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Augmented Renal Clearance in the Critically Ill: Prevalence, Risk Factors, and Implications for Beta-lactam Therapy

Andrew Alexander Udy

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Abstract

Background:

Beta-lactams are often used empirically in the intensive care unit (ICU), as they possess a wide spectrum of antibacterial activity. Most agents in this class are renally excreted, such that clinicians regularly modify dosing in the setting of kidney dysfunction. Rising plasma creatinine concentrations, or declining mathematical estimates of glomerular filtration, are commonly used for this purpose. Outside of this scenario, a 'one dose fits all' approach is typically employed, largely based on research from non-critically ill cohorts.

However, previous pharmacokinetic studies have demonstrated that many critically ill patients manifest significantly elevated beta-lactam clearance, often in parallel with augmented creatinine clearance (CL_{CR}). This in turn promotes sub-therapeutic concentrations for lengthy periods, potentially leading to treatment failure or the selection of resistant organisms. Currently little data are available that examine the epidemiology of this phenomenon, as augmented renal clearance (ARC) is poorly visible to the clinician.

The aims of this research were therefore to; a) examine the relationship between elevated CL_{CR} and plasma beta-lactam concentrations; b) explore the potential cardiovascular mechanisms promoting ARC; c) determine the prevalence of ARC in a heterogonous cohort of recently admitted patients with normal plasma creatinine (CR) concentrations; and d) evaluate the utility of mathematical estimates of glomerular filtration (GFR) in this setting.

Methods:

Relevant literature was reviewed concerning changes in renal function and beta-lactam pharmacokinetics in the critically ill. Four major clinical studies were performed; a) an analysis of plasma beta-lactam trough concentrations and CL_{CR} measures in select critically ill patients, b) a comparison of cardiac output and CL_{CR} in trauma and septic patients, c) a multicentre study of the prevalence of ARC in a cohort of recently admitted patients with normal plasma CR concentrations, and d) a comparison of mathematical estimates of GFR with measured CL_{CR} in this setting. Data were collected prospectively, with a timed urinary CL_{CR} employed as the primary measure of renal function. Demographic, anthropometric, therapeutic, illness-severity and outcome data were

recorded concurrently. Ethical approval was obtained for all clinical investigations (GC2008/054, HREC 2007/188, HREC/09/QRBW/192).

Results:

Fifty-two concurrent trough beta-lactam concentrations and CL_{CR} measures were utilised in the first study. Piperacillin was the most frequent beta-lactam prescribed (48%), while empirical cover and *Staphylococcus spp*. were the most common indications for therapy (62%). In only 58% (n=30) was the trough drug concentration ≥ the minimum inhibitory concentration (MIC), falling to 31% (n=16) when using 4 x MIC as the target. CL_{CR} values ≥ 130ml/min/1.73m^2 were associated with trough concentrations < MIC in 82% (p<0.001), and < 4 x MIC in 72% (p<0.001). CL_{CR} remained a significant predictor of sub-therapeutic concentrations in multivariate analysis.

Seventy-one patients contributed data to the second study (sepsis n=43, multitrauma n=28). Overall, 57.7% of the cohort manifested ARC, although there was a greater prevalence in trauma (85.7 versus 39.5%, p<0.001). An improved correlation between cardiac index (CI) and CL_{CR} was seen in septic (r=0.508, p=0.001), as compared to trauma (r=-0.012, p=0.951) patients. Those manifesting ARC were younger (p<0.001), male (p=0.012), with lower acute physiology and chronic health evaluation (APACHE) II (p=0.008) and modified sequential organ failure assessment (SOFA) scores (p=0.013), and higher cardiac indices (p=0.013). In multivariate analysis, age ≤ 50 years, trauma, and a modified SOFA score ≤ 4, were identified as significant risk factors. As a combined score, these parameters had greater utility in identifying ARC, compared with CI assessment alone.

Two-hundred and eighty-one patients were recruited into the multicentre study, contributing 1660 individual CL_{CR} measures. The mean (95% CI) age was 54.4 (52.5-56.4) years, APACHE II score 16 (15.2-16.7), and ICU mortality 8.5%. Overall, 65.1% manifested ARC on at-least one occasion during the first seven study days; the majority (74%) of whom did so on ≥ 50% of their CL_{CR} measures. Utilising a mixed effects model, the presence of ARC on study day 1, strongly predicted (p=0.019) sustained elevation of CL_{CR} in these patients over the first week in ICU.

One hundred and ten patients (n = 110) were included in the final analysis examining the utility of mathematical estimates of glomerular filtration. 63.6% were male, the mean age

was 50.9 (16.9) years, 57.3% received invasive mechanical ventilation, and 30% required vasopressor support. The mean CL_{CR} was 125 (45.1) ml/min/1.73m^2, compared to a Chronic Kidney Disease-Epidemiology Collaboration estimated glomerular filtration rate (CKD-EPI eGFR) of 101 (23.7) ml/min/1.73 m^2 ($p<0.001$). Moderate correlation was evident ($r=0.72$), although there was significant bias and imprecision (24.4 +/− 32.5 ml/min/1.73 m^2). In those patients with a CKD-EPI eGFR between 60–119 ml/min/1.73 m^2 ($n = 77$), 41.6% displayed ARC ($CL_{CR} \geq 130$ ml/min/1.73 m^2), while 7.8% had a $CL_{CR} < 60$ ml/min/1.73 m^2.

Conclusions:

Data from these investigations highlight the following key findings; i) ARC is strongly associated with sub-therapeutic beta-lactam concentrations; ii) younger patients admitted post trauma appear to be at greatest risk, likely a reflection of available organ reserve and systemic inflammation; iii) ARC is highly prevalent in recently admitted patients with normal plasma CR concentrations; and iv) mathematical estimates perform poorly in comparison to measured CL_{CR} in this setting.

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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Andrew Alexander Udy

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Publications During Candidature

Book Chapters

A. Udy and J. Lipman. Chapter 12 - Importance of High Creatinine Clearance for Antibacterial Treatment in Sepsis. In: **Sepsis Management PIRO and MODS.** Rello J, Lipman J, Lisboa T (Eds.) 2011, Springer-Verlag, Berlin Heidelberg.

A. Udy, JA. Roberts, J. Lipman. Augmented Renal Clearance (ARC) – un-ravelling the mystery of elevated antibiotic clearance. In: **Yearbook of Intensive Care and Emergency Medicine.** Vincent JL (Ed). 2010, Springer, Heidelberg.

Journal Articles, Abstracts and Letters

Roberts JA, **Udy AA**, Bulitta JB, Stuart J, Jarrett P, Starr T, Lassig-Smith M, Roberts NA, Dunlop R, Hayashi Y, Wallis SC, Lipman J. Doripenem population pharmacokinetics and dosing requirements for critically ill patients receiving continuous venovenous hemodiafiltration. **Journal of Antimicrobial Agents**, 2014; doi: pii: dku177.

Jamal J-A, Mat-Nor M-B, Mohamad-Nor F-S, **Udy AA**, Lipman J, Roberts JA. A national survey of renal replacement therapy prescribing practice for acute kidney injury in Malaysian intensive care units. **Nephrology**, 2014; doi: 10.1111/nep.12276.

Jamal J-A, **Udy AA**, Lipman J, Roberts JA. The impact of variation in renal replacement therapy settings on piperacillin, meropenem, and vancomycin drug clearance in the critically ill: An analysis of published literature and dosing regimens. **Critical Care Medicine**, 2014; 42(7): 1640-1650.

Udy AA, Morton FJA, Nguyen-Pham S, Jarrett P, Lassig-Smith M, Stuart J, Dunlop R, Starr T, Boots RJ, Lipman J. A comparison of CKD-EPI estimated glomerular filtration rate and measured creatinine clearance in recently admitted critically ill patients with normal plasma creatinine concentrations. **BMC Nephrology**, 2013; 14: 250.

Udy AA, Baptista JP, Lim NL, Joynt G, Jarrett P, Wockner L, Boots RJ, Lipman J. Augmented Renal Clearance in ICU: Results of a multicenter observational study of renal function in critically ill patients with normal plasma creatinine concentrations. **Critical Care Medicine**, 2014; 42(3): 520-527.

Udy AA, Roberts JA, Lipman J. Clinical implications of antibiotic pharmacokinetic principles. **Intensive Care Medicine**, 2013; 39(12): 2070-2082.

Sturgess DJ, Parmar D, Dulhunty J, Hegde R, Jarrett P, **Udy A**. An evaluation of plasma B-type natriuretic peptide as a marker of left ventricular diastolic dysfunction in non-cardiac critical care. **Anaesthesia and Intensive Care**, 2013; 41(5): 591-595.

Dulhunty JM, Roberts JA, Davis JS, Webb SA, Bellomo R, Gomersall C, Shirwadkar C, Eastwood GM, Myburgh J, Paterson DL, Starr T, **Udy AA**, Paul SK, Lipman J and the ANZICS Clinical Trials Group and ASID Clinical Research Network. A protocol for a multicentre randomised controlled trial of continuous beta-lactam infusion compared with intermittent beta-lactam dosing in critically ill patients with severe sepsis: the BLING II study. **Critical Care and Resuscitation**, 2013; 15(3): 179-185.

Udy AA, Roberts JA, Shorr AF, Boots RJ, Lipman J. Augmented renal clearance in septic and traumatized patients with normal plasma creatinine concentrations: Identifying at-risk patients. **Critical Care,** 2013; 17(1): R35.

Udy AA, Roberts JA, Lipman J. How should we dose antibiotics for pneumonia in the ICU. **Current Opinion in Infectious Diseases**, 2013; 26(2): 189-195.

Lonsdale DO, **Udy A**, Roberts JA, Lipman J. Antibacterial therapeutic drug monitoring in cerebrospinal fluid: Difficulty in achieving adequate drug concentrations. **Journal of Neurosurgery** 2012; 118(2): 297-301.

Hayashi Y, Lipman J, **Udy AA**, Ng M, McWhinney B, Ungerer J, Lust K, Roberts JA. β-Lactam therapeutic drug monitoring in the critically ill: Optimising drug exposure in patients with fluctuating renal function, and hypoalbuminaemia. **International Journal of Antimicrobial Agents** 2013; 41(2): 162-166.

Van der Merwe F, Wallis S, **Udy A**. Understanding the impact of critical illness on drug pharmacokinetics - scientifically robust study design. **Journal of Clinical Toxicology** 2012; S4:002. doi:10.4172/2161-0495.S4-002.

Udy A, Altukroni M, Jarrett P, Roberts JA, Lipman J. A comparison of pulse contour wave analysis and ultrasonic cardiac output monitoring in the critically ill. **Anaesthesia and Intensive Care** 2012; 40(4): 631-637.

Udy A, Roberts JA, De Waele JJ, Paterson DL, Lipman J. What's behind the failure of emerging antibiotics in the critically ill? Understanding the impact of altered pharmacokinetics and augmented renal clearance. **International Journal of Antimicrobial Agents** 2012; 39(6): 455-457.

Udy A, Varghese J, Altukroni M, Briscoe S, McWhinney B, Ungerer J, Lipman J, Roberts JA. Sub-therapeutic initial β-lactam concentrations in select critically ill patients: association between augmented renal clearance and low trough drug concentrations. **Chest** 2012; 142(1): 30-39.

Lipman J, **Udy AA**, Roberts JA. Do we understand the impact of altered physiology, consequent interventions and resultant clinical scenarios in the intensive care unit? The antibiotic story. **Anaesthesia and Intensive Care** 2011; 39(6): 999-1000.

Martin JH, Fay MF, **Udy A**, Roberts J, Kirkpatrick C, Ungerer J, Lipman J. Pitfalls of using estimations of glomerular filtration rate in an intensive care population. **Internal Medicine Journal** 2011; 41(7): 537-543.

Udy A, Roberts JA, Lipman J. Implications of augmented renal clearance in critically ill patients. **Nature Reviews-Nephrology** 2011; 7(9): 539-543.

Baptista JP, **Udy AA**, Sousa E, Pimentel J, Wang L, Roberts JA, Lipman J. Augmented renal clearance (ARC) in critically ill patients with SIRS and sepsis - Are estimates of renal function accurate? **Critical Care** 2011; 15(3): R139.

Hosein S, **Udy A**, Lipman J. Physiological changes in the critically ill patient with sepsis. **Current Pharmaceutical Biotechnology** 2011; 12(12): 1991-1995.

Udy A, Putt MT, Boots RJ, Lipman J. ARC - Augmented Renal Clearance. **Current Pharmaceutical Biotechnology** 2011; 12(12): 2020-2029.

Roberts JA, Taccone FS, **Udy AA**, Vincent JL, Jacobs F, Lipman J. Vancomycin dosing in critically ill patients – robust methods for improved continuous infusion regimens. **Antimicrobial Agents and Chemotherapy** 2011; 55(6): 2704-2709.

Roberts JA, Roberts MS, Semark A, **Udy AA**, Kirkpatrick CM, Paterson DL, Roberts MJ, Kruger P, Lipman J. Antibiotic dosing in the 'at-risk' critically ill patient: Linking pathophysiology with pharmacokinetic/pharmacodynamics in sepsis and trauma patients. **BMC Anesthesiology** 2011; 11(5).

Udy A, Boots RJ, Senthuran S, Stuart J, Deans R, Lassig-Smith M, Lipman J. Augmented Creatinine Clearance in Traumatic Brain Injury. **Anesthesia and Analgesia** 2010; 111(6): 1505-1510.

Udy A, Putt MT, Shanmugathasan S, Roberts JA, Lipman J. Augmented Renal Clearance (ARC) in the Intensive Care Unit - An illustrative Case Series. **International Journal of Antimicrobial Agents** 2010; 35(6): 606-608.

Udy A, Roberts JA, Boots RJ, Paterson DL, Lipman J. ARC - Augmented Renal Clearance: Implications for Antibiotic Dosing in the Critically Ill. **Clinical Pharmacokinetics** 2010; 49(1): 1-16.

Udy A, Roberts JA, Boots R, Lipman J. You only find what you look for: the importance of high creatinine clearance in the critically ill. **Anaesthesia and Intensive Care** 2009; 37(1): 11-13.

Conference Presentations

Not adjusting drug doses in critical illness, what's the risk? – Annual Scientific Meeting, College of Intensive Care Medicine, Brisbane, Australia, June 2014.

Implications of augmented renal clearance on antibiotic therapy in ICU patients – Clinical Infectious Diseases Forum, Pfizer Inc, Sydney, Australia, July 2013.

Augmented renal clearance (ARC) is common in multi-trauma patients without renal impairment. Australian and New Zealand Intensive Care Society (ANZICS) Annual Scientific Meeting, Adelaide, Australia, October 2012.

Sepsis Management: Antibacterial dosing in the ICU - Sedation and Analgesia Therapy, and Organ Function Protection Training Course, 1st Affiliated Hospital of Kunming Medical College, Kunming, China, August 2012.

Antimicrobial prescription in the ICU – physiologically sound dosing – 1st Annual Congress of the Faculty of Consulting Physicians of South Africa, Cape Town, Republic of South Africa, May 2012.

Antimicrobial Dosing in the Critically Ill – Society of Hospital Pharmacists of Australia, Continuing Education Session, Brisbane, Australia, October 2010.

Augmented renal clearance (ARC) in critically ill patients with SIRS and sepsis: are estimates of renal function accurate? Royal Brisbane and Women's Hospital Healthcare Symposium, Brisbane, Australia, October 2010.

Augmented Renal Clearance (ARC) in Traumatic Brain Injury. Annual Scientific Meeting, College of Intensive Care Medicine, Sydney, Australia, June 2010.

The Critical Care Patient – Society of Hospital Pharmacists of Australia, Infectious Diseases Symposium, Brisbane, Australia, August 2009.

Conference Posters / Abstracts

The Influence of Augmented Renal Clearance on Plasma Concentrations in Critically Ill Patients Receiving Beta-lactam Therapy. 11th Congress of the World Federation of Societies of Intensive and Critical Care Medicine (WFSICCM) – "Critical Care for All – Providing More for Less", Durban, Republic of South Africa 2013.

Augmented Renal Clearance: A Common and Sustained Finding in Patients without Renal Impairment during the First Seven Days in ICU. 11th Congress of the World Federation of Societies of Intensive and Critical Care Medicine (WFSICCM) – "Critical Care for All – Providing More for Less", Durban, Republic of South Africa 2013.

Minimally Invasive Cardiac Output Monitoring is Useful in Identifying Septic Critically Ill Patients with Augmented Renal Clearance (ARC). Australian and New

Zealand Intensive Care Society (ANZICS) Annual Scientific Meeting, Adelaide, Australia 2012.

Augmented renal clearance (ARC) in critically ill patients with SIRS and sepsis: Are estimates of renal function accurate? Royal Brisbane and Women's Hospital Healthcare Symposium, Brisbane, Australia 2010.

Augmented Renal Clearance (ARC) in Traumatic Brain Injury. Annual Scientific Meeting, College of Intensive Care Medicine, Sydney, Australia 2010.

Augmented Renal Clearance (ARC) in Traumatic Brain Injury. 30th International Symposium on Intensive Care and Emergency Medicine, Brussels, Belgium 2010.

Augmented Renal Clearance (ARC) in Traumatic Brain Injury. Royal Brisbane and Women's Hospital Healthcare Symposium, Brisbane, Australia 2009.

Publications Included in this Thesis

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Contributor	Statement of contribution
Udy A (Candidate)	Literature search and data synthesis (100%) Prepared the manuscript and figures (85%)
Roberts JA	Prepared & edited the manuscript (10%)
Lipman J	Prepared & edited the manuscript (5%)

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Contributor	Statement of contribution
Udy A (Candidate)	Literature search and data synthesis (100%) Prepared the manuscript and figures (85%)
Putt MT	Prepared & edited the manuscript (5%)
Boots RJ	Prepared & edited the manuscript (5%)
Lipman J	Prepared & edited the manuscript (5%)

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Udy A (Candidate)	Literature search and data synthesis (100%) Prepared the manuscript and figures (80%)
Roberts JA	Prepared & edited the manuscript (15%)
Lipman J	Prepared & edited the manuscript (5%)

Udy A, Roberts JA, Boots RJ, Paterson DL, Lipman J. ARC - Augmented Renal Clearance: Implications for Antibiotic Dosing in the Critically Ill. **Clinical Pharmacokinetics** 2010; 49(1): 1-16 – incorporated into **Chapter 3**.

Contributor(s)	Statement of contribution
Udy A (Candidate)	Literature search and data synthesis (100%) Prepared the manuscript (75%)
Roberts JA	Prepared & edited the manuscript (10%)
Boots RJ, Paterson DL, & Lipman J	Prepared & edited the manuscript (5% each)

Udy A, Roberts JA, De Waele JJ, Paterson DL, Lipman J. What's behind the failure of emerging antibiotics in the critically ill? Understanding the impact of altered pharmacokinetics and augmented renal clearance. **International Journal of Antimicrobial Agents** 2012; 39(6): 455-457 – incorporated into **Chapter 3**.

Contributor(s)	Statement of contribution
Udy A (Candidate)	Literature search and data synthesis (100%) Prepared the manuscript (80%)
Roberts JA, De Waele JJ, Paterson DL, & Lipman J	Prepared & edited the manuscript (5% each)

A. Udy and J. Lipman. Chapter 12 - Importance of High Creatinine Clearance for Antibacterial Treatment in Sepsis. In: **Sepsis Management PIRO and MODS.** Rello J, Lipman J, Lisboa T (Eds.) 2011, Springer-Verlag, Berlin Heidelberg – incorporated into **Chapter 3**.

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Udy A (Candidate)	Literature search and data synthesis (100%) Prepared the manuscript (90%)
Lipman J	Prepared & edited the manuscript (10%)

Udy A, Varghese J, Altukroni M, Briscoe S, McWhinney B, Ungerer J, Lipman J, Roberts JA. Sub-therapeutic initial beta-lactam concentrations in select critically ill patients: association between augmented renal clearance and low trough drug concentrations. **Chest** 2012; 142(1): 30-39 – incorporated as **Chapter 4**.

Contributor	Statement of contribution
Udy A (Candidate)	Study design & methodology (15%)

	Collated study data (30%) Performed the statistical analysis (90%) Prepared the manuscript (80%)
Varghese J	Study design & methodology (15%) Collated study data (50%) Performed the statistical analysis (10%) Prepared & edited the manuscript (5%)
Altukroni M	Collated study data (20%)
Briscoe S & McWhinney B	Performed the laboratory analysis (45% each)
Ungerer J	Performed the laboratory analysis (10%)
Lipman J	Prepared & edited the manuscript (5%)
Roberts JA	Study design & methodology (70%) Prepared & edited the manuscript (10%)

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Contributor	Statement of contribution
Udy AA (Candidate)	Study design & methodology (20%) Collected study data (90%) Performed the statistical analysis (80%) Prepared the manuscript (75%)
Roberts JA	Study design & methodology (70%) Collected data (10%) Prepared & edited the manuscript (10%)
Shorr AF	Performed the statistical analysis (20%) Prepared & edited the manuscript (5%)
Boots RJ	Prepared & edited the manuscript (5%)
Lipman J	Study design & methodology (10%) Prepared & edited the manuscript (5%)

Udy AA, Baptista JP, Lim NL, Joynt G, Jarrett P, Wockner L, Boots RJ, Lipman J. Augmented Renal Clearance in the ICU: Results of a multicenter observational study of

renal function in critically ill patients with normal plasma creatinine concentrations. **Critical Care Medicine**, 2014; 42(3): 520-527. – incorporated as **Chapter 6**.

Contributor	Statement of contribution
Udy AA (Candidate)	Study design & methodology (90%) Collected study data (40%) Performed the statistical analysis (80%) Prepared the manuscript (75%)
Baptista JP, Lim NL, & Joynt G	Collected study data (15% each) Prepared & edited the manuscript (5% each)
Jarrett P	Collected study data (15%)
Wockner L	Performed the statistical analysis (20%)
Boots RJ	Prepared & edited the manuscript (5%)
Lipman J	Study design & methodology (10%) Prepared & edited the manuscript (5%)

Udy AA, Morton FJA, Nguyen-Pham S, Jarrett P, Lassig-Smith M, Stuart J, Dunlop R, Starr T, Boots RJ, Lipman J. A comparison of CKD-EPI estimated glomerular filtration rate and measured creatinine clearance in recently admitted critically ill patients with normal plasma creatinine concentrations. **BMC Nephrology**, 2013; 14: 250 – incorporated as **Chapter 7**.

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Udy AA (Candidate)	Study design & methodology (100%) Collected study data (65%) Performed the statistical analysis (100%) Prepared the manuscript (90%)
Morton FJA, Nguyen-Pham S, Jarrett P, Lassig-Smith M, Stuart J, Dunlop R & Starr T	Collected study data (5% each)
Boots RJ & Lipman J	Prepared & edited the manuscript (5% each)

Contributions by Others to the Thesis

Professor Jeffrey Lipman (The University of Queensland) and Associate Professor Robert Boots (The University of Queensland) contributed significantly to the design, methodology, implementation, and interpretation of the studies presented. Professor Lipman conceived the central premise of these works, after decades working and researching in this area. His expert advice, mentorship and guidance were fundamental to completing the Higher Research Degree Candidature. Associate Professor Boots provided crucial revisions to many aspects, substantially improving the overall quality of the thesis.

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Statement of Parts of the Thesis Submitted to Qualify for the Award of Another Degree

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critical care medicine, infectious diseases, pharmacology, renal function

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Fields of Research (FoR) Classification

FoR code: 1103 Clinical Sciences 70%
FoR code: 1115 Pharmacology and Pharmaceutical Sciences 30%

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List of Abbreviations

95% CI – 95% Confidence Interval
AKI – Acute Kidney Injury
APACHE – Acute Physiology and Chronic Health Evaluation
ARC – Augmented Renal Clearance
AUC – Area Under the Curve
BMI – Body Mass Index
BSA – Body Surface Area
CG CL_{CR} – Cockcroft-Gault Calculated Creatinine Clearance
CI – Cardiac Index
CKD – Chronic Kidney Disease
CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration
CL - Clearance
CL_{CR} – Creatinine Clearance
CL_R – Renal Clearance
C_{max} – Maximum plasma concentration
C_{min} – Minimum plasma concentration
CO – Cardiac Output
CR – Creatinine
CV – Coefficient of Variance
CVP – Central Venous Pressure
eGFR – Estimated Glomerular Filtration Rate
EUCAST – European Committee of Antimicrobial Susceptibility Testing
$fT_{>MIC}$ – Time above MIC, as a fraction of the Dosing Interval
GFR – Glomerular Filtration Rate
HIV – Human Immunodeficiency Virus
HPLC – High Performance Liquid Chromatography
HR – Heart Rate
ICU – Intensive Care Unit
IDC – Indwelling Urinary Catheter
IDMS – Isotope Dilution Mass Spectrometry
IQR – Interquartile Range
LOS – Length of Stay
MAP – Mean Arterial Pressure

ME – Microbiologically Evaluable

MDRD – Modification of Diet in Renal Disease

MIC – Minimum Inhibitory Concentration

MITT – Microbiological Intention to Treat

MODS – Multiple Organ Dysfunction Syndrome

NP – Nosocomial Pneumonia

OR – Odds Ratio

PAC – Pulmonary Artery Catheter

PK – Pharmacokinetics

PD – Pharmacodynamics

ROC – Receiver Operating Characteristic

RR – Respiratory Rate

RRT – Renal Replacement Therapy

SAPS II – Simplified Acute Physiology Score

SD – Standard Deviation

SIRS – Systemic Inflammatory Response Syndrome

SOFA – Sequential Organ Failure Assessment

$T_{1/2}$ – Half-life

TBI – Traumatic Brain Injury

TDM – Therapeutic Drug Monitoring

WCC – White Cell Count

VAP – Ventilator Associated Pneumonia

V_d – Volume of Distribution

PART ONE - INTRODUCTION

Chapter 1

Overview

1.1 Introduction

Intensive care and hospital mortality rates for severe sepsis continue to be unacceptably high (1). Consensus guidelines on management have been published (2, 3), in an attempt to improve outcomes. A cornerstone of good clinical practice remains the timely application of antimicrobial agents (4-7), of both an appropriate dose and spectrum. Unfortunately, while drug development has largely stagnated, commonly encountered bacterial pathogens are continuing to evolve new resistance patterns, challenging the prescriber to improve antibacterial application (8). Tailoring antibacterial therapy to the patients' physiology therefore seems inherently logical (9).

Traditional antibacterial pharmaceutical research has largely focused on studies in healthy volunteers or hospitalised patients (10). Empirical dosing regimens in the critically ill, often extrapolated from such work, are mostly flawed. They fail to consider the distinctive demographic and physiology of this group (11), in particular the substantial changes in organ function that can be recognised. This will result in significant changes in key pharmacokinetic (PK) parameters, such as renal (CL_R) and total body clearance (CL) (12). This is turn may promote sub-therapeutic drug concentrations for lengthy periods of the dosing interval, treatment failure, and / or the development of antibacterial resistance (9).

The critically ill represent a unique population of hospitalised patients, manifesting physiology that is infrequently seen in a ward or outpatient setting, and often requiring invasive support to maintain homeostasis. A common feature is that of the systemic inflammatory response syndrome (SIRS), an innate humoral-based response to cellular inflammation and trauma (13-15). In the presence of either presumed or proven infection, this is then termed sepsis (16), while the development of end organ dysfunction and hypotension resistant to fluid resuscitation can be regarded as severe sepsis and septic shock respectively (16). Inadequately treated this can lead to multiple organ dysfunction (MODS) including the development of acute kidney injury (AKI) (17). In this setting, consideration of antibacterial dose reduction may be necessary, and is often the primary focus for clinicians.

However, the converse, *escalating* antibacterial doses in patients demonstrating supra-normal renal drug elimination or augmented renal clearance (ARC) is rarely considered in clinical practice (12). This is likely due to a lack of appreciation of this phenomenon, the poor sensitivity of standard diagnostic tests to identify ARC, and a paucity of clinical end-points to titrate antibacterial drug prescription against. To date, there has been scarce research in this area, limiting the conclusions that can be drawn from existing data. Both the underlying disease and the nature and frequency of invasive therapies provided in the ICU, are likely to contribute to this process. For prescribers, an appreciation of ARC and its implications for beta-lactam antibacterial drug exposure in this setting is essential.

1.2 Aims

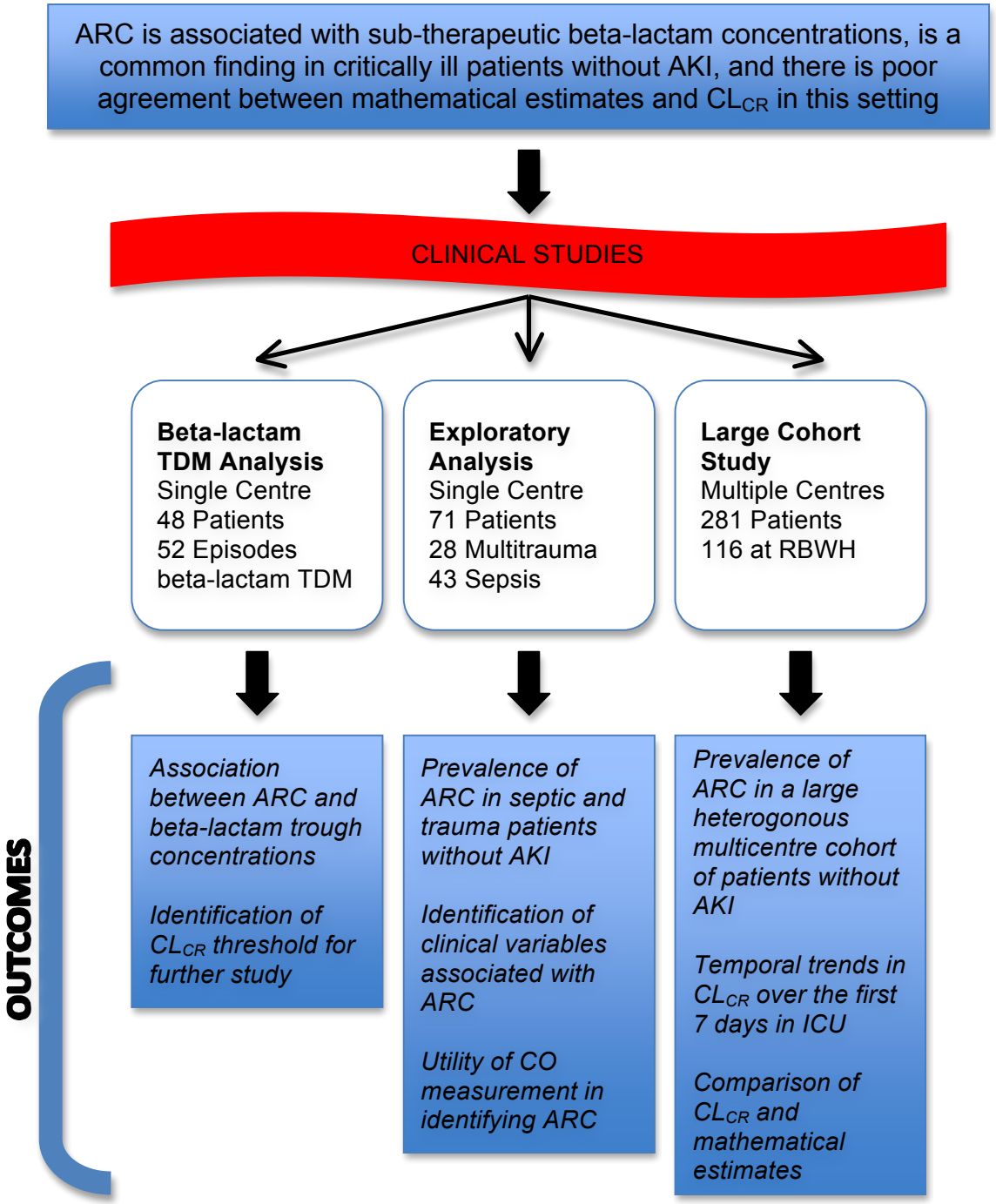
The broad aims of this research were to:

a) Examine the relationship between plasma beta-lactam concentrations and ARC in critically ill patients receiving standard doses
b) Explore the potential cardiovascular mechanisms promoting ARC in septic and traumatised patients admitted to the intensive care unit (ICU)
c) Determine the prevalence of ARC in a heterogonous population of recently admitted critically ill patients with normal plasma creatinine (CR) concentrations
d) Compare mathematical estimates of glomerular filtration and measured creatinine clearance (CL_{CR}) in critically ill patients without overt renal impairment
e) Review the implications of ARC for adequate beta-lactam exposure and future dosing strategies in the critically ill

1.3 Thesis Outline

Figure 1.1 outlines the framework of the thesis in relation to the clinical studies undertaken. Specific aims and hypotheses along with the relevant references to published work are provided in Table 1.1.

Figure 1.1 Schematic Outline of Clinical Studies Included in this Thesis



Caption: Schematic outline of the major clinical studies undertaken during the Higher Research Degree Candidature.

Table 1.1 Thesis Outline, Aims/Hypotheses, and References

Chapter	Title	Specific Aim/Hypothesis	References
PART ONE – Introduction			
2	ARC: Definition, Mechanisms and Risk Factors	-	Udy A, Roberts JA, Lipman J. Implications of augmented renal clearance in critically ill patients. Nature Reviews-Nephrology 2011; 7(9): 539-43 Udy A, Putt MT, Boots RJ, Lipman J. ARC - Augmented Renal Clearance. Current Pharmaceutical Biotechnology 2011; 12(12): 2020-9 Udy AA, Roberts JA, Lipman J. Clinical implications of antibiotic pharmacokinetic principles. Intensive Care Medicine, 2013; 39(12): 2070-82
3	ARC and Beta-lactam PK-PD in the Critically Ill	ARC has significant implications for effective beta-lactam dosing in the critically ill and may require novel dosing strategies	Udy A, Roberts JA, Boots RJ, Paterson DL, Lipman J. ARC - Augmented Renal Clearance: Implications for Antibiotic Dosing in the Critically Ill. Clinical Pharmacokinetics 2010; 49(1): 1-16 Udy A, Roberts JA, De Waele JJ, Paterson DL, Lipman J. What's behind the failure of emerging antibiotics in the critically ill? Understanding the impact of altered pharmacokinetics and augmented renal clearance. International Journal of Antimicrobial Agents 2012; 39(6): 455-7 A. Udy and J. Lipman. Chapter 12 - Importance of High Creatinine Clearance for Antibacterial Treatment in Sepsis. In: Sepsis Management PIRO and MODS. Rello J, Lipman J, Lisboa T (Eds.) 2011, Springer-Verlag, Berlin Heidelberg

			Udy AA, Roberts JA, Lipman J. Clinical implications of antibiotic pharmacokinetic principles. Intensive Care Medicine, 2013; 39(12): 2070-82
PART TWO – Clinical Studies			
4	Sub-therapeutic Beta-lactam Concentrations in Select Critically Ill Patients: Association Between ARC and Low Trough Drug Concentrations	Augmented CL_{CR} is strongly associated with sub-optimal beta-lactam plasma concentrations	Udy A, Varghese J, Altukroni M, Briscoe S, McWhinney B, Ungerer J, Lipman J, Roberts JA. Sub-therapeutic initial beta-lactam concentrations in select critically ill patients: association between augmented renal clearance and low trough drug concentrations. Chest 2012; 142(1): 30-39
5	ARC in Septic and Traumatized Patients with Normal Plasma Creatinine Concentrations: Identifying At-risk Patients	Elevated CL_{CR} is correlated with higher cardiac indices, and provides a useful method of identifying patients at risk of ARC	Udy AA, Roberts JA, Shorr AF, Boots RJ, Lipman J. Augmented renal clearance in septic and traumatized patients with normal plasma creatinine concentrations: Identifying at-risk patients. Critical Care, 2013; 17(1): R35
6	ARC in the ICU: Results of a Multicentre Observational Study of Renal Function in Critically Ill Patients with Normal Plasma Creatinine Concentrations	ARC is prevalent amongst patients with normal plasma CR concentrations recently admitted to critical care units	Udy AA, Baptista JP, Lim NL, Joynt G, Jarrett P, Wockner L, Boots RJ, Lipman J. Augmented Renal Clearance in the ICU: Results of a multicenter observational study of renal function in critically ill patients with normal plasma creatinine concentrations. Critical Care Medicine, 2014; 42(3): 520-527
7	A Comparison of CKD-EPI Estimated Glomerular Filtration Rate and Measured Creatinine Clearance in Recently Admitted Critically Ill Patients with Normal Plasma Creatinine Concentrations	Mathematical estimates perform poorly in comparison to CL_{CR} measures in critically ill patients with normal plasma CR concentrations	Udy AA, Morton FJA, Nguyen-Pham S, Jarrett P, Lassig-Smith M, Stuart J, Dunlop R, Starr T, Boots RJ, Lipman J. A comparison of CKD-EPI estimated glomerular filtration rate and measured creatinine clearance in recently admitted critically ill patients with normal plasma creatinine concentrations. BMC Nephrology, 2013; 14: 250
PART THREE - Discussion			
8	Discussion and Overall Findings	-	-

Chapter 2

ARC: Definition, Mechanisms and Risk Factors

2.1 Chapter Overview

This chapter provides a comprehensive review of the likely mechanisms and risk factors underpinning ARC in the critically ill. As this represents a new concept in critical care pharmacology, a simple definition is proposed, with the aim of promoting future research in this area.

A combination of text, figures, and tables from previously published manuscripts (as outlined in Chapter 1) form the majority of this chapter. Where appropriate, additional data have been included if they were published subsequent to these manuscripts, and further inform the thesis. The layout has been adjusted to fit the overall style of the thesis. The references are found alongside those for the other chapters, at the conclusion of the main body.

2.2 Introduction

The critically ill represent a unique patient population, unlike that encountered in either the outpatient or general ward setting. Their physiology is significantly disturbed (18), both as a consequence of the underlying disease process, and also as a result of invasive procedures and interventions (2, 3). In this setting, interpretation of standard diagnostic tests, and the application of conventional therapies, are often flawed, as they fail to consider the unique characteristics of this group. One such area is the assessment of renal function, and the application to antibacterial drug prescription in the ICU.

To a large extent, clinical and biochemical assessment of renal function in this setting is focused on identifying kidney injury, with a view to correcting potential causes, avoiding complications, and monitoring the need for renal replacement therapy (RRT). Although newer biomarkers are being investigated, plasma CR concentrations continue to be used widely as an indicator of the glomerular filtration rate (GFR), arguably the most important index of renal function (19). In this respect, elevated plasma CR concentrations are routinely interpreted as representing renal dysfunction, and prompt dose reduction of

renally eliminated drugs. However, the converse, *escalating* dosing in response to augmented elimination, is seldom considered in clinical practice.

This is largely a reflection of the poor utility of plasma CR concentrations when reported in the reference range, and the lack of objective feedback to allow optimisation of antibacterial drug dosing. This chapter explores the biological rationale and mechanisms underlying ARC in the critically ill, based on existing literature. The difficulty with interpreting standard tests of renal function is reviewed, along with those patients at greatest risk for ARC.

2.3 Defining ARC

ARC can be defined as the enhanced renal elimination of circulating solute (such as nitrogenous waste products or pharmaceuticals), and is quantified as the volume of plasma cleared of a given substance by the kidneys per unit time. In terms of the mechanisms involved, three important processes occur in the kidney - namely glomerular filtration, tubular re-absorption and tubular secretion. The relative contribution from each process will vary depending upon the solute in question, but the most widely accepted descriptor of renal function in both health and disease is the GFR (19). This defines the volume of plasma filtered by the kidney per unit time, and normal values are approximately 130 ml/min/1.73m^2 and 120 ml/min/1.73m^2 in young men and women respectively (19).

Defining ARC in terms of glomerular filtration is convenient, as it is both measurable and repeatable, such that trends can be followed over time, and in response to specific interventions. However, using the GFR for this purpose is complicated, as there is no consensus on the most accurate technique to quantify this at the bedside, nor what are the accepted normal values for any given population. In addition, the GFR provides no specific information on tubular function, which may be a key consideration for certain pharmaceuticals (20). Specifically, while data concerning such changes in critical illness are currently lacking, evidence for altered tubular drug handling has been reported outside of the ICU, such as in HIV infection (21), and may contribute significantly to altered renal drug elimination (22).

Despite these limitations, defining ARC in terms of an elevated GFR is attractive, particularly as previous authors have identified this as a key PK covariate in predicting

drug CL for renally eliminated agents (23-38). Any 'cut-off' would ideally be intimately related to a measure of drug CL or plasma concentrations, such that values above this figure would pre-dispose to inadequate drug exposure. Unfortunately, such data are not widely available. Importantly, any specific definition of ARC will only act as a pointer to potential sub-therapeutic drug exposure, prompting either implementation of therapeutic drug monitoring (TDM) or empirical application of higher dosing in those agents with a favourable therapeutic index.

2.4 Identifying ARC using Established Measures of Renal Function in the Critically Ill

Some form of estimate of renal function is routinely required by clinicians, both to guide and optimise ongoing therapy, and as a means of documenting and following deteriorating organ function. Clinical features, such as oliguria (urine output < 0.5 ml/kg/hr), and biochemical indices (such as plasma CR concentrations) are routinely used for such purposes. However, in these circumstances, the focus is on identifying renal impairment, as opposed to augmented function.

The most widely employed biochemical index of renal function is the plasma CR concentration. Creatinine is an amino-acid derivative (molecular mass 113 D) produced in the liver and muscle that is freely filtered by the glomerulus, and secreted by proximal tubular cells. Importantly, plasma concentrations will only rise once 60% of renal function is lost, and values within the 'normal' range, provide little if any information in the intensive care environment (39), particularly in relation to augmented function. Other indirect markers of renal function (such as blood urea nitrogen) or indeed newer indicators of kidney injury (such as Cystatin C) suffer from the same limitations. Gold-standard measures of GFR (such as inulin or iohexol CL, and radionucleotide studies) will provide the most accurate information, but are largely unavailable in a critical care setting.

In order to provide more useful information for prescribers and to improve the early identification of chronic kidney disease (CKD), mathematical estimates of glomerular filtration have been developed using simple laboratory and demographic measures. The Cockcroft-Gault equation was first published in 1973, and calculates an estimated CL_{CR} (CG CL_{CR}) using age, sex, weight and the plasma CR value (40). It has been widely adopted in pharmaceutical research. The newer modification of diet in renal disease (MDRD) formula was developed in a cohort of ambulatory patients with CKD, and both a

four and six variable equation have been employed (41). More recently the CKD Epidemiology Collaboration (CKD-EPI) equation has also entered clinical practice (42).

These mathematical estimates of GFR suffer from significant limitations in the critical care environment. In particular, while they may provide more information that plasma CR concentrations alone (43), neither equation was designed for use in this setting, and ongoing research confirms that they are less accurate, particularly with burns (44), trauma (45), in general critical care practice (46-48) and at higher filtration rates (49-51). In order to better model the dynamic nature of CR values in the critically ill, Jellife has proposed an estimate of CL_{CR} using two separate measurements (52). Although of significant merit, such equations still ignore the substantial underlying pathophysiology seen in critical illness, and suffer from the limitations of relying of plasma CR values alone (53).

A potentially more accurate, and easily accessible estimate of GFR is a measured CL_{CR} (54). Although less readily obtainable in the ambulatory patient, urinary catheterisation is frequent in the critically ill, making a timed urinary collection relatively easy. The duration of collection can be anywhere from 2 to 24hours (43, 55-59), with reasonable correlation between results (43). Eight-hour collections appear to provide the best balance between accuracy and feasibility (45), and can usually be reported daily, allowing the clinician to monitor trends and tailor therapy accordingly. The use of measured CL_{CR} in the ICU is also underscored by studies demonstrating a significant correlation with drug CL (26, 60, 61), allowing this to be employed as a surrogate of renal drug elimination.

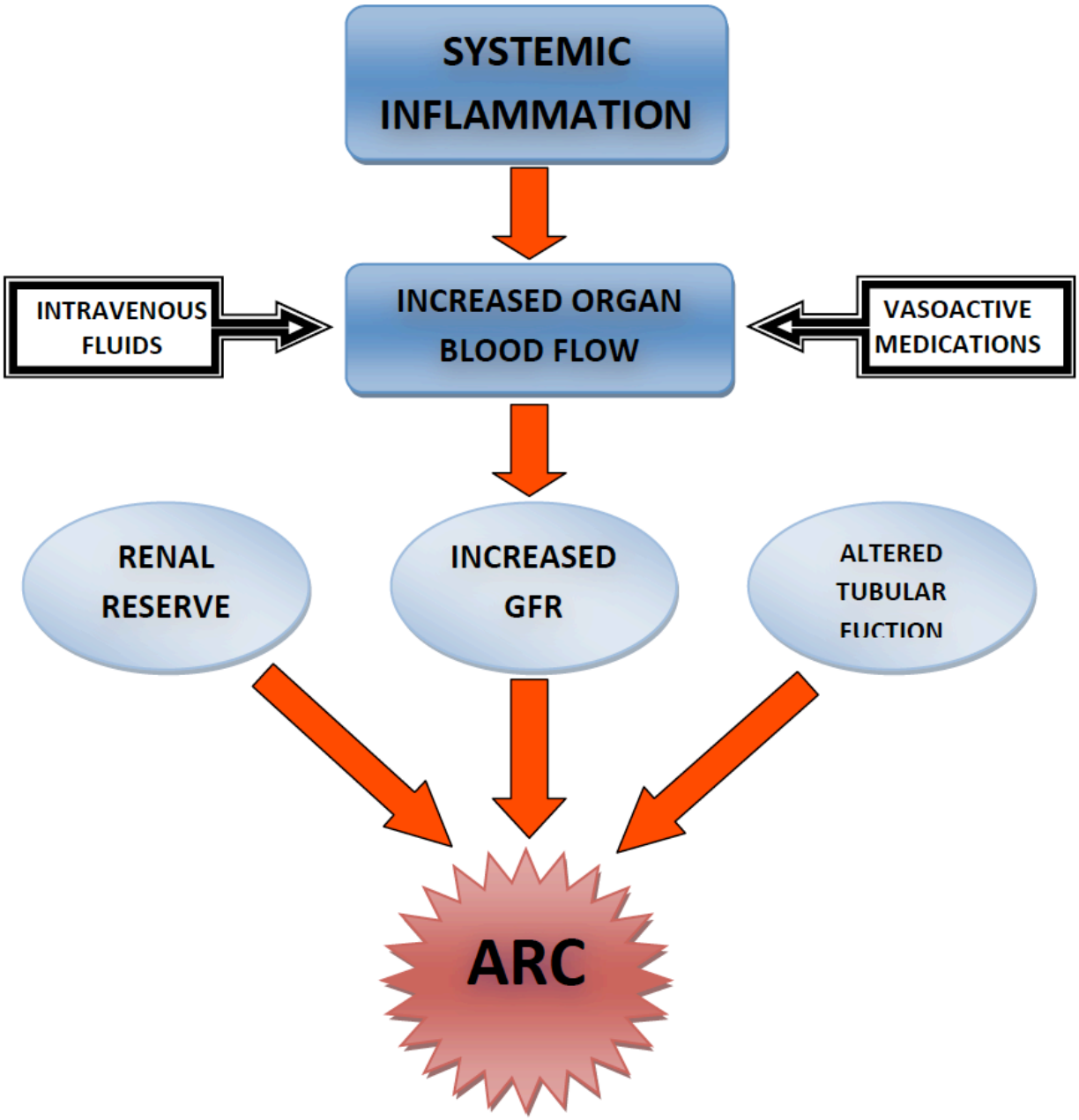
2.5 Mechanisms Underlying ARC

Patients requiring ICU admission often demonstrate SIRS that is largely driven by the underlying disease. A major component of this, particularly that seen with sepsis, is the development of a vasodilated or hyperdynamic cardiovascular state (62), characterised by a high cardiac output (CO) and increased major organ blood flow (63). How this alters renal function, and as a consequence renal drug elimination remains a matter of ongoing research. Many parallels can be drawn with pregnancy, where similar cardiovascular changes are encountered (64), along with markedly augmented renal blood flow (RBF) and glomerular filtration (65). As a consequence, increased renal drug CL, and reduction in the terminal elimination half-life, has been documented for many agents during pregnancy (66).

Leading international guidelines also recommend aggressive intravascular fluid loading and cardiovascular support in the early phases of sepsis management (2, 3, 67), which are likely to further exacerbate such changes. In this respect, evidence from large animal models demonstrate an increase in urine output and CL_{CR} with crystalloid administration (68), in addition to an increase in CO, RBF, and CL_{CR} (69, 70) following initiation of vasopressor support. As such, in the absence of AKI (where dose reduction would be appropriate), the use of aggressive resuscitative strategies in the critically ill may potentially augment renal drug delivery and elimination (71).

In addition to the disease process and interventions provided, the native renal response to catabolism and inflammation may also influence renal drug handling. This concept stems from early research demonstrating an increase in GFR following the administration of a high protein diet or infusion of amino acids (72). This *surge* in filtration has been termed the 'renal reserve', and suggests the normal human kidney is not working at full capacity under basal conditions. At times of biological stress, it is conceivable that this may promote higher filtration rates than otherwise would be observed (73). Importantly, this ‘reserve’ appears to decline with age, and in proportion to the baseline GFR (19). The implications in critical illness are currently poorly understood. Figure 2.1 graphically summarises the mechanisms likely to underpin ARC in the critically ill.

Figure 2.1 Mechanisms Relating to ARC in the Critically Ill



Caption: Mechanisms driving ARC in the critically ill; including the underlying systemic inflammatory state (leading to increased organ blood flow), administration of intravenous resuscitation fluids and vasoactive medications, and the recruitment of renal reserve.

The interaction between physiological reserve (most marked in younger patients), and systemic inflammation, is likely to be an important driver of this process. This was recently substantiated by Shimamoto et al., in which an increasing number of SIRS criteria were strongly associated with higher drug CL, and consequently lower plasma concentrations, in non-ventilated critically ill patients receiving standard doses of vancomycin (74).

2.6 Patients At Risk of ARC

Although a relatively new concept in critical care, some data exists that may guide identification of those patients at risk of ARC. Table 2.1 summarises risk factors associated with either elevated CL_{CR} or augmented drug CL from existing literature.

Table 2.1 Patients At Risk for ARC

Risk Factor	Key References
Younger Age	(59, 75)
Systemic Inflammation	(74)
Sepsis	(31, 32, 76-83)
Trauma and Surgery	(30, 45, 84-88)
Traumatic Brain Injury	(89-92)
Burns	(44, 93)
Haematological Malignancy	(94-100)
Ventilator Associated Pneumonia	(101)

In a single centre study of 4hr CL_{CR} in a cohort of general ICU patients, Fuster-Lluch et al. demonstrated an incidence of 'glomerular hyperfiltration' (CL_{CR} > 120ml/min/1.73m^2) of 17.9% on the day of admission (59). The prevalence peaked on day 5, and elevated CL_{CR} were more common in younger trauma and post-operative patients, with lower illness severity scores, higher urine outputs and diastolic blood pressure (59). Furthermore, increased CL of cefpirome (32), ceftriaxone (102), ceftazidime (76), piperacillin (77), ertapenem (25, 78, 103), vancomycin (79), teicoplanin (24), ciprofloxacin (80), levofloxacin (81), linezolid (82), and aminoglycosides (83), have been demonstrated in PK studies of general ICU patients. More recently, Claus and colleagues reported a > 50% incidence of at least one episode of ARC (CL_{CR} > 130 ml/min/1.73m^2) in a mixed cohort of medical and surgical patients receiving antimicrobial therapy in the ICU. Male gender and younger age were independently associated with ARC status (104).

2.6.1 Trauma and Surgery

Emergency post-operative and multitrauma victims frequently receive large quantities of fluid and blood products, in addition to undergoing often-repetitive surgical intervention. As such, they are at high risk of manifesting ARC, due to the underlying inflammatory state (13), coupled with fluid and vasoactive drug administration. The work by Brown et al. approximately thirty years ago still provides perhaps the best illustration of this phenomenon, with CL_{CR} reaching a peak of 190 ml/min/1.73m^2 in trauma patients on the 4th post-operative day (84). In addition, in those where CO was measured by trans-pulmonary thermodilution, a modest correlation was demonstrated with CL_{CR}, although septic patients and those receiving vasoactive medications were excluded (84).

In their work exploring the accuracy of shorter duration CL_{CR} collections, Cherry and colleagues observed a similar result, with significantly elevated CL_{CR} across all time points in trauma versus non-trauma patients (45). More recently Minville and colleagues also demonstrated a significant association between elevated 24-hour CL_{CR} (> 120 ml/min/1.73m^2) and admission post multitrauma. In multivariate logistic regression, age and trauma status were the only independent factors correlated with CL_{CR} (88).

In respect to antibacterial studies, Hanes et al. have reported increased CL of ceftazidime in trauma patients (85), while Toschlog and colleagues in a prospective study of once daily dosing of gentamicin demonstrated rapid drug elimination in over 50% of the trauma cohort, closely correlated with age and estimated CL_{CR} (87). In comparison, work by

Jacolot and colleagues investigating the use of cefpirome in traumatised patients with SIRS, failed to demonstrate any significant alterations in key PK parameters when compared with matched healthy controls (105). This is despite estimated CL_{CR} values being elevated in the trauma group (median = 147ml/min), although this was not of statistical significance. Of note, the mean length of stay (LOS) prior to antibiotic administration was 9 days, patients requiring vasopressors were excluded, and no haemodynamic data were reported (105).

In the surgical ICU, Shikuma et al. have demonstrated markedly elevated CL of piperacillin in a young cohort of critically ill patients with sepsis (86). In addition, wide inter-patient variation in key PK parameters was reported, as well as a moderate correlation between drug elimination and estimated CL_{CR} (86). Li et al. investigating the use of piperacillin for complicated intra-abdominal infection reported similar data. In this multicentre randomised clinical trial, a population PK model demonstrated drug CL greater than that reported in healthy volunteers, and identified CL_{CR} as a key covariate in predicting antibacterial PK (30).

2.6.2 Neurosurgery

Traumatic brain injury (TBI) and sub-arachnoid haemorrhage are two further sub-groups of critically ill patients likely to manifest ARC. This is a reflection of the injury process and patient demographic, as well as the treatment provided. Brain injury can occur in the setting of a global inflammatory process, such as that associated with multitrauma, or as an isolated insult (106). Importantly younger patients with relatively limited co-morbidity tend to be over-represented (in TBI), and ICU management largely focuses on the restoration of a normal haemodynamic profile. This commonly involves the use of resuscitation fluids and vasoactive medications, particularly in the defence of an adequate cerebral perfusion pressure (CPP) (107, 108). To add to this, concentrated saline solutions, or osmotic diuretics are often prescribed to reduce cerebral free water in the setting of refractory intracranial hypertension (109). Data confirms that CL_{CR} can be markedly elevated from baseline in this setting (Mean maximum CL_{CR} = 179 ml/min/1.73m^2), with measures continuing to be significantly elevated, even following withdrawal of brain specific therapy (CL_{CR} = 150 ml/min/1.73m^2) (92). Induced hypertension and hypervolaemia are also commonly employed in attempts to prevent delayed cerebral ischaemia following sub-arachnoid haemorrhage (110), and although unproven, may also promote ARC in this population.

2.6.3 Burns

Major burn injury represents a significant risk factor for ARC. The nature of the insult results in a biphasic haemodynamic response (111), with the early phase being characterised by relative hypovolaemia, due to ongoing leak of protein rich fluid across the capillary membrane (112). Aggressive fluid loading is the hallmark of emergency management, with many patients receiving large quantities of crystalloid resuscitation (113). AKI has been reported to occur in a significant number of burns patients, and is often multifactorial in aetiology (114).

The second phase is then characterised by marked hypercatabolism and inflammation lasting several days to weeks, and is further complicated by multiple visits to the operating theatre for ongoing debridement and grafting. At this time, CO and RBF can be markedly elevated leading to significantly augmented CL (93). This was demonstrated by Conil and colleagues, where 15 of 36 burns patients had a mean 24hr CL_{CR} of 174 ml/min in the second to third week post injury (44).

Not surprisingly, the CL of renally eliminated antibacterial agents would be expected to be high. Indeed, research has confirmed that cefepime (115), ceftazidime (116, 117), piperacillin (118), ticarcillin (119), imipenem (120), vancomycin (35, 121), tobramycin (93), amikacin (122), daptomycin (123) and ciprofloxacin (124) elimination is increased in this setting.

2.6.4 Additional Risk Factors

Two additional groups likely to manifest ARC are those with cystic fibrosis and haematological malignancy. Although data concerning changes in GFR with cystic fibrosis are conflicting (125), investigators have demonstrated augmented drug elimination in correlation with elevated inulin CL (126), and CL_{CR} (127) in this setting. Similarly changes in tubular drug handling have been demonstrated (128), and may help to explain some of the augmented drug CL observed.

Haematological malignancy or more specifically febrile neutropaenia appears to be another group where ARC is common (96). These patients routinely receive broad-spectrum empirical antibacterial therapy on admission to the ICU, and it is in this context that augmented renal drug CL have been noted (129). In particular, Pea et al. observed a

moderate inverse linear relationship between trough levels and estimated CL_{CR} in patients receiving high dose teicoplanin as empirical treatment for febrile neutropaenia (94). Significantly, higher dosing regimes than those currently recommended were required to achieve adequate concentrations (94). Similarly, augmented CL and/or higher dosing requirements have been demonstrated with ceftazidime (95), imipenem (96), amikacin (97), gentamicin (98), daptomycin (99), and vancomycin (100) in this setting. The mechanisms underlying this phenomenon are likely to involve SIRS, in addition to recruitment of 'renal reserve'.

2.7 Conclusions

ARC can be defined as the enhanced renal elimination of circulating solute, and is most conveniently considered in terms of an elevated GFR. An assessment of renal status is common in daily critical care practice, although is generally aimed at identifying kidney injury, rather than assessing renal function. Plasma CR concentrations are used widely for this purpose, although provide little value when reported in the normal reference range. Mathematical estimates of GFR are also likely to be of limited utility, given they were derived from non-critically ill cohorts. A measured urinary CL_{CR} provides the most pragmatic estimate of renal function currently available. Systemic inflammation, fluid loading and vasoactive drug administration are hallmarks of critical illness, likely contributing to ARC in many patients. Sub-groups at greatest risk include younger patients admitted post major trauma or surgery, those suffering TBI or burns injury, and in the setting of febrile neutropaenia. Augmented major organ blood flow and recruitment of renal reserve may be implicated. With the knowledge that sub-optimal application of antibacterial agents may promote increased morbidity, a greater understanding of the impact of ARC on drug exposure and clinical outcomes is required.

Chapter Three

ARC and Beta-lactam PK-PD in the Critically Ill

3.1 Chapter Overview

This chapter synthesises existing data concerning ARC and altered beta-lactam pharmacokinetics-pharmacodynamics (PK-PD) in the critically ill. The rationale for specific drug exposure targets is reviewed, along with the potential impact of ARC on PK-PD and clinical endpoints.

A combination of text, figures, and tables from previously published manuscripts (as outlined in Chapter 1) form the majority of this chapter. Where appropriate, additional data have been included if they were published subsequent to these manuscripts, and further inform the thesis. The layout has been adjusted to fit the overall style of the thesis. The references are found alongside those for the other chapters, at the conclusion of the main body.

3.2 Introduction

ARC in patients without organ dysfunction is being increasingly described in subsets of critically ill patients (12, 26, 56, 59, 61, 84, 89-91, 93, 130). In the context of antibacterial therapy, ARC will promote rapid renal drug elimination and sub-therapeutic concentrations, potentially leading to treatment failure or the selection of resistant microorganisms (12, 131). This has significant implications in patients with sepsis, whereby the consequences of inappropriate antibacterial therapy may be catastrophic (4-7).

The prescription of antibacterial agents in critically ill patients remains complex. Inter-patient variability is significant, with fluid shifts, altered capillary permeability, impaired vascular tone, organ dysfunction and multi-organ failure, all distorting the PK profile of many routinely prescribed agents (10). To date, ARC has been rarely considered in this context. However, the implications for beta-lactam PK are substantial, and require considerable review, as these agents are commonly used empirically in the ICU (132). This chapter outlines existing literature concerning beta-lactam elimination, and specifically

how this is altered in a critical care setting. In addition, the link between ARC, sub-therapeutic drug exposure, and clinical outcomes is explored.

3.3 Basic Pharmacological Principles

Clinical pharmacology is concerned with optimising the effects of pharmaceuticals on the body, such that a specific effect is achieved, while avoiding toxicity and side effects. Two major disciplines key to the application of this process, are that of pharmacokinetics (PK) and pharmacodynamics (PD). PK is primarily interested in the changes in drug concentration (ideally at the effect site) over time, and is graphically represented by a concentration time curve (See Figure 3.1). Typically this involves considering the absorption, distribution, metabolism and elimination of pharmaceuticals from the body. A variety of PK parameters can be employed to define this process for different agents, examples of which are defined below:

- Volume of distribution (V_d) = Hypothetical volume of fluid that the total amount of administered drug distributes into, generating a concentration equal to that measured in plasma.
- Clearance (CL) = Volume of plasma effectively cleared of the drug per unit time. Total drug CL is the combination of the clearances for each eliminating organ or tissue.
- Plasma half-life ($T_{1/2}$) = Time required for the plasma concentration to fall by one half.
- C_{max} = The maximum concentration measured after one dose. Ideally at the effect site, although commonly measured in plasma.
- C_{min} = The minimum concentration during a dosing period. Commonly determined in plasma prior to the next dose.
- Area under the curve (AUC) = The area under the concentration–time curve. Typically estimated from time zero to infinity using plasma concentrations.

The distribution of any given antibacterial agent will vary significantly depending upon its inherent pharmacochemical properties (such as molecular weight, and electrochemical charge) and its degree of plasma protein binding. Those agents with a higher affinity for lipids (lipophilic) will tend towards a higher V_d and longer elimination times, with extensive distribution into tissues and the intracellular space. In contrast, hydrophilic agents will primarily be limited to the extracellular space, favouring a lower V_d and more rapid

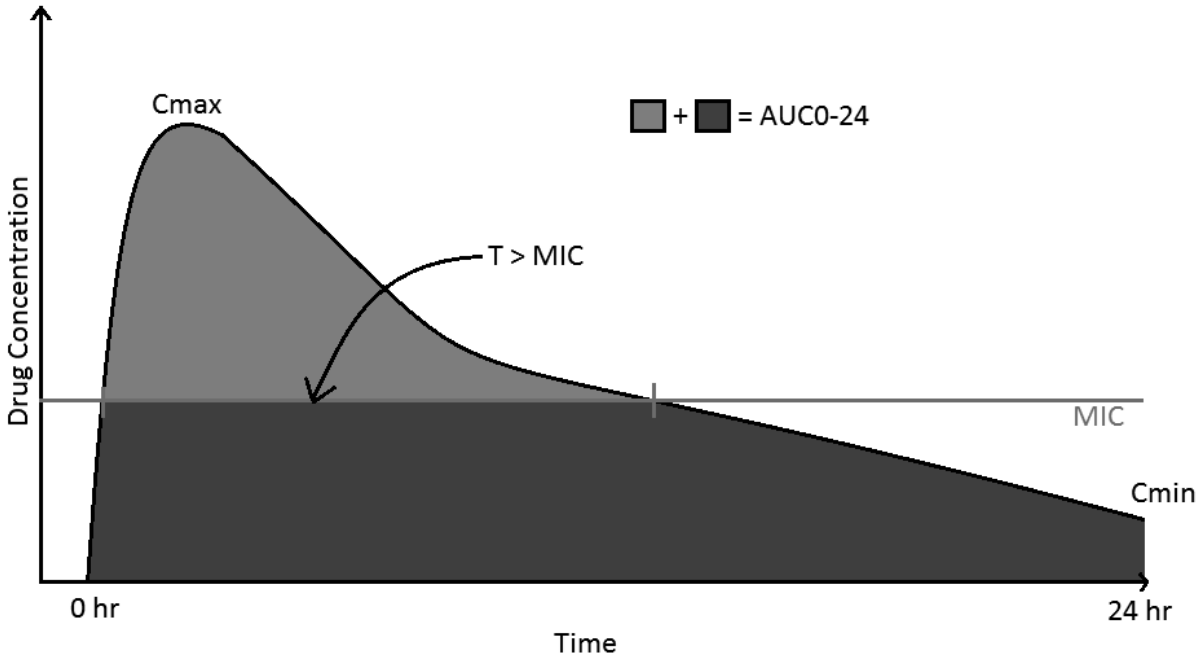
elimination. Those agents that are highly bound (to albumin or alpha-1 acid glycoprotein) may have very limited distribution (primarily in plasma) and a longer duration of action. Importantly, it is the free (or unbound) fraction that is pharmacologically active, and this will be influenced by plasma protein concentrations and binding competition from other agents.

PD in contrast involves the study of the effects of the drug, and is typically represented by a dose response curve. In terms of antibacterial agents, this refers to the ability of the agent to kill or inhibit the growth of an infecting organism following a given dose. Significantly, there is an important inter-play between the PK properties of these agents and their efficacy, which is referred to as the PK-PD characteristics. The PK-PD parameters of note for antibacterial agents are summarised below and in Figure 3.1:

- $fT_{\geq MIC}$ = Fraction of the dosing interval for which the concentration of the antibacterial agent remains at or above the minimum inhibitory concentration (MIC) for bacterial growth
- C_{max}/MIC = Ratio of the maximum antibacterial concentration (C_{max}) to the MIC of the infecting organism
- AUC_{0-24}/MIC = Ratio of the area under the concentration time curve during a 24-hour time period, to the MIC of the infecting organism.

Antibacterial agents can subsequently be classified on the basis of these PK-PD characteristics. Concentration-dependant killing (as is the case with aminoglycosides) relies on achieving a high C_{max}/MIC ratio at the site of infection (133, 134). In comparison, time-dependent agents (such as beta-lactams) require an extended $fT_{\geq MIC}$ (135). Some agents, such as the glycopeptides and fluoroquinolones demonstrate both time and concentration dependent features, such that achieving an adequate AUC_{0-24}/MIC ratio has been associated with successful bacterial kill (136, 137).

Figure 3.1 PK-PD Indices for Different Antibacterial Classes



Caption: Graphical depiction of Antibacterial PK-PD Indices. Time-dependent agents (such as the beta-lactams) require a suffient period where the drug concentration is at or above the MIC of the infecting pathogen. AUC – area under the curve, C_{max} – maximum plasma concentration, C_{min} – minimum plasma concentration, MIC – minimum inhibitory concentration, T > MIC – time above MIC

3.4 Beta-lactam PK-PD Targets

The beta-lactam group demonstrate time-dependent killing, such that $fT_{\geq MIC}$, is the best predictor of efficacy (138). Although optimum beta-lactam exposure in clinical practice is currently debated, in the absence of any significant post-antibiotic effect (PAE), dosing schedules should ideally aim to achieve sufficient drug concentrations for prolonged periods of the dosing interval (90-100% $fT_{\geq MIC}$) (139). In addition, trough concentrations 4-5 times the MIC are favoured, as bacterial killing is maximised (140, 141). The carbapenems (meropenem, imipenem, panipenem, ertapenem, doripenem, and biapenem) are a newer class of beta-lactams that also demonstrate time-dependent killing (142). However, *In vitro* models have suggested that the carbapenem PAE enables these agents to require less $fT_{\geq MIC}$ (143) for bacteriostatic activity (20% $fT_{\geq MIC}$) and bactericidal activity (40% $fT_{\geq MIC}$) (144). Given the PK-PD profile for this class of agents, rapid renal drug elimination in the setting of ARC is highly disadvantageous, leading to potentially sub-therapeutic levels for large portions of the dosing interval (25).

3.5 Beta-lactam CL in Critical Illness

The majority of agents in this class are renally eliminated (through a mixture of glomerular filtration and tubular secretion), and a number of studies have been published using different dosing regimens in the critically ill (Table 3.1). A correlation between CL_{CR} and drug CL has been reported for a number of agents (23, 28-33, 102, 117, 145-150). Work by Conil and colleagues also highlight the importance of renal function as a key covariate in piperacillin elimination, with a strong inverse relationship between measured CL_{CR} and trough concentrations (26). In addition, as illustrated in Table 3.1, increased beta-lactam drug CL and significant inter-individual variability has been widely reported in the critically ill (25, 32, 86, 102, 103, 151, 152).

Table 3.1 Studies of Beta-lactam Antibacterial Agents in Healthy Volunteers and the Critically Ill

Agent	CL in Healthy Volunteers (ml/min)*	CL and CL_{CR} in the Critically Ill (ml/min)*	Number and Population of Patients	Dose	Inter-patient Variability?	Increased CL?	Ref
Cefepime	CL = 138 (22) n=7 Dose: 2 g IV (153)	CL = 127 (33) CL_{CR} = 130.6 (32)	n=13, Sepsis	2 g IV 12hrly			(31)
		CL = 137.3 (45%)$^{+}$ CL_{CR} = 123.2 (54.6)	n=55, ICU patients	2 g IV 12hrly or 4 g IV CI	✓		(152)
		CL = 119.1 (59.6) CL_{CR} = 133.5 (67.4)	n=13, Burns	2 g IV 8hrly	✓		(117)
		CL = 125 (51) CL_{CR} = 54.6 (7.7)	n=7, Sepsis	2 g IV	✓		(154)
Cefpirome	CL = 101.7 (85-146.7)** n=9 Dose: 2 g IV (105)	CL = 158 (88-228)** CL_{CR} = 146.4 (72-252)**	n=12, Sepsis	2 g IV 12hlry	✓	✓	(32)
		CL = 126.7 (71.7-248.3)** CL_{CR} = 147 (82-190)**	n = 9, Trauma and Sepsis	2 g IV 12hrly	✓		(105)
		CL = 75 (11) CL_{CR} = 69.6 (21.2)	n=12, sepsis	2 g IV			(145)
Ceftriaxone	CL = 19.8 (2.5) n=12 Dose: 2 g IV(155)	CL = 41 (12) CL_{CR} = 114 (39)	n=9, Critically Ill, normal renal function	2 g IV Daily		✓	(102)
		CL = 26.3 (4.9) /1.73m^2 CL_{CR} = 93.7 (20.3) /1.73m^2	n=7, ICU patients normal renal function	2 g IV Daily		✓	(156)
		CL = 18 (5.5) CL_{CR} = 112 (29)	n=3, Critically Ill, normal renal function	1.5 g IV			(148)

Ceftazidime	CL = 116.5 (8.8) n=12 males Dose: 1 g IV(157)	CL = 124.9 (62.6) CL_{CR} = 119.2 (53.4)	n=17, Burns	1 g IV 4hrly	✓	✓	(117)
	CL = 97 (6.5) n=12 females Dose: 1 g IV(157)	CL = 99 (28.1) CL_{CR} = 102.8 (28.5)	n=8, Sepsis	2 g IV 8hrly	✓		(33)
		CL = 164.5 (62.3) CL_{CR} IB = 96.8 (21.6) CL_{CR} CI = 96.8 (23.3)	n=31, Trauma	2 g IV 8hrly or 60mg/kg/d CI	✓	✓	(85) (assuming weight = 70kg)
		CL = 151 (79.8) CL_{CR} = 61.1 (24.9)	n=15, Critically Ill	2 g IV 8hlry	✓	✓	(76)
		CL = 67.67 (5.83-185.5) **	n=21, Melioidosis	120mg/kg/d 8hrly IB or CI	✓		(23) (assuming weight = 70kg)
		CL IB = 85 (38.3-148.3) *** CL CI = 68.3 (23.3-148.3)*** CL_{CR} IB = 106 (59-160)*** CL_{CR} CI = 93 (36-215)***	n=18, Abdominal Sepsis	4.5 g IV CI or 1.5 g IV 8hrly	✓		(158)
Piperacillin	CL = 188 Dose: 4 g 8hrly (159)	CL = 396 (286) CL_{CR} = 116.5 (55.8)	n=11, Critically Ill	2.5 to 4 g IV	✓	✓	(86)
		CL= 1150 (1001 - 3530) $^{\$}$ CL_{CR} IB = 199 (91-233) $^{\$}$ CL_{CR} CI = 166 (103-237) $^{\$}$	n=13, Critically Ill	4g IV 6 or 8hrly as IB or CI (333 - 500mg/hr)	✓	✓	(77)
		CL_{CR} = 65 (6-216)**	n=70, Critically Ill	4 g IV 6 or 8hrly	✓	✓	(26)
		CL = 230 (34.6%) + CL_{CR} = 89 (22-150)**	n=52, Abdominal Sepsis	3 g IV 6hlrly or 12 g IV CI		✓	(30)

Meropenem	CL = 254 (16) n=6 Dose: 1 g IV(160)	CL = 191 (52.2) CL_{CR} = 61.2 (37.9)	n=10, Sepsis	1 g IV	✓		(151)
		CL = 155.8 (40.6) CL_{CR} = 71.1 (15)	n=8, Sepsis (CL_{CR} > 50ml/min)	1 g IV 8hrly	✓		(146)
		CL = 112 (70) CL_{CR} = 52 (51)	n=6, Septic Shock	1 g IV	✓		(161)
		CL = 170 (65) CL_{CR} = 50 (21.4)	n=11, Surgical infections	1 g IV 8hrly	✓		(147)
		CL IB = 156.67 (20) CL CI = 128.33 (23.3) CL_{CR} = 83.7 (53.1)	n=15, Critically Ill	2 g IV 8hrly or 3 g IV CI			(162)
		CL = 226.7 (23.3) CL_{CR} CI = 93 (69-161) [$] CL_{CR} IB = 106 (98-127) [$]	n=10, Sepsis	1g IV 8hrly or 3g IV CI	✓		(163)
Imipenem	CL = 186 (16) /1.73m^2 n=8 Dose: 1 g + 1 g cilastatin IV (164)	CL = 116.4 (42.3) CL_{CR} = 76.2 (33.67)	n=10, Sepsis	1 g + 1 g cilastatin IV	✓		(151)
		CL = 105 (13.3) CL_{CR} = 34.3 (10.3)	n=6, Critically Ill	500mg + 500mg cilastin IV 6-8hrly			(165)
		CL = 205 (70) CL_{CR} CI = 122 (33) CL_{CR} IB = 128 (35)	n=20, Nosocomial Pneumonia	1 g + 1 g cilastatin IV 8hrly or 2 g + 2 g cilastatin CI	✓	✓	(166)

Ertapenem	CL = 29.5 (3.4) n=16 Dose: 1 g IV (167)	CL = 200.5 (306.9) CL_{CR} = 96.8 (43.3)	n=8, Severe Sepsis	Dose: 1 g IV daily	✓	✓	(103)
		CL = 73.3 (63.3-81.7)[$] CL_{CR} = 74 (66-109)[$]	n=15, VAP	1 g IV daily		✓	(78)
		CL = 43.2 (23.7) CL_{CR} = 93.8 (52.4)	n=17, VAP	1 g IV daily		✓	(25)

* mean (SD), ** median (range), *** mean (range), $ median (IQR), + mean (inter-individual variability)

CL_{CR} – Creatinine Clearance, IV – Intravenous, CL_R – Renal Clearance, CL – Total (Body) Clearance, ARC – Augmented Renal Clearance, IB – Intermittent Bolus, CI – Continuous Infusion, VAP = Ventilator Associated Pneumonia

Although for some agents the mean PK data reported may not be greatly different from studies in healthy volunteers (Table 3.1), the significant inter-patient variability often observed indicates that summary statistics are not always accurate in describing this phenomenon. In addition, as many critically ill patients will manifest AKI and renal dysfunction, studies of small numbers in a heterogonous critically ill population will be underpowered to detect ARC. In those patients with 'normal' plasma CR concentrations, ARC is likely to be significantly more common (77, 163). Importantly these data provide a robust collection of PK-PD work that highlights the strong influence of altered renal function on beta-lactam PK, such that in the setting of ARC, pre-defined targets for optimal drug exposure are less likely to be achieved.

3.6 Linking ARC, Beta-lactam PK-PD Target Attainment and Clinical Outcomes

Limited data exists that explores the impact of ARC on beta-lactam PK-PD target attainment and clinical outcomes. Conil et al. examined C_{min} in seventy critically ill patients receiving standard doses of piperacillin. In patients with higher CL_{CR} (≥ 50 ml/min), C_{min} levels were unlikely to reach the break point for commonly encountered pathogens, particularly those with reduced susceptibility (26). However no difference in clinical outcomes was observed. McKinnon and colleagues evaluated the relationship between $fT_{\geq MIC}$ and clinical and microbiological outcomes in patients with bacteraemia and sepsis treated with cefepime or ceftazidime (168). Significantly greater clinical cure and bacteriological eradication than was seen in circumstances where 100% $fT_{\geq MIC}$ was achieved.

More recently, a large multi-national point prevalence study of antibacterial levels in critical illness has demonstrated that treatment failure was three times more likely, when $fT_{\geq MIC}$ was < 50% in those receiving beta-lactams (169). In addition, higher beta-lactam concentration to MIC ratios at both 50% and 100% of the dosing interval were associated with a greater probability of a positive clinical outcome in multivariate analysis. Using CG CL_{CR}, ARC (CG CL_{CR} ≥ 130ml/min) was strongly associated with lower drug concentrations (< MIC) at both time points (170).

In this context, it is noteworthy to consider the recent premature conclusion to the industry sponsored clinical trial (ClinicalTrials.gov Identifier: NCT00589693) examining the use of doripenem (DORIBAX®, Johnson & Johnson, Raritan, NJ 08869) in the treatment of

ventilator-associated pneumonia (VAP). Specifically, this phase III, prospective, multicentre, randomized, double blind study, aimed to assess the safety and efficacy of a fixed 7-day course of doripenem (1g, 4-hour infusion, q8hrly) compared with a fixed 10-day course of imipenem-cilastatin (1g, 1-hour infusion, q8hrly) as treatment for adult subjects hospitalized for at least 5 days, and diagnosed with VAP. The primary objective was to demonstrate the non-inferiority of doripenem in a microbiological intention to treat (MITT) and microbiologically evaluable (ME) population.

When terminated, 274 of the planned 524 subjects were randomised, with interim data analyses showing greater mortality, and lower clinical cure rates in those receiving doripenem. Although issues regarding diagnosis, patient selection, causative pathogen and ancillary interventions, separate to simple under-dosing, may confound this result (171), marked differences in clinical cure rates (favouring imipenem-cilastatin) were observed in patients with a CG CL_{CR} ≥ 150ml/min (172). Of note, separate PK-PD modelling has suggested that significantly higher daily doripenem doses (up to 2 g 8-hourly) might have been required for adequate drug exposure in these patients (173).

This result follows that of a separate industry sponsored clinical trial (ClinicalTrials.gov Identifier: NCT00229008) examining the efficacy and safety of a new extended spectrum cephalosporin; ceftobiprole, in nosocomial pneumonia (NP). Specifically, this phase III, multicentre, double-blind study, randomized 781 patients to receive either ceftobiprole (500mg, 2-hr infusion, q8hrly) and placebo (0.9% NaCl, 1-hr infusion, q12hrly) or ceftazidime (2g, 2-hr infusion, q8hrly) and linezolid (600mg, 1-hr infusion, q12hrly) for 7-14 days, for the treatment of NP or VAP. Clinical cure rate at 7-14 days after the last dose of study drug was the primary end-point. Overall, non-inferiority of ceftobiprole was reported for NP (75), although in sub-group analyses, a trend favouring ceftazidime/linezolid was consistently observed in VAP patients. In particular, younger patients (< 45yrs), and those with high CG CL_{CR} (≥ 150ml/min) demonstrated numerically worse clinical cure rates with ceftobiprole (75).

Finally, a recent prospective single-centre observational study has demonstrated an association between ARC (defined by a 24-hr CL_{CR} > 130ml/min/1.73m^2), and therapeutic failure (defined by a poor clinical response and the need for an alternative antibiotic) in critically ill patients receiving anti-infective therapy (104). Of interest, this observation was most evident in those receiving non-carbapenem beta-lactams.

3.7 Implications of ARC for Dosing Beta-lactams in the Critically Ill

These data serve to underline the importance of ARC in achieving adequate beta-lactam exposure in the critically ill, and raises important questions as to the optimal dosing strategy in this setting. Given the time-dependent kill characteristics of this class of agents and the increased CL documented in the critically ill, maintaining sufficient drug concentrations through out the dosing interval remains challenging. More frequent, extended or continuous dosing must be considered.

PK-PD data supports administration by extended or continuous infusion (23, 85, 174-180), although a clear clinical benefit remains uncertain. Lodise and colleagues examined the role of extended infusions of piperacillin-tazobactam in a retrospective cohort of critically ill patients with *Pseudomonas aeruginosa* infection. Extended infusions were associated with a significant improvement in 14-day survival in those patients with higher illness severity (181). Similar retrospective analyses have been performed in patients with ventilator associated pneumonia due to gram-negative bacilli, with continuous infusions of meropenem (182), ceftazidime (183), and piperacillin-tazobactam (184), all associated with improved rates of clinical cure, particularly with more difficult to treat organisms. In a small prospective study, Roberts et al. also reported a clinical advantage to continuous infusion of ceftriaxone, when patients received four or more days of therapy (174).

Confounding these results was a systematic review and meta-analysis performed in 2009, which reported no significant clinical advantage to continuous infusion of beta-lactams in hospitalized patients (185). More recently, Falagas and colleagues repeated this analysis focusing on piperacillin/tazobactam and carbapenem administration. Overall, lower mortality was demonstrated with extended or continuous infusions, although only 3 of 14 included studies were randomized controlled trials (186). Contrasting findings were recently reported from a single-centre before and after study, in which extended infusions of beta-lactams offered no advantage over intermittent dosing (187).

In the largest prospective study to date, a multicentre double-blind randomized controlled trial of continuous infusion of beta-lactams reported improved $fT_{\geq MIC}$, and clinical cure, in critically ill patients with severe sepsis (188). No significant difference was noted in ICU-free days or survival to hospital discharge (188), although further studies are ongoing.

Use of continuous or extended infusions in patients manifesting ARC represents an attractive approach, although to date there are no prospective data comparing dosing regimens in this setting. However, a recent observational study by Carlier et al. suggests that despite the use of such strategies, elevated CL_{CR} remains strongly associated with sub-optimal beta-lactam drug exposure (189). This in combination with the inferior clinical outcomes demonstrated in patients manifesting ARC (104), indicates that higher daily doses are also likely to be required. This is supported by dosing simulations reported for doripenem (173), meropenem (190, 191), cefepime (192), and piperacillin-tazobactam (193), in which adjustments in total dose, in addition to use of extended or continuous infusions are required.

3.8 Conclusions

Beta-lactams are commonly used empirically in the ICU. They are time-dependent agents, such that effective bacterial killing is reliant on achieving drug concentrations in excess of the MIC for prolonged periods of the dosing interval. They are predominantly renally eliminated. Many prior publications have demonstrated either elevated beta-lactam drug CL or marked inter-patient variability in the ICU, often in parallel with augmented CL_{CR}. Failure to achieve the required PK-PD targets (at least 50% $fT_{\geq MIC}$) has been associated with inferior clinical outcomes (169), while treatment failure has also been noted in those manifesting ARC in a mixed ICU cohort (104). ARC may have also confounded results from clinical trials of new or emerging antibacterial agents, potentially slowing the progression of these drugs into wider clinical practice (194). Although use of extended or continuous infusions of beta-lactams appears attractive in the critically ill, outcome data are currently lacking, with additional studies suggesting an increase in total daily dose may be required (189). Additional data concerning the prevalence of ARC in the critically ill, and improved methods to identify patients at risk of sub-therapeutic exposure are required to plan further studies in this area.

PART TWO – CLINICAL STUDIES

Chapter 4

Sub-therapeutic Initial Beta-lactam Concentrations in Select Critically Ill Patients: Association Between ARC and Low Trough Drug Concentrations

4.1 Chapter Overview

This chapter presents the findings from a single centre observational study of trough beta-lactam plasma concentrations in patients receiving empirical therapy in the ICU. The association between sub-optimal drug exposure and CL_{CR} is explored, in order to assist in identifying future patients manifesting ARC.

Text, figures, and tables from the published manuscript (as outlined in Chapter 1) are reproduced here. The layout has been adjusted to fit the overall style of the thesis. The references are found alongside those for the other chapters, at the conclusion of the main body.

4.2 Introduction

Sepsis continues to be a major cause of morbidity and mortality in the critically ill (1), with leading international guidelines stressing the importance of appropriate antibacterial administration (2). In this respect, optimising antibacterial exposure must be considered a clinical imperative, particularly with the expanding body of literature demonstrating a survival benefit with early, appropriate chemotherapy (6).

To maximise the efficacy of antibacterials, prescribers must not only consider the likely causative organism, but also the PK-PD implications of the underlying disease state, and ancillary interventions provided (135). Some consideration of the pathophysiology of critical illness and in its' influence on antibacterial handling and efficacy is essential, particularly as many dosing regimens have been derived outside of this setting. In this manner, *personalizing* drug prescription is paramount to improving the chances of clinical success, and reducing the opportunity for selection of drug resistant strains (131).

The beta-lactams are arguably the most commonly prescribed class of antibacterials in the critically ill (132). They are primarily hydrophilic in nature, with a low V_d, and

predominantly renally excreted. Bacterial killing is considered time-dependent, such that the duration the free (or unbound) drug concentration remains above the MIC of the infecting organism, is considered the primary PK-PD index of efficacy ($fT_{\geq MIC}$) (138). Ideally this should be 90-100% of the dosing interval, with maximal bacterial killing achieved at concentrations 4-5 x MIC (139-141, 195).

Changes in organ function in the critically ill will considerably impact the probability of achieving such targets with beta-lactam dosing. In particular, extra-vascular volume expansion with fluid loading and capillary leak may alter the V_d (135), while changes in renal function can significantly influence drug CL (71). In order to avoid drug accumulation and potential toxicity, dose reduction in the setting of renal dysfunction tends to be the primary concern for many clinicians, although increasing drug exposure in response to augmented drug elimination is seldom considered (12). This largely stems from a paucity of data concerning changes in drug CL in the critically ill, the limited sensitivity of plasma CR concentrations to identify augmented renal function, and the lack of routine TDM of beta-lactams in clinical practice.

Recently however, we have demonstrated that such measurements are feasible for a range of beta-lactams as part of a wider TDM program (196). Utilising these data, the aim of this study was to identify clinically significant risk factors, with particular emphasis on renal function that may promote sub-therapeutic beta-lactam trough concentrations, as a maker of sub-optimal drug exposure.

4.3 Materials and Methods

4.3.1 Study Population

Our institution operates a 30 bed tertiary level ICU that acts a major referral centre for the wider region. The only major patient groups not represented include; paediatrics, cardiac surgical patients, and solid organ transplant recipients. From February 2009, beta-lactam TDM has been available to tailor drug prescription, with utilisation of this service at the discretion of the treating physician and/or clinical pharmacist (196). In a smaller sub-group, where plasma CR concentrations alone have been considered a poor index of renal function, CL_{CR} collections have been obtained concurrently. These measures are typically obtained in patients considered 'at risk' of augmented drug CL; such as those admitted post-operatively, with sepsis or after major trauma (12), and without significant

derangement in plasma CR concentrations. This involves an 8-hour urine collection via an indwelling catheter, with determination of the plasma CR concentration at a point mid-way. This service is provided as a part of routine clinical care, and as such, informed consent was not considered necessary by our institutional review board (Royal Brisbane and Women's Hospital, Human Research Ethics Committee, GC2008/054).

4.3.2 Sampling

Blood samples were collected for TDM of the following beta-lactam antibacterials; ampicillin, dicloxacillin, penicillin, flucloxacillin, piperacillin, cefalothin, cefazolin, ceftriaxone, ceftazidime, cefepime, meropenem, and ertapenem. As initial dosing at our institution employs intermittent regimens, samples were drawn immediately prior to re-dosing, after at least four prior doses had been administered, thereby ensuring that all samples were obtained at 'steady-state', and limiting the impact of distribution kinetics. Sampling occurred over the same time-period as the 8-hour CL_{CR}. Empirical dose selection was at the discretion of the treating clinician, although consistent with the product information and in-line with local protocols. Continuous infusion is not employed empirically, but is considered if the subsequent trough level is sub-therapeutic, and the maximum recommended daily dose is already being prescribed. Total blood concentrations of each antibacterial were determined, with the unbound fraction being calculated using data from previously published studies (196).

4.3.3 Beta-lactam assay

Beta-lactam antibacterial levels were measured using a validated high performance liquid chromatography (HPLC) assay method, details of which have previously been published (197). In brief, the assay requires 200 µL of plasma and the sample preparation involves protein precipitation with acetonitrile and removal of lipid-soluble components by chloroform wash. The results of the assay are reported typically within 12 hours of sampling. The calibration curves for all the beta-lactam antibacterials were linear over the concentration ranges of 1 to 500 mg/L with correlation coefficients (r^2) = 0.998. Within-run precision (n=10) across three levels was = 3.1% CV. Inter-run precision (n=10) was = 6.9% CV and the limit of quantification was 1mg/L.

4.3.4 Therapeutic Drug Monitoring Targets and Susceptibility Data

Although specific PD targets for beta-lactam dosing are the subject of debate, recent clinical data supports maintenance of longer $fT_{\geq MIC}$ in the critically ill (ideally 100% of the

dosing interval) (168, 181). Furthermore, given that bactericidal activity is reported to be maximal at 4-5 x MIC of the known or suspected pathogen (140, 195), this represents a logical target trough plasma concentration to ensure adequate tissue penetration, clinical cure, and limited opportunity for drug resistance. Given the controversy concerning appropriate targets for antibacterial therapy, we elected to analyse the results obtained in terms of a conservative 100% $fT_{\geq MIC}$ as well as a more 'aggressive' 100% $fT_{\geq 4 \times MIC}$.

Where possible, beta-lactam concentrations were compared with susceptibility data of known or suspected pathogens, with breakpoints identified from the local antibiogram. Where local data were not available, the highest MIC in the susceptible range was selected as the dosing target from breakpoints published by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (http://www.eucast.org/clinical_breakpoints). The MIC (either known or presumed) employed in dose modification, was also categorised as 'low', 'moderate', or 'high', on the basis of the EUCAST distinctions. In those patients where no organism was isolated, if treatment was commenced within 48hrs of admission, infection was presumed to be secondary to a community acquired pathogen. Alternatively, a health-care or hospital acquired infection was presumed in those starting treatment > 48hours after admission.

4.3.5 Statistical Analysis

Continuous data are presented as the mean (SD). Categorical data are presented as counts and/or percentages. Sub-therapeutic unbound trough concentrations were defined as < MIC and < 4 x MIC respectively. Comparisons between groups utilised an Independent Student T-test test for continuous data, and a Chi-square or Fishers Exact test for categorical data, where analysis assumptions were met. Following identification of important covariates in univariate testing ($p<0.15$), a multivariate logistic regression model (single step, forced entry) was constructed to determine the primary determinants of sub-therapeutic trough concentrations. CL_{CR} as the primary covariate of interest, was entered as a linear (continuous) variable. Goodness of fit of the model was assessed by the Hosmer-Lemeshow statistic. A receiver operator characteristic (ROC) curve was constructed utilising the largest sub-group receiving the same antibacterial, to examine threshold CL_{CR} values. All analyses employed IBM SPSS Statistics version 19 (Chicago, IL), and a p-value < 0.05 was considered as statistical significance.

4.4 Results

Fifty-two concurrent trough beta-lactam concentrations and CL_{CR} measures, from forty-eight patients (four patients had beta-lactam concentrations determined twice due to a change in antibacterial agent), were used in analysis. Demographic details, including a breakdown of the antibacterial agents employed, and suspected or known pathogens, are presented in table 4.1. Admission diagnosis was classified as primarily neurological (eg. subarachnoid haemorrhage), post-operative, sepsis, or trauma. As demonstrated, piperacillin was the most frequent beta-lactam employed (48%), while empirical cover and *Staphylococcus spp*. were the most common indications for antibacterial therapy (62%). The mean (SD) recorded CL_{CR} was 134 (90) ml/min/1.73m^2, with > 90% of plasma CR concentrations being < 120 µmol/l (1.4mg/dl).

Table 4.1 Demographic Data for Those Patients (n=48) Receiving Beta-lactam Therapeutic Drug Monitoring in the Intensive Care Unit

Variable	
Male / Female, n (%)	34 (70.8) / 14 (29.2)
Age, yrs, mean (SD)	52.9 (20.9)
ICU LOS, days, mean (SD)	14.6 (11.2)
APACHE II, mean (SD)	20.3 (6.8)
SAPS II, mean (SD)	39.6 (16.1)
Height, cm, mean (SD)	171.4 (11.2)
Weight, kg, mean (SD)	85.4 (22.2)
Admission Diagnosis, n (%): - Neurological - Post-operative - Sepsis - Trauma	 9 (18.8) 15 (31.3) 11 (22.9) 13 (27.1)
Beta-lactam (n=52), n (%): - Penicillin - Fluclox/Dicloxacillin - Cefazolin - Ceftriaxone - Piperacillin - Meropenem	 2 (3.8) 11 (21.2) 1 (1.9) 4 (7.7) 25 (48.1) 9 (17.3)
Time to TDM Sampling from Admission (n=52), days, mean (SD)	6.5 (6.1)
Pathogen, (n=55)*, n (%): - Empirical cover - Staphylococcus Species - Enterobacteriaceae - Pseudomonas Species - Acinetobacter Species - Haemophilus influenzae - Streptococcus Species	 17 (30.9) 17 (30.9) 16 (29.1) 2 (3.6) 1 (1.8) 1 (1.8) 1 (1.8)
Plasma CR concentration (n=52), µmol/L, mean (SD)	80 (42)
Measured CL_{CR} (n=52), ml/min/1.73m^2, mean (SD)	134 (90)

* > 1 potential pathogen isolated in three cases

APACHE - Acute Physiology and Chronic Health Evaluation, SAPS - Simplified Acute Physiology Score, ICU LOS - Intensive Care Unit Length of Stay, CL_{CR} - Creatinine Clearance, CR – Creatinine, TDM - Therapeutic Drug Monitoring

The majority of patients were being mechanically ventilated on the day of study (85%), although only 25% were receiving vasopressors. The most common site of infection (presumed or confirmed) was the respiratory tract (52%). The mean (SD) fluid balance over the course of the measured CL_{CR} was -35 (1145) ml. Tables 4.2 and 4.3 demonstrate the differences in demographic and therapy related variables between those with sub-therapeutic and therapeutic concentrations (target; MIC and 4 x MIC respectively). In only 58% (n=30) of instances was the trough drug concentration ≥ MIC, falling significantly to 31% (n=16) when using 4 x MIC as the target.

Table 4.2 Comparison of Demographic, Therapeutic and Infection Related Variables Between Those with Unbound Trough Concentrations < MIC, and ≥ MIC

Variable	Drug Concentration < MIC (n=22)	Drug Concentration ≥ MIC (n=30)	p-value
Male / Female, n (%)	15 (68.2) / 7 (31.8)	22 (73.3) / 8 (26.7)	0.685
Age, yrs, mean (SD)	40.1 (19.6)	60.3 (18.1)	<0.001
APACHE II, mean (SD)	18.8 (6.6)	21.3 (6.8)	0.182
SAPS II, mean (SD)	36.6 (16.8)	41.8 (15.2)	0.249
Measured CL_{CR}, ml/min/1.73m^2, mean (SD)	188 (101)	95 (56)	<0.001
Known / Suspected Source, n (%):			
- Skin/Soft Tissue/Bone	3 (13.6)	4 (13.3)	1.000
- Respiratory Tract	13 (59.1)	14 (46.7)	0.376
- Abdomen	1 (4.5)	5 (16.7)	0.226
- Bacteraemia	3 (13.6)	3 (10.0)	0.689
- Central Nervous System	2 (9.1)	3 (10.0)	1.000
- Urinary Tract	0 (0)	1 (3.3)	1.000
Mechanical ventilation, n (%)	18 (81.8)	26 (86.7)	0.708
Fluid Balance, ml, mean (SD)	108 (1119)	-140 (1172)	0.446
Vasopressor, n (%)	4 (18.2)	9 (30.0)	0.331
β-lactam, n (%):			
- Fluclox/Dicloxacillin	6 (27.3)	5 (16.7)	0.495
- Piperacillin	10 (45.5)	15 (50.0)	0.746
- Meropenem	4 (18.2)	5 (16.7)	1.000
- Other	2 (9.1)	5 (16.7)	0.685
Target MIC, n (%):			
- Low	5 (22.7)	12 (40.0)	0.190
- Moderate	3 (13.6)	8 (26.7)	0.319
- High	14 (63.6)	10 (33.3)	0.030
Nil Organism identified, n (%)	4 (18.2)	13 (43.3)	0.056
ICU mortality, n (%)	1 (4.5)	2 (6.7)	1.000

APACHE - Acute Physiology and Chronic Health Evaluation, SAPS - Simplified Acute Physiology Score, ICU - Intensive Care Unit, CL_{CR} - Creatinine Clearance

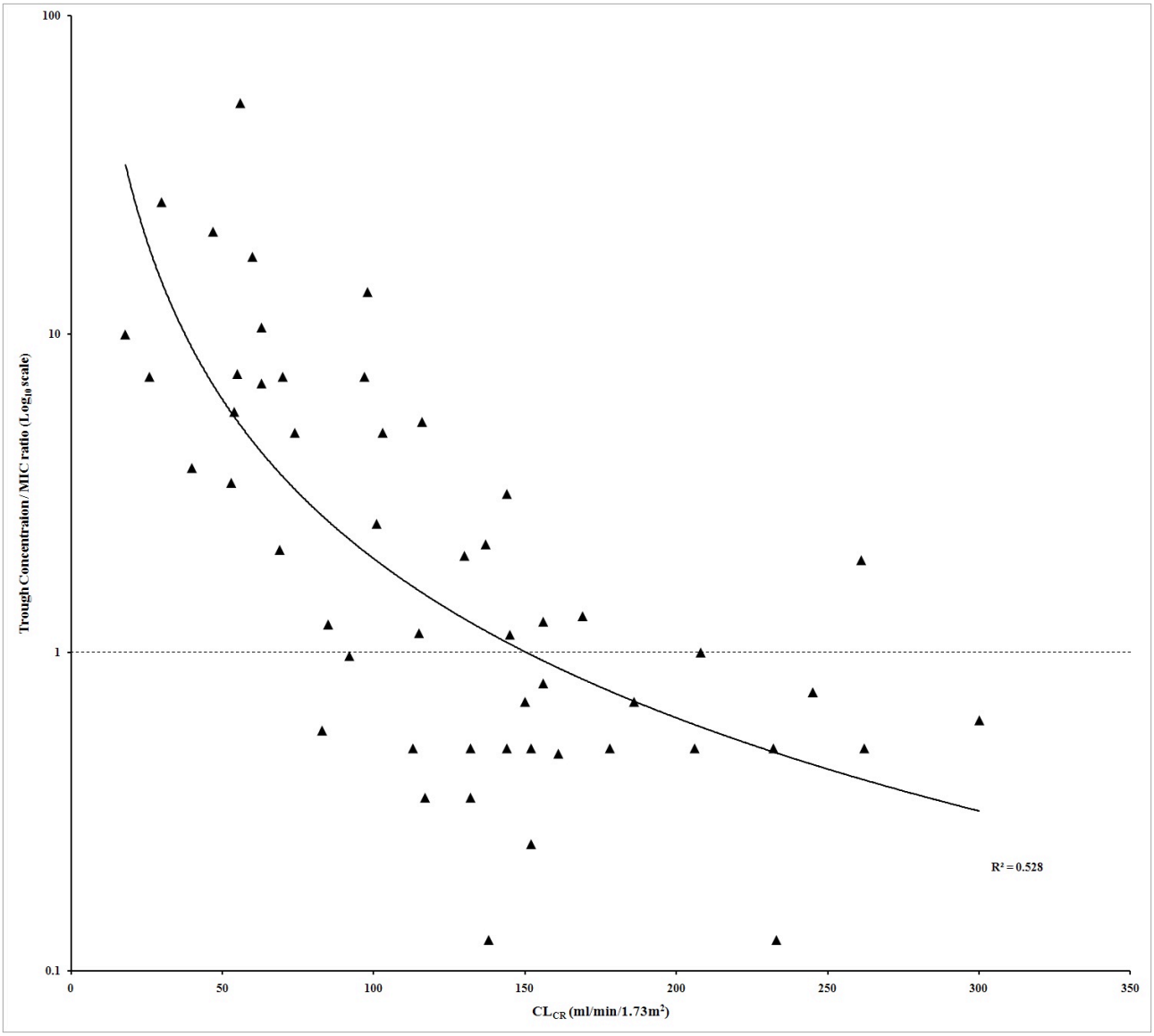
Table 4.3 Comparison of Demographic, Therapeutic, and Infection Related Variables Between Those with Unbound Trough Concentrations < 4 x MIC, and ≥ 4 x MIC

Variable	Drug Concentration < 4 x MIC (n=36)	Drug Concentration ≥ 4 x MIC (n=16)	p-value
Male / Female, n (%)	28 (77.8) / 8 (22.2)	9 (56.3) / 7 (43.8)	0.184
Age, yrs, mean (SD)	45.8 (20.2)	65.1 (16.9)	0.002
APACHE II, mean (SD)	19.4 (6.3)	22.2 (7.6)	0.173
SAPS II, mean (SD)	36.9 (15.1)	45.9 (16.5)	0.059
Measured CL_{CR}, ml/min/1.73m^2, mean (SD)	165 (91)	64 (28)	< 0.001
Known / Suspected Source, n (%):			
- Skin / Soft Tissue / Bone	4 (11.1)	3 (18.8)	0.662
- Respiratory Tract	22 (61.1)	5 (31.3)	0.047
- Abdomen	2 (5.6)	4 (25.0)	0.064
- Bacteraemia	5 (13.9)	1 (6.3)	0.653
- Central Nervous System	3 (8.3)	2 (12.5)	0.637
- Urinary Tract	0 (0)	1 (6.3)	0.308
Mechanical ventilation, n (%)	29 (80.6)	15 (93.8)	0.409
Fluid Balance, ml, mean (SD)	-17 (1117)	-75 (1242)	0.869
Vasopressor, n (%)	7 (19.4)	6 (37.5)	0.184
β-lactam, n (%):			
- Fluclox/Dicloxacillin	9 (25.0)	2 (12.5)	0.468
- Piperacillin	17 (47.2)	8 (50.0)	0.853
- Meropenem	5 (13.9)	4 (25.0)	0.431
- Other	5 (13.9)	2 (12.5)	1.000
Target MIC, n (%):			
- Low	9 (25.0)	8 (50.0)	0.076
- Moderate	7 (19.4)	4 (25.0)	0.719
- High	20 (55.6)	4 (25.0)	0.041
Nil Organism identified, n (%)	9 (25.0)	8 (50.0)	0.076
ICU mortality, n (%)	1 (2.8)	2 (12.5)	0.221

APACHE - Acute Physiology and Chronic Health Evaluation, SAPS - Simplified Acute Physiology Score, ICU LOS - Intensive Care Unit Length of Stay, CL_{CR} - Creatinine Clearance

As observed, there was a statistically significant difference in the value of the measured CL_{CR} between groups. In this respect, in instances where the trough concentration was < MIC, 82% had a CL_{CR} ≥ 130ml/min/1.73m^2 ($p<0.001$). Where the trough concentration was < 4 x MIC, 72% had a CL_{CR} ≥ 130ml/min/1.73m^2 ($p<0.001$). Those with trough concentrations < MIC and < 4 x MIC were also noted to be significantly younger, with higher MIC targets for suspected or known pathogens. There was also a greater incidence of respiratory tract infections in those with concentrations < 4 x MIC. There was no significant difference noted in gender, ICU mortality, beta-lactam employed, mechanical ventilation, vasopressor use, or fluid balance between groups. Figure 4.1 graphically depicts the trough drug concentration to MIC ratio as a function of the measured CL_{CR}.

Figure 4.1 Trough Drug Concentration / MIC Ratio (Log_{10} scale) as a Function of CL_{CR}



Caption: Plot of trough drug concentration to MIC ratio as a function of CL_{CR}. A value > 1 indicates a trough concentration > MIC of the known or suspected pathogen. A trend-line has been fitted with an R^2 value of 0.53. MIC - minimum inhibitory concentration.

Using a cut-off p-value < 0.15, variables were identified for inclusion in a multivariate logistic regression analysis, using a target concentration of MIC and 4 x MIC respectively. The results of this analysis are presented in Table 4.4. As demonstrated, CL_{CR} was identified as being a statistically significant contributor to the likelihood of obtaining a therapeutic concentration (target ≥ MIC OR: 0.986 (0.973-0.999), p=0.037; target ≥ 4 x MIC OR: 0.944 (0.902-0.989), p=0.015). In this respect, maintaining all other variables constant in the model, a 25 ml/min/1.73m^2 increase in the measured CL_{CR} (from that observed), is associated with a mean 60% reduction in the probability of obtaining a trough concentration ≥ 4 x MIC.

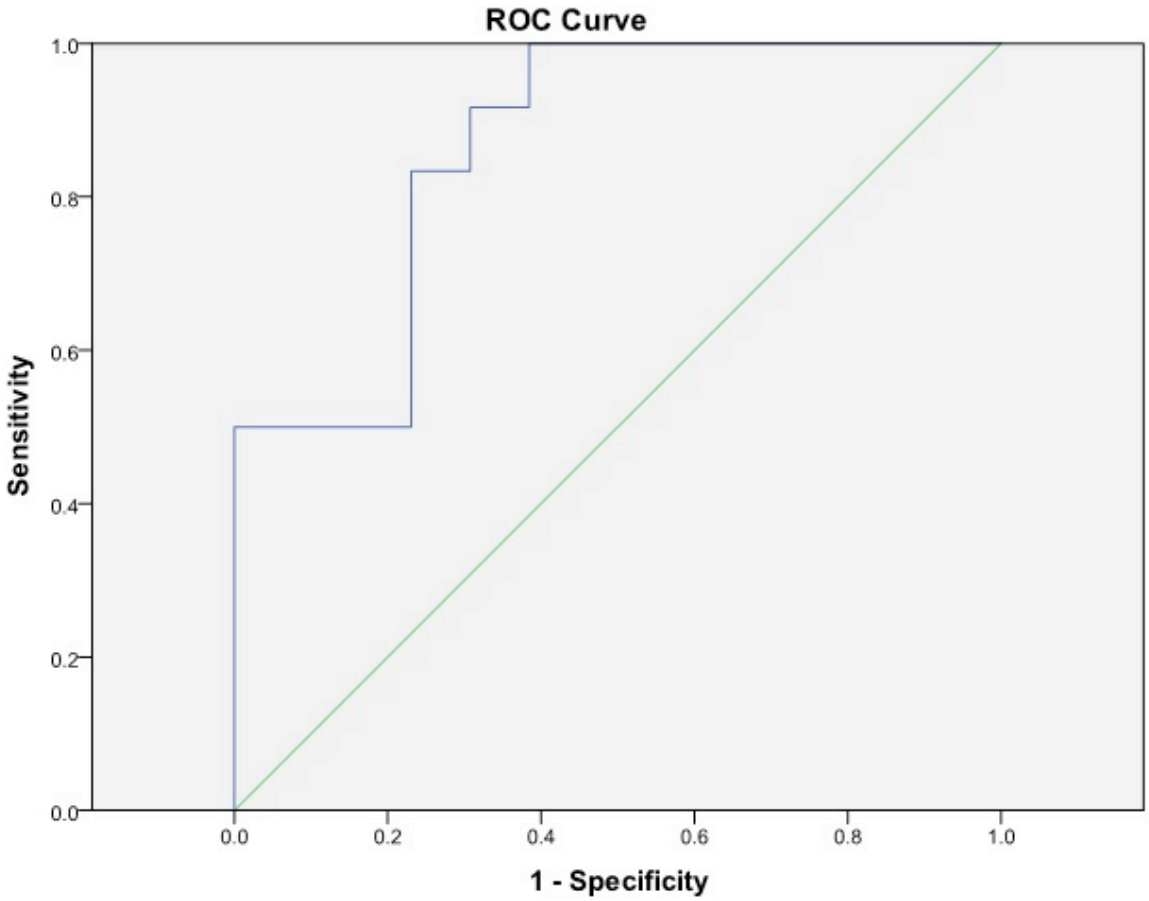
Table 4.4 Results of Single Step Forced Entry Logistic Regression Modelling, Using a Target Concentration ≥ MIC and ≥ 4 x MIC

Logistic Regression Model – Target Concentration = MIC		
Variable	**Odds Ratio (95% CI)**	**p-value**
Age	1.044 (0.999-1.091)	0.056
CL_{CR}	0.986 (0.973-0.999)	0.037
High MIC	2.205 (0.464-10.47)	0.320
Nil Organism	0.281 (0.040-1.971)	0.202
Logistic Regression Model – Target Concentration = 4 x MIC		
Variable	**Odds Ratio (95% CI)**	**p-value**
Age	0.992 (0.925-1.064)	0.820
SAPS II	1.042 (0.953-1.139)	0.372
CL_{CR}	0.944 (0.902-0.989)	0.015
Respiratory source	35.96 (0.974-1328)	0.052
Intra-abdominal source	0.698 (0.013-37.40)	0.860
Low MIC	3.306 (0.125-87.76)	0.475
High MIC	2.575 (0.067-98.38)	0.611
Nil Organism	0.158 (0.005-4.666)	0.285

CL_{CR} - Creatinine Clearance, APACHE - Acute Physiology and Chronic Health Evaluation, SAPS - Simplified Acute Physiology Score, MIC - Minimum Inhibitory Concentration

We further investigated statistical relationships in our dataset by performing a sub-group analysis on those patients receiving piperacillin for a known or suspected *Pseudomonas aeruginosa* infection (n=25, EUCAST MIC = 16mg/L). The ROC curve constructed to further examine the utility of CL_{CR} measures to accurately predict sub-therapeutic drug concentrations (< MIC) is presented in Figure 4.2. This demonstrates very good discrimination, with an area under the curve of 0.87 (p=0.002), and a 77% sensitivity, and 83% specificity for CL_{CR} values ≥ 110ml/min/1.73m^2.

Figure 4.2 Receiver Operating Characteristic (ROC) Curve for CL_{CR} vs Trough Concentration ≥ 16mg/l in 25 Patients Receiving Piperacillin



Caption: The area under the curve is 0.87. A CL_{CR} ≥ 110ml/min/1.73m^2 displays a sensitivity of 77% and specificity of 83% for predicting a trough piperacillin concentration < 16mg/l. A diagonal reference line is also provided.

4.5 Discussion

These data demonstrate that in select critically ill patients receiving beta-lactam therapy, there is a strong association between augmented CL_{CR} and sub-therapeutic unbound plasma trough concentrations. Although such an observation is predictable, based on the established PK characteristics of these agents, this work is unique in contemporary literature, given the number of agents employed, and the strength of the relationship demonstrated in both univariate and multivariate analysis. This highlights the concern that in many critically ill patients (largely those with seemingly 'normal' renal function), standard dosing is likely to provide inadequate beta-lactam exposure, potentially predisposing to treatment failure or the selection of drug resistant strains.

Previous authors have demonstrated that CL_{CR} is a key covariate in determining drug CL for a range of beta-lactams in the critically ill (23, 28, 30-33, 102, 117, 145, 146, 149, 150). In particular, Lipman et al. have demonstrated a near linear relationship between measured CL_{CR} and cefepime/cefpirome elimination (31, 32), while more recently Conil and colleagues have shown an inverse relationship between trough piperacillin concentrations and 24-hour measured CL_{CR} (26). Such work confirms the significant relationship between CL_{CR} and beta-lactam elimination, although the present study extends this finding to a broader range of agents commonly employed in this setting.

Although a significant proportion of critically ill patients will develop renal dysfunction during their ICU stay (17), an increasingly recognised observation in this population is that of elevated CL_{CR} values. This phenomenon has been recently termed ARC, and defines the enhanced renal elimination of circulating solute, such as waste products or pharmaceuticals (71). Although a relatively new term, many authors are describing this finding in a variety of subsets of critically ill patients (59, 84, 88, 92), and was a feature in over 50% of the cohort included in this analysis (mean CL_{CR} = 134ml/min/1.73m^2).

Specifically, Minville and colleagues have very recently described augmented CL_{CR} in a cohort of stable polytrauma victims (88), while similar findings have been observed in those receiving directed therapy for traumatic brain injury (92). Brown and colleagues also report CL_{CR} reaching a peak of 190ml/min/1.73m^2 in traumatised post-operative patients (84), while more recent research has demonstrated that younger, trauma and post-operative admissions, with lower illness severity scores, are more likely to manifest higher

CL_{CR} on admission (59). These findings are in keeping with our cohort, and provide some indication of sub-groups where beta-lactam TDM or regular CL_{CR} measurement may be useful in optimising drug exposure.

The physiological processes driving such changes in beta-lactam PK largely stem from the underlying inflammatory state, and invasive interventions provided. In this respect, many critically ill patients will manifest SIRS (15), characterised by a low systemic vascular resistance and high CO (62). In experimental models of gram-negative sepsis, this 'hyperdynamic' circulation has been associated with increases in blood flow to major organs, including RBF (63). This in turn results in greater delivery of solute to the kidney, and is likely to contribute to the higher CL observed in septic patients without renal dysfunction.

Such changes can be further exacerbated by the application of vasoactive medications (69), and large volume fluid resuscitation (68), both of which are routinely employed in septic patients, usually as part of goal-directed therapy (2). Similarly, aggressive haemodynamic targets are often employed in managing subarachnoid haemorrhage, particularly in attempts to ensure adequate cerebral perfusion, and prevent delayed cerebral ischaemia (110). Although we could not demonstrate a difference in the application of vasopressor agents between groups, this study was not powered for such an observation. Other 'at-risk' groups demonstrating similar changes in cardiovascular physiology include pregnancy (64), and burns victims (111).

Our findings raise the possibility that a significant proportion of critically ill patients will receive inadequate beta-lactam exposure, despite the application of 'standard' empiric dosing regimens. In addition, without easily defined and repeatable measures to guide therapy (such as blood pressure when titrating anti-hypertensives), recognizing this scenario can be problematic. Although our data does not demonstrate a difference in ICU mortality, this study is significantly under-powered for such an observation. This is not surprising given the number of potential confounders, although separate research has demonstrated improved clinical cure and bacterial eradication with 100% $fT_{\geq MIC}$ for beta-lactam antibacterials (168).

Further clinical investigation is clearly required. Specifically, the use of extended interval or continuous infusion strategies (to ensure higher beta-lactam concentrations over longer

intervals) has a sound PK-PD rationale (135), although outcome data continues to be scarce (185). Controlled trial data is perhaps flawed in this setting however, as the substantial changes in organ function encountered in the critically ill are rarely considered. The role of such dosing regimens in the setting of ARC remains un-tested.

The significance of the likely pathogen is also demonstrated in our analysis. In this respect, a higher MIC target was observed in those with sub-therapeutic concentrations in univariate analysis, although this was not significant in multivariate modelling. It still remains a logical conclusion however, that when targeting therapy towards more resistant pathogens (with higher MICs'), sub-therapeutic drug concentrations are likely to be more common. This is further demonstrated by our ROC analysis utilising piperacillin trough levels, which suggests that even relatively normal CL_{CR} values (110ml/min/1.73m^2) can predict sub-therapeutic drug concentrations when targeting more resistant pathogens. Importantly, dosing studies in the 'non-critically ill' are perhaps unlikely to enrol patients with CL_{CR} values significantly above this threshold, thereby validating current dosing regimens *outside* of the ICU. However, given the demonstrable changes in organ function with critical illness, such thresholds clearly require further assessment in a larger critically ill population.

This study has a number of potential limitations. Firstly, we have single data points only for analysis, and as such our findings do not attempt to describe the changes in beta-lactam PK throughout the ICU stay. In this respect, it is anticipated that there could be significant intra-individual variability due to the dynamic nature of critical illness. Furthermore, as we only have a single plasma concentration, it is not possible to determine drug CL. Secondly, we have chosen to employ 8-hour CL_{CR} measures, as compared with more traditional 24-hour collections. This represents the preferred practice at our institution, and previous authors have shown equivalence when using such measures (45). Thirdly, our data represents a relatively small select cohort from a single centre, and as such, may lack application in a wider setting. Finally, we have measured total drug concentrations, with correction for protein binding based on published literature. As protein binding is complex in critical illness, such assumptions may not be correct, although assays for free drug concentrations are not readily available currently.

4.6 Conclusions

In conclusion, this study has demonstrated a strong association between elevated CL_{CR} measures and sub-therapeutic trough concentrations for a range of beta-lactams in critically ill patients, regardless of whether a target of MIC or 4 x MIC is employed. Multivariate modelling confirms CL_{CR} as a significant covariate for predicting low trough concentrations, despite differences in illness severity, age, and MIC. Given the strong possibility that many critically ill patients receive inadequate beta-lactam exposure with standard dosing, we recommend the routine application of CL_{CR} measurement in the critically ill where ARC is suspected, to either guide the application of beta-lactam TDM where available, or the application of higher empirical dosing.

Chapter 5

ARC in Septic and Traumatized Patients with Normal Plasma Creatinine Concentrations: Identifying At-risk Patients

5.1 Chapter Overview

This chapter outlines the results of a prospective observational study of demographic and physiological risk factors for ARC in traumatized and septic patients receiving empirical beta-lactam therapy. In addition, the relationship between cardiac index (CI) and CL_{CR} is explored, in order to further elucidate the potential mechanisms underpinning ARC in these patients.

Text, figures, and tables from the published manuscript (as outlined in Chapter 1) are reproduced here. The layout has been adjusted to fit the overall style of the thesis. The references are found alongside those for the other chapters, at the conclusion of the main body.

5.2 Introduction

Accurate pharmaceutical prescription remains uniquely challenging in the critically ill. Many dosing schedules are simply extrapolated from data derived from healthy volunteers or ambulatory patients, without consideration of the pathophysiology (11) or clinical heterogeneity, often encountered in this setting. Capillary leak, fluid loading, decreased protein binding, use of vasoactive medications and altered excretory organ function, will significantly distort the 'normal' PK profile of many agents (135). Most concerning is the potential effects on antibacterial drug exposure, given the wealth of data demonstrating improved outcomes with early appropriate therapy (4-6). Although infrequently considered, such issues may not only confound the successful individual use of many pharmaceuticals, but also the planning, methodology and interpretation of clinical trials in this population (194).

A key PK variable of interest is drug CL, with previous data demonstrating notably elevated values in subsets of critically ill patients (71). This phenomenon has recently been termed ARC (198) and may significantly impact the successful application of many

renally eliminated agents by promoting sub-therapeutic drug exposure (18, 198). Although specific data concerning drug CL in critical illness remains sparse, elevated urinary CL_{CR}, as a marker of ARC, has been documented in sepsis (61), VAP (101), TBI (92), burns (44), multitrauma (88), and post-operatively (84). Furthermore, elevated CL_{CR} has been closely linked with sub-therapeutic beta-lactam antibacterial trough concentrations (26, 199) in addition to being significantly correlated with renal drug elimination (71).

Identification of patients manifesting ARC remains clinically challenging, principally as many agents (most notably antibacterials) manifest 'silent' PD indices, making under-dosing substantially less visible (12). Although various mathematical estimates of glomerular filtration are widely applied (40, 41), each was primarily designed for use outside of the ICU, making application in this setting flawed (46, 200) and of little value in guiding therapy. While a measured CL_{CR} has greater utility (54), a defined urinary collection period is required, thereby limiting application to initial dose selection. Improved methods to identify patients with ARC using simple bedside assessment are urgently required.

The physiological alterations promoting ARC remain poorly understood. In large animal models of gram-negative sepsis, elevated CO, low systemic vascular resistance, and increased major organ blood flow have been demonstrated (63). Application of aggressive fluid resuscitation (201) and vasopressor support (69) further augments this process, leading to substantial changes in renal function. Many parallels can be drawn with pregnancy, where similar cardiovascular changes are associated with augmented RBF and glomerular filtration (65). As such, in the absence of established AKI, the innate hemodynamic response to critical illness, coupled with common clinical interventions, may promote increased solute delivery to the kidneys and subsequent augmented renal elimination.

In this respect, assessment of CO offers a logical, pragmatic and physiologically sound method of rapidly assessing patients for the presence of ARC. To our knowledge, there has been little data reported on this application, representing a new, unique, indication for cardiovascular monitoring. Importantly, although CO assessment has historically employed invasive techniques (such as pulmonary artery catheterization), a variety of new devices are making continuous CO measurement accessible, feasible and safe (202). The aims of this pilot prospective observational study were, therefore, to: a) describe the prevalence of

ARC in a cohort of septic and traumatized critically ill patients receiving beta-lactam therapy; b) correlate CL_{CR} and cardiac function in these patients; and c) examine demographic, physiological and illness severity characteristics that may help to identify patients manifesting ARC.

5.3 Materials and Methods

5.3.1 Study Population

Patients were enrolled consecutively as part of a wider open label study examining beta-lactam antibacterial PK in critical illness, the methodology of which has been published elsewhere (203). In brief, patients were eligible for enrolment if they were: a) 18 to 80 years of age; and b) receiving piperacillin-tazobactam for treatment of presumed or confirmed nosocomial infection, while manifesting SIRS (15), or were receiving cefazolin as prophylaxis following multitrauma. This, therefore, represents a convenience sample of multitrauma and septic critically ill patients admitted to our institution. This manuscript reports a separate, independent analysis, focusing on ARC. The study protocol was approved by our institutional human research ethics committee (HREC 2007/188) and informed consent was obtained from either the patient or their substitute decision maker in all cases.

5.3.2 Study Protocol

An in-depth physiological and PK investigation was performed over a single six-hour dosing interval following antibacterial infusion (203). Pulse contour analysis, utilizing the Vigileo® system (software version 1.10), connected to an existing intra-arterial catheter via a Flo Trac® (Edwards Lifesciences, Irvine, CA, USA) sensor, was employed as the primary method of measuring CO. Demographic data including patient age, gender, body weight and height were inputted, following which the sensor was levelled to the phlebostatic axis and 'zeroed' to atmospheric pressure. The system provides continuous CO data utilizing the heart rate and an index of stroke volume (obtained from the arterial pressure waveform), which is automatically averaged and updated. CI ($L/min/m^2$) is then calculated as the CO (L/min) divided by the body surface area (BSA) (m^2). Three CI measurements were recorded at 0, 180, and 300 minutes, after which the mean value was calculated for use in subsequent analysis.

CL_{CR} was measured as the primary method of determining kidney function. All urine was collected via an indwelling catheter over three two-hour time periods (0 to 120, 120 to 240, and 240 to 360 minutes, respectively), following which urinary volume and CR concentration were determined by laboratory analysis. CR measurement in plasma and urine utilized automated analyzers employing a modified Jaffe (alkaline picrate) technique, representing an isotope dilution mass spectrometry (IDMS) traceable assay. Plasma CR concentrations measured on the day of investigation were used to calculate each CL_{CR} (normalized to a BSA of 1.73m^2), after which the mean value was used in further analysis.

Additional data, including the requirement for mechanical ventilation, vasopressor support, modified sequential organ failure assessment (SOFA) score (excluding the neurological component) and 24-hour fluid balance, were also recorded on the day of drug administration. Admission acute physiology and chronic health evaluation (APACHE) II score, in addition to ICU and in-hospital clinical outcomes, were also recorded. Given that changes in cardiovascular physiology are unlikely to promote enhanced renal elimination in the setting of evolving AKI, patients with a plasma CR concentration greater than the upper limit of the reported reference range (>110 µmol/L) were excluded from further analysis. ARC was defined as a CL_{CR} ≥130ml/min/1.73m^2, given previous data demonstrating an association with sub-therapeutic beta-lactam concentrations, when using standard doses (199).

5.3.3 Statistics

Continuous data are presented as the mean (SD) or median [IQR]. Categorical data are presented as counts (%). Correlation was assessed by means of a scatter graph and Pearson correlation coefficient (r). Comparisons between groups utilized an Independent Student T-test or Mann-Whitney U test for continuous data, and a Chi-square or Fishers Exact test for categorical data, where analysis assumptions were met. A backward conditional logistic regression model was developed to describe risk factors for ARC in multivariate analysis. Covariates were identified if the associated *P*-value was <0.15 in univariate testing, and the Hosmer-Lemeshow statistic was used to assess goodness of fit. Receiver operator characteristic (ROC) curves were constructed to examine the accuracy of any variable to predict ARC. A *P*-value <0.05 was considered as indicating statistical significance, and all analyses were performed using SPSS version 19 (Chicago, IL, USA).

5.4 Results

Eighty patients were enrolled in the open label PK study, fifty meeting the criteria for sepsis, and the remaining thirty admitted post multitrauma. One patient was excluded from further analysis as no CI measurements were available, while a further eight patients were excluded due to a plasma CR concentration >110 µmol/L on the day of study. Laboratory, demographic, illness severity and outcome data for the remaining seventy-one patients (sepsis n = 43, trauma n = 28) are presented in Table 5.1. As expected, young male patients dominated the trauma group, although illness severity scores were similar between diagnostic categories. Data collection occurred a median of 1.60 [1.20 to 2.13] days post admission in the trauma sub-group, compared with 4.11 [1.68 to 6.83] days in sepsis (P <0.001). Crude ICU (4.2%) and in-hospital (8.5%) mortality were remarkably low.

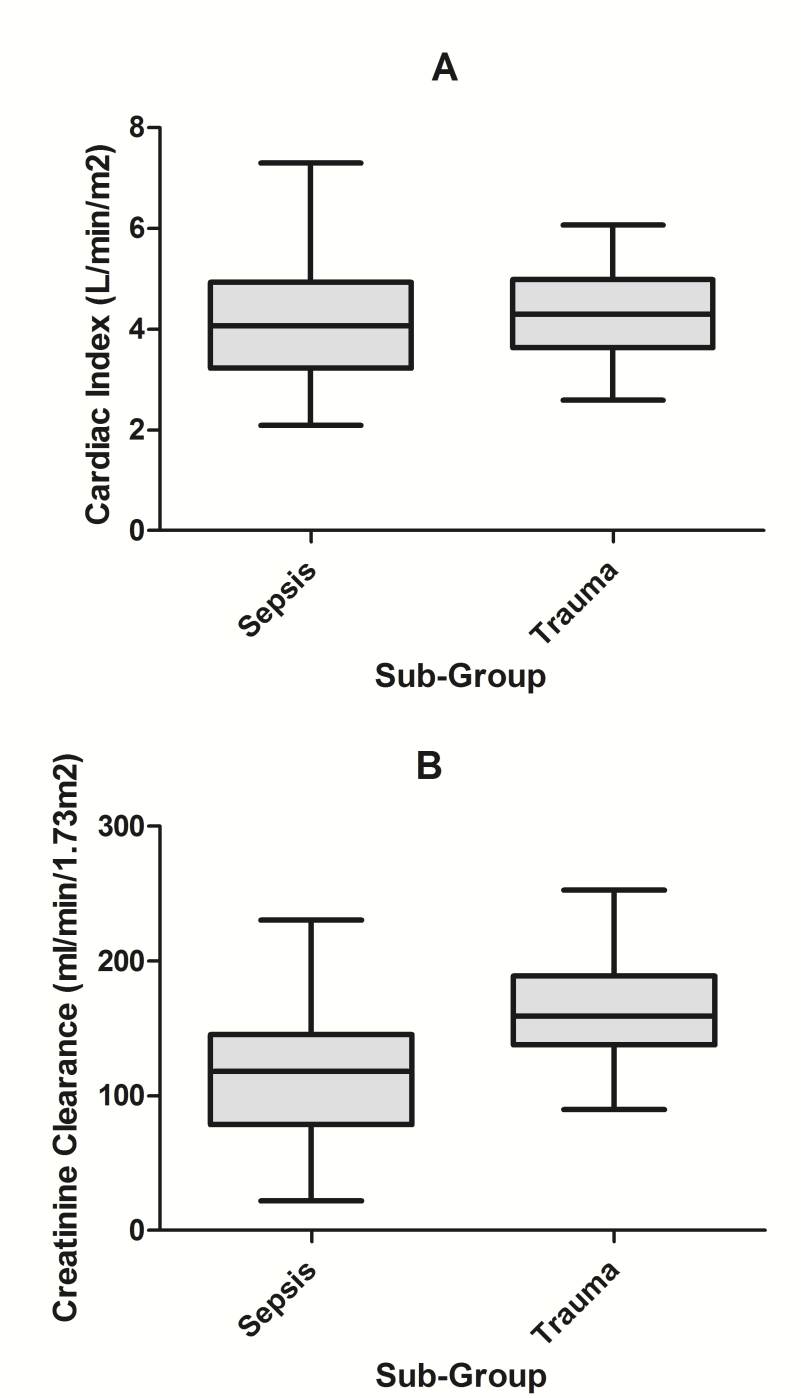
Table 5.1 Laboratory, Demographic and Illness-severity Data of All Patients (n = 71)

Variable	All patients (n = 71)	Trauma (n = 28)	Sepsis (n = 43)	*P*-value[a]
Age, years, mean (SD)	42.4 (16.6)	36.4 (13.9)	46.3 (17.1)	0.013
Male gender, number (%)	45 (63.4)	23 (82.1)	22 (51.2)	0.008
BSA, m^2, mean (SD)	1.98 (0.26)	2.01 (0.25)	1.96 (0.27)	0.415
APACHE II score, mean (SD)	17.9 (7.15)	16.1 (7.68)	19.0 (6.62)	0.096
Modified SOFA score, median [IQR]	3 [2-5]	3.5 [2-5]	3 [2-5]	0.659
Use of Vasopressors, number (%)	20 (28.2)	11 (39.3)	9 (20.9)	0.093
Mechanical ventilation, number (%)	66 (93.0)	26 (92.9)	40 (93.0)	1.000
24hour Fluid balance, ml, mean (SD)	656 (1,886)	1,209 (1903)	295 (1,806)	0.045
Plasma CR, µmol/L, mean (SD)	66.1 (18.1)	62.7 (13.2)	68.4 (20.5)	0.157
CI, L/min/m^2, mean (SD)	4.20 (1.10)	4.30 (0.86)	4.13 (1.23)	0.507
CL_{CR}, ml/min/1.73m^2, mean (SD)	135 (51.8)	166 (42.5)	114 (47.2)	<0.001
Augmented renal clearance, n (%)	41 (57.7)	24 (85.7)	17 (39.5)	< 0.001
ICU length of stay, days, mean (SD)	16.0 (11.1)	13.3 (10.2)	17.8 (11.4)	0.090
ICU mortality, number (%)	3 (4.20)	1 (3.6)	2 (4.7)	1.000
Hospital mortality, number (%)	6 (8.50)	3 (10.7)	3 (7.0)	0.674

[a]Comparison between sub-groups. APAHCE II, Acute Physiology and Chronic Health Evaluation; BSA, body surface area; CI, cardiac index; CL_{CR}, creatinine clearance; CR, creatinine concentration; SOFA, Sequential Organ Failure Assessment.

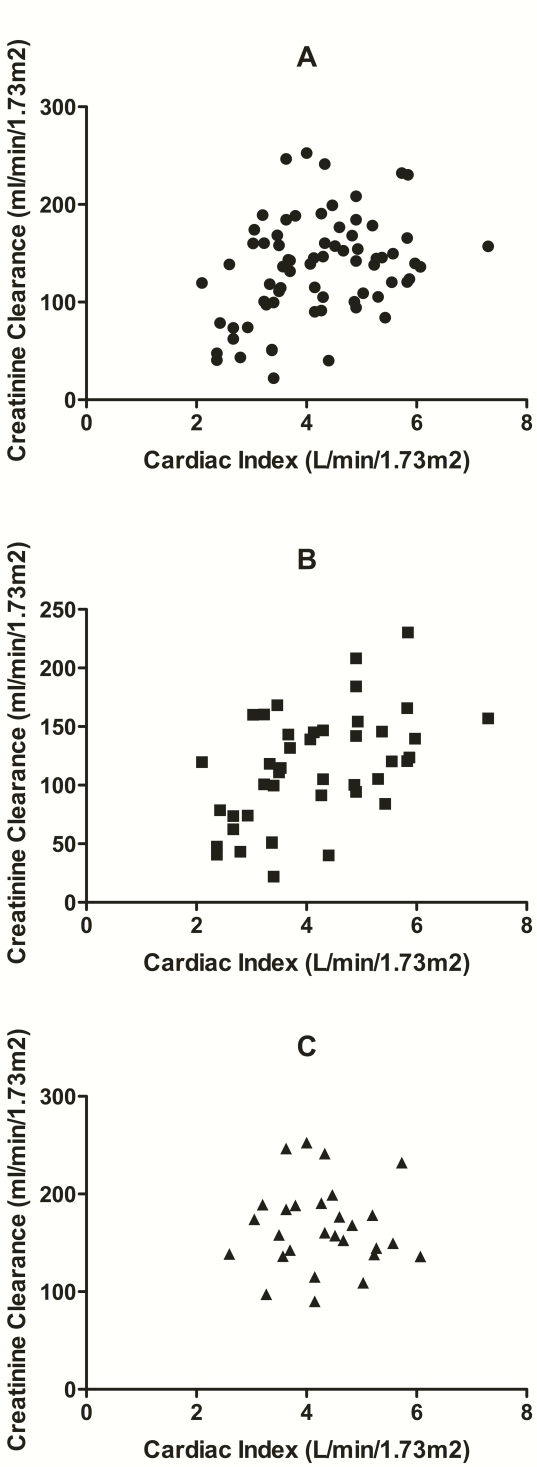
Overall, 57.7% of the cohort manifested ARC (CL_{CR} ≥130ml/min/1.73m^2), although higher CL_{CR} values were noted in traumatized patients (166 (42.5) versus 114 (47.2) ml/min/1.73m^2, *P* <0.001), leading to a greater prevalence in this group (85.7% versus 39.5%, *P* <0.001). The range of CI and CL_{CR} measures observed in each diagnostic sub-group are presented in Figure 5.1. In all patients (n = 71), a weak, statistically significant correlation was evident between CI and CL_{CR} (r = 0.346, *P* = 0.003), although this was primarily due to the relationship observed in septic patients (r = 0.508, *P* = 0.001), as no correlation (r = -0.012, *P* = 0.951) was evident in trauma patients (see Figure 5.2).

Figure 5.1 Box Plot of CI (L/min/m^2) and CL_{CR} (ml/min/1.73m^2) in Trauma and Septic Patients



Caption: Box plot (median, interquartile range, maximum and minimum) of cardiac index, L/min/m^2 (**A**) and creatinine clearance, ml/min/1.73m^2 (**B**) in trauma (n = 28) and septic (n = 43) patients. Higher CL_{CR} values were demonstrated in those admitted post trauma (*P* <0.001).

Figure 5.2 Correlation of CI (L/min/m^2) and CL_{CR} (ml/min/1.73m^2)



Caption: Scatter graphs of cardiac index (L/min/m^2) and creatinine clearance (ml/min/1.73m^2) in all patients (**A**), septic patients (**B**) and trauma patients (**C**). The Pearson correlation coefficient (r) for all patients was r = 0.346 (*P* = 0.003), septic patients r = 0.508 (*P* = 0.001), and trauma patients r = -0.012 (*P* = 0.951).

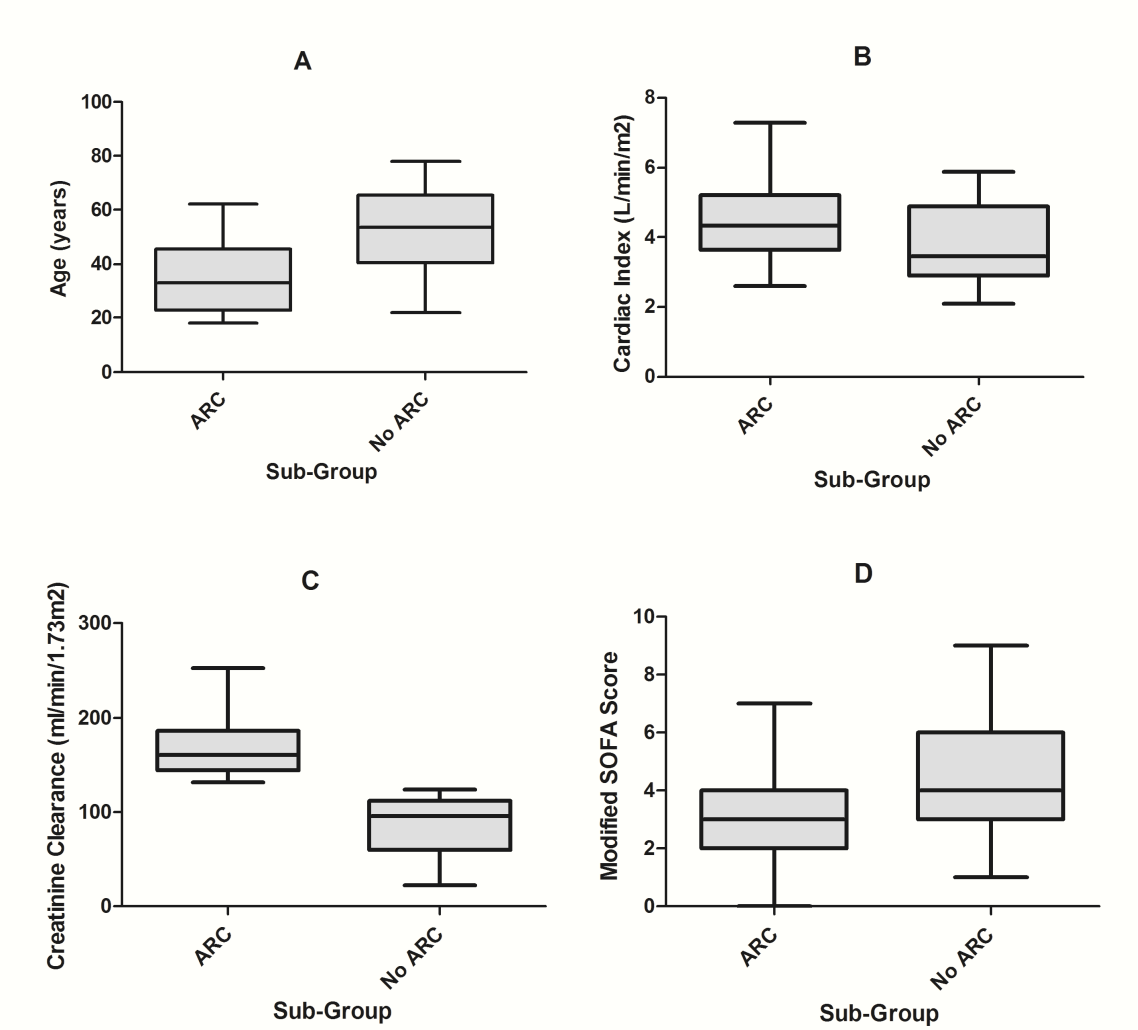
Differences in demographic, illness severity, physiological and laboratory data on the basis of ARC status are provided in Table 5.2. As illustrated, those manifesting ARC tended to be younger (*P* <0.001), male (*P* = 0.012), with lower APACHE II (*P* = 0.008) and modified SOFA scores (*P* = 0.013) and higher cardiac indices (P = 0.013). The range of values recorded for age, CI, CL_{CR} and modified SOFA score are presented graphically in Figure 5.3.

Table 5.2 Demographic, Diagnostic and Treatment-related Data in Those With and Without ARC

Variable	ARC (n = 41)	No ARC (n = 30)	*P*-value
Age, years, mean (SD)	34.1 (11.7)	53.7 (15.5)	<0.001
Male gender, number (%)	31 (75.6)	14 (46.7)	0.012
BSA, m^2, mean (SD)	1.98 (0.25)	1.99 (0.28)	0.850
APACHE II score, mean (SD)	16.0 (6.33)	20.4 (7.49)	0.008
Modified SOFA score, median [IQR]	3 [2-4]	4 [3-6]	0.013
Use of vasopressors, number (%)	9 (22.0)	11 (36.7)	0.173
Mechanical ventilation, number (%)	39 (95.1)	27 (90.0)	0.644
24hr Fluid balance, ml, mean (SD)	428 (2011)	967 (1684)	0.237
CI, L/min/m^2, mean (SD)	4.47 (1.01)	3.80 (1.12)	0.013
CL_{CR}, ml/min/1.73m^2, mean (SD)	170 (32.9)	86.8 (29.5)	<0.001
Category			
Trauma, number (%)	24 (58.5)	4 (13.3)	<0.001
Sepsis, number (%)	17 (41.5)	26 (86.7)	<0.001

APACHE II, Acute Physiology and Chronic Health Evaluation score; BSA, body surface area; CI, cardiac index; CL_{CR}, creatinine clearance; SOFA, Sequential Organ Failure Assessment.

Figure 5.3 Box Plot of Age (years), CI (L/min/m^2), CL_{CR} (ml/min/1.73m^2) and Modified SOFA Score in Patients With and Without ARC

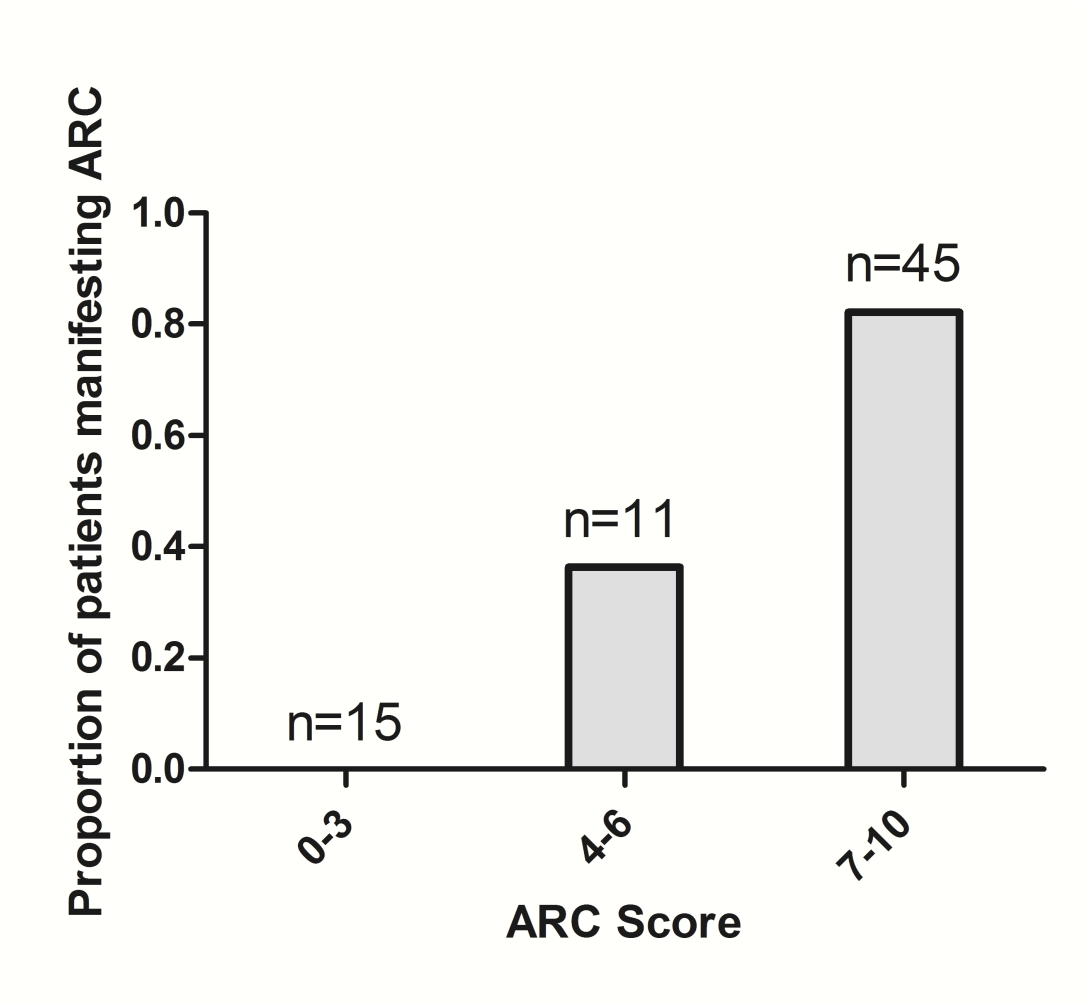


Caption: Box plot (median, interquartile range, maximum and minimum) of age, years (**A**), cardiac index, L/min/m^2 (**B**), creatinine clearance, ml/min/1.73m^2 (**C**) and modified SOFA score (**D**), in those with (n = 41) and without (n = 30) augmented renal clearance. Younger age (*P* <0.001), higher cardiac indices (*P* = 0.013) and lower modified SOFA scores (*P*= 0.013) were observed in those manifesting augmented renal clearance.

Linear variables associated with ARC were then dichotomized to facilitate multivariate logistic regression. Cut-points were identified from visual inspection of the data (Figure 5.3). Specifically, age ≤50 years, CI ≥3.5 L/min/m^2 and modified SOFA score ≤4, along with gender and diagnostic sub-group, were entered as categorical variables into a backward conditional regression model. APACHE II scores were not included, as these are co-linear with age and SOFA, and poorly validated in trauma. This analysis identified age ≤50 years (adjusted odds ratio (OR) 28.6, 95% CI 4.4 to 187.2), trauma (adjusted OR 16.1, 95% CI 3.0 to 87.7) and modified SOFA score ≤4 (adjusted OR 5.1, 95% CI 1.0 to 25.0) as statistically significant risk factors for ARC. The r^2 value was 0.59, and the Hosmer-Lemeshow statistic had a significance value of P = 0.834, suggesting acceptable goodness of fit. There was no improvement in model performance when continuous variables were utilized.

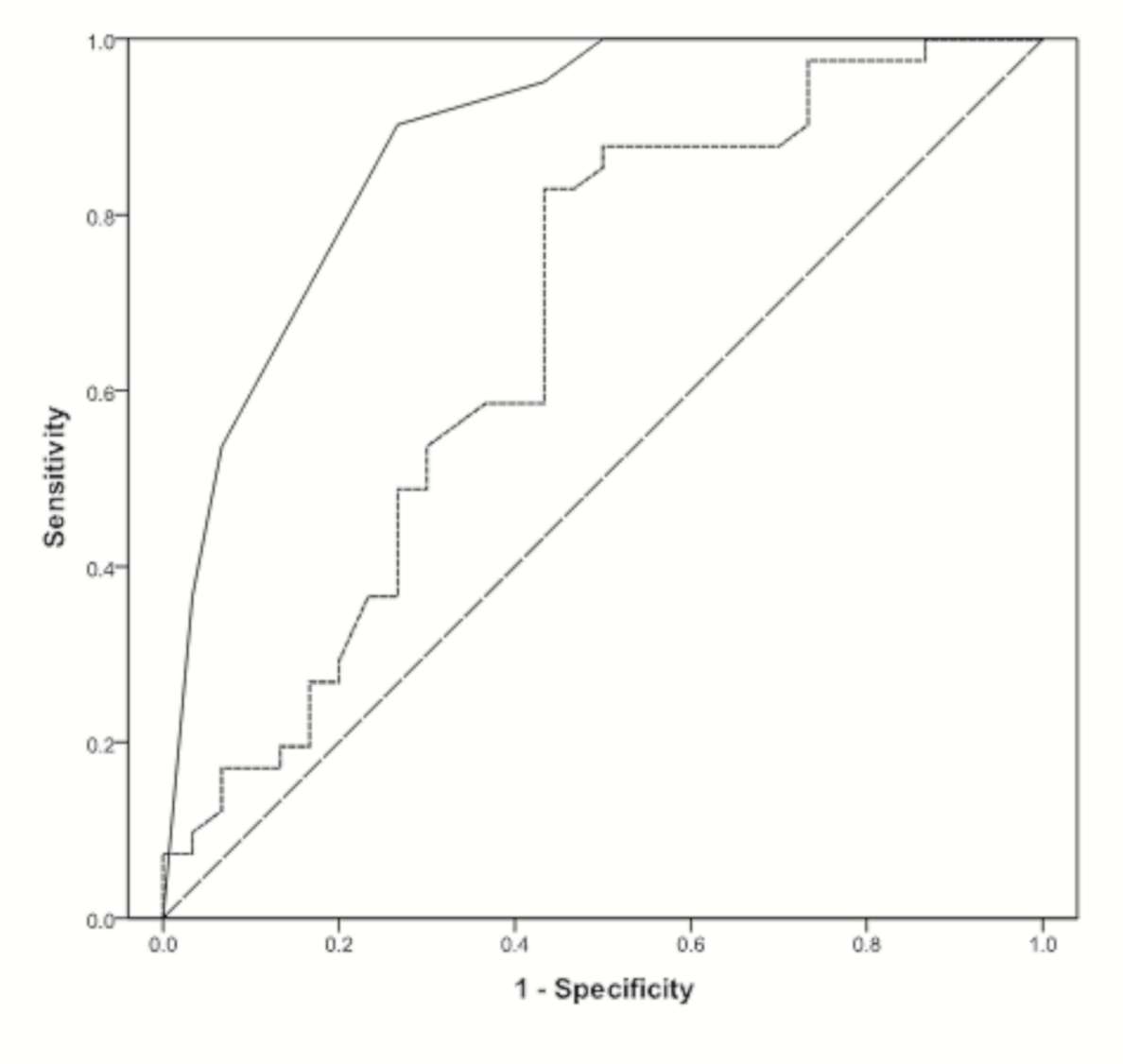
To further illustrate the relative significance of these covariates, a weighted scoring system was constructed based on the adjusted ORs and their proportions to each other. Age ≤50 years was assigned six points, admission post-trauma three points and modified SOFA score ≤4 one point. Scores were then summated for each patient, with higher totals strongly associated (P <0.001) with ARC (see Figure 5.4). This model was also compared with CI measurement as a predictor of ARC status using ROC analysis (see Figure 5.5). CI values alone demonstrate an area under the curve (AUC) of 0.67 (95% CI 0.54 to 0.81, P = 0.013), whereas the combined ARC score has improved accuracy, with an AUC of 0.89 (95% CI 0.80 to 0.97, P <0.001). Separate ROC curves were also constructed utilizing CI values in each diagnostic sub-group (figures not displayed). In those manifesting trauma, CI was less discriminating, with an AUC of 0.57 (95% CI 0.31 to 084, P = 0.646), although this variable performed better in sepsis, AUC 0.72 (95% CI 0.57 to 0.87, P = 0.015).

Figure 5.4 Proportion of Patients Manifesting ARC with Increasing ARC Risk Scores



Caption: Summated risk scores were grouped into three categories (0 to 3, 4 to 6, 7 to 10) and the proportion of patients manifesting augmented renal clearance determined in each. Higher scores were strongly associated with a greater prevalence of augmented renal clearance (*P* <0.001).

Figure 5.5 Receiver Operating Characteristic (ROC) curve of CI (L/min/m^2) and ARC Risk Score in Predicting ARC



Caption: ROC curve of cardiac index, L/min/m^2 (dashed line) and ARC risk score (solid line). Cardiac index demonstrates an AUC of 0.67 (95% CI 0.54 to 0.81, *P* = 0.013), whereas the ARC risk score has improved accuracy, with an AUC of 0.89 (95% CI 0.80 to 0.97, *P* <0.001). A diagonal reference line (AUC = 0.5) is also provided.

5.5 Discussion

This pilot investigation, in the context of a larger study examining beta-lactam antibacterial PK in the critically ill (203), has explored the relationship between CI and CL_{CR} in a cohort of septic and traumatized patients with normal plasma CR concentrations. Overall, ARC was present in more than 50%, similar to a previous report in critically ill patients receiving anti-infective therapy (104). A greater prevalence of ARC was noted in those suffering multitrauma (85.7%). In univariate analysis, a statistically significant association between higher CI and ARC (P = 0.013) was observed, while in multivariate modelling, age (≤50 years), diagnostic category (trauma) and modified SOFA score (≤4) were identified as significant risk factors for ARC.

These findings principally suggest that the underlying disease process and physiological reserve, more than any specific cardiovascular parameter, are implicated in the development of ARC. This is highly clinically relevant, given the potential for significant sub-therapeutic drug exposure when employing 'standard' doses in such patients. Relevant examples include increased clinical failure (168) or drug resistance (131) with beta-lactam antibacterial therapy or sub-optimal venous thromboembolism prophylaxis in those receiving low molecular weight heparin (204).

Multitrauma has already been identified as a significant risk factor for ARC (18, 88, 92) and this is further confirmed by our findings. The absence of any correlation between CI and CL_{CR} in trauma is likely related to the higher CL_{CR} measures observed in this group, the narrow range of recorded cardiac indices (see Figure 5.1) and the smaller sample size. Furthermore, recruitment of renal reserve (73), typically seen in states characterized by protein loading (205), may potentially augment glomerular filtration in this setting, independent of changes in CI.

Importantly, the high prevalence of ARC observed in the trauma sub-group, despite the limited value of CI measurement as a discretionary variable, has considerable potential ramifications for both future study design (194) and daily prescribing practice. Specifically, this finding reminds the clinician that a 'one size fits all' approach to drug dosing in critical illness, is flawed and requires adjustment for a number of variables, least of which is diagnostic category. The recent poor results from clinical trials of emerging antibacterial agents in VAP (194) further illustrate this concept. Selecting a single dosing regimen for all

study participants is unlikely to accommodate the range of clinical and physiological characteristics encountered.

The lower prevalence of ARC (39.5%) and greater variability in CL_{CR} and CI in the septic sub-group (Figure 5.1) reflects the heterogeneity of this syndrome and the wider spectrum of age and underlying co-morbid disease. Such variables significantly impact the available physiological reserve and, as such, the likelihood of manifesting augmented CL. This is evidenced by the strong overall association between ARC, lower modified SOFA scores and age, findings which are consistent with previous literature (59). Identification of additional drivers of ARC in septic patients is not possible with the current dataset, although this is likely to reflect the interaction between the innate inflammatory response and available organ reserve.

Previous data examining the relationship between CI and renal solute elimination in critical illness are limited. Specifically, Brown *et al*. sequentially assessed CL_{CR} in fifty relatively young critically ill post-operative trauma and non-trauma patients while simultaneously measuring CI via a pulmonary artery catheter (PAC) (84). After exclusion of those receiving inotropes or diuretics and those with sepsis or renal failure, a modest correlation was established between CI and CL_{CR} ($r = 0.63$, $P < 0.01$) (84). Our study extends these findings, with data distinct from a peri-operative setting and suggests a modest correlation between CI and CL_{CR} in critically ill septic patients ($r = 0.508$, $P = 0.001$).

The influence of common critical care interventions on cardiovascular and renal function remains to be accurately determined. Specifically, although improvements in CL_{CR} following intravenous fluid administration (68, 201) and use of vasopressor agents (69, 70) have been noted in large animal models, we did not observe any statistically significant difference in either the requirement for vasopressors ($P = 0.173$) or 24-hour fluid balance ($P = 0.237$) in those manifesting ARC. Importantly, these data could be misleading, as they represent information obtained around the time of drug dosing only and, therefore, fail to consider any prior interventions.

Minimally invasive pulse contour CO analysis was employed in this study primarily due to ease of application and decreasing use of PACs in routine clinical practice (206). Although mixed results have been reported in prior validation studies (207), particularly with the earlier software (208), later iterations have improved the accuracy of the device (209), with

an acceptable percentage error (207) and concordance rate (210) in comparison to PAC thermodilution. Aortic valve abnormalities are still likely to cause discrepancy (211) through distortion of the pulse contour, although they were not actively screened for in our analysis. Importantly, despite the growing use of pulse contour CO analysis in clinical practice, its use in general intensive care remains controversial (212) and must be recognized as a limiting factor in this analysis.

Despite the perceived inaccuracies of any specific device(s), our findings indicate a potential new, unique, direction for minimally invasive CI monitoring in critically ill septic patients. The modest correlation observed between CI and CL_{CR}, in addition to the ROC analysis, suggests that elevated values may be viewed as a clinical 'trigger' in patients without AKI, to re-consider the dosing strategy in use, particularly in relation to antibacterial therapy. While additional prospective studies utilizing drug PK data are urgently required, clinical trials examining the efficacy of new agents in this setting must be cognisant of these findings (194). Importantly, our data is limited temporally, such that we do not report changes in CI and CL_{CR} during the ICU stay. As critical illness represents a highly dynamic state, ongoing CI measurement may be even more useful in tailoring drug prescription over time.

We have not included specific drug PK data in these analyses for the following reasons: a) routine measurement of drug levels (beta-lactam or otherwise) is infrequent; b) CI and CL_{CR} assessment are much more accessible in clinical practice; and c) CL_{CR} (allowing identification of ARC) was the primary end-point of interest. In addition, ARC may influence drug handling for many different pharmaceuticals, as CL_{CR} is recognized as a key PK covariate for renally eliminated agents (26, 198, 199). It is acknowledged that CL_{CR} is not a 'gold standard' measure of glomerular filtration (such as inulin CL), albeit tubular CR secretion is unlikely to influence the result at higher filtration rates (213). Two-hour urinary collections were employed, as prior research has reported acceptable accuracy compared with longer time-periods (43). The implications of the proposed ARC scoring system are also acknowledged, with the current findings being primarily speculative. Separate, large, multicentre validation studies are required, in order to establish its external validity, and assess any potential clinical utility.

5.6 Conclusions

To our knowledge, this is the first study to correlate CI and CL_{CR} in a range of critically ill patients, in addition to investigating the application of pulse contour CO monitoring as a means of identifying augmented renal solute elimination. Our findings suggest that diagnostic category, illness severity, age and organ function are likely to significantly influence the probability of developing ARC and should be more regularly considered in future study design and daily prescribing practice. Specifically, these factors may be useful in identifying patients at risk of altered drug handling in critical illness. While additional PK data are required, these results provide a robust basis on which to undertake larger clinical investigation, specifically focusing on the development of improved drug dosing algorithms in the critically ill.

Chapter 6

ARC in the ICU: Results of a Multicentre Observational Study of Renal Function in Critically Ill Patients with Normal Plasma Creatinine Concentrations

6.1 Chapter Overview

This chapter presents the results from an international multicentre observational study of CL_{CR} in recently admitted critically ill patients with normal plasma CR concentrations. The overall prevalence of ARC is determined during the first seven days in ICU, in addition to providing data on temporal trends.

Text, figures, and tables from the published manuscript (as outlined in Chapter 1) are reproduced here. The layout has been adjusted to fit the overall style of the thesis. The references are found alongside those for the other chapters, at the conclusion of the main body.

6.2 Introduction

Accurate assessment of organ function in the critically ill remains uniquely challenging. Such patients routinely manifest an inflammatory response, which in combination with invasive interventions, results in physiology that is infrequently encountered in other settings (214). Regular clinical examination and use of select biomarkers dominate modern critical care practice, being primarily employed to identify and monitor evolving organ dysfunction. Enhanced or augmented organ performance is often of less concern, based on the premise that this is unlikely to lead to adverse outcomes.

However, changes in renal function, and therefore drug handling can significantly distort the normal PK profile of many commonly prescribed agents (71, 198). As a consequence, the clinician may adjust the dosing regime. Usually, progressive AKI, often recognised by a rising plasma CR concentration, will impair the elimination of renally cleared agents, leading to drug accumulation. Consequently dose reduction is generally appropriate to avoid drug toxicity.

The converse, dose escalation in the presence of augmented renal drug elimination, is infrequently reported in clinical practice (194). This largely results from the lack of 'visibility' of this phenomenon, due to the poor discrimination of plasma CR concentrations, when reported within the 'normal' reference range (12). There is, however, increasing evidence supporting the presence of ARC in critically ill patients (215). ARC is defined as the enhanced renal elimination of circulating solute (18). Specifically, elevated CL_{CR}, has been reported in burns (44), TBI (92), polytrauma (88), sepsis (61), VAP (101), and general intensive care practice (59, 84).

While there is a paucity of specific data detailing renal drug CL in the critically ill, CL_{CR} is a routinely used surrogate, representing a key covariate describing renal drug elimination (71). Mathematical estimates of CL_{CR} have been proposed, however these were principally designed for use in an ambulatory or ward-based setting, and are inaccurate in the critically ill (46, 200). As such, a directly measured urinary CL_{CR} is the most accurate and reproducible measure of renal function routinely available (54).

Currently little data exists that describes the epidemiology of ARC, particularly in respect to its' prevalence, and natural history. The impact of ARC on drug PK is not only relevant for daily practice, but also the implementation and interpretation of clinical trials of new or emerging pharmaceuticals (194). As such, there is significant uncertainty regarding the design of robust investigations that account for this phenomenon. The aims of this multicentre prospective observational study were therefore to examine the prevalence and natural history of ARC in a cohort of critically ill patients with normal plasma CR concentrations, with a view to informing future clinical study and current prescribing practice.

6.3 Materials and Methods

6.3.1 Setting

This multicentre observational study was undertaken in four, tertiary-level, university affiliated, ICUs in Australia, Singapore, Hong Kong and Portugal. Ethical approval was obtained from the institutional review board of each participating site, with written informed consent obtained from either the patient or their nominated substitute decision-maker. The lead site was the Royal Brisbane and Women's Hospital, Australia, with ethical approval granted by the Human Research Ethics Committee (HREC/09/QRBW/192).

6.3.2 Study Population

Study participants had to have an expected ICU LOS > 24 hours, no evidence of absolute renal impairment (admission plasma CR < 120 µmol/L), and no history of prior RRT or CKD. Patients were excluded if: a) either invasive haemodynamic monitoring (principally an intra-arterial cannula) or an indwelling urinary catheter (IDC) were not employed as part of standard management; b) they were < 18 years of age; c) they were pregnant; d) rhabdomyolysis was clinically suspected or the admission plasma creatinine kinase was > 5000 IU/L; or e) they were in the 'risk' category or greater for AKI, as defined by the RIFLE criteria (216). Convenience sampling was employed at each participating site. Patients undergoing an operative procedure within 24 hours prior to admission were classified as 'surgical'. Planned post-operative admissions were considered 'elective'.

6.3.3 Interventions

Demographic and outcome data, including age, gender, anthropometric measures, admission diagnosis, APACHE II scores, ICU and hospital LOS, and ICU mortality were recorded prospectively. Modified (excluding the neurological and renal components) SOFA scores, physiological variables, ventilation parameters, 24-hour fluid balance, vasopressor / inotrope administration, diuretic use, and antibacterial administration were recorded daily. Data collection commenced within 48 hours of ICU admission, and was discontinued at: a) ICU discharge; b) death; c) development of severe renal impairment (CL_{CR} < 30ml/min/1.73m^2); d) institution of RRT; e) removal of invasive monitoring or IDC; f) withdrawal of informed consent; or g) day 28, whichever came first.

An 8-hour CL_{CR} was the primary method of measuring renal function. Urine was collected via the IDC between midnight and 0800hrs daily, following which urinary volume and CR concentration were determined by laboratory analysis. Concurrent plasma CR concentrations were obtained, following which CL_{CR} was calculated utilising the standard formula. CR measurement in plasma and urine utilised automated analysers employing a modified Jaffe (alkaline picrate) technique, representing an IDMS traceable assay. As per convention, CL_{CR} values were subsequently normalised to a BSA of 1.73m^2. ARC was defined as an 8-hour CL_{CR} ≥ 130ml/min/1.73m^2, given the association with sub-therapeutic antibacterial concentrations, when using standard doses (199).

6.3.4 Statistical Analysis

Continuous data are presented as the mean (95% CI). Where continuous data were non-normal, a log transformation was applied; all summary statistics were calculated on the log scale, and back transformed for ease of interpretation. When a log transform was not appropriate, data are presented as median [IQR]. Categorical data are presented as counts (%). Non-paired analysis of continuous data utilised an independent Students t-test for two groups, or one-way ANOVA for multiple groups. When data exhibited non-normality and could not be transformed, a Mann-Whitney U or Kruskal-Wallis H test was used alternatively. Paired comparisons employed a paired Students t-test. Independent associations between categorical data were explored by Chi-square test or Fishers Exact test, where appropriate. To model changes in CL_{CR} over time, a mixed-effects model with a random intercept and random slope was constructed. These models are desirable in situations where data is missing not at random (due to patients being discharged from the ICU). As there are limited baseline data concerning ARC in critical illness, no specific power analysis was possible. *Apriori* a sample size > 250 patients was deemed sufficient for exploratory analysis. No assumptions were made for missing data and proportions were adjusted for the number of patients with available data. A two-sided *P*-value < 0.05 was considered as statistical significance, and all analyses were performed using SPSS version 21 (IBM Corporation, Armonk, New York).

6.4 Results

6.4.1 Demographic Data

During the study period, 932 patients were admitted to participating ICUs, of which 281 patients were recruited into the study, contributing 1660 individual CL_{CR} measures. Demographic, admission and illness severity data are presented in Table 6.1. The cohort was relatively young (54.4 (52.5-56.4) years), with most requiring admission to ICU on an emergent basis, with or without an antecedent operation. Routine admissions were scarce (<10%). Illness severity scores were moderately low, despite the non-elective nature of the cohort. Data collection commenced on day 1 [1-2], with patients remaining in the ICU for a median of 4 [2-10] days. As determined by protocol, admission plasma CR concentrations were within the 'normal' range (mean 72 (69-75) µmol/L). ICU mortality was 8.5%.

Table 6.1 – Demographic, Admission, and Illness severity Data

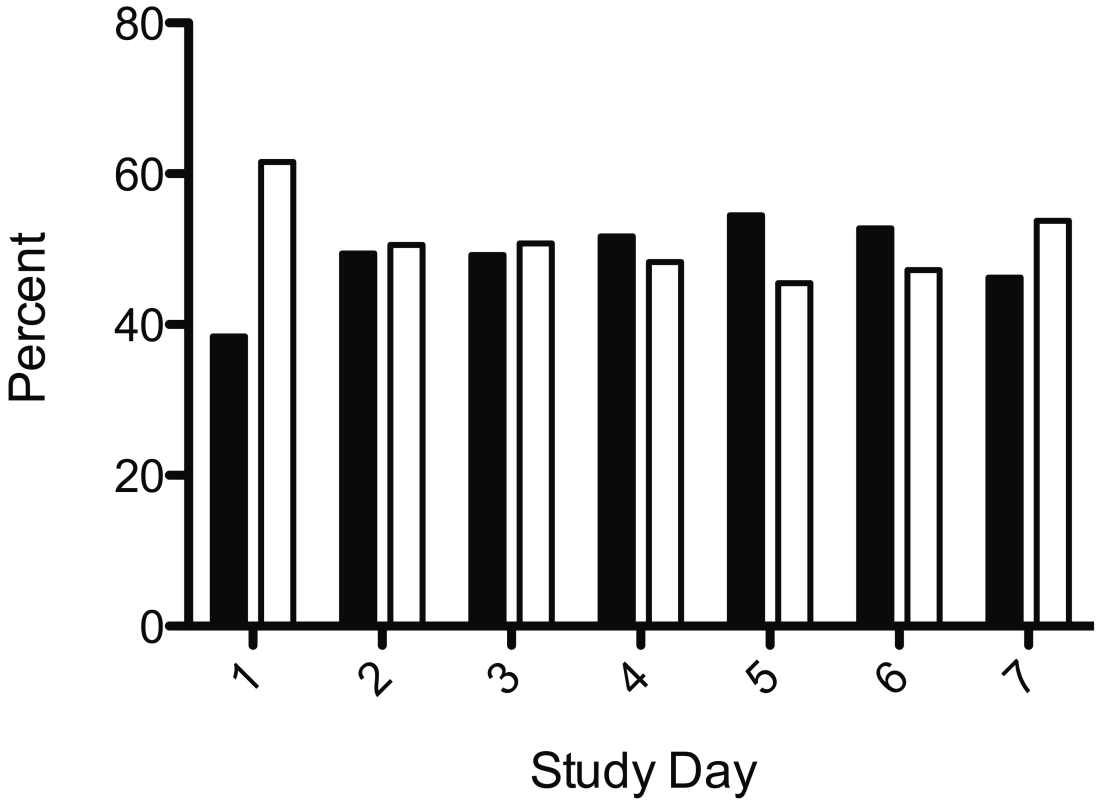
Variable	
Age, years, mean (95% CI)	54.4 (52.5-56.4)
Gender, male, n (%)	178 (63.3)
Weight, kg, mean (95% CI)	72.4 (70.1-74.6)
Height, m, mean (95% CI)	1.66 (1.65-1.68)
BMI, kg/m^2, mean (95% CI)	26.0 (25.3-26.6)
BSA, m^2, mean (95% CI)	1.80 (1.77-1.83)
APACHE II score, mean (95% CI)	16.0 (15.2-16.7)
Modified SOFA score (max), median [IQR]	3 [2-6]
Mechanical ventilation (at any point), n (%)	206 (73.8)
Vasopressor / inotropes (at any point), n (%)	111 (39.5)
Participating site, n (%) - Australia - Singapore - Hong Kong - Portugal	 116 (41.3) 81 (28.8) 59 (21.0) 25 (8.9)
Admission category, n (%) - Elective - Emergency - Surgical emergency - Trauma	 26 (9.3) 93 (33.1) 126 (44.8) 36 (12.8)
ICU Day of enrolment, median [IQR]	1 [1-2]
Plasma CR concentration (Day 1), µmol/L, mean (95% CI)	72 (69-75)
CR excretion rate, mg/kg/day, (Day 1), mean (95% CI)	19.2 (17.8-20.5)
CL_{CR}, $ml/min/1.73m^2$ (Day 1), mean (95% CI)	108 (102-115)
ICU length of stay, days, median [IQR]	4 [2-10]
ICU Mortality, n (%)	24 (8.5)

APACHE – acute physiology and chronic health evaluation, BMI – body mass index, BSA – body surface area, CL_{CR} – creatinine clearance, CI – confidence interval, CR – creatinine, ICU – intensive care unit, IQR – interquartile range, SOFA – sequential organ failure assessment

6.4.2 Prevalence of ARC

Overall, 65.1% (n=183) of the cohort manifested ARC on at-least one occasion during the first seven study days. On study day 1, ARC was evident in 108 patients (prevalence = 38.4%), with the majority of new cases occurring on study day 2 (n=41), and day 3 (n=13). The number of evaluable patients fell to 231 on study day 2, with the prevalence of ARC increasing to 49.4% (n=114). Of the fifty patients not completing a second CL_{CR}, 64% (n=32) did not manifest ARC. Figure 6.1 demonstrates the prevalence of ARC, as a fraction of the patients remaining in the study, through to day 7. From day 2, the prevalence of ARC remained relatively constant (~50%) with the highest prevalence (54.5%, n=67) recorded on study day 5. 43.4% of patients remaining in the ICU, who did not manifest ARC on day 1, went on to do so at least once in the subsequent six days. 34.9% of patients never displayed ARC on any CL_{CR} measure in the first seven days. Of those patients manifesting ARC, the majority (74%) did so on ≥ 50% of their CL_{CR} measures.

Figure 6.1 Daily Prevalence of ARC to Study Day 7



ARC =	108	114	87	74	67	56	43
n =	281	231	177	143	123	106	93

Caption: Percentage of patients with ARC (solid bars), compared to no ARC (open bars), on each study day. The total number (n) of patients remaining in the study, and those manifesting ARC are provided

6.4.3 Characteristics of patients displaying ARC

Comparison of admission, demographic, and illness severity data between groups (ARC vs no ARC) are presented in Table 6.2. Differences in physiological and treatment variables on study days 1, 4, and 7 are provided in Appendix A (Supplemental Digital Content). Patients manifesting ARC (at any point in the first seven study days) tended to be younger, male, multitrauma victims, receiving mechanical ventilation. On study day 1, the absence of ARC was associated with higher modified SOFA scores (P=0.007), the application of vasopressor or inotropic support (P=0.015), and a lower 24-hr urine output (P=0.004). Frusemide use was more common in those not manifesting ARC. Differences in the minimum mean arterial pressure (study day 1), and body temperatures (study day 4) were also observed, although these deviations are unlikely to be clinically meaningful. No difference was observed in the provision of enteral nutrition between groups. Significantly lower plasma CR concentrations (P<0.01), and high CR excretion rates (P<0.001) were consistently noted in those manifesting ARC (Appendix A, Supplemental Digital Content).

Table 6.2 Demographic, Therapeutic, and Illness severity Data in Those With and Without ARC at Any Time During the First Seven Study Days

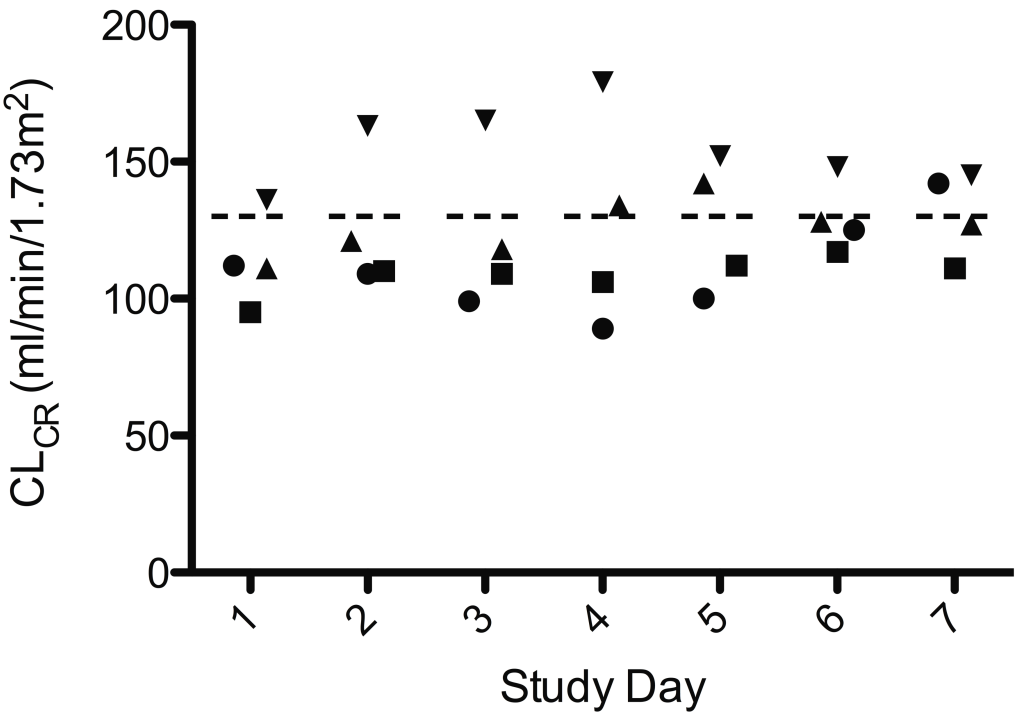
Variable	ARC (n=183)	No ARC (n=98)	*P*-value
Age, years, mean (95% CI)	49.1 (46.8-51.4)	64.4 (61.6-67.2)	<0.001
Gender, Male, n (%)	124 (67.8)	54 (55.1)	0.036
Weight, kg, mean (95% CI)	73.3 (70.6-76.0)	70.6 (66.6-74.7)	0.266
Height, m, mean (95% CI)	1.67 (1.66-1.69)	1.65 (1.63-1.67)	0.077
BMI, kg/m^2, mean (95% CI)	26.0 (25.3-26.8)	25.8 (24.5-27.1)	0.750
BSA, m^2, mean (95% CI)	1.82 (1.78-1.85)	1.77 (1.72-1.81)	0.106
APACHE II, mean (95% CI)	15.7 (14.7-16.6)	16.6 (15.3-17.8)	0.265
Modified SOFA score (max), median [IQR]	3 [2-6]	3 [2-6]	0.711
Mechanical ventilation (at any point), n (%)	150 (82.4)	56 (57.7)	<0.001
Vasopressor / inotropes (at any point), n (%)	76 (41.5)	35 (35.7)	0.342
Norepinephrine (at any point), n (%)	66 (36.1)	30 (30.6)	0.358
Dopamine (at any point), n (%)	14 (7.7)	5 (5.1)	0.417
Admission category, n (%)			
- Elective	13 (7.1)	13 (13.3)	0.089
- Emergency	54 (29.5)	39 (39.8)	0.081
- Surgical Emergency	86 (47.0)	40 (40.8)	0.321
- Trauma	30 (16.4)	6 (6.1)	0.014
ICU length of stay, days, median [IQR]	5 [3-11]	3 [2-6]	<0.001
ICU mortality, n (%)	14 (7.7)	10 (10.2)	0.465

APACHE – acute physiology and chronic health evaluation, ARC – augmented renal clearance, BMI – body mass index, BSA – body surface area, CI – confidence interval, ICU – intensive care unit, IQR – interquartile range, SOFA – sequential organ failure assessment

6.4.4 Natural history of ARC & Comparison between admission types

Figure 6.2 displays mean CL_{CR} as a function of admission type to study day 7. In the overall cohort, a significant rise is noted on study day 2 (Day 2 - 121 (113-129), Day 1 - 108 (102-115) ml/min/1.73m^2, *P*=0.001). Significant differences in demographics, anthropometric measures, illness severity, and interventions exist between diagnostic groups (Table 6.3). In addition, CL_{CR} varies both between, and within the groups. Of note, CL_{CR} on study day 2 rises significantly in trauma (*P*=0.013) and surgical emergency admissions (*P*=0.015), although no significant difference was identified in elective cases (*P*=0.916) or emergency admissions (*P*=0.121). Sustained increases in CL_{CR} appear to occur in trauma victims and surgical emergency admissions primarily (Figure 6.2).

Figure 6.2 Daily CL_{CR} Measures by Admission Type to Study Day 7



Elective	26	15	11	8	6	5	5
Emergency	93	77	58	47	41	38	33
Surgical Emergency	126	110	84	67	59	46	42
Trauma	36	29	24	21	17	17	13

Caption: Mean CL_{CR} in elective (●), emergency (■), surgical emergency (▲), and trauma (▼) patients to study day 7. The dashed line represents the cut-off for ARC (130ml/min/1.73m^2). The number of patients of each admission type remaining in the study per day is provided.

Table 6.3 Comparison of Demographics, Anthropometric Measures, Illness severity, and Interventions Between Admission Types

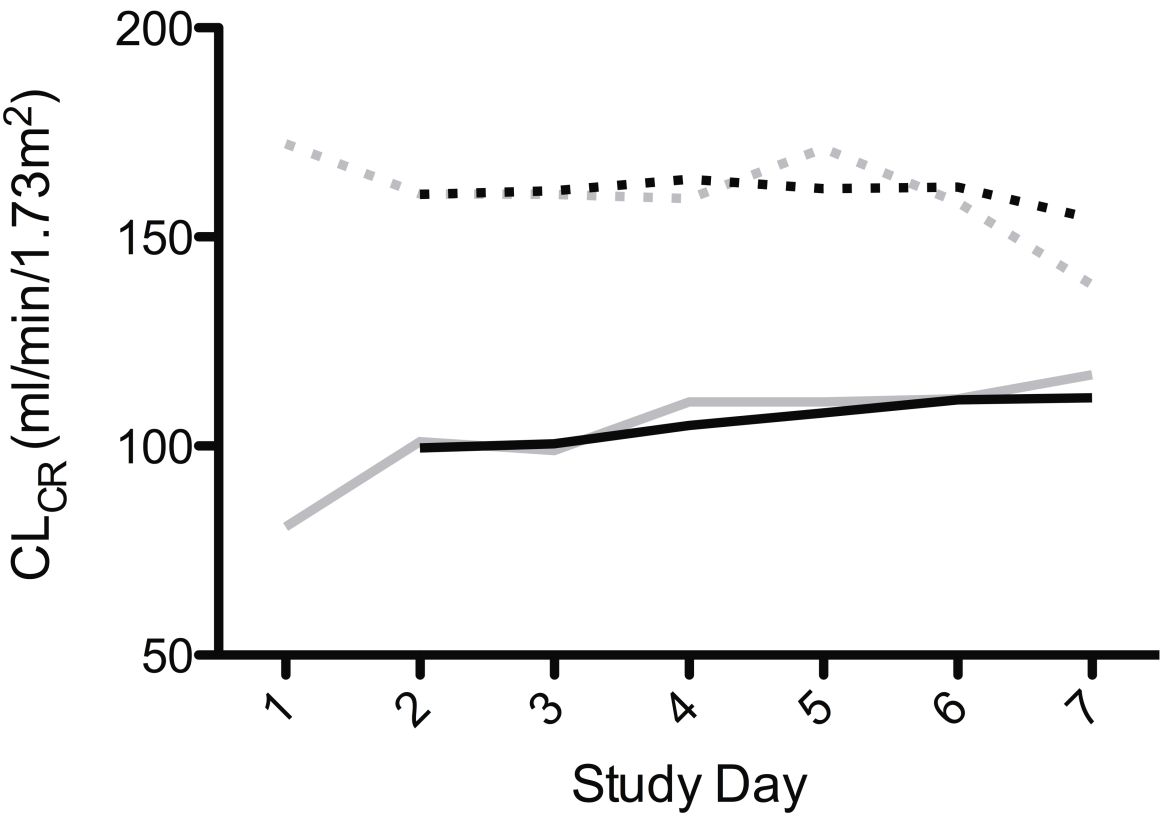
Variable	Elective	Emergency	Surgical Emergency	Trauma	*P*-value
Age, years, mean (95% CI)	58.5 (53.8-63.3)	56.3 (53.0-59.6)	56.2 (53.4-59.0)	40.7 (34.5-46.9)	<0.001
Gender, Male, n (%)	15 (57.7)	50 (53.8)	79 (62.7)	34 (94.4)	<0.001
Weight, kg, mean (95% CI)	73.7 (68.3-79.1)	72.7 (67.8-77.6)	69.8 (67.2-72.4)	79.5 (72.7-86.2)	0.059
Height, m, mean (95% CI)	1.68 (1.64-1.72)	1.65 (1.63-1.67)	1.66 (1.64-1.67)	1.72 (1.69-1.75)	0.001
BMI, kg/m^2, mean (95% CI)	26.1 (24.4-27.8)	26.5 (25.0-28.0)	25.3 (24.5-26.1)	26.8 (24.7-28.9)	0.344
BSA, m^2, mean (95% CI)	1.83 (1.76-1.90)	1.78 (1.73-1.84)	1.77 (1.73-1.81)	1.92 (1.84-1.99)	0.008
APACHE II, mean (95% CI)	13.4 (11.4-15.4)	17.0 (15.6-18.4)	16.3 (15.2-17.4)	14.2 (12.2-16.1)	0.017
Modified SOFA score (max), median [IQR]	3 [1.5-5.5]	4 [2-6]	3 [2-5]	4 [3-6]	0.014
Vasopressor / inotrope (at any point), n (%)	7 (26.9)	46 (49.5)	45 (35.7)	13 (36.1)	0.089
Mechanical ventilation (at any point), n (%)	7 (26.9)	72 (78.3)	99 (78.6)	28 (80.0)	<0.001
ICU length of stay, days, median [IQR]	3.5 [2-4.5]	4 [3-12]	5 [2-9]	4.5 [2-11.5]	0.239

APACHE – acute physiology and chronic health evaluation, BMI – body mass index, BSA – body surface area, CI – confidence interval, CL_{CR} – creatinine clearance, IQR – interquartile range, SOFA – sequential organ failure assessment

Variations in CL_{CR} as a function of ARC status on study day 1, are presented in Figure 6.3. Significant differences exist between groups on each study day, although greater within group variability is noted in those without ARC initially. Specifically, a significant increase in CL_{CR} is noted on study day 2 in those not previously manifesting ARC (P<0.001), which is not the case in those with documented augmented CL already. However, the presence of ARC initially is associated with a sustained elevation of CL_{CR}, over the first seven study days (Figure 6.3).

A mixed-effects model was generated to account for variable ICU LOS. Modelling occurred from study day 2, in order to mitigate the influence of factors outside ICU. Significant covariates included; hospital location, age, ARC status on day 1, daily modified SOFA scores, and frusemide administration. Vasopressor use was not included given the strong correlation with modified SOFA scores, while gender, mechanical ventilation, 24-hr fluid balance and admission type were not predictive of daily CL_{CR}. As illustrated (Figure 6.3), ARC status on stay day 1 significantly predicts CL_{CR} from day 2 to day 7, with values being markedly lower in those without ARC initially (P=0.019). Changes in modified daily SOFA scores are only significant in those without ARC, whereby increasing scores promote lower CL_{CR} values (P<0.001). Age was highly significant, with patients' ≥ 65 years having log CR_{CL} values on average 0.46 units lower than those < 40 years (P<0.001). Hospital location was included as an adjusting variable in order to account for differences in case-mix. Of note, frusemide administration was associated with lower CL_{CR} values (P<0.001).

Figure 6.3 Mixed Effects Model Comparing Those With and Without ARC on Study Day 1



Caption: Mean CL_{CR} (grey lines), and results from the model (black lines). The solid lines represent those without ARC on study day 1, and the dotted lines, those with ARC on study day 1.

6.5 Discussion

This paper reports the findings of a multicentre observational study examining the frequency of ARC in critically ill patients with normal plasma renal indices on admission. Major observations include a high prevalence overall, with ~65% of patients manifesting ARC on at least one occasion in the first seven study days. ARC on day 1 is also strongly associated with higher clearances over the subsequent six days, a finding that is not simply related to ongoing fluid loading. Although plasma CR concentrations were consistently lower in those manifesting ARC, the sustained elevation in CL_{CR} and CR excretion rates, and the lack of any significant difference in 24-hour fluid balance, strongly supports this assertion.

These data suggest that a significant proportion of patients will manifest sustained augmented renal solute elimination over the first week in ICU, a consideration not immediately obvious to the clinician or prescriber. Importantly, ARC will significantly impact drug PK for a variety of renally eliminated pharmaceuticals (such as low molecular weight heparins, aminoglycosides, glycopeptides, and beta-lactams (198)), leading to sub-therapeutic concentrations and potentially adverse clinical outcomes (104, 168, 204).

Brown et al. reported similar data in their work examining CR, osmolar, and free water CL in fifty critically ill post-operative patients (84). In those patients admitted to the surgical ICU with trauma, CL_{CR} values were elevated on day 1 (mean 140ml/min/1.73m^2), peaked on day 4 (mean 190ml/min/1.73m^2), and returned to initial levels by day 7. A strong inverse relationship was also demonstrated between age and CL_{CR}, as measured on the second post-operative day (84). Similar observations have been reported in more contemporary research (59, 88, 92, 215), while the present study confirms these findings in a larger, multicentre dataset.

The mechanisms driving such variation in renal function in the critically ill remain poorly understood. Increased major organ blood flow has been demonstrated in large animal models of gram-negative sepsis (63), similar to changes observed in human pregnancy (65), which may promote enhanced renal solute elimination. Recent clinical investigation however has demonstrated at best, only a weak correlation between pulse contour derived CI and CL_{CR} in critical illness (215). Of note, the high prevalence of ARC in this patient group suggests this might represent the 'expected' response to systemic inflammation, as

an indicator of accessible physiological reserve. Whether the absence of ARC can be used as a useful diagnostic or prognostic indicator represents an important area for future clinical investigation.

The true biological influence of trauma and surgery in the pathogenesis of ARC remains uncertain, given the confounding influence of age (217). Specifically, age was identified as the most significant covariate in predicting the development of ARC in mixed-effects modeling, suggesting that the high prevalence in trauma, may simply be a reflection of the underlying demographic. As illustrated, the trauma sub-group was almost exclusively young men, with greater body size, who were frequently ventilated. As such, systemic inflammation coupled with a greater physiological reserve may account for the higher clearances observed, rather than any unique mechanism. While an increase in glomerular filtration in response to protein loading may also be implicated (73, 205), no difference in the provision of enteral nutrition was noted between patients with and without ARC.

Of note is the significant increase in CL_{CR} between day 1 and 2, which appears to drive some of the with-in subject variability, particularly in those not manifesting ARC initially. Interpreting this finding is complex, given the number of patients not completing a second CL_{CR}, and the potential impact of pre-ICU care. Relatively poor renal function despite normal plasma CR concentrations on admission to the ICU has been previously reported (39), and may suggest the presence of 'occult' AKI, in parallel with a greater disease burden. This is reflected in the higher modified SOFA scores, greater vasopressor requirements, and lower urine outputs in patients without ARC on day 1. In those remaining in the study, renal function appears to improve, possibly associated with ICU intervention, or disease evolution.

Identifying a specific pattern of intra-patient variation, particularly in relation to ICU intervention, remains complex. Vasopressor administration increases RBF and glomerular filtration in large animal models (218), although the relationship in critical illness is much more dynamic. The inverse association between vasopressor administration and CL_{CR} on day 1 illustrates this. Of interest, the majority of participants received norepinephrine, such that exploring the influence of differing vasoactive agents is limited in the current dataset. The true clinical significance of mechanical ventilation is also uncertain, and likely reflects the ubiquitous nature of this intervention and longer LOS in ARC patients. The association between frusemide administration and lower CL_{CR} is also unclear; although this may

represent clinician directed diuretic therapy in the context of worsening azotaemia, or overly aggressive attempts at fluid diuresis.

6.6 Limitations

In order to maximize data efficiency, a mixed effects model was generated to infer results, despite participants contributing an unequal number of CL_{CR} measures. This represents a well-recognized statistical technique uniquely suited to dealing with missing information, and strengthens the overall study findings. Four separate institutions contributed data, significantly improving the generalizability and external validity of our findings. We recognize however that the prevalence of ARC will vary significantly with case-mix, and in this manner, assessment of CL_{CR} in individual institutions is highly recommended.

8-hour collections were employed as the primary outcome measure, as prior research has suggested this time-period provides the best balance between feasibility and accuracy (45). In addition, the observed CR excretion rates are within the range reported for the general populous (219). We acknowledge that CL_{CR} is not a 'gold standard' measure of glomerular filtration (such as inulin CL), although tubular CR secretion is unlikely to confound the results at higher filtration rates (213). Of note, we have not collected data on patient ethnicity, which represents an unexplored variable in this analysis.

The prevalence of ARC reported is consistent with recent data (104), although the exclusion of patients unlikely to remain in the ICU for > 24hrs, and those with established or evolving AKI, has resulted in a select study population. This is reflected in the moderate overall APACHE II score and ICU mortality, although the majority of patients were mechanically ventilated, and ~40% received vasopressor or inotrope therapy. As such, although the prevalence of ARC may be lower in the wider ICU population, this analysis provides a unique longitudinal view of CL_{CR} in a significant fraction of critically ill patients. We do not report on specific PK end-points, therapeutic outcomes, or antibiotic resistance patterns, as such data were beyond the aims of this study. In addition, while ARC was associated with a longer ICU LOS, it should be recognized that this study was not designed to assess any specific clinical outcomes.

6.7 Conclusions

The findings from this prospective, multicentre, observational study suggest a substantial group of patients that will manifest significantly elevated renal solute elimination over the first seven days in ICU, not overtly obvious to the clinician. In addition, the observation of relatively low CL_{CR} in some patients reinforces the concept that an assessment of 'renal function', as opposed to simply identifying 'kidney injury', is necessary. Recognition of patients at risk of ARC allows the targeted use of CL_{CR} measurement (not routine in most units), to monitor changes in renal function. Future studies should focus on expanding current knowledge regarding the implications for accurate dosing of renally eliminated pharmaceuticals in patients with ARC. In addition, given the high prevalence of ARC in this study (65.1%), further investigation to assess the potential impact on individual clinical outcomes is warranted.

Chapter 7

A Comparison of CKD-EPI Estimated Glomerular Filtration Rate and Measured CL_{CR} in Recently Admitted Critically Ill Patients with Normal Plasma Creatinine Concentrations

7.1 Chapter Overview

This chapter explores the utility of mathematical estimates of glomerular filtration to accurately reflect measured CL_{CR} in recently admitted critically ill patients with normal plasma CR concentrations. Bias and precision are determined in the context of previously discussed ARC thresholds.

Text, figures, and tables from the published manuscript (as outlined in Chapter 1) are reproduced here. The layout has been adjusted to fit the overall style of the thesis. The references are found alongside those for the other chapters, at the conclusion of the main body.

7.2 Background

Accurate assessment of renal function is a priority in the management of critically ill patients. Clinicians regularly utilize such information to help guide drug dosing, optimize fluid, acid–base, and electrolyte management, tailor nutritional requirements, and assess the need for RRT. Rising plasma CR concentrations often trigger clinical interventions, including dose reduction of renally eliminated agents. In contrast, plasma CR concentrations within the reported reference range appear to be less useful. Normal values in the critically ill have been associated with both augmented CL_{CR} (215), and occult AKI (39).

Driven primarily by a desire to more effectively monitor and screen for CKD, formulae using simple demographic variables have been developed to estimate the glomerular filtration rate (eGFR). The most commonly applied include the MDRD (41), and newer CKD-EPI (42) equations. Their application is based principally on large cohort studies that effectively stratify patients in terms of long-term clinical risk (220, 221). This has led to recommendations for widespread laboratory reporting of eGFR (222, 223).

While these initiatives represent key developments in improving the quality of care for patients with CKD, some clinicians have expressed concern about the ubiquitous application of eGFR, particularly in dose modification (224). Use of formulae to help guide drug dosing represents an attractive approach, although an ability to trigger both dose reduction and escalation is required. Currently there is a paucity of data examining whether eGFR could be used in place of conventional measures for such a purpose, particularly in the critical care environment. The aim of this study was therefore to compare CKD-EPI eGFR with measured urinary CL_{CR}, in a cohort of recently admitted critically ill patients with normal plasma CR concentrations.

7.3 Methods

7.3.1 Setting

This study was performed in a tertiary level, university affiliated, metropolitan ICU, over a two-month period. Enrolment utilized convenience sampling. Ethical approval was obtained from the institutional Human Research Ethics Committee (HREC/09/QRBW/192), with written informed consent obtained from either the patient or their nominated substitute decision-maker.

7.3.2 Study population

Study participants had to have an anticipated ICU LOS > 24 hours, a plasma CR concentration < 121 µmol/L, and no history of prior RRT or CKD. Patients were excluded if: a) either invasive haemodynamic monitoring or an IDC were not employed as part of standard management; b) they were < 18 years of age; c) they were pregnant; d) rhabomyolysis was clinically suspected or the admission plasma creatinine kinase was > 5000 IU/L; or e) they were in the 'risk' category or greater for AKI, as defined by the RIFLE criteria (216). Patients undergoing an operative procedure within 24 hours prior to admission were classified as 'surgical'. Planned post-operative admissions were considered 'elective'.

7.3.3 Interventions

Demographic and illness severity characteristics, including; age, gender, anthropometric measures, diagnosis, and APACHE II scores were recorded on admission. Modified (excluding the neurological component) SOFA scores, ventilation parameters, 24-hour

fluid balance, vasopressor administration, and diuretic use, were recorded prospectively at the time of CL_{CR} assessment. ICU and hospital LOS, and ICU mortality were determined for all patients. Data capture occurred within 48 hours of admission to the ICU, as determined by staff availability and admission time.

An 8-hour measured CL_{CR} was obtained using the following method. Urine was collected via the IDC between midnight and 0800 hrs, following which urinary volume and CR concentration were determined by laboratory analysis. Concurrent plasma CR concentrations were obtained at a point mid-way through the urinary collection, following which CL_{CR} was calculated using the formula listed below. CR measurement in plasma and urine utilised automated analysers employing a modified Jaffe (alkaline picrate) technique, representing an isotope dilution mass spectrometry (IDMS) traceable assay.

As per convention, CL_{CR} values were normalised to a BSA of 1.73 m^2. The abbreviated 175 MDRD (175 eGFR), CKD-EPI (CKD-EPI eGFR), and CG CL_{CR} equations were used to calculate estimates for comparison, as outlined below. ARC was defined as a measured 8-hr $CL_{CR} \geq 130$ ml/min/1.73 m^2, given the association with sub-therapeutic drug concentrations, when using standard doses of renally eliminated antibiotics (199, 225).

7.3.4 List of Equations Employed

$BSA = 0.007184 \times (Ht)^{0.725} \times (Wt)^{0.425}$

$CL_{CR} = (U_{CR} \times U_{Vol}/P_{CR} \times 480) \times 1.73/BSA$

CG CL_{CR} = [(140 – age) × Wt × (1.23 if male, 1.04 if female)]/P_{CR} × 1.73/BSA

175 eGFR = $175 \times (P_{CR} \times 0.0113)^{-1.154} \times age^{-0.203}$ (× 0.742 if female)

CKD-EPI eGFR

Females, $P_{CR} \leq 62 = 144 \times (P_{CR} \times 0.0113/0.7)^{-0.329} \times 0.993^{age}$

Females, $P_{CR} > 62 = 144 \times (P_{CR} \times 0.0113/0.7)^{-1.209} \times 0.993^{age}$

Males, $P_{CR} \leq 80 = 141 \times (P_{CR} \times 0.0113/0.9)^{-0.411} \times 0.993^{age}$

Males, $P_{CR} > 80 = 141 \times (P_{CR} \times 0.0113/0.9)^{-1.209} \times 0.993^{age}$

Where CL_{CR} = 8-hr Creatinine Clearance (ml/min/1.73 m^2), U_{CR} = Urinary Creatinine Concentration (µmol/L), U_{Vol} = Urinary volume (ml), P_{CR} = Plasma Creatinine Concentration (µmol/L), BSA = Body Surface Area (m^2), Ht = Height (cm), Wt = Weight (kg), CG CL_{CR} = Cockcroft-Gault Creatinine Clearance (ml/min/1.73 m^2), 175 eGFR = Abbreviated Modification of Diet in Renal Disease 175 formula (ml/min/1.73 m^2), and CKD-

EPI eGFR = Chronic Kidney Disease Epidemiology Collaboration Equation (ml/min/1.73 m^2), age (in years).

7.3.5 Statistical analysis

Continuous data are presented as the mean (SD) or median [IQR] depending on adherence to a normal distribution. Normality was assessed by visual inspection, and a one-sample Kolmogorov-Smirnov test. Categorical data are presented as counts (%). Correlations were assessed using a Pearson correlation coefficient (r). Precision and bias were examined using a Bland-Altman plot, with the bias representing the mean difference between each variable, and precision being one SD from the mean. Comparison of continuous data utilized a paired Students *T*-test. A two-sided *P*-value < 0.05 was considered as statistical significance, and all analyses were performed using SPSS version 21 (IBM Corporation, Armonk, New York) and PRISM version 5 (GraphPad Software Inc, La Jolla, California).

7.4 Results

One hundred and ten patients (n = 110) were included in the study, with all participants completing an 8-hr CL_{CR}. Demographic, admission, illness severity and outcome data are presented in Table 7.1. As illustrated, approximately two-thirds of the cohort was male, the patients were relatively young (50.9 (16.9) years), greater than 50% received invasive mechanical ventilation, and about one-third required vasopressor support. Less than 15% were elective cases, with the majority manifesting systemic inflammation, with or without undergoing prior surgery. As per protocol, plasma CR concentrations were within the normal reference range (68.5 (21.8) µmol/L), and did not change significantly in the following 24 hrs (*P* = 0.157), where data were available. The mean 8-hr CL_{CR} was 125 (45.1) ml/min/1.73 m^2, 48.2% (n = 53) manifested ARC, and 10 (9.1%) had a CL_{CR} < 60 ml/min/1.73 m^2.

Table 7.1 Demographic, Illness severity and Treatment Data

Variable	N = 110
Age, years, mean (SD)	50.9 (16.9)
Gender, male/female, n (%)	70 (63.6)/40 (36.4)
Height, m, mean (SD)	1.71 (0.09)
Weight, kg, mean (SD)	80.9 (22.4)
Body surface area, m^2, mean (SD)	1.92 (0.24)
APACHE II, mean (SD)	16.1 (6.20)
Modified SOFA, median [IQR]	3 [2-5]
Admission type, n (%)	
- Elective	15 (13.6)
- Emergency	33 (30.0)
- Surgical Emergency	37 (33.6)
- Trauma	25 (22.7)
Mechanical ventilation, n (%) (n = 108)	63 (57.3)
Intravenous Contrast administration, n (%) (n = 109)	30 (27.3)
Frusemide administration, n (%)	13 (11.8)
Mannitol administration, n (%)	4 (3.6)
Vasopressors, n (%)	33 (30.0)
Systemic Inflammatory Response Syndrome, n (%)	95 (86.4)
Plasma CR concentration, µmol/L, mean (SD)	68.5 (21.8)
Plasma CR concentration + 24 hrs, µmol/L, mean (SD) (n = 80)	63.0 (19.6)
ICU length of stay, days, median [IQR]	4 [2-10]
ICU mortality, n (%)	11 (10)

APACHE-Acute physiology and chronic health evaluation, ICU-Intensive care unit, SOFA-sequential organ failure assessment.

A comparison of measured 8-hr CL_{CR} and 175 eGFR, CG CL_{CR}, and CKD-EPI eGFR in all patients, and each diagnostic category separately, are presented in Table 7.2. Scatter graphs using all data points are provided in Figure 7.1. Equivalent Bland-Altman plots are presented in Figure 7.2. Across all groups, the observed bias is greatest with the CKD-EPI equation. A significant proportional error is also apparent, with higher average values significantly correlated with a larger positive bias (Figure 2C, r = 0.705, $P < 0.001$). This was not evident with either the 175 eGFR (r = 0.102, $P = 0.289$), or CG CL_{CR} (r = 0.103, $P = 0.285$) formulae.

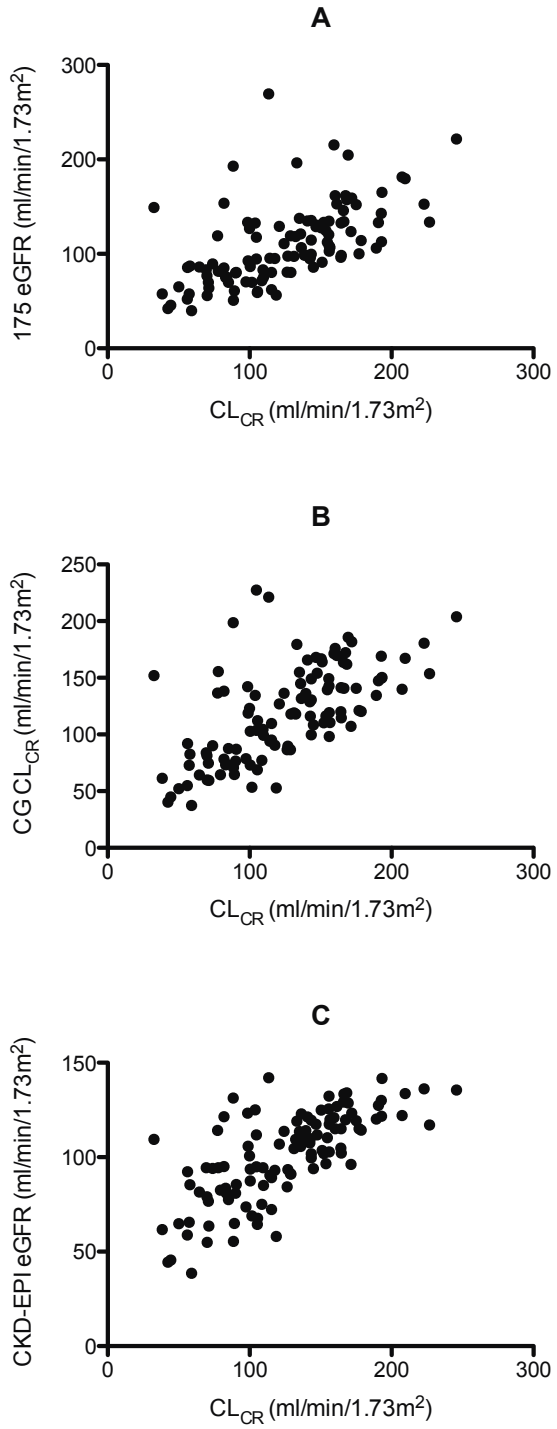
Table 7.2 Comparison, Correlation, Bias and Precision Between Measured 8-hr CL_{CR} and Mathematical Estimates in All Patients, and Each Diagnostic Sub-group

	Mean (SD)	r (*P*-value)	Bias +/− precision
All Patients (n = 110)			
CL_{CR}, ml/min/1.73 m^2	125 (45.1)		
175 eGFR, ml/min/1.73 m^2	110 (41.6)*	0.600 (<0.001)	15.6 +/− 38.9
CG CL_{CR}, ml/min/1.73 m^2	119 (41.7)	0.638 (<0.001)	6.23 +/− 37.1
CKD-EPI eGFR, ml/min/1.73 m^2	101 (23.7)*	0.720 (<0.001)	24.4 +/− 32.5
Elective Admissions (n = 15)			
CL_{CR}, ml/min/1.73 m^2	118 (27.2)		
175 eGFR, ml/min/1.73 m^2	115 (51.2)	0.325 (0.237)	2.77 +/− 49.5
CG CL_{CR}, ml/min/1.73 m^2	119 (44.1)	0.531 (0.042)	−1.04 +/− 37.5
CKD-EPI eGFR, ml/min/1.73 m^2	101 (20.0)**	0.488 (0.065)	17.2 +/− 24.7
Emergency Admission (n = 33)			
CL_{CR}, ml/min/1.73 m^2	113 (50.0)		
175 eGFR, ml/min/1.73 m^2	114 (47.9)	0.624 (<0.001)	−0.77 +/− 42.5
CG CL_{CR}, ml/min/1.73 m^2	123 (49.1)	0.599 (<0.001)	−10.4 +/− 44.3
CKD-EPI eGFR, ml/min/1.73 m^2	99 (27.6)**	0.692 (<0.001)	13.8 +/− 36.8
Surgical Emergency Admission (n = 37)			
CL_{CR}, ml/min/1.73 m^2	125 (46.4)		
175 eGFR, ml/min/1.73 m^2	101 (37.2)*	0.741 (<0.001)	23.7 +/− 31.3
CG CL_{CR}, ml/min/1.73 m^2	108 (37.5)**	0.753 (<0.001)	16.4 +/− 30.6
CKD-EPI eGFR, ml/min/1.73 m^2	95 (23.7)*	0.779 (<0.001)	29.5 +/− 31.6
Trauma Admission (n = 25)			
CL_{CR}, ml/min/1.73 m^2	146 (39.5)		
175 eGFR, ml/min/1.73 m^2	114 (32.0)*	0.745 (<0.001)	32.7 +/− 26.5
CG CL_{CR}, ml/min/1.73 m^2	129 (33.8)**	0.757 (<0.001)	17.4 +/− 26.1
CKD-EPI eGFR, ml/min/1.73 m^2	111 (17.4)*	0.772 (<0.001)	35.2 +/− 28.4

* $P < 0.001$, when compared to CL_{CR} ** $P < 0.05$, when compared to CL_{CR}.

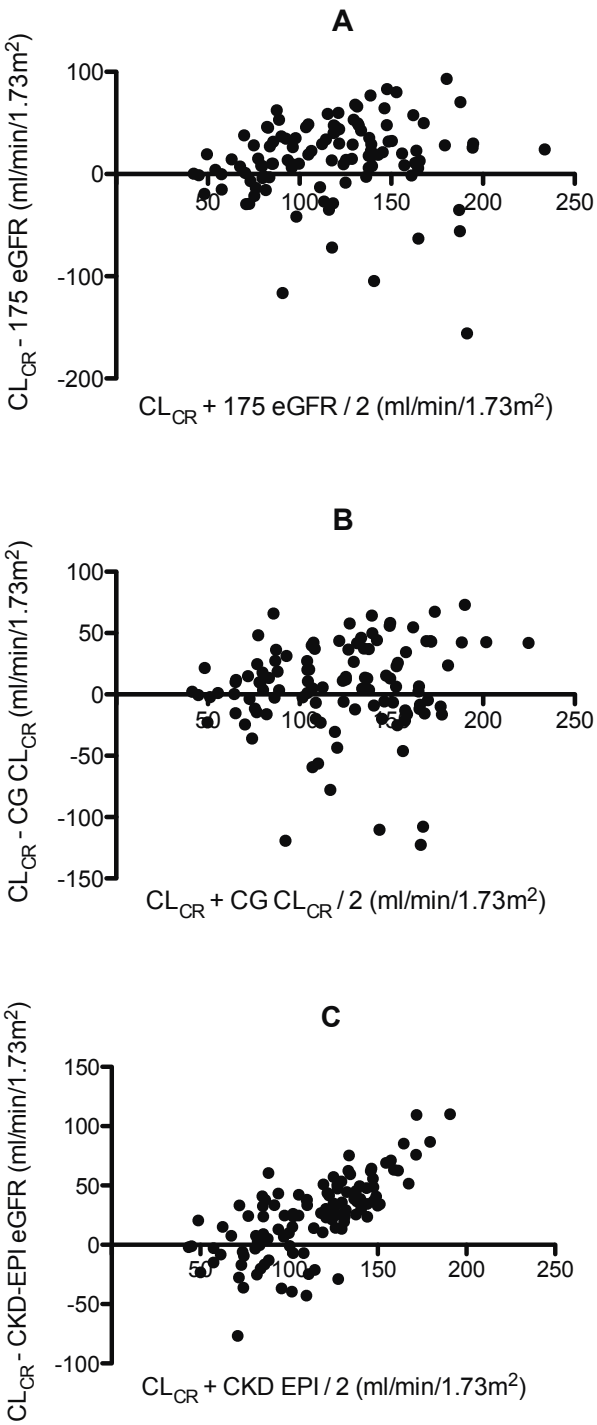
CL_{CR} = 8-hr Creatinine Clearance, CG CL_{CR} = Cockcroft-Gault Creatinine Clearance, 175 eGFR = Abbreviated Modification of Diet in Renal Disease 175 formula, CKD-EPI eGFR = Chronic Kidney Disease Epidemiology Collaboration Equation, r = Pearson correlation coefficient.

Figure 7.1 Scatter Graphs of CL_{CR} Versus Mathematical Estimates in All Patients



Caption: CL_{CR} on the x-axis compared with 175 eGFR (panel **A**), CG CL_{CR} (panel **B**), and CKD-EPI eGFR (panel **C**), on the y-axis. CL_{CR} = 8-hr Creatinine Clearance, 175 eGFR = Abbreviated Modification of Diet in Renal Disease 175 formula, CG CL_{CR} = Cockcroft-Gault Creatinine Clearance, CKD-EPI eGFR = Chronic Kidney Disease Epidemiology Collaboration Equation

Figure 7.2 Bland-Altman Plots of CL_{CR} Versus Mathematical Estimates in All Patients



Caption: Comparison of the difference between CL_{CR} and 175 eGFR (panel **A**), CG CL_{CR} (panel **B**), and CKD-EPI eGFR (panel **C**) on the y-axis, versus the average value obtained on the x-axis. CL_{CR} = 8-hr Creatinine Clearance, 175 eGFR = Abbreviated Modification of Diet in Renal Disease 175 formula, CG CL_{CR} = Cockcroft-Gault Creatinine Clearance, CKD-EPI eGFR = Chronic Kidney Disease Epidemiology Collaboration Equation.

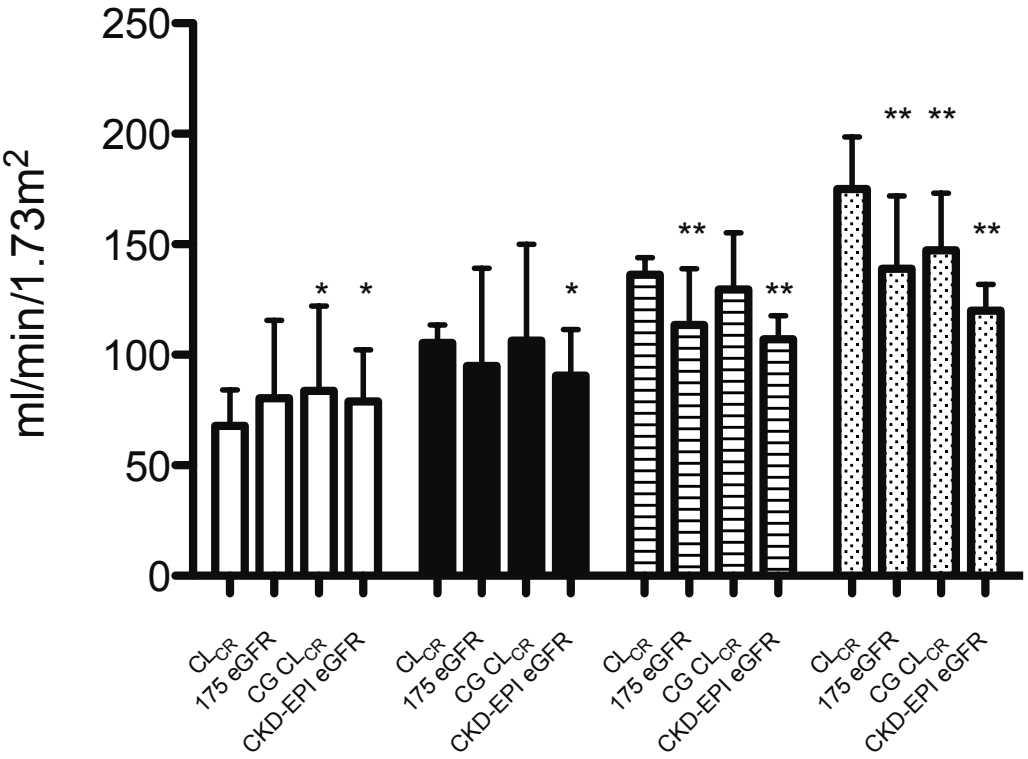
8-hr CL_{CR} values were used to categorize patients into four groups; < 90, 90–119, 120–149, and ≥ 150 ml/min/1.73 m^2. Comparisons with each mathematical estimate are presented in Table 7.3 and Figure 7.3. As illustrated, CKD-EPI eGFR was generally higher than CL_{CR} in the lower range (< 90 ml/min/1.73 m^2), although the opposite was observed at higher values. Correlation was generally poor in each group (Table 7.3). In those patients with a calculated CKD-EPI eGFR between 60–119 ml/min/1.73 m^2 (n = 77), 8-hr CL_{CR} values were significantly higher (118 (38.3) vs 96 (16.6) ml/min/1.73 m^2, $P < 0.001$), 41.6% (n = 32) displayed ARC, and 7.8% (n = 6) had a CL_{CR} < 60 ml/min/1.73 m^2.

Table 7.3 Correlation, Bias and Precision Across Different Ranges of CL_{CR}

	r (*P*-value)	Bias +/− precision (ml/min/1.73 m^2)
CL_{CR} < 90 ml/min/1.73 m^2 (n = 28)		
175 eGFR	0.223 (0.253)	−12.6 +/− 35.2
CG CL_{CR}	0.278 (0.152)	−15.9 +/− 37.2
CKD-EPI eGFR	0.351 (0.067)	−11.1 +/− 23.2
CL_{CR} 90–119 ml/min/1.73 m^2 (n = 23)		
175 eGFR	0.065 (0.767)	10.5 +/− 44.4
CG CL_{CR}	0.066 (0.763)	−0.93 +/− 43.9
CKD-EPI eGFR	−0.067 (0.760)	14.8 +/− 22.8
CL_{CR} 120–149 ml/min/1.73 m^2 (n = 23)		
175 eGFR	0.047 (0.832)	22.7 +/− 26.1
CG CL_{CR}	0.369 (0.083)	6.62 +/− 23.9
CKD-EPI eGFR	0.347 (0.104)	29.2 +/− 10.8
CL_{CR} ≥ 150 ml/min/1.73 m^2 (n = 36)		
175 eGFR	0.427 (0.009)	36.1 +/− 31.3
CG CL_{CR}	0.399 (0.016)	27.8 +/− 27.2
CKD-EPI eGFR	0.460 (0.005)	55.0 +/− 20.9

CL_{CR} = 8-hr Creatinine Clearance, CG CL_{CR} = Cockcroft-Gault Creatinine Clearance, 175 eGFR = Abbreviated Modification of Diet in Renal Disease 175 formula, CKD-EPI eGFR = Chronic Kidney Disease Epidemiology Collaboration Equation, r = Pearson correlation coefficient.

Figure 7.3 Comparison of CL_{CR} with Mathematical Estimates Over Different Ranges



Caption: CL_{CR} compared with 175 eGFR, CG CL_{CR}, and CKD-EPI eGFR over different ranges. CL_{CR} < 90 (open), 90–119 (solid), 120–149 (lines), and ≥ 150 (dots) ml/min/1.73 m^2. * $P < 0.05$, ** $P < 0.001$. CL_{CR} = 8-hr Creatinine Clearance, 175 eGFR = Abbreviated Modification of Diet in Renal Disease 175 formula, CG CL_{CR} = Cockcroft-Gault Creatinine Clearance, CKD-EPI eGFR = Chronic Kidney Disease Epidemiology Collaboration Equation.

7.5 Discussion

To our knowledge, this is the first report of CKD-EPI eGFR performance in a cohort of Australian patients recently admitted to the ICU. These data demonstrate significant disparity between CKD-EPI eGFR and measured CL_{CR} in patients with normal plasma CR concentrations. Despite an overall reasonable correlation, bias and precision were unacceptable across a range of values. This highlights that clinicians must carefully consider which estimate of renal function they use in clinical decision-making, as these may be very dissimilar. A modest fraction of study participants displayed CL_{CR} measures significantly higher than might be expected, a finding that requires further evaluation.

Albeit the CKD-EPI equation is relatively new in Australian practice, ours is not the only study to explore the use of eGFR formulae in the critically ill. Martin and colleagues examined the utility of MDRD eGFR and CG CL_{CR} in comparison to 8-hr CL_{CR} in a cohort of mainly traumatised patients (46). CL_{CR} measures were markedly elevated, with significant bias reported with both equations. In ~350 recently admitted patients, Herrera-Gutierrez et al. demonstrated significant bias when comparing CG CL_{CR} to measured values (43). This was particularly evident in patients with elevated CL_{CR} (≥ 100 ml/min/1.73 m^2), where CG estimates were markedly lower. Other studies in surgical intensive care (45), and burns injury (44), have reported similar observations.

Hoste and colleagues examined the relationship between 1-hr CL_{CR}, CG CL_{CR}, and MDRD eGFR in twenty-eight adult patients recently admitted to the ICU (39). Here, 25% had a 1-hr CL_{CR} < 60 ml/min/1.73 m^2, despite a normal plasma CR concentration. Even with a lower range of CL_{CR} measures, neither equation was considered specific enough for clinical use (39). In our study, fewer patients manifest this level of renal impairment (n = 10, 9.1%), limiting any definitive conclusions. However, these patients often (n = 6, 60%) had a normal or near-normal calculated CKD-EPI eGFR (60–119 ml/min/1.73 m^2).

Baptista and colleagues were the first to explore the role of eGFR in the setting of ARC, comparing CG CL_{CR} and MDRD eGFR with measured CL_{CR} in eighty-six critically ill patients (200). Calculated values were significantly less than measured CL_{CR}, with considerable bias and imprecision. In a retrospective analysis of 390 patients with ARC admitted to a single centre, Grootaert and colleagues similarly reported poor agreement between CG CL_{CR}, MDRD eGFR and 24-hr measured CL_{CR} (226).

Confounding these analyses however, is often the lack of an exogenous marker of GFR. Despite this, markedly elevated renal drug elimination has been noted in many sub-groups of critically ill patients (71), in parallel with higher CL_{CR} (61). Furthermore, recent research suggests elevated CL_{CR} measures (> 130 ml/min/1.73 m^2) are associated with sub-therapeutic drug concentrations (199, 225) and worse clinical outcomes (104), in critically ill patients receiving antimicrobial therapy. While the implications of this phenomenon require substantial validation, the observation that ~40% of patients with a normal or near-normal CKD-EPI eGFR (60–119 ml/min/1.73 m^2) actually manifest ARC, suggests such thresholds are not simply transferrable to different estimates of renal function.

This realization is consistent with these formulae being developed outside of an ICU environment; generating results that fail to consider the unique characteristics of critical illness (18, 214). Of note, bias appeared to be greatest in emergent surgical and trauma admissions (Table 7.2), sub-groups where ARC has been previously well documented (84, 88). Recent data from Shimamoto et al. suggests systemic inflammation is a key factor, with increasing SIRS criteria associated with elevated renal vancomycin CL (74). This has important ramifications for clinical practice, where use of variable estimates of renal function may result in disparate conclusions (12, 227), potentially leading to inadequate drug dosing (228).

We wish to acknowledge the following limitations. This paper reports the findings from a single-centre only, and therefore may not be representative of case-mix at other institutions. Despite this, the majority of study participants manifested SIRS; over half received invasive mechanical ventilation; and 30% required vasoactive support. Illness severity scores were moderate, and consistent with tertiary level ICU practice. Our inclusion criteria were designed to select a cohort of patients with normal plasma CR concentrations, as assessing renal function in the context of drug dosing remains challenging in this group. In addition, the CKD-EPI equation is reported to have improved accuracy compared to older eGFR estimates (229), particularly in patients with normal or near-normal renal function (230).

We have employed 8-hr urinary collections, as recommended by prior research (45). This method is not a gold standard measure of GFR, such that tubular CR secretion, and errors in measurement may have confounded our results. Without employing an exogenous

filtration maker (such as inulin), it is impossible to determine which estimate is closer to the 'true' filtration rate. As such, use of endogenous CL_{CR} may have resulted in systematically higher values. Despite this, CL_{CR} remains a common modifier of drug dosing in clinical practice, with recent data suggesting important PK (199, 225), and clinical (104) implications. Unfortunately no readily accessible, pragmatic, error free measure of GFR is currently available. This analysis principally serves to remind the clinician of the inherent discrepancy between estimates of GFR in the ICU.

7.6 Conclusion

In conclusion, this study has examined CKD-EPI eGFR in comparison to 8-hr measured CL_{CR} in a cohort of recently admitted critically ill patients with normal plasma CR concentrations. Our results suggest poor agreement between these techniques in this population. Whether this represents a true limitation of CKD-EPI eGFR, or an intuitive discrepancy based on the problems with endogenous CL_{CR}, remains uncertain. Notwithstanding this, until additional data are available on the utility of CKD-EPI eGFR for drug dose adjustment, particularly in identifying ARC, we would recommend clinicians consider using CL_{CR} for this purpose.

PART THREE - DISCUSSION

Chapter 8

Discussion, Key Findings, and Future Directions

8.1 Discussion

The critical care environment is often defined by logistic, administrative, and human resources factors. In this respect, 'critical illness' is a highly non-specific term, reflecting a diverse range of patients, and pathophysiology. Interventions are generally applied to this group in an unmalleable fashion, such that individual patient characteristics are less emphasised in therapeutic guidelines (3). A relevant example is blood pressure management in septic shock, where pre-existing physiology or comorbidity is infrequently considered. Even more pertinent is drug administration, where dose adjustment is only practiced in the setting of drug eliminating organ dysfunction, or with an easily 'titrate-able' end-point. Outside of these scenarios, a 'one dose fits all' approach is generally applied.

This represents a logistically attractive solution, such that protocols and procedures can be developed to support clinical practice, particularly 'out-of-hours'. However, this ignores the clinical heterogeneity confounding critical care practice, such that patients vary significantly in terms of their presenting illness, associated interventions, and organ function. Systemic inflammation, endothelial dysfunction, haemodynamic instability, intravenous fluid loading, use of vasoactive medications, and organ dysfunction, will greatly impact the clinical course for many patients. Importantly these factors will distort the PK profile of many pharmaceuticals used in this setting. Consequently doses determined from non-critically ill cohorts are unlikely to reliably reproduce the same drug exposure, potentially resulting in inferior clinical outcomes.

This scenario has perhaps no greater implications than for antibacterial application in the critically ill. This class of pharmaceuticals are prescribed ubiquitously in the ICU, often in the setting of diagnostic uncertainty, and without any immediate clinical feedback to guide dosing. Failure to provide timely and effective chemotherapy has also been strongly associated with inferior clinical outcomes (4-7), highlighting the clinical imperative to optimise drug exposure. For beta-lactams, this involves maintaining drug concentrations above the MIC of the likely pathogen for sufficient periods of the dosing interval (168). In the critically ill, this remains a challenging task, primarily related to the complex interaction

between patient physiology, drug PK, and microbial susceptibility. This triad of 'man, molecule and microbe' means that a single 'standard' dose is unlikely to be sufficient for many patients, such that clinicians must individualise drug prescription much more frequently.

This thesis has primarily focused on alterations in renal physiology, thought to underpin some of the variability in beta-lactam PK observed in the critically ill. These data highlight a number of important findings. Many of the patients included in these studies did manifest CL_{CR} measures significantly higher than has been reported in the general population (19), reinforcing that ARC is more than simply an academic construct. Specifically, in the multicentre dataset ~65% manifest at least one episode of ARC in the first seven study days, indicating that clinicians are likely to encounter this phenomenon on a regular basis. In addition, the presence of ARC on day one was an important predictor of elevated CL_{CR} over the remaining week (231), implying that an early assessment of renal function is warranted when antibacterial dosing is being considered.

The association between elevated CL_{CR} and low beta-lactam trough concentrations, as demonstrated in the analysis of our TDM data, underlines the PK-PD implications of these findings. Sub-therapeutic concentrations (C_{min} < MIC) were identified in ~40% of study participants, while CL_{CR} was a significant predictor of insufficient levels in multivariate modelling. While this finding is somewhat expected, given the established renal route of elimination for these agents, the identification of a useful CL_{CR} threshold will allow for further research in this area. In addition, although beta-lactam TDM is the gold standard in dose adjustment, this service is infrequently available in clinical practice. As such CL_{CR} measures are likely to be much more readily available, acting as a trigger for dose escalation or alternative methods of administration where appropriate.

Our study findings have also further identified which patients are at greatest risk of ARC. The significance of age as a defining factor is a constant finding. Younger patients, often admitted post major trauma, appear to constitute a major at-risk group. While chronological decline in renal function is well described, ARC appears to be more than simply a reflection of 'young kidneys'. Rather it is driven by the interplay between physiological reserve (which is greatest in younger patients without major comorbidity), and systemic inflammation. The lack of associated organ dysfunction (as manifest by lower SOFA scores), indicates ARC is unlikely to be encountered with greater illness

severity. While the development of AKI has clear prognostic implications in the ICU, it remains to be determined whether the absence of ARC (as the expected renal response) has any additional implications.

While it was hypothesised that cardiovascular alterations would drive ARC in many patients, this remains largely an assertion. No correlation was identified between CI and CL_{CR} in our trauma population. This is likely a consequence of the narrow range of cardiac indices and generally higher CL_{CR} measures observed in this group. In septic patients, a moderate correlation was demonstrated, a reflection of the greater heterogeneity associated with this syndrome. In ROC analysis, CI was less discriminating than the combination of age, trauma status, and SOFA score, reinforcing that intrinsic changes in kidney function (with inflammation) may have a greater role in ARC. In this context, CI and CL_{CR} may rise in parallel, a reflection of organ reserve, although increased major organ blood flow may not be sole driver of increased clearances. The 'ARC Risk Score' developed from this analysis also provides a useful tool to guide current prescription and future research, although validation in a much larger cohort is required.

The clinical imperative to consider renal function, as opposed to identifying kidney injury has also been highlighted by this research. In this respect, plasma CR concentrations alone were not representative of renal function in many study participants, providing little useful data when adjusting drug doses. Mathematical estimates of renal function, based primarily on these values have become commonplace in hospital practice. However there application to critical care practice, particularly drug dose modification, has been questioned (224), in that these estimates should not only trigger dose reduction, but also escalation. Our analyses support these concerns, demonstrating that these equations have poor utility in identifying ARC, with significant bias and imprecision compared to CL_{CR} measures. This is primarily a reflection of these formulae being developed from cohorts of non-critically ill patients, where significant acute systemic inflammation is likely to be absent.

8.2 Limitations

These data suffer from certain limitations that must be considered in the interpretation and application of this thesis. The use of CL_{CR} as the primary method of measuring renal function does not represent a gold-standard assessment of GFR. Creatinine undergoes

both filtration and tubular secretion, such that CL_{CR} may systematically over-estimate the patients true GFR. While this represents a source of significant bias in patients with declining renal function, the implications at higher filtration rates are less certain (232). In addition, serial measurements are reported to be accurate in following changes in GFR over time (213). The application of this measure is based on the following considerations; a) exogenous markers of GFR are infrequently available in clinical practice, such that extrapolation to daily dosing decisions is limited; b) CL_{CR} represents a more useful measure of renal function than plasma CR concentrations alone; c) a wealth of PK data has identified CL_{CR} as a key covariate in predicting antibacterial renal drug elimination; and d) CL_{CR} is a widely available, repeatable, and inexpensive intervention that can be applied on a global scale. In addition, although quantifying the true GFR would be ideal, the validity of any absolute figure is perhaps less important, than identifying patients likely to manifest sub-therapeutic drug exposure with standard dosing. As such, elevated CL_{CR} can be used as a marker of likely augmented beta-lactam drug clearance, prompting the institution of TDM, or empirically higher doses, where the agent has a favourable therapeutic index.

Some of these data are drawn from selected cohorts of critically ill patients, such that application to the wider ICU population remains uncertain. In particular, the analysis of beta-lactam TDM trough concentrations in comparison to 8-hr measured CL_{CR} (199), may suffer from selection bias, due to the enrolment of patients likely to manifest distorted PK. Although this may have influenced the prevalence of sub-therapeutic concentrations (C_{min} < MIC), the robust association with elevated CL_{CR} remains a highly applicable finding. The use of EUCAST breakpoints (where no causative organism was identified) to inform the adequacy of drug exposure could have also introduced additional bias. Importantly, our data are consistent with large international point prevalence studies, where approximately 30% of infected critically ill patients are culture negative (233). Use of these breakpoints allows consideration of a ‘worst case scenario’, although in some patients this degree of drug exposure may not be clinically necessary. This represents a valid concern, but as such susceptibility data are infrequently available at the time of commencing antibacterial therapy, these analyses remain highly informative. As such, until further information is available to tailor ongoing therapy, the clinician should aim to ‘cover’ all potential causative organisms. Equally the impact of sub-optimal drug exposures on resistance patterns remains uncertain, further reinforcing the need to employ robust initial dosing strategies.

The descriptive analyses presented in this thesis have focused on identifying patients at-risk of ARC. Measured CL_{CR} has been used as a surrogate of beta-lactam renal clearance, given prior data reinforcing its' utility in this context (see Chapters 2 and 3). However, it must be reinforced that alterations in beta-lactam renal elimination are only a single component in this complex clinical interaction. Anthropometric irregularities (e.g. morbid obesity), changes in protein binding, altered volume of distribution, and use of extracorporeal modalities will also significantly impact antibacterial PK. As such, this research has focused on the impact of augmented renal function, although this must be considered in the context of any additional factors that will influence drug exposure. Recent data from the Defining Antibiotic Levels in Intensive (DALI) care unit patients study (169) demonstrated that treatment failure was three times more likely when $fT_{\geq MIC}$ was < 50%. However, the required drug levels for therapeutic success are unlikely to be constant across all patient groups, or even potentially within the same patient over time. Indeed, in cases where the patient is receiving prophylaxis against infection, or a less virulent organism has been identified, more modest degrees of drug exposure may only be necessary. Although this is a crucial area for additional research, data from this thesis suggests that ARC will none the less have important implications.

The clinical ramifications of this phenomenon are also currently limited. Although there is an increasing literature base examining this area of critical care practice, a robust link between ARC, sub-therapeutic beta-lactam exposure, and inferior clinical outcomes remains to be established. This thesis highlights that ARC is likely to occur in younger patients, with lower illness severity scores, such that any effect on mortality is likely to be very small, and difficult to detect. Indeed, ICU mortality in those patients displaying ARC on at least one occasion in the multicentre study was 7.7%, compared to 10.2% in those that never manifest ARC (231). This implies that a significantly larger sample would be required to achieve a statistically robust result. More appropriate end-points could include treatment failure, microbiological resistance patterns, ICU and hospital LOS, in addition to health economic outcomes. Of note, the observation that ARC may be associated with a survival advantage represents an intriguing area for ongoing study. In particular, elevated CL_{CR} may in fact represent a maker of adequate physiological reserve, whereby the host is able to generate supra-normal organ function in the setting of systemic infection. As such, the absence of infection related organ dysfunction might have equally important prognostic implications, although temporal associations with antibiotic drug exposure require significant additional research.

8.3 Key Findings

Summary findings from this research are listed below:

- ARC is associated with low beta-lactam trough concentrations in critically ill patients receiving standard doses
- Younger age and admission post-trauma are important risk factors
- ARC is associated with less severe organ dysfunction
- CL_{CR} is moderately correlated with CI in critically ill septic patients
- ARC is prevalent in recently admitted patients with normal plasma CR concentrations
- ARC on day one is highly predictive of elevated CL_{CR} over the first week in ICU
- There is poor agreement between measured CL_{CR} and mathematical estimates in critically ill patients with normal plasma CR concentrations
- ARC has important ramifications for beta-lactam dosing, that require further study

8.4 Future Directions

The clinical and dosing implications of these findings require additional investigation. Specifically, prospective clinical studies examining the impact of varying dosing strategies (such as extended or continuous infusion) in the setting of ARC are needed. These should be powered to identify significant differences in both PK-PD and clinical endpoints. The combination of ARC and borderline bacterial susceptibility represents a key area for future research, as it is this sub-group where treatment failure is of greater concern. Importantly the ICU represents common area for intermediate pathogens.

Wider dissemination of these data is also required. The idea of a ‘one dose fits all’ approach to beta-lactam antibacterial application in the ICU is fundamentally flawed. Prescribers must be encouraged to consider their dosing decisions in the context of the likely pathogens, but also the patients underlying physiology. Individualising or tailoring drug prescription represents a key goal in translating this research to the bedside. For drug developers and pharmaceutical companies, greater emphasis must be placed on considering these issues prior to large-scale clinical investigation of new or emerging agents. This will ensure that poor efficacy is not simply a reflection of inadequate dosing, such that these agents can enter wider clinical practice successfully.

Finally the implications of ARC on microbiological resistance patterns deserve attention. This represents a global problem in both developed and developing nations. Responsible, directed, and adequate antibacterial dosing represents a key strategy in ensuring therapeutic longevity for many agents. This must be considered a priority in clinical practice and critical research programmes. How ARC is implicated in this process represents an important area for future study.

References

1. Finfer S, Bellomo R, Lipman J, et al. Adult-population incidence of severe sepsis in Australian and New Zealand intensive care units. Intensive Care Med 2004;30(4):589-596.
2. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008;36(1):296-327.
3. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med 2013;39(2):165-228.
4. Ibrahim EH, Sherman G, Ward S, et al. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest 2000;118(1):146-155.
5. Kollef MH, Sherman G, Ward S, et al. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest 1999;115(2):462-474.
6. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006;34(6):1589-1596.
7. MacArthur RD, Miller M, Albertson T, et al. Adequacy of early empiric antibiotic treatment and survival in severe sepsis: experience from the MONARCS trial. Clin Infect Dis 2004;38(2):284-288.
8. Paterson DL, Lipman J. Returning to the pre-antibiotic era in the critically ill: the XDR problem. Crit Care Med 2007;35(7):1789-1791.
9. Udy AA, Roberts JA, Lipman J. Clinical implications of antibiotic pharmacokinetic principles in the critically ill. Intensive Care Med 2013;39(12):2070-2082.
10. Roberts JA, Lipman J. Antibacterial dosing in intensive care: pharmacokinetics, degree of disease and pharmacodynamics of sepsis. Clin Pharmacokinet 2006;45(8):755-773.
11. Lipman J, Udy AA, Roberts JA. Do we understand the impact of altered physiology, consequent interventions and resultant clinical scenarios in the intensive care unit? The antibiotic story. Anaesth Intensive Care 2011;39(6):999-1000.
12. Udy A, Roberts JA, Boots RJ, et al. You only find what you look for: the importance of high creatinine clearance in the critically ill. Anaesth Intensive Care 2009;37(1):11-13.

13. Kohl BA, Deutschman CS. The inflammatory response to surgery and trauma. Curr Opin Crit Care 2006;12(4):325-332.
14. Nuytinck HK, Offermans XJ, Kubat K, et al. Whole-body inflammation in trauma patients. An autopsy study. Arch Surg 1988;123(12):1519-1524.
15. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992;101(6):1644-1655.
16. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med 2003;29(4):530-538.
17. Bagshaw SM, Uchino S, Bellomo R, et al. Septic acute kidney injury in critically ill patients: clinical characteristics and outcomes. Clin J Am Soc Nephrol 2007;2(3):431-439.
18. Udy AA, Putt MT, Shanmugathasan S, et al. Augmented renal clearance in the Intensive Care Unit: an illustrative case series. Int J Antimicrob Agents 2010;35(6):606-608.
19. Stevens LA, Coresh J, Greene T, et al. Assessing kidney function--measured and estimated glomerular filtration rate. N Engl J Med 2006;354(23):2473-2483.
20. Gross AS, McLachlan AJ, Minns I, et al. Simultaneous administration of a cocktail of markers to measure renal drug elimination pathways: absence of a pharmacokinetic interaction between fluconazole and sinistrin, p-aminohippuric acid and pindolol. Br J Clin Pharmacol 2001;51(6):547-555.
21. Tett S, Moore S, Ray J. Pharmacokinetics and bioavailability of fluconazole in two groups of males with human immunodeficiency virus (HIV) infection compared with those in a group of males without HIV infection. Antimicrob Agents Chemother 1995;39(8):1835-1841.
22. Tett SE, Kirkpatrick CM, Gross AS, et al. Principles and clinical application of assessing alterations in renal elimination pathways. Clin Pharmacokinet 2003;42(14):1193-1211.
23. Angus BJ, Smith MD, Suputtamongkol Y, et al. Pharmacokinetic-pharmacodynamic evaluation of ceftazidime continuous infusion vs intermittent bolus injection in septicaemic melioidosis. Br J Clin Pharmacol 2000;50(2):184-191.
24. Barbot A, Venisse N, Rayeh F, et al. Pharmacokinetics and pharmacodynamics of sequential intravenous and subcutaneous teicoplanin in critically ill patients without vasopressors. Intensive Care Med 2003;29(9):1528-1534.

25. Burkhardt O, Kumar V, Katterwe D, et al. Ertapenem in critically ill patients with early-onset ventilator-associated pneumonia: pharmacokinetics with special consideration of free-drug concentration. J Antimicrob Chemother 2007;59(2):277-284.
26. Conil JM, Georges B, Mimoz O, et al. Influence of renal function on trough serum concentrations of piperacillin in intensive care unit patients. Intensive Care Med 2006;32(12):2063-2066.
27. del Mar Fernandez de Gatta Garcia M, Revilla N, Calvo MV, et al. Pharmacokinetic/pharmacodynamic analysis of vancomycin in ICU patients. Intensive Care Med 2007;33(2):279-285.
28. Ikawa K, Morikawa N, Ikeda K, et al. Pharmacokinetic-pharmacodynamic target attainment analysis of biapenem in adult patients: a dosing strategy. Chemotherapy 2008;54(5):386-394.
29. Ikawa K, Morikawa N, Uehara S, et al. Pharmacokinetic-pharmacodynamic target attainment analysis of doripenem in infected patients. Int J Antimicrob Agents 2009;33(3):276-279.
30. Li C, Kuti JL, Nightingale CH, et al. Population pharmacokinetics and pharmacodynamics of piperacillin/tazobactam in patients with complicated intra-abdominal infection. J Antimicrob Chemother 2005;56(2):388-395.
31. Lipman J, Wallis SC, Rickard C. Low plasma cefepime levels in critically ill septic patients: pharmacokinetic modeling indicates improved troughs with revised dosing. Antimicrob Agents Chemother 1999;43(10):2559-2561.
32. Lipman J, Wallis SC, Rickard CM, et al. Low cefpirome levels during twice daily dosing in critically ill septic patients: pharmacokinetic modelling calls for more frequent dosing. Intensive Care Med 2001;27(2):363-370.
33. Young RJ, Lipman J, Gin T, et al. Intermittent bolus dosing of ceftazidime in critically ill patients. J Antimicrob Chemother 1997;40(2):269-273.
34. Llopis-Salvia P, Jimenez-Torres NV. Population pharmacokinetic parameters of vancomycin in critically ill patients. J Clin Pharm Ther 2006;31(5):447-454.
35. Dailly E, Le Floch R, Deslandes G, et al. Influence of glomerular filtration rate on the clearance of vancomycin administered by continuous infusion in burn patients. Int J Antimicrob Agents 2008;31(6):537-539.
36. Pea F, Furlanut M, Negri C, et al. Prospectively validated dosing nomograms for maximizing the pharmacodynamics of vancomycin administered by continuous infusion in critically ill patients. Antimicrob Agents Chemother 2009;53(5):1863-1867.

37. Lortholary O, Tod M, Rizzo N, et al. Population pharmacokinetic study of teicoplanin in severely neutropenic patients. Antimicrob Agents Chemother 1996;40(5):1242-1247.
38. Pea F, Brollo L, Viale P, et al. Teicoplanin therapeutic drug monitoring in critically ill patients: a retrospective study emphasizing the importance of a loading dose. J Antimicrob Chemother 2003;51(4):971-975.
39. Hoste EA, Damen J, Vanholder RC, et al. Assessment of renal function in recently admitted critically ill patients with normal serum creatinine. Nephrol Dial Transplant 2005;20(4):747-753.
40. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.
41. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130(6):461-470.
42. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150(9):604-612.
43. Herrera-Gutierrez ME, Seller-Perez G, Banderas-Bravo E, et al. Replacement of 24-h creatinine clearance by 2-h creatinine clearance in intensive care unit patients: a single-center study. Intensive Care Med 2007;33(11):1900-1906.
44. Conil JM, Georges B, Fourcade O, et al. Assessment of renal function in clinical practice at the bedside of burn patients. Br J Clin Pharmacol 2007;63(5):583-594.
45. Cherry RA, Eachempati SR, Hydo L, et al. Accuracy of short-duration creatinine clearance determinations in predicting 24-hour creatinine clearance in critically ill and injured patients. J Trauma 2002;53(2):267-271.
46. Martin JH, Fay MF, Udy A, et al. Pitfalls of using estimations of glomerular filtration rate in an intensive care population. Intern Med J 2011;41(7):537-543.
47. Poggio ED, Nef PC, Wang X, et al. Performance of the Cockcroft-Gault and modification of diet in renal disease equations in estimating GFR in ill hospitalized patients. Am J Kidney Dis 2005;46(2):242-252.
48. Snider RD, Kruse JA, Bander JJ, et al. Accuracy of estimated creatinine clearance in obese patients with stable renal function in the intensive care unit. Pharmacotherapy 1995;15(6):747-753.
49. Lin J, Knight EL, Hogan ML, et al. A comparison of prediction equations for estimating glomerular filtration rate in adults without kidney disease. J Am Soc Nephrol 2003;14(10):2573-2580.

50. Poggio ED, Wang X, Greene T, et al. Performance of the modification of diet in renal disease and Cockcroft-Gault equations in the estimation of GFR in health and in chronic kidney disease. J Am Soc Nephrol 2005;16(2):459-466.
51. Rule AD, Larson TS, Bergstralh EJ, et al. Using serum creatinine to estimate glomerular filtration rate: accuracy in good health and in chronic kidney disease. Ann Intern Med 2004;141(12):929-937.
52. Jelliffe R. Estimation of creatinine clearance in patients with unstable renal function, without a urine specimen. Am J Nephrol 2002;22(4):320-324.
53. Jones CA, McQuillan GM, Kusek JW, et al. Serum creatinine levels in the US population: third National Health and Nutrition Examination Survey. Am J Kidney Dis 1998;32(6):992-999.
54. Pickering JW, Frampton CM, Walker RJ, et al. Four hour creatinine clearance is better than plasma creatinine for monitoring renal function in critically ill patients. Crit Care 2012;16(3):R107.
55. Pong S, Seto W, Abdolell M, et al. 12-hour versus 24-hour creatinine clearance in critically ill pediatric patients. Pediatr Res 2005;58(1):83-88.
56. Sladen RN, Endo E, Harrison T. Two-hour versus 22-hour creatinine clearance in critically ill patients. Anesthesiology 1987;67(6):1013-1016.
57. Wells M, Lipman J. Measurements of glomerular filtration in the intensive care unit are only a rough guide to renal function. S Afr J Surg 1997;35(1):20-23.
58. Wells M, Lipman J. Pitfalls in the prediction of renal function in the intensive care unit. A review. S Afr J Surg 1997;35(1):16-19.
59. Fuster-Lluch O, Geronimo-Pardo M, Peyro-Garcia R, et al. Glomerular hyperfiltration and albuminuria in critically ill patients. Anaesth Intensive Care 2008;36(5):674-680.
60. Kees MG, Hilpert JW, Gnewuch C, et al. Clearance of vancomycin during continuous infusion in Intensive Care Unit patients: correlation with measured and estimated creatinine clearance and serum cystatin C. Int J Antimicrob Agents 2010;36(6):545-548.
61. Lipman J, Wallis SC, Boots RJ. Cefepime versus cefpirome: the importance of creatinine clearance. Anesth Analg 2003;97(4):1149-1154.
62. Parrillo JE, Parker MM, Natanson C, et al. Septic shock in humans. Advances in the understanding of pathogenesis, cardiovascular dysfunction, and therapy. Ann Intern Med 1990;113(3):227-242.

63. Di Giantomasso D, May CN, Bellomo R. Vital organ blood flow during hyperdynamic sepsis. Chest 2003;124(3):1053-1059.
64. Mabie WC, DiSessa TG, Crocker LG, et al. A longitudinal study of cardiac output in normal human pregnancy. Am J Obstet Gynecol 1994;170(3):849-856.
65. Dunlop W. Serial changes in renal haemodynamics during normal human pregnancy. Br J Obstet Gynaecol 1981;88(1):1-9.
66. Anderson GD. Pregnancy-induced changes in pharmacokinetics: a mechanistic-based approach. Clin Pharmacokinet 2005;44(10):989-1008.
67. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345(19):1368-1377.
68. Wan L, Bellomo R, May CN. The effects of normal and hypertonic saline on regional blood flow and oxygen delivery. Anesth Analg 2007;105(1):141-147.
69. Di Giantomasso D, May CN, Bellomo R. Norepinephrine and vital organ blood flow during experimental hyperdynamic sepsis. Intensive Care Med 2003;29(10):1774-1781.
70. Di Giantomasso D, Morimatsu H, Bellomo R, et al. Effect of low-dose vasopressin infusion on vital organ blood flow in the conscious normal and septic sheep. Anaesth Intensive Care 2006;34(4):427-433.
71. Udy AA, Roberts JA, Boots RJ, et al. Augmented renal clearance: implications for antibacterial dosing in the critically ill. Clin Pharmacokinet 2010;49(1):1-16.
72. Castellino P, Giordano C, Perna A, et al. Effects of plasma amino acid and hormone levels on renal hemodynamics in humans. Am J Physiol 1988;255(3 Pt 2):F444-449.
73. Thomas DM, Coles GA, Williams JD. What does the renal reserve mean? Kidney Int 1994;45(2):411-416.
74. Shimamoto Y, Fukuda T, Tanaka K, et al. Systemic inflammatory response syndrome criteria and vancomycin dose requirement in patients with sepsis. Intensive Care Med 2013;39(7):1247-1252.
75. Noel G, Strauss R, Shah A, et al. Poster K-486. Ceftobiprole versus Ceftazidime combined with Linezolid for Treatment of Patients with Nosocomial Pneumonia. In: ICAAC/IDSA; 2008.
76. Gomez CM, Cordingly JJ, Palazzo MG. Altered pharmacokinetics of ceftazidime in critically ill patients. Antimicrob Agents Chemother 1999;43(7):1798-1802.
77. Roberts JA, Roberts MS, Robertson TA, et al. Piperacillin penetration into tissue of critically ill patients with sepsis--bolus versus continuous administration? Crit Care Med 2009;37(3):926-933.

78. Boselli E, Breilh D, Saux MC, et al. Pharmacokinetics and lung concentrations of ertapenem in patients with ventilator-associated pneumonia. Intensive Care Med 2006;32(12):2059-2062.
79. Pea F, Porreca L, Baraldo M, et al. High vancomycin dosage regimens required by intensive care unit patients cotreated with drugs to improve haemodynamics following cardiac surgical procedures. J Antimicrob Chemother 2000;45(3):329-335.
80. Conil JM, Georges B, de Lussy A, et al. Ciprofloxacin use in critically ill patients: pharmacokinetic and pharmacodynamic approaches. Int J Antimicrob Agents 2008;32(6):505-510.
81. Pea F, Di Qual E, Cusenza A, et al. Pharmacokinetics and pharmacodynamics of intravenous levofloxacin in patients with early-onset ventilator-associated pneumonia. Clin Pharmacokinet 2003;42(6):589-598.
82. Adembri C, Fallani S, Cassetta MI, et al. Linezolid pharmacokinetic/pharmacodynamic profile in critically ill septic patients: intermittent versus continuous infusion. Int J Antimicrob Agents 2008;31(2):122-129.
83. Beckhouse MJ, Whyte IM, Byth PL, et al. Altered aminoglycoside pharmacokinetics in the critically ill. Anaesth Intensive Care 1988;16(4):418-422.
84. Brown R, Babcock R, Talbert J, et al. Renal function in critically ill postoperative patients: sequential assessment of creatinine osmolar and free water clearance. Crit Care Med 1980;8(2):68-72.
85. Hanes SD, Wood GC, Herring V, et al. Intermittent and continuous ceftazidime infusion for critically ill trauma patients. Am J Surg 2000;179(6):436-440.
86. Shikuma LR, Ackerman BH, Weaver RH, et al. Effects of treatment and the metabolic response to injury on drug clearance: a prospective study with piperacillin. Crit Care Med 1990;18(1):37-41.
87. Toschlog EA, Blount KP, Rotondo MF, et al. Clinical predictors of subtherapeutic aminoglycoside levels in trauma patients undergoing once-daily dosing. J Trauma 2003;55(2):255-260; discussion 260-252.
88. Minville V, Asehnoune K, Ruiz S, et al. Increased creatinine clearance in polytrauma patients with normal serum creatinine: a retrospective observational study. Crit Care 2011;15(1):R49.
89. Albanese J, Leone M, Garnier F, et al. Renal effects of norepinephrine in septic and nonseptic patients. Chest 2004;126(2):534-539.

90. Benmalek F, Behforouz N, Benoist JF, et al. Renal effects of low-dose dopamine during vasopressor therapy for posttraumatic intracranial hypertension. Intensive Care Med 1999;25(4):399-405.
91. Vincent F, El-Khoury N, Bonnard G, et al. Should a renal dose of norepinephrine stimulate hyperfiltration in head trauma patients? Chest 2005;127(6):2282-2283.
92. Udy A, Boots R, Senthuran S, et al. Augmented creatinine clearance in traumatic brain injury. Anesth Analg 2010;111(6):1505-1510.
93. Loirat P, Rohan J, Baillet A, et al. Increased glomerular filtration rate in patients with major burns and its effect on the pharmacokinetics of tobramycin. N Engl J Med 1978;299(17):915-919.
94. Pea F, Viale P, Candoni A, et al. Teicoplanin in patients with acute leukaemia and febrile neutropenia: a special population benefiting from higher dosages. Clin Pharmacokinet 2004;43(6):405-415.
95. Nyhlen A, Ljungberg B, Nilsson-Ehle I. Pharmacokinetics of ceftazidime in febrile neutropenic patients. Scand J Infect Dis 2001;33(3):222-226.
96. Lamoth F, Buclin T, Csajka C, et al. Reassessment of recommended imipenem doses in febrile neutropenic patients with hematological malignancies. Antimicrob Agents Chemother 2009;53(2):785-787.
97. Romano S, Fdez de Gatta MM, Calvo MV, et al. Population pharmacokinetics of amikacin in patients with haematological malignancies. J Antimicrob Chemother 1999;44(2):235-242.
98. Higa GM, Murray WE. Alterations in aminoglycoside pharmacokinetics in patients with cancer. Clin Pharm 1987;6(12):963-966.
99. Bubalo JS, Munar MY, Cherala G, et al. Daptomycin pharmacokinetics in adult oncology patients with neutropenic fever. Antimicrob Agents Chemother 2009;53(2):428-434.
100. Fernandez de Gatta MM, Fruns I, Hernandez JM, et al. Vancomycin pharmacokinetics and dosage requirements in hematologic malignancies. Clin Pharm 1993;12(7):515-520.
101. Ambrose PG, Bhavnani SM, Ellis-Grosse EJ, et al. Pharmacokinetic-pharmacodynamic considerations in the design of hospital-acquired or ventilator-associated bacterial pneumonia studies: look before you leap! Clin Infect Dis 2010;51 Suppl 1:S103-110.
102. Joynt GM, Lipman J, Gomersall CD, et al. The pharmacokinetics of once-daily dosing of ceftriaxone in critically ill patients. J Antimicrob Chemother 2001;47(4):421-429.

103. Brink AJ, Richards GA, Schillack V, et al. Pharmacokinetics of once-daily dosing of ertapenem in critically ill patients with severe sepsis. Int J Antimicrob Agents 2009;33(5):432-436.
104. Claus BO, Hoste EA, Colpaert K, et al. Augmented renal clearance is a common finding with worse clinical outcome in critically ill patients receiving antimicrobial therapy. J Crit Care 2013;28(5):695-700.
105. Jacolot A, Incagnoli P, Edouard AR, et al. Pharmacokinetics of cefpirome during the posttraumatic systemic inflammatory response syndrome. Intensive Care Med 1999;25(5):486-491.
106. Ott L, McClain CJ, Gillespie M, et al. Cytokines and metabolic dysfunction after severe head injury. J Neurotrauma 1994;11(5):447-472.
107. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. IX. Cerebral perfusion thresholds. J Neurotrauma 2007;24 Suppl 1:S59-64.
108. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. I. Blood pressure and oxygenation. J Neurotrauma 2007;24 Suppl 1:S7-13.
109. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. II. Hyperosmolar therapy. J Neurotrauma 2007;24 Suppl 1:S14-20.
110. Sen J, Belli A, Albon H, et al. Triple-H therapy in the management of aneurysmal subarachnoid haemorrhage. Lancet Neurol 2003;2(10):614-621.
111. Papp A, Uusaro A, Parviainen I, et al. Myocardial function and haemodynamics in extensive burn trauma: evaluation by clinical signs, invasive monitoring, echocardiography and cytokine concentrations. A prospective clinical study. Acta Anaesthesiol Scand 2003;47(10):1257-1263.
112. Barton RG, Saffle JR, Morris SE, et al. Resuscitation of thermally injured patients with oxygen transport criteria as goals of therapy. J Burn Care Rehabil 1997;18(1 Pt 1):1-9.
113. Latenser BA. Critical care of the burn patient: the first 48 hours. Crit Care Med 2009;37(10):2819-2826.
114. Palmieri T, Lavrentieva A, Greenhalgh DG. Acute kidney injury in critically ill burn patients. Risk factors, progression and impact on mortality. Burns 2010;36(2):205-211.
115. Bonapace CR, White RL, Friedrich LV, et al. Pharmacokinetics of cefepime in patients with thermal burn injury. Antimicrob Agents Chemother 1999;43(12):2848-2854.

116. Conil JM, Georges B, Lavit M, et al. A population pharmacokinetic approach to ceftazidime use in burn patients: influence of glomerular filtration, gender and mechanical ventilation. Br J Clin Pharmacol 2007;64(1):27-35.
117. Conil JM, Georges B, Lavit M, et al. Pharmacokinetics of ceftazidime and cefepime in burn patients: the importance of age and creatinine clearance. Int J Clin Pharmacol Ther 2007;45(10):529-538.
118. Shikuma LR, Ackerman BH, Weaver RH, et al. Thermal injury effects on drug disposition: a prospective study with piperacillin. J Clin Pharmacol 1990;30(7):632-637.
119. Adam D, Zellner PR, Koeppe P, et al. Pharmacokinetics of ticarcillin/clavulanate in severely burned patients. J Antimicrob Chemother 1989;24 Suppl B:121-129.
120. Dailly E, Kergueris MF, Pannier M, et al. Population pharmacokinetics of imipenem in burn patients. Fundam Clin Pharmacol 2003;17(6):645-650.
121. Dolton M, Xu H, Cheong E, et al. Vancomycin pharmacokinetics in patients with severe burn injuries. Burns 2010;36(4):469-476.
122. Conil JM, Georges B, Breden A, et al. Increased amikacin dosage requirements in burn patients receiving a once-daily regimen. Int J Antimicrob Agents 2006;28(3):226-230.
123. Mohr JF, 3rd, Ostrosky-Zeichner L, Wainright DJ, et al. Pharmacokinetic evaluation of single-dose intravenous daptomycin in patients with thermal burn injury. Antimicrob Agents Chemother 2008;52(5):1891-1893.
124. Garrelts JC, Jost G, Kowalsky SF, et al. Ciprofloxacin pharmacokinetics in burn patients. Antimicrob Agents Chemother 1996;40(5):1153-1156.
125. Rey E, Treluyer JM, Pons G. Drug disposition in cystic fibrosis. Clin Pharmacokinet 1998;35(4):313-329.
126. Hedman A, Alvan G, Strandvik B, et al. Increased renal clearance of cefsulodin due to higher glomerular filtration rate in cystic fibrosis. Clin Pharmacokinet 1990;18(2):168-175.
127. Jusko WJ, Mosovich LL, Gerbracht LM, et al. Enhanced renal excretion of dicloxacillin in patients with cystic fibrosis. Pediatrics 1975;56(6):1038-1044.
128. Wang JP, Unadkat JD, al-Habet SM, et al. Disposition of drugs in cystic fibrosis. IV. Mechanisms for enhanced renal clearance of ticarcillin. Clin Pharmacol Ther 1993;54(3):293-302.
129. Lortholary O, Lefort A, Tod M, et al. Pharmacodynamics and pharmacokinetics of antibacterial drugs in the management of febrile neutropenia. Lancet Infect Dis 2008;8(10):612-620.

130. Conil JM, Georges B, Fourcade O, et al. Intermittent administration of ceftazidime to burns patients: influence of glomerular filtration. Int J Clin Pharmacol Ther 2007;45(3):133-142.
131. Roberts JA, Kruger P, Paterson DL, et al. Antibiotic resistance--what's dosing got to do with it? Crit Care Med 2008;36(8):2433-2440.
132. Dulhunty JM, Webb S, Paterson D, et al. A survey of antibiotic prescribing practices in Australian and New Zealand intensive care units. Critical Care and Resuscitation 2010;12(3):162-170.
133. Buijk SE, Mouton JW, Gyssens IC, et al. Experience with a once-daily dosing program of aminoglycosides in critically ill patients. Intensive Care Med 2002;28(7):936-942.
134. Moore RD, Lietman PS, Smith CR. Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. J Infect Dis 1987;155(1):93-99.
135. Roberts JA, Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. Crit Care Med 2009;37(3):840-851.
136. Forrest A, Nix DE, Ballow CH, et al. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. Antimicrob Agents Chemother 1993;37(5):1073-1081.
137. Moise-Broder PA, Forrest A, Birmingham MC, et al. Pharmacodynamics of vancomycin and other antimicrobials in patients with Staphylococcus aureus lower respiratory tract infections. Clin Pharmacokinet 2004;43(13):925-942.
138. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis 1998;26(1):1-10.
139. Turnidge JD. The pharmacodynamics of beta-lactams. Clin Infect Dis 1998;27(1):10-22.
140. Vogelman B, Craig WA. Kinetics of antimicrobial activity. J Pediatr 1986;108(5 Pt 2):835-840.
141. Vogelman BS, Craig WA. Postantibiotic effects. J Antimicrob Chemother 1985;15 Suppl A:37-46.
142. Mouton JW, Touzw DJ, Horrevorts AM, et al. Comparative pharmacokinetics of the carbapenems: clinical implications. Clin Pharmacokinet 2000;39(3):185-201.
143. Bustamante CI, Drusano GL, Tatem BA, et al. Postantibiotic effect of imipenem on Pseudomonas aeruginosa. Antimicrob Agents Chemother 1984;26(5):678-682.
144. Drusano GL. Prevention of resistance: a goal for dose selection for antimicrobial agents. Clin Infect Dis 2003;36(Suppl 1):S42-50.

145. Joukhadar C, Klein N, Mayer BX, et al. Plasma and tissue pharmacokinetics of cefpirome in patients with sepsis. Crit Care Med 2002;30(7):1478-1482.
146. Kitzes-Cohen R, Farin D, Piva G, et al. Pharmacokinetics and pharmacodynamics of meropenem in critically ill patients. Int J Antimicrob Agents 2002;19(2):105-110.
147. Lovering AM, Vickery CJ, Watkin DS, et al. The pharmacokinetics of meropenem in surgical patients with moderate or severe infections. J Antimicrob Chemother 1995;36(1):165-172.
148. Van Dalen R, Vree T, Baars IM. Influence of protein binding and severity of illness on renal elimination of four cephalosporin drugs in intensive-care patients. Pharmaceutisch Weekblad Scientific Edition 1987;9(2):98-103.
149. Roos JF, Lipman J, Kirkpatrick CM. Population pharmacokinetics and pharmacodynamics of cefpirome in critically ill patients against Gram-negative bacteria. Intensive Care Med 2007;33(5):781-788.
150. Tam VH, McKinnon PS, Akins RL, et al. Pharmacokinetics and pharmacodynamics of cefepime in patients with various degrees of renal function. Antimicrob Agents Chemother 2003;47(6):1853-1861.
151. Novelli A, Adembri C, Livi P, et al. Pharmacokinetic evaluation of meropenem and imipenem in critically ill patients with sepsis. Clin Pharmacokinet 2005;44(5):539-549.
152. Georges B, Conil JM, Seguin T, et al. Cefepime in intensive care unit patients: validation of a population pharmacokinetic approach and influence of covariables. Int J Clin Pharmacol Ther 2008;46(4):157-164.
153. Barbhaiya RH, Forgue ST, Gleason CR, et al. Pharmacokinetics of cefepime after single and multiple intravenous administrations in healthy subjects. Antimicrob Agents Chemother 1992;36(3):552-557.
154. Kieft H, Hoepelman AI, Knupp CA, et al. Pharmacokinetics of cefepime in patients with the sepsis syndrome. J Antimicrob Chemother 1993;32 Suppl B:117-122.
155. Patel IH, Chen S, Parsonnet M, et al. Pharmacokinetics of ceftriaxone in humans. Antimicrob Agents Chemother 1981;20(5):634-641.
156. Heinemeyer G, Link J, Weber W, et al. Clearance of ceftriaxone in critical care patients with acute renal failure. Intensive Care Med 1990;16(7):448-453.
157. Sommers DK, Walters L, Van Wyk M, et al. Pharmacokinetics of ceftazidime in male and female volunteers. Antimicrob Agents Chemother 1983;23(6):892-896.
158. Buijk SL, Gyssens IC, Mouton JW, et al. Pharmacokinetics of ceftazidime in serum and peritoneal exudate during continuous versus intermittent administration to patients with severe intra-abdominal infections. J Antimicrob Chemother 2002;49(1):121-128.

159. Batra VK, Morrison JA, Lasseter KC, et al. Piperacillin kinetics. Clin Pharmacol Ther 1979;26(1):41-53.
160. Bax RP, Bastain W, Featherstone A, et al. The pharmacokinetics of meropenem in volunteers. J Antimicrob Chemother 1989;24 Suppl A:311-320.
161. Karjagin J, Lefeuvre S, Oselin K, et al. Pharmacokinetics of meropenem determined by microdialysis in the peritoneal fluid of patients with severe peritonitis associated with septic shock. Clin Pharmacol Ther 2008;83(3):452-459.
162. Thalhammer F, Traunmuller F, El Menyawi I, et al. Continuous infusion versus intermittent administration of meropenem in critically ill patients. J Antimicrob Chemother 1999;43(4):523-527.
163. Roberts JA, Kirkpatrick CM, Roberts MS, et al. Meropenem dosing in critically ill patients with sepsis and without renal dysfunction: intermittent bolus versus continuous administration? Monte Carlo dosing simulations and subcutaneous tissue distribution. J Antimicrob Chemother 2009;64(1):142-150.
164. Norrby SR, Bjornegard B, Ferber F, et al. Pharmacokinetics of imipenem in healthy volunteers. J Antimicrob Chemother 1983;12 Suppl D:109-124.
165. Tegeder I, Schmidtko A, Brautigam L, et al. Tissue distribution of imipenem in critically ill patients. Clin Pharmacol Ther 2002;71(5):325-333.
166. Sakka SG, Glauner AK, Bulitta JB, et al. Population pharmacokinetics and pharmacodynamics of continuous versus short-term infusion of imipenem-cilastatin in critically ill patients in a randomized, controlled trial. Antimicrob Agents Chemother 2007;51(9):3304-3310.
167. Majumdar AK, Musson DG, Birk KL, et al. Pharmacokinetics of ertapenem in healthy young volunteers. Antimicrob Agents Chemother 2002;46(11):3506-3511.
168. McKinnon PS, Paladino JA, Schentag JJ. Evaluation of area under the inhibitory curve (AUIC) and time above the minimum inhibitory concentration (T>MIC) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections. Int J Antimicrob Agents 2008;31(4):345-351.
169. Roberts JA, Paul SK, Akova M, et al. DALI: Defining Antibiotic Levels in Intensive care unit patients: Are current beta-lactam antibiotic doses sufficient for criticall ill patients? Clin Infect Dis 2014;58(8):1072-1083.
170. Udy A, Roberts JA, Akova M, et al. The influence of augmented renal clearance on plasma concentrations in critically ill patients receiving beta-lactam therapy. In: 11th Congress of the World Federation of Societies of Intensive and Critical Care Medicine; Durban, South Africa; 2013.

171. Kollef MH. Review of recent clinical trials of hospital-acquired pneumonia and ventilator-associated pneumonia: a perspective from academia. Clin Infect Dis 2010;51 Suppl 1:S29-35.
172. Kollef MH, Chastre J, Clavel M, et al. A randomized trial of 7-day doripenem versus 10-day imipenem-cilastatin for ventilator-associated pneumonia. Crit Care 2012;16(6):R218.
173. Roberts JA, Lipman J. Optimal doripenem dosing simulations in critically ill nosocomial pneumonia patients with obesity, augmented renal clearance, and decreased bacterial susceptibility. Crit Care Med 2013;41(2):489-495.
174. Roberts JA, Boots R, Rickard CM, et al. Is continuous infusion ceftriaxone better than once-a-day dosing in intensive care? A randomized controlled pilot study. J Antimicrob Chemother 2007;59(2):285-291.
175. Lipman J, Gomersall CD, Gin T, et al. Continuous infusion ceftazidime in intensive care: a randomized controlled trial. J Antimicrob Chemother 1999;43(2):309-311.
176. Georges B, Conil JM, Cougot P, et al. Cefepime in critically ill patients: continuous infusion vs. an intermittent dosing regimen. Int J Clin Pharmacol Ther 2005;43(8):360-369.
177. McNabb JJ, Nightingale CH, Quintiliani R, et al. Cost-effectiveness of ceftazidime by continuous infusion versus intermittent infusion for nosocomial pneumonia. Pharmacotherapy 2001;21(5):549-555.
178. Mouton JW, Vinks AA, Punt NC. Pharmacokinetic-pharmacodynamic modeling of activity of ceftazidime during continuous and intermittent infusion. Antimicrob Agents Chemother 1997;41(4):733-738.
179. Nicolau DP, McNabb J, Lacy MK, et al. Continuous versus intermittent administration of ceftazidime in intensive care unit patients with nosocomial pneumonia. Int J Antimicrob Agents 2001;17(6):497-504.
180. Roberts JA, Paratz J, Paratz E, et al. Continuous infusion of beta-lactam antibiotics in severe infections: a review of its role. Int J Antimicrob Agents 2007;30(1):11-18.
181. Lodise TP, Jr., Lomaestro B, Drusano GL. Piperacillin-tazobactam for Pseudomonas aeruginosa infection: clinical implications of an extended-infusion dosing strategy. Clin Infect Dis 2007;44(3):357-363.
182. Lorente L, Lorenzo L, Martin MM, et al. Meropenem by continuous versus intermittent infusion in ventilator-associated pneumonia due to gram-negative bacilli. Ann Pharmacother 2006;40(2):219-223.
183. Lorente L, Jimenez A, Palmero S, et al. Comparison of clinical cure rates in adults with ventilator-associated pneumonia treated with intravenous ceftazidime administered by

continuous or intermittent infusion: a retrospective, nonrandomized, open-label, historical chart review. Clin Ther 2007;29(11):2433-2439.

184. Lorente L, Jimenez A, Martin MM, et al. Clinical cure of ventilator-associated pneumonia treated with piperacillin/tazobactam administered by continuous or intermittent infusion. Int J Antimicrob Agents 2009;33(5):464-468.

185. Roberts JA, Webb S, Paterson D, et al. A systematic review on clinical benefits of continuous administration of beta-lactam antibiotics. Crit Care Med 2009;37(6):2071-2078.

186. Falagas ME, Tansarli GS, Ikawa K, et al. Clinical outcomes with extended or continuous versus short-term intravenous infusion of carbapenems and piperacillin/tazobactam: a systematic review and meta-analysis. Clin Infect Dis 2013;56(2):272-282.

187. Arnold HM, Hollands JM, Skrupky LP, et al. Prolonged infusion antibiotics for suspected gram-negative infections in the ICU: a before-after study. Ann Pharmacother 2013;47(2):170-180.

188. Dulhunty JM, Roberts JA, Davis JS, et al. Continuous infusion of beta-lactam antibiotics in severe sepsis: a multicenter double-blind, randomized controlled trial. Clin Infect Dis 2013;56(2):236-244.

189. Carlier M, Carrette S, Roberts JA, et al. Meropenem and piperacillin/tazobactam prescribing in critically ill patients: does augmented renal clearance affect pharmacokinetic/pharmacodynamic target attainment when extended infusions are used? Crit Care 2013;17(3):R84.

190. Pea F, Viale P, Cojutti P, et al. Dosing nomograms for attaining optimum concentrations of meropenem by continuous infusion in critically ill patients with severe gram-negative infections: a pharmacokinetics/pharmacodynamics-based approach. Antimicrob Agents Chemother 2012;56(12):6343-6348.

191. Crandon JL, Ariano RE, Zelenitsky SA, et al. Optimization of meropenem dosage in the critically ill population based on renal function. Intensive Care Med 2011;37(4):632-638.

192. Nicasio AM, Ariano RE, Zelenitsky SA, et al. Population pharmacokinetics of high-dose, prolonged-infusion cefepime in adult critically ill patients with ventilator-associated pneumonia. Antimicrob Agents Chemother 2009;53(4):1476-1481.

193. Felton TW, Hope WW, Lomaestro BM, et al. Population pharmacokinetics of extended-infusion piperacillin-tazobactam in hospitalized patients with nosocomial infections. Antimicrob Agents Chemother 2012;56(8):4087-4094.

194. Udy AA, Roberts JA, De Waele JJ, et al. What's behind the failure of emerging antibiotics in the critically ill? Understanding the impact of altered pharmacokinetics and augmented renal clearance. Int J Antimicrob Agents 2012;39(6):455-457.
195. Mouton JW, den Hollander JG. Killing of Pseudomonas aeruginosa during continuous and intermittent infusion of ceftazidime in an in vitro pharmacokinetic model. Antimicrob Agents Chemother 1994;38(5):931-936.
196. Roberts JA, Ulldemolins M, Roberts MS, et al. Therapeutic drug monitoring of beta-lactams in critically ill patients: proof of concept. Int J Antimicrob Agents;36(4):332-339.
197. McWhinney BC, Wallis SC, Hillister T, et al. Analysis of 12 beta-lactam antibiotics in human plasma by HPLC with ultraviolet detection. J Chromatogr B Analyt Technol Biomed Life Sci;878(22):2039-2043.
198. Udy AA, Roberts JA, Lipman J. Implications of augmented renal clearance in critically ill patients. Nat Rev Nephrol 2011;7(9):539-543.
199. Udy AA, Varghese JM, Altukroni M, et al. Subtherapeutic initial beta-lactam concentrations in select critically ill patients: association between augmented renal clearance and low trough drug concentrations. Chest 2012;142(1):30-39.
200. Baptista JP, Udy AA, Sousa E, et al. A comparison of estimates of glomerular filtration in critically ill patients with augmented renal clearance. Crit Care 2011;15(3):R139.
201. Wan L, Bellomo R, May CN. A comparison of 4% succinylated gelatin solution versus normal saline in stable normovolaemic sheep: global haemodynamic, regional blood flow and oxygen delivery effects. Anaesth Intensive Care 2007;35(6):924-931.
202. Morgan P, Al-Subaie N, Rhodes A. Minimally invasive cardiac output monitoring. Curr Opin Crit Care 2008;14(3):322-326.
203. Roberts JA, Roberts MS, Semark A, et al. Antibiotic dosing in the 'at risk' critically ill patient: Linking pathophysiology with pharmacokinetics/pharmacodynamics in sepsis and trauma patients. BMC Anesthesiol 2011;11:3.
204. Robinson S, Zincuk A, Strom T, et al. Enoxaparin, effective dosage for intensive care patients: double-blinded, randomised clinical trial. Crit Care;14(2):R41.
205. Bosch JP, Saccaggi A, Lauer A, et al. Renal functional reserve in humans. Effect of protein intake on glomerular filtration rate. Am J Med 1983;75(6):943-950.
206. Wiener RS, Welch HG. Trends in the use of the pulmonary artery catheter in the United States, 1993-2004. Jama 2007;298(4):423-429.

207. Mayer J, Boldt J, Poland R, et al. Continuous arterial pressure waveform-based cardiac output using the FloTrac/Vigileo: a review and meta-analysis. J Cardiothorac Vasc Anesth 2009;23(3):401-406.
208. Zimmermann A, Kufner C, Hofbauer S, et al. The accuracy of the Vigileo/FloTrac continuous cardiac output monitor. J Cardiothorac Vasc Anesth 2008;22(3):388-393.
209. Zimmermann A, Steinwendner J, Hofbauer S, et al. The accuracy of the Vigileo/FloTrac system has been improved--follow-up after a software update: a blinded comparative study of 30 cardiosurgical patients. J Cardiothorac Vasc Anesth 2009;23(6):929-931.
210. McGee WT, Horswell JL, Calderon J, et al. Validation of a continuous, arterial pressure-based cardiac output measurement: a multicenter, prospective clinical trial. Crit Care 2007;11(5):R105.
211. Lorsomradee S, Cromheecke S, De Hert SG. Uncalibrated arterial pulse contour analysis versus continuous thermodilution technique: effects of alterations in arterial waveform. J Cardiothorac Vasc Anesth 2007;21(5):636-643.
212. Giustiniano E, Morenghi E, Ruggieri N, et al. Cardiac output by Flotrac/VigileoTM validation trials: are there reliable conclusions? Reviews on recent clinical trials 2012;7(3):181-186.
213. Kim KE, Onesti G, Swartz C. Creatinine clearance and glomerular filtration rate. Br Med J 1972;1(5796):379-380.
214. Hosein S, Udy AA, Lipman J. Physiological changes in the critically ill patient with sepsis. Curr Pharm Biotechnol 2011;12(12):1991-1995.
215. Udy AA, Roberts JA, Shorr AF, et al. Augmented renal clearance in septic and traumatized patients with normal plasma creatinine concentrations: Identifying at-risk patients. Crit Care 2013;17(1):R35.
216. Bellomo R, Ronco C, Kellum JA, et al. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004;8(4):R204-212.
217. Christensen MC, Ridley S, Lecky FE, et al. Outcomes and costs of blunt trauma in England and Wales. Crit Care 2008;12(1):R23.
218. Di Giantomasso D, May CN, Bellomo R. Norepinephrine and vital organ blood flow. Intensive Care Med 2002;28(12):1804-1809.

219. Oterdoom LH, Gansevoort RT, Schouten JP, et al. Urinary creatinine excretion, an indirect measure of muscle mass, is an independent predictor of cardiovascular disease and mortality in the general population. Atherosclerosis 2009;207(2):534-540.
220. Matsushita K, Mahmoodi BK, Woodward M, et al. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. JAMA 2012;307(18):1941-1951.
221. White SL, Polkinghorne KR, Atkins RC, et al. Comparison of the prevalence and mortality risk of CKD in Australia using the CKD Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) Study GFR estimating equations: the AusDiab (Australian Diabetes, Obesity and Lifestyle) Study. Am J Kidney Dis 2010;55(4):660-670.
222. Johnson DW, Jones GR, Mathew TH, et al. Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: new developments and revised recommendations. Med J Aust 2012;197(4):224-225.
223. Mathew TH, Johnson DW, Jones GR, et al. Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: revised recommendations. Med J Aust 2007;187(8):459-463.
224. Martin JH, Fay MF, Ungerer JP. eGFR--use beyond the evidence. Med J Aust 2009;190(4):197-199.
225. Baptista JP, Sousa E, Martins PJ, et al. Augmented renal clearance in septic patients and implications for vancomycin optimisation. Int J Antimicrob Agents 2012;39(5):420-423.
226. Grootaert V, Willems L, Debaveye Y, et al. Augmented renal clearance in the critically ill: how to assess kidney function. Ann Pharmacother 2012;46(7-8):952-959.
227. Wargo KA, English TM. Evaluation of the chronic kidney disease epidemiology collaboration equation for dosing antimicrobials. Ann Pharmacother 2010;44(3):439-446.
228. Chung J, Oh JM, Cho EM, et al. Optimal dose of vancomycin for treating methicillin-resistant Staphylococcus aureus pneumonia in critically ill patients. Anaesth Intensive Care 2011;39(6):1030-1037.
229. Levey AS, Stevens LA. Estimating GFR using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. Am J Kidney Dis 2010;55(4):622-627.
230. Stevens LA, Schmid CH, Greene T, et al. Comparative performance of the CKD Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease

(MDRD) Study equations for estimating GFR levels above 60 mL/min/1.73 m2. Am J Kidney Dis 2010;56(3):486-495.

231. Udy AA, Baptista JP, Lim NL, et al. Augmented Renal Clearance in the ICU: Results of a Multicenter Observational Study of Renal Function in Critically Ill Patients With Normal Plasma Creatinine Concentrations. Crit Care Med 2014; 42(3): 520-527.

232. Kim KE, Onesti G, Ramirez O, et al. Creatinine clearance in renal disease. A reappraisal. Br Med J 1969;4(5674):11-14.

233. Vincent JL, Rello J, Marshall J, et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA 2009; 302(21): 2323-2329.

Appendix A – Physiological and treatment variables in those with and without ARC on study day 1, day 4, and day 7.

	Study Day 1 (n=281)		Study Day 4 (n=143)		Study Day 7 (n=93)	
Variable	**ARC**	**No ARC**	**ARC**	**No ARC**	**ARC**	**No ARC**
Mod SOFA score, median [IQR]	2 [1-4]	3 [2-5.5]	2 [1-4]	2 [1-5]	2 [1-5]	3 [1-3]
Max MAP, mmHg, mean (95% CI)	105 (102-107)	104 (102-106)	110 (106-114)	109 (105-113)	107 (104-113)	110 (106-114)
Min MAP, mmHg, mean (95% CI)	74 (72-76)	70 (69-72)	77 (74-80)	75 (72-78)	81 (78-85)	79 (75-83)
Max CVP, mmHg, mean (95% CI)	14 (13-16)	14 (13-15)	15 (13-16)	15 (14-17)	14 (12-15)	14 (13-16)
Min CVP, mmHg, mean (95% CI)	6 (5-6)	6 (5-6)	5 (4-6)	6 (5-8)	5 (4-7)	5 (4-7)
Max HR, /min, mean (95% CI)	99 (95-103)	103 (100-106)	100 (96-105)	103 (96-110)	101 (95-106)	105 (98-111)
Min HR, /min, mean (95% CI)	70 (66-73)	74 (71-76)	74 (70-78)	76 (72-80)	75 (70-79)	78 (73-83)
Max RR, /min, mean (95% CI)	22 (21-23)	24 (22-25)	25 (24-27)	24 (22-26)	28 (26-31)	27 (24-29)
Min RR, /min, mean (95% CI)	13 (12-13)	13 (13-14)	15 (14-16)	15 (14-17)	15 (14-17)	15 (14-17)
Max Temp, ^{o}C, mean (95% CI)	37.8 (37.7-38.0)	37.9 (37.7-38.0)	38.4 (38.2-38.5)	38.0 (37.8-38.2)	38.5 (38.3-38.8)	38.2 (37.9-38.4)
Min Temp, ^{o}C, mean (95% CI)	36.4 (36.1-36.7)	36.2 (36.1-36.4)	37.1 (36.9-37.3)	36.7 (36.6-36.9)	37.1 (36.9-37.3)	36.9 (36.6-37.2)
WCC, x 10^{9}/L, mean (95% CI)	12.3 (10.8-13.7)	13.6 (11.1-16.1)	10.5 (9.24-11.8)	10.6 (9.43-11.8)	12.0 (10.8-13.3)	11.4 (10.2-12.6)
Mechanical Ventilation, n (%)	78 (72.9)	121 (70.3)	55 (74.3)	47 (69.1)	27 (62.8)	39 (78.0)
Any vasopressors / inotrope, n (%)	25 (23.1)	64 (37.0)	16 (21.6)	17 (24.6)	13 (30.2)	7 (14.0)
Norepinephrine administration, n (%)	19 (17.6)	57 (32.9)	12 (16.2)	15 (21.7)	9 (20.9)	6 (12.0)
Dopamine administration, n (%)	7 (6.5)	9 (5.2)	5 (6.8)	3 (4.3)	3 (7.0)	1 (2.0)

Receiving enteral nutrition, n (%)	62 (57.4)	99 (57.2)	53 (71.6)	53 (76.8)	34 (79.1)	42 (84.0)
Frusemide administration, n (%)	10 (9.3)	30 (17.5)	12 (16.2)	25 (36.8)	11 (26.2)	20 (40.0)
Mannitol administration, n (%)	13 (12.0)	14 (8.1)	5 (6.8)	5 (7.5)	1 (2.4)	0 (0.0)
Antibiotic administration, n (%)	80 (74.1)	141 (82.0)	46 (62.2)	56 (82.4)	32 (74.4)	38 (76.0)
IV contrast administration, n (%)	21 (19.6)	33 (19.3)	3 (4.2)	1 (1.5)	2 (4.9)	1 (2.0)
24-hr UO, ml, mean (95% CI)	2206 (1934-2478)	1776 (1616-1935)	2763 (2460-3066)	2461 (2181-2742)	3392 (2761-4024)	2722 (2339-3104)
Plasma CR concentration, µmol/L, mean (95% CI)	60 (57-63)	79 (75-83)	55 (52-59)	73 (67-80)	55 (50-60)	66 (60-73)
CR excretion rate, mg/kg/day, mean (95% CI)	25.0 (22.0-28.0)	15.5 (14.7-16.4)	23.3 (21.5-25.1)	15.2 (14.0-16.4)	22.0 (20.0-23.9)	14.9 (13.6-16.2)
CL_{CR}, ml/min/1.73m^2, mean (95% CI)	172 (164-181)	81 (76-85)	178 (168-188)	88 (81-95)	169 (159-180)	95 (88-103)
24-hr Total fluid balance, ml, mean (95% CI)	722 (424-1019)	1042 (803-1281)	264 (-13-541)	231 (-84-509)	-338 (-790-114)	-201 (-533-132)

ARC – augmented renal clearance, CI – confidence interval, CR – creatinine, CL_{CR} – creatinine clearance, CVP – central venous pressure, HR – heart rate, IQR – interquartile range, MAP – mean arterial pressure, RR – respiratory rate, SOFA – sequential organ failure assessment, UO – urine output, WCC – white cell count (in blood)