Altered Pharmacokinetics and Pharmacodynamics of Drugs in the Intensive Care Unit

by

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Abstract

Critical illness is unique for its complex nature which very often requires a range of professional expertise to provide the most comprehensive care possible, hence the need for a multidisciplinary approach. One of the most important aspects to accurate drug dosing and dose individualization in critically ill patients is their renal function. This is especially true considering its dynamic changes during the course of treatment warranting multiple dose adjustments to renally eliminated drugs. However, renal function assessment in the critically ill overlooks the possibility for hyper-functioning kidneys, known as augmented renal clearance (ARC), which could contribute to therapeutic failures in the intensive care unit (ICU). Therefore, our research aimed to conduct a systematic review and meta-analysis of prevalence and risk factors of ARC in the critically ill, offering a step towards early identification of those at risk, allowing timely medication optimization. Moreover, ARC alters the disposition of renally eliminated medications currently used in the intensive care unit, resulting in underdosing and potential therapy failure. Our research addresses the rising concern of inadequate dosing in patients with ARC by summarizing the currently available evidence in a narrative review. Our research addressed an example of a life threatening neurocritical care condition, namely aneurysmal subarachnoid hemorrhage (aSAH). Subarachnoid hemorrhage (SAH) results from bleeding in the subarachnoid space often caused by head trauma or more commonly, a ruptured brain aneurysm resulting in aSAH. Delayed cerebral ischemia (DCI) and cerebral vasospasm are the main complications that contributes to unfavorable outcomes in patients with aSAH. Nimodipine is the only drug shown to decrease the incidence of DCI and improve patient outcomes**.** Therefore, current guidelines suggest that all aSAH patients receive oral nimodipine for 21 days. Patients with no difficulty swallowing swallow nimodipine whole capsules or tablets; otherwise, nimodipine liquid must be drawn from capsules, tablets need to be crushed or the commercially available liquid product to be used to facilitate administration through an enteral feeding tube (FT). It is not clear whether these techniques of administration are equivalent. Hence, our research aimed to examine if different nimodipine formulations and administration techniques via FT were associated with the safety and effectiveness of nimodipine.

In the first project of our research, we generated a random-effects meta-analytic model and forest plots for a total of 70 studies resulting in a pooled ARC prevalence (95% CI) of 39 %

(34.9-43.3). Prevalence for neuro, trauma, mixed and sepsis ICUs were 74 (55-87), 58 (48-67), 36 (31-41) and 33 (21-48), respectively. Age, male sex and trauma were associated with ARC with pooled OR (95% CI) of 0.95 (0.93-0.96), 2.36 (1.28-4.36), 2.60 (1.21-5.58), respectively. This supports our hypothesis that certain critically ill populations will have higher risk of developing ARC more than other cohorts.

The results of the second project of our research summarized the extent to which ARC influences the probability of target attainment in several medications requiring dosing changes to mitigate the risk of therapeutic failure. The results demonstrated the need for higher than standard doses and reduced dosing intervals in patients with ARC. These results provide clinicians with a guide to navigate drug dosing requirements for patients with ARC and to anticipate aspects of treatment where deviation from standard dosing regimens could be prudent.

With regards to the third project of our research, results from 727 patient records showed that administration of nimodipine oral liquid product was independently associated with higher prevalence of diarrhea compared to other administration techniques/formulations (OR 2.31, 95%CI 1.46 - 3.66, *p*-value < 0.0001 and OR 3.22, 95% CI 1.61-6.41, *p*-value = 0.001, for old and new commercially available formulations, respectively). It also showed that bedside withdrawal of liquid from nimodipine capsules prior to administration was significantly associated with higher prevalence of nimodipine dose reduction or discontinuation secondary to blood pressure reduction (OR 2.82, 95%CI 1.57-5.06, *p*-value = 0.001). Moreover, tablet crushing and bedside withdrawal of liquid from capsules prior to administration were associated with increased odds of DCI (OR 6.66, 95%CI 3.48-12.74, *p*-value < 0.0001 and OR 3.92, 95%CI 2.05-7.52, *p*-value<0.0001, respectively). However, no differences were observed between groups in the rates of angiographic vasospasm or mortality. Our findings suggest that different enteral nimodipine formulation and administration techniques are associated with variable propensity for diarrhea, hypotension and DCI and highlights the need to determine the optimal formulation/technique for enteral nimodipine administration. In summary, ARC is a prevalent phenomenon in critically ill adults that alters drug disposition and affects target attainment and the risk of adverse drug reactions. Moreover, neurocritical care and trauma patients are at a higher risk of developing ARC and special attention is prudent when it comes to drug dosing in these subpopulations. Additionally, we concluded that the tolerability and

efficacy of nimodipine treatment in aSAH patients is significantly dependent on the method of delivery.

Preface

This thesis is an original work by Fatma Hefny. The research projects, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name "Nimodipine Pharmacokinetic Variability and its Impact on Outcomes in Patients with Aneurysmal Subarachnoid Hemorrhage: A Prospective Observational Study", Pro00085618 and project Name "Comparison of Nimodipine Formulations and Administration Techniques via Enteral Feeding Tubes in Patients with Aneurysmal Subarachnoid Hemorrhage: A Multicenter Retrospective Cohort Study", Pro00103859.

This thesis contains **two** published journal articles:

Chapter 2 is a published article. I (Fatma Hefny) contributed to the reviewing, data collection, writing, data analysis and citing the articles, and creating the final draft.

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Chapter 3 is a published article. I (Fatma Hefny) contributed to the reviewing, data collection, writing, data analysis and citing the articles, creating the final draft and revision of the manuscript.

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This work is dedicated to

This work is lovingly dedicated to my husband **(Mohamed Ebeed)** and my family for their continuous and unwavering support throughout the journey leading to this point, and the loving memory of my late uncle **(Mohamed Desouky),** God rest his soul, for being a source of inspiration and unconditional support, and my mentor (**Dr. Sherif Mahmoud**) for the inspiration, guidance and for granting me the opportunity to realize a dream of mine and helping me every step of the way, I am forever grateful.

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TABLE OF CONTENTS

CHAPTER 1 INTRODUCTION 1

1.1 BACKGROUND 1

1.1.1 CRITICAL ILLNESS 1

1.1.1.1 Overview on Critical Illness 1

1.1.1.2 Pharmacotherapeutics in critically ill patients 1

1.1.1.3 Altered pharmacokinetics (PK) in critical illness 2

1.1.1.4 Altered pharmacodynamics (PD) in critical illness 10

1.1.2 AUGMENTED RENAL CLEARANCE (ARC) 11

1.1.2.1 Definition of ARC 11

1.1.2.2 Pathophysiology of ARC 12

1.1.2.3 Prevalence of ARC 12

1.1.2.4 Risk factors of ARC 12

1.1.2.5 Implications of ARC 13

1.1.3 ANEURYSMAL SUBARACHNOID HEMORRHAGE (ASAH) 13

1.1.3.1 Epidemiology 13

1.1.3.2 Etiology and Risk Factors for Increased aSAH 14

1.1.3.3 Pathophysiology of Cerebral Aneurysms 15

1.1.3.4 Aneurysms and The Cerebral Circulation 16

1.1.3.5 Diagnosis and Grading of aSAH 17

1.1.3.6 Surgical Management of aSAH 19

1.1.3.7 Complications of aSAH 19

1.1.3.8 Prognosis of aSAH 20

1.1.3.10 The Role of Nimodipine in the pharmacotherapy of aSAH 20

1.2 RATIONALE 21

1.3 OBJECTIVES 22

1.4 OVERALL HYPOTHESES 22

1.5 LINKAGE 23

CHAPTER 2 PREVALENCE AND RISK FACTORS OF AUGMENTED RENAL CLEARANCE: A SYSTEMATIC REVIEW AND META-ANALYSIS 29

CHAPTER 3 DRUG DOSING IN CRITICALLY ILL ADULT PATIENTS WITH AUGMENTED RENAL CLEARANCE 57

CHAPTER 4 COMPARISON OF NIMODIPINE FORMULATIONS AND ADMINISTRATION TECHNIQUES VIA ENTERAL FEEDING TUBES IN PATIENTS WITH ANEURYSMAL SUBARACHNOID HEMORRHAGE: A MULTICENTER RETROSPECTIVE COHORT STUDY 83

Chapter 5 DISCUSSION 109

BIBLIOGRAPHY 115

Chapter 1 References 115

Chapter 2 References 120

Chapter 3 References 127

Chapter 4 References 132

Chapter 5 References 133

Appendix 135

List of Tables

1.TABLE 1.1: SUMMARY OF PK CHANGES IN CRITICAL ILLNESS (3) 2
2.TABLE 1.2: THE AETIOLOGICAL FACTORS AND ASSOCIATED DISEASE CONDITIONS WITH aSAH (63) 15
3. TABLE 1.3 aSAH GRADING SCALES 18
4.TABLE 2.1. SUMMARY CHARACTERISTICS OF STUDIES INCLUDED IN ARC SYSTEMATIC REVIEW AND META-ANALYSIS OF PREVALENCE AND RISK FACTORS. 35
5.TABLE 2.2. SUMMARY CHARACTERISTICS OF INDIVIDUAL STUDIES REPORTING OTHER RISK FACTORS. 39
6.TABLE 3.1. DOSING RECOMMENDATIONS FOR CRITICALLY ILL ADULT PATIENTS WITH AUGMENTED RENAL CLEARANCE (ARC). 76
7.TABLE 4.1. BASELINE CHARACTERISTICS OF THE STUDY POPULATION 92
8.TABLE 4.2. PHARMACOTHERAPY REPORTED IN THE CURRENT STUDY 93
9.TABLE 4.3. HOSPITAL COURSE AND PATIENT OUTCOMES 100
10.TABLE 4.4 ADJUSTED ODDS RATIOS OF ENTERAL NIMODIPINE ADMINISTRATION GROUPS AND STUDY ENDPOINTS 101
12.SUPPLEMENTARY TABLE 2.1. FULL SEARCH STRATEGY 135
13.SUPPLEMENTARY TABLE 2.2. APPRAISAL OF INDIVIDUAL STUDIES INCLUDED IN THIS REVIEW 137
14.SUPPLEMENTARY TABLE 3.1: FULL SEARCH STRATEGY 141
15.SUPPLEMENTARY TABLE 3.2. SEARCH RESULTS 143
16.SUPPLEMENTARY TABLE 3.3. STUDY SUMMARIES 144

List of Figures

1.Figure 2.1. Flow chart of the study search and screening 34
2.Figure 2.2 Forest plot of the prevalence of ARC in mixed intensive care unit (ICU) population. 41
3.Figure 2.3. Forest plot of the prevalence of ARC in neurocritical care (A) 42
4.Figure 2.4. Forest plot of the prevalence of ARC in sepsis intensive care unit (ICU) (A) and other population (B). 43
5.Figure 2.5. Funnel plot of studies reporting prevalence. 44
6.Figure 2.6. Forest plot of risk factors for augmented renal clearance. 45
7.Figure 4.1. comparison of the prevalence of diarrhea by center 95
8.Figure 4.2. comparison of the prevalence of dose reduction or discontinuation by center 97
9.Figure 4.3. comparison of the prevalence of DCI by center 99
10.Supplementary Figure 2.1: Forest plot of ARC prevalence in mixed ICU (MEASURED and calculated CrCl) 139
11.Supplementary Figure 2.2: Forest plot of OR of diabetes, SOFA score, and APACHEII score as risk factors for ARC 140

List of abbreviation and symbols

AAG	Alpha-acid glycoprotein
ACA	Anterior Cerebral Artery
ACOMM	Anterior communicating artery
AED	Antiepileptic drugs
APACHE II	Acute Physiology and Chronic Health Evaluation II
aSAH	Aneurysmal Subarachnoid Hemorrhage
AUC	Area under the concentration-time curve
AUC0-3h	Area under plasma drug concentration-time -curve from 0 time to 3 hours
BBB	Blood brain barrier
BMI	Body mass index
CKD	Chronic kidney disease
CL	Clearance
Cmax	Maximum (or peak) serum concentration
CSF	Cerebrospinal fluid
Css	Steady plasma concentrations
CT	Computed tomography
CYP	Cytochrome P450
DCI	Delayed Cerebral Ischemia
DSA	Digital subtraction angiography
DVT	Deep venous thrombosis
ECMO	Extracorporeal membrane oxygenation
EVD	External ventricular drainage
FT	Feeding Tube
GCS	Glasgow Coma Score
ICH	Intracerebral hemorrhage
ICU	Intensive care unit
IS	Internal standard
IV	Intravenous
IVH	Interventricular hemorrhage
Kg	Kilogram
L	Litre
LC- MS/MS	Liquid chromatography, tandem mass spectrometry
LLOQ	Lowest limit of quantification
MCA	Middle Cerebral Artery
mg	Milligram
min	Minutes
mL	Millilitre
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
NG	Nasogastric tube
OR	Odds ratio
PCOMM	Posterior communicating artery
PK	Pharmacokinetics

REDCap	Research electronic data capture
ROC	Area under the receiver operating characteristic
SD	Standard deviation
t ½	Half-life
TCD	Transcranial Doppler ultrasonography
Tmax	Time at which Cmax is attained
TNF-α	Tumor necrosis- α
Vd	Volume of distribution
WFNS	World Federation of Neurological Surgeons Scale
µg	Microgram
µL	Microliter

CHAPTER 1 INTRODUCTION

1.1 BACKGROUND

1.1.1 CRITICAL ILLNESS

1.1.1.1 OVERVIEW ON CRITICAL ILLNESS

Critical illness is defined as any life-threatening condition that requires pharmacological treatment and/or mechanical support to the function of vital organ functions to reduce the risk of death (1). Critical illness can be precipitated by sepsis, surgery, trauma, or by complications of acute or chronic diseases. Following the onset of the triggering event, various neuronal and inflammatory cascades initiate an orchestrated stress response. The activated stress response involves a wide range of changes in the homeostasis and changes in the systemic circulation with direct and indirect effects together reducing energy-consuming anabolism and activate energy-producing catabolic pathways. This centrally activated hormonal and metabolic "fight-or-flight" state is thought to be the main response to critical illnesses.

1.1.1.2 PHARMACOTHERAPEUTICS IN CRITICALLY ILL PATIENTS

Appropriate drug therapy for critically ill patients is the key to ensuring comprehensive care. The dynamic, complex and heterogeneous nature of critically ill patients combined with limited evidence often leads to off-label drug use and a high degree of individualization of drug regimens. Although evidence-based standard drug therapy regimens are essential in assisting intensive care unit (ICU) clinicians with providing high-quality care, clinicians need to face instances where data are limited, or a clear consensus is absent. Additionally, the pharmacokinetics (PK) and pharmacodynamics (PD) of drugs used in critically ill patients show significant deviations from the patient groups whose data informed the conventional dosing regimens. As a result, critically ill patients are at higher risk for adverse drug events (ADEs) and more-severe ADEs, and such events lead to longer length of stay and higher costs (2). Therefore, an understanding of drug PK/PD in the critically ill is essential to ensure safe and effective drug regimens. Failure to proactively predict and monitor for changes to the PK and PD of a drug in a critically ill patient can contribute to clinical failures or ADEs. The role of a pharmacist as a member of a multidisciplinary ICU team is indispensable to reduce the incidence of ADEs. Therefore, multidisciplinary teams, including clinicians with a thorough

understanding of drug PK and PD such as an ICU-trained pharmacist, are pivotal in providing comprehensive care.

1.1.1.3 ALTERED PHARMACOKINETICS (PK) IN CRITICAL ILLNESS

PK describes the movement of a drug through the body and is divided into four major components: absorption, distribution, metabolism, and elimination. Table 1.1 summarizes the PK changes in critical illness.

1.TABLE 1.1: SUMMARY OF PK CHANGES IN CRITICAL ILLNESS (3)

Parameter	Common Changes Observed in Critical Illness	Potential Pharmacokinetic Change
Absorption	• Diminished GI or subcutaneous perfusion due to shock and the use of vasopressors • Reduced GI motility in the postoperative setting • Use of enteral nutrition formulas	• Reduction in time to peak concentration and AUC • Reduction in time to peak concentration and AUC • Reduction in AUC
Distribution	• Fluid resuscitation • Reduction in circulating albumin • Increase in circulating AAG • Reduced tissue perfusion secondary to shock states	• Increase in Vd and reduced peak concentration of hydrophilic drugs • Increase in free drug concentration and Vd for drugs bound to albumin • Reduction in free drug concentration and Vd for drugs bound to AAG • Reduction in free drug concentration in peripheral tissues
Metabolism	• Induction of hepatic enzymes by critical illness or drugs • Inhibition of hepatic enzymes by critical illness or drugs • Acute reduction in hepatic blood flow	• Increase in hepatic clearance of low-ER drugs • Reduction in hepatic clearance of low-ER drugs • Reduction in hepatic clearance of high-ER drugs
Elimination	• Acute kidney insufficiency • Augmented renal function • Altered active transport of medications • Renal replacement therapies	• Reduction in renal clearance for renally eliminated drugs • Increase in renal clearance for renally eliminated drugs • Variable effect • Variable effect

AAG 5 a1 acid glycoprotein; AUC 5 area under the curve, ER 5 extraction ratio; Vd 5 volume of distribution.
This table is copied from Introduction to Drug Pharmacokinetics in the Critically Ill Patient by Brian S. Smith et al. (3)

1.1.1.3.1 ABSORPTION

Alterations in pharmacokinetics of drugs due to critical illness includes changes in the systemic absorption of orally administered drugs. Critically ill patients receive multiple oral medications in unadjusted doses, overlooking the changes in their systemic absorption and risking therapeutic failure. A recent review conducted in our lab regarding oral drug absorption in the ICU reported altered drug absorption in critically ill patients and suggested the need for alternative measures to lower the risk of therapeutic failure (4). These measures aiming to mitigate the alterations in drug absorption in critically ill patients include holding tube feeding around medication administration times, adopting alternative dosing regimens with higher doses of orally administrated drugs and using alternate routes of administration such as parenteral routes where possible (4).

Multiple drug-specific factors can affect drug absorption, including its particle size, solubility, lipophilicity, ionization, and dissociation rate (5). It has been well established in the literature that in states of hypotension and shock, the body physiologically responds by shunting blood to its vital organs, including the heart and the brain. Subsequently, blood flow to other systems, including the gastrointestinal tract is decreased.

Vasopressor use is one of the factors affecting absorption in critically ill patients. Studies have demonstrated that vasopressors, such as, dopamine, epinephrine, and norepinephrine, have different effects on both gastrointestinal perfusion and oxygen consumption (6). However, the impact of gastrointestinal perfusion on drug absorption has not been evaluated, and the impact of this on drug absorption is not well defined in the literature (7). Patient and drug specific factors may also further add to this variability. It is important to consider the general lack of data evaluating the impact of vasopressor use in critically ill adults on oral drug absorption (8). Intravenous drug delivery in critically ill patients receiving vasopressors is often used to ensure a patient receives the desired dose of a drug.

Delayed gastric emptying is also one of the aspects that complicate oral absorption in critically ill patients. Reasons for delayed or slowed gastric emptying include but not limited to surgery, postoperative ileus, trauma, head injury, burns, sepsis, and opiate use (9). Clinicians need to also be aware that delayed gastric emptying can delay the onset of the action of enterally administered drugs (10). Furthermore, feeding tubes are often used to facilitate enteral delivery in critically ill patients who are either mechanically ventilated or unable to swallow. Drugs

administered via feeding tube entail multiple challenges. For instance, drugs can adsorb to the plastic of the tube's internal lumen, impeding drug delivery. Tubes also bear the risk of clogging due to residual drug adhered to the lumen. Additionally, enteral feeding solutions tend to increase the pH of the stomach, which leads to reducing the absorption of drugs that require an acidic pH (11). Phenytoin is an example of medications that are subject to variable absorption in the presence of enteral feeding solutions. Additionally, first pass metabolism is an important factor contributing towards altered bioavailability of orally administered drugs in all patients, especially the critically ill. This is more pronounced considering the alterations in hepatic clearance since it is the primary site of first pass metabolism. Altered hepatic clearance is discussed in more detail in section 1.1.1.3.3.

1.1.1.3.2 DISTRIBUTION

Drug distribution is the process of disposition of a parent drug across the body's compartments such as the blood or the central compartment and the tissue compartment. The efficacy and/or toxicity of this drug highly relies on its ability to distribute and reach certain tissues. This is also a key concept to understand why there are instances of a weak or absent correlation between the plasma levels of a drug and its pharmacodynamic effect. Volume of distribution (VD) is a PK variable describing the relationship between the dose of a drug and the serum concentration reflecting it. Hydrophilic drug compounds tend to remain in the central compartment and are characterized with a lower Vd value close to 0.65 L/kg (12). In other words, the higher the Vd the more extensive the drug is distributed throughout the body's compartments. On the other hand, lipophilic drug compounds are characterized with a higher Vd to reflect their wider drug distribution in the tissue compartment. It is important to consider the ability of a particular drug to penetrate or distribute into tissues when assessing this drug therapy. Hydrophilic drugs generally remain in the plasma water volume, showing a Vd closely approximating 0.65 L/kg. However, lipophilic medications often will exhibit higher Vd.

Fluid resuscitation is an often-necessary intervention in many critically ill patients. The additional infused fluid volume leads to an increase the volume of the body's total water content, resulting in decreased serum concentrations of hydrophilic drugs. Furthermore, due to the increase in fluid volume, many patients with vasodilatory shock will also exhibit capillary leak syndrome. There is an increased potential for increased third spacing when these two phenomena occur simultaneously, leading to an increase in the interstitial volume and alterations in the intravascular volume which can increase or decrease. Increased Vd in

critically ill patients in comparisons to non-critically ill patients can affect numerous lifesaving hydrophilic drug classes, such as antimicrobials (13). Therapeutic drug monitoring and loading doses are strategies that are often employed to achieve the targeted serum concentrations when the Vd is increased (14, 15).

Alteration of plasma protein binding is another important factor affecting Vd and drug distribution. Albumin and α-1 acid glycoprotein (AAG) are the two most predominant plasma proteins that drugs are bound to. Acidic drugs, such as phenytoin bind to albumin. Basic drugs, such as lidocaine bind to AAG (16). Many conditions affect plasma protein levels in critically ill patients. Concentrations of AAG have been shown to increase in critically illness (17). Accelerated protein catabolism and increased vascular permeability are two examples that result in decreased albumin concentrations due to stress response or trauma (18, 19). These changes are especially concerning taking into consideration that many drugs frequently used in ICU settings are plasma protein bound. While therapeutic drug effects are attributed to the free or unbound drug fraction in most cases, it is important to consider in critically ill patients with hypoalbuminemia, that highly protein-bound drugs will have a greater fraction of free drug, leading to increased pharmacologic effects, even if total drug level remains unchanged. It is common practice while managing non-critically ill patients to monitor total drug concentrations which would be especially misleading in critically ill patients with low plasma protein levels.

To illustrate, midazolam, a sedative often used in the ICU, can be highly influenced by critical illness. A threefold increase in midazolam Vd was demonstrated in a cohort of critically ill patients, resulting in a prolonged half life. One proposed explanation for the increased Vd is hypoalbuminemia resulting in an increase in the free proportion of midazolam, which is a lipophilic medication readily distributed to the adipose tissues (20, 21). More interestingly, A linear relationship was shown between serum albumin concentration and the induction time of midazolam. Lower albumin concentrations associated with shorter time to induction, consistent with the notion that the lower serum albumin levels increase free midazolam levels leading to a quicker response (22). To summarise, highly albumin-bound drugs in hypoalbuminemia exhibit greater free proportions and potentially an increased pharmacologic effect as well as a greater risk for tolerability issues. The impact of hypoalbuminemia should be considered by clinicians when using highly albumin bound drugs. Dose adjustment or switching to an alternative agent with lower albumin binding could also be a valid option. Additionally, adjustments for decrements in albumin levels or substituting the measurement of

total drug levels for a direct measurement of free drug levels should be considered when using therapeutic drug monitoring in the setting of hypoalbuminemia.

Similarly, AAG plasma protein levels have been shown to increase in the acute phase inflammatory disease states (17). This increase would be important to consider when using AAG-bound medications drugs as this will result in a reduction in the circulating free drug levels. Morphine is an example of AAG-bound drugs where the Vd is reduced by approximately 40% and its clearance is reduced by more than 66%. The clinical implications of such pharmacokinetic alterations could mean prolonging the effects of morphine and increasing the risk of adverse drug reactions and side effects (23).

Lastly, among the pharmacokinetic alterations occurring in critically ill patients are changes in regional tissue perfusion. Hypoperfusion is a common complication in critically ill patients, where hemodynamic changes can adversely affect tissue perfusion, hence decreasing the delivery of hydrophilic drugs via blood passing through the capillary circulation. This, in turn, impairs drug delivery to the tissues and limits their efficacy at the site of action. This is especially true in the case of peripheral tissues and non-central organs with compromised blood supply. For instance, piperacillin into skeletal muscles and adipose tissues has been found to be impaired in septic shock patients (24). The research team in this study used micro-dialysis in patients with septic shock and compared the results to healthy controls. A staggering 5-to-10-fold reduction in the distribution of piperacillin into the skeletal muscles and adipose tissues was demonstrated in septic shock patients, despite the successful attainment of the targeted piperacillin plasma concentrations.

1.1.1.3.3 METABOLISM

Drugs are metabolized in a myriad of different body tissues, including the liver, kidneys, gastrointestinal tract (GIT), heart, lungs, brain and even the skin. The liver, however, is the predominant drug metabolism site. In the case of critical illness, hepatic enzyme activity is altered, serum protein concentration and blood flow to the liver are also changed. This can result in significant changes in the rate and extent of hepatic drug clearance. A good understanding of the physiologic changes surrounding critical illness, which affect drug metabolism is essential for clinicians to anticipate and mitigate changes in drug pharmacokinetics that can be reflected in adverse drug reactions or therapeutic failures.

Hepatic clearance is defined as the volume of blood that can be completely cleared of the drug per unit time by the liver (25, 26). The removal of drugs by the liver from the blood is directly proportional to the hepatic blood flow and the drug's hepatic extraction ratio. The hepatic extraction ratio is the fraction of the drug removed from the blood by the liver in one pass. Drugs can be classified as having high extraction ratio (>0.7), intermediate extraction ratio (0.3-0.7), or low extraction ratio (<0.3) (5). The hepatic clearance of high extraction ratio drugs such as fentanyl and midazolam depend mainly on the hepatic blood flow and is less affected by liver function changes. On the contrary, low extraction ratio drugs clearance such as phenytoin and warfarin hepatic clearance is less affected by hepatic blood flow changes and more dependent on liver function changes. Considering whether a drug exhibits a high or low hepatic extraction ratio is essential in predicting the effect changes in hepatic blood flow and liver enzyme activity might have on its hepatic drug clearance.

Hepatic drug metabolism consists of two phases. Phase 1 metabolism involves oxidation, reduction, and hydrolysis reactions aiming to alter the parent drug into either an active or an inactive drug metabolite or more than one metabolite. Phase 2 metabolism, on the other hand involves the addition of large polar molecules the parent drug molecule or its metabolite resulting from phase 1 metabolism. Phase 2 involves glucuronidation, sulfation, or acetylation reactions, converting the molecule to a more water-soluble form and hereby enhancing its solubility and subsequent elimination. Metabolites can be active, usually less potent than their parent compound, but can be more active or even toxic. The cytochrome P450 (CYP450) enzyme family is mainly responsible for phase 1 drug metabolism. The activity of CYP450 enzymes can be induced or inhibited by conditions or drugs critically ill patients are subject to (27). Moreover, many CPY450 enzymes, e.g., CYP2D6, CYP2C19, and CYP2C9 exhibit genetic polymorphisms that often lead to variability in the rates of intrinsic hepatic metabolism among patients.

Critically ill patients are often presenting with disease states that can affect the activity of hepatic metabolizing enzymes. It should be taken in consideration how alterations in CYP450 activity have the potential to prolong or reduce the therapeutic effects of parent drugs. Moreover, they can increase the burden of toxic metabolites, as well as delay the response of prodrugs that require hepatic metabolic activation. For example, the activity of the CYP450 enzyme in severe burn injury can become reduced significantly. Phase 2 metabolism, however, is typically is not affected in this case (28).

Another significant example of such conditions is renal dysfunction, which is known to alter the renal elimination of drugs through urine. But it can also impact the hepatic drug metabolism of drugs. Decreases in both phase 1 and phase 2 metabolism in the setting of renal dysfunction have been reported in animal studies (29). Both the drug uptake into hepatocytes and the biliary excretion of drugs, has been shown to decrease in the setting of kidney injury (30). In cirrhotic patients the number of functional hepatocytes is reduced which can in turn lead to a significant drop in hepatic enzyme metabolic activity (31). Cholestasis is another example where delays in the drugs biliary excretion has been shown to negatively affect CYP450 function (32). Trauma, surgery, and hemorrhagic shock are also conditions seen in critically ill patients where the subsequent inflammatory response has been shown to have different effects on CYP450 enzyme activity. Studies suggest a reduction in CYP3A4, CYP2C19, and CYP2E1 activity and an increase in CYP2C9 activity (33, 34).

Therapeutic hypothermia is a treatment often employed in the ICU aiming to lower the body temperature to reduce long-term injury such as in cardiac arrest. Therapeutic hypothermia can also affect CYP450 metabolic activity. Decrements in the hepatic clearance of phenytoin, midazolam, fentanyl, remifentanil, phenobarbital, and vecuronium have been reported in studies (35, 36). This reduction can be attributed to the reduced speed of chemical reactions, reduced enzyme affinity for the drug, or a combination of both. Lipid solubility, protein binding, hepatic blood flow are examples of other factors which can be altered due to hypothermia. These alterations continue to be changed during the rewarming phase, hence the importance of vigilant therapeutic drug monitoring in this setting especially with narrow therapeutic index drugs. The clinical impact of drug pharmacokinetic changes during hypothermia is still not strong enough to warrant changes to current drug regimens.

1.1.1.3.4 EXCRETION

The primary mechanism responsible for the renal clearance of most drugs is glomerular filtration. Generally, the renal clearance of drugs has a direct proportional relationship to the kidney's glomerular filtration rate (GFR). In critically ill patients however, acute kidney injury (AKI) is a common complication during the course of their stay. AKI can also be precipitated by numerous factors, leading to GFR reduction and subsequently decelerated renal drug clearance. Additionally, critically ill patients with comorbid chronic kidney disease of different stages require careful consideration in their dosing regimens. In both of these cases, using alternative dosing regimens or switching to non-renally cleared drugs are important alternative

measures in critically ill patients with AKI and/or CKD. Evidence suggests that patients with AKI receive higher doses of medications than the maximum recommended dose and are at a higher risk for experiencing ADEs (37, 38). Dose reduction are often required for maintenance doses in the case of renal impairment. However, it is important to consider that usual doses or higher loading doses of the same drugs may be required to account for increased Vd, as discussed in section 1.1.1.3.3.

However, although renal impairment is a fairly common in critically ill patients, it is important not to overlook instances where the renal clearance is accelerated or augmented. Normal GFR is commonly described as 120-130 mL/min/1.73 m^2, critically ill patients often exhibit GFR values much higher than normal range values. Subsequently, renal drug clearance is accelerated and the risk of therapeutic failure increases (39). Factors such as sepsis, trauma, surgery, burns, and vasopressors increase renal blood flow and subsequently increase renal drug clearance. This is especially important to consider with antimicrobials that are primarily renally eliminated, such as β-lactams and glycopeptides. Research recently showed a direct correlation between lower plasma drug levels and accelerated renal clearance in the critically ill (39). In these instances, modification of dosing regimens might be necessary if the drug is primarily renally eliminated. However, the decision to increase the dosing frequency or increase the dosing amounts depend on PD properties of the drug since serum concentrations do not always reflect PD targets. Augmented renal clearance (ARC) will be discussed in detail in Chapters 2 and 3.

Although not being primary processes involved in renal drug clearance, tubular secretion and reabsorption can also be altered in critical illness. Multiple transport systems are responsible for the disposition of organic anionic and cationic drug molecules in the kidneys. Tubular secretion and reabsorption of these medications takes place primarily in the proximal tubules, by the cells present on plasma cell membranes. Tubular secretion is an active process where drugs are being transported from the interstitial fluid side into the nephron lumen of through an anion-cation transport system that can be saturated. For instance, quinidine and digoxin if administered together, can result in higher than expected digoxin concentrations and increased risk of toxicity due to two molecules competing for the same transport proteins (40).

Tubular reabsorption is the process where the reabsorption of an ultra-filtrate occurs, subsequently increasing drug concentrations again in the tubule lumen and promoting the drug's passive diffusion into the plasma following the concentration gradient. For instance,

urine alkalization increases basic drugs' reabsorption trapping the drug in its non-ionized form. On the contrary, it enhances the elimination of acidic drugs by trapping the drug in its ionized form. An example of this is alkalinizing the urine to a pH of 7.5 using sodium bicarbonate to enhance the elimination of salicylates to mitigate the effects of an overdose.

In addition, approximately 4% of critically ill patients with AKI require renal replacement therapy (RRT) (41). Multiple RRT modalities, including hemofiltration, ultrafiltration, intermittent hemodialysis and peritoneal dialysis are used in these cases. Multiple factors affect drug clearance in this case including membrane properties, dialysate properties, and drug properties. Generally, large molecular weight drugs as well as drugs that are highly protein bound, and drugs with large Vd are less affected by RRT since they are less likely to be removed by RRT.

These discussed PK changes in critically ill patients can potentially augment or reduce the effect of the affected drugs, increasing the risks of either ADEs, therapeutic failures or both. However, multiple strategies have been incorporated into practice to mitigate the effect of PK alterations. These include gradually titrating IV infusions towards individualized end points, such as titrating vasopressors to target a specific mean arterial pressure (MAP). Sedatives are also titrated to a target pain score, and planned interruptions of sedative and analgesic infusions are made to prevent over-sedation and over-analgesia and facilitate mechanical ventilation weaning (42).

1.1.1.4 Altered pharmacodynamics (PD) in critical illness

PD describes the pharmacologic response resulting from the drug once it reaches its receptor or site of action. Critically ill patients, being a special group of patients where altered pathophysiology results in significant variability in their pharmacokinetic parameters which then also impacts on the pharmacodynamics. Poor clinical outcomes have often been associated with failure to achieve pharmacodynamic targets for some drugs, such as antimicrobials and antiepileptic drugs in augmented renal clearance. Therefore, it is important to consider the alterations involved in the critically ill and to use the knowledge of pharmacokinetic/pharmacodynamic properties of drugs to optimize dosing regimens not only to maximize effectiveness but also minimize and mitigate toxicity and reduce the risk of therapeutic failure.

Pharmacodynamic alterations in drug response could also occur independently from a pharmacokinetic precursor. For instance, hypothermia is sometimes used in patients post cardiac arrest and in neurocritical care. As discussed in section 1.1.1.3.3, therapeutic hypothermia's effects on drug pharmacokinetics by altering its metabolism and elimination. Moreover, hypothermia also affects drug response in a rather unpredictive fashion - unlike PK changes - with either reduced or no change in the potency, depending on drug class. Thus, intensivists should be aware of the complex interplay of alterations in drug metabolism, elimination and response on drug disposition and response during hypothermia. This includes close monitoring of drug levels when possible and the monitoring of drug outcomes such as the depth of neuromuscular blockade and the employment of sedation scores. The effect of hypothermia on the toxicity of a given drug level compared to normothermia, however, remains an area of ongoing research.

1.1.2 AUGMENTED RENAL CLEARANCE (ARC)

When assessing a patient's kidney function particularly in a critical care setting, clinicians typically consider one of two possibilities: either normal renal function, or renal impairment; with most of the attention paid towards dosing adjustments in the presence of impaired renal function and/or the use of renal replacement therapy. This conventional view might in fact be overlooking a third category of patients who may be exhibiting hyperfunctioning kidneys or what is known as augmented renal clearance (ARC). This phenomenon, while not yet fully understood, may potentially be the rationale behind a range of therapeutic failures for renally eliminated drugs (43-45). This is mainly due to the fact that ARC is typically undetected unless clinicians proactively monitor for its presence and the lack of solid evidence on the dosing of renally eliminated medications subject to an accelerated elimination, leading to subtherapeutic levels and sub-optimal outcomes.

In the recent years, there has been a growing number of reports recognizing the significance of ARC (46, 47).

1.1.2.1 DEFINITION OF ARC

ARC has most commonly been defined in the literature as a creatinine clearance (CrCl) higher than 130 ml/min/1.73m^2. However, there is not yet an agreed-upon cut-off for the CrCl above which a patient is diagnosed with ARC; nor a staging system for patients having CrCl more than 150 ml/min/1.73m^2 or even 200 ml/min/1.73m^2 analogous to renal impairment stages.

Studies vary in their definition of ARC in terms of CrCl cut-off. Most studies define ARC as CrCl ≥ 130 mL/min/1.73 m^2; other definitions used are CrCl ≥ 120 mL/min/1.73 m^2, CrCl ≥ 150 mL/min/1.73 m^2 , CrCl ≥ 140 mL/min/1.y m^2 , CrCl ≥ 155 mL/min/1.73 m^2 , CrCl ≥ 160 mL/min/1.73 m^2 , and CrCl ≥ 108 mL/min/1.73 m^2.

1.1.2.2 Pathophysiology of ARC

The pathophysiology of ARC is largely unknown, but it is thought to be closely tied to the vigorous sympathetic response associated with severe critical illness, alterations in vascular tone, cardiac output and major organs blood flow, resulting in a hyperdynamic state and augmented glomerular filtration rate (46, 48). This is in addition to the effects of administration of fluids and vasopressors aimed at maintaining organ perfusion (48, 49).

1.1.2.3 Prevalence of ARC

ARC prevalence has been reported to range from 18 to 80% in general critically ill population (46, 50-57). However, different patient sub-populations within critically ill patients are at different risks of developing ARC.

1.1.2.4 Risk factors of ARC

Younger age, polytrauma and lower severity illness have been identified as risk factors. The limited ability of CrCl estimating equations to accurately predict ARC has motivated the creation of scores with greater predictive ability for identifying patients at risk of ARC. Baptista et al. presented a model where the best diagnostic value for ARC was obtained using the combination of urinary creatinine < 45 mg/mL and age < 65 years, with a specificity of 0.88 but a low sensitivity of 0.60 (58). Udy et al. presented another score based on the results of a multivariate analysis, their score employed the modified SOFA score, admission post-trauma and age to predict ARC (59). Higher scores were strongly associated with a greater prevalence of ARC. Recently, Barletta et al. also developed the (ARCTIC) Augmented Renal Clearance in Trauma Intensive Care scoring system to predict ARC in trauma patients (60). They performed a multivariate analysis to identify independent predictors of ARC. The risk factors included in the final ARCTIC score were age below 56 years, age between 56 and 75 years, serum creatinine <0.7 mg/dL and male sex. An ARCTIC score of 6 or higher had a sensitivity of 0.84 and a specificity of 0.68 of predicting ARC. It's important to consider that all these studies selected patients with normal serum creatinine levels. Therefore, the application of

ARC scores may not apply in patients with serum creatinine higher than 1.3 mg/dL even though the actual creatinine levels are not being included in the scores. Scores to detect patients at risk of ARC are a practical tool to use in ICUs to help proactively identify patients at the highest risk of ARC, and warrant the need to measure urinary CrCl to definitively diagnose those patients.

However, the developed scoring tools were generated based on general critically ill/trauma population rather than patients with severe neurological illnesses potentially not capturing neurocritical care patients with additional risks for ARC.

1.1.2.5 Implications of ARC

The presence of ARC in critically ill patients may have a negative impact on the attainment of therapeutic levels of many drugs. Almost all the scarce references published about this research question are focused on antimicrobial therapy, where ARC is very important because it could condition not only the drug efficacy but also the development of resistance. ARC can also influence the pharmacokinetic profile of antimicrobial drugs that are renally cleared and known to have a direct correlation between their renal clearance and CrCl, such as beta lactams, vancomycin or aminoglycosides. According to their activity pattern, antimicrobial drugs can be classified into three groups: concentration-dependent killing along with prolonged effects (aminoglycosides, fluoroquinolones, polymyxins, daptomycin or metronidazole), time-dependent activity with no or very short persistent effects (b-lactams) and concentration-independent killing with prolonged persistent effects (tetracyclines, tigecycline, macrolides, azithromycin, clindamycin, linezolid, chloramphenicol, trimethoprim, sulphonamides and vancomycin). For the first and the third groups, the PK/PD indexes that best correlated with efficacy are the maximum serum concentration (Cmax)/minimum inhibitory concentration (MIC) ratio or the area under the concentration-time curve (AUC)/MIC ratio, because the prolonged persistent effects protect against regrowth when the active drug concentration falls below the MIC. For the second group, time-dependent activity, the PK/PD index that best correlated with efficacy is the duration of time that free antimicrobial concentrations exceeded the MIC.

1.1.3 ANEURYSMAL SUBARACHNOID HEMORRHAGE (ASAH)

1.1.3.1 Epidemiology

Aneurysmal SAH accounts for 5% of all strokes and 85% of all spontaneous subarachnoid haemorrhages. The overall global incidence of aSAH follows a decreasing trend. The global incidence of aSAH has decreased from 10.2 in 100,000 to the 6.1 in 100,000 population in the last 30 years. Moreover, aSAH incidence also varies by geographic location. The changes in incidences of aSAH are thought to be related to the higher age of the population and genetic component (61, 62).

Although aSAH is more common in males at a younger age, females have a higher incidence of aSAH in the elderly population. With each year increase in age beyond the age of 35 years, the chances of cerebral aneurysm bleeding increase in by 1.03 folds. Despite the current advancements in diagnosing and managing aSAH medically and surgically, aSAH is responsible for significantly higher mortality, morbidity, and disease burden out of all stroke patients. The mortality due to aSAH is approximately 40% in the first 30 days, and the survivors' favorable outcome is less than 25% (61, 62).

1.1.3.2 Etiology and Risk Factors for Increased aSAH

Numerous factors and diseases contribute to the aetiology of the development of a cerebral aneurysm and its rupture, resulting in aSAH. **Table (1.2)** summarizes the etiological factors and associated disease conditions with aSAH.

2.TABLE 1.2: THE AETIOLOGICAL FACTORS AND ASSOCIATED DISEASE CONDITIONS WITH ASAH (63)

Infectious arterial vasculitis	**Mycotic (infectious) aneurysm**
	Meningovascular lues
	Lyme disease
	Gnathostomiasis (Gnathostoma spinigerum)
Immune vasculitis	Primary CNS angiitis
	Polyarteritis nodosa
	Wegener's vasculitis
	Churg-Strauss syndrome
	Behçet's disease
Other cerebrovascular diseases	Arteriovenous angioma
	Dural arteriovenous fstula
	Spinal arterial aneurysm
	Intracranial arterial dissection
	Venous sinus thrombosis
	Cerebral amyloid angiopathy
	Moyamoya disease
Tumour	Intracranial and intraspinal tumour
Haematology	Sickle cell anaemia
Drugs	Anticoagulants and thrombolytic therapy
Substance abuse	Cocaine and amphetamine

This table is copied from Ahmed AE GA, Mohamed AO, Khair B. Aneurysmal subarachnoid hemorrhage. ICU Book. 2017:73-99. (63)

Among the modifiable risk factors involved in the development and rupture of cerebral aneurysms, are smoking, hypertension, dyslipidemia, alcohol and recreational drug abuse, and low body mass index (BMI). Among the non-modifiable risk factors involved in an increased aSAH risk are sex, familial disorders and connective tissue disorders.

1.1.3.3 PATHOPHYSIOLOGY OF CEREBRAL ANEURYSMS

Cerebral aneurysms are classified based on their pathogenesis and their shape form. The saccular aneurysm is the most common form and is commonly called the berry aneurysm, due to the berry-shaped or multi-lobe appearance. Saccular aneurysms are spontaneously formed and are responsible for 85% of aSAH cases. Tumours, trauma, and infections are among the contributing risk factors in the formation of cerebral aneurysms. Bacterial or fungal infections

can also cause focal necrotic areas on the arterial wall resulting in the formation of an aneurysm. Another type of aneurysms are fusiform aneurysms. These are spindle-shaped bulgings on the artery wall, caused most often secondary to atherosclerosis. Dissecting aneurysms are a third type of cerebral aneurysms and are caused by the dissection of the vessel wall either secondary to a traumatic injury or are spontaneously formed.

The exact mechanism of a cerebral aneurysm's formation is unclear. However, the initiating factors are both pathological and structural changes in the vessel wall composition. Additional predisposing genetic factors, environmental factors, and epidemiological factors also further contribute to the cerebral aneurysm formation.

1.1.3.4 Aneurysms and The Cerebral Circulation

Approximately 85% of cerebral aneurysms occur in the anterior cerebral circulation. Moreover, 20% of patients will develop multiple aneurysms, most commonly located bilaterally at the mirror site. As the aneurysm develops, a neck and dome are formed. Aneurysm rupture occurs at the dome site as the dome wall progressively thins and tears. Factors that further increase the risk of the aneurysm rupture are aneurysms diameter > 7 mm, tip of the basilar artery aneurysms, bifurcations aneurysms or aneurysms formed at the origin of posterior communicating arteries (PCOMM). Following the initial rupture of the aneurysm, a small amount of blood escapes into the subarachnoid space triggering the initial headache. However, there are cases where the blood can not be detected in computerised tomography (CT) leading to the patient getting initially discharged then admitted later with more significant aSAH and more severe or persistent symptoms. Therefore, the initial headache is often referred to as a sentinel headache. The signs and symptoms following ruptured cerebral aneurysms arise either due to the mass effect or the blood present in the subarachnoid and ventricular spaces (64).

Aneurysm rupture due to anterior communicating artery (ACOMM) or middle cerebral artery (MCA) bifurcation causes bleeding into the surrounding brain tissues leading to intracerebral haemorrhage (ICH). This in turn gives rise to pressure-related symptoms such as hemiparesis, and aphasia. While the blood present in the subarachnoid and ventricular spaces leads to hydrocephalus, cerebral vasospasm, and cerebral ischemia (64). The risk of re-bleeding from the ruptured aneurysm is at its peak in the initial 7 days post aSAH. This is due to the natural thrombolysis mechanism which displaces the clot plug from the rupture site. Rebleeding in these cases leads to higher morbidity and mortality (64). Moreover, due to obstruction to the flow of cerebrospinal fluid (CSF), acute hydrocephalus can occur hours after aSAH, late

hydrocephalus can also occur around 2 weeks post aSAH due to blockage of CSF absorption in the subarachnoid villi by the blood in subarachnoid and ventricular space. Additionally, cerebral vasospasm risk peaks from the occurrence of the ictus and until day 14 post-ictal. The highest incidence however, occurs on day seven post-ictal. Cerebral vasospasm occurs due to spasm of the major cerebral arteries causing increasing headaches, declines in the level of consciousness, and focal neurological deficits that may not have been present post-ictal. If the vasospasm persists, cerebral ischemia, infarctions, and brain oedema are among the complications (64). The primary and secondary brain injuries secondary to the ruptured aneurysm, can also be complicated by non-neurological organ dysfunction such as cardiac complications, electrolyte disturbances, and deep venous thrombosis, leading to higher morbidity and mortality (64).

1.1.3.5 Diagnosis and Grading of aSAH

1.1.3.5.1 DIAGNOSIS OF ASAH

As one of the most devastating neurosurgical emergencies, aSAH has a staggering mortality rate of ~ 60% in the first 180 days and < 16% of aSAH survivors return to their previous state. The two most important strategies to prevent aSAH complications and improve outcome are early diagnosis and immediate intervention. Unfortunately, early diagnosis of aSAH during initial assessment is extremely challenging, especially considering the limitations of radiological investigations as well as lumbar punctures which increases the risk of misdiagnosis (65, 66).

Diagnostic investigations are done when aSAH is suspected and for high-risk patients. Diagnostic investigations include Lumbar puncture (LP), Magnetic resonance image (MRI), non-contrast brain scan, Computed tomography angiography (CTA), and Digital subtraction angiography (DSA).

1.1.3.5.1 GRADING OF ASAH

It is important to consider that aSAH is a heterogeneous disorder demonstrating a varied range of initial presentations and final outcomes. The outcome of aSAH is affected by many patient-related factors, disease-related factors, and surgical/medical interventions. The clinical features of the initial presentation of aSAH significantly affect the prognosis. A substantial amount of research has been conducted to develop aSAH grading scales to quantify and grade the severity of the initial neurological insult. The aim of grading aSAH is to aid clinical decisions and

predict the outcome. Currently, the World Federation of Neurological Surgeons (WFNS) Scale, Hunt and Hess Scale, the Fisher Scale and the Glasgow Coma Score (GCS) are the most widely used aSAH grading scales (65, 67, 68). Higher grades on Hunt and Hess and WFNS scales reflect higher hemorrhage severity and poor neurological function and are associated with higher overall mortality. Higher grades on Fisher scale, however, reflect a thicker layer of blood, and is predictive of symptomatic vasospasm after SAH (65, 67, 68).

3. TABLE 1.3 aSAH GRADING SCALES

TABLE 1.3.A WFNS SCALE

WFNS Grade	Glasgow Coma Scale Score	Motor Deficit
1	15	
2	13-14	Absent
3	13-14	Present
4	7-12	
5	3-6	Present or absent

WFNS, World Federation of Neurological Surgeons

TABLE 1.3.B HUNT AND HESS SCALE

Hunt and HESS Grade *	Description
1	Asymptomatic or mild headache
2	Cranial nerve palsy and moderate to severe headache, nuchal rigidity
3	Focal neurologic deficit, confusion, lethargy
4	Stuporous, hemiparesis, early decerebrate posture
5	Comatose, decerebrate rigidity, morbid appearance

* One point is added for associated systemic illnesses that may include: hypertension, diabetes mellitus, atherosclerosis, chronic obstructive pulmonary disease, or documented severe vasospasm.

TABLE 1.3.C FISHER SCALE

Fisher Grade	Blood on CT scan
1	No SAH identified
2	Diffuse or vertical layers <1 mm thick
3	Localized clot and/or vertical thickness >1 mm
4	Intracerebral or intraventricular hemorrhage

CT, computed scan; SAH, subarachnoid hemorrhage

1.1.3.6 Surgical Management of aSAH

In patients who survive the initial bleed, the aneurysm site is targeted to prevent re-bleeding and other complications. Coiling endovascular treatment by has emerged as a less invasive technique compared to surgically clipping of the aneurysm (69). Interventional Neuroradiology (INR) is a subspecialty of neurosurgery, radiology, and neurology where imaging-based techniques that are minimally invasive are used for the management of central nervous system diseases. Currently, endovascular treatment is recommended for all aSAH especially aneurysms in the posterior circulation and cavernous carotid aneurysms. This is mainly due to its minimally invasive nature and the shorter ICU/hospital stay and quicker patient recovery associated with it. Non-ruptured aneurysms with high bleeding risks justifying the intervention are also recommended to be endovascularly treated. Similarly, High risk patients with multiple co-morbidities such as old age and bad neurological status are also recommended to be endovascularly treated (70).

The main disadvantage to coiling aneurysms is that high rate of aneurysm recurrence associated with it. The recurrence rate post coiling is approximately 6% in large aneurysms and 30% in giant aneurysms which leads to the need of a complementary treatment. Additionally, the cost of endovascular coiling is higher than surgical clipping of cerebral aneurysms (71).

The current guidelines for management of aSAH recommend both endovascular coiling and clipping, where endovascular coiling should be considered first. The current trends suggest that endovascular techniques will be the future of cerebral aneurysms management (72).

1.1.3.7 Complications of aSAH

The high morbidity and mortality associated with aSAH has a devastating impact on the brain and other organs. Despite the significant improvement in its management strategies in the last thirty years, the mortality rate before admission and 30 days after admission remains high, approximating 15%, and 35% respectively. aSAH outcomes largely depends on the severity of initial ictus and the following complications. aSAH course in the ICU ranges from a few days to a few weeks and is typically accompanied by neurological and non-neurological complications. Neurological complications include vasospasm, delayed cerebral ischemia, re-bleeding, brain edema, hydrocephalus, and seizures. Non-neurological complications include but not limited to fever, hyperglycemia, anemia, cardiac complications, electrolyte disturbances, and deep venous thrombosis (73, 74).

Complications of aSAH significantly determines the prognosis. Re-bleeding in the early phase is the most severe complication and requires immediate re-treatment. Acute hydrocephalus is another complication that requires CSF diversion, commonly achieved using extraventricular drain (EVD). Vasospasm and DCI commonly occur between day 3 and 21. Patients at high risk for developing DCI are closely monitored with bedside transcranial Doppler (TCD) ultrasonography. If DCI is suspected, immediate perfusion-weighted imaging is required.

1.1.3.8 Prognosis of aSAH

A devastating 60% of aSAH patients die within the initial 6 months of the initial bleed. Numerous complications increase the morbidity and mortality risk in aSAH patients. The combination of the primary neurological insult following the aneurysm rupture and the secondary neurological and non-neurological complications thereafter, aggravates the overall outcome. Outcome prediction is pivotal for effective management of aSAH. However, further research is needed to develop the use of biomarkers for aSAH prognostication. Large size cerebral aneurysms and advanced age signals poorer prognosis. Early diagnosis, intervention, and administration of nimodipine are the mainstay of preventing further brain injury and optimize the outcome.

1.1.3.10 The Role of Nimodipine in the pharmacotherapy of aSAH

Calcium channel blockers play a crucial role in reducing the incidence of post-aSAH arteriopathy, thereby improving patients' functional outcomes. Nimodipine acts by inhibiting the influx of calcium ions through voltage-gated L-type calcium channels of vascular smooth muscles, therefore, causing vasodilation. Nimodipine has been shown to dilate blood vessels and prevent vasoconstriction particularly in small arterioles whose diameters are 70-100µm (75, 76). Despite that, nimodipine reported benefits in SAH patients were not related to its effects on vasospasm suggesting other potential mechanisms. Furthermore, nimodipine elevates adenosine levels in the central nervous system with subsequent inhibition of the excitatory neurotransmitter glutamate, a potential neuroprotective mechanism (77). Administered as a standard regimen of 60 mg every 4 hours for 21 days, nimodipine is the only oral calcium channel blocker that has been shown to decrease the rates of DCI and improve neurological outcomes in randomized controlled trials (and hence recommended by clinical guidelines (Class I; Level of Evidence A) (72, 74, 78-80).

Oral nimodipine is available in soft gelatin capsules and oral liquid forms in the United States (US). In Canada the only dosage form currently available is nimodipine tablets. Conscious and capable patients swallow whole nimodipine tablets or capsules. In Canadian institutions, for those patients who are unable to swallow whole tablets due to mechanical ventilation, altered mental status, dysphagia, or other reasons, nursing staff crush nimodipine tablets, suspend it in water and administer it through enteral feeding tubes (FT). However, the tablets should not be crushed prior to administration as this may decrease its intended bioavailability and clinical effectiveness according to the nimodipine manufacturer's monograph (81). In US institutions where the nimodipine soft gelatin capsules are available, the liquid is often siphoned from the soft gelatin capsule shell in clinical practice. This is done either by the nursing staff in the intensive care unit (ICU) and administered through FT by oral syringes, or by the pharmacy staff to prepare an extemporaneously prepared liquid which is then measured in oral syringes and administered through FT. In US institutions where a nimodipine oral liquid product (Nymalize®) is available, it is directly administered through the FT. The dose in this case is either measured from 6mg/ml nimodipine bottles or premeasured 30 mg and 60 mg oral syringes. It is not clear, however, whether these formulations and techniques of administration are equivalent and equally well tolerated. Anecdotal evidence suggests that patients receiving the nimodipine oral liquid product exhibit a higher incidence of diarrhea. In addition, some studies suggest that that the bioavailability of nimodipine is reduced when administered through FT, especially in more severe aSAH (82, 83).

1.2 RATIONALE

Being a special population, critically ill patients need special consideration to optimize their care and minimize therapeutic failures and ADRs. To that end, it is essential to recognize the pharmacokinetic and pharmacodynamic alterations in this patient population as they play a vital role in guiding clinical decision making. While standardized drug regimens may offer a reasonable starting point for most drug treatments. Therapeutic drug monitoring (TDM) techniques and alternate drug regimens maybe necessary for target attainment in critically ill patients. Hence the importance of understanding the PK/PD alterations in critically ill patients. Multiple knowledge gaps are needed to be addressed in order to guide these alternative drug regimens and TDM strategies. Our research addressed the knowledge gap pertaining to the prevalence and risk factors of ARC in different critically ill patient populations, summarized the available evidence on drug dosing requirements and performed a direct comparison

between different formulations and techniques of administration of nimodipine in neurocritical care patients aiming to determine the optimum method of delivery of nimodipine in aSAH patients.

1.3 OBJECTIVES

Overall objectives of this thesis were:

- To summarize the available evidence pertaining the prevalence and risk factors of ARC in critically ill patients. This objective was achieved by conducting a systematic review and meta-analysis of prevalence and risk factors of ARC in the critically ill to aid in the early identification of those at risk, to make for a timely medication optimization.
- To address the concern of inadequate dosing in critically ill adult patients with ARC. This objective was achieved by summarizing the currently available evidence in a narrative review and to provide clinicians with dose recommendation insights for renally eliminated agents in adult critically ill patients with ARC.
- To investigate and compare the effects of different nimodipine administration delivery techniques on patient safety and efficacy endpoints. This objective was achieved by conducting a retrospective chart review cohort study. The primary aim of the study was to investigate the impact of nimodipine administration techniques on the safety in patients with SAH. The secondary aim was to compare the impact of nimodipine mode of administration on outcomes in patients with SAH.

1.4 OVERALL HYPOTHESES

In ARC research projects, we hypothesized that the propensity to develop ARC will be inequivalent in different critically ill subpopulations. Neurocritical care and Trauma ICU patients will have higher prevalence of ARC compared to other ICU patients. In aSAH projects, after adjusting for disease severity and other confounders, we hypothesized that the prevalence of diarrhea and hypotension in patients who received liquid nimodipine will higher than those who received the crushed tablets or liquid drawn from capsules.

1.5 LINKAGE

This thesis contains multiple projects that are all part of larger research looking into the pharmacokinetic and pharmacodynamic alterations in critically ill patients. Firstly, we researched the prevalence and risk factors of ARC, a condition that accelerates the renal clearance of renally eliminated drugs. We hypothesized that different critically ill patient populations have different propensities towards developing ARC. Moreover, we researched the impact of ARC on dosing requirements in critically ill patients and the effect of ARC on target attainment in multiple drug treatments. Secondly, we researched the potential difference between different formulations and techniques of nimodipine delivery and their potential association with poorer safety and efficacy endpoints in patients with aSAH, a debilitating neurocritical care emergency.

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CHAPTER 2 PREVALENCE AND RISK FACTORS OF AUGMENTED RENAL CLEARANCE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Purpose: Kidney function assessment in the critically ill overlooks the possibility for hyperfunctioning kidneys, known as augmented renal clearance (ARC), which could contribute to therapeutic failures in the intensive care unit (ICU). The aim of this research is to conduct a systematic review and meta-analysis of prevalence and risk factors of ARC in the critically ill, a step towards early identification of those at risk, allowing timely medication optimization.

Methods: MEDLINE, Embase, Cochrane Library, CINAHL, Scopus, ProQuest Dissertations and Theses Global databases were searched on October 27, 2020. We included studies conducted in critically ill adults that reported the prevalence and/or risk factors of ARC. We evaluated studies quality using Joanna Briggs Institute appraisal tool. Case reports, reviews, editorials and commentaries were excluded. We generated a random-effects meta-analytic model using the inverse variance method and visualized the pooled estimates using forest plots. (Prospero registration: CRD42021246417).

Results: Seventy studies were included. The pooled prevalence (95% CI) was 39%(34.9-43.3). Prevalence for neuro, trauma, mixed and sepsis ICUs were 74(55-87), 58(48-67), 36(31-41) and 33(21-48), respectively. Age, male sex and trauma were associated with ARC with pooled OR(95% CI) of 0.95(0.93-0.96), 2.36(1.28-4.36), 2.60(1.21-5.58), respectively. Limitations included variations in ARC definition, inclusion and exclusion criteria and studies design.

Conclusion: ARC is prevalent in critically ill patients especially neurocritical care and trauma ICU population. Young age, male sex and trauma are risk factors for ARC in those with apparently normal renal function. Further research on optimal dosing of drugs in the setting of ARC is warranted.

Keywords: augmented renal clearance, critically ill, glomerular hyperfiltration, neurocritical care, GFR.

2.1 INTRODUCTION

Critical illness is unique for its complex nature which very often requires a range of professional expertise to provide the most comprehensive care possible, hence the need for a multidisciplinary approach. When assessing a patient's kidney function particularly in a critical care setting, clinicians typically consider one of two possibilities: either normal renal function, or renal impairment; with most of the attention paid towards dosing adjustments in the presence of impaired renal function and/or the use of renal replacement therapy. This conventional view might in fact be overlooking a third category of patients who may be exhibiting hyperfunctioning kidneys or what is known as augmented renal clearance (ARC). This phenomenon, while not yet fully understood, may potentially be the rationale behind a range of therapeutic failures for renally eliminated drugs (1-3). This is mainly due to the fact that ARC is typically undetected unless clinicians proactively monitor for its presence and the lack of solid evidence on the dosing of renally eliminated medications subject to an accelerated elimination, leading to subtherapeutic levels and sub-optimal outcomes. The pathophysiology of ARC is largely unknown, but it is thought to be closely tied to the vigorous sympathetic response associated with severe critical illness, alterations in vascular tone, cardiac output and major organs blood flow, resulting in a hyperdynamic state and augmented glomerular filtration rate (4, 5). This is in addition to the effects of administration of fluids and vasopressors aimed at maintaining organ perfusion (5, 6). ARC has most commonly been defined as a creatinine clearance (CrCl) higher than 130 ml/min/1.73m^2 (7-9). However, there is not yet an agreed-upon cut-off for the CrCl above which a patient is diagnosed with ARC; nor a staging system for patients having CrCl more than 150 ml/min/1.73m^2 or even 200 ml/min/1.73m^2 analogous to renal impairment stages.

In the recent years, there has been a growing number of reports recognizing the significance of ARC (4, 10). ARC prevalence has been reported to range from 18 to 80% in general critically ill population (4, 11-18). However, reported studies varied in their patient population, sample sizes, inclusion and exclusion criteria and ARC definition, thus impeding accurate identification of ARC prevalence and risk factors among intensive care unit (ICU) patients. Therefore, the aim of this research is to conduct a systematic review and meta-analysis of the available literature on ARC and attempt to provide pooled estimates of its prevalence and contributing risk factors in various

critically ill populations. To our knowledge, this is the first combined systematic review and meta-analysis of ARC in the critically ill. Our work represents a step towards defining the prevalence and risk factors of ARC, facilitating early identification of those at risk for ARC allowing timely medication optimization.

2.2 METHODS

This review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (19). Prospero protocol registration number: CRD42021246417.

2.2.1 Database Search Method

The medical librarian (JYK) developed comprehensive searches on October 27, 2020 in the following databases: MEDLINE (via Ovid), Embase (Ovid), Cochrane Library (Wiley), CINAHL, Scopus, and ProQuest Dissertations and Theses Global. Search strategies included keywords and controlled vocabulary related to augmented renal clearance in critical care (**S1 Supplementary Table 2.1**). There were no date or language limits applied. To better facilitate the screening process, the research team used Covidence, a web-based systematic review screening tool (www.covidence.org). In addition to subscription databases, the first 200 results from Google Scholar were evaluated for inclusion. Bibliographies from included studies were also reviewed.

2.2.2 Inclusion and Exclusion Criteria

We included human studies conducted in critically ill adult populations that reported ARC prevalence and/or risk factors in our analysis. Studies also needed to have a clearly defined criteria for ARC and reported what method was used to measure or calculate CrCl. We excluded studies that focused on pediatric patients or patients with renal dysfunction (e.g., acute kidney injury), as well as studies conducted in populations that would have altered renal elimination (e.g., cystic fibrosis, burn patients). Case reports, reviews, editorials and commentaries were also excluded.

2.2.3 Study Screening

Study screening and selection were conducted independently by SHM and AS using Covidence. This was completed in two steps: (1) An Initial title and abstract screening was done. (2) The relevant abstracts were then introduced to a full-text review. The authors used discussion to come to a consensus about any arising conflicts during the screening process. Non-English language studies were translated using the Google Translate web-based document translator, when possible.

2.2.4 Data Extraction

The data were extracted independently by AS and FH from each of the included studies and then cross-checked to verify the integrity and completeness of the information. Any inconsistencies were resolved by discussion with SHM. The extracted data included: Study design, exclusion and inclusion criteria, intensive care unit (ICU) type, ARC definition, diagnoses, patient demographics and ARC prevalence and risk factors contributing to ARC along with their measures of association. For studies that did not specify a cut-off for ARC but reported individual CrCl values, a value of > 130 ml/min/1.73m^2 was applied to determine ARC prevalence.

2.2.5 Risk of Bias Assessment

All the included studies were individually assessed for their risk of bias by employing the "Joanna Briggs Institute Critical Appraisal Instrument for Studies Reporting Prevalence Data" (https://jbi.global/sites/default/files/2020-08/Checklist_for_Prevalence_Studies.pdf). This critical appraisal tool assessed nine aspects to assess the quality of each study: (1) Was the sample frame appropriate to address the target population? (2) Were study participants sampled in an appropriate way? (3) Was the sample size adequate? (4) Were the study subjects and the setting described in detail? (5) Was the data analysis conducted with sufficient coverage of the identified sample? (6) Were valid methods used for the identification of the condition? (7) Was the condition measured in a standard, reliable way for all participants? (8) Was there appropriate statistical analysis? (9) Was the response rate adequate, and if not, was the low response rate managed appropriately?

2.2.6 Data Analysis

The statistical analysis was performed by FH in consultation with a biostatistician using the package in R Statistical Software (Version 4.0.3, R Foundation for Statistical Computing, Vienna, Austria) and RStudio Interface (Version 1.3.1093, RStudio, Boston, MA, USA) (20-22). For the meta-analysis of prevalence, the function metaprop was used to pool the meta-analytic estimate of prevalence of ARC using the reported number of cases and the total number of subjects in each included trial. We generated a random-effects meta-analytic model using the inverse variance method for weights, DerSimonian-Laird estimator (23, 24) for T^2 as the measure of true between-study variance, Jackson method for confidence interval of T^2 (25) and a Logit transformation to the calculated individual studies prevalence. Additionally, we examined I^2 statistic (the estimate of residual heterogeneity that is not due to sampling variation alone) and Cochrane Q statistic

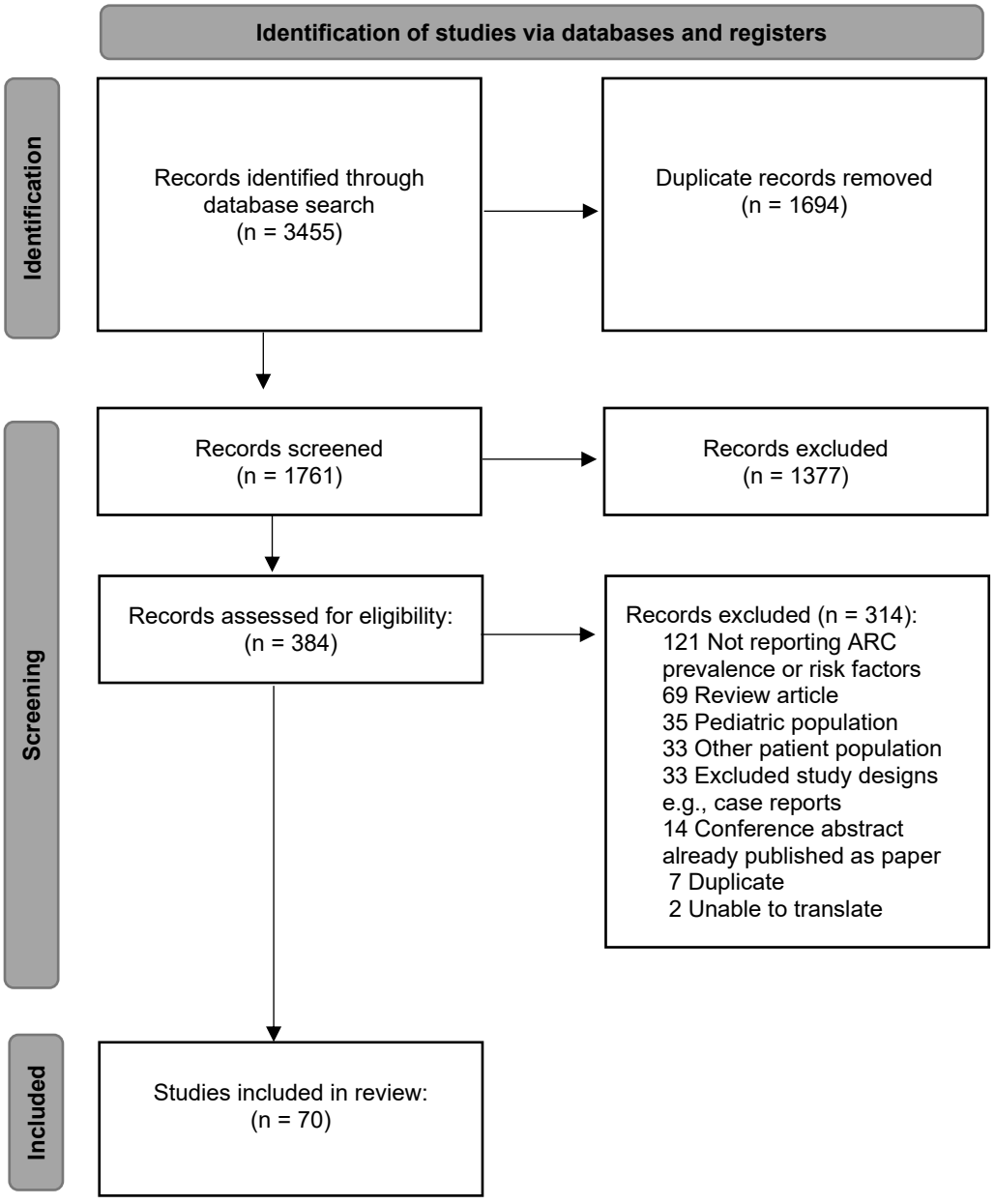
(describes the total heterogeneity not stemming from random error). The analyses were then visualized graphically using forest plots. To assess the risk of publication bias, Egger's test (26) was conducted and tested for significance, and a funnel plot was used to visualize the individual studies' effect sizes against their estimate of precision. Studies reporting data for more than one distinct patient populations, each population was entered separately in the meta-analysis. For the meta-analysis of risk factors, the function "metagen" from the package "meta" in R was utilized. It was used to synthesize the meta-analytic odds ratio size of the commonly reported risk factors: age, male sex, trauma, Sequential Organ Failure Assessment (SOFA) score, Acute Physiology and Chronic Health Evaluation (APACHE II), and diabetes on ARC from their reported odds ratios of multivariate logistic regression.

2.3 RESULTS

2.3.1 Study Selection and Characteristics

As depicted in **Figure 2.1**, comprehensive searches identified 3455 records across all databases. A total of 1761 records remained for screening after the removal of duplicate records. After title and abstract screening, 384 records were subject to a full-text screening ending with a total of 70 included records Observational studies constituted the majority of collected evidence at 68 studies, along with 1 randomized controlled trial (27) and 1 prospective non-randomized interventional study (28). **Table 2.1** depicts a summary of the studies included in this systematic review and meta-analysis of prevalence and risk factors. **Table 2.2** depicts a summary of the studies reporting other risk factors not-included in the meta-analysis. **S2 Supplementary Table 2.2** depicts the risk of bias assessment of the included studies using the Joanna Briggs Institute critical appraisal instrument for studies reporting prevalence data. The average score of all studies was 94.4%.

1.FIGURE 2.1. FLOW CHART OF THE STUDY SEARCH AND SCREENING



4.TABLE 2.1. SUMMARY CHARACTERISTICS OF STUDIES INCLUDED IN ARC SYSTEMATIC REVIEW AND META-ANALYSIS OF PREVALENCE AND RISK FACTORS.

Author	Year	Population	Study Design	Clearance Determination*		ARC definition ≥*	N	Prevalence (%)	Male n (%)	Age*	Main Diagnoses	Identifiable risk factors	Renal Impairment
Joynt et al.(29)	2001	Sepsis ICU	prospective observational	m	24h Urine	130	11	36.4	7(63.6)	45±16	Sepsis	not reported	Excluded
Fuster-Lluch et al.(30)	2008	Mixed ICU	prospective observational	c	NKF	120	89	18.0	67(75.3)	60.5(18-86)	Several	not reported	Excluded
Baptista et al. Portugal (31)	2011	Mixed ICU	prospective observational	m	24h Urine	130	120	35.8	87(72.5)	55.9±21.1	Sepsis, Trauma	not reported	Excluded
Baptista et al. Australia (31)	2011	Mixed ICU	prospective observational	m	8h Urine	130	89	48.3	64(71.9)	40±18.9	Sepsis, Trauma	not reported	Excluded
Minville et al. PolyTrauma (32)	2011	Trauma ICU	retrospective observational	m	24h Urine	120	144	54.9	108(75)	42±18	Poly trauma ICU	Age Trauma	Excluded
Minville et al. Non-PolyTrauma (32)	2011	Trauma ICU	retrospective observational	m	24h Urine	120	140	19.3	88(62.8)	58±17	Non trauma ICU	Age Trauma	Excluded
Lautrette et al.(33)	2012	Sepsis ICU	retrospective observational	m	24h Urine	140	32	25.0	15 (46.8)	54±16	Infectious meningitis	not reported	Included
Baptista et al.(34)	2012	Sepsis ICU	prospective observational	m	24h Urine	130	93	39.8	69(74.2)	58(34-75)	Trauma, Sepsis, Other.	not reported	Excluded
Grootaert et al.(35)	2012	Mixed ICU	retrospective observational	m	24h Urine	120	1317	29.6	247(18.8)	59(48-67)	Several	not reported	Unclear
Carlier et al.(36)	2013	Mixed ICU	prospective observational	m	24h Urine	130	61	31.1	51(85)	56(48-67)	Infections	not reported	Excluded
Udy et al. Sepsis(37)	2013	Sepsis ICU	prospective observational	m	6h Urine	130	43	39.5	22(51.2)	46.3±17.1	Sepsis	Age, Trauma, mod. SOFA	Included
Udy et al. Trauma(37)	2013	Trauma ICU	prospective observational	m	6h Urine	130	28	85.7	23(82.1)	36.4±13.9	Trauma	Age, Trauma, mod. SOFA	Included
Minkute et al.(38)	2013	Mixed ICU	retrospective observational	c	C&G	130	36	50.0	29(80.5)	49.75(21)	Several	not reported	Excluded
Udy et al.(39)	2013	Mixed ICU	prospective observational	m	8h Urine	120	110	53.6	70(63.6)	50.9±16.9	Several	not reported	Excluded
Claus et al.(40)	2013	Mixed ICU	prospective observational	m	24h Urine	130	128	51.6	86(67.2)	59(49-67.8)	Several	Age, APACHEII, Male sex	Excluded
Baptista et al. group 2 (41)	2014	Sepsis ICU	prospective observational	m	8h Urine	130	25	40.0	17(68)	59.9±17.2	Several	not reported	Excluded
Baptista et al. group 1 (41)	2014	Sepsis ICU	retrospective observational	m	8h Urine	130	79	36.7	52(66)	57.8±15.5	Several	not reported	Excluded

Baptista et al.(42)	2014	Mixed ICU	prospective observational	m	8h Urine	130	54	55.6	39(72.2)	54.2±16.9	Several	not reported	Excluded
Campassi et al.(43)	2014	Mixed ICU	prospective observational	m	24h Urine	120	363	28.4	103(28.4)	56.5±16	Several	Age, DM	Excluded
Udy et al. Multicenter (44)	2014	Mixed ICU	prospective observational	m	8h Urine	130	281	65.1	178(63.3)	54.4(52.5-56.4)	Several	not reported	Excluded
Adnan et al. (45)	2014	Mixed ICU	prospective observational	m	24h Urine	130	49	38.8	37(75.5)	34(24-47)	Trauma, others	not reported	Excluded
Ruiz et al. (46)	2015	Mixed ICU	prospective observational	m	24h Urine	130	360	33.3	246(68.3)	50±19	Polytrauma, Non-polytrauma	Age, Polytrauma	Excluded
Huttner et al. (47)	2015	Sepsis ICU	prospective observational	c	C&G	130	100	64.0	75(73.5)	46±10.55	Several	not reported	Excluded
Dias et al. (48)	2015	Neuro ICU	retrospective observational	c	C&G	130	18	88.9	16(89)	41±15.6	TBI, Polytrauma	not reported	Included
May et al. (49)	2015	Neuro ICU	prospective observational	m	24h Urine	130	20	100.0	8(40)	52.14±10.36	SAH	not reported	Excluded
De Waele et al. (50)	2015	Mixed ICU	retrospective observational	m	24h Urine	130	1081	55.9	687(63.6)	62(20.5)	Several	not reported	Excluded
Steinke et al. (51)	2015	Surgical ICU	retrospective observational	m	18h Urine	130	100	16.0	61(61)	66(57-74)	Infection, others	not reported	Included
Chu et al. (52)	2016	Sepsis ICU	retrospective observational	c	C&G	130	148	47.3	97(65.5)	55.3±14.9	Infection	not reported	Excluded
Kawano et al. (53)	2016	Mixed ICU	prospective observational	m	8h Urine	130	111	38.7	62(55.9)	67(53-770	Several	Age, DM, Weight, APACHEII, others	Excluded
Saour et al. (54)	2016	Trauma ICU	retrospective observational	c	MDRD	120	775	61.3	581(75)	37.7±17	Several	not reported	Excluded
Abd El Naeem et al. (55)	2017	Mixed ICU	prospective observational	m	24h Urine	130	50	40.0	32(64)	71±15	Sepsis, others	not reported	Excluded
Barletta et al. (56)	2016	Trauma ICU	retrospective observational	m	12h Urine	130	65	69.2	48(74)	48±18	TBI, other traumas	not reported	Unclear
Declercq et al. Trauma Surgery (57)	2016	Surgical non-ICU	prospective observational	m	8h Urine	130	129	34.9	75(58)	62(46-75)	Trauma surgery	Age, Sex	Excluded
Declercq et al. Abdominal Surgery (57)	2016	Surgical non-ICU	prospective observational	m	8h Urine	130	103	30.1	76(74)	63(51-71)	Abdominal surgery	Age	Excluded
Hirai et al.(3)	2016	Mixed ICU	retrospective observational	c	C&G	130	292	16.4	185(63.4)	72(62.8-82)	Several	Age, Brain injury, others	Excluded
Ehmann et al.(58)	2017	Mixed ICU	prospective observational	c	C&G	130	48	10.4	27(56.3)	55.5(32-69.9)	Sepsis, others	not reported	Included
Burnham et al.(59)	2017	Sepsis ICU	retrospective observational	c	MDRD	130	494	5.5	260(52.6)	59.9±15.8	Sepsis	Age, sepsis severity, others	Included
Carrie et al. RVI (60)	2018	Trauma ICU	retrospective observational	m	24h Urine	130	30	66.7	27(90)	48(32-67)	Polytrauma, TBI	not reported	Excluded
Udy et al. TBI(61)	2017	Neuro ICU	prospective observational	m	8h Urine	150	11	100.0	9(81.8)	37(24-49)	TBI	not reported	Included

Barletta et al. ARCTIC(62)	2017	Trauma ICU	prospective observational	m	12h Urine	130	133	66.9	101(76)	48±19	TBI, fractures, others	Age, Sex	Excluded
Dhaese et al.(63)	2018	Surgical ICU	prospective observational	m	8h Urine	130	110	31.8	75(68.2)	60±14.4	Several	not reported	Excluded
Tamatsukuri et al.(64)	2018	Sepsis ICU	prospective observational	m	8h Urine	130	17	35.3	11(64.7)	60(19.5)	Sepsis	not reported	Excluded
Carrie et al. main study(2)	2018	Sepsis ICU	prospective observational	m	24h Urine	150	79	55.7	62(78)	52(33-68)	Sepsis	not reported	Excluded
Carrie et al. PIP/TAZO(65)	2018	Sepsis ICU	prospective observational	m	24h Urine	130	59	61.0	47(80)	53±21	Polytrauma, non-trauma surgery	not reported	Excluded
Carrie et al. TBI(66)	2018	Neuro ICU	prospective observational	m	24h Urine	130	223	73.1	184(83)	36(23-57)	TBI, VAP	not reported	Included
Kawano et al.(67)	2018	Sepsis ICU	retrospective observational	c	Japanese equation	130	280	6.8	145(51.8)	74(64-83)	Infection	Age, Sex, DM, others	Excluded
Tsai et al.(68)	2018	Mixed ICU	prospective observational	m	8h Urine	130	97	32.0	60(46)	50±18	Sepsis, Trauma, others	not reported	Excluded
Wong et al.(69)	2018	Mixed ICU	prospective observational	c	C&G	130	330	58.2	198(60)	53.4±17.7	Infection	not reported	Included
Ishii et al.(70)	2018	Mixed ICU - Non-ICU	retrospective observational	c	Japanese equation	120	177	26.0	109(62)	73(63-80)	Tumors, Brain injury	not reported	Excluded
Udy et al. BLINGII(27)	2018	Sepsis ICU	randomized controlled trial	m	8h Urine	130	254	17.7	151(59.4)	63(52-71)	Infection	not reported	Included
Ollivier et al(71)	2019	Mixed ICU	prospective observational	m	24h Urine	150	21	85.7	17(81)	36(27-60)	Trauma, Surgery	not reported	Included
Wu et al.(72)	2019	Mixed ICU	prospective observational	m	24h Urine	130	100	46.0	66(66)	60(47-71)	Several	Age, SOFA, Weight, others	Excluded
Aitullina et al.(73)	2019	Mixed ICU	retrospective observational	c	not reported	108	97	16.5	65(67)	63(51-73.5)	Several	not reported	Included
Weber et al.(74)	2019	Oncology ICU	prospective observational	m	24h Urine	120	24	37.5	14(58.3)	59(39.8-63.5)	Febrile neutropenia	not reported	Excluded
Izumisawa et al. Hematomalignancy(75)	2019	Oncology Non-ICU & ICU	retrospective observational	c	C&G	120	261	8.4	146(55.9)	65.6±13.6	Hematologic malignancy	not reported	Excluded
Izumisawa et al. Non-Malignancy(75)	2019	Oncology Non-ICU & ICU	retrospective observational	c	C&G	120	261	11.1	175(67)	67.2±16.9	Non malignancy	not reported	Excluded
Chu et al.(76)	2019	Mixed ICU - Non-ICU	retrospective observational	c	C&G	130	315	59.0	213(67.6)	56.3(19)	Infection	not reported	Excluded
Villanueva et al.(77)	2019	Trauma ICU	retrospective observational	c	C&G	160	70	50.0	57(81.4)	47.5(31-61)	TBI, Spinal injury	not reported	Excluded
Morbitzer et al. aSAH(78)	2019	Neuro ICU	prospective observational	m	8h Urine	130	50	94.0	16(32)	57.2±10.7	SAH	not reported	Excluded
Morbitzer et al. ICH(78)	2019	Neuro ICU	prospective observational	m	8h Urine	130	30	50.0	18(60)	70±13.7	ICH	not reported	Excluded
Mulder et al.(79)	2019	Trauma ICU	retrospective observational	m	24h Urine	130	207	57.0	141(68)	45±20	Trauma	Age, Sex, others	Excluded

Bricheux et al(80).	2019	Hospitalized	retrospective observational	c	C&G	130	300	26.7	203(68)	59±17	Abdominal infection, Pneumonia	not reported	Unclear
Helset et al.(81)	2020	Mixed ICU	prospective observational	m	24h Urine	130	83	25.3	61(73.5)	54.5(38-63)	Several	not reported	Unclear
Gijsen et al.(7)	2020	Mixed ICU	retrospective observational	m	24h Urine	130	4267	35.2	2669(62.5)	65(54-74)	Several	not reported	Excluded
Barrasa et al.(82)	2020	Mixed ICU	prospective observational	m	10h Urine	130	17	23.5	12(70.6)	61.7	Several	not reported	Included
Lannou et al. (83)	2020	Neuro ICU	prospective observational	m	24h Urine	130	60	53.3	53(88)	48(32-60)	TBI, Multiple trauma	not reported	Excluded
Aréchiga-Alvarado et al. (84)	2020	Mixed ICU	prospective observational	c	C&G	130	63	50.8	56(88.9)	33.25(47.5)	Infection	not reported	Unclear
Carrie et al. Amikacin(85)	2020	Surgical ICU	retrospective observational	c	C&G	130	70	20.0	53(76)	65(51-73)	Infection	not reported	Unclear
Saito et al.(86)	2020	Oncology ICU	retrospective observational	c	own predictive model	130	133	41.4	80(60.2)	64(25-86)	Haematologic malignancies	Age, Sex, Scr, others	Included
Lannou et al. Editorial Letter(87)	2020	Neuro ICU	retrospective observational	m	24h Urine	155	30	76.7	not reported	33(47-57)	Brain trauma	not reported	Included
Cojutti et al.(28)	2020	Oncology ICU	prospective interventional	c	MDRD	130	75	36.0	47(62.7)	58(51-66)	Febrile neutropenia	not reported	Included
Brown et al.(88)	2020	Hospitalized	retrospective observational	m	8h Urine	130	85	25.9	43(50.6)	55(41-70)	Several	not reported	Excluded
Chen et al.(89)	2020	Neuro ICU	retrospective observational	c	C&G	130	104	25.0	71(68.3)	44.5(18.5)	Cerebral tumor, Stroke, TBI	not reported	Excluded
Baptista et al.(90)	2020	Mixed ICU	retrospective observational	m	8h Urine	130	454	24.9	293(64.5)	66(52-76)	Several	Age, Sex, Trauma, others	Included
Nei et al.(91)	2020	Mixed ICU	retrospective observational	c	CKD-EPI	130	368	4.1	208(56.5)	66.8(55.7-76.6)	TBI, Trauma, Sepsis, others	Age, ICH, SOFA, Trauma, others	Included

APACHE II = Acute Physiology and Chronic Health Evaluation; ARC = Augmented Renal Clearance; aSAH = aneurysmal subarachnoid hemorrhage; CG = Cockcroft Gault equation; CKD-EPI = Chronic Kidney Disease Epidemiology; CrCl = creatinine clearance; ICH = intracranial hemorrhage; ICU = intensive care unit; MDRD =modification of diet in renal disease method; NKF = national kidney foundation equation; SAH = subarachnoid hemorrhage; SAPS II = Simplified Acute Physiology Score; SCr = serum creatinine; SOFA = sequential organ failure assessment score; TBI = traumatic brain injury. *Age reported in median (IQR) or mean ± SD, ARC cut-off reported in 130 mL/min/1.73 m^2, Clearance Determination method: m = measured, c = calculated.

5.TABLE 2.2. SUMMARY CHARACTERISTICS OF INDIVIDUAL STUDIES REPORTING OTHER RISK FACTORS.

Author	Year	Population	Sample Size	Clearance Determination	Identified Risk Factor(s)	Odds Ratio (95% CI)	Study inclusion in prevalence meta-analysis
Hirai et al.(3)	2016	Mixed Hospital	292	Calculated	Febrile Neutropenia	2.76 (1.11 - 6.67)	✓
					Fluid Infusion ≥ 1500 ml/day	2.53 (1.27 - 5.16)	
					Traumatic Brain Injury	5.11 (1.49 - 17.57)	
Nei et al.(91)	2020	Mixed ICU	368	Calculated	Charlson Comorbidity Index	0.80 (0.16 - 1.00)	✓
					Intracerebral Hemorrhage	2.82 (1 - 69.1)	
Kawano et al.(53)	2016	Mixed ICU	111	Measured	Post-Operative Without Sepsis	0.28 (0.07 - 1.04)	✓
Wu et al.(72)	2019	Mixed ICU	100	Measured	Loop Diuretics	0.32 (0.11 - 0.93)	✓
					Age < 50	4.02 (1.54 - 10.51)	
Udy et al.(37)	2013	Mixed ICU	71	Measured	Age </= 50	28.6 (4.4 - 187.2)	✓
Ramos et al.(92)	2017	Mixed ICU	36	Measured	24h Sodium Excretion	0.99 (0.98 - 1.00)	✗
Saito et al.(86)	2020	Oncology Hospital	133	Calculated	Serum Creatinine	0.89 (0.83 - 0.94)	✓
					Leukemia	9.4 (2.4 - 36.8)	
					Fever	2.4 (0.78 - 7.1)	
Burnham et al.(59)	2017	Sepsis ICU	494	Calculated	African American Ethnicity	3.45 (1.40 - 8.50)	✗
					Sepsis Severity	0.54 (0.30 - 0.97)	
Mulder et al.(79)	2019	Trauma ICU	207	Measured	Packed RBC Transfusion	0.31 (0.15 - 0.66)	✓
Eidelson et al.(93)	2018	Trauma ICU	154	Measured	Admission Hematocrit	1.18 (1.04 - 1.33)	✗
Barletta et al.(62)	2017	Trauma ICU	133	Measured	Serum Creatinine < 0.7 mg/dL	12.5 (3 - 52.6)	✓
					Age < 56	58.3 (5.2 - 658.9)	
					Age 56 - 75	13.5 (1.2 - 151.7)	

2.3.2 ARC Definition

Of the 70 included studies, 68 studies reported prevalence data. Studies varied in their definition of ARC in terms of CrCl cut-off. Most studies [52 records (76.5%)] defined ARC as CrCl ≥ 130 ml/min/1.73m^2; other definitions used were CrCl ≥ 120 ml/min/1.73m^2 [9 records (13.2%)], CrCl ≥ 150 ml/min/1.73m^2 [3 records (4.4%)], CrCl ≥ 140 ml/min/1.73m^2 [1 record (1.5%)], CrCl ≥ 155 ml/min/1.73m^2 [1 record (1.3%)], CrCl ≥ 160 ml/min/1.73m^2 [1 record (1.5%)], and CrCl ≥ 108 ml/min/1.73m^2 [1 record (1.5%)].

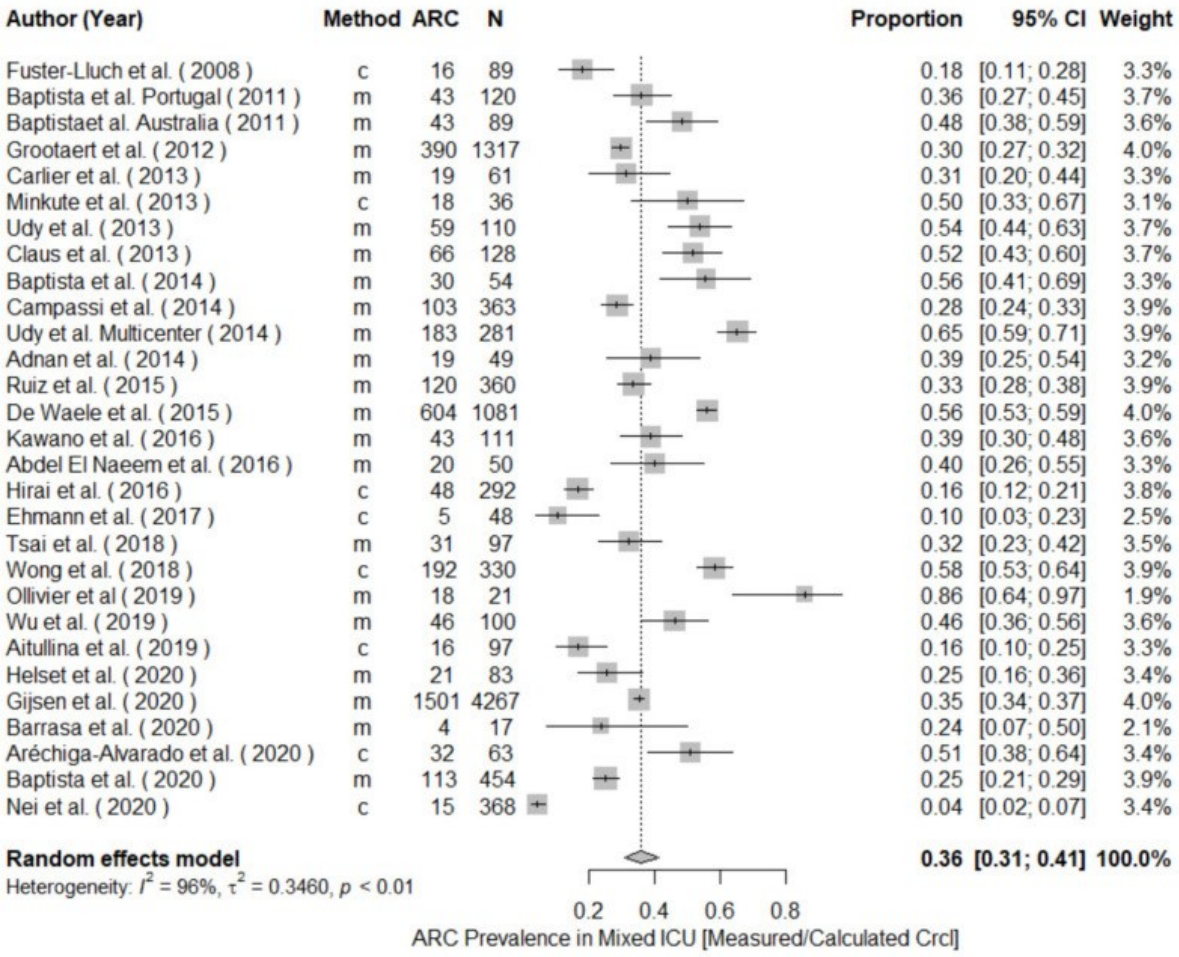
2.3.3 ARC Prevalence

Reports on the prevalence of ARC in this meta-analysis ranged between 4% and 100% in various critically ill populations; with an interquartile range of 25.9-55.8%, which suggests that ARC has a very common occurrence. Our meta-analysis of prevalence included 68 studies representing 76 samples: 29 (38.2%) from mixed ICUs, 14 (18.4%) from sepsis ICUs, 9 (11.8%) from neuro ICUs, 9 (11.8%) from trauma ICUs, and 15 (19.7%) including patients from surgical, oncology, and other critically ill and non-critically ill hospitalized patients **(Table 2.1)**. CrCl determination methods varied among studies where 52 (68.4 %) studies measured CrCl utilizing 6-24h urine collection method and 24 (31.6%) studies calculated CrCl using various equations. Among the studies that calculated CrCl, the majority used Cockcroft & Gault's formula (n=15).

The meta-analysis of prevalence of all included studies yielded a pooled prevalence of 39% (34.9%-43.3%) including patients from mixed, neuro, sepsis, trauma, surgical, and oncology critical care units; as well as non-ICU patients. The highest ARC occurrence was detected in neurocritical care patients with a 74% pooled prevalence across the 9 studies (**Figure 2.3A**), followed by 58% in trauma ICUs across 9 studies (**Figure 2.3B**), 36% in mixed ICUs across 29 studies (**Figure 2.2**), 33% in sepsis ICUs (**Figure 2.4A**), and 27% in the other patient populations collectively (**Figure 2.4B**). A meta-analysis of ARC prevalence only in studies that measured CrCl yielded a prevalence of 44.26% (39.91-48.69) while in studies that calculated mathematical estimates of CrCl, the pooled prevalence was 28.3% (19.91-38.52) showing a stark underestimation in the case of calculated CrCl (**S3 Supplementary Figure 2.1**). To assess the risk of publication bias, a funnel plot was used to visualize the individual studies' effect sizes against

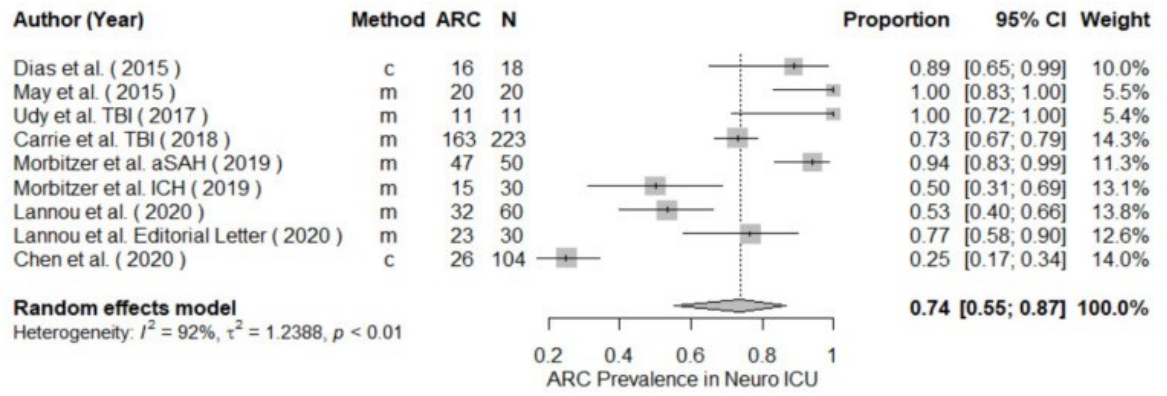
their estimate of precision (**Figure 2.5**). Egger's test (26) was conducted to test for funnel plot's asymmetry; the result was insignificant (p-value > 0.05), suggesting no publication bias.

2.FIGURE 2.2 FOREST PLOT OF THE PREVALENCE OF ARC IN MIXED INTENSIVE CARE UNIT (ICU) POPULATION.

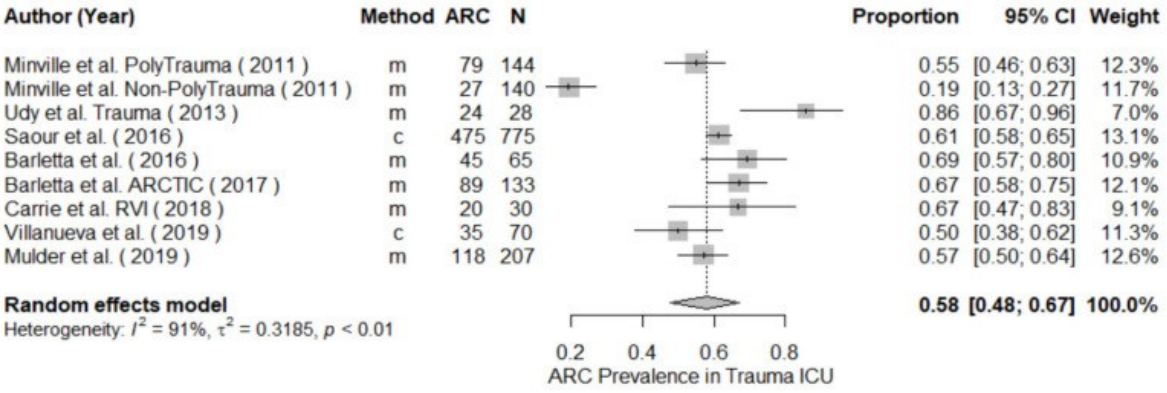


3.FIGURE 2.3. FOREST PLOT OF THE PREVALENCE OF ARC IN NEUROCRITICAL CARE (A) AND TRAUMA INTENSIVE CARE UNIT (ICU) POPULATION (B)

A



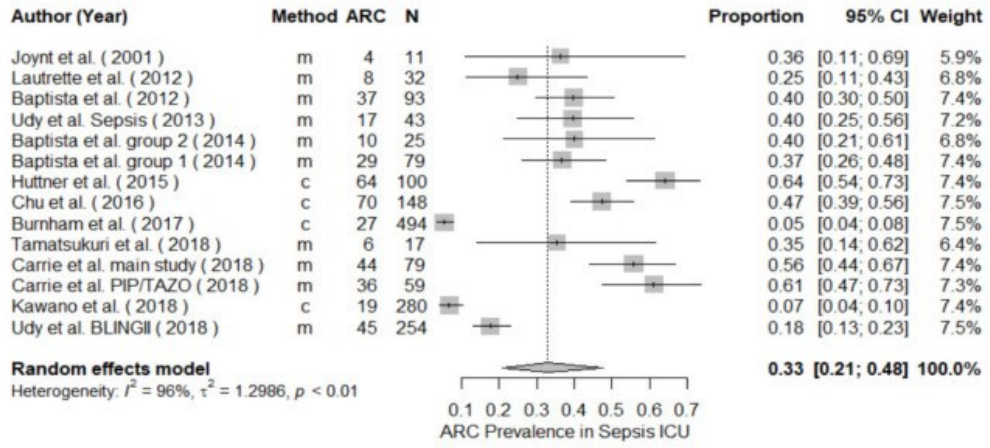
B



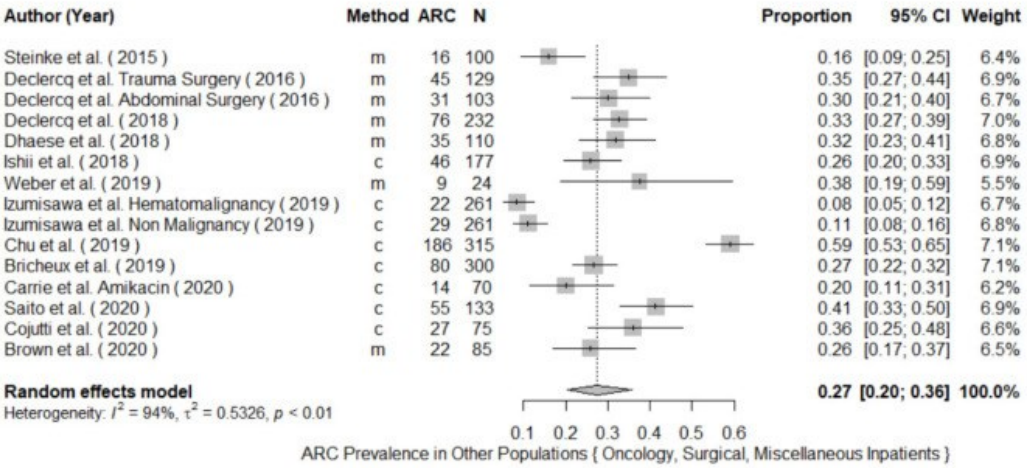
Clearance Determination method: m = measured, c = calculated; CI, confidence interval; N, study size.

4.FIGURE 2.4. FOREST PLOT OF THE PREVALENCE OF ARC IN SEPSIS INTENSIVE CARE UNIT (ICU) (A) AND OTHER POPULATION (B).

A

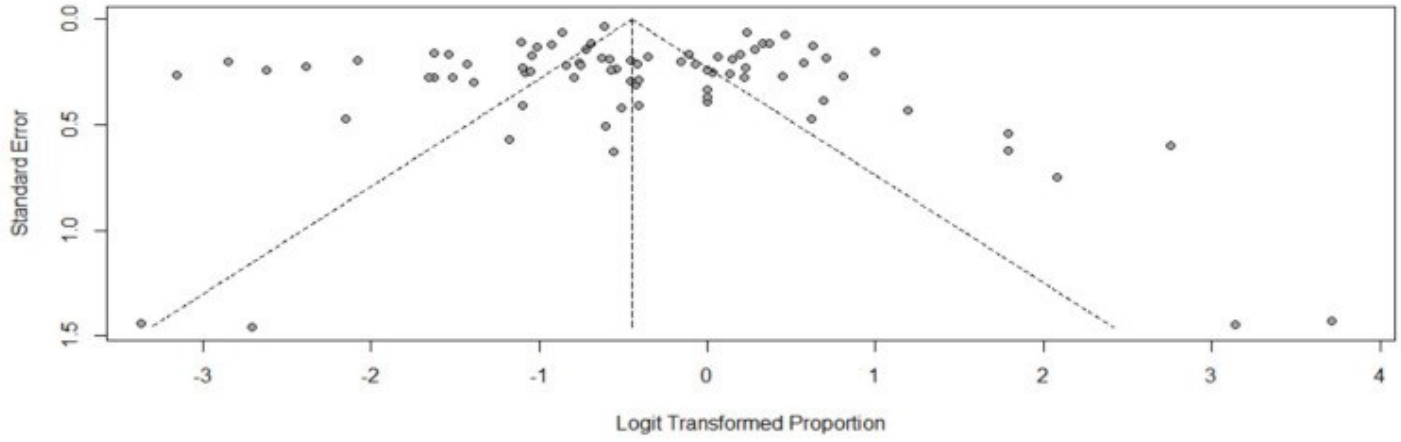


B



Clearance Determination method: m = measured, c = calculated; CI, confidence interval; N, study size.

5.FIGURE 2.5. FUNNEL PLOT OF STUDIES REPORTING PREVALENCE.

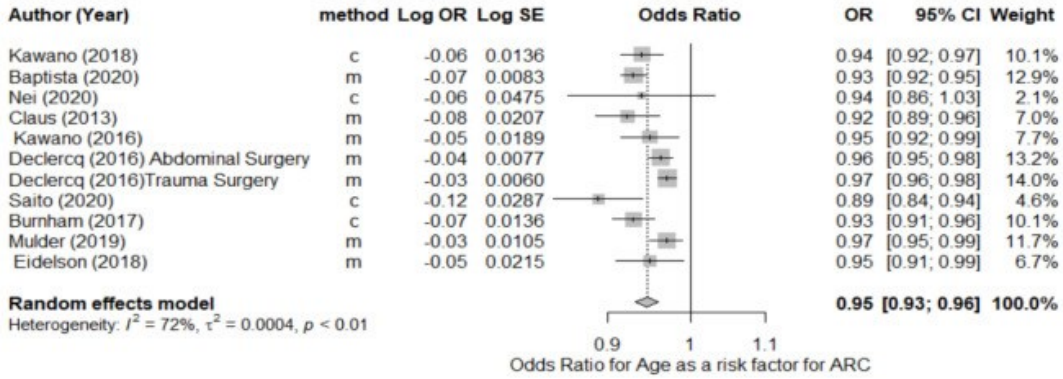


2.3.4 ARC Risk Factors

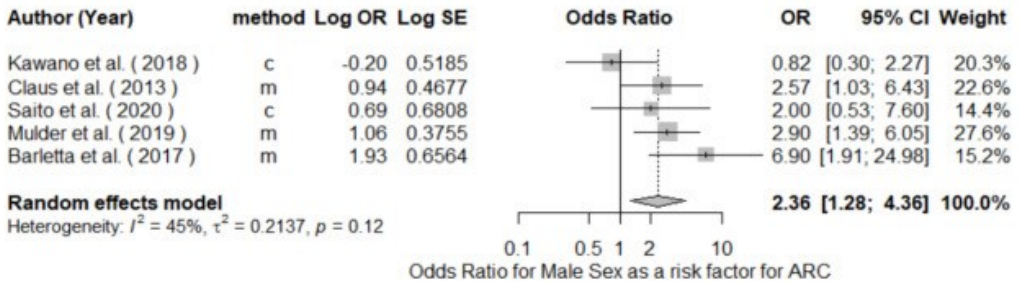
Reported risk factors included in the meta-analysis were age (as a continuous variable), male sex, trauma, SOFA and APACHEII disease severity scores, and diabetes. Among the reported risk factors, age, male sex and trauma were significantly associated with ARC with pooled odds ratio (95% CI) estimates of 0.95 (0.93-0.96), 2.36 (1.28-4.36), and 2.60 (1.21-5.58), respectively (**Figure 2.6**). SOFA, APACHEII and diabetes were not significantly associated with ARC with pooled odds ratio (95% CI) estimates of 0.86 (0.7301-1.0112), 1.00 (0.9471-1.0589) and 1.21 (0.4623-3.1689), respectively (**S4 Supplementary Figure 2.2**).

6.FIGURE 2.6. FOREST PLOT OF RISK FACTORS FOR AUGMENTED RENAL CLEARANCE.

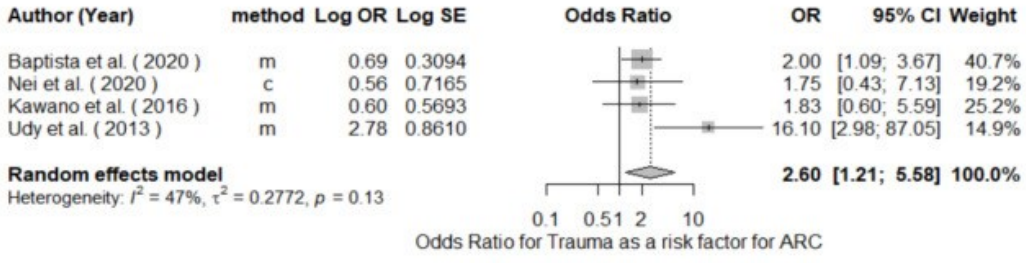
A



B



C



A, age (as continuous variable); B, male sex; C, trauma. Clearance Determination method: m = measured, c = calculated; CI, confidence interval; OR, odds ratio; SE, standard error.

2.4 DISCUSSION

ARC is a phenomenon where renal clearance is accelerated beyond normal range, it has also been referred to as glomerular hyperfiltration or enhanced renal clearance. ARC bears the risk of causing therapeutic failure of predominantly renally cleared drugs, which could be especially detrimental in critically ill populations. Numerous studies have described the association between ARC and higher rates of failure to attain therapeutic levels and compromised effectiveness of various drugs and the need for a more frequent administration and/or higher dosages. Standard doses of renally eliminated medications are typically used in patients with "normal" renal function. However, pharmacodynamic targets that are consistently obtained in other populations with typical dosing are not met in the presence of ARC. Studies suggested that ARC might be associated with subtherapeutic concentrations of antimicrobials and other drugs, (34, 94-96) antimicrobial therapy failure,(97) increased odds of recurrent infections,(18) and poor seizure control (98). Our systematic review and meta-analysis demonstrated the common occurrence of ARC in critical care settings with higher prevalence among neurocritical care and trauma patients compared to mixed ICU population. In addition, risk factors consistently found to be associated with ARC includes age, male sex, and trauma. The differences in the pooled ARC prevalence demonstrates that different critically ill populations are not at an equivalent risk for ARC and highlights the importance of screening for ARC in select patient populations as well as the need to develop new screening tools that accounts for these risk differences. To our knowledge, this is the first combined systematic review and meta-analysis of the prevalence and risk factors of ARC.

In our random effects meta-analysis for ARC prevalence, patients with neurocritical care population demonstrated the highest prevalence of ARC (74%). ARC incidence has been reported to range much higher in neurocritical care patients compared to general critically ill population (4, 11-18). To illustrate, in a study of 20 traumatic brain injury (TBI) patients, 85% had ARC (14). In a study of patients with hemorrhagic stroke, ARC has been reported in 50% of intracerebral hemorrhage (ICH) (n=30) and 94 % of subarachnoid hemorrhage (n=50) patients (16). In addition, ICH has been found to predict ARC in a retrospective study of heterogenous ICU patients, supporting the notion that neurological injury pose additional ARC risk (91). This could be attributed to the possibility that patients with neurological injuries might have additional ARC

risks. Neurocritical care patients tend to be relatively younger patients with single comorbidities and otherwise unimpaired organ systems and lower incidence of renal impairment. Furthermore, neurological injury could play an additional role in the pathophysiology of ARC; however, further studies are needed to confirm such association (48, 99).

The employment of an accurate determination method for glomerular filtration rate is essential for ARC screening and diagnosis. Although using serum creatinine to assess kidney function has limitations, CrCl measurement using 8-24h urine collection is the most agreed upon accurate method for the measurement of renal function in the clinical setting without the need of administrating an exogenous substance such as inulin. Moreover, due to the impracticality of routine and frequent measurement of CrCl in clinical settings, calculating CrCl using mathematical estimations derived from population parameters are often employed to allow for a more rapid determination. Commonly used formulae used to draw mathematical estimates of CrCl include the Cockcroft Gault equation (CG), Modification of Diet in Renal Diseases (MDRD), and Chronic Kidney Disease-Epidemiology (CKD-EPI). Each of those methods have their own merits and downfalls. Several studies assessed the relative accuracy of different mathematical estimates of CrCl in patients exhibiting ARC. It has been found that all mathematical estimations of CrCl grossly underestimate the actual CrCl when compared with their respective measured CrCl in patients with ARC (31, 39, 42, 45, 46, 51, 56, 100-102). Similarly, we found that the mathematical estimations of CrCl grossly underestimated the prevalence in ARC when compared to measured CrCl. To illustrate, the meta-analysis of prevalence of ARC in the same population (mixed ICU patients) was 23% in studies using mathematical estimates whereas studies using measured CrCl showed a 42% prevalence. Therefore, we recommend obtaining a patient's measured CrCl at least once on admission for a more judicious assessment if they are at risk for ARC. Special consideration must also be taken in immobile patients, children, burn patients or patients with conditions causing lower muscle mass or amputations to account for the reduced production of creatinine in these cases which could result in falsely low serum creatinine levels leading to incorrect diagnosis of augmented renal clearance.

It has been consistently shown in studies reporting risk factors of ARC that ARC patients tend to be younger males (<50 years old) with lower critical illness severity scores. These patients also

tend to have single organ impairment with unimpaired kidney function and a history of recent trauma. In our analysis, among the reported risk factors, age, male sex, and trauma were significantly associated with ARC with pooled odds ratio (95% CI) estimates of 0.95 (0.93-0.96), 2.36 (1.28-4.36), and 2.60 (1.21-5.58), respectively. The aforementioned risk factors have been utilized to develop clinical prediction tools needed for early identification of patients at higher risk for developing ARC. An ARC scoring system with 60% sensitivity and 95% specificity was introduced by Baptista et al (103) where urinary creatinine higher than 45 mg/mL, age less than 65 years, and Blood Urea Nitrogen (BUN) less than 7 mmol/L serve as predictors of ARC. Moreover, Udy et al developed a scoring system that is based on age less than 50 years old, history of recent trauma, and SOFA score ≤ 4 (37). This tool demonstrated 100% sensitivity and 71% specificity when validated by Akers et al (104). Furthermore, Barletta et al (62) developed the augmented renal clearance in trauma intensive Care (ARCTIC) scoring system which eliminated the need to calculate a SOFA score in order to assess the patients' risk for developing ARC, which can be impractical in some patient settings. The risk factors employed in the assessment tool were serum creatinine, sex and age, and it stratified patients into high risk (ARCTIC score ≥ 6) and low risk (ARCTIC score <6). Employing predictive tools like ARC or ARCTIC in routine screening of critically ill patients could be valuable in the way of early recognition and timely management of ARC patients. However, the developed scoring tools were generated based on general critically ill/trauma population rather than patients with severe neurological illnesses potentially not capturing neurocritical care patients with additional risks for ARC.

Our systematic review is limited by the characteristics of the included studies. The main body of evidence comes from retrospective observational studies which requires caution in the interpretation of results. In addition, variations in ARC definitions, the method of determining CrCl, studies inclusion and exclusion criteria may impede accurate comparisons among studies. For example, 65% of the studies in the meta-analysis have excluded patients with existing acute and/or chronic renal impairment with various stages, impeding the possibility of extrapolating their results outside of the sampling context; as well as overestimating ARC occurrence in these samples compared to others where patients with renal impairment were included (9, 61, 66, 91). However, in our analysis we took into consideration the heterogeneity of the included studies and our pooled estimates are a reasonable representation of the body of literature.

2.5 CONCLUSION

ARC is a prevalent phenomenon in critically ill patients especially neurocritical care and trauma ICU population. Young age, male sex, and trauma are risk factors for ARC in those with apparently normal renal function. The estimation of CrCl using mathematical estimates of GFR grossly underestimates the prevalence of ARC in the critical care setting, therefore measured CrCl through urine collections is prudent. Further research on optimal dosing of drugs in the setting of ARC is warranted.

Registration and protocol: This review was registered in international prospective register of systematic reviews (PROSPERO). Registration number CRD42021246417 and protocol can be accessed in the following link: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021246417

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CHAPTER 3 DRUG DOSING IN CRITICALLY ILL ADULT PATIENTS WITH AUGMENTED RENAL CLEARANCE

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ABSTRACT

Augmented renal clearance (ARC) is a phenomenon of enhanced renal function seen in critically ill patients. ARC alters the disposition of renally eliminated medications currently used in the intensive care unit, resulting in underdosing and potential therapy failure. Our review addresses the rising concern of inadequate dosing in patients with ARC by summarizing the currently available evidence. To our knowledge, this guide is the first to provide clinicians with dose recommendation insights for renally eliminated agents in adult critically ill patients with ARC. A comprehensive literature search using MEDLINE, Embase, Cochrane Library, CINAHL, Scopus, and ProQuest Dissertations and Theses Global was conducted until November 3, 2021. Screening and data extraction was conducted in two steps: title and abstract screening followed by full-text review. Full text review resulted in a total of 51 studies included in this review. The results demonstrated the need for higher than standard doses for meropenem, imipenem and vancomycin and reduced dosing intervals for ceftriaxone in patients with ARC. The potential need for increased dosing frequency in ARC patients was also found for both enoxaparin and levetiracetam. In conclusion, ARC has been shown to influence the probability of target attainment in several medications requiring dosing changes to mitigate the risk of therapeutic failure.

Keywords: Augmented Renal Clearance, Drug Dosing, Antibiotics, Antiepileptics, Low-Molecular Weight Heparins.

3.1 INTRODUCTION

Augmented renal clearance (ARC) is a phenomenon seen in critically ill patients that has been increasingly recognized in the recent years. It is most often defined as a creatinine clearance (CrCl) >130ml/min/1.73m^2 which is most accurately based on measured CrCl using 8-24h urine collection (1). Although the exact mechanisms causing ARC are not fully understood, many have been hypothesized. ARC may perhaps be a physiologic response to acute injury such as traumatic brain injury or body temperature change. Renal clearance may also be enhanced due to various treatments patients in the intensive care unit (ICU) receive, such as vasopressors and fluid resuscitation. It is also thought to be a consequence of the heightened sympathetic response associated with severe critical illness and systemic inflammatory responses such as in patients with traumatic brain injury and sepsis; as well as changes in vascular resistance, cardiac output and blood flow to major organs e.g. the kidneys, resulting in a hyperdynamic state and accelerated glomerular filtration rate. The prevalence of ARC has been reported to range between 14-80% making it a common phenomenon (1). The clinical relevance of ARC lies in the potential for enhancing the clearance of drugs primarily eliminated by the kidneys such as beta-lactam antimicrobials and certain antiepileptic drugs, potentially leading to therapeutic failure and potentially poor outcomes in this especially vulnerable patient population.

Multiple ARC risk factors have been reported by research teams. As mentioned, ARC is more prevalent in the critical care setting, especially in trauma patients. Age appears to be the most important and widely verified risk factor for ARC. Patients of younger age (<50 years of age) were at the highest risk of developing ARC. Additionally, ARC patients tend to be males, with lower critical illness severity scores (1). Therefore, it may be necessary to use risk assessment tools for more rapid identification of critically ill patients exhibiting ARC. A few tools have been developed for this purpose (2).

It is considered common practice to reduce doses in the presence of renal impairment, however, the scarcity of currently available evidence and the lack of a clear consensus supporting dosing requirements in the case of ARC have made it difficult for clinicians to optimise dosing regimens for ARC patients. Multiple studies have demonstrated that ARC impacts the plasma levels of

renally eliminated drugs commonly seen in a critical care setting, especially antimicrobials and antiepileptic drugs (AED). We discussed the phenomenon of ARC in our previous review (1); however, multiple studies have been published since our initial review. Therefore, the objective of this review is to provide an update to summarize the current evidence pertaining to the influence of ARC on the disposition of renally eliminated medications commonly used in the ICU. We hope that this guide will provide clinicians with dosing recommendation insights for multiple renally eliminated agents used in patients with ARC.

3.2 LITERATURE SEARCH

3.2.1 Search Strategy

A comprehensive database search was conducted by the medical librarian (JYK) on October 27, 2020 in the following databases: MEDLINE (via Ovid), Embase (Ovid), Cochrane Library (Wiley), CINAHL, Scopus, and ProQuest Dissertations and Theses Global with no date or language limits. The search was updated on November 3, 2021 to capture newly published research following the original search. Keywords related to ARC in the critically ill were used to conduct the search (see Supplementary Table 3.1 for details on keywords used). We utilized, the web-based review screening tool "Covidence" for the screening process (www.covidence.org).

3.2.2 Study Inclusion and Exclusion Criteria

Human studies conducted in critically ill adult populations and reporting drug dosing or pharmacokinetics in the setting of ARC (those with creatinine clearance > 130 ml/min/1.73m^2) were included. Studies were further sorted based on inclusion of specific medications. Studies focused on pediatrics, pregnant women, or studies conducted in populations with potentially altered renal elimination (e.g., cystic fibrosis, burn patients) were excluded. This is due to the physiological and pathological changes associated with these patient populations that would hinder the detection of ARC. In addition, reviews, editorials, case reports, pre-prints and commentaries were also excluded.

3.2.3 Study Screening

Study screening and selection from the October 27, 2020 database search were conducted independently by AS and SHM. An updated study screening and selection from November 3, 2021, were conducted independently by SHM and SS to include research published from October 2020 to November 2021. An initial title and abstract screening followed by a full-text review was conducted. Any conflicts were discussed among authors to reach a consensus.

3.2.4 Data Extraction

Data extracted included study design, study objectives, study population, drugs tested, method used and study findings.

3.3 RESULTS OF LITERATURE SEARCH & DISCUSSION

Literature search resulted in 3,455 and 3,941 articles across all databases on October 27, 2020, and November 3, 2021, respectively (**Supplementary Table 3.2**). A total of 1,761 and 347 unique articles remained for screening from these comprehensive searches. Full text screening yielded 51 articles for inclusion (**Supplementary Table 3.3)**.

Prospective observational studies constitute the main body of evidence in this review at 69% (n=34) of the total evidence. Retrospective observational studies constitute 31% (n=16) of the total evidence. This is in addition to a single prospective interventional study by Cojutti et al. discussing meropenem (3) Expectedly, the literature search concluded that renally eliminated drugs such as beta lactams and levetiracetam in ARC patients needed alternate dosing regimens where a loading dose might be needed, an extended infusion strategy employed or increased frequency or amount of dosing to achieve the same targets as in non-ARC patients. Although the currently available evidence is not exhaustive of all drugs used in the ICU and other settings where patients are at a higher risk of developing ARC e.g. oncology patients,it can be assumed that all renally eliminated drugs in this patient population will be at a higher risk of therapeutic failure or target non-attainment and it would be prudent to take precautions to mitigate for this risk.

Young age, male sex, and trauma are repeatedly defined in the literature as risk factors for ARC in those with apparently normal renal function and lower disease severity scores. Age, male sex and trauma were associated with ARC with pooled OR (95% CI) of 0.95 (0.93–0.96), 2.36 (1.28–4.36), 2.60 (1.21–5.58), respectively. Prevalence for neuro, trauma, mixed and sepsis ICUs were 74 (55–87), 58 (48–67), 36 (31–41) and 33 (21–48), respectively (4).

3.3.1 Carbapenems

3.3.1.1 Meropenem

Meropenem is a member of the carbapenem class of antimicrobials. It has a broad spectrum of activity and exhibits time-dependent killing. It is also eliminated 70% by the kidneys (5). In the case of critically ill patients, clinicians target a minimum of ≥50% *f*T > MIC (percent time of free drug remains above the minimum inhibitory concentration, MIC), and the preferred target is ≥100% *f*T > MIC. In some cases, experts prefer to target ≥100% *f*T >4 times the MIC (6-8). Three prospective observational studies have described the impact of ARC on meropenem treatments (9-11). In an early study, Kitzes-Cohen et al. have reported that lower plasma concentrations of meropenem were seen with increasing kidney function (9). Ehmann et al. corroborated this observation (10). Additionally, standard meropenem doses were insufficient in achieving desired concentrations in the majority of patients with ARC (9, 10). The authors suggested that a meropenem dosing of 2000 mg every 8 hours will greatly enhance the probability of target attainment (9, 10). A dose of 2000mg every 8 hours was also identified as an alternative strategy by Tamatsukuri et al. with the additional recommendation of administration via prolonged infusion over 180 minutes for each dose (11). However, these studies were limited by a small sample size as well as a lack of correlation to clinical outcomes. An interventional study exploring the effects of TDM-based optimization on treatment outcomes also exists (3). Cojutti et al. found that based on therapeutic drug monitoring (TDM), 30.1% of patients required dose adjustment and this strategy resulted in a promising overall cure rate of 90%. In this study mortality was also significantly associated with ARC (OR 10.846, CI 95% 1.534-76.672, P=0.017) (3).

Conclusion: ARC results in lower plasma concentration of meropenem; this can lead to therapeutic failure and negative clinical outcomes. Because of this, higher dosing is recommended (9, 10). A dose of 2000mg every 8 hours is likely needed; prolonged infusion may also improve drug

exposure (9-11). Therapeutic drug monitoring of meropenem could also be of benefit in these patients. Further studies focused on these strategies are needed.

3.3.1.2 Imipenem/cilastatin

Imipenem is a carbapenem antimicrobial agent. It has a broad spectrum of activity and demonstrates time dependent bacterial killing. It is also 70% renally eliminated (5). In the case of critically ill patients, clinicians target a minimum of ≥50% *f*T > MIC, and the preferred target is ≥100% *f*T > MIC. In some cases, experts prefer to target ≥100% *f*T >4 times the MIC (6-8). A retrospective study demonstrated that when patients received 500 mg every 6 hours (2g/day), frequent treatment failure and infrequent toxicity was documented (12). The authors also found that when patients received higher doses (3-4g/day) instead of standard dosing (2g/day) they reported fewer counts of treatment failures without any increase in toxicity. Huttner et al. performed a prospective observational study in which patients received standard doses of 500mg four times daily as well (13). They reported ARC as a predictor for undetectable trough levels, though this study was underpowered to determine any associations to clinical failure. These two studies suggest a possibility that standard dosing may be insufficient and increased doses could be warranted (12, 13).

Patel et al. 2021 conducted a prospective observational study to determine the probability of target attainment using various dosing regimens of imipenem/cilastatin/relebactam in patients with hospital acquired bacterial pneumonia/ventilator acquired bacterial pneumonia (14). ARC was defined as CrCl ≥150 ml/min calculated using the Cockcroft-Gault equation. A dose of imipenem/relebactam 500/250mg every 6hr established a joint probability of target attainment (PTA) of 99% for a target trough of 30% fT>MIC (14). Further studies analyzing the correlation between target trough concentration and clinical success are needed.

Conclusion: ARC may lead to lower concentrations of imipenem in some patients receiving standard doses of 500 mg every 6 hours, which has the potential to result in therapeutic failure and negative effects on clinical outcomes (12, 13). Increased doses could be considered for patients exhibiting ARC who are indicated for treatment with imipenem and experiencing clinical failure at standard doses. Doses of 1g every 6 hours could be considered for these individuals (12). Further

studies administering increased doses to patients with ARC in which safety and clinical outcomes are documented, are required. With regards to imipenem/relebactam, standard doses of 1.25g (500mg imipenem/ 500mg cilastatin/250mg relebactam) dosed every 6 hours consistently showed high PTA for such doses in patients with ARC (14). This may indicate that no further dose increases are necessary in patients with ARC being treated for infection with imipenem/relebactam. Further studies are needed to identify the relationship between target attainment and clinical success.

3.3.2 Cephalosporins:

3.3.2.1 Ceftriaxone

Ceftriaxone is a third-generation cephalosporin antimicrobial. It has a relatively broad spectrum of activity, with specific efficacy against gram negative pathogens; it accomplishes bacterial killing in a time-dependent manner. Up to 67% of the drug is eliminated by the kidneys (5). In the case of critically ill patients, clinicians target a minimum of ≥50% *f*T > MIC, and the preferred target is ≥100% *f*T > MIC. In some cases, experts prefer to target ≥100% *f*T >4 times the MIC (7, 8, 15). Three prospective observational studies describe ceftriaxone dosing in the context of ARC (16-18). Increased kidney function leads to a decrease in plasma concentrations of ceftriaxone when standard dosing is used (17). The insufficiency of standard dosing of ceftriaxone is further described by Ollivier et al. They found that CrCl > 150ml/min is significantly associated with under-dosing, defined as trough concentrations < 2mg/L (OR 8.8, CI 95% 2.5-30.7, P<0.01) (16). The authors suggested that a reduced dosing interval of 2000mg every 12 hours would be better suited for target attainment (16). However, these studies were limited by a small sample size and the inability to associate findings with clinical outcomes. Wong et al. found that ARC was a predictive factor for treatment failure. They suggested that ceftriaxone allowed for increased drug exposure throughout the dosing interval compared to other β-lactams, due to the attainment of a strict target of 100%fT>4xMIC in a majority of patients who received it (18). A retrospective observational study evaluating the effects of an increased dosing regimen of ceftriaxone also exists (19). Carrie et al. found that 2000 mg twice daily dosing was effective in reducing therapeutic failure and relapse of infection without increased adverse effects (19).

Conclusion: Ceftriaxone may be a promising agent in improving target attainment, possibly due to its high protein binding which allows for prolonged half-life, ensuring concentrations remain above target for the duration of the dosing interval (19). However, it is not spared from reduced plasma concentrations in the setting of ARC which can lead to higher rates of therapeutic failures (16, 17, 19). Higher doses or reduced dosing intervals may be warranted (16). Doses of 2000mg every 12 hours are likely required (16). Further studies regarding increased doses of ceftriaxone, and its safety, in patients with ARC are necessary.

3.3.3 Aminoglycosides:

3.3.3.1 Amikacin

Amikacin is a member of the aminoglycoside class of antimicrobials. It demonstrates concentration dependent bacterial killing and is often used to treat severe gram-negative infections. It is eliminated nearly 100% unchanged by the kidneys (5). There is one retrospective observational study that has discussed amikacin's use in patients with ARC (20). Carrie et al. found that an increase in renal clearance is associated with an increased clearance of amikacin, which results in lower plasma concentrations. Using the Monte Carlo simulation, the authors determined the standard loading dose of 25mg/kg ABW to be effective in reaching maximum blood concentration (Cmax)/MIC targets for most patients(20). However, patients exhibiting CrCl >130ml/min may need higher than licensed loading doses of up to 35mg/kg ABW (20). An increase in maintenance dose has been explored in a prospective observational study (21). Arechiga-Alvarado et al. reported that an increase in creatinine clearance leads to lower concentrations of amikacin. Monte Carlo simulations suggested that for patients with ARC infected with pathogens with high minimum inhibitory concentrations, maintenance doses of up to 70mg/kg could be warranted (21). However, this study was limited by a small sample size and both studies based the dosing recommendations only on simulation data. Furthermore, the safety of doses as high at 70mg/kg need to be explored in future studies. Both of the above studies investigated extended interval/once daily dosing (20, 21).

Conclusion: ARC results in increased amikacin clearance and subsequent decreased plasma concentrations (20). Low plasma concentrations of amikacin have the potential to increase instances of therapeutic failure which would be detrimental in terms of increased mortality and

emergence of resistant pathogens (20). For this reason, higher than licensed doses may be needed to reach the recommended pharmacokinetic/pharmacodynamic targets (20, 21). An increase of either the loading dose or maintenance dose may be effective in improving achievement of desired drug levels in patients with ARC (20, 21). Further studies are required to assess the safety and clinical benefit of such dose increases.

3.3.4 Glycopeptides:

3.3.4.1 Vancomycin

Vancomycin is a glycopeptide antimicrobial agent. It has a narrow spectrum of activity against primarily gram-positive pathogens, including resistant strains of Staphylococcus. It is excreted by the kidneys as 80-90% unchanged drug (5). The ideal monitoring parameter for vancomycin is area under the curve to minimum inhibitory concentration (AUC: MIC) ratio of greater than 400. However, in clinical practice a steady state trough value of 10-20mg/L is often used as a surrogate target. Current standard dosing involves a loading dose of 25-30mg/kg followed by a maintenance dose of 15mg/kg administered at various intervals determined by the patients calculated CrCl. The recommended dosing interval for patients with CrCl >80ml/min is every 12 hours (22).

Multiple studies have discussed the impacts of ARC on vancomycin plasma concentrations (23-26). The clearance of vancomycin is drastically increased in patients with ARC ranging from 1.6 to up to 3.5 times the expected values (23, 26). The authors also demonstrated that this was associated with sub-therapeutic levels as well as a need for overall higher doses (26). Multiple studies suggested that standard dosing of vancomycin consistently results in subtherapeutic vancomycin levels and higher doses are required (19, 24, 25, 27, 28). To illustrate, Chen et al. found that only 19.23% of patients in the ARC group were able to achieve target trough levels of >10mg/L (24). In addition, He et al. 2020 conducted a retrospective observational study and found that 77.7% of patients with ARC vs 68.8% of patient without ARC had subtherapeutic (<10mg/L) vancomycin trough concentrations when given vancomycin maintenance doses of 15mg/kg every 12 hours IV infusion. They also demonstrated that only 17.9% and 4.3% of patients with ARC were able to reach trough levels between 10-15 and 15-20mg/L, respectively (25). The authors suggested a dose of 46mg/kg/day in patients with ARC to achieve trough levels of at least 10mg/L (25). Contrary to these studies Zhao et al. found that standard doses of 1000mg q12hr

would result in PTA (defined as targeted AUC between 400-650mg.h/L) of 62.56% in patients with CrCl between 150-179 ml/min (29). Results of this study were based solely on Monte Carlo simulations with a mean patient TBW (total body weight) of 63.4kg and thus may not be representative of adult populations with higher TBW(29). Furthermore, two prospective observational studies have discussed the need for high loading doses for patients with ARC (30, 31). Baptista et al. and Campassi et al. administered loading doses of 1000-1500mg and 15mg/kg, respectively with maintenance doses of 30mg/kg/day (30, 31). It was reported that only half of the ARC patients were able to achieve therapeutic trough levels with this dosing strategy (30, 31). The authors suggested a need for an increased loading dose of 2g as well as a need for TDM for these patients (30). A need for maintenance doses over 40mg/kg/day was also reinforced by the findings of Helset et al. (2020). In their prospective observational study they found that ARC patients demonstrated an overall lower AUC:MIC despite receiving an average dose of 44.4mg/kg/day (32).Two retrospective observational studies found that when patients with ARC received doses of 1000mg every 12 hours, the majority were not able to achieve trough concentration >10mg/L (23, 27). The authors suggested that increased frequency be considered. A retrospective study by Minkute et al. has reported that ARC patients are at risk of under-dosing (defined as trough below 5.2 ug/ml) and that nearly double the standard dose is likely required. The authors further suggested that a decreased dosing interval to every 6 to 8 hours be considered (28).

Lastly, both a prospective observational study and retrospective analysis have discussed the promising effects of the use of nomogram-based dosing in patients with ARC (33, 34). Bapstista et al. (2014) administered dosing concurrent with a developed nomogram based on 8h urine CrCl measurement. With this dosing strategy all ARC patients were able to achieve target trough levels within the first day of treatment (33). This study was limited by a small sample size. However, Ishii et al. (2018) showed promising results when using a nomogram based on calculations of estimated glomerular filtration rate (eGFR) using the Japanese Society of Nephrology equation. This equation is essentially the Modification of Diet in Renal Disease Study (MDRD) equation multiplied by a Japanese coefficient of 0.741(34). This dosing resulted in no significant differences between trough concentrations of ARC and non-ARC patients. Unfortunately, the nomogram was not detailed within the study.

Conclusion: Patients with ARC are at an increased risk for subtherapeutic trough concentrations of vancomycin, this reduced drug exposure has the potential to cause therapy failure and other negative clinical outcomes (23, 24, 26) . The most promising option may be dosing based on a nomogram for various renal functions (33, 34). However, nomograms may be unavailable or not feasible in practice. Based on the data presented an increase in loading dose and/or maintenance dose could also be considered to allow ARC patients rapid and continuous achievement of desired vancomycin levels. Loading doses of 2g may be most effective in achieving target trough concentrations quickly (30). Additionally, maintenance doses of 45mg/kg/day would be a more realistic starting dose for patients with ARC (32). Lastly, it is necessary that patients with ARC receive more frequent TDM with subsequent dose adjustment. Development and validation of a CrCl based dosing nomogram is a promising step forward for patients with extremes of renal function requiring vancomycin therapy (33, 34). Further studies administering increased doses or frequencies are needed to determine safety and efficacy. It is also important to note that patients with ARC receiving higher doses are at a higher risk of developing ADRs if the CrCl was not monitored closely, and doses adjusted accordingly.

3.3.5 Oxazolidinones:

3.3.5.1 Linezolid

Linezolid is an oxazolidinone antimicrobial agent that exhibits concentration dependent killing with time dependence, with the ideal monitoring parameter of AUC:MIC (22). Use is primarily in the treatment of severe gram-positive infections (35). Linezolid is partially eliminated by the kidneys with about 30% of the unchanged drug excreted in the urine (5). Currently, there is no clear definition for linezolid's target parameters, an AUC24hours: MIC >119 mg/L/hour has been proposed (36, 37), an alternative target trough concentration ≥ MIC has been proposed (38).

A prospective observational study has addressed the impact of ARC on linezolid plasma concentrations and demonstrated the benefit of continuous infusion in this setting (35). Barrasa et al. reported that with increasing renal function, linezolid clearance is increased, which results in reduced plasma concentrations. Patients with ARC have a particularly low probability of target attainment; when receiving a standard dose of 600mg every 12 hours no patients with ARC were able to achieve PK/PD targets (35). However, 70% of patients with ARC who received linezolid

as a continuous infusion of 50mg/hour, reached desired targets (35). The authors also used Monte Carlo simulation to determine optimal dosing regimens. They report the rate of target attainment could further be increased to 93% if a continuous infusion of 75mg/hour is used (35). This study was limited by a lack of correlation with either dosing strategy with clinical outcomes.

Conclusion: Enhanced renal clearance results in lower plasma concentrations of linezolid, this has the potential to lead to therapeutic failure and subsequent negative clinical outcomes. Continuous infusion may allow for increased drug exposure in patients with ARC, which would allow for an increased probability of achieving and maintaining desired targets (35). A dosing strategy including continuous infusion of 50-75 mg/hour may be beneficial for target attainment in patients exhibiting ARC (35). Further studies regarding the benefit of continuous infusion of linezolid on clinical outcomes of patients with ARC are needed.

3.3.6 Penicillin:

3.3.6.1 Piperacillin/Tazobactam

Piperacillin is a penicillin which belongs to the β-lactam class of antimicrobials. It is often administered in conjunction with tazobactam, a β-lactamase inhibitor. It has a broad spectrum of activity and like other β -lactams, exhibits time dependent bactericidal activity. Both piperacillin and tazobactam are eliminated by the kidneys, about 68% and 80%, respectively (5). In the case of critically ill patients, clinicians target a minimum of ≥50% *f*T > MIC, and the preferred target is ≥100% *f*T > MIC. In some cases, experts prefer to target ≥100% *f*T >4 times the MIC (6-8).

Three prospective observational studies have discussed the effects of ARC on PK/PD target attainment of piperacillin/tazobactam therapy (13, 39, 40). Wu et al. (2019) demonstrated that ARC patients were less likely to achieve targets of 50%fT>MIC and 100%fT>MIC. It has been suggested that critically ill patients should have treatment targets above these, specifically %T>4xMIC (39). This was examined by Carrie et al. (2018) where the authors found that when targeting concentrations of >4xMIC, CrCl>170ml/min was statistically associated with under-dosing, adding that patients with therapeutic failure had significantly higher CrCl. The authors concluded that TDM is required to ensure adequate drug exposure in patients with ARC (40). However, in this study multiple β lactams were included as well as treatment consisting of multiple antimicrobial agents (40). Huttner et al. (2015) found that with the administration of

various β -lactams, including piperacillin/tazobactam at 4.5g three times daily, patients with ARC were 3.3 times more likely to have undetectable trough levels. Again, this finding was generalized to various β -lactams but suggests that this dose of piperacillin/tazobactam is likely not sufficient for patients who exhibit ARC (13).

A dose of 4g/0.5g every 8 hours delivered by 3-minute bolus infusions, was also unlikely to allow ARC patients to attain PK/PD targets in a prospective observational study by Andersen et al. (2018). The authors suggested that increasing the frequency of administration to 4g every 6 hours or administering prolonged infusion, either 3 hours or continuously, would be more effective (41). However, only 4 patients with ARC were included in this study (41). They also concluded that if 4g every 6 hours was administered it would provide 100%fT>MIC as long as MIC was 2.0mg/L, so this recommendation would likely remain insufficient in the context of empirical dosing for high MIC pathogens (41). Every 6-hour dosing was addressed in a prospective cohort study by Weber et al. (2019). It was reported that a dose of 4g/0.5g every 6 hours was insufficient to attain targets of 50% and 100%fT>MIC in all patients, regardless of ARC, though increased CrCl was associated with lower trough levels (42). This study was composed of a small number of hematological malignancy patients and findings cannot be generalized to all critical care settings but may suggest that even infusions of 4g every 6 hour may not be sufficient (42). A cross-sectional study by Akers et al. (2014) showed that patients with high ARC scores had increased piperacillin/tazobactam clearance as well as reduced AUC, compared to the low ARC score group. They utilized PK simulation data to suggest that continuous infusion of 12g/day or intermittent infusions of 4-6g every 4 hours or 6-8g every 6 hours would allow for target attainment above MIC of 16mg/L (43). This study only included 13 patients and patients were only classified based on ARC scores, CrCl was not used for comparison of groups (43). Lastly, when patients received a 4.5g loading dose, followed by 4.5g every 6 hours administered by 3-hour infusion, half of the patients did not achieve the target (>16mg/L), 80% of these patients had ARC (44). This study was limited by a small sample size but suggests that a dosing frequency of every 6 hours and prolonged infusion may not be sufficient to achieve desired targets for patients with ARC, especially those who are infected with high MIC pathogens (44).

Three prospective observational studies have reported the effects of continuous infusion on piperacillin/tazobactam therapy in patients with ARC (19, 45, 46). Carrie et al. (2018) administered 4g/0.5g loading and 16g/2g maintenance doses. With this dose, the rate of underexposure (defined as at least 1/ 3 concentration samples being under 16mg/L) was higher in ARC patients, however the underexposure rate for the overall sample was only 19% (45). The authors utilized simulation to determine that a continuous infusion of 20g/2.5g/day would allow for the highest probability of target attainment without excessive dosing (resulting in concentrations > 150mg/L) (45). Another study performed by Carrie et al. in 2019 administered the suggested increased dose to hospital acquired pneumonia/ventilator acquired pneumonia (HAP/VAP) patients with ARC (19). They reported that when maintenance doses were increased from 16g/day (control group) to 20g/day (treatment group) therapeutic failure was reduced by 13% (19). Lastly, Dhaese et al. (2018) utilized Monte Carlo simulation to determine that high dose piperacillin/tazobactam, 4g loading dose and 24g/day as continuous infusion, would not allow patients with CrCl >90ml/min to reach targets of 100%fT>MIC (16mg/L). The authors raise the question regarding if additional agents should be added or if a different therapy should be employed altogether (46). Interestingly, a nested cohort sub-study of the BLINGII trial showed no difference in clinical outcomes of ARC patients when either continuous infusion or intermittent infusion was used (47). However, this was a generalized finding for multiple β -lactams and not piperacillin/tazobactam specifically.

Conclusion: ARC results in lower levels of piperacillin/tazobactam, this has the potential to cause underexposure and lead to negative clinical outcomes. TDM, if available, should be considered for these patients to ensure adequate exposure to medication. Data for continuous infusion are promising. Perhaps continuous infusion of 20g/2.5g/day would allow increased likelihood of target attainment for patients with ARC (45). Further studies are required to determine efficacy and safety of such dose changes in ARC patients. Additionally, larger studies are needed to determine impact on clinically significant outcomes.

3.3.6.2 Ceftolozane/Tazobactam

Ceftolozane/Tazobactam is a cephalosporin/beta lactamase inhibitor combination product often used to treat gram-negative infections resistant to other drugs. Common recommended dosing for treatment of infections ranges from 1.5-3g q8hr. Ceftolozane and tazobactam are renally eliminated as >95% and >80% unchanged drug, respectively (5).

Two prospective observational studies investigated the appropriateness of ceftolozane/ tazobactam 3g q8hr dosing in patients with ARC (48, 49). Nicolau et al. 2021 determined that 11/14 critically ill patients enrolled in the study demonstrated ARC (CrCl ≥ 130mL/min). Eighty two percent of patients with ARC demonstrated ceftolozane fT>MIC 4ug/mL for up to 6 hours after the dose was administered and sixty four percent of patients with ARC were able to demonstrate this for up to 8 hours(48). Sixty four percent of patients with ARC demonstrated tazobactam fT> 1ug/mL (threshold) for up to 4 hours post administration (48). The authors concluded that adequate target levels were maintained for the 8-hour interval between doses for ceftolozane/tazobactam. It should be noted that the generalizability of this study is reduced due to its sample size (n=14). Shorr et al. 2021 conducted a larger study using the patients enrolled in the phase 3 ASPECT-NP trial to investigate the same dose. Monte Carlo simulations where developed based on patients HABP/VABP with varying renal functions. ARC was defined as CrCl ≥ 130mL/min (49). Over 99% of simulated patients achieved the ceftolozane target of 50% fT> MIC of 4ug/mL in plasma in all renal function groups including ARC (49). 80% of patients achieved the tazobactam target of 35% fT> Ct of 1ug/mL across all renal function groups including ARC (49). Although a high PTA was shown for tazobactam in patients with ARC, PTA did trend down as ARC increased across groups. No statistical difference was shown in 28 day all-cause mortality between non-ARC and ARC groups treated with ceftolozane/tazobactam in intention to treat (0.2 [95% CI, −9.6 to 10.6]) and microbiologic intention to treat groups (−1.4 [95% CI,−11.6 to 9.4]) (49). The authors concluded ceftolozane/tazobactam 3g q8h is an appropriate dose for patients with ARC based on these findings.

Conclusion: Doses of ceftolozane/tazobactam in critically ill adults of 3g q8h have been shown to achieve high probability of target attainment in patients with ARC (48, 49). Few clinical outcomes such as all-cause mortality have also been shown to exhibit no difference in patients with or

without ARC treated with ceftolozane and tazobactam (49). Ceftolozane/tazobactam 3g q8hr is likely an appropriate dose for critically ill adults with ARC however further analysis that compares target concentration attainment to clinically relevant results such as infection resolution are needed.

3.3.7 Low-Molecular weight heparins:

3.3.7.1 Enoxaparin

Enoxaparin is a commonly used low molecular weight heparin, up to 40% of the drug is excreted by the kidneys(5). For venous thromboembolism prophylaxis in moderate to high risk patients, a peak factor Xa level of 0.2 to 0.4 units/mL or trough level of 0.1 to 0.2 units/mL is usually targeted (50). A prospective observational study provides information about the effects of ARC on prophylactic enoxaparin dosing (51). Patients with ARC exhibited target anti-factor Xa levels at hour 4 but these levels dropped significantly by hours 12 and 24(51). This suggests that the duration of activity of enoxaparin may be shortened by enhanced renal clearance in patients with ARC, possibly rendering the need for dose adjustment (51). However, the significance of anti-factor Xa monitoring at 12 and 24 hours is not fully known. This study is also limited by a small sample size, and data regarding the development of clots was not collected.

Conclusion: The duration of action of enoxaparin may be shortened in patients with ARC, this could potentially lead to an increased risk for clot formation. An increased frequency of dosing to 40mg twice daily should be considered for clot prophylaxis in these patients. Further studies exploring a shortened dosing interval and the impacts on clot formation in critically ill patients with ARC are needed.

3.3.8 Anti-epileptics:

3.3.8.1 Levetiracetam

Levetiracetam is an AED which is used to treat multiple seizure types as well as seizure prophylaxis in certain care settings. It is eliminated renally with 66% of the unchanged drug excreted in the urine (5). Therapeutic drug monitoring of levetiracetam targets a plasma concentration between 12 and 46 mg/mL(52, 53).

A prospective observational study by Ong et al. in 2021 on neurosurgical ICU patients targeting a trough concentration of 6mg/L showed Monte Carlo simulations demonstrating PTA >80% in patients with ARC who were dosed with levetiracetam 1000mg Q8H (54). Three prospective observational studies further discussed levetiracetam administration in patients with ARC (55-57). La et al. have reported that a standard dose of 1000mg twice daily, resulted in sub-therapeutic concentrations in patients with ARC. Two of the studies also utilized Monte Carlo simulation to determine an optimized dosing strategy. May et al. determined three times daily dosing is needed to reach desired plasma concentrations of levetiracetam. Three times daily dosing was also suggested by Spencer et al. as an alternative, as they reported an increased probability of target attainment when a dose of 500mg every 8 hours was simulated. They also documented similar findings for a dose of 1000 mg twice daily. Again, these studies were limited by small sample size, and did not discuss development of seizures in ARC patients specifically. Additionally, dosing suggestions were based on simulation data alone. Two prospective observational studies conducted by Bilbao-meseguer et al. and Sime et al. also demonstrated levetiracetam dosing in critically ill patients with ARC using doses as high as 6g/day (58, 59). Bilbao-meseguer et al. 2021 performed Monte Carlo simulations using data from adult ICU patients to demonstrate PTA using various dosing regimens in patients with CrCl ranges (80-240ml/min). They found 500mg BID to be inadequate in all critically ill patients with or without ARC and found doses as high as 1500mg q12hr to only guarantee target trough concentrations in those with CrCl < 80ml/min. The study concluded doses as high as 1500-2000 mg Q8H were required to achieve target trough concentrations in those with ARC (58). Sime et al. 2021 also developed Monte Carlo simulations and found patients with ARC had a PTA of 0 for trough concentrations of ≥46mg/L with doses as high as 6g/day however these doses demonstrated a PTA ≤ 80% for a target trough concentration of 6mg/L. These studies results should be interpreted with caution due to the small sample sizes and wide range in target trough concentrations (6-46mg/L) included in both studies (58, 59). Further safety data on dose regimens this high should be analyzed before implemented.

Conclusion: ARC results in lower plasma levels of levetiracetam, this could lead to therapeutic failure and the increased development of seizures in these patients. It appears that an increase in dose or frequency is needed. Dosing regimens of 500mg every 8 hours or 1000-2000mg every 12 hours can be currently recommended for seizure prophylaxis in patients exhibiting ARC as they

may allow for the achievement of therapeutic plasma levels (1, 56, 57). Additionally, loading doses may be used to further increase drug exposure. Though some studies suggest that further dose increases may be warranted up to 6g/day (58, 59), further studies which attempt to administer increased doses and report seizure occurrence and adverse event profiles in patients with ARC are necessary to determine the safety of efficacy of such doses.

3.3.9 Other considerations:

It is important to note that ARC is one of multiple pathophysiological changes due to critical illness need to be taken into account when following drug therapy guidelines in various disease states. Numerous changes including but not limited to altered plasma protein binding, extracorporeal membrane oxygenation (ECMO), alterations in gastric pH and the rate and extent of absorption of orally administered drugs, and reductions in hepatic blood flow or enzyme activity. These changes can consequently affect the pharmacokinetics of different drugs. Therefore, they should be taken into consideration before adopting unadjusted dosing regimens in critically ill patient settings, putting them at a risk for therapy failure, longer hospitalizations and increased adverse drug events(60).

3.3.10 Limitations:

This literature review is limited by the inherent drawbacks to non-systematic reviews. In addition, some of the proposed dosing regimens are derived from pharmacokinetic simulations as opposed to controlled clinical trials. Although we aimed to provide clinicians with a summary of the available evidence to aid in the dosing of key renally eliminated drugs in critical care settings, there is a current lack of a clear consensus of high quality critically appraised evidence to support the dosing regimens of some of the reported drugs such as linezolid and enoxaparin.

3.4 CONCLUSION

In conclusion, our review summarizes the evidence on medications relevant to the care of critically ill adults which may require alternate dosing regimens in patients with ARC, addressing an area of rising concern. ARC has been repeatedly shown to negatively influence the probability of target trough level attainment in many life-saving medications, potentially increasing the risk of therapeutic failure. We have provided a table with recommended doses for 10 medications for

critically ill adult patients with CrCl >130ml/min/1.73 m2 based on multiple studies (**Table 3.1***)*. Further research is required to investigate the correlation between target trough level attainment and clinical outcomes as well as the safety of higher doses such as those reported in our recommendation table.

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Authors contributions: Conceptualization and design, SHM; Database search, JYK; Study screening and selection, SHM, AS, SS; Data extraction and summarization, FH, CM, SS, AS; resolution of conflict in study selection and interpretation, SHM; Drafting the first version of the manuscript, CM, SS; revision and approval of the final manuscript, All authors.

6.TABLE 3.1. DOSING RECOMMENDATIONS FOR CRITICALLY ILL ADULT PATIENTS WITH AUGMENTED RENAL CLEARANCE (ARC).

Drug	Literature Suggested Target	Recommended Dose	Evidence [sample size]
Meropenem	In the case of critically ill patients, clinicians target a minimum of ≥50% *f*T > MIC, and the preferred target is ≥100% *f*T > MIC. In some cases, experts prefer to target ≥100% *f*T >4 times the MIC (6, 8, 15, 61)	• Suggested dose: 2000 mg IV every 8 hours • Prolonged (each dose to be infused over at least 3 hours) or continuous infusion may also improve drug exposure • TDM, if present	Three prospective observational studies: • Kitzes-Cohen et al (2002) [n=14](9) • Ehmann et al. (2017) [n=48](10) • Tamatsukuri et al. (2018) [n=17](11) One interventional study suggesting TDM: • Cojutti et al. (2020) [n=75](3)
Imipenem/cilastatin*	In the case of critically ill patients, clinicians target a minimum of ≥50% *f*T > MIC, and the preferred target is ≥100% *f*T > MIC. In some cases, experts prefer to target ≥100% *f*T >4 times the MIC (6, 8, 15, 61)	• Suggested dose: 1000 mg IV every 6 hours may be considered; however further studies are needed	One retrospective study: • Bricheux et al. (2019) [n=300] (12) One prospective observational study • Huttner et al. (2015) [n=100](13)
Ceftriaxone	In the case of critically ill patients, clinicians target a minimum of ≥50% *f*T > MIC, and the preferred target is ≥100% *f*T > MIC. In some cases, experts prefer to target ≥100% *f*T >4 times the MIC (6, 8, 15, 61)	• Suggested dose: 2000 mg IV every 12 hours	Three prospective observational studies: • Ollivier et al. (2019) [n=21](16) • Joynt et al. (2001) [n=12](17) • Wong et al. (2018) [n=373](18) One retrospective observational study: • Carrie et al. (2019) [n=177](19)
Amikacin	Extended interval dosing: Trough: < 2 mg/L Peak (not generally monitored): 40-60 mg/L A 6-14 hour level could be of value for dose adjustment based on nomogram	• Suggested dose: 20-30 mg/kg IV once daily (extended interval dosing) • Dose based on IBW (use ABW if ABW < IBW; used DW if ABW is more than 20% IBW) • Adjust further dosing based on TDM	One retrospective observational study: • Carrie et al. (2020) [n=70](20) One prospective observational study: • Arechiga-Alvarado et al. (2020) [n=50](21)
Vancomycin	The ideal monitoring parameter for vancomycin is area under the curve to minimum inhibitory concentration (AUC/ MIC) ratio of greater than 400. However, a targer steady state trough value of 10-20mg/L is often used as a surrogate target.	• Suggested dose: LD: 25-30 mg/kg (ABW; max dose 3000 mg) IV followed by MD of at least 15 mg/kg (ABW) every 8 hours IV (MD doses of 20 mg/kg every eight hours have been used) • Adjust further dosing based on TDM • Dosing as per a CrCl based nomogram may be beneficial, if present • Continuous infusion of 40-60 mg.kg/day has been suggested (target Css of 20-25 mg/L)	13 retrospective observational studies: • Chu et al. (2020) [n=95](23) • Hirai et al. (2016) [n=292](26) • Chen et al. (2020) [n=104](24) • Izumisawa et al. (2019) [n=684](62) • He et al.(2020) [n=280](25) • Villanueva et al. (2019) [n=70](63) • Chu et al. (2016) [n=148](27) • Minkute et al. (2013) [n=109](28) • Baptista et al. (2014) [n=104](33) • Ishii et al. (2018) [n=177](34) • Vermis et al. (2014) [n = 96] Abstract (64) • Chu et al. (2020) [n=292] (65) • Mikami et al. 2021 [n=65] (66) Six prospective observational studies • Baptista et al. (2012) [n=93](30) • Campassi et al. (2014) [n=363](31)

Drug	Literature Suggested Target	Recommended Dose	Evidence [sample size]
			• Zhao et al.(2021) [n=209](29) • Helset et al. [n=83] (2020) (32) • Weigel et al. (2014) [n = 287] Abstract (67) • Sridharan et al. 2020 [n=80] (68)
Linezolid*	There is no clear definition for linezolid's target parameters, an AUC24hours: MIC >119 mg/L/hour has been proposed (36, 37), an alternative target trough concentration ≥ MIC has been proposed(38).	• Insufficient evidence • Continuous IV infusion of 50-75 mg/hour has been suggested (1200 mg/day) • TDM if available	One prospective observational study: • Barrasa et al. (2020) [n=43](35)
Piperacillin/Tazobactam	In the case of critically ill patients, clinicians target a minimum of ≥50% *f*T > MIC, and the preferred target is ≥100% *f*T > MIC. In some cases, experts prefer to target ≥100% *f*T >4 times the MIC(6-8).	• Continuous IV infusion of 18-22.5g/day may be beneficial • TDM with subsequent dose adjustments can help guide dosing	One retrospective observational study: • Carrie et al. (2019) [n=177](19) Nine prospective observational studies: • Huttner et al. (2015) [n=100](13) • Wu et al. (2019) [n=100](39) • Carrie et al. (2018) [n=79](40) • Andersen et al. (2018) [n=22](41) • Carrie et al. (2018) [n=59](45) • Dhaese et al. (2018) [n=110](46) • Carlier et al (2013) [n=61](44) • Weber et al. (2019) [n=24](42) • Akers et al. (2014) n=[13](43)
Ceftolozane/Tazobactam	In the case of critically ill patients, clinicians target a minimum of ≥50% *f*T > MIC, and the preferred target is ≥100% *f*T > MIC. In some cases, experts prefer to target ≥100% *f*T >4 times the MIC(6-8)	• Suggested dose: 3000 mg IV every 8 hours	Two prospective observational studies: • Nicolau et al. 2021 [n=14](48) • Shorr et al. 2021 [n=5152](49)
Enoxaparin*	For venous thromboembolism prophylaxis in moderate to high risk patients, a peak factor Xa level of 0.2 to 0.4 units/mL or trough level of 0.1 to 0.2 units/mL is usually targeted (50)	• Insufficient evidence • A dose of at least of 40 mg subcutaneous twice daily is likely needed for prophylaxis	Two prospective observational study: • Abdel El Naeem et al. (2017) [n=50](51) • Ramos et al. (2018)(69)
Levetiracetam	Suggested reference range: 12 and 46 mg/mL(52, 53)	• Suggested dose: 1.5-2 g IV every 12 hours	Six prospective observational studies: • La et al. (2018) [n=25] Abstract (55) • May et al. (2014) [n=20] Abstract (56) • Spencer et al. (2011) [n=12](57) • Ong et al. 2021 [n=20](54) • Bilbao-Meseguer et al. 2021 [n=27](58) • Sime et al. 2021 [n=30](59)

ABW, actual body weight; CrCl, creatinine clearance; Css, steady state concentration; IBW, ideal body weight; DW, dosing weight [DW= 0.4 (ABW – IBW) +IBW]; HABP, hospital-acquired baceterial pneumonia; LD, loading dose; *f*T > MIC, percent time concentration above the minimum inhibitory concentration (MIC); MD, maintainance dose; TDM, therapeutic drug monitroing; VABP, ventilator-acquired bacterial pneumonia. * No substantial evidence to support the proposed dosing recommendation.

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CHAPTER 4 COMPARISON OF NIMODIPINE FORMULATIONS AND ADMINISTRATION TECHNIQUES VIA ENTERAL FEEDING TUBES IN PATIENTS WITH ANEURYSMAL SUBARACHNOID HEMORRHAGE: A MULTICENTER RETROSPECTIVE COHORT STUDY

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Key words: nimodipine; aneurysmal subarachnoid hemorrhage; diarrhea; vasospasm; enteral administration; delayed cerebral ischemia

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ABSTRACT

Background: Delayed cerebral ischemia (DCI) is the main complication that contributes to unfavorable outcomes in patients with aneurysmal subarachnoid hemorrhage (aSAH). Nimodipine is the only drug shown to decrease the incidence of DCI and improve patient outcomes ***(Class I; Level of Evidence A)***. Therefore, current guidelines suggest that all aSAH patients receive oral nimodipine for 21 days. Patients with no difficulty swallowing will swallow the whole capsules or tablets; otherwise, nimodipine liquid must be drawn from capsules, tablets need to be crushed or the commercially available liquid product to be used to facilitate administration through an enteral feeding tube (FT). It is not clear whether these techniques of administration are equivalent. Therefore, the overall goal of the study was to determine if different nimodipine formulations and administration techniques via FT were associated with the safety and effectiveness of nimodipine.

Methods: This was a retrospective multicenter observational cohort study conducted in 21 hospitals across North America. Medical records of patients admitted with aSAH were reviewed. Those who received nimodipine by enteral FT for ≥ 3 days were included. Patient demographics, disease severity, nimodipine administration and study outcomes (prevalence of diarrhea, nimodipine dose reduction (from 60 mg Q4h to 30 mg Q2h) or discontinuation secondary to hypotension and DCI) were collected. Descriptive statistics were used to present the data. Predictors of the study outcomes were analyzed using regression modeling.

Results: A total of 727 patients were included. Administration of nimodipine oral liquid product was independently associated with higher prevalence of diarrhea compared to other administration techniques/formulations (OR 2.31, 95%CI 1.46 - 3.66, *p*-value < 0.0001 and OR 3.22, 95% CI 1.61-6.41, *p*-value = 0.001, for old and new commercially available formulations, respectively). Bedside withdrawal of liquid from nimodipine capsules prior to administration was significantly associated with higher prevalence of nimodipine dose reduction or discontinuation secondary to blood pressure reduction (OR 2.82, 95%CI 1.57-5.06, *p*-value = 0.001). Tablet crushing and bedside withdrawal of liquid from capsules prior to administration were associated with increased odds of DCI (OR 6.66, 95%CI 3.48-12.74, *p*-value < 0.0001 and OR 3.92, 95%CI 2.05-7.52, *p*-value<0.0001, respectively). No differences were observed between groups in the rates of mortality.

Conclusions: Our findings suggest that different enteral nimodipine formulation and administration techniques are associated with the propensity for diarrhea, hypotension and DCI.

This could be attributed to excipient differences, inconsistency and inaccuracy in medication administration and altered nimodipine bioavailability. Further studies are needed to determine the optimal formulation/technique for enteral nimodipine administration.

Key words: nimodipine; aneurysmal subarachnoid hemorrhage; diarrhea; vasospasm; enteral administration; delayed cerebral ischemia

4.1 INTRODUCTION

Aneurysmal subarachnoid hemorrhage (aSAH) is a neurological emergency resulting from blood extravasating into the subarachnoid space secondary to ruptured brain aneurysm. The average mortality rate following aSAH is estimated to range from 30 to 50%, with approximately one-third of aSAH survivors experiencing debilitating cognitive and functional disabilities (1-3). Delayed cerebral ischemia (DCI) and vasospasm are the primary complications contributing to unfavorable outcomes following aSAH. Calcium channel blockers play a crucial role in significantly reducing the incidence of post-SAH arteriopathy, subsequently improving patients' functional outcomes. Nimodipine, administered as 60 mg every 4 hours for 21 days, is the only oral calcium channel blocker that has been shown to decrease the rates of DCI and improve neurological outcomes and hence recommended by clinical guidelines (Class I; Level of Evidence A). (1, 3).

In the United States (US), oral nimodipine is available in soft gelatin capsules and oral liquid forms, while in Canada the only dosage form currently available is nimodipine tablets. Conscious and capable patients swallow whole nimodipine tablets or capsules. However, in Canadian institutions, for those patients who are unable to swallow whole tablets due to mechanical ventilation, altered mental status, dysphagia, or other reasons, nursing staff crush nimodipine tablets, suspend it in water and administer it through enteral feeding tubes (FT). Nevertheless, according to the nimodipine manufacturer's monograph, the tablets should not be crushed prior to administration as this may decrease its intended bioavailability and clinical effectiveness (4). In US institutions where the nimodipine soft gelatin capsules are available, the liquid is often siphoned from the soft gelatin capsule shell in clinical practice. This is done either by the nursing staff in the intensive care unit (ICU) and administered through FT by oral syringes, or by the pharmacy staff to prepare an extemporaneously prepared liquid which is then measured in oral syringes and administered through FT. In US institutions where a nimodipine oral liquid

product (Nymalize®) is available, it is directly administered through the FT. The dose in this case is either measured from 6mg/ml nimodipine bottles or premeasured 30 mg and 60 mg oral syringes. It is not clear, however, whether these formulations and techniques of administration are equivalent and equally well tolerated. Anecdotal evidence suggests that patients receiving the nimodipine oral liquid product exhibit a higher incidence of diarrhea. In addition, some studies suggest that that the bioavailability of nimodipine is reduced when administered through FT, especially in more severe aSAH (5, 6). However, the evidence is sparse, suggesting the need to address this knowledge gap. Therefore, the overall goal of the study was to determine if different nimodipine formulations and administration techniques via FT were associated with the safety and effectiveness of nimodipine in aSAH.

The primary objective of the study was to compare the safety of enteral nimodipine formulations and administration techniques. Safety endpoints included the prevalence of diarrhea and nimodipine dose reduction or discontinuation secondary to blood pressure reduction. The secondary objective was to determine if nimodipine administration techniques are associated with patient outcomes, including angiographic evidence of vasospasm using digital subtraction angiography, DCI (as defined in the methods section) and hospital mortality. To our knowledge, this is the first study of this scale to perform such comparisons.

4.2 METHODS

4.2.1 Study Design

This was a multicenter, retrospective, observational cohort study conducted across 21 hospitals in North America. Site investigators individually obtained ethics approval, each from their corresponding institutional review board (IRB) and were subject to the governing regulations set by their IRBs. For this study design, informed consent was not required. The study was performed in compliance with the Declaration of Helsinki ethical standards and its later amendments or comparable sets of ethical standards in each jurisdiction.

4.2.2 Study Population

Medical records of patients admitted to any of the participating hospitals and treated with nimodipine were reviewed. Inclusion criteria were non-traumatic SAH diagnosis, age 18 years or older and those who received nimodipine through enteral FT for 3 or more days and admitted within the dates of January 1st 2016, to July 31st, 2020.

4.2.3 Data Extraction

Study data were collected and managed using REDCap electronic data capture tool hosted at the University of Alberta (Edmonton, Alberta, Canada) (7, 8). Data collected included patients' demographics (age, height, weight, and biological sex), aneurysm location, aneurysm treatment (e.g., endovascular coiling, surgical clipping), Fisher scale and Hunt and Hess grade, and presence of pre-existing liver disease (liver cirrhosis or Child Pugh class B or C). Body mass index (BMI) was also calculated for each patient. The nimodipine administration record was collected and included dose, frequency, duration, formulation and technique of administration. The lowest systolic blood pressure (SBP) value before the start of nimodipine and 24 hours after initiation and SBP values reported at the time of dose change or discontinuation were recorded. In addition, administration and duration of liver microsomal enzyme (LME) inducing and inhibiting medications, vasopressors and laxatives were recorded for the first 21 days of hospital stay or until discharge, whichever came first.

Primary endpoints included occurrence and duration of diarrhea and nimodipine dose-reduction or discontinuation (attributed to blood pressure reduction or hypotension as documented in the patient's record). Secondary endpoints included reporting of DCI and hospital mortality. Other outcomes collected were the hospital and intensive care unit (ICU) length of stay and discharge disposition.

4.2.4 Definitions

Diarrhea was defined as the reporting of 3 or more loose or liquid stools per day or documentation of diarrhea in the patient's chart by the medical team. DCI was defined as the documentation of a new onset focal neurological impairment (such as hemiparesis or aphasia), cerebral infarction or a decrease of at least 2 points in Glasgow Coma Score (GCS) that cannot be explained by other causes (10). LME inducers included phenytoin, fosphenytoin, carbamazepine, pentobarbital, phenobarbital, primidone and rifampin. LME inhibitors included fluconazole, verapamil, amiodarone, diltiazem, nicardipine, erythromycin, valproic acid and protease inhibitors.

4.2.5 Data Analysis

Patients were stratified into five main groups corresponding to their nimodipine formulation and administration technique: Group 1 (6 reporting centers, n =178) included patients who received extemporaneously prepared liquid drawn from soft gelatin capsules performed by

trained compounding pharmacy staff; Group 2 (6 reporting centers, n = 96) included patients who received liquid drawn from soft gelatin capsules performed at bedside by the nurse; Group 3 (3 reporting centers, n = 127, Canada) included patients who received crushed nimodipine tablets; Group 4 (11 reporting centers, n = 252) included patients who received the commercially available nimodipine oral liquid product (Nymalize® - old formulation) (11) and Group 5 (4 reporting centers, n = 74) included patients who received the commercially available newly reformulated and premeasured nimodipine liquid (Nymalize® - new formulation) oral syringes which, according to the manufacturer, now contains nearly 44% less polyethylene glycol (PEG) excipient than the original formula (Group 4) (12). If the patient was exposed to more than one enteral formulation or administration technique, they were assigned to the group with highest number of administration days.

Continuous variables (being not normally distributed) were presented as median with interquartile range (IQR) and were compared using Kruskal–Wallis test followed by Dunn's multiple comparison test with Bonferroni correction for multiple comparisons. Categorical variables were presented as frequency and percentage n (%) and were compared using $\chi 2$ or Fisher exact test, as appropriate. The association between covariates (including stratified nimodipine administration groups) and study endpoints were analyzed using univariate logistic regression. Biologically plausible variables, potential confounders (variables seems to significantly differ across the groups) and/or those with p values of < 0.2 were controlled for in the multivariate logistic regression models and adjusted odds ratios (OR) were determined. The fit of the final models with the variables controlled for in the models was confirmed by using Hosmer–Lemeshow goodness-of-fit test. Models' discrimination was compared using the area under the receiver operating characteristic (ROC) curve. Missing data, if any, were handled by complete case analysis. A p value < 0.05 was set as the level of significance. Data analysis was conducted using STATA software version 15 (STATA Corporation, College Station, Texas).

4.3 RESULTS

A total of 842 patient charts from 21 reporting hospitals were reviewed; 115 patient records were excluded as they received enteral nimodipine for less than 72 hours. Therefore, a total of 727 patient records satisfied the inclusion criteria and were analyzed. **Table 4.1** details the baseline

characteristics of the patients included in the study. Females comprised 68% of the study population and the median (IQR) age was 60 (51-69) years. The majority of aneurysms were treated by endovascular coiling [450 (61.9%)], while 170 (23.4%) were treated by surgical clipping. As depicted in **Table 4.1**, groups were similar in terms of baseline characteristics and admission Hunt and Hess grade. However, inter-groups differences were identified. Groups differed in terms of weight, BMI, aneurysm location, aneurysm securing technique (e.g., coiling, clipping, etc.) and Fisher scale, which we attempted to control for the multivariate logistic regression models. **Table 4.2** depicts nimodipine administration regimens in the study groups. The median (IQR) number of days patients received nimodipine collectively was 18 (11-21), and the median (IQR) number of days nimodipine was administered via enteral FT was 12 (7-20) with no significant difference among the study groups. Patients also spent a median (IQR) of 11 (5-17) days receiving nimodipine 60 mg every 4h and 2 (0-8) days receiving 30 mg every 2h. As shown in **Table 4.2**, 109 patients (15%) received LME inducers and 12 (1.7%) received LME inhibitors. Six hundred and seventy patients (92.2%) received any laxative during the reporting period and 627 (86.2%) received an antibacterial drug. A total of 419 (57.6%) patients received vasopressors. These exposures were addressed and accounted for using multiple logistic regression as mentioned in the methods and will be further elaborated below.

7.TABLE 4.1. BASELINE CHARACTERISTICS OF THE STUDY POPULATION

Characteristic		Group 1: Liquid drawn from capsules by the pharmacy department (n =178)	Group 2: Liquid drawn from capsules in the intensive care unit (n=96)	Group 3: Crushed nimodipine tablets (n=127)	Group 4: Nimodipine liquid product (old formulation) (n=252)	Group 5: nimodipine liquid product (new formulation) (n=74)	All patients (n=727)	*P*-value
Number of reporting hospitals[a]		6	6	3	11	4	21	-
Age (years) median (IQR)		58 (50-70)	60 (48-68)	61 (51-68)	60 (51-70)	57.5 (53-67)	60 (51-69)	0.976
Female		127 (71)	67 (69.8)	85 (66.9)	170 (67.5)	45 (60.8)	494 (68)[g]	0.572
Height (cm) median (IQR)		165.1 (160-172.7)[c]	165.1 (160-172.7)[d]	167.3 (160-175)[e]	165.1 (158-173)[f]	165 (158-175)	165.1 (160-173)	0.548
Weight (kg) median (IQR)		79.5 (67.1-95.3)	74.45 (62.4-90)	73 (60-89.7)[b]	73.7 (62.6-85)	71.35 (59.8-92.8)[b]	74.40 (62.6-90)	0.012
Body Mass Index (BMI) median (IQR)		28.3 (24.7-33.2)[c]	27.4 (21.9-31.6)[d]	26.2 (23-29.4)[b,e]	26.6 (23.7-30.5)[b,f]	25.4 (22.5-31.4)[b]	26.99 (23.6-31.2)[g]	0.0018
BMI categories	**Underweight**	3 (1.7)[c]	4 (4.2)[d]	7 (5.7)[e]	4 (1.6)[f]	8 (10.8)	26 (3.6)[g]	< 0.0001
	Normal	47 (26.6)	31 (32.6)	39 (31.97)	84 (34.15)	25 (33.8)	226 (31.7)	
	Overweight	52 (29.4)	29 (30.5)	49 (40.2)	93 (37.8)	19 (25.7)	242 (33.9)	
	Obese	75 (42.4)	31 (32.6)	27 (22.1)	65 (26.4)	22 (29.7)	220 (30.8)	
Aneurysm location	**ACA**	29 (16.3)	7 (7.3)	6 (4.7)	43 (17.1)	20 (27)	105 (14.4)	< 0.0001
	MCA	34 (19.1)	15 (15.6)	33 (25.98)	48 (19.1)	12 (16.2)	142 (19.5)	
	ACOM	15 (8.43)	30 (31.25)	42 (33.07)	38 (15.08)	9 (12.2)	134 (18.4)	
	PCOM	28 (15.7)	17 (17.7)	17 (13.4)	45 (17.9)	7 (9.5)	114 (15.7)	
	Angio negative/Unknown	19 (10.7)	1 (1)	2 (1.6)	17 (6.75)	6 (8.1)	45 (6.2)	
	Other/Multiple locations	53 (29.78)	26 (27.1)	27 (21.3)	61 (24.21)	20 (27)	187 (25.7)	
Aneurysm treatment	**Clipping**	34 (19.1)	39 (40.6)	35 (27.6)	50 (19.8)	12 (16.2)	170 (23.4)	< 0.0001
	Coiling	107 (60.1)	52 (54.2)	82 (64.6)	161 (63.9)	48 (64.9)	450 (61.9)	
	Other treatment[h]	37 (20.8)	5 (5.2)	10 (7.9)	41 (16.3)	14 (18.9)	107 (14.7)	
Fisher grade	**Low grade (1-2)** **Grade 1** **Grade 2**	12 (7.1)[i] 5 (2.96) 7 (4)	4 (4.6)[j] 1 (1.1) 3 (3.4)	7 (6.4)[k] 0 (0) 7 (6.4)	24 (10.9)[l] 3 (1.4) 21 (9.5)	15 (21.7)[m] 2 (2.9) 13 (18.8)	62 (9.5)[n] 11 (1.7) 51 (7.8)	0.004
	High grade (3-4) **Grade 3** **Grade 4**	157 (92.9) 56 (33.1) 101 (59.8)	84 (95.5) 17 (19.3) 67 (76.1)	102 (93.6) 13 (11.9) 89 (81.7)	197 (89.1) 69 (31.2) 128 (57.9)	54 (78.3) 15 (21.7) 39 (56.5)	594 (90.6) 170 (25.9) 424 (64.6)	
Hunt & Hess grade	**Low grade** **Grade 1** **Grade 2** **Grade 3**	102 (59.7)[o] 21 (12.3) 33 (19.3) 48 (28.1)	58 (61.1)[d] 8 (8.4) 20 (21.1) 30 (31.6)	41 (48.2)[p] 3 (3.5) 17 (20) 21 (24.7)	144 (57.8)[q] 21 (8.4) 51 (20.5) 72 (28.9)	33 (47.8)[m] 6 (8.7) 14 (20.3) 13 (18.8)	378 (56.5)[r] 59 (8.8) 135 (20.2) 184 (27.5)	0.189
	High grade **Grade 4** **Grade 5**	69 (40.4) 40 (23.4) 29 (16.96)	37 (39) 26 (27.4) 11 (11.6)	44 (51.8) 16 (18.8) 28 (32.9)	105 (42.2) 49 (19.7) 56 (22.5)	36 (52.2) 23 (33.3) 13 (18.8)	291 (43.5) 154 (23) 137 (20.5)	

All data are presented as n (%) unless otherwise specified; ACA, anterior cerebral artery; ACOM, anterior communicating artery; IQR, interquartile range; MCA, middle cerebral artery; PCOM, posterior communicating artery; a, some centers reported more than one administration technique/formulation; b, significantly different from group 1; c, n=177; d, n=95; e, n=122; f, n=246; g, n=714; h, other: deconstructive

strategy, pipeline embolization, partial Clipping then pipeline stenting, collagen plug, glue embolization, endovascular drain , onyx embolization; i, n=169; j, n=88; k, n=109; l, n=221; m, n=69; n, n=656; o, n=171; p, n=85; q, n=249; r, n=669. Reported p-values are referring to whether between group differences exist.

8.TABLE 4.2. PHARMACOTHERAPY REPORTED IN THE CURRENT STUDY

	Group 1: Liquid drawn from capsules by the pharmacy department (n =178)	Group 2: Liquid drawn from capsules in the intensive care unit (n=96)	Group 3: Crushed nimodipine tablets (n=127)	Group 4: Nimodipine liquid product (old formulation) (n=252)	Group 5: nimodipine liquid product (new formulation) (n=74)	All patients (n=727)	*P*-value
Total number of days of nimodipine median (IQR)	19 (12-21)	17 (12-21)	19 (11-21)	17 (9.75-21)	18.5 (11-21)	18 (11-21)	0.06
Number of days of enteral nimodipine	12 (6-20)	10.5 (6-19)	13 (7-20)	12 (6-19)	12.5 (7-21)	12 (7-20)	0.741
Number of days of oral nimodipine	0 (0-6)	1 (0-6)	0 (0-6)	0 (0-4)	0 (0-5)	0 (0-5)	0.073
Nimodipine dosing median (IQR)							
Number of days of nimodipine 60 mg q4h	10 (4-17)[a]	11 (4.5-16)[a]	16 (7-20)	10 (4-15)[a]	7 (2-14)[a]	11 (5-17)	0.0001
Number of days of nimodipine 30 mg q2h	3 (0-11)[a]	3 (0-9)[a]	0 (0-3)	2.5 (0-7.25)[a]	6 (0-14)[a, b]	2 (0-8)	0.0001
LME inducer use[c] n(%)	17 (9.6)	14 (14.6)	57 (44.9)	19 (7.5)	2 (2.7)	109 (15)	< 0.0001
Phenytoin n(%)	1 (0.6)	10 (10.4)	55 (43.3)	16 (6.4)	1 (1.4)	83 (11.4)	< 0.0001
Number of days of LME inducer [median (IQR)]	2 (2-3)	5 (4-11.5)	5.5 (2-10)	6 (2-12.5)	5.5 (4.75-6.25)	5 (2-10)	0.140
LME inhibitor use[d] n(%)	8 (4.5)	3 (3.1)	0 (0)	1 (0.4)	0 (0)	12 (1.7)	0.003
Any laxative use n (%)	175 (98.3)	95 (99)	124 (97.6)	210 (83.3)	66 (89.2)	670(92.2)	< 0.0001
Stool softener	121 (68)	89 (92.7)	1(0.8)	188 (74.6)	61 (82.4)	460 (63.3)	< 0.0001
Osmotic laxative	135 (75.8)	50 (52.1)	106 (83.5)	101 (40.1)	27 (36.5)	419 (57.6)	< 0.0001
Stimulant laxative	162 (91)	86 (89.6)	80 (63)	169 (67.1)	65 (87.8)	562 (77.3)	< 0.0001
Antibacterial use n(%)	153 (86)	88 (91.7)	116 (91.3)	202 (80.2)	68 (91.9)	627 (86.2)	0.005
Number of days of antimicrobials [median (IQR)]	5.5 (1-10)	8.5 (5-12)[b, e]	8 (4-11)[b, e]	5 (1-11)	6 (3-10)	6 (2-11)	0.0004
Vasopressor use n(%)	103 (58)	71 (74)	59 (46.5)	140 (55.6)	46 (62.2)	419 (57.6)	0.001
Number of days of vasopressors [median (IQR)]	1 (0-6)[f]	4 (0-7)	0 (0-5)[f]	1 (0-4)[f]	2.5 (0-6)	1(0-5)	0.0003

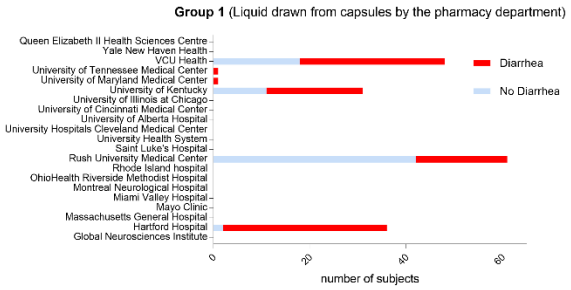
Number of days (continuous data) are presented as median (IQR); categorical data are presented as n(%); LME, liver microsomal enzyme; a, significantly different from group 3; b, significantly different from group 4; c, LME inducers included phenytoin, fosphenytoin, phenobarbital, pentobarbital and carbamazepine; d, LME inhibitors included fluconazole, verapamil, amiodarone, nicardipine, diltiazem, erythromycin and valproic acid; e, significantly different from group 1; f, significantly different from group 2. Reported p-values are referring to whether between group differences exist.

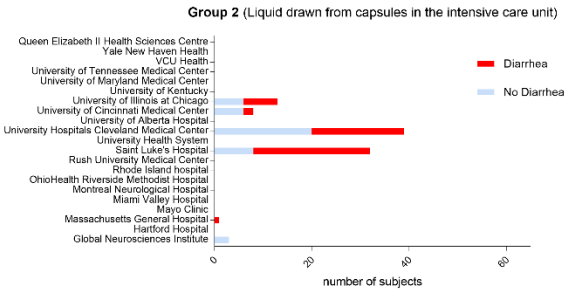
4.3.1 Impact of nimodipine formulations and administration techniques on diarrhea prevalence

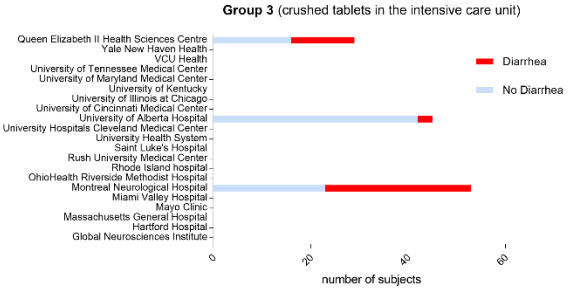
Of the 727 included patients, 444 (61%) experienced diarrhea. The prevalence of diarrhea among the study cohort groups ranged between 36.2% and 78.4% (**Table 4.3**). The highest prevalence was observed in Group 5 receiving the new reformulated Nymalize® at 78.4%; followed by Group 4 receiving the original Nymalize® formulation at 72.2%. The lowest prevalence was observed in Group 3 (crushed tablets) at 36.2%. Diarrhea lasted for a median (IQR) of 2 (0-6) days among the entire population. Groups 4 and 5 had significantly higher number of days of diarrhea compared to the other groups (**Table 4.3**). The median (IQR) numbers of diarrhea days were 4 (0-9) and 4 (1-7) in Groups 4 and 5, respectively; while for groups 1, 2 and 3, number of days were 1 (0-4), 1 (0-3) and 0 (0-2), respectively.

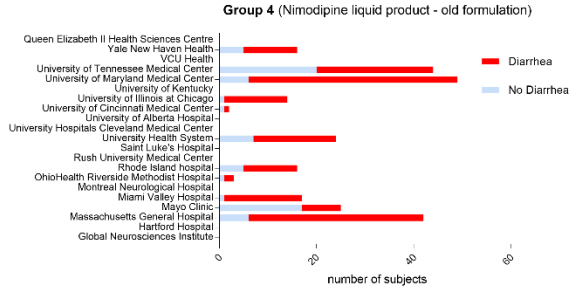
Univariate followed by multivariate logistic regression analyses were performed to identify covariates associated with diarrhea. After controlling for antibacterial use, laxative use, BMI and Fisher grade, compared to Group 1 as a reference (baseline group), Groups 4 and 5 were significantly associated with increased odds of diarrhea (OR 2.31, 95%CI 1.46 - 3.66, p-value < 0.0001 and OR 3.22, 95%CI 1.61-6.41, p-value = 0.001, respectively). On the other hand, Group 3 was significantly associated with decreased odds of diarrhea (OR 0.32, 95%CI 0.19 - 0.54, p-value < 0.0001) compared with Group 1. We selected Group 1 to be the baseline group because this is where the liquid has been accurately extracted from the capsules at the pharmacy departments of the participating hospitals, representing the best possible measure taken to prevent decrements to the amount or the bioavailability of nimodipine. (**Table 4.4**). To check if the observed findings are not driven by a single center, we examined the unadjusted prevalence of diarrhea in individual institutions. As depicted in Supplementary Figure 4.1, most centers within Groups 4 and 5 receiving the commercially available formulations, had higher prevalence of diarrhea.

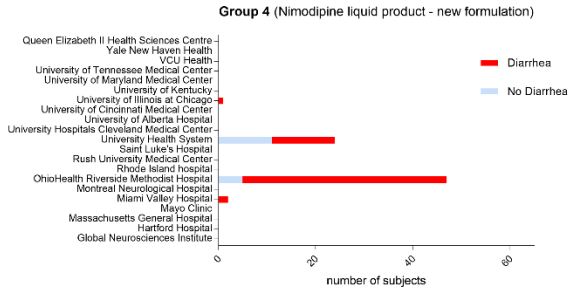
7.FIGURE 4.1. COMPARISON OF THE PREVALENCE OF DIARRHEA BY CENTER







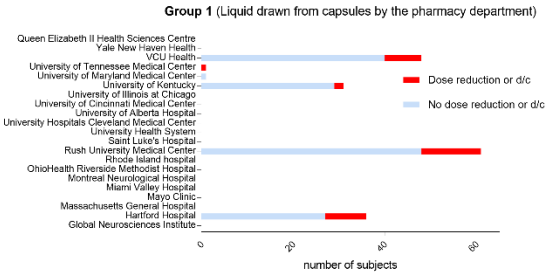


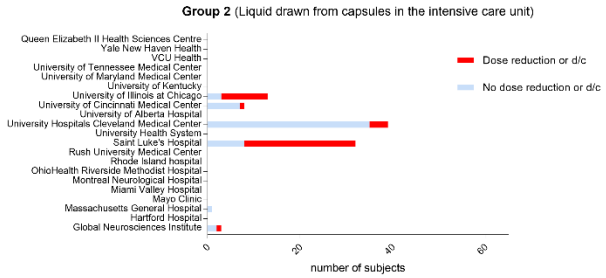


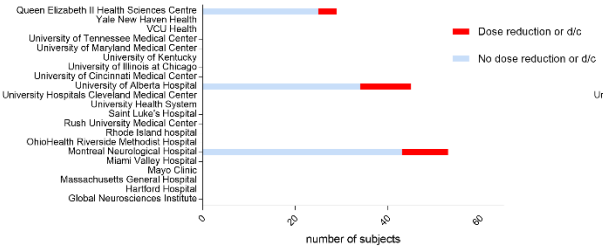
4.3.2 Impact of nimodipine formulations and administration techniques on nimodipine dose reduction or discontinuation secondary to hypotension

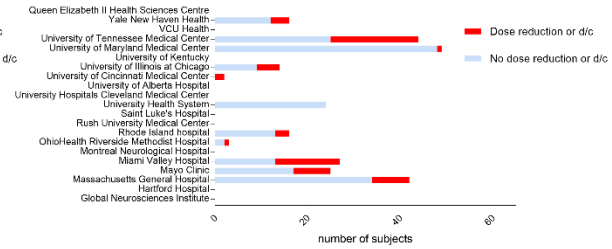
Nimodipine dose reduction (from 60 mg Q4h to 30 mg Q2h) or discontinuation secondary to hypotension was reported in 171 (23.5%) patients (**Table 4.3**), with Group 2 (liquid drawn at bedside) having the highest prevalence (41.7%, *p*-value = 0.0003). Using multivariate logistic regression, after controlling for age, BMI and Fisher grade, Group 2 was significantly associated with dose reduction and discontinuation (OR 2.82, 95%CI 1.57-5.06, p-value = 0.001) (**Table 4.4**). To check if the observed findings are not driven by a single center, we examined the unadjusted prevalence of nimodipine dose reduction or discontinuation secondary to blood pressure reduction in individual institutions. As depicted in Supplementary Figure 4.2, it seems that the high prevalence observed Group 2 was driven by two centers.

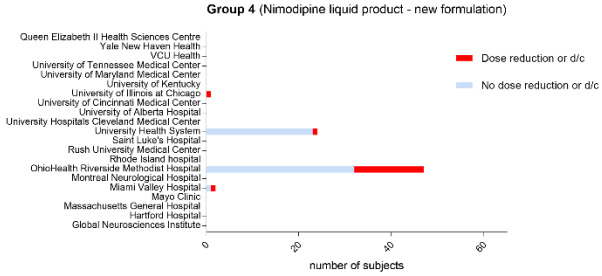
8.FIGURE 4.2. COMPARISON OF THE PREVALENCE OF DOSE REDUCTION OR DISCONTINUATION BY CENTER







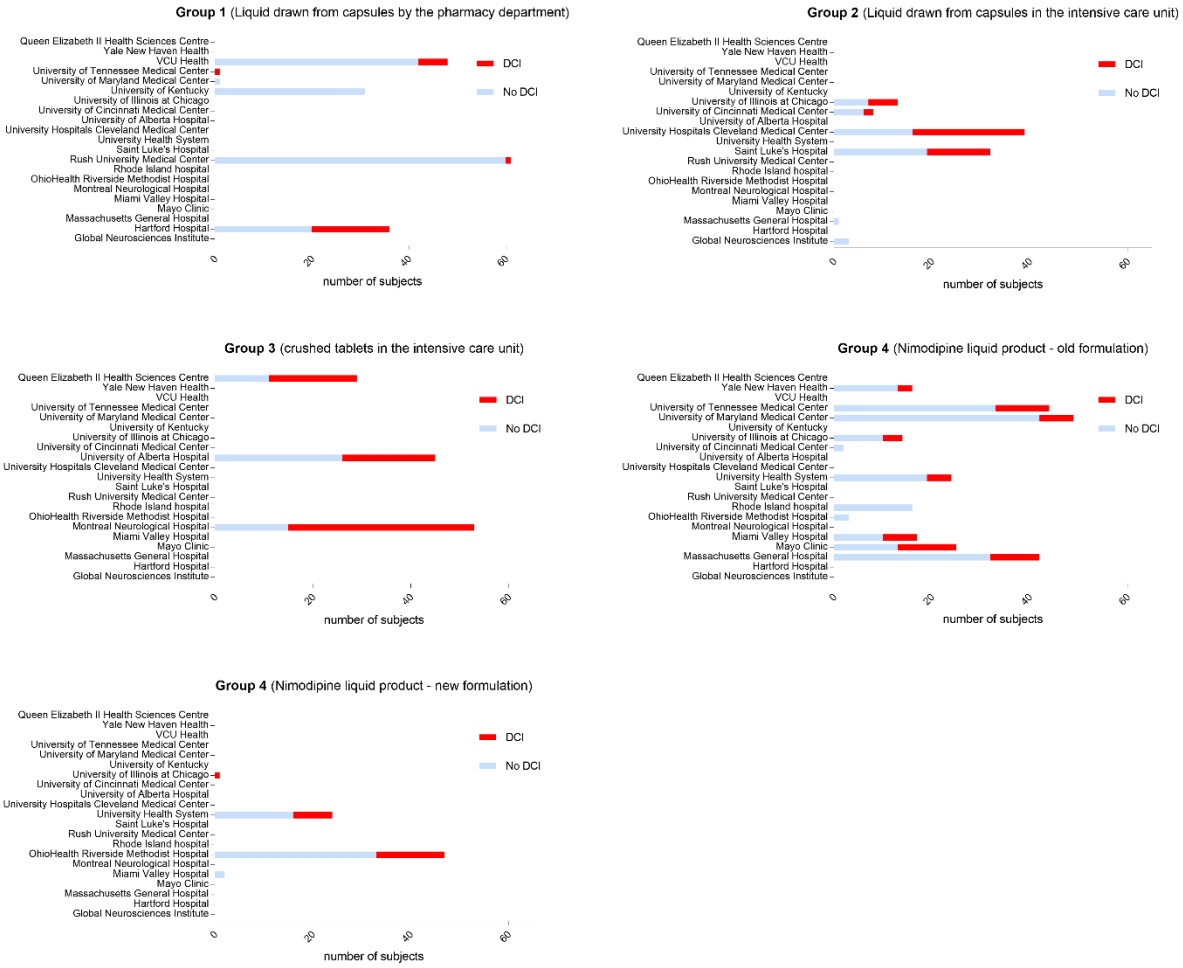




4.3.3 Impact of nimodipine formulations and administration techniques on patient outcomes

Secondary endpoints included DCI and hospital mortality (**Table 4.3**). A total of 225 (31%) patients experienced DCI. The magnitude of group-wise differences in DCI was higher than expected. There was a statistically significant difference ($p < 0.0001$) in DCI prevalence among the study groups (**Table 4.3**). The highest prevalence was observed in Group 3 (crushed tablets) at 59.1% followed by Group 2 (liquid drawn at bedside) at 45.8%. The lowest prevalence was observed in Group 1 (liquid drawn by pharmacy) at 13.5%. After controlling for age, BMI, aneurysm location, aneurysm treatment, Fisher grade, and LME inducer use, Groups 2, 3, 4 and 5, were significantly associated with increased odds of DCI compared to Group 1 as a reference, where Groups 2 and 3 had the highest adjusted OR (**Table 4.4**). To check if the observed findings are not driven by a single center, we examined the unadjusted prevalence of DCI in individual institutions. As depicted in Supplementary Figure 4.3, it seems that institutions in Groups 2 and 3 had higher prevalence of DCI compared to other groups. None of the groups were associated with mortality after controlling for age, Hunt and Hess grade and female sex (**Table 4.4**).

9.FIGURE 4.3. COMPARISON OF THE PREVALENCE OF DCI BY CENTER



9.TABLE 4.3. HOSPITAL COURSE AND PATIENT OUTCOMES

		Group 1: Liquid drawn from capsules by the pharmacy department (n =178)	Group 2: Liquid drawn from capsules in the intensive care unit (n=96)	Group 3: Crushed nimodipine tablets (n=127)	Group 4: Nimodipine liquid product (old formulation) (n=252)	Group 5: nimodipine liquid product (new formulation) (n=74)	All patients (n=727)	*P*-value
Diarrhea		105 (59)	53 (55.2)	46 (36.2)	182 (72.2)	58 (78.4)	444 (61)	< 0.0001
Number of days of diarrhea		1 (0-4)[a, b, c]	1 (0-3)[a, b]	0 (0-2)[a, b]	4 (0-9)	4 (1-7)	2 (0-6)	0.0001
Mean SBP reduction[d]		-12.5 (-27 to 0)	-7 (-23 to 5)	-6 (-24 to 6)	-9 (-21 to 5)	-4.5 (-20 to 6)	-9 (-23 to 5)	0.105
Nimodipine discontinuation[e]		55 (31)	32 (33.3)	56 (44.1)	62 (24.6)	24 (32.4)	229 (31.5)	0.004
Nimodipine dose reduction[e]		86 (48.3)	61 (63.5)	46 (36.2)	72 (28.6)	30 (40.5)	295 (40.6)	< 0.0001
Nimodipine dose reduction or discontinuation secondary to hypotension		33 (18.5)	40 (41.7)	25 (19.7)	55 (21.8)	18 (24.3)	171 (23.5)	0.0003
SBP value at the time of nimodipine dose reduction or discontinuation secondary to hypotension (mmHg)		113 (99-130)[c]	110 (99-131)[c]	128 (107-160)	111 (97-121)[c]	106 (95-118)[c]	113 (99-130)[c]	< 0.0001
DCI		24 (13.5)	44 (45.8)	75 (59.1)	59 (23.4)	23 (31.1)	225 (31)	< 0.0001
Onset day of DCI		6.5 (3-10)	6 (4-9)	5 (2-7)	6 (4-10)	5 (4-9)	5 (3-9)	0.083
Discharge outcome	Discharged home	45 (25.3)	12 (12.5)	13 (10.2)	63 (25)	12 (16.2)	145 (19.9)	< 0.0001
	Transfer to acute care hospital	46 (25.8)	4 (4.2)	36 (28.4)	30 (11.9)	32 (43.2)	148 (20.4)	
	Transfer to continuing care	62 (34.8)	59 (61.5)	46 (36.2)	103 (40.9)	16 (21.6)	286 (39.3)	
	Died	25 (14)	21 (21.9)	32 (25.2)	56 (22.2)	14 (18.9)	148 (20.4)	
ICU LOS		17(13-22)[a, c]	18(14-21)[a, c]	15(9-20)	15(10-20)	15.5(12-19)	16(11-21)	0.0001
Hospital LOS		22(15-27)[c]	21(17-27)[c]	27(19-42)	18(11.5-26.5)[c]	21(14-25)[c]	21(15-28)	0.0001

Continuous data are presented as median (IQR); categorical data are presented as n (%); DCI, delayed cerebral ischemia; SBP, systolic blood pressure; a, significantly different from group 4; b, significantly different from group 5; c, significantly different from group 3; d, calculated by subtracting the lowest SBP 24h before nimodipine initiation from the lowest SBP 24h after nimodipine initiation; e, due to any cause. Reported *p*-values are referring to whether between group differences exist.

10.TABLE 4.4 ADJUSTED ODDS RATIOS OF ENTERAL NIMODIPINE ADMINISTRATION GROUPS AND STUDY ENDPOINTS

	Group 1: Liquid drawn from capsules by the pharmacy department	Group 2: Liquid drawn from capsules in the intensive care unit	Group 3: Crushed nimodipine tablets	Group 4: Nimodipine liquid product (old formulation)	Group 5: nimodipine liquid product (new formulation)
Diarrhea[a]	Reference	OR 0.84, CI 0.49 - 1.43, p = 0.512	OR 0.32, CI 0.19 - 0.54, p < 0.0001	OR 2.31, CI 1.46 - 3.66, p < 0.0001	OR 3.22, CI 1.61 – 6.41, p = 0.001
Dose reduction or D/C[b]	Reference	OR 2.82, CI 1.57 – 5.06, p = 0.001	OR 1.08, CI 0.58 – 2.01, p = 0.806	OR 1.25, CI 0.75 – 2.08, p = 0.391	OR 1.37, CI 0.69 – 2.75, p = 0.369
DCI[c]	Reference	OR 3.92, CI 2.05 – 7.52, p < 0.0001	OR 6.66, CI 3.48 – 12.74, p < 0.0001	OR 2.02, CI 1.15 – 3.54, p = 0.014	OR 3.16, CI 1.55 – 6.42, p = 0.001
Hospital mortality[d]	Reference	OR 1.86, CI 0.93 - 3.75, p = 0.082	OR 1.84, CI 0.91 – 3.72, p = 0.087	OR 1.61, CI 0.92 – 2.83, p = 0.095	OR 1.29, CI 0.58 – 2.86, p = 0.533

CI, 95% confidence interval; DCI, delayed cerebral ischemia; Dose reduction of D/C, nimodipine dose reduction of discontinuation secondary to blood pressure reduction; OR, adjusted odds ratio; a, controlled for any laxatives use, antibacterials use, body mass index (BMI) and Fisher grade (n=648); b, controlled for age, BMI and Fisher grade (n=648); c, controlled for age, BMI, aneurysm location, aneurysm treatment, Fisher grade and liver microsomal enzyme inducer use (n = 648); d, controlled for age, female sex and Hunt and Hess grade (n=669).

4.4 DISCUSSION

In this study we compared available enteral nimodipine formulations and administration techniques in terms of tolerability and effectiveness. Our findings suggest that enteral nimodipine formulations and administration techniques are associated with the propensity for diarrhea, hypotension, and DCI.

In our study, patients in Groups 4 and 5 (both commercially available nimodipine liquid formulations) had the highest diarrhea prevalence and Group 3 (crushed tablets) had the lowest prevalence. Data on the prevalence of diarrhea among aSAH patients are limited. Our findings are similar to anecdotes and clinical experience suggesting diarrhea is highly prevalent in patients receiving the nimodipine oral liquid product (12). In a single center study conducted by Brooker et al, 82.4% of those who received the nimodipine oral liquid product developed diarrhea (12). However, the study was limited by its small sample size. On the other hand, the prevalence of diarrhea reported in drug product monographs were much lower than our study, ranging from 1.7-4.2% (11, 13). These data are merely derived from the results of clinical studies where the patient population received nimodipine capsules as opposed to nimodipine liquid. In addition, 92.2% and 86.2% of our cohort received laxatives and antibacterials, respectively, potentially contributing to the increased prevalence of diarrhea. However, despite controlling for these covariates, the association between the formulation and administration technique and diarrhea still existed. This could be attributed to variation in the amount of excipients in each formulation, notably the amount of PEG content, an ingredient with laxative properties, evidenced by the high odds of diarrhea in groups 4 and 5 receiving the commercially available nimodipine oral liquid products containing a high PEG content. Although the reformulated oral liquid product has been marketed for the benefit of containing double the nimodipine concentration (6 mg/ml) compared to the original formulation, allowing for administration of half the liquid volume for the same dosage (and approximately 44% less PEG), Group 5 still demonstrated high odds of diarrhea. Therefore, it is recommended to exercise caution when using nimodipine oral liquid product and to reduce the concomitant use of laxatives. Contrarily, other formulations and administration techniques (Groups 1, 2 and 3) had a lower propensity for diarrhea, suggesting better tolerability in this regard.

Despite it being the only preventive treatment for DCI after aSAH, the main challenge limiting the dosing of nimodipine is hypotension. Oral or intravenous nimodipine administration yields a cerebrospinal spinal fluid (CSF) concentration that is ten-fold lower than the plasma concentration (14). Hypotension starts to occur at a 30 ng/ml plasma nimodipine concentration (14). This hypotension safety risk hampers the ability to determine if higher doses of oral nimodipine would prove more effective. Further clinical studies are currently attempting to evaluate the safety and effectiveness of local delivery options as a way of bypassing or curbing systemic limitations (15-20). In our study, we found the highest prevalence of nimodipine dose reduction or discontinuation due to blood pressure reduction was seen in Group 2. The rationale behind this finding is unclear. This could be attributed to institutional practice differences in their threshold for initiating vasopressors and discontinuing or reducing the dose of nimodipine especially since Group 2 had the highest percentage of vasopressor use compared to other groups. It should be noted, that due to the retrospective nature of the study, we are unable to determine the exact cause of hypotension in those patients, which could have been attributed to SAH-related cardiovascular and cerebrovascular dysfunctions rather than nimodipine-induced blood pressure reduction and the results should be interpreted with caution.

Although the prevalence of DCI in the study population is consistent with existing literature, Groups 2 (liquid drawn at bedside) and 3 (crushed tablets) demonstrated the highest odds of developing DCI (21). This raises the concern that enteral nimodipine formulation and administration techniques may not be equivalent in terms of their effectiveness. This could be attributed to altered nimodipine systemic exposure secondary to inconsistency in medication administration and variations in nimodipine oral bioavailability notably for Groups 2 and 3. To illustrate, Oyler et al. have found that simulated bedside extraction of 30 mg nimodipine capsule contents provided inconsistent and lower yield compared to pharmacy-compounded oral syringes (22.6±4.6 mg vs. 30.4±0.59 mg, respectively, p-value = 0.001), suggesting potential inaccuracies of bedside extraction of capsule contents (as done in Group 2) (22). In addition, the observed differences are less likely due to variations in the FT placement as approximately 93% of the participating hospitals reportedly utilize gastric positioning of the FT. With regard to nimodipine tablets, the manufacturer recommends against tablet crushing (as done in Group 3) as this may reduce nimodipine bioavailability and effectiveness (4). A few small studies have corroborated the

manufacturer's recommendation. To illustrate, Kumana et al. have reported reduced systemic exposure in a patient where nimodipine was administered as crushed tablets via a gastric tube (23). Abboud et al. compared enteral and parenteral nimodipine plasma concentrations in patients switched from intravenous to oral routes. They have reported lower bioavailability in patients receiving nimodipine tablets via an FT compared to those who swallowed whole tablets (24). Moreover, in a single center retrospective study, Isse et al. have reported an association between nimodipine administration technique and patient outcomes where patients receiving crushed nimodipine tablets enterally had worse outcomes compared to those who received whole tablets after controlling for disease severity (5). However, this study was a single center study with small sample size, limiting its generalizability. Furthermore, nimodipine is light-sensitive and is subject to photodegradation if not administered immediately or stored properly, further contributing to administration inconsistencies (25, 26). This would be of relevance to Groups 2 and 3 as in both cases nimodipine dose needs to be prepared in the ICU before administration, which may remain in the medicine cup or oral syringe for variable times resulting in various degrees of photodegradation. Another factor that influences nimodipine exposure is the use of LME inducers. Although Groups 2 and 3 had the highest use of LME inducers, the median number of days on LME inducer was less than one week in both groups. In addition, it was controlled for as a confounder in our regression modeling and administration group remained an independent predictor for DCI. Taken together, it would be prudent to avoid crushing nimodipine tablets (Group 3) or to administer liquid drawn from soft gelatin capsules performed at bedside by the nurse (Group 2) for enteral administration techniques as common practice. Alternative administration techniques and formulations should be considered.

Our study is limited by the retrospective nature of the study design. Hence, there might have been other unforeseen or uncaptured confounders such as institutional practice variations and other patient-extrinsic factors (e.g., health systems and socioeconomic factors) across the reporting sites that may have contributed to the study findings. Those factors may be overrepresented within different nimodipine administration groups. Although, we were unable to control for institutional practice differences due to collinearity with nimodipine groups and other unknown confounder, we carefully looked at outcomes shown to be significant (diarrhea, DCI and nimodipine discontinuation) in individual institutions and it seems that the study findings are not driven by a single center (Supplementary Figures S1-S3). Another limitation is the variability of data

collection across study centers. However, we tried to standardize all study definitions across the reporting sites to minimize such limitation.

Although we have tried to control for as many confounders as possible to account for these variations, with the existence of inter-group differences, the findings of the present study should be interpreted with caution and further prospective studies are warranted to overcome such limitations.

4.5 CONCLUSION

Aneurysmal Subarachnoid hemorrhage is a devastating medical emergency that needs prompt medical and surgical care. The proven benefit of nimodipine in the aSAH population warrants that every patient should receive it, if tolerated. Our findings suggest that different enteral nimodipine formulation and administration techniques are associated with the propensity for diarrhea, hypotension and DCI. Observed differences in diarrhea prevalence could be attributed to variation in the amount of excipients in each formulation, notably the amount of PEG content, an ingredient with laxative properties, rather than nimodipine, the active ingredient, potency changes. Therefore, differences in diarrhea not necessarily parallels differences in DCI and BP changes. On the other hand, factors affecting nimodipine potency (inconsistency and inaccuracy in medication preparation, dose measurement and administration and altered nimodipine bioavailability) could contribute, at least in part, to the observed DCI changes; however, this did not translate into parallel differences in BP changes. The reason for this discrepancy is unclear which could be attributed to institutional practice differences in their threshold for initiating vasopressors and discontinuing or reducing the dose of nimodipine. Although we have tried to control for as many confounders as possible to account for these variations, with the existence of inter-group differences, the findings of the present study should be interpreted with caution. Further studies are needed to determine the optimal enteral nimodipine formulation and administration technique for aSAH patients unable to swallow oral nimodipine capsules.

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Conflict of Interest

The authors declare that they have no conflicts of interest

Statement of Human Rights and Informed Consent

The study was approved by the Health Research Ethics Board (HERB) of the University of Alberta. Participating centers individually obtained approval, each from their corresponding institutional review board (IRB) and were subject to the governing regulations set by their IRBs. For this study design, informed consent was not required. The study was performed in compliance with the Declaration of Helsinki ethical standards and its later amendments or comparable sets of ethical standards in each jurisdiction.

Author Contributions

SHM and GMB primarily contributed to study conception and design, but all authors had input on study design and execution. Data collection was conducted by all authors. Data analysis was performed primarily by FRH and SHM; all authors had input on data interpretation. FRH, SHM, and GMB primarily wrote the manuscript, but all authors were able to review and revise. All authors approved the final version of the manuscript.

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CHAPTER 5 DISCUSSION

Critical illness is defined as any life-threatening condition that requires pharmacological treatment and/or mechanical support to the function of vital organ functions to reduce the risk of death. Pharmacotherapy in critically ill patients is particularly challenging due to the heterogeneous nature of these patients combined with the often limited evidence available on drug dosing in critically ill patients. This often leads to off-label drug use and a high degree of individualization of drug regimens. The significant deviations of PK and PD of drugs used in critically ill patients compared to the patient groups whose data informed the conventional dosing regimens also add the challenge.

ARC is prevalent in critically ill patients where renal clearance is exceeds 130 ml/min/1.73m^2. ARC poses the risk of causing therapeutic failure of predominantly renally cleared drugs, which are often life saving in these patients. It has been found to be associated with higher rates of failure to attain therapeutic levels and compromised effectiveness of various drugs. Standard doses of renally eliminated medications typically used in patients with "normal" renal function are insufficient to attain pharmacodynamic targets in the presence of ARC. Studies suggested that ARC might be associated with subtherapeutic concentrations of antimicrobials (1-4), higher risk of therapeutic failure (5), increased odds of recurrent infections (6), and poor seizure control (7).

The finding of our research demonstrated the common occurrence of ARC in critical care settings with higher prevalence among neurocritical care and trauma patients compared to mixed ICU population. Our synthesized ARC prevalence emphasized the extent to which different critically ill populations are at an inequivalent risk for ARC. It also highlighted the importance of screening for ARC in select patient populations, and the need to develop new screening tools that accounts for these risk differences. Our meta-analytic estimates of age, male sex and trauma as risk factors for ARC, with pooled OR (95% CI) of 0.95 (0.93–0.96), 2.36 (1.28–4.36), 2.60 (1.21–5.58), respectively , highlight the importance of proactively screening for ARC in those with apparently normal renal function and lower disease severity scores. Our meta-analytic estimates of prevalence for neuro, trauma, mixed and sepsis ICUs - 74 (55–87), 58 (48–67), 36 (31–41) and 33 (21–48), respectively- highlight the importance of prioritizing ARC screening for higher risk sub-

populations such as neuro and trauma ICU patients and possibly warranting measurements of their urinary creatinine to rule out ARC (8).

The clinical relevance of ARC lies in its implications on drug dosing of renally eliminated drugs often used in the ICU. It's been consistently reported that ARC patients often need alternate drug regimens to compensate for the accelerated clearance. Although the currently available evidence is not exhaustive of all drugs used in the ICU or other settings, it can be assumed that all renally eliminated drugs in this patient population will be at a higher risk of therapeutic failure or target non-attainment and it would be prudent to take precautions to mitigate for this risk such as TDM.

It is important to remember that ARC is one of multiple pathophysiological changes such as alterations in gastric pH and the rate and extent of absorption of orally administered drugs, and reductions in hepatic blood flow or enzyme activity. These need to be taken into account when following standard drug regimens (9).

Our research into the role of nimodipine in aSAH treatment is a direct application on the pharmacokinetic and pharmacodynamic alterations in critically ill patients. aSAH is associated with a high morbidity and mortality burden and nimodipine is currently the only recommended drug therapy for improving patient outcomes. We compared the tolerability and effectiveness of enteral nimodipine formulations and techniques in the treatment of aSAH in our cohort study. Our findings suggesting that enteral nimodipine formulations and administration techniques are associated with the propensity for diarrhea, hypotension and DCI highlights the importance of optimizing technique of delivery of nimodipine in this vulnerable patient population.

With regards to safety, patients receiving commercially available liquid nimodipine had the highest odds of experiencing diarrhea where patients receiving crushed tablets had the lowest odds despite controlling for covariates such as laxatives and antibacterials. Although data on the prevalence of diarrhea among aSAH patients are limited, our findings are consistent with anecdotes and clinical experience suggesting diarrhea is highly prevalent in patients receiving nimodipine oral liquid (10). It is important to note that the prevalence of diarrhea reported in drug product monographs were much lower than the findings of our study, ranging from 1.7-4.2% (11, 12). Additionally,

although the reformulated oral liquid product has been marketed for the benefit of containing double the nimodipine concentration (6 mg/ml) and approximately 44% less PEG than the original formulation, patients receiving the product still demonstrated higher odds of diarrhea. Therefore, recommend caution when using nimodipine oral liquid product and to reduce the concomitant use of laxatives, as well as consider other formulations with arguably better tolerability in this regard.

Also in the safety regard, the main challenge limiting the dosing of nimodipine is hypotension (13). Our results suggest that the highest prevalence of nimodipine dose reduction or discontinuation due to hypotension was seen in patients receiving nimodipine liquid drawn from capsules by the pharmacist. Although the rationale behind this finding is unclear, it could be attributed to institutional practice differences in their threshold for initiating vasopressors and discontinuing or reducing the dose of nimodipine especially. However, due to the retrospective nature of the study, we are unable to conclusively determine if the hypotension in those patients, is nimodipine-induced. Therefore, we recommend caution interpreting these results; as well as considering other pathophysiological changes that might contribute to this finding e.g. reduction in hepatic blood flow or enzymatic activity, alterations in gastric pH and the extent of absorption of oral drugs.

With regards to the effectiveness side of the comparison; although the prevalence of DCI in our study population is consistent with existing literature, our results show patients receiving liquid drawn from capsules at bedside and patients receiving crushed tablets demonstrated the highest odds of developing DCI (14), suggesting that enteral nimodipine formulation and administration techniques may not be equivalent in terms of their effectiveness. This could be attributed to altered nimodipine systemic exposure secondary to inconsistency in medication administration and variations in nimodipine oral bioavailability notably for patients receiving liquid from capsules drawn at bed side or crushed tablets since they are both done by the nursing staff. This interpretation is supported by evidence suggesting potential inaccuracies of bedside extraction of capsule contents (15) and the notion that it the observed differences are less likely due to variations in the FT placement as approximately 93% of the participating hospitals reportedly utilize gastric positioning of the FT.

In patients receiving crushed nimodipine tablets, the manufacturer recommends against tablet crushing as this may reduce nimodipine bioavailability and effectiveness (16). A few small studies have corroborated the manufacturer's recommendation (17-19). Therefore, it would be prudent to avoid crushing nimodipine tablets or to consider alternative formulations such as liquid drawn from soft gelatin capsules for enteral administration techniques as common practice.

To address our limitations, although we were unable to control for institutional practice differences due to collinearity with nimodipine groups and other unknown confounder, we carefully looked at outcomes shown to be significant (diarrhea, DCI and nimodipine discontinuation) in individual institutions and it seems that the study findings are not driven by a single center (Supplementary Figures S4.1-S4.3). Another limitation is the variability of data collection across study centers. However, we aimed to standardize all study definitions across the reporting sites to minimize such limitation. Additionally, we attempted to control for as many confounders as possible to account for these variations. However, with the existence of inter-group differences, the findings of the present study should be interpreted with caution as further prospective studies are warranted to overcome such limitations.

To conclude, ARC is a prevalent phenomenon in critically ill adults and particularly neurocritical care and trauma patients, as well as younger patients with lower disease severity scores. Further prevalence studies are needed to develop risk scores that account for the risk differences between critically ill sub-populations towards developing ARC and provide clinicians with practical and accurate predictive tools to screen for ARC. Patients affected by ARC are consistently in need of alternate drug regimens to compensate for the accelerated clearance of renally eliminated drugs Further studies are also needed to further understand the clinical impact of ARC and target attainment failure of drugs affected by ARC.

We concluded that aSAH patients receiving nimodipine via different formulations or techniques of delivery show different propensities towards tolerability e.g., diarrhea and hypotension, and effectiveness endpoints e.g., DCI. Further research is needed to determine the optimal available delivery technique of nimodipine especially in critically ill adults who are unable to swallow, as well as explore new formulations that overcome the pitfalls of the available ones. Further research

into alternate regimens that could overcome the drawbacks of currently used formulations such as crushed tablets are also needed, as well as possible practice policy changes to improve the availability of superior formulations.

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APPENDIX

11.SUPPLEMENTARY TABLE 2.1. FULL SEARCH STRATEGY

Database	Search Strategy
MEDLINE **Ovid MEDLINE(R) ALL** 1946 to October 26, 2020	1. augmented renal clearance.mp. 2. augmented kidney clearance.mp. 3. ((increas* or enhanc* or high*) adj3 (kidney or renal) adj1 (function or clearance)).mp. 4. ((increas* or high*) adj3 (creatinine clearance or drug clearance or med* clearance)).mp. 5. (ultrafiltrat* adj3 (kidney or renal)).mp. 6. glomerular hyperfiltration.mp. 7. 3 or 4 or 5 or 6 8. exp *Intensive Care Units/ 9. (ICU or intensive care or critical care or critical* ill* or acute care).ti,ab,kf. 10. exp *Critical Care/ 11. (sepsis or septic shock or trauma or brain injur* or brain bleed* or cerebral bleed* or intracerebral or intracranial or stroke* or infection* or meningitis or subarachnoid or h#emorrhag*).ti,ab,kf. 12. 8 or 9 or 10 or 11 13. 7 and 12 14. 1 or 2 or 13 15. animal/ 16. human/ 17. 15 not (15 and 16) 18. (veterinary or rabbit or rabbits or animal or animals or mouse or mice or rodent or rodents or rat or rats or hamster* or pig or pigs or porcine or horse* or equine or cow or cows or bovine or goat or goats or sheep or ovine or canine or dog or dogs or feline or cat or cats or zebrafish).ti. 19. 17 or 18 [animal studies] 20. 14 not 19 21. limit 20 to comment 22. limit 20 to editorial 23. 21 or 22 24. 20 not 23
Embase **Ovid Embase** 1974 to 2020 October 26	1. augmented renal clearance.mp. 2. augmented kidney clearance.mp. 3. ((increas* or enhanc* or high*) adj3 (kidney or renal) adj1 (function or clearance)).mp. 4. ((increas* or high*) adj3 (creatinine clearance or drug clearance or med* clearance)).mp. 5. (ultrafiltrat* adj3 (kidney or renal)).mp. 6. glomerular hyperfiltration.mp. 7. 3 or 4 or 5 or 6 8. exp *intensive care unit/ 9. (ICU or intensive care or critical care or critical* ill* or acute care).ti,ab,kw. 10. exp *intensive care/ 11. (sepsis or septic shock or trauma or brain injur* or brain bleed* or cerebral bleed* or intracerebral or intracranial or stroke* or infection* or meningitis or subarachnoid or h#emorrhag*).ti,ab,kw. 12. 8 or 9 or 10 or 11 13. 7 and 12 14. 1 or 2 or 13 15. animal/ 16. human/ 17. 15 not (15 and 16) 18. (veterinary or rabbit or rabbits or animal or animals or mouse or mice or rodent or rodents or rat or rats or hamster* or pig or pigs or porcine or horse* or equine or cow or cows or bovine or goat or goats or sheep or ovine or canine or dog or dogs or feline or cat or cats or zebrafish).ti. 19. 17 or 18 [animal studies] 20. 14 not 19 21. limit 20 to editorial 22. 20 not 21
CINAHL	S1 augmented renal clearance S2 augmented kidney clearance S3 (increas* or enhanc* or high*) N2 ("kidney function" or "kidney clearance" or "renal function" or "renal clearance") S4 (increas* or high*) N2 ("creatinine clearance" or "drug clearance" or "med* clearance") S5 (ultrafiltrat* N3 (kidney or renal)) S6 "glomerular hyperfiltration"

	S7 S3 OR S4 OR S5 OR S6 S8 (MM "Intensive Care Units+") S9 TI (ICU or "intensive care" or "critical care" or "critical* ill*" or "acute care") OR AB (ICU or "intensive care" or "critical care" or "critical* ill*" or "acute care") S10 (MM "Critical Care+") S11 TI (sepsis or "septic shock" or trauma or "brain injur*" or "brain bleed*" or "cerebral bleed*" or intracerebral or intracranial or stroke* or infection* or meningitis or subarachnoid or h#emorrhag*) OR AB (sepsis or "septic shock" or trauma or "brain injur*" or "brain bleed*" or "cerebral bleed*" or intracerebral or intracranial or stroke* or infection* or meningitis or subarachnoid or h#emorrhag*) S12 S8 OR S9 OR S10 OR S11 S13 S7 AND S12 S14 S1 OR S2 OR S13 S15 (MH "Animals+") S16 (MH "Human") S17 S15 NOT (S15 AND S16) S18 TI veterinary or rabbit or rabbits or animal or animals or mouse or mice or rodent or rodents or rat or rats or hamster* or pig or pigs or porcine or horse* or equine or cow or cows or bovine or goat or goats or sheep or ovine or canine or dog or dogs or feline or cat or cats or zebrafish S19 S17 OR S18 S20 S14 NOT S19 S21 S14 NOT S19 [Limit to Commentary] S22 S14 NOT S19 [Limit to Editorial] S23 S21 OR S22 S24 S20 NOT S23
Scopus	(TITLE-ABS-KEY ("augmented renal clearance" OR "augmented kidney clearance") OR TITLE-ABS-KEY ((((increas* OR enhanc* OR high*) W/2 ("kidney function" OR "kidney clearance" OR "renal function" OR "renal clearance")) OR ((increas* OR high*) W/2 ("creatinine clearance" OR "drug clearance" OR "med* clearance")) OR (ultrafiltrat* W/3 (kidney OR renal)) OR "glomerular hyperfiltration") AND (icu OR "intensive care" OR "critical care" OR "critical* ill*" OR "acute care" OR sepsis OR "septic shock" OR trauma OR "brain injur*" OR "brain bleed*" OR "cerebral bleed*" OR intracerebral OR intracranial OR stroke* OR infection* OR meningitis OR subarachnoid OR hemorrhag* OR haemorrhag*))) AND NOT TITLE (veterinary OR rabbit OR rabbits OR animal OR animals OR mouse OR mice OR rodent OR rodents OR rat OR rats OR hamster* OR pig OR pigs OR porcine OR horse* OR equine OR cow OR cows OR bovine OR goat OR goats OR sheep OR ovine OR canine OR dog OR dogs OR feline OR cat OR cats OR zebrafish) AND (EXCLUDE (DOCTYPE , "ed"))
Cochrane Library via Wiley	#1 augmented renal clearance #2 augmented kidney clearance #3 (increas* or enhanc* or high*) NEAR/2 ("kidney function" or "kidney clearance" or "renal function" or "renal clearance") #4 (increas* or high*) NEAR/2 ("creatinine clearance" or "drug clearance" or "med* clearance") #5 (ultrafiltrat* NEAR/3 (kidney or renal)) #6 "glomerular hyperfiltration" #7 (1-#6) #8 [mh "intensive care units"[mj]] #9 ICU or "intensive care" or "critical care" or "critical* ill*" or "acute care" #10 [mh "critical care"[mj]] #11 sepsis or "septic shock" or trauma or "brain injur*" or "brain bleed*" or "cerebral bleed*" or intracerebral or intracranial or stroke* or infection* or meningitis or subarachnoid or hemorrhag* or haemorrhag* #12 (2-#11) #13 #7 AND #12 #14 #1 OR #2 OR #13
ProQuest Dissertations and Theses Global	noft("augmented renal clearance" OR "augmented kidney clearance") OR noft(((increas* NEAR/2 ("kidney function" OR "kidney clearance" OR "renal function" OR "renal clearance")) OR (enhanc* NEAR/2 ("kidney function" OR "kidney clearance" OR "renal function" OR "renal clearance")) OR (high* NEAR/2 ("kidney function" OR "kidney clearance" OR "renal function" OR "renal clearance")) OR (increas* NEAR/2 ("creatinine clearance" OR "drug clearance" OR "med* clearance")) OR (high* NEAR/2 ("creatinine clearance" OR "drug clearance" OR "med* clearance")) OR (ultrafiltrat* NEAR/3 (kidney OR renal)) OR "glomerular hyperfiltration") AND (icu OR "intensive care" OR "critical care" OR "critical* ill*" OR "acute care" OR sepsis OR "septic shock" OR trauma OR ("brain injured" OR "brain injuries" OR "brain injury") OR "brain bleed*" OR "cerebral bleed*" OR intracerebral OR intracranial OR stroke* OR infection* OR meningitis OR subarachnoid OR hemorrhag* OR haemorrhag*)) NOT ti(veterinary OR rabbit OR rabbits OR animal OR animals OR mouse OR mice OR rodent OR rodents OR rat OR rats OR hamster* OR pig OR pigs OR porcine OR horse* OR equine OR cow OR cows OR bovine OR goat OR goats OR sheep OR ovine OR canine OR dog OR dogs OR feline OR cat OR cats OR zebrafish)

Google Scholar	augmented renal clearance OR enhanced renal function OR enhanced renal clearance OR increased kidney function OR increased kidney clearance

12.SUPPLEMENTARY TABLE 2.2. APPRAISAL OF INDIVIDUAL STUDIES INCLUDED IN THIS REVIEW

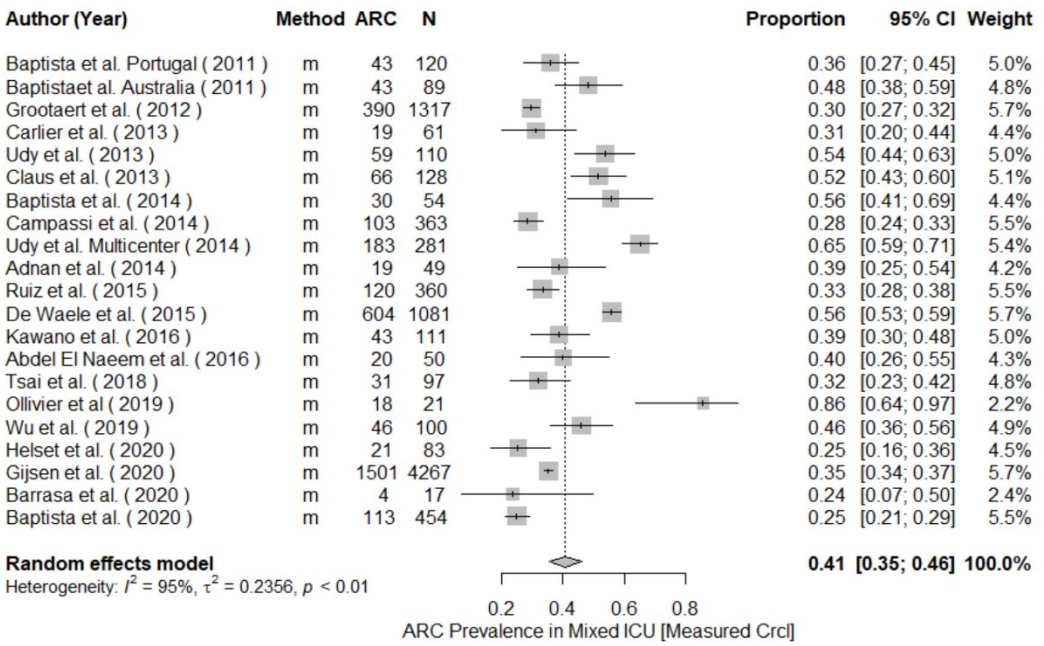
Prevalence/Incidence Studies	A	B	C	D	E	F	G	H	I	Total
Adnan (2014) (3)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	**8/9**
Abdel el Naeem (2017) (4)	Yes	Unclear	No	Yes	Yes	Yes	Yes	Yes	Yes	**7/9**
Aréchiga-Alvarado et al. (5)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**9/9**
Aitullina (2019) (6)	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	**7/9**
Baptista (2011) (7)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	**8/9**
Baptista (2012) (8)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	**8/9**
Baptista (2014) (9)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**9/9**
Baptista et al.(2014) (10)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**9/9**
Baptista (2020) (11)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**9/9**
Barletta (2016) (12)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	**8/9**
Barletta (2017) (13)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	**8/9**
Barrasa (2020) (14)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	**8/9**
Bricheux (2019) (15)	Unclear	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	**7/9**
Brown (2020) (16)	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	**7/9**
Burnham (2017) (17)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	**8/9**
Campassi (2014) (18)	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	**7/9**
Carlier (2013) (19)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	**8/9**
Carrie (2018a) (20)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	**8/9**
Carrie (2018b) (21)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	**8/9**
Carrie (2019a) (22)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	**8/9**
Carrie (2019b) (23)	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	**6/9**
Carrie (2020) (24)	Unclear	Yes	No	Yes	Yes	No	Yes	Yes	Yes	**6/9**
Chen (2020) (25)	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	**7/9**
Chu (2016) (26)	Yes	Unclear	No	Yes	Yes	No	Yes	Yes	Yes	**6/9**
Chu (2019) (27)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	**8/9**
Claus (2013) (28)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	**8/9**
Cojutti (2020) (29)	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	**6/9**
Dhaese et al. (2018) (30)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**9/9**
Declercq (2016) (31)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**9/9**
DeWaele (2015) (32)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**9/9**
Dias (2015) (33)	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	**7/9**
Ehmann (2017) (34)	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	**6/9**
Eidelson et al.(35)	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	**7/9**
Fuster-Lluch (2008) (36)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**9/9**

Gijsen (2020) (37)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**9/9**
Grootaert (2012) (38)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**9/9**
Helset (2020) (39)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	**8/9**
Hirai (2016) (40)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	**8/9**
Huttner (2015) (41)	Yes	Unclear	No	Yes	Yes	No	Yes	Yes	Yes	**6/9**
Ishii (2018) (42)	Yes	Yes	No	Yes	No	No	Yes	No	Yes	**5/9**
Izumisawa (2019) (43)	Unclear	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	**7/9**
Joynt (2001) (44)	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	**7/9**
Kawano et al.(2016) (45)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**9/9**
Kawano (2018) (46)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**9/9**
Lannou (2020) (47)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	**8/9**
Lannou editorial letter (2020) (48)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	**8/9**
Lautrette (2012) (49)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	**8/9**
May (2015) (50)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	**8/9**
Minkute (2013) (51)	Unclear	Yes	No	Yes	Yes	No	Yes	Yes	Yes	**6/9**
Minville (2011) (52)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	**8/9**
Morbitzer (2019) (53)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**9/9**
Mulder (2019) (54)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	**8/9**
Nei (2020) (55)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	**8/9**
Ollivier (2019) (56)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	**8/9**
Ramos (2017)(57)	Yes	Yes	No	No	Unclear	Yes	Yes	Yes	Yes	**6/9**
Ruiz (2015) (58)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**9/9**
Saito (2020) (59)	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	**7/9**
Saour (2016) (60)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	**8/9**
Steinke (2015) (61)	Yes	Yes	No	Yes	Unclear	Yes	No	Yes	Yes	**6/9**
Tamatsukuri (2018) (62)	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	**7/9**
Tsai (2018) (63)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	**8/9**
Udy (2013) (64)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	**8/9**
Udy (2013b) (65)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	**8/9**
Udy (2014) (66)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**9/9**
Udy (2017) (67)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	**8/9**
Udy (2018) (68)	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**8/9**
Villaneuva (2019) (69)	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	**7/9**
Weber (2019) (70)	No	Yes	No	Yes	Yes	Yes	Yes	No	Yes	**6/9**
Wong (2018) (71)	Unclear	Yes	Yes	Yes	No	No	Yes	Yes	Yes	**6/9**
Wu (2019) (72)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	**8/9**

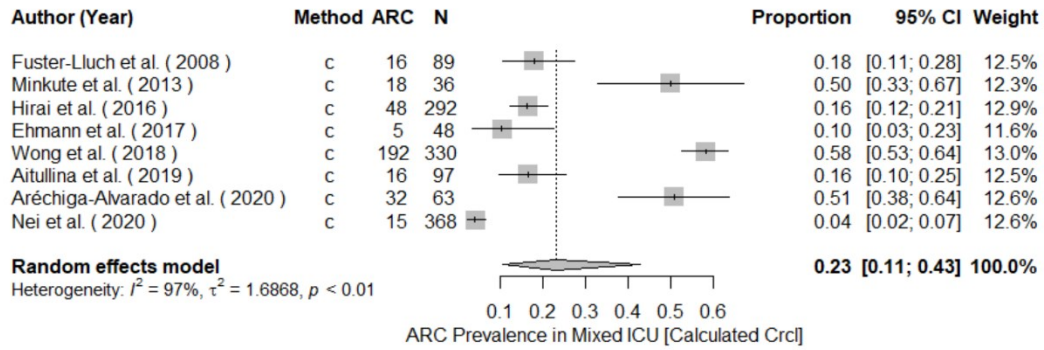
A: Was the sample frame appropriate to address the target population? **B:** Were study participants sampled in an appropriate way? C: Was the sample size adequate? **D:** Were the study subjects and the setting described in detail? **E:** Was the data analysis conducted with sufficient coverage of the identified sample? **F:** Were valid methods used for the identification of the condition? **G:** Was the condition measured in a standard, reliable way for all participants? **H:** Was there appropriate statistical analysis? **I:** Was the response rate adequate, and if not, was the low response rate managed appropriately?

10.SUPPLEMENTARY FIGURE 2.1: FOREST PLOT OF ARC PREVALENCE IN MIXED ICU (MEASURED AND CALCULATED CRCL)

A



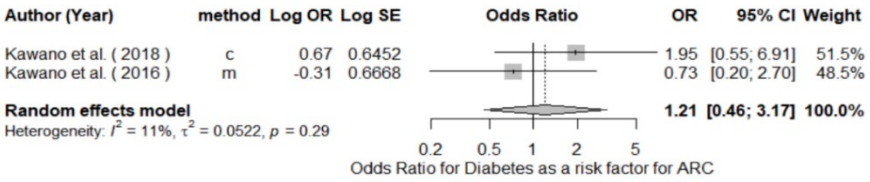
B



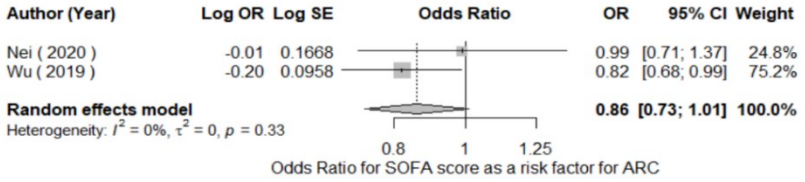
Supplementary Figure 1. Forest plot of the prevalence of ARC in mixed intensive care unit (ICU) population. A, studies reporting measured creatinine clearance (m); B, studies reported calculated creatinine clearance (c). CI, confidence interval; N, study size.

11.SUPPLEMENTARY FIGURE 2.2: FOREST PLOT OF OR OF DIABETES, SOFA SCORE, AND APACHEII SCORE AS RISK FACTORS FOR ARC

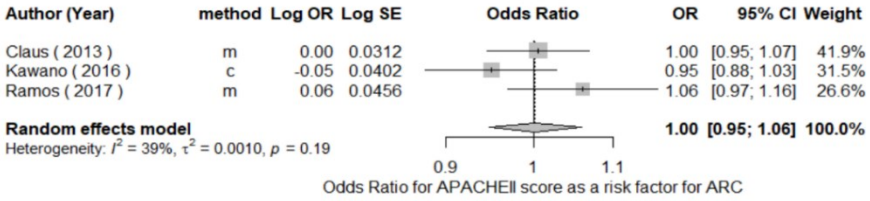
A



B



C



Supplementary Figure 2. Forest plot of risk factors for augmented renal clearance. A, diabetes; B, Sequential Organ Failure Assessment (SOFA) score ; C, Acute Physiology and Chronic Health Evaluation (APACHE II) . Clearance Determination method: m = measured, c = calculated; CI, confidence interval ; OR, odds ratio; SE, standard error.

13. SUPPLEMENTARY TABLE 3.1: FULL SEARCH STRATEGY

Database	Search Strategy
MEDLINE Ovid MEDLINE(R) ALL 1946 to November 03, 2021	1. augmented renal clearance.mp. 2. augmented kidney clearance.mp. 3. ((increas* or enhanc* or high*) adj3 (kidney or renal) adj1 (function or clearance)).mp. 4. ((increas* or high*) adj3 (creatinine clearance or drug clearance or med* clearance)).mp. 5. (ultrafiltrat* adj3 (kidney or renal)).mp. 6. glomerular hyperfiltration.mp. 7. 3 or 4 or 5 or 6 8. exp *Intensive Care Units/ 9. (ICU or intensive care or critical care or critical* ill* or acute care).ti,ab,kf. 10. exp *Critical Care/ 11. (sepsis or septic shock or trauma or brain injur* or brain bleed* or cerebral bleed* or intracerebral or intracranial or stroke* or infection* or meningitis or subarachnoid or h?emorrhag*).ti,ab,kf. 12. 8 or 9 or 10 or 11 13. 7 and 12 14. 1 or 2 or 13 15. animal/ 16. human/ 17. 15 not (15 and 16) 18. (veterinary or rabbit or rabbits or animal or animals or mouse or mice or rodent or rodents or rat or rats or hamster* or pig or pigs or porcine or horse* or equine or cow or cows or bovine or goat or goats or sheep or ovine or canine or dog or dogs or feline or cat or cats or zebrafish).ti. 19. 17 or 18 [animal studies] 20. 14 not 19 21. limit 20 to comment 22. limit 20 to editorial 23. 21 or 22 24. 20 not 23
Embase Ovid Embase 1974 to 2021 November 03	1. augmented renal clearance.mp. 2. augmented kidney clearance.mp. 3. ((increas* or enhanc* or high*) adj3 (kidney or renal) adj1 (function or clearance)).mp. 4. ((increas* or high*) adj3 (creatinine clearance or drug clearance or med* clearance)).mp. 5. (ultrafiltrat* adj3 (kidney or renal)).mp. 6. glomerular hyperfiltration.mp. 7. 3 or 4 or 5 or 6 8. exp *intensive care unit/ 9. (ICU or intensive care or critical care or critical* ill* or acute care).ti,ab,kw. 10. exp *intensive care/ 11. (sepsis or septic shock or trauma or brain injur* or brain bleed* or cerebral bleed* or intracerebral or intracranial or stroke* or infection* or meningitis or subarachnoid or h?emorrhag*).ti,ab,kw. 12. 8 or 9 or 10 or 11 13. 7 and 12 14. 1 or 2 or 13 15. animal/ 16. human/ 17. 15 not (15 and 16) 18. (veterinary or rabbit or rabbits or animal or animals or mouse or mice or rodent or rodents or rat or rats or hamster* or pig or pigs or porcine or horse* or equine or cow or cows or bovine or goat or goats or sheep or ovine or canine or dog or dogs or feline or cat or cats or zebrafish).ti. 19. 17 or 18 [animal studies] 20. 14 not 19 21. limit 20 to editorial 22. 20 not 21
CINAHL	S1 augmented renal clearance S2 augmented kidney clearance S3 (increas* or enhanc* or high*) N2 ("kidney function" or "kidney clearance" or "renal function" or "renal clearance") S4 (increas* or high*) N2 ("creatinine clearance" or "drug clearance" or "med* clearance") S5 (ultrafiltrat* N3 (kidney or renal)) S6 "glomerular hyperfiltration" S7 S3 OR S4 OR S5 OR S6 S8 (MM "Intensive Care Units+")

	S9 TI (ICU or "intensive care" or "critical care" or "critical* ill*" or "acute care") OR AB (ICU or "intensive care" or "critical care" or "critical* ill*" or "acute care") S10 (MM "Critical Care+") S11 TI (sepsis or "septic shock" or trauma or "brain injur*" or "brain bleed*" or "cerebral bleed*" or intracerebral or intracranial or stroke* or infection* or meningitis or subarachnoid or h#emorrhag*) OR AB (sepsis or "septic shock" or trauma or "brain injur*" or "brain bleed*" or "cerebral bleed*" or intracerebral or intracranial or stroke* or infection* or meningitis or subarachnoid or h#emorrhag*) S12 S8 OR S9 OR S10 OR S11 S13 S7 AND S12 S14 S1 OR S2 OR S13 S15 (MH "Animals+") S16 (MH "Human") S17 S15 NOT (S15 AND S16) S18 TI veterinary or rabbit or rabbits or animal or animals or mouse or mice or rodent or rodents or rat or rats or hamster* or pig or pigs or porcine or horse* or equine or cow or cows or bovine or goat or goats or sheep or ovine or canine or dog or dogs or feline or cat or cats or zebrafish S19 S17 OR S18 S20 S14 NOT S19 S21 S14 NOT S19 [Limit to Commentary] S22 S14 NOT S19 [Limit to Editorial] S23 S21 OR S22 S24 S20 NOT S23
Scopus	(TITLE-ABS-KEY ("augmented renal clearance" OR "augmented kidney clearance") OR TITLE-ABS-KEY ((((increas* OR enhanc* OR high*) W/2 ("kidney function" OR "kidney clearance" OR "renal function" OR "renal clearance")) OR ((increas* OR high*) W/2 ("creatinine clearance" OR "drug clearance" OR "med* clearance")) OR (ultrafiltrat* W/3 (kidney OR renal)) OR "glomerular hyperfiltration") AND (icu OR "intensive care" OR "critical care" OR "critical* ill*" OR "acute care" OR sepsis OR "septic shock" OR trauma OR "brain injur*" OR "brain bleed*" OR "cerebral bleed*" OR intracerebral OR intracranial OR stroke* OR infection* OR meningitis OR subarachnoid OR hemo rrhag* OR haemorrhag*))) AND NOT TITLE (veterinary OR rabbit OR rabbits OR animal OR animals OR mouse OR mice OR rodent OR rodents OR rat OR rats OR hamster* OR pig OR pigs OR porcine OR horse* OR equine OR cow OR cows OR bovine O R goat OR goats OR sheep OR ovine OR canine OR dog OR dogs OR feline OR cat OR cats OR zebrafish) AND (EXCLUDE (DOCTYPE , "ed"))
Cochrane Library via Wiley	#1 augmented renal clearance #2 augmented kidney clearance #3 (increas* or enhanc* or high*) NEAR/2 ("kidney function" or "kidney clearance" or "renal function" or "renal clearance") #4 (increas* or high*) NEAR/2 ("creatinine clearance" or "drug clearance" or "med* clearance") #5 (ultrafiltrat* NEAR/3 (kidney or renal)) #6 "glomerular hyperfiltration" #7 #8 [mh "intensive care units"[mj]] #9 ICU or "intensive care" or "critical care" or "critical* ill*" or "acute care" #10 [mh "critical care"[mj]] #11 sepsis or "septic shock" or trauma or "brain injur*" or "brain bleed*" or "cerebral bleed*" or intracerebral or intracranial or stroke* or infection* or meningitis or subarachnoid or hemorrhag* or haemorrhag* #12 #13 #7 AND #12 #14 #1 OR #2 OR #13
ProQuest Dissertations and Theses Global	noft("augmented renal clearance" OR "augmented kidney clearance") OR noft(((increas* NEAR/2 ("kidney function" OR "kidney clearance" OR "renal function" OR "renal clearance")) OR (enhanc* NEAR/2 ("kidney function" OR "kidney clearance" OR "renal function" OR "renal clearance")) OR (high* NEAR/2 ("kidney function" OR "kidney clearance" OR "renal function" OR "renal clearance")) OR (increas* NEAR/2 ("creatinine clearance" OR "drug clearance" OR "med* clearance")) OR (high* NEAR/2 ("creatinine clearance" OR "drug clearance" OR "med* clearance")) OR (ultrafiltrat* NEAR/3 (kidney OR renal)) OR "glomerular hyperfiltration") AND (icu OR "intensive care" OR "critical care" OR "critical* ill*" OR "acute care" OR sepsis OR "septic shock" OR trauma OR ("brain injured" OR "brain injuries" OR "brain injury") OR "brain bleed*" OR "cerebral bleed*" OR intracerebral OR intracranial OR stroke* OR infection* OR meningitis OR subarachnoid OR hemorrhag* OR haemorrhag*)) NOT ti(veterinary OR rabbit OR rabbits OR animal OR animals OR mouse OR mice OR rodent OR rodents OR ra t OR rats OR hamster* OR pig OR pigs OR porcine OR horse* OR equine OR cow OR cows OR bovine O R goat OR goats OR sheep OR ovine OR canine OR dog OR dogs OR feline OR cat OR cats OR zebrafish)

Google Scholar	augmented renal clearance OR enhanced renal function OR enhanced renal clearance OR increased kidney function OR increased kidney clearance

14. Supplementary Table 3.2. Search Results

Database	2020 Results	2021 Results
MEDLINE	637	754
Embase	1165	1349
CINAHL	239	265
Scopus	1181	1321
Cochrane Library	220	236
ProQuest Dissertations & Theses Global	13	16
TOTAL	3,455	3,941

15.SUPPLEMENTARY TABLE 3.3. STUDY SUMMARIES

Authors	Study Type	Objective	Population	Methods	Findings	Limitations	Conclusion
Meropenem							
Kitzes-Cohen et al (2002) (73)	Prospective Observational	Determine the PK/PD of meropenem in severely ill patients with sepsis and determine if recommended dose resulted in plasma concentrations higher than MIC of bacterial isolated	n = 14, patients in ICU with severe sepsis + blood or other culture growing bacteria susceptible to meropenem	Patients split into 2 groups based on CrCl, group 1 having CrCl >50ml/min and group 2 having CrCl <50ml/min. Patients in G1 received 1g q8h and G2 1g q12h. Blood samples drawn after administration at predefined intervals. The time when meropenem conc. were higher than 4xMIC were also determined.	Between groups there were significant differences in CL and MRT as well as half life. In both groups only patients infected with less resistant strains (MIC <1mg/L) have desired plasma concentrations during 100% of dosing interval. Patients in Group 1 with less susceptible organisms only maintained desired concentration for 4 to 6h, and duration of treatment was increased in these patients.	small sample size, don't know how they determined CrCl	The standard doses are OK for less resistant organisms but are likely not for less susceptible pathogens like A. baumanii and P.aeruginosa and in these patients continuous infusion may be warranted to achieve sustained levels above target concentration.
Ehmann et al. (2017) (34)	Prospective Observational study	Investigate target attainment of standard meropenem dosing in critically ill patients, to quantify the impact of renal function on meropenem exposure and how this relates to target attainment.	n = 48, adult patients with severe infection being treated with meropenem	all patients received standard doses of meropenem as 30-min infusion (1000mg q8h). Multiple arterial blood samples were collected over a period of 4 days (based on these C4h and C8h were calculated). CrCl was estimated according to the Cockcroft Gault equation - this was done daily based on serum creatinine measurements. Patients were stratified into following groups based on renal function: severe RI (15-29), mod RI (30-59), mild RI (60-89), normal (90-129) and ARC (>130). PK/PD target attainment was assessed for MIC of 2mg/L and 8mg/L based on EUCAST breakpoints for relevant pathogens. Targets were 100% T>MIC and 50% T>4xMIC. They looked at if calculated C4h and C8h concentrations exceeded those thresholds. Target attainment was	For non-CRRT patients with pathogens with MIC 2mg/L both targets were obtained in approx. half of patients. When data was extrapolated to 2000mg target attainment was substantially higher. For MIC of 8mg/L target attainment (100% T>MIC) occurred in 1/5th of patients and was even lower for the other target (4xMIC). When extrapolated for a dose of 2000mg, the likelihood of target attainment for 100% T>MIC doubled and quadrupled for 50%T>4xMIC. For non-CRRT patients	did not measure CrCl, based findings off of extrapolated concentrations (not actual), did not relate targets to actual infective pathogens	PK/PD target attainment was overall unlikely when critically ill patients were receiving a dose of 1000mg q8h, especially if they had ARC. Doses of 2000mg q8h may be warranted for certain patient subgroups (i.e. ARC, less susceptible pathogens) in order to attain desired targets.

				also evaluated for doses of 2000mg based on extrapolated C4h and C8h values.	augmented RF to mild RI was a risk factor for non-attainment for MIC of 2mg/L. For MIC 8mg/L moderate RI was also identified as a risk factor.		
Tamatsukuri et al. (2018) (62)	Prospective observational	determine optimum population PK model of meropenem in patients with sepsis with ARC, and evaluated dosing regimens based on renal function	n = 17, adult patients receiving meropenem in the ICU	Patients treated with 1 to 3g/day over 30-60ming infusion. Blood levels drawn and predefined intervals based on renal function. CrCL measured with 8h urine collection and ARC defined as CrCl >130ml/min.	Plasma MEPM levels were significantly lower in ARC. Empirical tx: for CFR>90% 2g q8h via 180 min infusion was needed for ARC patients. Definitive tx (for P.aeruginosa): PTA>90% achieved with 1g q8h and 2g q8h if infused over 180mins.	small sample, dosing recommendations hypothesized	patients with ARC may benefit from prolonged infusion (180min) of meropenem +/- dose increase (2g)
Cojutti et al. (2020) (29)	prospective interventional study	assess the role of real-time TDM-guided optimization of CI meropenem on maximizing empirical treatment and preventing break-through infection and/or colonization with carbapenem resistant Enterobacteriaceae (CRE) among oncohaematological patients with febrile neutropenia	n=75 adult patients with oncohaematological disease who were admitted and received empirical escalation therapy with meropenem for the treatment of febrile neutropenia	If patients did not clinically improve in 48-72hrs meropenem was initiated with 1g LD over 30 mins followed by 1g q8h over 8hrs (for CrCl>60ml/min). All patients underwent TDM on days 2 or 3 and then again q48-72h until treatment was over. With each TDM SCr, eCrCl and CRP were reassessed. ARC was defined as eCrCl >130. Target Css was 8-16 mg/L (derived from recommendation of 4-8x MIC of Enterbacteriaeae and P.aeruginosa which is 2mg/L). TDM dose adjustments were provided by clinical pharmacologists and were based on personal interpretation. Patients were followed up for 3m and if they were readmitted, rectal swabs were collected to determine CRE colonization.	Meropenem doses were adjusted in 30.1% of TDM reassessment (split for increased and decreased). For patients receiving definitive-empirical or targeted treatment with meropenem, all-cause mortality was 10% and overall cure rate was 90%. Mortality was significantly associated with ARC (OR 10.8). 15 (20%) patients had definitive targeted therapy, of these 12 patients had meropenem susceptible pathogens and all attained the desired PD targets (Css/MIC = 4-8). None of the 3 patients who had resistant pathogens attained the targets (2 achieved Css/MIC of 1 and were cured, the other did not and died). 84% of total patients were readmitted and none of them had CRE colonization.	dosing recommendations were based on personal assessments of various pharmacologists, very specific patient population, Cotreatment with other agents	CI + TDM readjustment may optimize drug exposure of meropenem among FN patients with susceptible pathogens; a target of Css 8-16 mg/L should be used. This dosing strategy may also prevent the emergence of CRE colonization.

Imipenem							
Bricheux et al. (2019)(15)	Retrospective Observational	to report clinical outcomes of patients receiving imipenem in the context of drug concentrations - to gain further understanding for the use of TDM for beta-lactam agents like imipenem primary outcome = incidence of toxicity (included events deemed possibly, probably) overall and with highest trough conc secondary outcomes = incidence of clinical failure (recurrence or death) overall and with undetectable or below 2 and 4mg/L as well as the median concentration in patients with or without clinical toxicity or failure	n=300 any hospitalized adult patients, undergoing imipenem TDM for suspected or confirmed infection	most pts had received standardized doses of 500mg QID (15min infusion) researchers calculated if levels were trough (99% were), institutional guidelines suggest target trough levels of 2-20mg/L. CrCl was calculated using CG, ARC defined as CrCl >130	TOXICITY - Only 5% of patients had AEs the were at least possibly related to imipenem treatment (only 1 had certainly related). Patients with highest quartile concentrations (>7.7mg/L) did not experience more toxicity than those with lower conc. But patients who did have side effects had slightly higher trough concentrations. Both patients experiencing and not experiencing toxicity had similar median doses received, duration of hospital stay, and renal clearance. FAILURE - 29% of patients had clinical failure. Patients with failure did not have lower imipenem concentrations. Also found that patients with P.aeurginosa infections + trough <2mg/L were more likely to have treatment failure (underpowered due to small subgroup) and that patients who did not receive a subsequent dose increase after trough below 2mg/L were also more likely to have treatment failure (not stat. sig) OTHER - It appeared patients with ARC had decreased likelihood of treatment failure. Patients with ARC were	Did not define "toxicity" that they were looking for. Did not discuss data collection methods. States ARC is a protective mechanism against treatment failure, which is unexpected.	Due to overall infrequency of toxicity and frequency of treatment failure authors question if standard dose of 2g/day is optimal for patients with severe infection (found that those receiving 3-4g/day did not experience more toxicity but instead trended towards no treatment failure). Author questions the utility of imipenem TDM for imipenem given that, in this population, plasma levels could predict neither toxicity nor failure with strong statistical significance.

					less likely to have failure (if MIC is low)		
Huttner et al. (2015) (41)	Prospective Observational	Determine link between ARC, low B-lactam concentrations and clinical outcomes ● Primary outcome = clinical response 28 days after inclusion ● Secondary outcome = ARC prevalence, subthreshold and undetectable concentrations	n=100 patients aged 18-60 requiring intensive care and diagnosed with suspected or confirmed infection warranting treatment with B-lactam antibiotic (imipenem/cilastin - 500mg QID, meropenem - 2g TID, piperacilin/tazobactam - 4.5g TID and cefepime - 2g BID).	TDM performed for peak, intermediate and trough concentrations on days 1, 2, 3 and 5 of therapy. CrCl calculated using CG during the first week and days 14 and 28. Intermediate and trough concentrations were compared to non-species-specific breakpoints (EUCAST) for each B-lactam. If concentration was equal to or lower than breakpoint it was defined as subtherapeutic.	64% of sample patients had ARC (younger, fewer comorbidities and lower APACHE II score). ARC strongly predicted undetectable trough concentrations. Based on logistical regression models, there was no association between ARC and clinical failure. Sub analysis of microbiologically confirmed infection showed no link between ARC, subtherapeutic levels and clinical failure.	Infections not all documented, did not calculate CrCl, did not use MIC for actual pathogen, patients on dual antibiotic therapy were not excluded	Confirmed strong association between ARC and reduced B-lactam concentrations (ARC patients 3.3x more likely to have at least one undetectable trough concentration). Effect of this finding on clinical outcomes cannot be identified at this time.
Patel et al. 2021 (74)	Prospective observation population study	To evaluate the effects of covariates on Imipenem/relebactam (IPM and REL) exposures and to analyze pharmacokinetic/pharmacodynamic probability of target attainment (PTA) in patients with HABP/VABP.	n=1197. Patients were included if they were in previous phase 3 clinical trials PN014 and PN017. Patients were also pooled from an additional 10 previous studies.	The authors used a PK/PD model developed using nonlinear mixed effects. Data was added to this model from 2 previously phase 3 clinical studies: RESTORE IMI 2 (pn014) and PN017. Clinical and demographic covariates were included to assess their influence on PK characteristics of IMP/REL (imipenem and relebactam). CrCL was calculated using the CG equation. Simulation were made to determine the joint PTA for PK/PD targets for IMP/REL to confirm the dose regimen for those with HABP/VABP with various renal functions (augmented renal clearance (CrCl ≥150 ml/min), normal renal function, (CrCl ≥90 to <150 ml/min), renal impairment (mild, CrCl ≥60 to <90 ml/min; moderate, CrCl ≥30 to <60 ml/min; or severe, CrCl ≥15 to <30 ml/min),	1,000,000 virtual patients were simulated based on the study participants. Joint PTA at steady state was >99% for patients with HABP/VABP, regardless of renal function category, using targets of 30% *f*T>MIC for IPM and *f*AUC0–24/MIC greater than or equal to 8 for REL at an IPM/REL MIC breakpoint of less than or equal to 2 μg/ml at a fixed concentration of 4 μg/ml REL.	This study used CG equation to calculate CrCL instead of the gold standard 24hour urine collection method which is more accurate. Covariates were assumed to remain the same as their baseline's values in critically ill patients which is likely not true for certain covariates such as CrCl which is known to be unstable. Funding was provided by MSD which is	Adequate joint PTA for IMP/REL was achieved in both ventilated and non-ventilated patients with HABP/VABP across all renal function categories. Support the recommended 500/500/250-mg IMI/REL q6hr dose with no adjustment based on ventilation status.

				and end-stage renal disease (CrCl <15 ml/min)).		where multiple authors work causing a potential risk of bias.	
Ceftriaxone							
Ollivier et al. (2019) (56)	Prospective Observational	Determine whether ARC negatively impacts ceftriaxone PK/PD target attainment in critically ill patients	n = 21, adult patients treated with ceftriaxone for a first episode of presumed or documented infection. Excluded if renal impairment or receiving renal replacement therapy.	All patients received a dose of 2g once daily. On days 1 to 3 patients underwent TDM of unbound ceftriaxone concentration as well as 24hr CrCl measurements. Underdosing was defined as trough unbound conc. Below 2mg/L. If pathogen was known they also defined underdosing as fT>MIC <100% and fT>4xMIC <100%. Used monte carlo simulation for multiple dosing regimens (2 or 3g once daily and 1 or 2g twice daily) for various renal function groups (no ARC, moderate ARC 150-200 and severe ARC) to determine optimal dosing regimen.	Rate of underdosing was 62% with strong association with CrCl. If patients had CrCl >150 this was associated with underdosing with OR 8.8. There was no statistical association between underdosing and therapeutic failure. Findings through MS are as follows: proportion of patients who failed to achieve fT>MIC 100% was sig higher if CrCl was over 200ml/min. PTA for moderate ARC was 55% and only 45% for severe ARC. A dose of 2g BID allowed PTA of 99% for MIC of 2mg/L regardless of renal clearance.	small sample size	Patients with ARC are less likely to achieve desired treatment targets especially with less susceptible pathogens. Dosing of 2g BID may be better suited for increased PTA.
Joynt et al. (2001) (44)	Prospective Observational	Determine the PK profile of normal recommended dose of ceftriaxone in critically ill patients and to establish if it allows for plasma concentrations which are adequate for antibacterial efficacy	n=12, critically ill patients with severe sepsis and normal serum creatinine concentrations	all patients received 2g qd via 30 min infusion and blood levels were drawn within the first 24h and on day 3. 24h urine volume and urine CrCl were also measured	They found correlation between CrCl and total ceftriaxone CL. In critically ill patients with normal renal function Vd increased, CL increased, and this resulted in prolonged t1/2. 3 patients had high CrCl, and they all showed plasma ceftriaxone concentrations below desired threshold for a substantial proportion of the dosing interval. Based on MIC of 8mg/L, half of patients in the cohort failed to maintain concentrations	very small sample size, cannot link findings to clinical outcomes	authors recommend a dose change for critically ill patients with normal renal function (LD 300mg followed by CI of 1g over 24hrs)

					at this level for the entire dosing regimen and the 3 patients with high CrCl did not reach this level for a substantial part of the dosing interval.		
Wong et al. (2018) (71)	Prospective Observational	To describe the achievement of unbound b-lactam antibiotic concentration targets in a therapeutic drug monitoring (TDM) programme in critically ill patients, and the factors associated with failure to achieve a target concentration.	n = 373, critically ill patients receiving B-lactam (ampicillin, benzylpenicillin, flucloxacillin, piperacillin, ceftriaxone, cefazolin, meropenem) + TDM	The treating physician and clinical pharmacist determined empirical dosing and performed dose adjustment (see algorithm in paper). Blood samples were obtained once steady state had been reached (after administration of at least 4 doses). Plasma unbound concentrations were measured directly using validated assay. Demographic, clinical, and microbiological data was collected. CrCl was calculated using the CG equation and ARC was >130 ml/min. PK/PD target of 50%fT>MIC and 100%fT>4xMIC were analyzed, MIC was either available or they used EUCAST breakpoints.	39.1% of cohorts had ARC - they received higher doses. 90.1% of patients achieved target of 50% fT>MI (except for ampicillin which showed only 60%), this was reduced to 36.6% with target of 100%fT>4xMIC (except for benzylpenicillin 80% and ceftriaxone 71.4%). But with benzylpenicillin and ceftriaxone patients were more likely to exceed 100%fT>10xMIC and require dose reductions (however overexposure was associated with impaired renal function). ARC was identified as a factor to predict failure of target achievement, so extended periods of administration. Failure to achieve PK/PD targets was not associated with negative clinical outcomes.	single centre study, CrCl was not measured with 24hr urine samples, did not take into account synergistic antibiotic use, for the vast majority we did not actually know MIC that should be targeted.	Patients with ARC are more likely to not achieve PK/PD targets when receiving B-lactam in an ICU setting. So, dosing strategies need to be redefined, especially for this patient population. Ampicillin may not be suited for empirical treatment in this population. Benzylpenicillin and ceftriaxone (highly protein bound agents) may be better suited for patients with ARC as they showed the highest likelihood of target attainment. Potential for overexposure may be reduced if used in patients with ARC (there is little evidence that 100%fT>10xMIC is going to result in toxicity).
Carrie et al. (2019) (75)	Retrospective observational study	The main objective was to compare the clinical outcome of ARC patients treated by conventional or increased β-lactam dosing regimens for a first episode of	n = 177 (88 in control and 89 in treatment), patients who displayed ARC the first day of treatment, while being treated for	compared two 15-month periods before and after change in local antibiotic therapy protocol. 24-hr urinary samples completed for CrCl, ARC defined as >150ml/min. For the latter period, patients who had CrCl >150ml/min received higher than licensed doses of amoxi/clav,	Therapeutic failure or relapse was 10% in the treatment group and 23% in the control group. No antibiotic related side effects were reported in the treatment group. There	retrospection → selection and interpretation bias, did not perform MIC and TDM reporting	Higher than licensed dosing regimens of B-lactams (see table within paper) may be safe and effective in reducing the rate of therapeutic failure and recurrence of HAP-VAP in the setting of critically ill patients with ARC.

		hospital or ventilator-acquired pneumonia (HAP-VAP).	HAP-VAP with B-lactams	cefotaxime, ceftriaxone, and piperacilin/tazobactam. MIC was defined by the lab or if not available EUCAST. Study endpoints included (primarily) therapeutic failure = persistent or worsening symptoms with the need for escalation of empiric therapy and recurrence = second HAP-VAP with at least one of the initial causative bacterial strains, (secondary) side effects, secondary acquisition of antimicrobial resistance, duration of ventilation, length of stay in ICU, status of patient at discharge.	was no statistical difference in MV duration, ICU stay or mortality rate between the two periods.		
Amikacin							
Carrie et al. (2020) (24)	Retrospective Observational	Characterize PK of amikacin in critically ill patients with Open-Abdomen and Negative-Pressure Wound Therapy (OA/NPT) and assess the appropriateness of recommended regimens for empirical MIC coverage.	n=70, critically ill patients treated by OA/NPT and receiving amikacin with TDM were included.	Based on concentration values from TDM, PK modeling was performed considering the effect of multiple covariates. Monte Carlo simulations were employed to determine the FTA for PK/PD targets (Cmax/MIC ratio of >/= 8 and [AUC0-24]/MIC of >/= 75) for multiple renal functions and doses. Authors hypothesized patients treated with OA/NPT would have sig. Changes in Vd and or CL which would justify higher than licensed dosing regimens.	Patients with OA/NPT had higher Vd than expected for critically ill patients but amount of fluid collected by the NPT did not improve PK model building so the influence is complex. CrCl and ABW as covariates influencing amikacin CL and Vd. Desired Cmax/MIC ratio can be achieved in most patients with ABW LD of 25 to 30mg/kg. But, LD of 30 to 35 mg/kg ABW, may be necessary for patients with CrCl of >130ml/min especially if high MIC pathogen.	percentage of standard error as <50% for PK parameters Can't link results to clinical response (small sample), data collected retrospectively, CrCl not measured	PK/PD targets can be achieved in most patients using LD of 25 to 30mg/kg ABW but higher doses (up to 35mg/kg) are likely needed in patients with ARC infected with less susceptible pathogens.
Arechiga-Alvarado et al. (2020) (5)	Prospective Observational	Evaluate PK of amikacin in Mexican patients with different renal functions receiving once daily dosing regimens and the influence of clinical and demographic covariates that may influence	n = 50, adult patients with suspected or proven infection and getting treatment with once-daily IV amikacin with at least one determination of	Patients received IV treatment with dosing determined by the treating physician. Plasma samples were taken. CG equation used for CrCl determination. Simulations were performed with the population model for dose selection (targets of Cmax/MIC of 8 or more and AUC/MIC>75).	CrCl had significant influence on amikacin CL.	small sample	CrCl significantly influences CL of amikacin. For low susceptibility pathogens doses of up to 60-70mg/kg may be needed to ensure target attainment.

		optimization of the drug. Propose a dosage regimen achieving therapeutic targets	amikacin plasma concentration.				
Vancomycin							
Chu et al. (2020) (76)	Retrospective Observational	Establish a PPK model to better describe the pharmacokinetic behavior of vancomycin and clarify PPK characteristics in Chinese ARC patients.	n = 95 patients aged 11-82 years, hospitalized, suspected or confirmed infection caused by gram positive and receiving vancomycin (pregnant and renal replacement not included)	All patients received vancomycin via IV infusion at intermittent intervals of 6, 8, or 12h and total daily doses between 1000 and 4000mg. All patients had ARC (CrCl > 130ml/min), CrCl estimated by CG equation. To determine steady state levels were drawn 30 mins before subsequent dose.	CL was 8.515 L/h and Vd was 155.4 L which is 2.5-3.5x values reported in literature. Univariate analysis showed age, CrCl, BUN to be covariants for CL. But multivariate analysis did not show this conclusion and only age influenced CL.	retrospective, small sample, children included	Clearance of vancomycin is higher in patients with ARC
Chen et al. (2020) (25)	Retrospective Observational	Study the effect of ARC on vancomycin TDM in patients undergoing neurosurgery	n = 104, adult patients treated with vancomycin after neurosurgery + normal liver and kidney function with TDM employed	Patients undergoing vancomycin therapeutic drug monitoring were assigned to the normal renal function or ARC group (CrCl > 130ml/min, calculated by CG). Target was 10 to 20 mg/L. The baseline characteristics, vancomycin therapeutic drug monitoring data, and prognosis were compared and analyzed.	Age, weight, and CrCl were significantly different between groups. Total dosage and duration were lower in the ARC group (maybe switched to other agents after they did not reach initial targets)? Mean vancomycin trough conc. was 6.45mg/L (compared to 10.72mg/L). Rate of target achievement was only 19.23% (compared to 41.03%). The proportion of patients in the three trough concentration groups (<10, 10-20 and >20) was also significantly different between groups. Trough concentration was correlated with age and CrCl. Neither of the groups had adverse reactions, and outcomes	small sample, retrospective, did not measure CrCl	In this cohort patients with ARC tended to be young, weigh more and be previously healthy. More likely to have subtherapeutic trough levels and require individualized doses based on TDM.

					were not significantly different.		
He et al. 2020(77)	Retrospective observational	To provide PK/PD parameters of serum vancomycin and analyze the optimal dosage regimen in critically ill patients with ARC.	n=280 critically ill patients that were tested for steady state vancomycin serum concentrations during January 2013 – November 2018 in a tertiary level hospital. Exclusion criteria: CrCl <80 ml/min, pregnant or lactating individuals.	Patients were assigned to two groups: ARC (CrCl > 130ml/min) or non-ARC (CrCL <130 ml/min). CrCl was determined using CG equation. Patients were given vancomycin 15mg/kg q12 hours over a 2 hr iv infusion. Vancomycin serum concentration was measured and PK parameters of vancomycin were estimated using Bayesian estimator. AUC/MIC was calculated using the MIC for each gram-positive bacteria (staph aureus, enterococcus faecalis and enterococcus faecium). TDM was conducted and doses that achieved target tough levels were recorded.	Patient with ARC had higher vancomycin clearance and lower trough serum vancomycin concentration values than on-ARC patients. Subtherapeutic trough concentrations (<10mg/L) were shown in 77.7% of ARC patients vs 68.8% of non-ARC patients ($p<0.05$). Higher through concentrations were harder to obtain in both ARC and non-ARC group. A daily dose of 46mg/kg is needed to attain a tough concentration of 10mg/L in patients with ARC.	Used CG formula to calculate CrCl instead of 24 hour urine collection which is more accurate. The Bayesian estimator used was developed in a Spanish population however this study was conducted to reflect results in a Chinese population. This may affect how accurately the Bayesian model reflects PK parameters of vancomycin in this population. ARC group contained 90 males vs. only 49 females. The average age of patients in the ARC group was statistically different than that of the non-ARC group ($p<0.05$) with the ARC group being a younger. This study did not compare clinical outcomes such as resolution of infections or infection related complications between the ARC	A higher dose of vancomycin is needed in critically ill patients with ARC. TDM guided dose adjustment should be considered to achieve the target therapeutic range. Further studies are needed to establish dosing guidelines in ICU patients with ARC treated with vancomycin.

						and non-ARC group.	
Hirai et al. (2016) (40)	Retrospective Observational	Investigate the risk factors for ARC and to evaluate the influence of ARC on the PK of vancomycin	n = 292 patient with normal serum creatinine receiving IV vancomycin	CrCl was estimated from serum creatinine concentrations based on CG equation. ARC was defined as CrCl > 130ml/min. Blood sampling was performed at least 3 days after treatment was initiated.	16.4% had ARC (less than 65 years old, brain injury, febrile neutropenia, mean volume of infusion fluid >1500ml/d risk factors for ARC). Patients with ARC had 1.6x higher CL of vancomycin. ARC group received higher doses and still exhibited lower trough levels and AUC. Subtherapeutic levels (<10mcg/ml) were identified in 68.8% of ARC patients and 32.8% in non-ARC.	did not discuss LD use	Clinicians should consider adjustments of initial dosage of vancomycin and appropriate TDM-guided dose optimization to achieve targeted therapeutic range, especially in patient with ARC
Chu et al. (2016) (78)	Retrospective Observational	Evaluate the effects of ARC on serum vancomycin concentration	n = 148 patients receiving vancomycin dose of 1000mg q12h and undergoing serum monitoring	All patients received 1000mg q12h, after 3 or 4 maintenance doses serum samples were collected before the next dose. Dosage adjustments were made if necessary. CrCl was determined using CG equation, ARC was >130ml/min.	78 patients had ARC. ARC patients were younger, lower SCr and higher GFR (determined by MDRD). Trough concentration for ARC patients was 9.2 +/- 5.4 ug/ml with 62.9% having vancomycin trough concentrations below 10 ug/ml.	retrospective, way more males than female, single center, CrCl was not measured	Patients with ARC are at higher risk for below target vancomycin trough concentrations. An increased LD or increased dosing frequency is necessary for patients with ARC
Minkute et al. (2013) (51)	Retrospective Observational	Determine the incidence of ARC in patients with different medical conditions employing steady state trough vancomycin serum concentrations for analysis.	n = 109 patients in various clinical settings	CrCl was estimated using CG equation and done every vancomycin serum concentrations measurement day, ARC defined by CrCl >130ml/min. Patients were divided into ARC group and control group. Vancomycin was prescribed according to routine use and ranged from 1000 to 4000mg/day. Concentration measurements were based on clinical judgement only. When the vancomycin serum concentrations was obtained before the next dose at steady state the case would be included for further analysis. Trough target was between 5.2 and 10.3 ug/ml. Various degrees of ARC were tested for impact of	Mechanical ventilation, hemodynamic instability and patient age were determinants of ARC. ARC resulted in statistically higher risk of under dosage (OR 1.84). Even though patients with ARC received higher average dose (22.9mg/kg/day compared to 13.5mg/kg/day). Every increase of CrCl by 40ml/min predicts a decrease in Css (steady state trough conc) by 1.49mg/ml.	Many different doses, different intervals for plasma measurements, all of which were determined by multiple physicians. CrCl was estimated and not measured. Recommendation is speculative and they did not test dosing in the study	Subtherapeutic vancomycin serum concentrations dominated in ARC patients, this finding should be considered while prescribing vancomycin. MV and hemodynamic instability may be predictors of ARC. Therefore, if there is a young patient, who is hemodynamically unstable and/or mechanically ventilated, CrCl >130 but especially if over 150ml/min and required vancomycin they may benefit from decreased dosing interval (q8h or q6h) and more prompt monitoring of trough concentrations (before 24hrs after initial dose).

				vancomycin serum concentrations. Patient factors and patient medical conditions were tested to determine relationship to ARC.			
Zhao et al. 2021 (79)	Prospective observational	The purpose of this study is to determine the pharmacokinetic of vancomycin in Chinese adults and the recommend dosage for patients with different renal function, including patients with ARC.	N=209. Chinese adult patients (39.2% ICU, 60.8% admitted to other departments) hospitalized between January 2010 and June 2018. Patients were included if they received intermittent IV vancomycin therapy, had data recorded, including age, gender, TBW, SCr and at least one serum vancomycin measurement.	Patient demographics and lab data were extracted. Serum concentration of vancomycin was determined. PK modeling was conducted to analyze covariates. Monte Carlo simulation were then performed for each renal function classification: 15–29 mL/min, 30–44 mL/min, 45–59 mL/min, 60–89 mL/min, 90–119 mL/min, 120–149 mL/min, 150–179 mL/min, 180–209 mL/min, 210–239 mL/min, 240–269 mL/min, and 270–299 mL/min. CrCl was calculated using the CG equation. ARC was defined as CrCl>130ml/min. Dosing intervals were set at 8, 12 or 24 h with 250–2500 mg per dose. The probability of target (steady state 24-h area under the curve (AUC24): 400–650 mg·h/L, steady state trough concentration (Ct): 10–20 mg/L) attainment was calculated.	51/209 (24.4%) of patients had ARC. Patients with ARC showed 1.3- 2.1 times higher drug clearance than patients with normal kidney function. CrCl was identified as the most significant covariate that affected elimination of vancomycin. Dosing regimens were recommended as follows: For patients with CrCl 120-149ml/min a dose of 1750mg q24hr will result in a PTA of 62.33%, for CrCl 150-179ml/min a dose regimen of 1000mg q12hr will result in a PTA of 62.56% and for CrCl >180 750mg q8hr will result in a PTA of 61.69%.	Limited sample size means reduced generalizability. CrCl was calculated using the CG equation instead of the gold standard 24hour urine collection method which may have influenced accuracy of estimated clearance.	Established a population pharmacokinetic model for vancomycin in adult patients with different renal function, including patients with ARC. An initial dosing regimen of vancomycin was proposed for patients with insufficient, normal and augmented renal clearance.
Baptista et al. (2012) (8)	Prospective observational	Evaluate the effect of ARC on vancomycin serum concentrations in critically ill patients	n = 93 adult patients, ventilated with severe sepsis or septic shock receiving empiric or directive treatment with vancomycin.	Patients received LD 1000mg (weight <70kg) or 1500mg (weight >70kg) over 1h followed by continuous infusion of 30mg/kg/day. Serum levels measured on the first 3 days of treatment. Adequate treatment for gram-positive organisms was defined as 13.8-20.7umol/L. If needed, dose adjustments were made. 24h CrCl measurement performed on patients, with ARC defined as CrCl >130ml/min. Patients were divided into group A (no ARC) and group B (ARC).	40% of patients in the cohort demonstrated ARC. These patients were significantly younger, less severely ill, with trauma as the leading cause of admission. The serum vancomycin concentrations in Group B were significantly lower on all 3 days of testing. 10.8% had therapeutic levels on D1, 31.4% on D2 and 51.6% on D3.	Did not discuss data origin/collection. Rationale for their treatment targets	ARC is associated with subtherapeutic serum vancomycin levels, this study suggests these patients may need a more aggressive LD and well as TDM

Campassi et al. (2014) (18)	Prospective observational	Determine the incidence and associated factors of ARC and the effects on vancomycin concentrations and dosing in ICU patients.	n=363 patients admitted to clinical-surgical ICU (exclusion: under 21 years old, no bladder catheter in place, no 24hr urine collection available, plasma creatinine of >1.3mg/dL)	24 hr urine samples were collected and CrCl was calculated. ARC defined as CrCl >120 ml/min. Patients were grouped based on the presence of ARC. Possible risk factors were analyzed. In patients with confirmed gram-positive infection, vancomycin was started with LD 15 mg/kg followed by CI of 30mg/kg/day targeting plasma concentration of 15-25ug/ml. Dosage adjustments were made if needed. Serum levels were measured on the first 3 days of treatment.	28% of the cohort developed ARC. ARC patients were younger, had obstetric or trauma admission, lower APACHE II scores. Logistic regression analysis showed younger age and absence of diabetes as the only independent predictors of ARC. 12/44 patients getting vancomycin had ARC. These patients had lower concentrations and required higher doses (after 72h doses required were almost 50% higher than the other group). After 24hr of treatment no ARC patient had achieved target trough levels.	CrCl was only evaluated at admission.	ARC is a common finding and linked to age and absence of diabetes. Patients with ARC had lower plasma concentrations of vancomycin despite receiving increased dosing.
Helset et al. (2020) (39)	Prospective observational	The aim of this study was to identify patients at risk of therapeutic failure defined as vancomycin AUC/minimum inhibitory concentration (AUC0-24/MIC) <400, and to examine possible effects of different MICs, the variability in renal clearance and continuous renal replacement therapy (CRRT), and the relevance of vancomycin therapy.	n = 83 (20 patients per group), adult patients enrolled from various ICU settings (general, cardio, and neurosurgical) treated with vancomycin of over 72 hours.	The patients were divided into four groups according to renal function and CRRT-mode as follows: normal (CrCl >60 and <129) or augmented renal clearance (> 130) and continuous venovenous hemodialysis or -hemofiltration. Doses were infused at a maximum rate of 1g/h with a median frequency of 2x/day. Vancomycin trough levels were measured at 24, 48, and 72 hours after therapy initiation prior to next dose. Peak levels were drawn 1hr after infusion. Urine collection used for CrCl measurements started at initiation and continued q24hrs. Relevance of vancomycin therapy was retrospectively evaluated based on microbiological results and indications for therapy by three ID specialists.	ARC patients were given stat. higher maintenance doses (44.4mg/kg) compared to other groups. ARC patients had higher CL and shorter T1/2 compared to normal renal clearance groups which resulted in lower AUC/MIC values. For all groups, when looking at MIC of 2 and 4 mg/L, the target was reached at 8% and 0% respectively. Only ⅓ of patients needed treatment and of this median MIC was 1.0mg/L and patients belonging to all groups had AUC/MIC >400 but majority were part of CRRT group.	Patients who required vancomycin treatment had appropriate levels so are findings clinically significant? They didn't breakdown how many patients required treatment were from each group just that majority was from CRRT	All patients with ARC (even with MIC <1) + any patient with pathogens of MIC >1 mg/L are at risk of subtherapeutic AUC/MIC ratio when treated empirically with vancomycin. Daily CrCl measurements and TDM are needed in non-CRRT patients. Author suggests continuous infusion as a possible dosing option for ARC patients.

Baptista et al. (2014)(9)	Group 1 (retrospective), group 2 (prospective)	Develop a dosing nomogram for the administration of vancomycin by CI for the first 24h of therapy based on 8h measured urinary CrCl. And then to evaluate its efficiency in a separate cohort of critically ill septic patients.	Group 1 (n=79), ventilated, adult patients with severe sepsis or septic shock starting empirical or directive treatment that includes vancomycin. Group 2 (n=25), critically ill septic patients receiving vancomycin at discretion of ICU physicians.	Group 1 - Dosing protocol (described in previous study above), daily TDM performed morning following initiation of treatment. Used 8h urine collection to determine CrCl. Relationship between the clearance of vancomycin and 8 h CrCl was used to define a dosing nomogram for vancomycin for different 8 h CLCR that targets Css of 25 mg/L. ARC defined as 8h CrCl of >130ml/min. Group 2 - 8h urine collection determined CrCl. Received dosing as per nomogram and had serum levels drawn on day 1 following start of treatment. To determine the efficacy of the nomogram that had been developed. Treatment target was 20-30 mg/L.	In group 1, 51% of patients achieved the target, compared to 84% in group 2. In patients with ARC in group 1, 28% achieved target whereas all of the ARC patients in group 2 reached target. There were no side effects reported in group 2 but 6.3% of patients in group 1 had nephrotoxicity reported.	second cohort was smaller, no info on collection of retrospective data	Patients with ARC appeared to be more likely to experience subtherapeutic vancomycin levels within the first 24h of treatment. Using the nomogram appeared to increase target attainment, especially in ARC patients.
Ishii et al. (2018) (42)	Retrospective Observational	Evaluate the validity of a renal function-based nomogram for vancomycin dosing, and to investigate the association of specific conditions related to ARC with the accuracy of the nomogram.	n = 177, patients receiving IV vancomycin + concentration data + dosed based on nomogram (<18 yrs, renal replacement and eGFR <30ml/min were excluded)	Patients received vancomycin doses based on nomogram. Blood sampling done at least 3 days after initiation. eGFR calculated using the Japanese Society of Nephrology formula from SCr concentrations. The associations between age, renal function, and conditions with subtherapeutic concentration (<10ug/ml) was evaluated.	46% of patients had trough <10, 7% had trough >20. Univariate analysis showed age as the only variable associated with subtherapeutic levels. There was no significant difference between trough concentrations when patients were analyzed in CrCl groups.	retrospective, did not consider LD, is GFR equation validated, nomogram not detailed in study	This study suggests that this nomogram (which I couldn't find) may be useful in avoiding subtherapeutic concentrations of vancomycin in patients with risk factors for ARC.
Vermis et al. (2014) (80)	Retrospective Observational - abstract	investigate the prevalence of ARC in a hematological population and evaluate correlation with higher clearance and increased vancomycin dosing	n = 96, patients with hematological malignancies receiving vancomycin in a tertiary care hospital	Patients received LD 15 mg/kg followed by maintenance of 30mg/kg via CI. Therapeutic levels were 20ug/ml. CrCl was estimated using CG equation. ARC was defined as CrCl > 120ml/min	ARC was a factor in 73/112 treatment courses. It was statistically related to age, neutropenia and chemotherapy. Patients with ARC reached therapeutic levels on day 5 with average maintenance of 41.7 mg/kg/day and patients without reached on day	ARC could have been a factor in 1 to 100% of the treatment course.	Regular monitoring of drug concentration and subsequent dose adjustment is needed. A dosing regimen with increased LD 25 mg/kg (for all patients) and maintenance of 40 mg/kg for patients with CrCl >130 ml/min may be beneficial.

					3 with average 32.7mg/kg/day.		
Weigel et al. (2014)(81)	Prospective Observational - abstract	Does ARC measured by MDRD lead to subtherapeutic serum vancomycin concentrations	n = 287 patients in general ICU who received CI vancomycin	Patients received LD of 20 mg/kg, TDM performed, and maintenance doses were adjusted to target concentration of 20-25 mg/L. eGFR was calculated using MDRD and ARC was defined as eGFR > 130	Subtherapeutic levels were more frequent in patients with ARC (55.2 compared to 29.3%)	abstract	If a patient has ARC higher standard maintenance doses of vancomycin will be needed to reach therapeutic concentrations.
Chu et al. (2020) (27)	Retrospective Observational	Analyze the influence of factors on the steady-state trough concentration of vancomycin, especially in patients with ARC	n = 292 patients, between 12-90years with documented are assumed infection with gram-positive organisms, receiving 1000mg q12h with monitoring completed.	Demographic, clinical factor, vancomycin doses and concentrations were retrospectively gathered and analyzed. CG formula was used to calculate CrCl and ARC was defined as over 130 ml/min.	Median trough concentration of vancomycin in ARC patients was 7.7 ug/ml. Patients within the therapeutic range was only 32.8%. With over 60% having concentrations <10ug/ml. Data suggests age had a more profound correlation with trough concentrations than CrCl.	retrospective, included children in the study	Patients with ARC are at an increased risk of vancomycin trough levels <10ug/ml. Patients with ARC should be identified as early as possible and TDM should be performed for dosing changes.
Villanueva et al. (2019) (69)	Retrospective Observational	To determine if institutional vancomycin pharmacy dosing protocol will achieve higher rates of initial therapeutic troughs	n = 70, critically ill trauma patients treated with the institutional vancomycin protocol with appropriately drawn steady state trough (1hr before 4th or 5th dose) - exclusion: CrCl <60 ml/min, Scr >1.5mg/dL, renal replacement therapy.	Dosing protocol was 15mg/kg to 20mg/kg + 25 mg/kg LD, maintenance intervals determined based on CrCl. Target 15mg/L to 10mg/L. CrCl calculated using CG. ARC defined as >160ml/min.	Only 15% of patients had initial levels at target. No statistically significant differences between the group that did and did not achieve targets. But more patients had CrCl > 160 in the group that didn't achieve as well as lower rates of ever achieving therapeutic trough. The patients with initial trough below 10 mg/L were categorized as having lower Scr, higher CrCl and higher ARCTIC score.	small, retrospective, did not measure CrCl	Dosing protocol (15-20mg/kg + 25mg/kg LD at various intervals) did not result in target attainment in critically ill trauma patients. Continuous infusion may be a strategy worth exploring in this patient population.
Izumisawa et al. (2019) (43)	Retrospective Observational	Perform a large scale investigation toward the effect of hematologic malignancy on the PK parameters of vancomycin	n = 684, adult Japanese patients with (261) and without (261) hematological malignancy who received vancomycin with	Patients split into hematologic malignancy and non-hematologic malignancy, then split into more groups based on having normal renal function (CrCl >60 and <120) and ARC (CrCl >120). CrCl calculated using CG equation. Patient	Vancomycin daily dose and trough concentration was higher in hematologic malignancy group. CL was higher and t1/2 was shorter for the malignancy group.	retrospective, generalizability	Patients with hematological malignancy must have vancomycin therapy carefully monitored.

			proper TDM completed (trough levels drawn 3 or more days after initiation). Excluded patients on renal replacement therapy.	background, lab values, dose, and PK were analyzed and compared.	When comparing group, A and B with heme malignancy they found average doses were higher in group B, yet trough concentrations were not significantly different.		
Mikami et al. 2021 (82)	Retrospective Observational	to evaluate the clinical applicability of urinary CrCl for determining the initial dose of vancomycin in critically ill patients and to assess vancomycin trough plasma concentration/maintenance daily dose (C/D) ratio in patients with ARC.	n=65. Critically ill patients who received vancomycin IV from April 2014-July 2020 in the emergency department of Hokkadio University hospital. Exclusion criteria: <18, RRT, changed vancomycin maintenance dose during start of therapy and initial TDM.	Patient characteristics and laboratory data were collected from medical records. Renal function was estimated using CrCl (8hr urine collection) ,CG equation and KineticGFR equation. Correlation between estimated renal function (using each of the above formulas) on the first day of vancomycin administration and C/D ratio was evaluated. Physician/pharmacist determined the LD and maintenance dosing. Patients were divided into those with or within renal function changes (defined as change in CrCl >30 ml/min from the beginning of vancomycin administration to initial TDM) and patients with or without ARC (Actual ARC Defined as CrCl >130ml/min on first day of vancomycin administration). Difference in C/D ratio between ARC and non-ARC groups (borderline ARC and non-ARC) were evaluated as a secondary outcome.	CrCl formula tended to show a stronger negative correlation with D/C ratio than the other two formulas in all groups except in the non-ARC group. Actual ARC group had significantly lower C/D ratio than non-ARC group (0.24 vs 0.52kg/L). No significant difference was found between the Actual and borderline ARC group or the borderline and non-ARC group.	The study had a low patient population number, this meant some groups did not meet the required sample size set for correlation analysis. The study was only conducted at one hospital limiting generalizability. The study did not compare C/D ratio to clinical outcomes such as infection resolution, limiting the clinical relevance of these findings.	CrCl may have clinical applicability in determining initial dose of vancomycin in critically ill patients. Patients with ARC require higher vancomycin doses than non-ARC patients. It is necessary to continuously monitor renal function using CrCl because renal function in critically ill patients often changes daily. Further studies are needed to verify these results.
Sridharan et al. 2020 (83)	Prospective Observational	To assess the incidence of ARC and compare the drug utilization in this group with those having a normal renal clearance	n=80. Patients 21-60 yr old with normal Scr (53-97umol/L). Exclusion criteria: history of renal disease.	Patient demographics, laboratory results, clinical outcome and ICU length of stay were extracted. CrCl was assessed using 24hour urine collection. CG and MDRD equation were also used to assess CrCl to compare CrCL obtained from urine collection The pearsons correlation tests were used to assess this. Vancomycin (target 10-20 mg/L) and gentamicin (target <2mg/L) trough levels were collected as part of care. Monte Carlo simulations were only carried out for	Both CG equation (r=0.46, p=0.001) and MDRD equation (r-0.26, p= 0.001) were significantly correlated with urinary CrCl. 42/80 (52.5%) of patients had ARC. 8/28 (28.6%) vancomycin trough levels were within the recommended range vs 4/4 (100%) gentamicin levels were within the	Small sample size means low generalizability of these results. The study did not provide information regarding dosing regimens used in patients for either vancomycin or gentamicin. This leads to the inability to rule	Critically ill adults are likely to have ARC and are more likely to achieve subtherapeutic vancomycin concentrations.

				vancomycin to compare CrCl and trough concentrations in patients with or without ARC. ARC was defined at CrCl>130ml/min.	recommended range in the 29 patients who had ARC. 6/23 (26.1%) vancomycin trough levels were within range and 1/1 (100%) gentamicin trough concentrations were within range in the 16 patients WITHOUT ARC). 90% of patients with ARC are likely to have trough concentrations 5.63-7.78mg/L (10-20mg/L) vs 7.75-9.66mg/L in those without ARC.	out subtherapeutic dosing as a confounding variable which could result in subtherapeutic trough concentrations. The study did not indicate time of blood sampling therefore we cannot determine if trough concentrations represent steady state.	
Linezolid							
Barrasa et al. (2020)(14)	Prospective Observational	Assess influence of ARC on PK of linezolid in critically ill patients. Evaluate the effect of continuous infusion on the probability of therapeutic success	adult patients in ICU and suffered from infection treated with linezolid	Part 1: measured conc. with standard dosing (600mg q12h over 30mins) in groups of patients based on renal function - group I CrCl <60, group II CrCl >60 and <130, group III CrCl >130, part 2: measured conc. following continuous infusions (50mg/h) in patients with renal function >40 (group 4 >40 and <130, group 5 crcl >130). Targeting linezolid AUC/MIC > 80 and %T>MIC>85%	PART 1: linezolid concentration was remarkably lower in group III, significant differences in half-life (t1/2), CL, AUC24, and Cmin. Patients with ARC did not achieve PK/PD targets, whereas 80% of patient in the other groups did. This was the case with ARC patients who received 600mg q12h and q8h as per Monte Carlo simulation. PART 2: ARC patients had reduced C and AUC but 70% of patients achieved and maintained linezolid conc. above target, compared to 94% of patients without ARC. No adverse effects were observed. Based on simulation a CI of 75mg/h probability of target attainment in 93% of patients who had ARC.		Linezolid administered as continuous infusion (either 50mg/h - equivalent to current standard dosing or 75mg/h) is an alternative for patients with ARC. Provides justification for the use of TDM in patients with ARC.

Piperacillin/Tazobactam							
Wu et al. (2019)(72)	Prospective Observational	Incidence and risk factors of ARC and its effect on B-lactam PK/PD in Asian populations admitted to ICU	n=100 adult patients in ICU for >24hr without CKD	Blood samples collected if patient received piperacilin/tazobactam, cefepime, meropenem at mid-dosing interval and prior to next dose (after at least 4 prior doses had been given). Used P. aeruginosa breakpoint as target MIC. Analyzed results in terms of %fT>MIC	ARC group was significantly younger with lower SOFA score. Loop diuretics showed lower occurrence of ARC. For more aggressive treatment targets like 50%fT>4MIC, 100%fT>MIC and 100%fT>4MIC patients with ARC were less likely to achieve targets. More patients achieved the PK/PD target of 100%fT>MIC with ICU survival than those with ICU mortality. But there was no stat. Difference between ICU survival in ARC and non-ARC groups.	small sample size, did not calculate unbound	Patients with ARC are less likely to attain necessary PK/PD targets, impact on clinical outcomes cannot be determined (survival of ARC patients could be due to young age and less organ failure and not B-lactam levels) studies matched for age and SOFA may be necessary to compare clinical outcomes.
Carrie et al. (2018) (21)	Prospective Observational	To determine whether ARC impacts negatively on PK/PD target attainment in patients treated by high doses of B-lactams administered continuously for a first infection in a surgical ICU. The secondary objective was to test the association between ARC, sub exposure to B-lactams and clinical outcomes.	n=79, adult patients, critically ill without renal impairment treated by one of the monitored B-lactams for a documented infection (exclusion criteria - renal impairment, undocumented infection, initial inappropriate antimicrobial therapy, died before 15 days after termination of therapy)	Cefazolin, cefotaxime, piperacilin/tazobactam, cefepime, ceftazidime, meropenem were administered at standard dosing. Patients were included on day 1 of antibiotic therapy, TDM and CrCl were reported on days 1-3. For CrCl, patients underwent 24-h urine samples. For TDM, blood was collected at 24, 48 and 72hrs. Underdosing was defined as free drug concentration under the MIC of the known pathogen and sub-exposure was defined as at least 1 sample under the MIC of the known pathogen. Defined bactericidal activity as 4x MIC (if MIC not known they used EUCAST break-point). Therapeutic failure was defined as persistent or recurrent fever, organ dysfunction, clinical and biological symptoms of the initial infection with a need for escalating antibiotics during or 15 days after treatment.	With PK/PD target at >4xMIC the rate of underdosing was 12% with significant association with CrCl (CrCl >170 stat. Associated with B-lactam underdosing). Other variables associated with underdosing included younger age, higher weight and higher MIC. Mean CrCl values were significantly higher in patients with therapeutic failure and sub-exposure. Sub-exposure was associated with therapeutic failure.	Had lots of patients receiving combination antibiotic therapy, levels and CrCl only taken for 3 days, majority receiving piperacillin so does it apply to all agents?	More aggressive clinical targets may be needed in critically ill patients (4xMIC for the entire dosing interval). When CrCl is >170 there is increased risk for sub-exposure to antimicrobial agents and this is associated with therapeutic failure. TDM may be employed in patients with ARC especially those infected with less susceptible pathogens or infections with limited penetration of antimicrobial agents.

Andersen et al. (2018) (84)	Prospective Observational	Develop a PK model to assess the piperacillin PK profile in septic patients. Make correlation to target attainment and assess efficacy of different dosing regimens.	n=22 adult patients admitted with sepsis (known or suspected infection) to a medical ward. Patients on renal replacement therapy were excluded.	All patients received piperacilin/tazobactam at 4g/0.5g q8h via 3 min intermittent infusion. Blood samples were collected over 1 dosing interval for 3 consecutive days. Wanted to evaluate targets of 50%fT>MIC and 100%fT>MIC using clinical breakpoint for P.aeurginosa (16mg/L). Using simulations, they tested intermittent, extended and continuous regimens at various daily doses. ARC was defined as 130ml/min and CrCl was calculated using the CG equation.	4 patients in the cohort had ARC. An increase in CrCl from 83.9 to 174 ml/min predicted to lead to an increase in total B-lactam CL of 79.5%. The max MIC for 100%fT>MIn patients with CrCl >130ml/min was only 0.125mg/L, which suggests ARC patients are less likely to achieve targets. Found prolonged infusion and higher intermittent dose improved results. Extended infusion (4 g every 6 h [q6h]) over 3 h would be sufficient to achieve a 50% fTMIC in all patients, while continuous infusion (CI; 8 g) was needed in order to achieve a 100% fTMIC. When using IA at 4g q6h the max MIC for a pathogen resulting in 100%fT>MIC was 2.0mg/L which is considered sufficient.	small sample, estimated CrCl, simulation data dose recommendation	In patients with sepsis, piperacilin/tazobactam doses administered by prolonged infusion (infusions over 3h or CI) or increased frequency (4g q6h) may result in more favorable PK/PD target attainment.
Weber et al. (2019) (70)	Prospective Observational	Evaluate fT>MIC with q6h piperacilin/tazobactam dosing in hematology patients with chemo-induced neutropenia. Assess impact of PK/PD target attainment on clinical outcomes.	n=24, Patients undergoing chemotherapy for hematological malignancies presenting with first fever and receiving piperacilin/tazobactam	Patients received piperacilin/tazobactam 4g/0.5g q6h. 24h urine samples were performed for CrCl calculation. Plasma concentrations were assayed at 50% and 100% of dosing interval and compared to target MIC breakpoint of 16 mg/L to determine likelihood of 50%fT>MIC and 100%fT>MIC. Also recorded clinical cure, length of stay, duration of antibiotics, and clinical treatment success.	Only 4% of patients achieved 100% fT>MIC and 50% achieved 50% fT>MIC. Higher CrCl was significantly associated with lower trough drug concentration. Of patients who had clinical failure none achieved 100%fT>MIC and about half achieved 50%fT>MIC. Duration of therapy and time to clinical cure were longer in those who did not attain 100%fT>MIC but this was not statistically significant.	small sample size, generalizability	Dose of 4g q6h was not suitable for this population especially if they had increased CrCl (ARC)

Akers et al. (2014) (85)	Prospective Observational	Assess diagnosis of ARC score, compare PK of low vs high ARC score groups. Assess target attainment for multiple dosing recommendations of piperacillin	n = 13 critically ill patients	Pharmacokinetic data from trauma/surgical intensive care unit patients receiving piperacillin/tazobactam were evaluated. We combined intermediate scores into a single low score group and compared pharmacokinetic parameters against the high ARC score group. Diagnostic performance was evaluated using median clearance and volume of distribution, area under the antibiotic time-concentration curve (AUC), and achievement of free concentrations greater than a minimum inhibitory concentration (MIC) of 16 mg/mL for at least 50% of the dose interval. Alternative dosing strategies were explored in silico.	More rapid CL and larger Vd observed among patients with high ARC score. These factors may reduce antibiotic exposure which was also reflected in reduced AUCs compared with patients with low ARC scores. Higher ARC scores were also found to be 100% sensitive for predicting suboptimal drug levels for pathogens with MIC of 16ug/ml. Sufficient dosing was found to be an extended interval of 12g/day (500mg/h), for intermittent 4 to 6g q4h or 6 to 8g q6h would be required. Also found that extended dosing allowed for a 50% (or more) cost reduction compared to various intermittent dosing.	used MDRD equation, only 13 patients included,	critically ill patients with ARC may benefit from extended dosing (12g/day at 500mg/h) especially for less susceptible pathogens with MIC 16ug/ml
Dhaese et al. (2017)(86)	Prospective Observational	evaluate the population PK and PTA of piperacillin when infused continuously in critically ill patients (because current PK models for continuous infusion are estimated from intermittent infusion studies)	Evaluated 270 plasma samples of 110 patients in ICU being treated with piperacillin (excluded those undergoing extracorporeal membrane oxygenation or renal replacement therapy)	received continuous infusion piperacilin/tazobactam, standard dose was 16/2g/piperacillin/tazobactem/24hr but dose was increased or decreased based on renal clearance. CrCl determined by 8hr urinary collection. Levels were determined in the lab and Monte Carlo simulation used based on various doses, CrCl, and MICs.	high dose (4g loading, 24g/day) + CI was not sufficient to achieve adequate exposure of 100% fT>MIC against susceptible P.aeruginosa isolates (MIC <16mg/L) when renal CL was >90. For MIC of 16mg/L (worst case scenario) max dose continuous infusion only provided adequate exposure for CrCl of less than 65. In a substantial amount of patients even high dose continuous was not enough (31.5% of patients had ARC defined as CrCl >130).		current dosing is based on II data and that dosing is potentially not effective for some ICU patients. Suggestions based on this → piperacilin/tazobactam use as monotherapy in patients with high CrCl and infected with high MIC bacteria may not be sufficient (use combination, TDM, different agents). Author suggests a PK model that is based on CI is needed.

Carrie et al. (2018)(22)	Prospective Observational	To determine whether ARC impacts negatively on piperacilin/tazobactam unbound concentration in critically ill patients receiving 16g/2g/day administered continuously. The secondary outcome was to determine optimal dosing of piperacilin/tazobactam for empirical antimicrobial therapy in critically ill patients with various renal clearance and pathogen susceptibility.	n=59, adult ICU patients with sepsis, excluded if CrCl <40 or renal replacement therapy.	Patients received 4g/0.5g LD and 16g/2g by continuous infusion. Samples collected at 24, 48 and 72hrs. For days 1-3 of treatment patients underwent 24-h urine samples to calculate CrCl - patients put into groups as no ARC (>40 and <130) moderate ARC (>130 and <200) and severe ARC (>200). Therapeutic failure was defined as persistent or recurrent fever, organ dysfunction, clinical and biological symptoms of the initial infection with a need for escalating antibiotics during or within 15 days of treatment. Underexposure was based on at least one sample below the highest MIC as per EUCAST - 16mg/L for PIP and 2mg/L for TAZ (wanted to base off of "worst case" scenario because it is important that empirical treatment covers this). They also looked at excessive dosing which was defined as free drug conc. >150mg/L for PIP	PIP underexposure was 19% with a stat. association to CrCl. The rate of PIP underexposure was higher in ARC patients. Patients with CrCl >170 did not achieve PK/PD targets when receiving 16g/2g/24hr via CI. In patients with ARC a 20g/2.5g/24hr dosing regimen was associated with highest probability to reach 16mg/L target, without risk of excessive dosing (as per simulation).	simulation data - need for clinical outcome trials, small sample	Higher than licensed doses of piperacilin/tazobactam (20g/2.5g/24hr) may be needed for patients with CrCl >170ml/min, and even at these doses study suggests patients were well under the 150mg/L threshold for neurological toxicity.
Carlier et al (2013)(19)	Prospective Observational	Link ARC to PK/PD target attainment in critically ill patients receiving meropenem or piperacilin/tazobactam	n = 61, adults without renal dysfunction receiving meropenem or piperacilin/tazobactam as an extended infusion	CrCl via 24hr urine sample, ARC defined as CrCl >130ml/min, patients received standard doses of meropenem (1g LD followed by 1g q8h via extended infusion over 3hrs) and piperacilin/tazobactam (4.5g LD followed by 4.5g q6h via extended infusion over 3hr). Blood samples drawn and analyzed. Concentrations compared to target MICs for P.aeruginosa - 16mg/L for piperacilin/tazobactam and 2mg/L for meropenem as per EUCAST breakpoints.	48% of patients did not achieve PK/PD target (100%fT>MIC) and of these almost 80% had ARC. Patients who did not achieve the target were younger, had higher CrCl and higher weight. 48% of patients had ARC and of this majority (76%) did not reach PK/PD target. A lower target of 50%fT>MIC was also assessed, finding that of the ARC patients 37% of patients did not even achieve this target.	small sample	Standard dosing of meropenem and piperacilin/tazobactam resulted in nearly half of critically ill patients in this cohort not achieving PK/PD target, with patients experiencing ARC at increased risk.
Ceftolozane/Tazobactam							
Nicolau et al. 2021 (87)	Prospective Observational	To determine whether established ceftolozane/tazobactam (C/T) dosing is adequate for patients	n=14. Critically ill patients >18, with CrCl >180ml/min (CG equation) within 24 hr. of	CrCl was measured using 8 hr urine sample. ARC was defined as CrCl >130 ml/min. Patients received 3g of C/T via 60 min IV infusion. PK sampling was at time 0 (predose), 1,2,4,6 and 8 hours after	11/14 patients showed to have CrCl >130ml/min using 8 hr urine collection and were confirmed to have ARC. Mean plasma	Small sample size reduced generalizability. Used CrCl 8 hour collection instead of the gold	3g C/T dose reached clinically meaningful plasma concentrations. Dosing q8 hour is associated with reaching PK/PD targets and is generally well tolerated in critically ill patients with ARC. Therefore C/T 3g q8 hr is

		with ARC and bacterial infection	dosing and had a documented or suspected infection.	the start of infusion. Noncompartmental analysis was conducted on the concentration data. The study further determined fT>MIC of 4ug/ML for Ceftolozane and fT> threshold = 1ug/ml for >20% of the dosing interval for tazobactam. Safety and tolerability was assessed based on the incidence of AE and serious AE.	clearance and volume of distribution was higher in patients with ARC vs healthy patients for ceftolozane and tazobactam. Ceftolozane fT>MIC of 4ug/mL was achieved in 9/11 patients with ARC for up to 6 hours after administration. This was also seen in 7/11 patients with ARC for up to 8 hours after administration. Tazobactam fT>1mg/ML (threshold) was achieved for 2 hr in all patients and up to 4hr after administration in 7/11 patients with ARC. Saftey and tolerance data showed C/T was well tolerated in critically ill population. The most common AE were constipation and hypotension (18.2%).	standard 24hr collection to determine CrCl. fT>MIC of 4ug/mL and ft>1ug/mL for Ceftolozane and Tazobactam respectively were not compared against clinical outcomes reducing the clinical relevance of these targets. Some of the study authors are currently employed by the company which funded the study resulting in potential conflicts of interest.	likely to be efficacious of critically ill patients with ARC without additional dose adjustments needed.
Shorr et al. 2021(88)	Prospective Observational	To examine 28-day all-cause mortality (ACM) and clinical and per-participant micro- biologic cure rates at the test-of-cure (TOC) visit among participants with ARC (CrCl>130 mL/min) and those with normal renal function (CrCl 80 to 130 mL/min).	N=5152. Patients from the phase 3 ASPECT-NP trial, >18 years of age with HABP/VABP (persistent, worsening or new nosocomial pneumonia despite >48 hours of antibacterial therapy). Exclusion criteria: only gram-positive pathogen was isolated, ESRD, peritoneal or hemodialysis,	Patients were categorized into normal renal function group (CrCl 80-130ml/min) or ARC Group (CrCl >130ml/min). CG formula was used to calculate CrCl. PK models informed Monte Carlo simulations to assess PTA in plasma and pulmonary epithelial lining fluid (ELF) for C/T. PK/PD target for ceftolozane was 50% of the dosing period that the free drug concentration >MIC (fT>MIC of 4ug/mL). PK/PD target for tazobactam 35% fT>Ct with a threshold concentration of 1ug/mL. Authors also measured all-cause mortality and clinical cure and per-patient microbiologic cure rates at the test-of-cure visit.	>99% of all simulated patients were estimated to achieve the ceftolozane target (50% fT>MIC of 4ug/mL) in plasma and ELF across different ARC categories. Tazobactam target (35% fT>Ct of 1ug/mL) was achieved in 80% of simulated patients. High PTA for tazobac- tam was estimated for all patients but incremental decrease in PTA was observed with increased ARC across ARC categories.	CrCl was calculated using the CG equations instead of the gold standard 24hr urine collection making it less accurate. CrCl categorization was only done at baseline and therefore patients who had ARC at baseline but then reverted to normal renal function would have had a dose adjustment but remained in the	Findings demonstrate high PTA with C/T 3 g dosed every 8 h in patients with HABP/VABP and in critically ill participants with and without ARC, with- out a need for further dose modification.

			urine output <20mL/hr over 24 hour period, received >24hr of systemic/inhaled antibacterial agent with gram negative activity 72hours prior to study agent.			ARC group. Many of the study authors work for the company that funded the study which could be a conflict of interest.	
Enoxaparin							
Abdel El Naeem et al. (2017)(4)	Observational (prospective)	determine impact of ARC on therapeutic action of enoxaparin measured by anti-factor Xa activity	critically ill, >18 years old, stay >48hrs, requiring enoxaparin prophylaxis (given 40mg/QD)	50 critically ill patients divided into two groups (ARC and normal kidney function) based on 24hr CrCl measurement. Anti-factor Xa measured in both groups at 4, 12 and 24hr post administration.	Anti-factor Xa levels similar in both groups at 4h but measurement at 12 and 24h showed ARC group with significantly reduced levels.	Did not follow-up regarding development of DVT in both groups, did not follow-up regarding overall clinical outcomes of patients, and are levels at hours 12 and 24 relevant?	ARC patients showed shortened activity of enoxaparin, need for increased dose or administration frequency. Need larger study conducted with extended follow-up to address development of clots as well as other clinically important outcomes.
Ramos et al. (2018)(89)	Observational (prospective) - abstract	investigate impact of ARC on the PK of enoxaparin	ICU patients, <65 years of age, normal SCr, requiring enoxaparin prophylaxis	13 patients included, 6 developed ARC (defined by CrCl >130ml/min/1.73m2, measured via 24h urine collection), of these 6, 5 patients achieved therapeutic range of enoxaparin during second day of treatment	found no relationship between ARC and therapeutic failure	dose of enoxaparin not specified, did not investigate thromboembolic events	Dosing adjustment may not be required in ICU patients receiving prophylactic enoxaparin. Though a larger study which incorporates data on development of clots is required.
Levetiracetam							
La et al. (2018)(90)	Prospective Observational	Identify optimal dosing strategies for patients receiving levetiracetam for seizure prophylaxis secondary to TBI	ICU TBI patients	25 patients included, receiving 1000mg IV bid, CrCl and max. levetiracetam levels measured during first 7 days of admission	median maximum levetiracetam concentrations 2.3-4.6mg/L (subtherapeutic, suggested reference range: 6-20mg/L), 20% of patients had seizures	didn't use confirmed reference ranges	Standard dosing regimens may not be effective in TBI patients exhibiting ARC, further investigation needed to determine required dosing.
May et al. (2014)(91)	Prospective Observational - abstract	measure CrCl in aneurysmal SAH patients and evaluate how it may impact renally cleared medications	ICU patients with SAH	20 patients enrolled, baseline CrCl measured, and concentration-time dependent profiles were simulated for multiple IV doses of levetiracetam using Monte Carlo Simulation (MCS)	Measured CrCl was much greater than estimated. MCS suggested that levetiracetam dosing did not achieve target levels unless three times daily dosing was used.	simulation, dosing data provided is vague	In ICU patients with SAH an increased dose of levetiracetam (i.e. TID dosing) may be required for adequate therapeutic effects

Spencer et al. (2011)(92)	Prospective Observational	Characterize the steady-state pharmacokinetics of IV levetiracetam used as seizure prophylaxis in patients following neurological injury. Determine which dosing regimen resulted in levetiracetam levels within therapeutic range of 6-20ug/ml	neurocritical care patients with SAH, TBI, or SDH requiring seizure prophylaxis, >18 years of age, with venous access already established (exclusion: multi-system trauma, kidney impairment, low hemoglobin)	12 neurocritical care patients received levetiracetam 500mg infused over 15 minutes q12h. Blood samples collected after a minimum of 4 doses of therapy and serum levetiracetam levels obtained. Used Monte Carlo simulation for multiple dosing regimens.	Levetiracetam systemic clearance was faster, and half-life was shorter in neurocritical patients (compared to those of healthy volunteers and adults in status epilepticus). Additionally, Vd was decreased. Doses of 500-1000mg q8h and 1500-2000mg q12h provided greatest probability of achieving target concentrations between 6-20ug/ml	results based on simulation, relationship between serum concentration and clinical efficacy cannot be established, did not measure CrCl, small sample	Increasing dose or frequency increased probability of achieving trough >6ug/ml but also increased probably of trough >20ug/ml. Doses of 500 mg every 8 hours and 1000 mg every 12 hours achieved trough concentrations of at least 6 µg/ml with greater than 50% probability while achieving trough concentrations greater than 20 µg/ml with less than 10% probability. PK is altered → increased dose/frequency may be required in critically ill patients.
Bilbao-Meseguer et al. 2021 (93)	Prospective Observational	To evaluate the adequacy of levetiracetam dosing in patients with normal or augmented renal clearance (ARC) admitted to the ICU by population modelling and simulation	N=27 patients. Critically ill patients over 18 years old, admitted to ICU and treated with levetiracetam with a CRCL > 50ml/min measured in urine.	Each patient received 500, 1000 or 1500mg of levetiracetam q12hr via 30 min IV infusion. Blood samples were taken pre dose (0hr), 0.5hrs and 12hr after administration. Samples with assayed for interpretation. A PK model of levetiracetam was developed with a focus on ARC using this data. ARC defined as CrCl >130ml/min/1.73^2 measured in urine. Monte Carlo simulations were performed to predict levetiracetam Cmin and PTA under these dosing regimens with patients with various CrCl (80-240ml/min). Patient samples and data provided by Basque Biobank and processed with ethical approval.	500mg q12hr was insufficient in critical patients with normal or augmented renal function. Maximum dose approved in the summary of product (1500mg q12hr) only guaranteed target trough concentration in patients with CrCL<80ml/min. Doses of 1500-2000mg q8hr needed to achieve PTA >80% in those with CrCl >160-200 ml/min. Mild improvements in achieving Cmin were shown with infusion time of 2hr in those with CrCl >240 ml/min.	Small population size leads to lack of external validation of the PK model developed. Investigations used a target trough concentration 12-46mg/L and a lower target trough range of >6mg/L. Study would have benefitted by the well accepted and universally accepted therapeutic range. This study did not discuss clinical outcomes of seizure prevention in patients with ARC being treated with these doses.	CrCl effects levetiracetam exposure which puts patients with ARC at risk of subtherapeutic levels. 500mg q12hr is an inadequate dose for patients with or without ARC. Doses as high as 1500mg q12hr may be insufficient for those with ARC and further studies are needed to assess effective dosing regimens.
Sime et al. 2021(94)	Prospective Observational	To develop a population pharmacokinetic model for levetiracetam In	n=30. Patients treated In the ICU >18 years of age, with severe TBI with GCS of	Demographic and clinical data was collected from the hospital. Levetiracetam dosing was at the discretion of the treating intensivist (po/IV). Blood samples were	21/30 participants has ARC defined as CrCl >130ml/min. For the simulated dosing	Small sample size reduces generalizability of study results. Study did not	TDM and urinary creatinine clearance should be measured in critically ill patients with TBI or SAH. Even a high-dose approach (up to 6 g of levetiracetam

		patients with severe TBI and aneurysmal SAH, and use it to describe optimal dosing regimens.	<8 on admission or GSC >8 on admission & CT imaging consistent with severe TBI including SAH, epidural hemorrhage, intra-cerebral hemorrhage, or difuse axonal injury; OR aneurysmal SAH, planned administration of IV or PO levetiracetam for treatment or prophylaxis, Scr <170umol/L, arterial line or planned insertion, indwelling catheter or planned insertion and consent.	collected after a minimum of 4 doses at 0 (predose), 15, 30, 60, 120, 360 and 480 min. A non-parametric PK model was developed. Monte Carlo simulations generated concentration-time profiles and PTA for the following dosing regimens both IV and PO: 1000mg q12hr, 1000mg q8hr, 1500mg q12hr, 15000mg q8hr, 2000mg q12hr and 2000mg q8hr. These concentration-time profiles and PTA for various dosing regimens were shown for CrCL profiles ranging from 80-240ml/min). CrCl was measured as urinary creatinine clearance.	regimens, on average, the median trough concentration reduced by 50% for every 40ml/min increase in CrCL. For IV continuous infusion, a lower reduction (30%) was observed for every 40mL/min increase in CrCl. In patient with CrCl >120ml/min none of the regimens had a PTA >72%. In patients with ARC the PTA > 46 mg/L is almost 0 for doses as high as 6 g/day. Patients with CrCL >160ml/min would have a ≤ 80% PTA >6mg/L using doses up to 6 g/day.	specify urinary creatinine clearance collection time (gold standard is 24hour urine collection), therefore CrCl accuracy is not known.	a day) does not guarantee achieving trough concentrations within currently accepted target ranges in patients with ARC. Therefore, clinicians should be vigilant in the potential need to use higher doses and dose titrate, if necessary, in these patients.
Ong et al. 2021(95)	Prospective observational	Describe the population PK of levetiracetam using a nonparametric approach to design a optimal dosing regimen for critically ill neurosurgical patients.	N= 20. Age >21 and admission to neurosurgical ICU for elective brain tumor resection, SAH or TBI and received at least once IV dose of levetiracetam for seizure prophylaxis. Exclusion criteria: Hx of seizures and on active treatment, subjects of barbiturate coma for ICP or status epilepticus, pregnant or breastfeeding.	Demographic and laboratory data were collected for each patient. CG equation was used to estimate CrCl and ARC was defined as CrCl> 150mL/min. Levetiracetam dose was left up to discretion of the primary neurosurgical team. Each dose as administered over 15-30 min IV infusions. Blood samples were collected before administration (0hr), 0.5hr, 1hr, 6hr and 12hr after dose administration. Nonparametric analysis was done on blood samples for population PK modeling. 1000 Monte Carlo simulations were used to determine the PTA (>6mg/L target). PTA was calculated using IV doses of 500mg BID, 100mg BID, 1500mg BID and 1000mg Q8hr.	1/3 (30%) of patients presented with ARC on the day of blood sampling. All subjected were given at least 3 doses of levetiracetam at the point of blood sampling. The Monte Carlo simulation showed 500mg BID IV provided a PTA of 63.4% (low). 1000mg BID and 1000mg q8hr provided a PTA of 80% in patients without and with ARC respectively.	Small sample size and narrow weight and CrCl range therefore not all clinically relevant covariates could be described, and this reduces the generalizability of results. CrCl was calculated using CG equation instead of 24-hour urine collection reducing accuracy. PK/PD targets were not compared to clinical outcomes (seizure	Standing dosing of levetiracetam 500mg BID IV was insufficient to achieve therapeutic trough concentrations in most neurosurgical ICU patients. A higher dose of at least 1000mg bid IV is recommended for patients without renal impairment.

						prevention) in this study, therefore the PTA with different dosing regimens may lack clinical relevance.	