[#]	*50 [18]*	*47 [17]*	*61 [18]*	*<0.01*[*]
Male gender	*60 (46)*	*38 (39)*	*21 (62)*	*0.02*[†]
Anthropometrics[#]				
Weight (kg)	81 [28]	79 [27]	86 [32]	0.24[*]
Height (m)	*1.67 [0.09]*	*1.66 [0.08]*	*1.70 [0.08]*	*0.02*[*]
BSA (m^2)	1.87 [0.28]	1.85 [0.27]	1.94 [0.31]	0.10[*]
Admission category				
Sepsis	*67 (51.1)*	*59 (60.8)*	*8 (23.5)*	*<0.01*[†]
Trauma	16 (12.2)	10 (10.3)	6 (17.6)	0.28[†]
Major surgery	*26 (19.8)*	*12 (12.4)*	*14 (41.2)*	*<0.01*[†]
Diabetes	*57 (43.5)*	*49 (50.5)*	*8 (23.5)*	*<0.01*[†]
Baseline $eGFR_{CKD-EPI}$				
>90 mL/min/1.73m^2	86 (65.5)	66 (68.0)	20 (58.8)	0.33[†]
61-90 mL/min/1.73m^2	*23 (17.6)*	*11 (11.3)*	*12 (35.3)*	*<0.01*[†]
30-60 mL/min/1.73m^2	15 (11.5)	13 (13.4)	2 (13.3)	0.35[†]
<30 mL/min/1.73m^2	7 (5.3)	7 (7.2)	0 (0.0)	0.19[†]
Baseline $eGFR_{CKD-EPI}$ (mL/min/1.73m^2)	99 [81-115]	102 [74-118]	93 [83-108]	0.21
APACHE II score on admission	22 [18-27]	22 [18-27]	21 [18-30]	0.72
SOFA score on admission	6 [4-10]	7 [4-10]	6 [4-9]	0.50
Baseline SCr (µmol/L)	66 [55-87]	65 [55-93]	70 [60-77]	0.79
ICU length of stay (days)	4 [2-6]	4.0 [2.0-6.5]	4.5 [3.0-6.3]	0.49
Hospital length of stay (days)	9 [5-19]	9 [5.0-17]	8 [5-23]	0.98
ICU mortality	4 (3)	2 (2)	2 (6)	0.28[†]
Hospital mortality	8 (6)	5 (5)	3 (9)	0.43[†]

Abbreviation: BSA, body surface area; $eGFR_{CKD-EPI}$, estimated glomerular filtration rates calculated from the Chronic Kidney Disease Epidemiology collaboration equation; APACHE II score, Acute Physiology and Chronic Health Evaluation II score; SOFA score, Sequential Organ Failure Assessment score; SCr, serum creatinine concentration; ICU, intensive care unit

Data is presented in median [interquartile range] and n (%); *p*-values were obtained from Mann Whitney U-test unless otherwise stated

[#]Data is presented in mean [standard deviation]

[*]*p*-values were obtained from Student's T-test

[†]*p*-values were obtained from Chi-squared test

Table 4.3 Prevalence of ARC, rAKI, AKI and ARF

	All (n=131)	Indigenous (n=97)	Non-indigenous (n=34)	*p*-value
ARC (%)	38 (29.0)	31 (32.0)	7 (20.6)	0.21
ARF	11 (8.4)	9 (9.3)	2 (5.9)	0.54
AKI	13 (9.9)	11 (11.3)	2 (5.9)	0.36
rAKI	19 (14.5)	14 (14.4)	5 (14.7)	0.97

Abbreviation: ARC, augmented renal clearance; ARF, acute renal failure; AKI, acute kidney injury; rAKI, risk of AKI

p-values were obtained from Chi-squared test

Table 4.4 Frequency of ARC, rAKI, AKI and ARF

	All samples (n = 445)	Indigenous (n = 328)	Non-Indigenous (n = 117)	*p*-value
ARC (%)	96 (21.6)	81 (24.7)	15 (12.8)	<0.01
ARF	24 (5.4)	20 (6.1)	4 (3.4)	0.27
AKI	31 (7.0)	24 (7.3)	7 (6.0)	0.63
rAKI	35 (7.9)	28 (8.5)	7 (6.0)	0.38

Abbreviation: ARC, augmented renal clearance; ARF, acute renal failure; AKI, acute kidney injury; rAKI, risk of AKI

p-value was obtained from Chi-squared test

Table 4.5 Comparison of Indigenous patients with and without ARC

Variable	All (n=97)	ARC (n=31)	No ARC (n=66)	*p*-value
Age (y)[#]	*46.8 [16.9]*	*37.3 [14.8]*	*51.3 [16.0]*	*<0.01*[*]
Male gender	38 (39.2)	16 (51.6)	22 (33.3)	0.09[†]
Weight (kg)[#]	79.0 [26.7]	73.5 [20.0]	81.6 [29.2]	0.17[*]
Diabetes	*49 (50.5)*	*9 (29.0)*	*40 (60.6)*	*<0.01*[†]
Sepsis admission	59 (60.8)	18 (58.1)	41 (62.1)	0.70[†]
Trauma admission	10 (10.3)	5 (16.1)	5 (7.6)	0.28[†]
Major surgery	*12 (12.4)*	*8 (25.8)*	*4 (6.1)*	*0.02*[†]
APACHE II Score on admission	22 [18-27]	23 [19-27]	22 [18-26]	0.28
SOFA Score on admission	7 [4-10]	8 [5-11]	6 [3-10]	0.29
Baseline SCr (µmol/L)	*65 [55-93]*	*59 [50-66]*	*71 [59-130]*	*<0.01*
Baseline $eGFR_{CKD-EPI}$ ($mL/min/1.73m^2$)	*102 [74.2-118]*	*117 [107-129]*	*94 [45-113]*	*<0.01*
Baseline $eGFR_{CKD-EPI}$				
> 90ml/min/1.73m²	*66 (68.0)*	*29 (93.5)*	*37 (56.1)*	*<0.01*[†]
61-90 ml/min/1.73m²	11 (11.3)	2 (6.5)	9 (13.6)	0.49[†]
30-60 ml/min/1.73m²	*13 (13.4)*	*0 (0.0)*	*13 (19.7)*	*<0.01*[†]
< 30 ml/min/1.73m²	7 (7.2)	0 (0.0)	7 (10.6)	0.09[†]
ICU length of stay (days)	4.0 [2.0-6.5]	4.0 [2.0-8.0]	4.0 [2.8-6.3]	0.82
Hospital length of stay (days)	9.0 [5.0-16.5]	9.0 [6.0-13.0]	10.0 [5.0-17.8]	0.61
ICU mortality	2 (2.1)	0 (0.0)	2 (3.0)	1.00[†]
Hospital mortality	5 (5.2)	0 (0.0)	5 (7.6)	0.17[†]

Abbreviation: ARC, absolute augmented renal clearance; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Sequential Assessment; SCr, serum creatinine concentration; $eGFR_{CKD-EPI}$, estimated glomerular filtration rate calculated from the Chronic Kidney Disease – Epidemiology Collaboration equation; ICU, intensive care unit

Data is presented in median [interquartile range] or n (%) unless otherwise stated; *p*-values were obtained from Mann Whitney U-test unless otherwise stated

Data in italics are statistically significant

[#]Data is presented in mean [standard deviation]

[*]*p*-values were obtained from Student's T-test

[†]*p*-values were obtained from Chi-squared test

Table 4.6. Comparison of different methods of determining CrCL for the first occasion of sampling

	Reference Method	Comparator	Bias	Precision	95% LOA - Lower	95% LOA - Upper
Non-indigenous						
	$CrCL_m$	$eGFR_{CKD-EPI}$	16.3	29.6	-41.6	74.3
	$CrCL_m$	$CrCL_{CG}$ (TBW)	8.2	43.1	-76.2	92.7
	$CrCL_m$	$CrCL_{CG}$ (LBW_J)	39.7	33.1	-25.2	104.7
	$CrCL_m$	$CrCL_{CG}$ (LBW_B)	26.5	37.6	-47.1	100.2
	$CrCL_m$	$CrCL_{CG}$ (LBW_H)	39.4	32.8	-25.0	103.7
Indigenous						
	$CrCL_m$	$eGFR_{CKD-EPI}$	10.0	29.6	-48.1	68.1
	$CrCL_m$	$CrCL_{CG}$ (TBW)	-3.2	41.4	-84.4	78.0
	$CrCL_m$	$CrCL_{CG}$ (LBW_J)	27.6	31.1	-33.3	88.5
	$CrCL_m$	$CrCL_{CG}$ (LBW_B)	10.3	34.1	-56.4	77.1
	$CrCL_m$	$CrCL_{CG}$ (LBW_H)	27.4	32.9	-37.0	91.8

Abbreviation: LOA, Limits of Agreement; $CrCL_m$, measured creatinine clearance; $eGFR_{CKD-EPI}$, estimated glomerular filtration rate calculated from the Chronic Kidney Disease – Epidemiology collaboration equation; $CrCL_{CG}$ (TBW), creatinine clearance calculated from the Cockcroft-Gault equation based on patient's today body weight; $CrCL_{CG}$ (LBW_J /LBW_B/LBW_H), creatinine clearance calculated from the Cockcroft-Gault equation based on patient's lean body weight, using James, Boer and Hume's formula, respectively

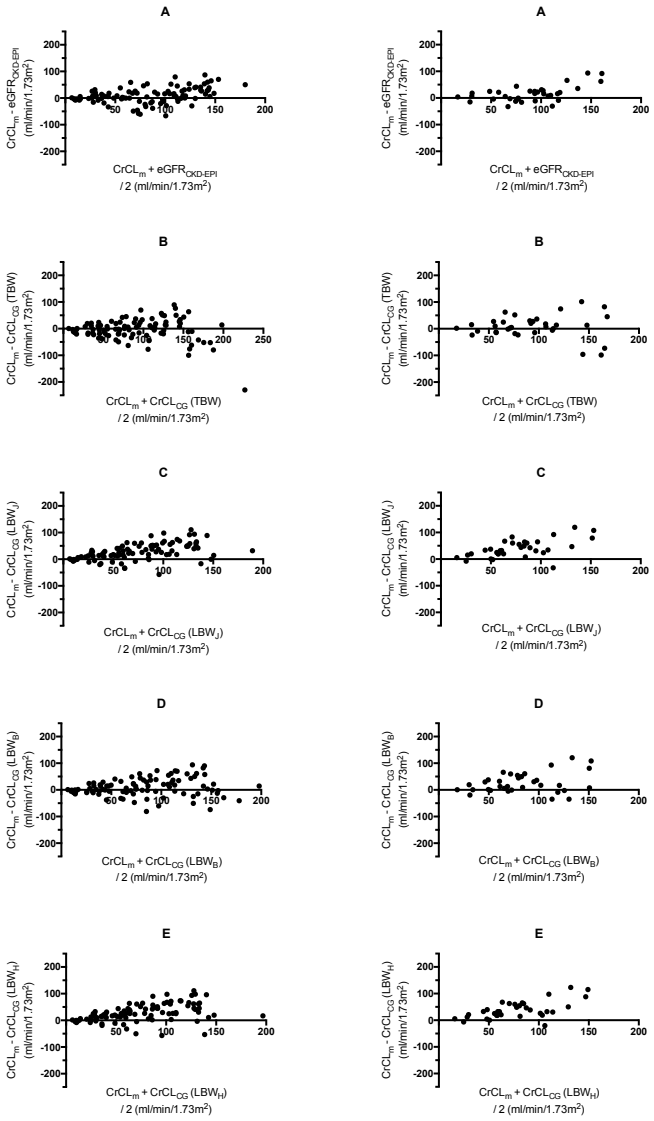

Figure 4.2. Bland-Altman plots for comparison of measured CrCL with A) $eGFR_{CKD-EPI}$, B) $CrCL_{CG}$ (TBW), C) $CrCL_{CG}$ (LBW_J); $CrCL_{CG}$ (LBW_B), D) $CrCL_{CG}$ (LBW_J) and E) $CrCL_{CG}$ (LBW_H), on the first sampling day.

Abbreviation: $CrCL_m$, measured creatinine clearance; $eGFR_{CKD-EPI}$, estimated glomerular filtration rate calculated with the Chronic Kidney Disease – Epidemiology collaboration equation; $CrCL_{CG}$ (TBW), creatinine clearance calculated with the Cockcroft-Gault equation based on total body weight; $CrCL_{CG}$ (LBW_J), creatinine clearance calculated with the Cockcroft-Gault equation based on lean body weight (James equation); $CrCL_{CG}$ (LBW_B), creatinine clearance calculated with the Cockcroft-Gault equation based on lean body weight (Boer equation); $CrCL_{CG}$ (LBW_H), creatinine clearance calculated with the Cockcroft-Gault equation based on lean body weight (Hume equation)

4.2.5 Discussion

4.2.5.1 Key Findings

To our knowledge, this is the first study to describe $CrCL_m$ in critically ill Australian Indigenous patients. We observed a high prevalence of ARC in this group; thirty-one of 97 (32.0%) Indigenous patients manifested ARC, despite the fact this cohort is known to have a significantly fewer nephrons. Furthermore, we identified significant associations between ARC and younger age, major surgery, the absence of diabetes, and a baseline $eGFR_{CKD\text{-}EPI}$ >90mL/min/1.73m^2. All mathematical equations exhibited poor accuracy in comparison to $CrCL_m$, suggesting limited utility in the critical care setting.

4.2.5.2 Relationship with Previous Studies

The prevalence of ARC detected in the Indigenous group is consistent with that reported in other critically ill populations (30-65%), albeit at the lower range (64). A probable explanation is that patients with CKD or high SCr were excluded in most other studies exploring the epidemiology of ARC. Approximately 2% of the Australian Indigenous population self-report to have CKD, which is 10 times more than non-Indigenous Australians (329). The unusually high prevalence of CKD in this unique population may further contribute to the relatively low prevalence of ARC reported in our data.

Numerous risk factors for ARC have been identified, including: male gender, younger age, multiple trauma, mechanical ventilation, sepsis and use of inotropes (318, 320). In our study, we found a significant association between ARC and younger age, major surgery, the absence of diabetes, and baseline $eGFR_{CKD\text{-}EPI}$ >90mL/min/1.73m^2. The exceptionally high prevalence of diabetes in the Australian Indigenous population is likely to explain its inverse association with ARC, as poorly controlled diabetes is commonly associated with CKD. Of note, critically ill Indigenous patients in the Australian ICU setting are 10-15 years younger compared with non-Indigenous comparators (321), and was a consistent finding in our study.

The limited accuracy of the eGFR equations in comparison to $CrCL_m$ is in agreement with previously published data (330). The mathematical equations are heavily dependent on SCr, which does not immediately reflect the transient fluctuations of renal function observed in critical illness.

The precision and bias are similar between most equations, although $CrCL_{CG}$ marginally manifests the lowest bias and highest precision. However, a recent study suggested $eGFR_{CKD\text{-}EPI}$ as the most accurate formula for optimising vancomycin therapy in critically ill patients, as compared with $CrCL_{CG}$ and modification of diet in renal disease (MDRD) eGFR (67). Of note, $eGFR_{CKD\text{-}EPI}$ is likely to underestimate the GFR in critically ill patients and its accuracy worsens significantly with higher CrCL (67, 102, 331).

4.2.5.3 Study implications

ARC was identified in approximately 1 in 3 Indigenous patients, reminding the clinician that any wholesale assumptions about renal function in this group are likely to be flawed. As such, obtaining routine $CrCL_m$ for all critically ill Indigenous patients without overt AKI or CKD, appears warranted, in order to ensure the clinician has accurate knowledge of renal function.

Traditionally, a reduction in renal function (identified by a rise in SCr) in the setting of critical illness, triggers dose adjustment for renally eliminated drugs according to recommendations from available evidence-based guidelines. However, a SCr in the normal laboratory range usually does not lead to further investigation of its pharmacological implications. Indeed, most Australian ICU laboratory reporting systems currently provide eGFR results greater than 90mL/min/1.73m^2 just as '>90mL/min/1.73m^2', indicating the patient has 'adequate' renal function. However, as described in this study, the prevalence of ARC was not insignificant in critically ill Indigenous patients. This information would not be routinely reported in a clinical setting, with some $CrCL_m$ being as high as 205 mL/min/1.73m^2, which clearly mandates differing dosing requirements to 90 mL/min/1.73m^2.

Such findings require greater attention in clinical practice as the presence of ARC has been correlated with sub-therapeutic levels of drugs that are predominantly renally eliminated, which encompasses most commonly used antibiotics in the ICU (77, 317). ARC has also been reported in studies describing the PK of commonly used antibiotics in critically ill Australian Indigenous patients with severe sepsis, where significantly higher doses and/or dosing frequencies are recommended (332, 333). Such dose optimisation should be considered imperative, as the presence of ARC in critically ill patients requiring antibiotics has been correlated with worse clinical outcomes (320). Nonetheless, a consensus has yet to be reached regarding the best approach to antibiotic dosing in the presence of ARC.

4.2.5.4 Strengths and Limitations

There are some limitations to this study. $CrCL_m$ includes creatinine excreted by tubular secretion, creating a source of error when compared with actual GFR, especially for patients with low $CrCL_m$ (102). While it would have been ideal to use an exogenous filtration marker (such as inulin or radionucleotide analogues), the application of such is not practical in the ICU. Furthermore, $CrCL_m$ is widely recommended for use in critical illness (322, 334), and is often considered a surrogate of GFR in routine clinical practice.

The sample size in our study is not large enough to investigate further sub-groups or undertake longitudinal analyses. In this case, it may be that the difference in prevalence of ARC between Indigenous and non-Indigenous patients would reach statistical significance using a larger sample. In this fashion, our study still provides compelling observational data concerning renal function in critically ill Indigenous patients, representing an at-risk group for which there is a paucity of contemporary data. In particular, our study provides unique data comparing the accuracy of varying methods to estimate GFR in this setting.

Finally, as this is not a PK/PD study, alterations of PK or clinical outcomes due to the presence of ARC for patients requiring pharmacotherapy cannot be assessed. Importantly however, a large number of studies have previously established the association between ARC and sub-optimal drug exposure.

4.2.5.5 Future Studies

A large prospective multi-centre study is needed to clarify the relationship between the manifestation of ARC and clinical outcomes in critically ill Australian Indigenous patients requiring antimicrobial therapy. Furthermore, PK studies are also needed to describe optimal antimicrobial doses for different levels of ARC.

4.2.6 Conclusion

Critically ill Australian Indigenous patients have a high prevalence of ARC, leading to a significant risk of underdosing with renally excreted drugs. Risk factors of ARC in critically ill Indigenous patients include younger age, the absence of CKD, the absence of diabetes and recent major surgery. All mathematical equations tested demonstrated limited accuracy in comparison with $CrCL_m$, and hence urinary $CrCL_m$ should be obtained whenever ARC is suspected.

4.2.7 Acknowledgements

We would like to acknowledge the ICU team and nursing staff of Alice Springs Hospital for their support and assistance with sample collection and other relevant tasks for this study.

4.2.8 Funding

This work was supported by a PhD Scholarship provided by the National Health and Medical Research Council of Australia (D.T.); Scholarship provided by the Australian Academy of Science's Douglas and Lola Douglas (D.T.); Alice Springs Specialists' Private Practice Trust Fund (D.T.); and in part by the Australian National Health and Medical Research Council Fellowship (APP1048652 to J.A.R.). We also wish to acknowledge funding from the Australian National Health and Medical Research Council for Centre of Research Excellence (APP1099452).

4.2.9 Transparency declarations

All authors: none to declare.

4.3 Conclusion

This Chapter has described the high prevalence of ARC in critically ill Australian Indigenous patients. A numerically higher prevalence of ARC is observed when compared with the non-Indigenous patients, which was likely due to their younger age. The factors correlated with ARC include younger age, the absence of CKD, the absence of diabetes and recent major surgery. Since all tested CrCL equations manifested limited correlation with $CrCL_m$, urinary $CrCL_m$ should be obtained whenever ARC is suspected to optimise drug dosing. When obtaining $CrCL_m$ is not possible, $eGFR_{CKD\text{-}EPI}$ can be considered to estimate patient's renal function.

Chapter 5 Optimising meropenem dosing in critically ill Australian Indigenous patients with severe sepsis

5.1 Synopsis

Currently, there is no available PK data for meropenem in the critically ill Australian Indigenous patients. The aim of this Chapter was to describe the population PK of meropenem in severely septic Australian Indigenous patients in comparison to non-Indigenous patients. The Monte Carlo dosing simulations performed in this Chapter also provides a set of dosing recommendations for critically ill Australian Indigenous patients which aimed to optimise PK/PD target attainment.

5.2 Published manuscript entitled "Optimising meropenem dosing in critically ill Australian Indigenous patients with severe sepsis"

The manuscript entitled "Optimising meropenem dosing in critically ill Australian Indigenous patients with severe sepsis" has been published in *International Journal of Antimicrobial Agents*.

The co-authors contributed to the manuscript as follows: The conducting of this population PK study was performed by the PhD Candidate, Danny Tsai under the supervision of Prof. Jason A. Roberts. Data collection was performed by the PhD candidate, Danny Tsai under the guidance of Prof. Jason A Roberts. Drug assay was performed by Dr Steven Wallis and the PhD candidate Danny Tsai. The description of the drug assay methods in the manuscript was written by Dr Steven Wallis. PK modelling was performed by Prof. A Roberts. The PhD Candidate, Danny Tsai, took the leading role in manuscript preparation and writing. Prof. Jason A. Roberts took the leading role in critical review and revision of the manuscript. Critical review was performed by Dr Penelope Stewart, Dr Stephen Gourley, Dr Rajendra Goud, Dr Saliya Hewagama, Dr Sushena Krishnaswamy, Dr Steven Wallis, Prof. Jeffrey Lipman and Prof. Jason A. Roberts.

The manuscript is presented as per the accepted manuscript. The figures and tables have been inserted into the text in locations close to where they were referred to. The abbreviations and numberings of pages, figures and tables have been adjusted to comply with the format of this thesis. The references can be found in the references section of the thesis.

Optimising meropenem dosing in critically ill Australian Indigenous patients with severe sepsis

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5.2.1 Abstract

Objectives Currently there are no PK data to guide antibiotic dosing in critically ill Australian Indigenous patients with severe sepsis. This study aimed to determine whether the population PK of meropenem were different between critically ill Australian Indigenous and critically ill Caucasian patients.

Methods Serial plasma and urine samples as well as clinical and demographic data were collected over two dosing intervals from critically ill Australian Indigenous patients. Plasma meropenem concentrations were assayed by validated chromatography. Concentration-time data were analysed with data from a previous PK study in critically ill Caucasian patients using Pmetrics. The population PK model was subsequently used for Monte Carlo dosing simulations to describe optimal doses for these patients.

Results Six Indigenous and five Caucasian subjects were included. A two compartment model described the data adequately with meropenem CL and V_c described by CrCL and patient TBW respectively. Patient ethnicity was not supported as a covariate in the final model. Significant differences were observed for meropenem CL between the Indigenous and Caucasian groups, median 11.0 (range 3.0–14.1) vs 17.4 (4.3–30.3) L/h, $p< 0.01$, respectively. Standard dosing regimens (1g IV 8-hourly 30-min infusion) consistently achieved target exposures at the MIC breakpoint in the absence of ARC.

Conclusion No significant interethnic differences in meropenem PK between the Indigenous and Caucasian groups were detected and CrCL was found to be the strongest determinant of appropriate dosing regimens.

5.2.2 Introduction

Sepsis has been a major health issue in the Australian Indigenous population and is associated with a high morbidity and mortality rate (2, 4, 30). It remains one of the highest health concerns of which about 60% of deaths in the Indigenous patient population of the largest Central Australian remote hospital were related to infection, in comparison to 25% in the non-Indigenous patient population from 2000 to 2005. Fifty-six per cent of the infection-related deaths were attributed to bacterial sepsis (3).

Meropenem is a broad spectrum antibiotic commonly used in the ICU (335). Its PK/PD properties show a time dependent bacterial kill characteristic with a target of maintaining free drug concentration above the MIC for at least 40% of the dosing interval (>40%$fT_{>MIC}$). (336). However, significant changes in V_d) and drug CL observed in critically ill patients can alter the possibility of achieving this target (18). These PK changes are difficult to predict, especially in the absence of TDM.

Conventional dosing guidelines are usually followed in critically ill Indigenous patients, however, a recent systematic review suggested described PK differences between ethnicities for some antibiotics (337). Indeed, young and healthy Indigenous adults are reported to have 30% less nephrons than non-Indigenous comparators, as well as having a mean kidney volume which is 27% greater (44). From an anthropometrics perspective, the Australian Indigenous have lower body mass, higher central fat and slimmer limbs (338). Furthermore, they were shown to have similar allele frequency as South Asians for some cytochrome P450 enzymes (45). Whether these physiological differences affect meropenem PK in the acute setting is unknown. Currently there is no available data on the antibiotic PK of critically ill Indigenous patients in Australia.

This study aims to compare the population PK of meropenem in Australian Indigenous patients with severe sepsis and critically ill Caucasian patients with sepsis.

5.2.3 Materials and methods

5.2.3.1. Institution where this work was carried out

Department of Intensive Care Medicine, Alice Springs Hospital, Alice Springs, Northern Territory, Australia.

5.2.3.2 Setting

This was a prospective, observational cohort study investigating the PK of meropenem. Ethical approval was obtained from local (Central Australian Human Research Ethics Committee, approval code HREC-13-149) and university (The University of Queensland Human Research Ethics Committee, approval code 2013000904) Ethics Committees.

5.2.3.3 Study population

The inclusion criteria were: (1) Australian Indigenous; (2) ≥18 years of age; (3) confirmed or suspected severe sepsis within the previous 48 hours; (4) prescribed meropenem; and (5) an arterial line *in situ*. The exclusion criteria were (1) CrCL <15 mL/min; (2) requiring haemodialysis or CRRT; and (3) pregnancy.

5.2.3.4 Study protocol

The dose of meropenem (DBL Meropenem®; Hospira Australia, Melbourne, Australia) was determined by the treating clinicians and was made up in 100 mL sodium chloride 0.9% and infused intravenously over 30 minutes. Ten blood samples were collected in 2 mL lithium heparin tubes from the existing arterial line over one dosing interval at the following time-points 0, 15, 30, 45, 60, 90, 120, 180, 360 and 480 minutes from initiation of infusion. A second set of samples following the same regimen was obtained the next day. Demographics, clinical information, and routine laboratory test results performed on the study days were also collected.

5.2.3.5 Sample handling and storage

Blood samples were placed in a drug refrigerator at 2-8 °C immediately after sampling. Samples were then centrifuged at 5000 rpm for 6 minutes within 8 hours of collection. Both plasma and urine samples were aspirated into cryovials and stored in a freezer at -70 °C. Samples were packed with dry ice, and freighted to the Burns Trauma & Critical Care Research Centre, The University of Queensland for drug assay.

5.2.3.6 Drug assay

Plasma concentrations of meropenem were determined by validated high performance liquid chromatography with ultraviolet detection (HPLC-UV) on a Shimadzu Prominence instrument. Sample analysis was conducted in batches with calibration standards and quality controls in which batch acceptance criteria were applied. Before the chromatographic analysis was performed, acetonitrile was added to 100 μL aliquots of plasma combined with internal standard (cefotaxime) to precipitate proteins. Following centrifugation, the supernatant was isolated and washed with dichloromethane to remove acetonitrile and lipophilic components. Following centrifugation, the upper layer was isolated for chromatographic analysis.

For the chromatography, the stationary phase was a Waters XBridge C18 2.1 x 50 mm column. The mobile phase was 4% acetonitrile / 96% 50 mM phosphate buffer at pH 2.5 delivered isocratically. The eluent was monitored at 304 nm. For sample validation, the calibration curve was linear with a weighing of $1/x^2$ over the range 0.2 to 100 mg/L. The precision and accuracy at the LLOQs were ≤5.9%. The assay was validated against matrix effects (precision and accuracy within 4% at high and low concentrations). The assay's precision and accuracy was determined at both within-day and between-day, and was within 6.5% at all three concentrations tested.

5.2.3.7 Population PK modelling

Data collected from 6 Indigenous patients' plasma samples were combined with 5 critically ill Caucasian patients from a previously published study with a similar study protocol including concentration-time data that were available to us, and so that ethnicity of the patient group could be tested whether it significantly influences meropenem PK as a covariate (339). A two-compartment

model was developed with Nonparametric Adaptive Grid (NPAG) algorithm using the Pmetrics® software package (340) for R® (version 3.2.2). Demographic and clinical data (age, ethnicity, sex, weight, CrCL, SOFA score, serum albumin, SCr and vasopressor therapy requirement) which may influence meropenem PK were tested for inclusion into the model as covariates. If the covariate inclusion resulted in an improvement in the log likelihood (p<0.05) and/or improved the goodness of fit plots, they were included in the model.

5.2.3.8 Model diagnostics

Model evaluation was assessed by visual assessment of goodness of fit of the observed-predicted plots and the coefficient of determination of the linear regression of the observed-predicted values (r^2 close to 1, intercept close to 0) from each run. The predictive performance was assessed on mean prediction error (bias) and the mean biased adjusted squared prediction error (imprecision) of the population and individual posterior predictions.

5.2.3.9 Dosing simulations

Probability of target attainment (PTA) was obtained from Monte Carlo simulation (n = 1000) in Pmetrics®. This assesses the likelihood of achieving 40% $fT_{>MIC}$ (considering 2% protein binding) over the first 24 hours of various dosing regimens and levels of CrCL for MIC values between 0.125 to 32 mg/L. Results were then used to make dosing recommendations based on the lowest dosing regimen that still achieved 90% PTA.

5.2.3.10 Statistical analysis

Continuous data were presented in median (range) and categorical data presented as counts (%). Statistical difference was assessed for the demographic data and PK parameters between the Indigenous and Caucasian population by using Pearson's Chi-squared and Mann-Whitney U-tests in R®. A p value of <0.05 was considered as statistically significant.

5.2.4 Results

Six Indigenous and 5 Caucasian patients were included providing 216 plasma samples for analysis. The demographics and clinical information are presented in Table 4.1. In general, the Indigenous group was younger, had a lower CrCL and had more patients requiring vasopressor therapy, though not statistically significant. They also have significantly higher SOFA scores.

5.2.4.1 Population PK model building

A two compartment model was found to describe the data adequately, with CrCL and patient's actual body weight being the only tested covariates which significantly improved the PK model. The final model is described as:

$$\mathrm{TVCL} = \mathrm{CL}\,\mathrm{x}\frac{\mathrm{CrCL}}{100}$$

$$\mathrm{TVVc} = \mathrm{Vc}\,\mathrm{x}\left(\frac{\mathrm{TBW}}{80}\right)^{0.75}$$

Where TVCL is the typical value of meropenem CL in the population (includes Indigenous and non-Indigenous patients), CL is the population parameter estimate of meropenem CL, TVVc is the typical value of V_c, V_c is the population parameter estimate of volume of the central compartment and TBW is total body weight. The goodness of fit for the individual and population predicted vs observed plots were acceptable (Figure 4.1).

The combined and comparative population PK parameter estimates from two-compartment model are also presented in Table 4.1. CL was significantly lower for the Indigenous patients compared with the Caucasian patients (*p*-value 0.004). However, this difference in CL was well described by CrCL but not ethnicity, hence ethnicity was not included as a covariate in the final model.

Table 5.1 Demographics, clinical data and PK parameter estimates from two-compartment model

	Total (n=11)	**Indigenous** (n=6)	**Caucasian** (n=5)	**p value**[#]
Age (y)	48 (22-76)	45 (22-76)	55 (29-69)	0.329
Female	6 (55)	4 (67)	2 (40)	0.782[†]
Weight (kg)	80 (60-110)	73 (60-104)	80.0 (60-110)	0.519
Height (cm)	170 (157-185)	167.5 (157-176)	170 (165-185)	0.231
BMI (kg/m^2)	26.6 (23.7-34.1)	26.4 (23.7-34.1)	26.6 (20.8-30.3)	1.000
SrCr (μmol/L)	73 (37-301)	76 (37-301)	73 (43-109)	1.000
CrCL (mL/min)	105.7 (15.5-164.0)	98.2 (15.5-164.0)	105.7 (19.6-144.3)	0.662
Albumin (g/L)	32 (20-39)	32 (26-39)	28 (18-37)	0.782
Vasopressors	8 (73)	6 (100)	2 (40)	0.122[†]
SOFA score	10 (2-15)	11 (10-15)	3 (2-11)	***0.007***
V_c (L)	13.6 (9.7-18.4)	11.0 (9.8-17.0)	15.3 (9.7-18.4)	0.082
CL (L/h)	14.1 (3.0-30.3)	11.0 (3.0-14.1)	17.4 (4.3-30.3)	***0.004***
K_{cp} (h^{-1})	1.49 (0.57-5.32)	1.25 (0.57-1.73)	1.91 (0.69-5.32)	0.247
K_{pc} (h^{-1})	2.38 (0.77-16.6)	1.41 (1.07-2.37)	5.89 (0.77-16.6)	***0.017***

Abbreviation: BMI, body mass index; SrCr, serum creatinine; CrCL, creatinine clearance; SOFA, sequential organ failure assessment; V_c, central volume of distribution; CL, meropenem clearance; K_{cp}, distribution rate constant from central to peripheral compartment; K_{pc}, distribution rate constant from peripheral to central compartment.

Data is presented in median (range) or counts (%)

[#] p value was obtained from Mann-Whitney U test unless otherwise specified.

[†] p value was obtained from Pearson's Chi-squared test

Figures in bold and italic are statistically significant

5.2.4.2 Dosing simulations

Dosing recommendations for specific CrCL against different MICs were performed using the results of PTA for various regimens (different doses, dosing intervals and intermittent and continuous infusions) are presented in Table 4.2. Continuous infusions of the same daily dose achieved higher PTA when compared with 30-min infusion regimens, whereas an increase in CrCL resulted in a decline in PTA.

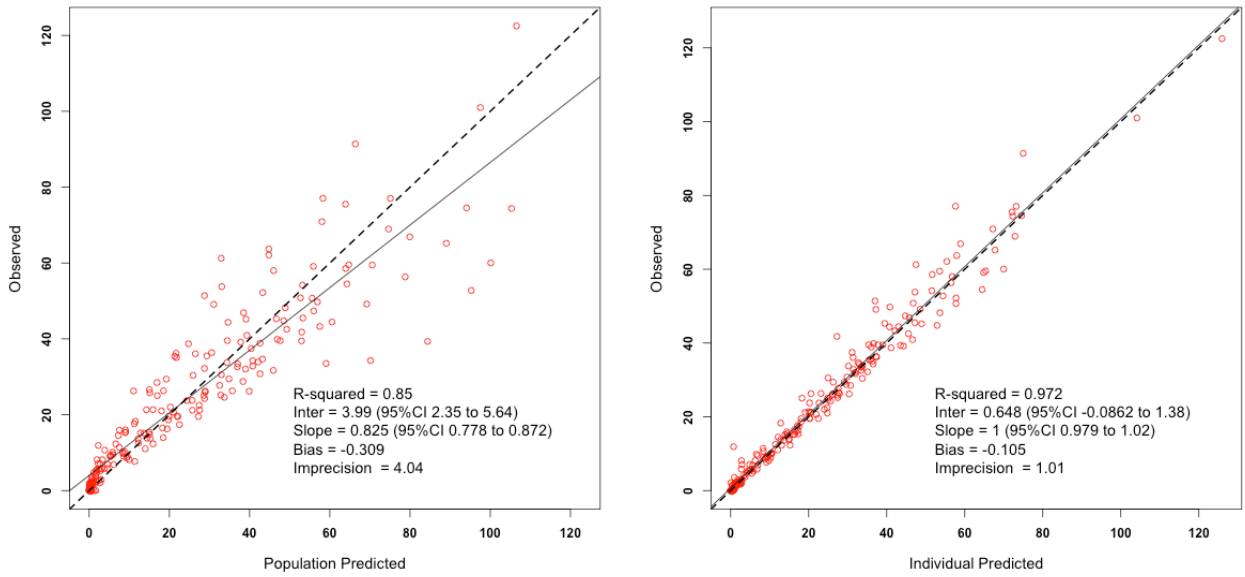

Figure 5.1. Diagnostic plots for the final covariate model. Observed versus population predicted concentrations (left) and individual predicted concentrations (right) in plasma. Data are presented in mg/L

Table 5.2. Dose recommendations for critically ill patients

CrCL (mL/min)	**Minimum Inhibitory Concentration**	
	≤0.25mg/L	**2mg/L**
≤20	0.5g 24-hourly	0.5g 24-hourly
21-50	0.5g 12-hourly	0.5g 12-hourly
51-100	0.5g q8h	1g q8h
101-130	1g q8h	1g q6h or 3g CI
131-170	1g q8h	1g q6h or 3g CI

Abbreviation: CrCL, creatinine clearance; CI, continuous infusion; q8h, eight hourly; q6h, six hourly.

5.2.5 Discussion

To our knowledge, this is the first study to investigate the population PK of meropenem in Australian Indigenous patients with severe sepsis. Our results suggest that Meropenem PK were not significantly different in Australian Indigenous patients relative to Caucasian comparators.

The principle difference between the two groups related to drug CL, which was adequately described by patient renal function defined as CrCL. This demonstrates that renal function remains the most important determinant of meropenem PK, and dosing regimens should be guided in accordance with the patient's CrCL. Although the median CrCL between the two groups was not significantly different, two of the Indigenous patients had a CrCL of 15-20 mL/min, which may have contributed to the significant difference in meropenem CL observed between the two groups. The estimated meropenem CL (11.0 L/h) in our Indigenous patients was also similar to results from previous studies in septic and critically ill patients with comparable CrCL (CL 7.8-11.5 L/h (341-343)). Of note, our Indigenous group was 10-30 years younger when compared with the patients in the previous studies (341-343), although the level of renal function was similar. This observation supports previous data reporting the significantly higher prevalence of chronic kidney diseases and poorer renal function in the Australian Indigenous population when compared to age-matched Caucasians (344).

The absence of interethnic differences in meropenem PK in our study aligns with previous observations demonstrating that interethnic PK differences are unlikely in antibiotics that are predominantly eliminated via glomerular filtration (337).

Importantly, in this study we have found a large interindividual variability in the meropenem PK in the studied patients. Significant fluctuations of drug CL and V_d is common in critically ill patients (345), and has been reported in other studies investigating meropenem PK (341, 343). These studies generally conclude that this profound variability in PK increases the likelihood of sub-therapeutic concentrations or drug accumulation and associated toxicities.

Our dosing simulations aiming for the 40% $fT_{>MIC}$ target revealed that a regimen of 500 mg twice daily gives an acceptable PTA for pathogens with an MIC of 2 mg/L (clinical breakpoint for most non-resistant Gram negative bacteria such as *Pseudomonas aeruginosa*, *Acinetobacter spp.*, *Haemophilus influenzae* and *Moraxella catarrhalis*) in patients with CrCL 20-50 mL/min.

However, 1 g thrice daily is needed in patient with CrCL of 100 mL/min. 1 g four times daily is likely required in patient with CrCL of 130mL/min.

Continuous infusions, however, consistently achieved better PK/PD target attainment as has been shown in previous studies (80). As expected, with increasing CrCL, higher daily doses or use of continuous infusion is required to achieve PK/PD targets. We would note that a standard dose of 1g thrice daily would be insufficient for patients with CrCL >100 mL/min for pathogens with a MIC of 2 mg/L or greater.

This study has some limitations. Specifically, the small sample size limited our power to detect other potential covariates affecting meropenem PK and also determine whether failure to achieve PK/PD targets was associated with an altered clinical outcome. Secondly, we collected samples on two dosing intervals and so may not have been able to describe all of the perturbations in PK that occurred over the duration of treatment. Finally, we did not collect samples from the site of infection (e.g. epithelial lining fluid in pneumonia) and therefore our dosing recommendations relate to achievement of target exposures in blood only.

5.2.6 Conclusions

This study has highlighted that CrCL remains the strongest determinant of meropenem PK in patients with severe sepsis. Although, we did not demonstrate any interethnic differences in meropenem PK between Indigenous and Caucasian Australians in this study, this may be, at least in part due to the low number of patients recruited and high interindividual PK variability.

5.2.7 Acknowledgements

We would like to acknowledge the ICU team and nursing staff of Alice Springs Hospital for their support and assistance with sample collection and other relevant tasks for this study.

5.2.8 Funding

This work was supported by a PhD Scholarship provided by the National Health and Medical Research Council of Australia (D.T.); Scholarship provided by the Australian Academy of Science's Douglas and Lola Douglas (D.T.); Alice Springs Specialists' Private Practice Trust Fund (D.T.); and in part by the Australian National Health and Medical Research Council Fellowship (APP1048652 to J.A.R.). We also wish to acknowledge funding from the Australian National Health and Medical Research Council for Centre of Research Excellence (APP1099452).

5.2.9 Transparency declarations

All authors: none to declare.

5.3 Conclusion

This Chapter describes the population PK of meropenem in severely septic Australian Indigenous patients. There were no clinically relevant differences in the meropenem PK observed when compared with non-Indigenous comparators. Although a large interindividual variability was observed in the meropenem PK in this patient group, it is well described by the CrCL and patient's TBW. A dosing regimen defined using Monte Carlo simulations is provided in the Chapter to guide dosing at various levels of CrCL.

Chapter 6 Optimising piperacillin dosing in critically ill Australian Indigenous patients with severe sepsis

6.1 Synopsis

Currently, there are no available PK data for piperacillin in the critically ill Australian Indigenous patients to inform appropriate dosing. The first section of this Chapter is a published manuscript aimed to describe the population PK of piperacillin in severely septic Australian Indigenous patients. The second section of this Chapter describes the probability of PK/PD target attainment with various dosing regimens using Monte Carlo dosing simulations.

6.2 Published manuscript entitled "Pharmacokinetics of piperacillin in critically ill Australian Indigenous patients with severe sepsis"

The manuscript entitled "Pharmacokinetics of piperacillin in critically ill Australian Indigenous patients with severe sepsis" is published in *Antimicrobial Agents and Chemotherapy*.

The co-authors contributed to the manuscript as follows: The conducting of this PK study was performed by the PhD Candidate, Danny Tsai under the supervision of Prof. Jason A. Roberts. Data collection was performed by the PhD Candidate, Danny Tsai under the guidance of Prof. Jason A Roberts. Drug assay was performed by Dr Steven Wallis. The description of the drug assay methods in the manuscript was written by Dr Steven Wallis. PK modelling was performed by the PhD Candidate Danny Tsai under the guidance of Prof. A Roberts. The PhD Candidate, Danny Tsai, took the leading role in manuscript preparation and writing. Prof. Jason A. Roberts took the leading role in critical review and revision of the manuscript. Critical review was performed by Dr Penelope Stewart, Dr Stephen Gourley, Dr Rajendra Goud, Dr Saliya Hewagama, Dr Sushena Krishnaswamy, Dr Steven Wallis, Prof. Jeffrey Lipman and Prof. Jason A. Roberts.

The manuscript is presented as per the accepted manuscript. The figures and tables have been inserted into the text in locations close to where they were referred to. The abbreviations and numberings of pages, figures and tables have been adjusted to comply with the format of this thesis. The references can be found in the references section of the thesis.

Pharmacokinetics of piperacillin in critically ill Australian Indigenous patients with severe sepsis

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6.2.1 Abstract

Objectives There are no PK data available to guide piperacillin dosing in critically ill Australian Indigenous patients despite numerous reported physiological differences. This study aimed to describe the population PK of piperacillin in critically ill Australian Indigenous patients with severe sepsis.

Methods A population PK study of Indigenous patients with severe sepsis was conducted in a remote hospital ICU. Plasma samples were collected over two dosing intervals and assayed by validated chromatography. Population PK modelling was conducted using Pmetrics®.

Results Nine patients were recruited and a two compartment model adequately described the data. Piperacillin CL, V_c, distribution rate constant from central to peripheral compartment and from peripheral to central compartment (K_{cp} and K_{pc}) were 5.6 ± 3.2 L/h, 14.5 ± 6.6 L, 1.5 ± 0.4 h^{-1} and 1.8 ± 0.9 h^{-1} respectively, where CL and V_c were found to be described by CrCL and TBW respectively.

Conclusion In this patient population, piperacillin demonstrated high interindividual PK variability. CrCL were found to be the most important determinant of piperacillin PK.

6.2.2 Introduction

Critically ill Australian Indigenous patients have a high mortality rate (2, 28, 321). They are reported to be younger, have greater disease severity and more co-morbidity upon admission into the ICU, of which sepsis and severe sepsis are common admission diagnoses (2, 28, 321). Unfortunately, the lack of evidence-based antibiotic dosing guidelines in the Indigenous population makes prescribing a significant challenge for clinicians.

The Australian Indigenous are reported to have various physiological differences when compared with non-Indigenous Australians. For instance, young and healthy Indigenous adults have approximately 30% less nephrons compared with the non-Indigenous counterparts (44). From an anthropometric perspective, they generally have slightly smaller total body weight (TBW), higher central fat and slimmer extremities (46). Whilst strong comparative data of interethnic antibiotic PK generally remains elusive, a recent systematic review has suggested the possibility of interethnic differences in antibiotic PK for numerous antibiotics (337).

Piperacillin is a broad spectrum antibiotic commonly used in the critically ill, and is considered to have time dependent bacterial kill characteristics. Its hydrophilic physicochemistry makes it prone to PK fluctuations in critically ill patients (346). To date, there is no data on piperacillin PK in critically ill Indigenous Australians.

The aim of this study was to describe the population PK of piperacillin in critically ill Australian Indigenous with severe sepsis.

6.2.3 Materials and methods

6.2.3.1 Setting

An observational population PK study was conducted in a 10 bed ICU at a teaching hospital in remote Central Australia. Ethics clearance was obtained from the local and university Ethics Committees (Central Australian Human Research Ethics Committee, approval HREC-13-149; The University of Queensland Human Research Ethics Committee, approval 2013000904).

6.2.3.2 Study protocol

The dosing regimen of piperacillin which was co-administered with tazobactam (Tazopip®; Aspen Pharmacare, Sydney, Australia) was at the discretion of the treating intensivist. Inclusion and exclusion criteria, details of sampling, demographic data collected and sample handling were previously published (333).

6.2.3.3 Drug assay

Piperacillin was measured in plasma (0.5 - 500 mg/L) by a validated ultra-high pressure liquid chromatography–mass spectroscopy/mass spectroscopy (UHPLC-MS/MS) method on a Shimadzu Nexera2 UHPLC system coupled to a Shimadzu 8030+ triple quadrupole mass spectrometer (Shimadzu, Kyoto, Japan). The methods for this assay have been described previously (347). The assay method was validated for linearity, matrix test, selectivity, lower limit of quantification, recovery, reinjection stability and precision and accuracy using the Food and Drug Administration criteria for bioanalysis (348). Precision was within 5.8% and accuracy was within 10.0% at the tested plasma quality control piperacillin concentrations of 1.5, 50 and 400 mg/L.

6.2.3.4 Population PK modelling

Concentration-time data obtained from the plasma samples were described by compartment models using the Pmetrics® software package (340) for R® (version 3.2.2). Demographic and clinical data collected were tested for inclusion into the PK model as covariates. The covariates which statistically improved the log likelihood ($p<0.05$) and/or improved the goodness of fit plots were retained in the final model.

6.2.3.5 Model diagnostics

Model evaluation was performed by visually assessing the goodness of fit of the observed-predicted plots and the coefficient of determination of the linear regression of the observed-predicted values (r^2 close to 1, intercept close to 0) from each run. The predictive performance was assessed on mean prediction error (bias) and the mean biased adjusted squared prediction error (imprecision) of the

population and individual posterior predictions. Visual predictive check plots (VPC) generated from the final model were also visually assessed whether the observed data were appropriately distributed within the simulated model.

6.2.3.6 Statistical analysis

Continuous data were presented in mean ± standard deviation or median ± interquartile range and categorical data presented as counts (%).

6.2.4 Results

Ten Indigenous patients were recruited and one patient was excluded due to inappropriate storage of samples. The demographics and clinical information are presented in Table 6.1. In total 139 plasma samples were available for PK analysis.

Table 6.1 Demographic and clinical data

	n=9
Age (y)	43 ± 11
Female	4 (44%)
Weight (kg)	76 ± 11
Height (cm)	170 ± 17
BMI (kg/m^2)	27 ± 7
SrCr (μmol/L)	95 ± 69
CrCL (mL/min)	91 ± 46
Albumin (g/L)	27 ± 5
Vasopressor use	8 (89%)
APACHE II score	23 ± 6
SOFA score	8 ± 2

Abbreviation: BMI, body mass index; SrCr, serum creatinine; CrCL, creatinine clearance; APACHE II, acute physiological and chronic health evaluation II; SOFA, sequential organ failure assessment score.

Data is presented in mean ± standard deviation or counts (%)

6.2.4.1 Population PK model building and model diagnostics

A two compartment model was found to describe the data adequately. Elimination from the central compartment (represented by CL) and intercompartmental distribution (represented by K_{cp} and K_{pc}) were modelled as first order processes using differential equations. CrCL and patient's TBW were the only covariates tested which significantly improved the PK model. The final model was described as:

$$\mathrm{TVCL} = \mathrm{CL\ x}\left(\left[\frac{\mathrm{CrCL}}{55}\right] + 0.45\right)$$

$$\mathrm{TVVc} = \mathrm{Vc\ x}\left(\frac{\mathrm{TBW}}{76}\right)^{0.75}$$

Where TVCL is the typical value of piperacillin clearance, CL is the population parameter estimate of piperacillin clearance, TVVc is the typical value of volume of distribution of the central compartment, V_c is the population parameter estimate of volume of the central compartment and TBW is total body weight. The final covariate model had a decrease in -2 log-likelihood of 33.6 from the base model and improved the goodness of fit plots. The population PK parameter estimates obtained the two-compartment model are presented in 6.2.

Table 6.2 PK parameter estimates from two-compartment model

	Total (n=9)	**CV** (%)	**Variance**	**Median**
V_c (L)	14.5 ± 6.6	45.7	44.0	12.2
CL (L/h)	5.6 ± 3.2	57.0	10.4	4.6
K_{cp} (h^{-1})	1.5 ± 0.4	28.2	0.2	1.5
K_{pc} (h^{-1})	1.8 ± 0.9	47.5	0.7	1.7

Abbreviation: V_c: volume of distribution in the central compartment; CL: drug clearance; K_{cp}: distribution rate constant from central to peripheral compartment; K_{pc}: distribution rate constant from peripheral to central compartment; CV: coefficient of variation.
Data is presented in mean ± standard deviation.

The goodness of fit for the individual and population predicted vs observed plots and the VPC were considered acceptable (Figure 6.1). The VPC showed an even distribution of the observed data across the percentiles of the simulated data.

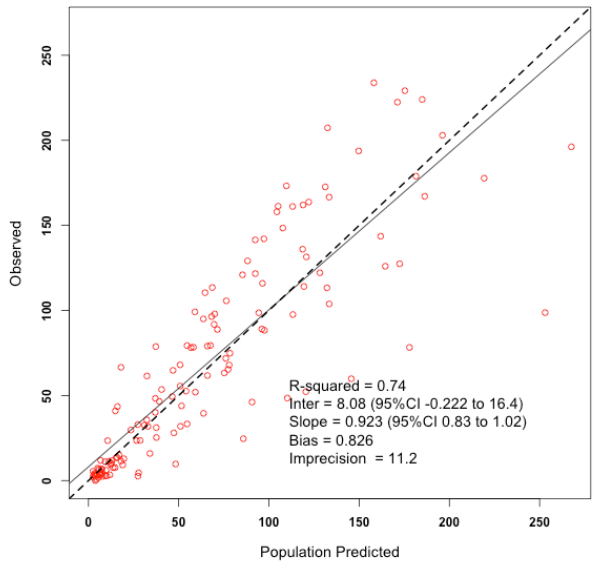
Table 6.3 compares the PK parameter estimates observed in our study with other published data from various patient populations (8, 317, 349-359). The parameter estimates from the present study generally show a lower mean piperacillin CL when compared with data on healthy volunteers and critically patients when CrCL were taken into consideration. On the other hand, V_c was similar across all patient groups.

6.2.5 Discussion

To the best of our knowledge, this is the first study to examine the population PK of piperacillin in critically ill Australian Indigenous patients with severe sepsis. We found that piperacillin PK in this population has high interindividual variability compared to healthy volunteers (349, 350), but similar compared to other critically ill or hospitalised patients (8, 317, 351-359). Nonetheless, we have also found that renal function, i.e. CrCL, remains the most important determinant of piperacillin dosing requirements.

The mean CL estimate observed in this study was 5.6 L/h, which is lower than previously described for healthy volunteers (12-14 L/h). However, individual estimates in our study group ranged from 2.8 to 14.2 L/h, which is not dissimilar to the range of other published data in critically ill or hospitalised patients (3 to 40 L/h) (8, 317, 351-359). Regarding piperacillin V_d, the V_c in this study was similar to other published data for both healthy volunteers and critically ill (8, 317, 350, 355). These data highlight why there is such high variability in piperacillin PK, where both supra and sub-therapeutic concentrations were common.

a.



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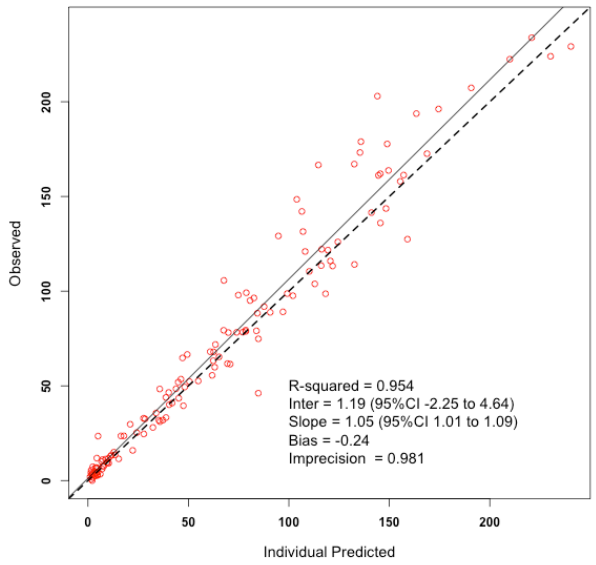

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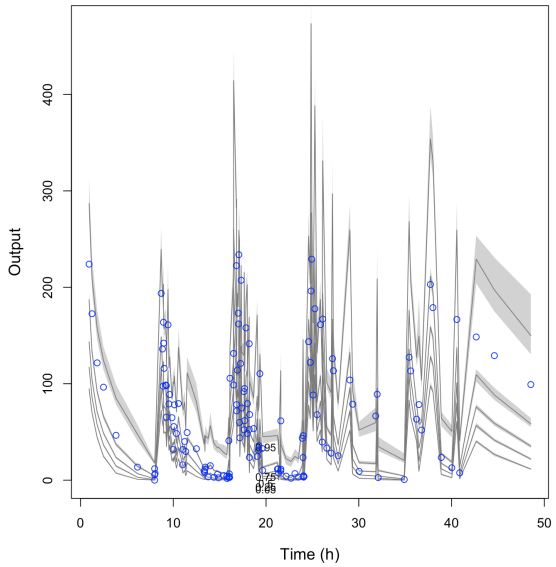

Figure 6.1 Diagnostics of final PK model – (a) Population predicted concentrations vs observed concentrations plot, (b) Individual predicted concentrations vs observed concentrations plot (where data presented on both x- and y-axes are Concentration in mg/L), (c) VPC plot (where Output on the y-axis is Concentration in mg/L)

Table 6.3 PK parameter estimates of piperacillin from published studies

Dose regimen	Population	No. of females	Age (y)	TBW (kg)	CrCL (mL/min)	SOFA	APACHE II	PK parameters	
								V_c (L/kg)	CL (L/h)
4g 30 min infusion (present study)	Severe sepsis Australian Indigenous	4/9	43 ± 11	76 ± 11	91 ± 46	7.8 ± 1.7	23 ± 6	0.19 ± 0.09	5.6 ± 3.2
60mg/kg 3 min bolus (349)	Healthy volunteers	0/12	20 - 30	69	NA	NA	NA	NA	*11.3 ± 1.3*
4g 3 min bolus (350)	Healthy volunteers	0/5	22 ± 0.4	70 ± 1.4	87 ± 5	NA	NA	0.16 ± 0.03	*15.3 ± 1.2*
4g 30 min infusion (351)	Abdominal infection	1/18	31 ± 9	76 ± 17	98 ± 26	NA	NA	NA	14.8 ± 4.0
4g 30 min infusion (352)	Elective colorectal surgery	9/18	67 ± 12	72 ± 11	72 ± 21	NA	NA	NA	11.6 ± 2.6
4g, administration duration not specified (353)	Community acquired pneumonia	14/53	65 ± 17	56 ± 12	81 ± 47	NA	NA	NA	8.2 ± 2.6
4g bolus (354)	Hospitalised patients	2/12	60 ± 12	70 ± 13	60 ± 31	NA	NA	NA	5.7
4g 20 min infusion (355)	Sepsis, critically ill	3/8	38 (22-65)	80 (74-86)	88 (53-101)	3 (3-3)	24 (18-26)	0.09 [0.07-0.12]	17.1 [14.4-20.6]
4g 20 min infusion (8)	Ventilator associated pneumonia, critically ill	3/7	42 (23-65)	85 (72-90)	166 (103-237)	3 (2-3)	24 (16-27)	0.17 [0.14-0.19]	NA
30 min infusion, dose not specified (356)	Sepsis/severe sepsis	?/14	NA	NA`	52 (21-123)	9 (5-14)	NA	NA	6.2 (1.1-30.7)
4g 20 min infusion (317)	Sepsis, critically ill	21/48	47 ± 18	88 ± 24	122 ± 59	3.5 (2-6)	19 ±7	0.23	16.3
30 min infusion, dose not specified (357)	Critically ill	26/38	62 (54-68)	70 (60-81)	47 (29-87)	11 (8-13)	20 ± 6.0	NA	2.3 (1.7-3.7)
4g 30 min infusion (358)	Critically ill	?/19	NA	NA	NA	NA	NA	NA	3.2 {0.8-32.8}
30 min infusion, dose varied (359)	Surgical critically ill	5/13	45 ± 19	79 ±18	139 ± 44	6 ± 2	15 ± 5	NA	40.4

Abbreviation: CrCL, creatinine clearance; SOFA, sequential organ failure assessment score; APACHE II, acute physiologic assessment and chronic health evaluation II score; V_c, volume of distribution of the central compartment; CL, drug clearance; NA, data not available.

Data presented as mean ± standard deviation or median (interquartile range)/[95% confidence interval/{range}].

Data in italics were not directly reported but calculated from PK data in the study .

It is likely that the high interindividual PK differences observed in this study prevented identification of any interethnic differences, if such an effect is indeed present. This conclusion is supported by a recent systematic review that suggests antibiotics which are eliminated predominantly via glomerular filtration are less likely to display interethnic PK differences (337), in part because the differences can be readily explained by renal function estimates. Whether the lower mean piperacillin CL observed in our study group, when CrCL was taken in consideration, is caused by a lower non-renal CL requires further investigation (351-353, 355, 356).

This study has some limitations. Firstly, only plasma piperacillin concentrations were assessed in this study, which do not reflect piperacillin concentration achieved in other tissue sites (360). Secondly, the study was not designed to investigate the unbound piperacillin concentration, and an assumption of 30% albumin binding was made for our dosing simulations. This is supported by previous literature (54). Lastly, patients recruited in this study met the severe sepsis criteria defined by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee (361), and the study recruitment took place prior to the publication of the new definition for 'sepsis' (362). We would like to acknowledge that the two definitions may result in slightly different patient groups, and there is little data currently available to define how different the groups may be.

In conclusion, this study has highlighted that CrCL is the strongest determinant of piperacillin PK in severely septic Australian Indigenous patients. Therefore, it should be considered essential to select the dosing regimens for individual patients according to their measured CrCL.

6.2.6 Acknowledgements

We would like to acknowledge the ICU team and nursing staff of Alice Springs Hospital for their support and assistance with sample collection and other relevant tasks for this study.

6.2.7 Funding information

This work was supported by a PhD Scholarship provided by the National Health and Medical Research Council of Australia (D.T.); Scholarship provided by the Australian Academy of Science's Douglas and Lola Douglas (D.T.); Alice Springs Specialists' Private Practice Trust Fund (D.T.); and in part by the Australian National Health and Medical Research Council Fellowship (APP1048652 to J.A.R.). We also wish to acknowledge funding from the Australian National Health and Medical Research Council for Centre of Research Excellence (APP1099452).

6.3 Monte Carlo dosing simulation and dosing recommendations

Based on the final two-compartment model described in section 6.2.4.1, a series of Monte Carlo dosing simulations have been performed to assess the PTA for various dosing regimens against different probable parameters. Subsequently, a set of dosing guideline was formulated based on the simulation results.

6.3.1 Methods

PTA was obtained from Monte Carlo dosing simulations (n = 1000) in Pmetrics® with the assumption of free drug ratio of 0.7 (54). PTA assesses the likelihood of achieving ≥50% $fT_{>MIC}$ over the first 24 hours of various dosing regimens and CrCL for MIC values between 0.125 to 64 mg/L. Dosing regimens used for simulation were 2 g 8-hourly, 2 g 6-hourly, 4 g 12-hourly, 4 g 8-hourly, 4 g 6-hourly and 4 g 4-hourly as 30 minute infusions; 8 g, 12 g, 16 g and 24 g as 24-hour continuous infusions. A total body weight of 80kg and CrCL of 20, 50, 100, 130 and 170 mL were used for the dosing simulation, which were a random selection of CrCL distribution seen in our patient population.

6.3.2 PTA results

Results of the dosing simulations for various dosing regimens against different CrCL are presented in Fig. 6.2. When compared with the 30-minute infusion regimens, the equivalent daily dose as a 24-hour continuous infusions achieved a higher PTA. An increase in CrCL resulted in a lower PTA especially at higher MICs.

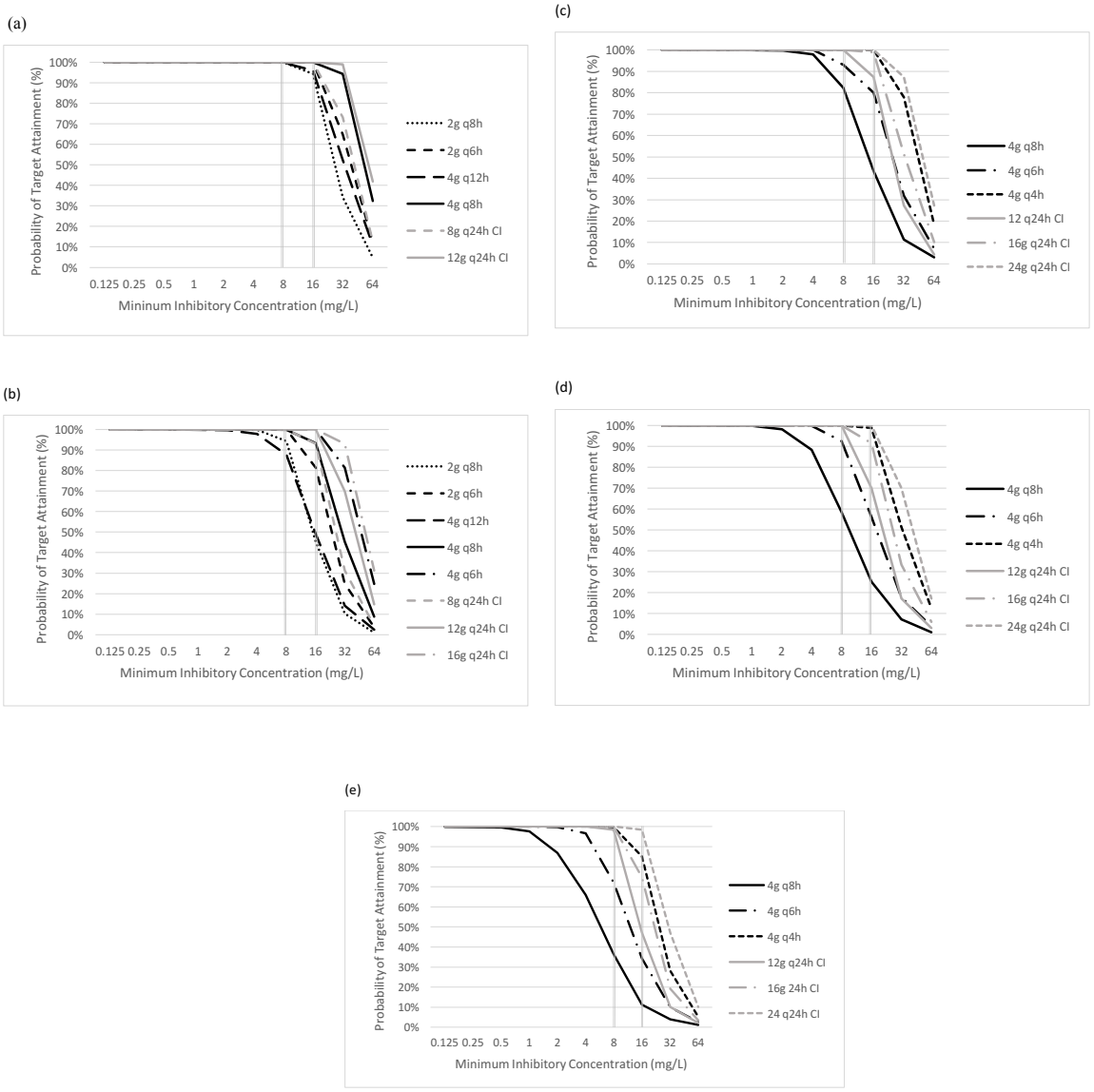

Figure 6.2 PTA for piperacillin dosing regimens comprising 30 minute intermittent infusions and 24 hour continuous infusions against CrCL of (a) 20, (b) 50, (c) 100, (d) 130 and (e) 170 mL/min

Abbreviation: q24h, twenty-four hourly; q12h, twelve hourly; q8h, eight hourly; q6h, six hourly; q4h, four hourly; CI, continuous infusion.

Table 6.4 Recommended piperacillin dosing regimen for various CrCL against MIC

CrCL (mL/min)	Minimum inhibitory concentration			
	≤2mg/L	**4mg/L**	**8mg/L**	**16mg/L**
≤20	4g q12h	4g q12h	4g q12h	4g q12h
21-50	4g q12h	4g q12h	4g q8h	4g q8h
51-100	4g q8h	4g q8h	4g q6h	4g q4h or 16g q24h CI
101-130	4g q8h	4g q6h	4g q6h	4g q4h or 16g q24h CI
131-170	4g q8h	4g q6h	4g q4h	24g q24h CI

Abbreviation: CrCL, creatinine clearance; q24h, twenty-four hourly; q12h, twelve hourly; q8h, eight hourly; q6h, six hourly; q4h, four hourly; CI, continuous infusion. CI, continuous infusion.

6.3.3 Discussion

Given the high variability in piperacillin PK observed in this study, it is not possible to devise a one-size-fits-all dosing regimen for this patient population. Our dosing simulations described that different dosing regimens are required to treat infections caused by pathogens with different clinical MIC breakpoints (e.g. 16, 8, 4 and 2 mg/L for non-resistant *Pseudomonas aeruginosa*, *Gram-positive/negative anaerobes*, Enterobacteriaceae, *Entercocccus spp.* and *Haemophilus influenzae* respectively) (363). Piperacillin dosing regimens suitable for this patient population are listed in Table 4. We would note that a regimen of 4 g 4-hourly is needed for a pathogen with a MIC of 16 mg/L in patients with a CrCL 51 – 130 mL/min. A continuous infusion of 24 g 24-hourly is needed when CrCL ≥130mL/min.

We would further note that TDM has previously been shown to improve PK/PD target attainment for piperacillin therapy (99, 364). Although most ICUs do not have access to such facilities to perform drug monitoring for penicillins, it should be used where possible (335).

6.4 Conclusion

This Chapter has highlighted that CrCL is the strongest determinant of piperacillin PK in severely septic Australian Indigenous patients. Therefore, it should be considered essential to select the dosing regimens for individual patients according to their measured CrCL whilst being aware of the MIC of the target bacteria to ensure maximal PK/PD target attainment. Our study also highlights the need to investigate the same for other commonly used antibiotics to enable us to optimise dosing and ultimately outcomes for Indigenous Australians with severe sepsis.

Chapter 7 Optimising ceftriaxone dosing in critically ill Australian Indigenous patients with severe sepsis

7.1 Synopsis

The aim of this Chapter was to describe the PK of total and unbound ceftriaxone in severely septic Australian Indigenous patients and compare to published data in other critically ill populations. A commonly used regimen in Central Australia, 1 g IV twelve-hourly, was assessed for its adequacy in attaining the PK/PD targets of typical targeted pathogens.

7.2 Published manuscript entitled "Total and unbound ceftriaxone pharmacokinetics in critically ill Australian Indigenous patients with severe sepsis"

The manuscript entitled "Total and unbound ceftriaxone pharmacokinetics in critically ill Australian Indigenous patients with severe sepsis" is published in the *International Journal of Antimicrobial Agents*.

The co-authors contributed to the manuscript as follows: The conducting of this PK study was performed by the PhD Candidate, Danny Tsai under the supervision of Prof. Jason A. Roberts. Data collection was performed by the PhD Candidate, Danny Tsai under the guidance of Prof. Jason A Roberts. Drug assay was performed by Dr Steven Wallis. The description of the drug assay methods in the manuscript was written by Dr Steven Wallis. PK analysis was performed by the PhD Candidate Danny Tsai under the guidance of Prof. A Roberts. The PhD Candidate, Danny Tsai, took the leading role in manuscript preparation and writing. Prof. Jason A. Roberts took the leading role in critical review and revision of the manuscript. Critical review was performed by Dr Penelope Stewart, Dr Stephen Gourley, Dr Rajendra Goud, Dr Saliya Hewagama, Dr Sushena Krishnaswamy, Dr Steven Wallis, Prof. Jeffrey Lipman and Prof. Jason A. Roberts.

The manuscript is presented as per the accepted manuscript. The figures and tables have been inserted into the text in locations close to where they were referred to in the text. The abbreviations and numberings of pages, figures and tables have been adjusted to comply with the format of this thesis. The references can be found in the references section of the thesis.

Total and unbound ceftriaxone pharmacokinetics in critically ill Australian Indigenous patients with severe sepsis

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7.2.1 Abstract

Objectives In the absence of specific data to guide optimal dosing, this study aimed to describe the PK of ceftriaxone in severely septic Australian Indigenous patients and assess the achievement of PD target of regimens prescribed.

Methods A PK study was conducted in a remote hospital ICU in patients receiving 1g 12-hourly dosing. Serial blood and urine samples were collected over one dosing interval on 2 consecutive days. Samples were assayed using a validated chromatography method for total and unbound concentrations. Concentration-time data collected were analysed with a non-compartmental approach.

Results One hundred plasma samples were collected from 5 included subjects. Ceftriaxone CL, volume of distribution at steady state (V_{dss}), elimination $T_{½}$ and elimination rate constant estimates were 0.9 (0.6-1.5) L/h, 11.2 (7.6-13.4) L, 9.5 (3.2-11.2) h and 0.08 (0.07-0.21) h^{-1} respectively. The unbound fraction of ceftriaxone ranged between 0.14 and 0.43, with a higher unbound fraction present at higher total concentrations. The unbound concentration at time 720 minutes for the first and second dosing intervals were 7.2 (4.8-10.7) and 7.8 (4.7-12.1) mg/L respectively, which exceeds the MIC of all typical target pathogens.

Conclusion The regimen of ceftriaxone 1 g twelve hourly is adequate for critically ill Australian Indigenous patients with severe sepsis caused by non-resistant pathogens.

7.2.2 Introduction

Sepsis and severe sepsis are two of the commonest ICU admission diagnoses for the Australian Indigenous population (2, 29). Up to 60% of all hospital deaths for Indigenous patients are related to infection, 56% of which were associated with bacterial sepsis (3).

A recent systematic review documented the significant differences in antibiotic PK that may occur between different ethnic groups (44). In relation to the Australian Indigenous, physiological differences which can alter antibiotic PK include having 30% less nephrons (44), sharing similar allele frequencies of some cytochrome P450 enzymes with the East Asian population (45) and having smaller body mass, higher central fat and thinner extremities when compared with the non-Indigenous (46).

Ceftriaxone is a third generation cephalosporin and is a commonly used antibiotic in the ICU. It shows a time dependent bacterial kill characteristic (38), where maximum bacterial kill effects are anticipated when plasma free drug concentration exceeds the MIC ($fT_{>MIC}$) for at least 60-70% of the dosing interval (339). It has mixed renal and biliary elimination, however, due to its uncommon PK properties of having a high binding to serum albumin (83-95%) and a relatively long $T_{½}$ of 6-8 hours, renal impairment rarely warrants dose adjustment (54, 365). The presence of hypoalbuminaemia, like numerous other conditions which are commonly seen in the critically ill, may lead to altered plasma ceftriaxone concentrations (18). In the absence of TDM, it can be difficult to prescribe drugs like ceftriaxone with confidence for critically ill patients and know that dosing is adequate.

There are very limited data on the effect of critical illness on the disposition of ceftriaxone, especially in the Australian Indigenous, hence this study aims to describe the PK of total and unbound ceftriaxone in critically ill Australian Indigenous patients with severe sepsis.

7.2.3 Material and methods

7.2.3.1 Setting

A prospective, observational PK study was conducted in the ICU of Alice Springs Hospital, a remote hospital in the Northern Territory of Australia. Ethics approval was granted from the local and university Ethics Committees (Central Australian Human Research Ethics Committee, approval HREC-13-149; The University of Queensland Human Research Ethics Committee, approval 2013000904) and written consent was obtained from all participants/next of kin.

7.2.3.2 Study population

The inclusion criteria were: (1) Australian Indigenous; (2) ≥18 years of age; (3) confirmed or suspected severe sepsis within the previous 48 hours; (4) clinical indication for ceftriaxone; and (5) arterial line and an indwelling urinary catheter *in situ*. The exclusion criteria were (1) CrCL <15 mL/min; (2) requirement of haemodialysis or CRRT; and (3) pregnancy.

7.2.3.3 Study protocol

The ceftriaxone (Ceftriaxone Sandoz®; Sandoz Pty Ltd, Sydney, Australia) dose and frequency were determined by the treating physician. Ceftriaxone was then reconstituted in 100 mL sodium chloride 0.9% and infused intravenously via a central venous catheter over 30 minutes. Ten 2mL blood samples were collected from the existing arterial line over the 12 h dosing interval at 0, 30, 60, 75, 90, 120, 180, 360, 480 and 720 minutes from initiation of infusion. A second set of samples with the same regimen was obtained the next day. Urine was collected throughout the duration of both dose intervals via an indwelling catheter. Demographics, clinical information and routine laboratory test results performed on the study days were also recorded.

All plasma samples were assayed for total ceftriaxone concentration (unbound and bound), and five plasma samples for each dosing interval (30, 90, 180, 360 and 720 minutes from initiation of infusion) were assayed for the unbound concentration.

7.2.3.4 Sample handling and storage

Immediately after blood and urine samples were collected, they were stored at 2-8 °C. One mL of collected urine sample was pipetted into a cryovial. Within 8 hours of sampling, the blood containing sampling tubes and the urine containing cryovials were centrifuged at 5000 rpm for 6 minutes. Plasma samples were then aspirated into cryovials and batched with the urine cryovials. They were then stored at -70 °C. The total urine sample was used for creatinine assay in Alice Springs Hospital pathology, with the measured CrCL subsequently determined. Upon completion of recruitment, plasma and urine samples were packed with dry ice and freighted to the Burns, Trauma & Critical Care Research Centre, The University of Queensland for drug assay.

7.2.3.5 Drug assay

7.2.3.5.1 Plasma samples

Total and unbound concentrations of ceftriaxone in plasma were measured by a validated ultra-high pressure liquid chromatography–mass spectroscopy/mass spectroscopy (UHPLC-MS/MS) method on a Shimadzu Nexera connected to a Shimadzu 8030+ triple quadrupole mass spectrometer. Clinical samples were assayed in batches alongside calibrators and quality controls and results were subject to batch acceptance criteria.

The free fraction was first isolated by ultrafiltraion at 37°C with Centrifree Ultrafiltration Device (Merck Millipore, Tullagreen, Ireland), and the ultrafiltrated plasma was then processed as a typical plasma sample in order to obtain the unbound concentration. Ionisation was by positive mode electrospray. Detection was monitored by MRMs at m/z 554.7→396.1 (ceftriaxone) and 557.7→399.1 (d3-ceftriaxone). Linearity was validated over the concentration range 2 to 200 mg/L (total) and 0.2 to 200 mg/L (unbound). Precision and accuracy was within 8.4% for total analysis and 12.3% for unbound analysis at all three concentrations tested. The unbound fraction of QCs (total ceftriaxone concentration) were 8.3% (low: 3 mg/L), 9.0% (med: 10 mg/L) and 12.6% (high: 80 mg/L). Unbound concentrations were measured with precision (n=6) of 9.2% (low), 4.1% (med) and 3.5% (high).

7.2.3.5.2 Urine samples

Concentrations of ceftriaxone in urine were measured from 10 to 10,000 mg/L by a validated high pressure liquid chromatography-ultra violet (HPLC-UV) method on a Shimadzu Prominence HPLC system. Urine samples were filtered and diluted with water in preparation for instrumental analysis. Ceftriaxone was monitored at 304 nm, and the assay method was validated for linearity, LLOQ, matrix effects and precision and accuracy using the Food and Drug Administration criteria for bioanalysis (348). The precision and accuracy were within 0.9% and 7.9%, respectively.

7.2.3.6 PK analysis

Data collected from plasma samples were analysed using a non-compartmental approach with the Pmetrics® software package (version 1.4.2) for R® (version 3.2.2). The unbound ceftriaxone samples were also contrasted with the corresponding total ceftriaxone concentration to determine the unbound fraction of ceftriaxone (described as a percentage) at different times over the dosing interval.

7.2.3.7 Statistical analysis

Continuous data were presented in median (range) and categorical data presented as counts (%). The amount of ceftriaxone recovered in urine was tested for correlation with the measured CrCL data using linear regression with Microsoft® Excel for Mac.

7.2.4 Results

Five Indigenous patients were included in this study and contributed a total of 100 blood samples. All patients received a dosing regimen of 1 g 12-hourly. The demographics, clinical information and PK parameter estimates are presented in Table 7.1. The concentration-time profile for the sampling occasions is shown in Figure 7.1, and the unbound fraction of ceftriaxone concentration throughout the dosing interval is presented in Figure 7.2, which shows a trend of a decreasing unbound fraction throughout the dosing interval that corresponds with decreasing drug concentrations. Figure 3 describes the correlation between unbound fraction and total ceftriaxone concentration for each individual patient. In general, higher ceftriaxone concentrations were found to correspond with higher unbound fractions.

There was no clear association observed between CrCL and the amount of ceftriaxone recovered in the urine over the dose interval (r^2 = 0.570). Furthermore, total ceftriaxone CL was not associated with changes in CrCL (r^2 = 0.227).

7.2.5 Discussion

We have found a high individual variability of PK parameter estimates. The median unbound trough concentration (fC_{720}) were 7.2 (4.8-10.7) and 7.8 (4.7-12.1) mg/L on first and second dosing intervals respectively, with no study participant manifesting a fC_{720} of less than 4 mg/L, which is higher than 4 x MIC breakpoint of all typical target pathogens (0.125, 0.125, 0.25, 0.5, 1 and 1 mg/L for *Neisseria gonorrhoeae, Haemophilus influenzae, Streptococcus pyogenes, Streptococcus pneumoniae,* Enterobacteriaceae*.,* and *Moraxella catarrhalis* respectively, in accordance to the European Committee on Antimicrobial Susceptibility Testing data (363)). Ceftriaxone is commonly prescribed as a once daily regimen, however, it has been reported that an improvement in clinical cure for critically ill patients receiving a continuous ceftriaxone infusion compared with those prescribed daily intermittent infusions of the same dose (7). Our study has demonstrated that a regimen of 1 g 12 hourly maintains PK/PD exposure above 4 x target MIC for all typical pathogens.

Table 7.1 Demographic, clinical data and PK parameter estimates

	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5	Total*
Age (y)	28	39	28	53	29	29 (28-53)
Female	Yes	No	Yes	No	No	2 (40%)
Weight (kg)	109	106	62	107	56	106 (56-109)
Height (cm)	165	172	165	181	174	172 (165-181)
BMI (kg/m^2)	40	36	23	33	18	33 (18-40)
CrCL (mL/min)	99	190	104	78	91	99 (78-190)
Bilirubin (μmol/L)	5	22	8	4	27	8 (4-27)
ALT (μmol/L)	29	145	21	304	1152	145 (21-1152)
Albumin (g/L)	28	23	24	23	27	24 (23-28)
APACHE II score	27	21	12	26	18	21 (12-27)
SOFA score	10	10	5	10	7	10 (5-10)
CL (L/h)	0.6	1.5	0.9	1.5	0.6	0.9 (0.6-1.5)
V_{dss} (L)	8.4	13.4	11.6	11.2	7.6	11.2 (7.6-13.4)
V_{dss} (L/kg)	0.08	0.13	0.19	0.10	0.14	0.13 (0.08-0.19)
k_e (h^{-1})	0.07	0.13	0.07	0.21	0.07	0.07 (0.07-0.21)
$T_{½}$ (h)	9.8	5.4	10.2	3.2	9.5	9.5 (3.2-10.2)
$AUC_{0-\infty}$ (mg.hr/L)	1788	664	1120	683	1763	1120 (664-1788)
C_{720A} (mg/L)	56.7	21.8	15.3	25.2	52.8	31.0 (15.3-56.7)
C_{720B} (mg/L)	60.8	22.6	30.4	36.1	-	33.2 (22.6-60.8)
***f*C_{720A}** (mg/L)	10.7	4.8	5.9	7.6	7.2	7.2 (4.8-10.7)
***f*C_{720B}** (mg/L)	12.1	4.7	5.0	10.7	-	7.8 (4.7-12.1)
Unbound fraction (%)	22	28	20	34	23	23 (20-34)

*Data presented in median (range)

Abbreviation: BMI, body mass index; CrCL, measured creatinine clearance; ALT, alanine transferase, APACHE II score, acute physiological and chronic health evaluation II score; SOFA score, sequential organ failure assessment score; CL (drug clearance); V_{dss}, volume of distribution at steady state; k_e, elimination rate constant; $T_{½}$, elimination half-life; AUC_{inf}, area under the concentration-time curve to time infinity; C_{720A}, total plasma ceftriaxone concentration 720 minutes from infusion of first dosing interval; C_{720B}, total plasma ceftriaxone concentration 720 minutes from infusion of second dosing interval; *f*C_{720A}, unbound ceftriaxone concentration 720minutes from infusion of first dosing interval; *f*C_{720B}, unbound ceftriaxone concentration 720minutes from infusion of second dosing interval; -, data not available.

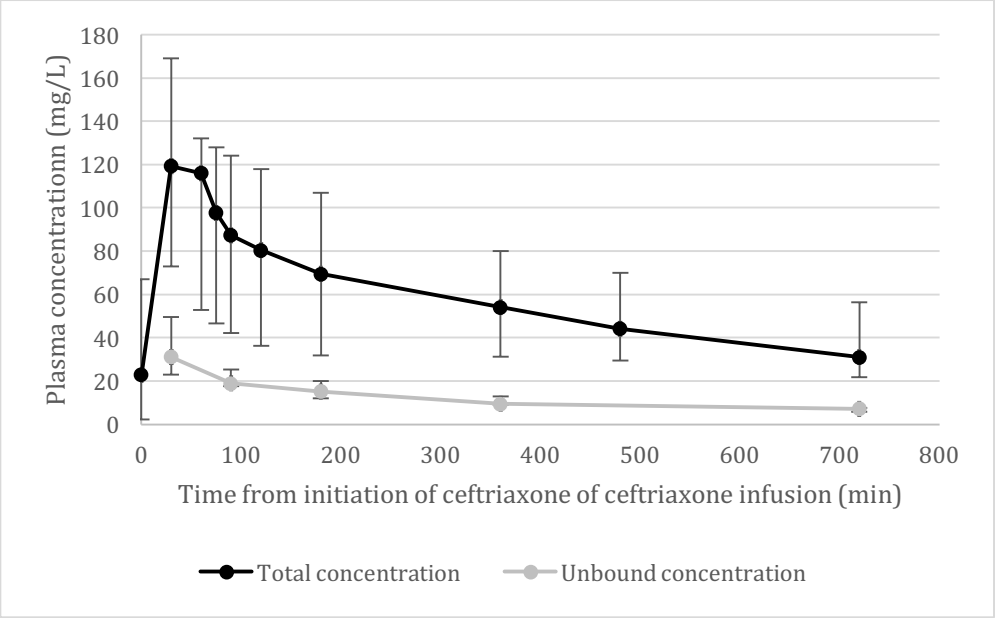

Figure 7.1 Total and unbound plasma ceftriaxone concentrations after initiation of intravenous infusion on the first dosing occasion (n=5)

Data is presented in median ± range

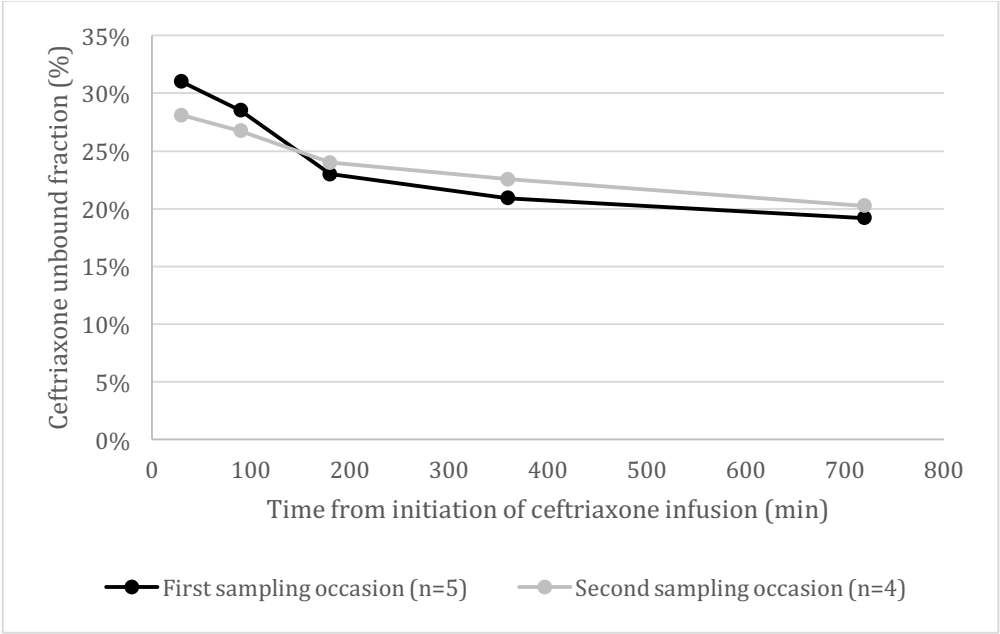

Figure 7.2 Ceftriaxone unbound fraction throughout a dosing interval on first and second dosing occasions

Data is presented in median

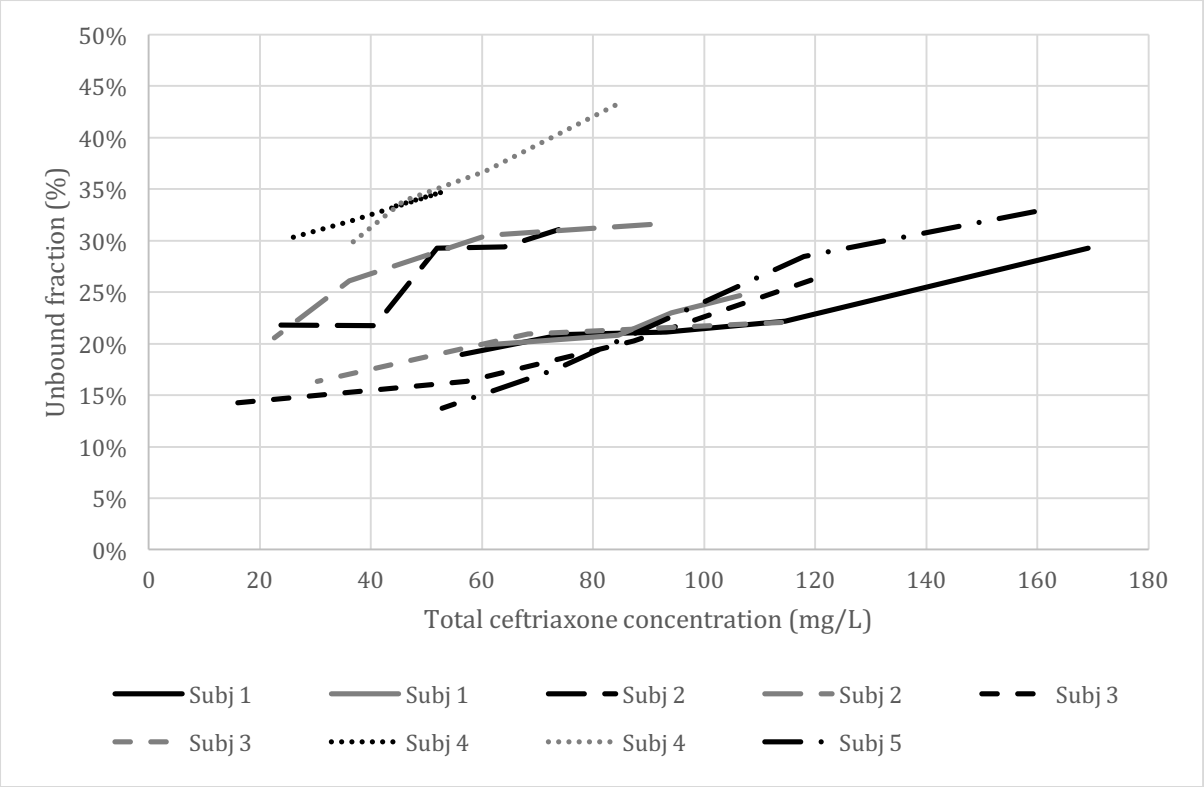

Figure 7.3. Ceftriaxone unbound fraction for different total ceftriaxone concentrations for each subject throughout a dosing interval on first and second dosing occasions

Abbreviation: Subj, subject.

Black lines represent data from the first sampling occasion, and grey lines represent data from the second sampling occasion.

Our subjects showed PK differences when compared with data obtained from healthy volunteers (median CL 0.89 vs 1.0, 1.1 L/h) (366, 367). When compared with other studies on critically ill patients, our subjects achieved a significantly lower CL against those with similar CrCL (112 mL/min vs 98 mL/min, CL 0.88 vs 2.4 L/h respectively) (368). Compared with those with lower CrCL (112 mL/min vs 26, 63 mL/min), a similar or lower CL is observed in our subjects (0.88 vs 1.2, 0.96 L/h) (368, 369), which suggests a lower non-renal CL, either due to less hepatic CL or unspecified interethnic differences. Furthermore, the lack of relationship between the CrCL and ceftriaxone recovered in urine as well as between CL and CrCL may be a result of the small sample size of this study, but it may also suggest differences in PK between this patient group and others.

This study may need to be repeated in a larger sample size to further mechanistically characterise any differences in CL.

A dramatically lower V_{dss} was observed in our subjects when compared with other published data on critically ill patients (10.4 vs 20.2, 20.0 L) (368, 369). When compared with healthy volunteers, the unbound fraction in our group was significantly higher (14-43% vs 5-15%) (370), but lower than other published data on critically ill patients (23% vs 33%) (369). Higher unbound concentration was seen in our patients with hyperbilirubinaemia and diabetes, which is in agreement with previous studies (369, 371), however, we did not find a correlation between hypoalbuminaemia and unbound fraction. The lower CL and V_{dss} seen in our group may have provided an explanation for the high fC_{720} observed.

There are a number of limitations to this study. Firstly, although this is the first study of ceftriaxone in this population, there were only five patients available for recruitment and a larger study may be needed to clarify the effect of hypoalbuminaemia, hyperbilirubinaemia and diabetes on the PK of unbound ceftriaxone in this patient group. Secondly, we did not collect samples from the site of infection, hence results concluded from this are restricted to ceftriaxone concentrations in the blood. Lastly, the study was not powered to test the effect of ceftriaxone exposure on clinical outcome.

7.2.6 Conclusions

There is a large interindividual variability in total and unbound ceftriaxone PK in this population, which may be driven by one or more different conditions including hyperbilirubinaemia, diabetes, hypoalbuminaemia and CrCL. Nonetheless, a regimen of 1 g 12-hourly is adequate to treat all typical pathogens.

7.2.7 Acknowledgements

We would like to acknowledge the ICU team and nursing staff of Alice Springs Hospital for their support and assistance with sample collection and other relevant tasks for this study.

7.2.8 Competing interest declarations

None to declare for all authors.

7.2.9 Funding

This work was supported by a PhD Scholarship provided by the National Health and Medical Research Council of Australia (D.T.); Scholarship provided by the Australian Academy of Science's Douglas and Lola Douglas (D.T.); Alice Springs Specialists' Private Practice Trust Fund (D.T.); and in part by the Australian National Health and Medical Research Council Fellowship (APP1048652 to J.A.R.). We also wish to acknowledge funding from the Australian National Health and Medical Research Council for Centre of Research Excellence (APP1099452).

7.3 Conclusion

This Chapter describes the PK of total and unbound ceftriaxone in Indigenous patients with severe sepsis and confirmed the regimen of 1 g IV 12-hourly was adequate in attaining the PK/PD target for pathogens typically targeted during systemic infections.

Overall, a large interindividual variability in PK was described. The CL and V_d in this study group were slightly lower than published data in other critically ill populations. All patients achieved the highest PK/PD target, which is maintaining the unbound plasma concentration for greater than 4x the MIC of all typical pathogens for the entire duration of each dosing interval. It follows, that the current regimen can be recommended in the study population.

Chapter 8 Optimising vancomycin dosing in critically ill Australian Indigenous patients with severe sepsis

8.1 Synopsis

Currently, there are no available PK data for vancomycin in the critically ill Australian Indigenous patients to inform dosing. This Chapter aims to describe the population PK of vancomycin in severely septic Australian Indigenous patients. The PK parameter estimates obtained from the final PK model were compared with published data from other critically ill populations. Furthermore, the PTA for various regimens was assessed with Monte Carlo dosing simulation. Subsequently, a set of dosing recommendation was presented.

8.2 Submitted manuscript entitled "Pharmacokinetics and optimised dosing of vancomycin in critically ill Australian Indigenous patients with severe sepsis"

The manuscript entitled "Pharmacokinetics and optimised dosing of vancomycin in critically ill Australian Indigenous patients with severe sepsis" has been submitted for publication.

The co-authors contributed to the manuscript as follows: The conducting of this PK study was performed by the PhD Candidate, Danny Tsai under the supervision of Prof. Jason A. Roberts. Data collection was performed by the PhD candidate, Danny Tsai under the guidance of Prof. Jason A Roberts. Drug assay was performed by Dr Steven Wallis. The description of the drug assay methods in the manuscript was written by Dr Steven Wallis. PK modelling was performed by the PhD Candidate Danny Tsai under the guidance of Prof. A Roberts. The PhD Candidate, Danny Tsai, took the leading role in manuscript preparation and writing. Prof. Jason A. Roberts took the leading role in critical review and revision of the manuscript. Critical review was performed by Dr Penelope Stewart, Dr Stephen Gourley, Dr Rajendra Goud, Dr Saliya Hewagama, Dr Sushena Krishnaswamy, Dr Steven Wallis, Prof. Jeffrey Lipman and Prof. Jason A. Roberts.

The manuscript is presented as per the submitted manuscript. The figures and tables have been inserted into the text in locations close to where they were referred to in the text. The abbreviations and numberings of pages, figures and tables have been adjusted to comply with the format of this thesis. The references can be found in the references section of the thesis.

Pharmacokinetics and optimised dosing of vancomycin in critically ill Australian Indigenous patients with severe sepsis

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8.2.1 Abstract

Objectives Vancomycin is a commonly used antibiotic due to the high burden of methicillin-resistant *Staphylococcus aureus* infections. This study aimed to describe the population PK of vancomycin in Australian Indigenous patients with severe sepsis.

Methods A population PK study was conducted in a remote Australian ICU. Serial plasma samples were collected over one to two dosing intervals and assayed by validated chromatography. Concentration-time data collected were analysed using Pmetrics software. The final population PK model was then used for Monte Carlo dosing simulations to determine optimal loading and intermittent maintenance doses.

Results Fifteen Indigenous subjects (8 females) were included for analysis with a median (IQR) age, weight and CrCL of 43 (34-46) years, 73 (66-104) kg and 99 (56-139) mL/min respectively. A two-compartment model described the data adequately. Vancomycin CL and V_c were described by CrCL and patient weight respectively. Median CL, V_c, K_{cp} and K_{pc} were 4.6 (3.8-5.6) L/h, 25.4 (16.1-31.3) L, 0.46 (0.28-0.52) h^{-1} and 0.25 (0.12-0.37) h^{-1} respectively. Therapeutic loading doses were significantly dependent on both TBW and CrCL, whereas maintenance doses were dependent on CrCL.

Conclusions This is the first report of vancomycin PK in this patient group. Descriptions of patient weight and CrCL were the most prominent determinants of optimised dosing regimens.

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8.2.2 Introduction

Critically ill and septic Australian Indigenous have high hospital morbidity and mortality rates (321). Empirical vancomycin therapy is commonly used in Indigenous patients presenting with sepsis in rural and remote health centres. This is due to the high prevalence of community acquired methicillin resistant *Staphylococcus aureus* (MRSA) colonisation and infections in patients from remote communities, especially in Central Australia (372, 373).

TDM is almost always utilised for vancomycin therapy in the ICU due to its narrow therapeutic window (335). Vancomycin exhibits a mixed concentration dependent and time dependent bacterial kill characteristic, that appears best represented by the $AUC_{0\text{-}24}$:MIC (38), and the commonly accepted PK/PD target is an $AUC_{0\text{-}24}$:MIC ratio of ≥400. Vancomycin is subject to significant PK changes in critical illness such as increases in V_d and increases or decreases in vancomycin CL due to ARC or AKI, respectively. These scenarios can dramatically complicate vancomycin dosing (18, 65).

A recent systematic review identified interethnic differences in PK for numerous antibiotics (337). Various physiological characteristics reported in the Australian Indigenous people raises the question whether PK differences exist when compared with the non-Indigenous populations. Relative to non-Indigenous comparators, young Indigenous adults are reported to have 30% less nephrons (44), smaller body mass, slimmer extremities and higher central fat (46) which together may be associated with altered CL and V_d of renally cleared drugs. As current guidelines are predominantly extracted from studies performed in Caucasian and Asian populations, the PK of antibiotics need to be described to ensure current dosing regimens are optimal for other patient populations.

This study aimed to describe the population PK of vancomycin in Indigenous Australians with severe sepsis and develop optimised dosing regimens that maximise the probability of PK/PD target attainment.

8.2.3 Participants and methods

A prospective, observational, population PK study was conducted in the ICU of an Australian remote teaching hospital.

8.2.3.1 Ethics

Ethical clearance was approved by the local (Central Australian Human Research Ethics Committee, approval HREC-13-149) and university (The University of Queensland Human Research Ethics Committee, approval 2013000904) Ethics Committees. Written consent was obtained from all participants/next of kin.

8.2.3.2 Study population

The inclusion criteria were: (1) Australian Indigenous; (2) ≥18 years of age; (3) confirmed or suspected severe sepsis (374) within the previous 48 hours; (4) prescribed with vancomycin; and (5) an arterial line *in situ*. The exclusion criteria were (1) CrCL <10 mL/min; (2) requiring haemodialysis or CRRT; and (3) pregnancy.

8.2.3.3 Study protocol

The vancomycin (DBL Vancomycin®; Hospira Australia, Melbourne, Australia) dose and dosing interval were determined by the treating physician and was administered via a central venous catheter. Blood samples were collected in lithium heparin tubes from patient's arterial line over one dosing interval at the following time-points: 0, 90, 180, 210, 240, 300, 360, 420, 480 and 720 minutes from initiation of infusion. A second set of samples was obtained the next day if feasible. Demographics, clinical information, and routine laboratory test results performed on the study days were also recorded.

8.2.3.4 Sample handling and storage

Blood samples were placed in a drug refrigerator at 2–8 °C after sampling. They were then centrifuged at 5000 rpm for 6 minutes within 8 hours of collection. The plasma supernatant was pipetted into 1 mL cryovials and stored in a freezer at -70 °C. At the end of subject recruitment, samples were packed with dry ice and freighted to the Burns Trauma & Critical Care Research Centre, The University of Queensland for drug assay.

8.2.3.5 Drug assay

Vancomycin was measured in plasma (0.2 to 100 mg/L) by a validated high pressure liquid chromatography-mass spectroscopy/mass spectroscopy (HPLC-MS/MS) method on a Shimadzu Nexera2 ultra-high pressure liquid chromatography (UHPLC) system coupled to a Shimadzu 8030+ triple quadrupole mass spectrometer (Shimadzu, Kyoto, Japan). For routine analysis, separations were performed using validated hydrophilic interaction liquid chromatography (HILIC), however a reverse phase chromatography was also validated to enable orthogonal analysis in cases of suspected chromatographic interference.

Sample (100 µL) was spiked first with internal standard (teicoplanin) and then treated with acetonitrile to precipitate proteins. Dichloromethane was then used to remove lipid soluble components from the aqueous supernatant. An aliquot of 0.5 µL of the aqueous supernatant was injected onto the HPLC-MS/MS.

Two separate, orthogonal chromatographies (HILIC or reversed phase columns with different gradients of the same mobile phase components) were validated for the measurement of vancomycin. Mobile Phase A was 0.1% formic acid in water (v/v), and Mobile Phase B was 100% acetonitrile with 0.1% formic acid (v/v). The default (HILIC) chromatography used a SeQuant zic-HILIC 2.1 x 20 mm (5.0 µm) analytical guard column and a gradient going from 80% B to 0% B and back again for a 5.5 min run-time. The alternative (reverse phase) chromatography used a Restek Pinnacle DB IBD column, 2.1 x 50 mm (1.9 µm) and the gradient went from 5% B to 95% B and back again for a 6.5 min run-time.

Vancomycin was monitored by positive mode electrospray at MRMs of 746.1→144.2 and 725.6→144.1. Teicoplanin was monitored in positive mode at 940.8→316.1.

The assay method was validated for linearity, LLOQ, matrix effects, recovery, reinjection stability and precision and accuracy using the Food and Drug Administration criteria for bioanalysis (348). The precision and accuracy were within 2.2% and 9.1% for the default HILIC chromatography.

8.2.3.6 Population PK modelling

Concentration-time data from the plasma samples were described by compartment models using the Pmetrics® software package (version 1.4.2) for R® (version 3.2.2). Various demographic and clinical data collected (e.g. weight, measured CrCL, sickness severity scores) were tested for inclusion into the model as covariates. The covariate was included into the model if it improved the log likelihood (p<0.05) and/or the goodness of fit plots.

8.2.3.7 Model diagnostics

Model evaluation was performed by visual assessment of goodness of fit of the population and individual predicted concentration vs observed concentration plots. The predictive performance was assessed on mean prediction error (bias) and the mean biased adjusted squared prediction error (imprecision) of the population and individual posterior predictions. Finally, VPC plots were generated from the final model. Appropriate distribution of the observed data within the simulated data was visually assessed.

8.2.3.9 Monte Carlo dosing simulation

Monte Carlo simulation was performed to determine optimal loading doses for various doses (15, 20, 25, 30, 35 and 40mg/kg), weights (60, 80 and 100kg) and CrCL (20, 50, 100, 130 and 170mL/min). The infusion rate used for all doses during simulation was 1000 mg/h. The simulations measured the probability of maintaining vancomycin concentration between 15 and 25 mg/L for a minimum of 80% of the dose interval from time 0 to 720 minutes.

The doses which achieved the highest PTA were subsequently incorporated into specified maintenance dosing regimens (500 mg 8, 12 and 24-hourly; 1000 mg 6, 8, 12 and 24-hourly; 2000

mg 8, 12 and 24-hourly) for further simulations. PTA of the maintenance regimens assessed the likelihood of maintaining the vancomycin concentration between 15 - 25 mg/L for at least 80% of 24 hours, 24 hours post end of loading dose interval.

Dosing simulations were repeated for the likelihood of attaining AUC:MIC ≥400 against different MICs (0.125 to 4 mg/L) for 24 hours, 24 hours post end of loading dose interval (36-60 hours post commencement of dosing for a CrCL of 20mL/min; 32-56 hours post commencement of dosing for CrCL ≥50 mL/min). The dosing regimens with the highest PTA were compared with the two different simulations for maintenance doses.

8.2.3.10 Statistical analysis

Continuous data were presented in median (IQR) and categorical data presented as counts (%).

8.2.4 Results

Fifteen Australian Indigenous patients were available for analysis inclusive of 216 blood samples. The demographics and clinical information are presented in Table 8.1.

Table 8.1 Demographic and clinical data

	n=15
Age (y)	43 (34-46)
Female	8 (53%)
Weight (kg)	73 (66-104)
Height (cm)	168 (160-172)
BMI (kg/m^2)	25 (24-34)
SrCr (μmol/L)	72 (58-98)
CrCL (mL/min)	99 (56-139)
Albumin (g/L)	26 (23-31)
Vasopressor	14 (93%)
APACHE II score	22 (19-27)
SOFA score	10 (6-10)

Abbreviation: BMI, body mass index; SrCr, serum creatinine; CrCL, creatinine clearance; APACHE II score, acute physiology and chronic health evaluation II score; SOFA score, sequential organ failure assessment score.

Data presented in median (interquartile range) or counts (%)

8.2.4.1 Population PK model building

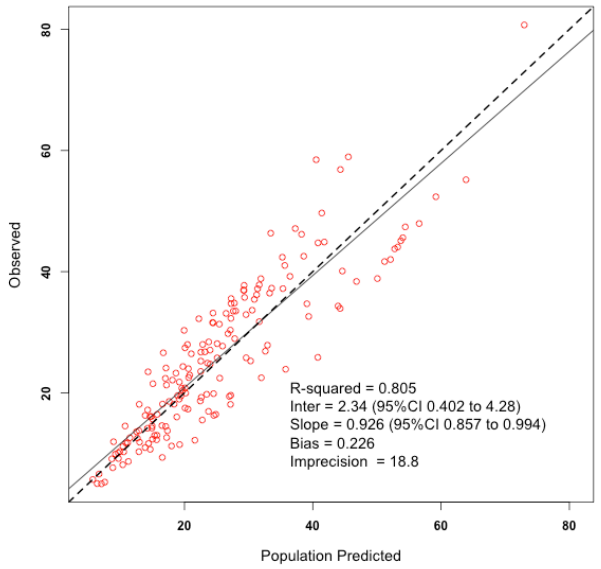
A two-compartment model described the data adequately. CrCL and total body weight (TBW) were the only covariates which improved the population PK model significantly. The final model is described as:

$$\mathrm{TVCL} = \mathrm{CL} \times \frac{\mathrm{CrCL}}{100}$$

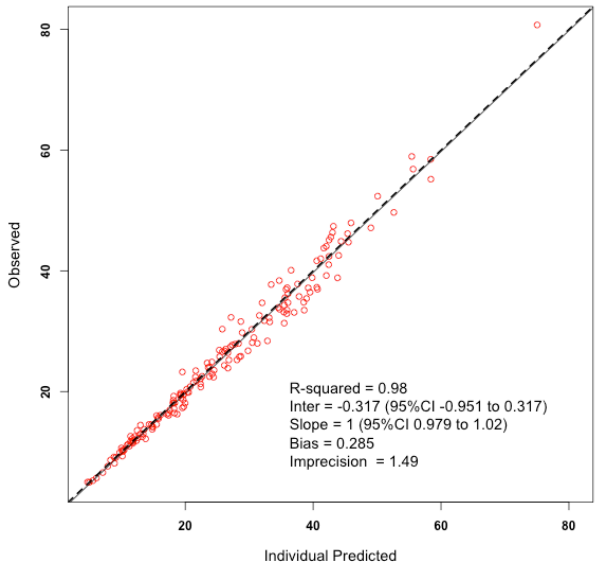
$$\mathrm{TVVc} = \mathrm{Vc} \times \left(\frac{\mathrm{TBW}}{80}\right)^{0.7}$$

Where TVCL is the typical value of vancomycin clearance, CL is the population parameter estimate of vancomycin clearance, TVV_c is the typical value of V_c, V_c is the population parameter estimate of volume of the central compartment and TBW is total body weight. The goodness of fit for the individual and population predicted concentrations vs observed concentrations plots and VPC were considered acceptable (Figure 8.1). The population PK parameter estimates described by the final model are presented in Table 8.2.

(a)



(b)



(c)

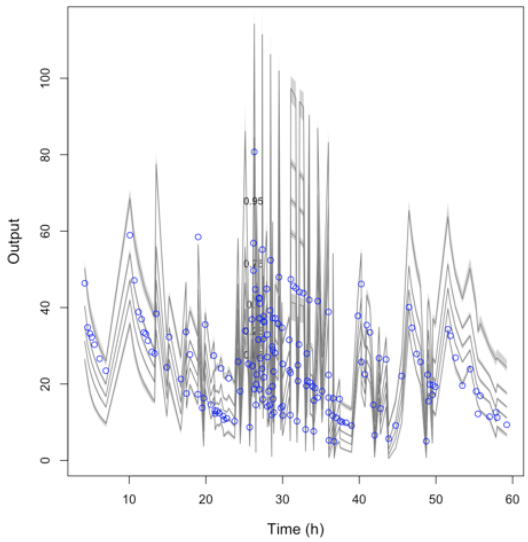


Figure 8.1 Diagnostics of the final population PK model – (a) Population predicted concentrations vs observed concentrations plot, (b) Individual predicted vs observed plot (Concentration in mg/L), (c) VPC plot (where Output on the y-axis is Concentration in mg/L)

Table 8.2 PK parameter estimates from two-compartment model

	n=15	CV (%)
V_c (L)	25.4 (16.3 - 31.3)	43.3
CL (L/h)	4.6 (3.8 - 5.6)	26.2
K_{cp} (h^{-1})	0.46 (0.28 – 0.52)	73.0
K_{pc} (h^{-1})	0.25 (0.12 - 0.37)	159.4

Abbreviation: V_c, volume of distribution in the central compartment; CL, drug clearance; K_{cp}, distribution rate constant from central to peripheral compartment; K_{pc}, distribution rate constant from peripheral to central compartment; CV, coefficient of variation.

Data presented in median (interquartile range)

8.2.4.2 Monte Carlo dosing simulation

The dosing simulations revealed the loading doses with highest PTA are dependent on both CrCL and TBW, whereas the maintenance dose associates significantly with CrCL. The PTA of a maintenance dosing regimens for a trough concentration within 15-25 mg/L 24 hours post the loading dose against various CrCL is presented in Table 8.3. Regimens with the highest PTA were then selected for the dosing table presented in Table 8.4.

The dosing simulations demonstrate that patients with lower TBW achieved slightly lower vancomycin concentrations when compared with higher TBW. Furthermore, the highest PTA of trough concentrations within 15-25 mg/L 24 hours post loading dose are mostly between 50-70%.

When comparing the PTA from the two dosing simulation targets (trough concentrations and AUC:MIC), we found a high correlation of dosing regimens with highest PTA between the two sets of simulations for an MIC of 1 mg/L. Regimens with the same total daily dose but different dosing intervals manifested similar PTA, and regimens with less dosing frequencies generally demonstrated a slightly lower PTA (eg. 1 g 8-hourly comparing to 1.5 g 12-hourly).

Table 8.3. PTA of achieving a trough concentration of 15-25mg/L 24 hours post dose interval of loading dose for various clinical scenarios based on patient weight and renal function

CrCL	20 mL/min			50 mL/min			100 mL/min			130 mL/min			170 mL/min		
TBW	60kg	80kg	100kg	60kg	80kg	100kg	60kg	80kg	100kg	60kg	80kg	100kg	60kg	80kg	100kg
0.5g 24-hrly	**0.53**	**0.68**	**0.73**	0.01	0.02	0.04	-	-	-	-	-	-	-	-	-
0.5g 12-hrly	0.243	0.21	0.18	0.21	0.30	0.41	-	-	-	-	-	-	-	-	-
0.5g 8-hrly	0.03	0.04	0.04	**0.69**	**0.70**	**0.69**	0.04	0.06	0.08	-	-	-	-	-	-
1g 24-hrly	0.35	0.28	0.22	0.09	0.15	0.23	0	0	0.01	-	-	-	-	-	-
1g 12-hrly	0.01	0.02	0.03	0.57	0.52	0.48	0.08	0.11	0.17	0.02	0.03	0.04	0	0	0.01
1g 8-hrly	-	-	-	-	-	-	**0.48**	**0.57**	**0.63**	0.16	0.23	0.28	0.04	0.05	0.07
1g 6-hrly	-	-	-	-	-	-	0.53	0.53	0.44	**0.49**	**0.49**	**0.61**	0.20	0.26	0.30
1.5g 12-hrly	-	-	-	0.13	0.08	0.06	0.31	0.39	0.48	0.08	0.13	0.18	0.02	0.03	0.04
2g 12-hrly	-	-	-	-	-	-	0.46	0.50	0.53	0.24	0.33	0.39	0.06	0.09	0.13
2g 8-hrly	-	-	-	-	-	-	-	-	-	0.49	0.42	0.38	**0.42**	**0.52**	**0.57**

Abbreviation: CrCL, creatinine clearance; TBW, total body weight; -, simulation not performed.
Figures in bold represented dosing regimens with the highest PTA.

Table 8.4 Vancomycin dosing algorithms recommended for various CrCL

CrCL (mL/min)	Loading dose	Time to next dose	Maintenance regimen
≤20	15mg/kg	12 hours	500mg 24-hourly
21-50	20mg/kg	8 hours	500mg 8-hourly
51-100	30mg/kg	8 hours	1g 8-hourly
101-130	35mg/kg	8 hours	1g 6-hourly
131-170	40mg/kg	8 hours	2g 8-hourly

Abbreviation: CrCL, measured creatinine clearance

8.2.5 Discussion

8.2.5.1 Summary of principal findings

A large interindividual variability was observed in the vancomycin PK which was significantly associated with differences in patient's TBW and CrCL. We found that optimal loading doses are heavily dependent on both TBW and CrCL, whereas maintenance doses are dependent on CrCL. We have presented a dosing table that can be used to maximise achievement of therapeutic concentrations for the first 24 hours post loading dose.

8.2.5.2 Findings of the present study in light of what was published before

The estimated median CL (4.6 L/h) in the Indigenous patients was similar to other published data in critically patients with comparable CrCL (3.5-5.9 L/h), and like previous studies, CrCL remained the most important determinant of vancomycin PK (375-377). This supports the finding highlighted in a recent systematic review, that interethnic differences in PK are unlikely for the CL of an antibiotic where glomerular filtration is the predominant mechanism of elimination (337). Furthermore, we observed a large interindividual variability for V_c in our patient group. The median V_c is 0.35 L/kg, which is similar to critically ill patients in other populations (0.19 - 0.41 L/kg) (375, 376). These results do not support the presence of interethnic PK differences for vancomycin, or that at the very least, they suggest that any population-level difference is not clinically significant.

Loading doses are now considered important for rapidly achieving effective vancomycin exposures in critically ill patients. This practice is supported by data demonstrating that low vancomycin exposure (AUC:MIC ratio <430 for Etest and <398.5 for broth microdilution methods of MIC determination) for the first 24-48 hours of therapy is an independent factor for higher mortality and treatment failure in MRSA bacteraemia (76, 378). In our dosing simulations, we found that the magnitude of loading dose required is affected by TBW and CrCL. The importance of CrCL is a novel observation, in some ways, with patients with a higher CrCL requiring the first maintenance dose to be administered earlier than in patients with lower CrCL. We proposed a first maintenance dose at 8 hours in these scenarios. The major output from our dosing simulations was the development of a dosing algorithm which incorporates loading doses and maintenance dosing regimens with the highest PTA.

8.2.5.3 Strengths and limitations

The Indigenous Australians are a unique ethnic group with very distinctive physiology. This study was able to recruit 15 Indigenous patients with severe sepsis, which is highly prevalent in Australian remote communities. There is currently very limited PK data available to guide optimal antibiotic dosing.

On the other hand, an association of PK/PD target attainment with an altered clinical outcome could not be assessed due to the small sample size. Furthermore, samples were not collected from the site of infection (e.g. epithelial lining fluid in pneumonia) and thus, our dosing recommendations relate to the achievement of target exposures in blood only. Finally, a larger sample size may have enabled other covariates to be included in the final model, although it is unlikely they would significantly alter the dosing algorithm.

8.2.5.4 Understanding possible mechanism

The impact of drug CL on loading doses for vancomycin therapy is usually neglected. However, the process of vancomycin elimination would have initiated shortly after it reaches a detected concentration in the plasma. For a drug that is predominantly eliminated via the renal route and with

a mixed concentration and time dependent PD property, CrCL naturally becomes a significant determinant of early achievement of therapeutic target.

8.2.5.5 Meaning of this study and implications for practice

It is generally accepted that a TDM target for vancomycin intermittent infusions is a trough concentration between 15-20 mg/L. However, this target has also been shown to poorly correlate with an AUC of 400 mg.h/L due to high interindividual variability (379). In our simulations, however, we have found a high correlation between PTA of AUC of 400 mg.h/L and trough concentration between 15-25 mg/mL. To some extent, this result supports the ongoing use of trough concentration measurements for TDM where it is not possible to more accurately characterise AUC:MIC in individual patients.

We would also point out that the commonly used empirical regimen of 1 g 12-hourly only achieved acceptable PTAs for patients with a CrCL of 50mL/min in our dosing simulations. Furthermore, the PTA of 50–70% for most recommended regimens denotes the requirement of dose adjustments for 30–50% of patients. Due to changes in renal function and PK alterations in critical illnesses, continuous TDM throughout the course of vancomycin therapy is still recommended.

Our dosing simulations have demonstrated drastically low PTA of AUC:MIC for MICs ≥1.5 mg/L for most maintenance dosing regimens, which is consistent with the association of a MIC ≥1.5mg/L and higher mortality (378). This observation emphasises the challenges in the treatment of MRSA infections with high MICs. Whilst the risk of toxicity also needs to be considered, unusually high doses may be required to attain the PK/PD target for increasing clinical cure and potentially survival in the presence of less susceptible pathogens.

8.2.5.6 Implications for future research

The dosing algorithm proposed in this study was aimed to achieve early PK/PD target attainment in the critically ill setting. A study is needed to compare the PTA of this algorithm with conventional dosing guidelines. Furthermore, multicentre clinical trials may also be needed to assess the clinical

outcomes in patients with confirmed MRSA infection, comparing those who have achieved early PK/PD target attainment to those who have not.

8.2.6 Acknowledgements

We would like to acknowledge the ICU team and nursing staff of Alice Springs Hospital for their support and assistance with sample collection and other relevant tasks for this study.

8.2.7 Funding

This work was supported by a PhD Scholarship provided by the National Health and Medical Research Council of Australia (D.T.); Scholarship provided by the Australian Academy of Science's Douglas and Lola Douglas (D.T.); Alice Springs Specialists' Private Practice Trust Fund (D.T.); and in part by the Australian National Health and Medical Research Council Fellowship (APP1048652 to J.A.R.). We also wish to acknowledge funding from the Australian National Health and Medical Research Council for Centre of Research Excellence (APP1099452).

8.2.8 Transparency declarations

None to declare for all authors.

8.3 Conclusion

This Chapter describes the PK of vancomycin in Indigenous patients with severe sepsis. Despite a large interindividual variability in the PK, the variability was adequately described by variations between patients in CrCL and TBW. PK parameter estimates obtained from the final model are comparable to data published in other critically ill populations. From the Monte Carlo dosing simulations, we have found that loading doses were heavily dependent on weight and CrCL, whereas maintenance doses were highly dependent on CrCL. As such, a table of different loading doses based on the patient's total body weight as well as CrCL have been proposed. This dosing algorithm aims to maximise early PK/PD target attainment and will be very useful for the Central Australian region where a high burden of MRSA is present.

Chapter 9 Summary of findings and future directions

9.1 Summary of findings and discussion

The overall aim of this thesis was to optimise commonly used antibiotics in critically ill Australian Indigenous patients with severe sepsis. The following is a summary of the major findings from projects conducted.

9.1.1 Interethnic differences in PK of antibiotics

The structured systematic review included in Chapter 2 investigates the presence of PK differences of antibiotics in different ethnic groups, as well as the probable mechanisms causing these differences.

Fifty articles were included in this analysis. We found that most differences were identified in antibiotics that are orally administered and are significantly eliminated via the hepatic route. Antibiotics with likely interethnic PK differences include ciprofloxacin, macrolides, clindamycin, tinidazole and some cephalosporins. On the other hand, PK differences were negligible for β-lactams, aminoglycosides, glycopeptides, most fluoroquinolones, linezolid and daptomycin. Furthermore, where a difference has been identified, it was most commonly found in the Asian population which generally manifested higher drug exposures up to 2-3 fold greater than Caucasian comparators. Such differences were mostly caused by a lower V_d and/or drug CL.

The PK mechanisms which contributed to these identified PK differences are most likely the polymorphisms associated with hepatic metabolism and active transporters in different parts of the body; different body size and composition; and high AGP binding fraction. On the other hand, interethnic PK differences are unlikely for antibiotics that are predominantly absorbed by passive diffusion and/or predominantly eliminated by glomerular filtration.

9.1.2 CrCL of critically ill Indigenous patients

The manuscript incorporated in Chapter 4 studied the $CrCL_m$ of 131 critically ill patients (97 Indigenous and 67 non-Indigenous). This prospective observational cohort study described the incidence of ARC and AKI in the two patient groups. Possible determinants of ARC in the Indigenous patient group were also examined. The accuracy of various mathematical equations calculating the eGFR and CrCL was also assessed, using $CrCL_m$ as reference.

Eight-hour urine was collected daily for all recruited patients, and $CrCL_m$ subsequently determined. A significantly higher prevalence of ARC (defined as ≥130mL/min) was detected in the Indigenous patient group (24.7% vs 13.7% of samples, $p<0.01$) while AKI was similar between the two groups (8.5% vs 8.5%, $p=1.00$). Up to 44% of Indigenous patients without CKD had ARC. Demographics associated with ARC include younger age, absence of diabetes, major surgery and higher baseline eGFR. All mathematical equations demonstrated limited correlation with $CrCL_m$. eGFR calculated with the CKD-EPI equations marginally manifests the highest correlation with $CrCL_m$.

Overall, the incidence of ARC in critically ill Indigenous patients was higher than non-Indigenous comparators, which was likely due to their younger age. $CrCL_m$ should be performed wherever possible to optimise dosing of renally cleared drugs.

9.1.3 Optimising meropenem dosing in critically ill Australian Indigenous patients with severe sepsis

The study incorporated in Chapter 5 is an observational population PK study performed on meropenem. Six Indigenous patients were recruited, and concentration-time data collected from serial plasma samples was combined with data obtained from 5 critically ill Caucasian patients with sepsis from a previously published study for PK analysis. Meropenem CL and V_c were described by CrCL and patient weight respectively. Patient ethnicity was not supported as a covariate in the final model, and was not included in the final model.

Although the CL was significantly lower in the Indigenous patient group when compared with the non-Indigenous patient group (median 11.0 (range 3.0–14.1) vs 17.4 (4.3–30.3) L/h, $p< 0.01$, respectively), the difference is described by lower CrCL in the Indigenous group rather than due to

the interethnic differences. A set of dosing guidelines was presented for patients with different CrCL against MICs for different typical pathogen targeted.

Thus, no clinically relevant interethnic differences in meropenem PK between the Indigenous and Caucasian groups were detected and CrCL was found to be the strongest determinant of appropriate dosing regimens. This finding supports the hypothesis suggested in Chapter 2, where interethnic PK difference is unlikely for antibiotics that are predominantly eliminated by glomerular filtration.

9.1.4 Optimising piperacillin dosing in critically ill Australian Indigenous patients with severe sepsis

The study incorporated in Chapter 6 is an observational population PK study performed on piperacillin. Nine Indigenous patients were recruited, and concentration-time data collected from serial plasma samples was used for PK analysis. The final model was used for Monte Carlo simulation with Pmetrics® to describe optimal doses of piperacillin. CL and V_c were 5.6 ± 3.2 L/h, 14.5 ± 6.6 L respectively, and were described by CrCL and total body weight respectively. A slightly lower CL in this population was found when compared with other published data, however, whether this difference is of any clinical significance is unclear. The dosing simulations concluded that a regimen of 4 g piperacillin 4-hourly is needed for a MIC of 16 mg/L for those with CrCL of 51–130 mL/min. A continuous infusion of 24 g/24 hours is needed when CrCL ≥130mL/min.

In conclusion, a lower mean CL in the Indigenous group was detected for piperacillin, although its clinical significance cannot be assessed. CrCL was found to be the strongest determinant of appropriate dosing regimens as piperacillin is predominantly renally eliminated. This finding supports the hypothesis suggested in Chapter 2, where interethnic PK difference was less likely for antibiotics that are predominantly eliminated via the kidneys. The small difference in piperacillin CL observed in this study may be contributed by differences in the hepatic CL. In this patient population, piperacillin demonstrated high interindividual PK variability, but it is well described by the CrCL. A dosing algorithm was suggested to optimise PK/PD target attainment.

9.1.5 Optimising ceftriaxone dosing in critically ill Australian Indigenous patients with severe sepsis

The study incorporated in Chapter 7 is an observational PK study performed on ceftriaxone. Five Indigenous patients with severe sepsis were recruited. Concentration-time data collected from serial plasma samples for a regimen of 1 g 12-hourly were analysed with a non-compartmental approach. The regimen of 1 g IV 12-hourly is a commonly used regimen in critically ill patients in Central Australia.

CL, V_{dss}, $T_{½}$ and elimination rate constant estimates were 0.9 (0.6-1.5) L/h, 11.2 (8.0-12.5) L, 9.5 (4.3-10.0) h and 0.07 (0.07-0.17) h^{-1} respectively. The unbound fraction of ceftriaxone ranged between 0.14 and 0.43, with a higher unbound fraction present at higher total concentrations. The CL and V_{dss} observed in this population were lower than data published in other populations.

Furthermore, the median (range) unbound concentration at time 720 minutes for the first and second dosing intervals were 7.2 (5.9-7.6) and 7.8 (4.9-11.0) mg/L respectively, which exceeds 4x MIC of all typical target pathogens.

In conclusion, the regimen of ceftriaxone 1 g IV twelve-hourly is adequate for critically ill Australian Indigenous patients with severe sepsis caused by non-resistant pathogens.

9.1.6 Optimising vancomycin dosing in critically ill Australian Indigenous patients with severe sepsis

The study incorporated in Chapter 8 is an observational population PK study performed on vancomycin. Fifteen Indigenous patients were recruited, and concentration-time data collected from serial plasma samples was used for PK analysis. A two-compartment model described the data adequately. CL and V_c were described by CrCL and patient weight respectively and were 4.6 (3.8-5.6) L/h and 25.4 (16.1-31.3) L respectively. The PK parameter estimates obtained from our study were similar to data published in other populations. Hence any interethnic differences in the PK of vancomycin are unlikely to be of a high clinical significance.

Results from the Monte Carlo dosing simulations showed that therapeutic loading doses were significantly dependent on both weight and CrCL, whereas maintenance doses were dependent predominantly on CrCL.

In conclusion, these results suggest an absence of interethnic PK differences for vancomycin, or that at the very least, that any population-level difference is not clinically significant. Although high interindividual variability exist in the population PK of vancomycin, the variation was well described by CrCL. A dosing algorithm was proposed to maximise early PK/PD target attainment in the critically ill Australian Indigenous patients.

9.2 Future directions for research

There are a number of areas which may require further attention for future research:

- A vancomycin dosing algorithm was recommended for Indigenous patients with severe sepsis in Chapter 8. This algorithm was based on a series of Monte Carlo dosing simulations. A clinical trial should be considered to compare the PK/PD target attainment rate between the regimens recommended in this thesis and those from existing dosing protocols. Furthermore, patient clinical outcome can also be assessed against PK/PD target attainment.

- A series of clinical trials could be conducted to assess the correlation between PK/PD target attainment and clinical outcome for commonly used antibiotics in the ICU for critically ill Australian Indigenous patients.

- In Chapter 6 and 7, a slightly lower mean drug CL was observed in the severely septic Indigenous patients for piperacillin and ceftriaxone. This results in slightly higher drug concentrations. Although this may increase the PTA, the incidence of toxicity is unknown. A large epidemiological study should be considered to describe the incidence of adverse drug events between Indigenous and non-Indigenous patients for conventional and optimised dosing regimens.

- All PK studies included into this thesis describe the antibiotic concentrations achieved in the plasma. However, antibiotic concentration achieved in the plasma cannot be directly extrapolated to other parts of the body. Studies exploring into antibiotic concentration in specific tissue sites are suggested for the Indigenous population.

- Approximately 20-25% of Indigenous patients admitted into the Central Australian ICU have end-stage renal failure, and RRT is required for these patients. As different types and modes of RRT can have different effects on the PK of the antibiotics used, PK studies in the critically ill Indigenous patients receiving RRT should be considered.

- Numerous anti-human immunodeficiency virus drugs were made into lower strength formulations in Thailand due to the significantly higher drug concentrations observed in Thai subjects compared with published data in other ethnic groups. This may be due to a lower hepatic CL (cytochrome P450) observed in Thai patients. PK studies in antimicrobials used for

chronic infections should also be considered for further study, especially those with a significant hepatic CL component.

- Gentamicin is a common antibiotic used in Indigenous neonatal patients. However, higher drug concentrations are commonly observed when conventional dosing regimen is used in clinical practice. A population PK study for this patient group can be considered to develop evidence-based dosing regimens for this important drug.

9.3 Conclusion

Optimisation of antibiotic dosing regimens can maximise PK/PD target attainment. Numerous factors may influence the probability of attaining these targets such as the physiological changes associated with critical illness. In our studies, we have demonstrated that there are likely no significant interethnic PK differences between the critically ill Australian Indigenous and non-Indigenous patients for meropenem, ceftriaxone, piperacillin and vancomycin. Although there is a possibility of interethnic PK differences in drug CL for antibiotics that are significantly eliminated via the hepatic route, it is unlikely to be clinically relevant. Furthermore, techniques which can improve PK/PD target attainment can be employed to maximise the anticipated clinical benefit. These techniques include accurate assessments of CrCL, evaluating risk factors for ARC, identify the MIC of the pathogen and use TDM. Nonetheless, extensive efforts are still required for future research in optimising antibiotic dosing in the critically ill Australian Indigenous patients.

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