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The Critically ill Patient with Augmented Renal Clearance: the Dark Side of the Kidney

Tese de Doutoramento em Ciências da Saúde - Ramo de Medicina, orientada pelo Prof. Doutor Paulo Martins e Prof. Doutor Jorge Pimentel e apresentada à Faculdade de Medicina da Universidade de Coimbra.

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THE CRITICALLY ILL PATIENT WITH AUGMENTED RENAL CLEARANCE: THE DARK SIDE OF THE KIDNEY

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Doctoral Thesis in the Doctoral Program in Health Sciences, branch of Medicine, under the supervision of Prof. Doutor Paulo Martins and Prof. Doutor Jorge Pimentel, presented to the Faculty of Medicine of the University of Coimbra.

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A verdade de hoje é o erro de amanhã – todo esse saber se afundará e a glória e a petulância que vinha nele.

Vergílio Ferreira

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ABSTRACT

Sepsis is a leading cause of morbidity and mortality among critically ill patients. Antimicrobial therapy remains a significant challenge and is one of the key treatments for sepsis. Knowledge of the pharmacokinetic and pharmacodynamic of antimicrobials is of paramount importance for the optimization of therapy. The profound physiopathological alterations generated by sepsis in the human organism frequently alter both pharmacokinetic and pharmacodynamic of antimicrobials; in addition, infections in critically ill patients are frequently caused by highly resistant pathogens, which make the optimization of antibiotic therapy in the critical care setting more difficult.

The kidney is the major route of elimination for an important number of antibiotics, which is why the correct evaluation of renal function is fundamental for the calculation of adequate dosing. Critically ill patients can develop acute kidney injury, with corresponding diminished renal clearance (increasing the risk of drug overdosing), or, less frequently, they may develop augmented renal clearance (increasing the risk of drug underdosing). Augmented renal clearance is defined as the enhanced renal elimination of circulating solutes compared with an expected baseline, and a cut-off value of higher than 130 mL/min/1.73 m^2 is currently accepted. Clinicians are very used to perform drug dosing adjustment for acute kidney injury, but the same is not true for the augmented renal clearance setting.

For the development of this thesis, six aims were defined:

1) To perform a comprehensive review on the subject of augmented renal clearance in the critically ill adult patient, encompassing its definition, epidemiology, physiopathology, clinical impact on drug exposure, prognostic and future research directions;

2) To add information regarding the prevalence of augmented renal clearance in critical care setting, and identifying clinical predictors of augmented renal clearance in the critically ill;

3) To assess the accuracy of commonly used equations for estimating renal function in critically ill patients to identify patients with augmented renal clearance;

4) To understand the impact of augmented renal clearance in the optimal treatment of septic critically ill patients with vancomycin;

5) To understand the interrelations between the renal clearance of creatinine and vancomycin.

6) To develop and validate a new nomogram for the treatment of critically ill patients using vancomycin in continuous infusion.

In pursuance of these objectives, we performed the following **seven** studies in distinct populations of adult critically ill patients, which are reproduced within this thesis:

1) A narrative review, under the subject of augmented renal clearance.

2) A prospective, observational and multicenter study (Australia, Singapore, Hong Kong, and Portugal), describing the prevalence and natural history of augmented renal clearance.

3) A retrospective single-center observational study, assessing the prevalence and risk factors for augmented renal clearance.

4) A prospective single-center observational study, and 5) a *post hoc* analysis of prospectively collected data in two-centers observational study (Portugal and Australia), both studies comparing different methods of evaluation of renal function.

6) A prospective single-center observational study, assessing the effect of augmented renal clearance in the treatment with vancomycin by continuous infusion.

7) A combined retrospective and prospective single-center interventional study, through a pharmacokinetic study, developing and validating of a new nomogram for the treatment of critically ill patients under vancomycin in continuous infusion.

After a comprehensive discussion gathering the results of these studies, within the scope of adult critically ill patients, we reached the following conclusions:

1 – The prevalence of augmented renal clearance is high, between 43.0 and 55.6% of patients with normal values of serum creatinine. This prevalence can reach 65% when considering patients manifesting augmented renal clearance on at least one occasion in the first seven days of study.

2 – Trauma, young age and male sex were independent risk factors for augmented renal clearance.

3 – Commonly used mathematical estimates are inaccurate for the correct evaluation of the renal function, particularly in the patient showing augmented renal clearance.

4 – Significant correlation was demonstrated between urinary creatinine clearance and vancomycin clearance, depicting the relevant role of renal function of the pharmacokinetic of this antimicrobial.

5 – Augmented renal clearance is strongly associated with subtherapeutic levels of serum vancomycin, on the first three days of treatment.

6 – The development of a new dosing nomogram for the treatment with vancomycin in continuous infusion, grounded in simple pharmacokinetic concepts, allows for the achievement of adequate treatment in the majority of the studied patients.

RESUMO

A sépsis é uma das principais causas de morbidade e mortalidade nos doentes críticos. A antibioterapia adequada constitui um dos pilares do tratamento da infecção grave; no entanto, embora aparentemente simples, a sua concretização continua a ser um desafio médico importante.

O conhecimento na área da farmacocinética e farmacodinâmica dos antimicrobianos é fundamental para a optimização da antibioterapia no doente com infecção. As profundas alterações fisiopatológicas no organismo humano observadas nos doentes sépticos alteram frequentemente tanto a farmacocinética quanto a farmacodinâmica da grande maioria dos fármacos.

O rim é a principal via de eliminação de muitos antibióticos, pelo que a correcta avaliação da função renal é fundamental para o cálculo da posologia adequada. Os doentes críticos podem desenvolver: 1) diminuição da depuração renal (aumentando o risco de sobredosagem de medicamentos); 2) aumento da depuração renal (aumentando o risco de subdosagem de medicamentos). A depuração renal aumentada é entendida como a eliminação renal aumentada de solutos circulantes em comparação com o esperado para uma função renal normal e é definida como >130mL/min/1,73m^2. Apesar de ser habitual os médicos realizarem o ajuste da dosagem de medicamentos nos doentes com diminuição da função renal, o mesmo não é verdade num cenário de depuração renal aumentada.

Para o desenvolvimento desta tese, foram definidos seis objetivos:

1) Realizar uma revisão completa e abrangente acerca da depuração renal aumentada no doente crítico adulto, incluindo considerações acerca da sua definição, epidemiologia, fisiopatologia, do seu impacto na exposição adequada aos fármacos, no prognóstico bem como quais as direcções futuras da investigação nesta área;

2) Caracterizar a prevalência da depuração renal aumentada nos doentes críticos e identificar os seus potenciais preditores clínicos;

3) Avaliar, em doentes críticos, a acuidade e precisão das equações comumente usadas na prática clínica para estimar a função renal, em especial naqueles doentes que exibem depuração renal aumentada;

4) Compreender o impacto da depuração renal aumentada na eficácia do tratamento com vancomicina em perfusão intravenosa contínua;

5) Compreender as relações de interdependência entre a depuração renal da creatinina e da vancomicina.

6) Desenvolver e validar um nomograma para o tratamento com vancomicina em perfusão intravenosa contínua no doente crítico.

Em busca desses objetivos, realizámos os seguintes **sete** estudos, no contexto do doente crítico adulto:

1) Uma revisão narrativa, versada ao tema depuração renal aumentada.

2) Um estudo prospectivo, observacional e multicêntrico (Austrália, Singapura, Hong Kong e Portugal), que descreve a prevalência e a história natural da depuração renal aumentada.

3) Um estudo observacional retrospectivo e monocêntrico, avaliando a prevalência e os factores de risco para depuração renal aumentada.

4) Um estudo observacional prospectivo e monocêntrico e 5) um outro, *post hoc* de dados colectados prospectivamente em estudo observacional bicêntrico (Portugal e Austrália), ambos comparando diferentes métodos de avaliação da função renal.

6) Um estudo observacional prospectivo e monocêntrico, avaliando o efeito da depuração renal aumentada no tratamento com vancomicina em perfusão intravenosa contínua.

7) Estudo combinado, retrospectivo e prospectivo, de intervenção e monocêntrico, com desenvolvimento e validação de novo nomograma para tratamento de doentes críticos submetidos a tratamento com vancomicina em perfusão intravenosa contínua.

Após adequada discussão integrada e no âmbito do doente crítico adulto, conclui-se:

1 – A prevalência de depuração renal aumentada é elevada – entre 43.0-55.6% dos doentes com valores normais de creatinina sérica. Essa prevalência pode chegar a 65% quando considerados os doentes que manifestaram depuração renal aumentada em pelo menos uma ocasião nos primeiros sete dias de estudo.

2 – Trauma (como causa de admissão em Medicina Intensiva), idade jovem e sexo masculino foram os três factores de risco independentes associados à exibição de depuração renal aumentada.

3 – As estimativas matemáticas comumente utilizadas na prática clínica são imprecisas e pouco fiáveis para a avaliação correcta da função renal, particularmente no doente que exibe depuração renal aumentada.

4 – Demonstrou-se correlação significativa entre as depurações renais da creatinina e da vancomicina.

5 – O aumento da depuração renal da creatinina está fortemente associado a níveis subterapêuticos de vancomicina sérica nos primeiros três dias de tratamento.

6 – O desenvolvimento de um novo nomograma posológico para o tratamento com vancomicina em perfusão intravenosa contínua no doente crítico, alicerçado em conceitos farmacocinéticos simples, é exequível e permite o tratamento adequado na maioria dos doentes estudados.

List of abbreviations and acronyms

ARC	Augmented Renal Clearance
AKI	Acute Kidney Injury
$AUC_{0\text{-}24h}$/MIC	Area Under the Plasma Concentration Time Curve to Minimum Inhibitory Concentration Ratio
AUC	Area Under the Curve
BSA	Body Surface Area
CDC	Center For Disease Control and Prevention
CHUC	Centro Hospitalar e Universitário de Coimbra
C_{Inf}	Continuous Infusion
CG	Cockcroft and Gault Equation
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration Equation
CL_{CR}	Urinary Creatinine Clearance
COVID-19	Coronavirus Disease 2019
CRT_S	Serum Concentration of Creatinine
CRT_U	Urinary Concentration of Creatinine
DALI	Defining Antibiotic Levels in Intensive Care Unit Patients
DDD	Defined Daily Dose
DGS	Direção Geral da Saúde
ECDC	European Centre for Disease Prevention and Control
EDTA	Diethylene Triamine Pentacetic Acid
EEA	European Economic Area
EPIC III	Extended Prevalence of Infection in Intensive Care Study
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
EU	European Union
FRR	Functional Renal Reserve
GFR	Glomerular Filtration Rate
ICU	Intensive Care Unit
LMWH	Low-Molecular-Weight Heparin
LPS	Lipopolysaccharides
m^2	Square Meter
MDRD	Modification of Diet in Renal Disease Equation
MIC	Minimum Inhibitory Concentrations
mL	Millilitre
min	Minute
MRSA	Methicillin-Resistant *Staphylococcus aureus*
PK/PD	Pharmacokinetic/Pharmacodynamic
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
TDM	Therapeutic Drug Monitoring
UFR	Urine Flow Rate
V_{SS}	Steady-State Serum Vancomycin Concentration

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CHAPTER 1. INTRODUCTION

THE BEGINNING

Observation is one of the stages of the scientific method and a fundamental element of research; it is when hypotheses are put forward, and later tested and confirmed. Frequently, this "observation stage" is the ignition that propels the process of structured research. This Doctoral Thesis is no exception, for casual observation is precisely what set the investigation process in motion, during my initial Critical Care formation/training in the Intensive Care Unit (ICU) at the Centro Hospitalar e Universitário de Coimbra (CHUC), where several critically ill patients were showing unusually high or very high values of urinary creatinine clearance (CL_{CR}), frequently above 130mL/minute. These data were recorded throughout the patient's stay, on an electronic medical record software (conceived by Dr. Victor Fernandes), specifically designed to incorporate the critical care routines and patient flow, used in our ICU until the year of 2011.

This Doctoral Thesis was conceived as a storyline, with a beginning, middle, and an end, with a common thread connecting all the research herein. This project encompasses original research exploring the epidemiology, diagnosis and clinical consequences, practical answers to the emerged questions, framed with a comprehensive narrative from the medical literature, reviewing and collecting the most relevant information regarding Augmented Renal Clearance (ARC) in critical care setting.

The title «**The Critically ill Patient with Augmented Renal Clearance: the Dark Side of the Kidney**» intends to shed a light on the lesser known and under-studied spectra of renal function, and to explore the clinical consequences of this condition in the critical care population.

Therefore, **the fundamental and combined question** brought forth is as follows:

What clinical characteristics are shown by critically ill patients who have unusually high values of CL_{CR}, which are considered beyond the accepted normal and physiological values observed in individuals with normal renal function, herein designated as ARC, and how may they be identified correctly? What are the clinical and therapeutic implications of ARC, and how to overcome them?

SEPSIS AND CRITICAL CARE

Sepsis is a life-threatening organ dysfunction due to a deregulated host response to infection [1] and is a leading cause of mortality and critical illness worldwide. In 2017, almost 49 million new cases of sepsis were recorded worldwide and 11 million related deaths were reported, corresponding to around 20% of global deaths [2]. ICU patients are particularly exposed to infection, for several reasons. *First*, severe infection is a frequent cause of ICU admission. *Second*, immunosuppression is associated with acute critical illness, either as a primary predisposing factor for severe infection, or as a consequence of the severe, acute and prolonged illness. *Third*, hospital-acquired infection is common in ICU setting. *Finally*, natural cellular barriers against infection are frequently broken due to the ubiquitous use of invasive devices and frequent major surgical procedures of ICU patients. In a recent 24-hour point prevalence study performed in 2017 and involving 1144 ICUs in 88 countries [the Extended Prevalence of Infection in Intensive Care (EPIC III) study] investigating 15.202 patients, the overall rate of suspected or proven infection was 54% [3]. In addition, the burden of hospital and ICU-acquired sepsis is especially high in the ICU [4]. More specifically, the in-hospital mortality of patients admitted in the ICU with sepsis or septic shock is around 20% and 43%, respectively [5]. Portuguese data are scarce, but indicate that around one quarter of hospitalizations in ICUs is due to community-acquired sepsis, corresponding to an in-hospital fatality around 38% [6,7].

Antibiotics are the most frequently prescribed drugs among hospitalized patients in the ICU. Recent data from the above mentioned EPIC III study showed that 70% of ICU patients received at least 1 antibiotic[3]. In 2017, the global consumption of antimicrobials in Portuguese hospitals was 1.53 Defined Daily Dose (DDD) per 1000 habitants, reflecting the high consumption of antimicrobials in Portugal [8]. Furthermore, the occurrence of pathogens with elevated minimum inhibitory concentrations (MIC) remains higher in ICU patients compared to non-ICU patients [9].

Rational use of antibiotics is a global emergency. Inappropriate prescription of empiric antimicrobial therapy occurs in up to 40% of cases[10]. In the set of all drugs, antimicrobials have two very distinct features. On the one hand, there is no *"end-of-needle"* effect allowing measurement of the antibiotic effectiveness, in opposition to others drugs, such as vasoactive drugs or analgesics that show a quick effect [11]. On the other hand, the relationship between the therapeutic effect on the patient and the antibiotic prescription is neither simple nor linear: the consequences of inadequate treatment (either because of bad choice, insufficient dosing, late onset, no de-escalation, short or too long treatment) are present not only for the target patient but also for the hospital and healthy communities, when, in the near future, the need for antimicrobial treatment arises (Figure A).

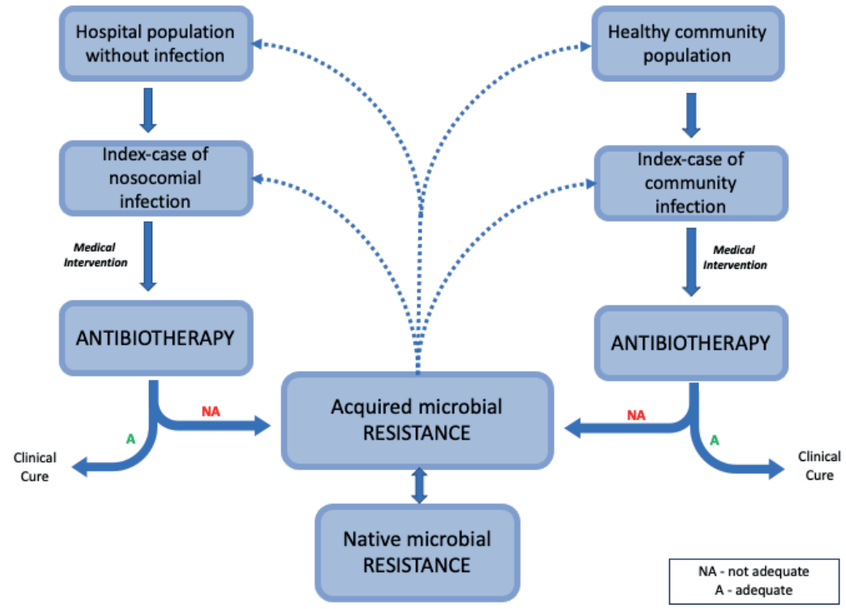

Figure A – Interconnections between antibiotherapy and microbial resistance

Misuse of antimicrobials may be responsible for therapeutic failure, higher mortality, higher toxicity, increase in costs and emergence of resistance of less susceptible, multidrug resistant, extensively drug resistant or pan–drug resistant organisms [12-17]. Importantly, infections with antibiotic-resistant agents are associated with increased risk of hospital mortality[3]. On the contrary, judicious use of antimicrobials includes choice of drugs with appropriate microbiologic spectrum, early initiation, adequate dosing/duration of treatment, re-evaluation, de-escalation, toxicological surveillance associated to the collection of appropriate samples for microbiologic analysis as soon as possible, as part of an effective stewardship antibiotic program [18-21].

Causative organisms can be difficult to identify in sepsis. The most common pathogens that cause septic shock are bacterial microorganisms [20]. In the United States of America, between 2015 and 2017, the most frequently reported pathogens across all types of adult healthcare-associated infections are *Escherichia coli* (17.5%) and *Staphylococcus aureus* (11.8%) [22]. Particularly, *Staphylococcus aureus* is a commensal and opportunistic gram-positive microorganism involved in infections of both community and healthcare settings. Specifically and in the ICU setting, *Staphylococcus aureus* was the most frequently reported agent of ventilator/intubation-associated pneumonia and of surgical site infection, and the third agent of central line-associated bloodstream infections. Its ability to form biofilm at endotracheal tubes, urinary and endovascular catheters promotes bacterial survival and multiplication, and amplifies the opportunity for transfer of antibiotic resistance genes within organisms [23].

The United States Centers for Disease Control and Prevention (CDC) classified 18 germs into one of three categories: urgent, serious, and concerning. Methicillin-resistant Staphylococcus aureus (MRSA) has been considered a «serious threat» in the Antibiotic *Resistance Threats in the United States,* published in December, 2019 [24]. In Europe, the report from the European

Centre for Disease Prevention and Control (ECDC), regarding data from invasive (blood and cerebrospinal fluid) isolates and including all European Union (EU) Member States and two European Economic Area (EEA) countries (Iceland and Norway), showed that the population-weighted mean percentage of MRSA was 16.4% in 2018 [25].

Concerning Portugal, pertaining to 3 810 invasive isolates tested, ECDC report showed that the rate of MRSA was 38.1% (36-40%, 95% of confidence interval) [8]. According to the epidemiological surveillance of health care associated infections in Portugal [Directorate-General for Health (Direção Geral da Saúde — DGS)], the percentage of invasive MRSA decreased by 8.2 percentage points, between 2014 and 2017 [26]. In the ICU of the CHUC, *S. aureus* was the most frequent etiologic agent of nosocomial pneumonia, where 44.4% of isolates were MRSA[27]. In 2019, after considering all the microbiologic isolates, *S. aureus* remains the most common in our ICU; however, nowadays the rate of MRSA is 26.6%, whereas in the hospital is 41% (unpublished data, provided by the Microbiology department of the CHUC's Clinical and Pathology Service). Despite the greater current offer of anti-MRSA drugs, vancomycin remains the mainstay for its parenteral therapy.

OVERVIEW OF KIDNEY FUNCTION

The acute critically ill patient has unique characteristics, and one of the most relevant is the interaction between organs and systems. No organ or system can be considered an isolated island, which is why the dysfunction of one organ inevitably interferes with the function of another one. They are susceptible to several influences, such as distant disrupted organs, major imbalance of body homeostasis or the exposure to the general effects of acute body injury, whereas related or not with infection.

Normal kidneys are not an exception. Kidneys are key organs exerting vital functions needed for the homeostasis of the human cells, such as the excretion of water and solutes, acid-base balance an endocrinal function and, as a core function, the excretion of waste products of metabolism in urine [28]. Likewise, kidneys are one of the most important routes of elimination for several drugs. This in particularly important while considering antimicrobials (or their active metabolites) that are predominantly cleared by the kidneys, i.e. carrying significant hydrophilic structure.

Accurate evaluation of renal function is essential to optimize dosing of drugs with important renal elimination. It is widely acknowledged that glomerular filtration rate (GFR) is the best overall index of renal function [29,30]. Therefore, accurate measuring of GFR constitutes the cornerstone of drug dosing calculation. Ideally, GFR should be measured with the use of exogenous filtration markers, such as inulin (gold-standard), iothalamate, diethylene triamine pentacetic acid (EDTA) or iohexol. However, these methods are cumbersome and expensive to perform in clinical practice. As an alternative, an endogenous marker can be used from a timed urine collection and blood sampling, allowing the estimation of GFR. Normal values of GFR vary according to age, sex, body surface and race, and are, on average, approximately 127-130 and 118-120 mL/min/1.73m^2 for men and women, respectively [29-31]

ESTIMATION OF GFR

From a practical point of view, creatinine is the most frequent used endogenous marker for the estimation of GFR, either by measurement of it clearance or by the use of creatinine-based mathematical formulae. Creatinine is a residual product of creatine from muscle metabolism and dietary meat intake and is released into the circulation at a relatively constant rate. Additional factors can influence the creatinine generation such as age, sex, race, body habitus and the presence of severe or chronic disease. Creatinine is freely filtered by the glomerulus but is far from an ideal marker (such as inulin), once it is secreted by the proximal tubular cells of the kidney.

Measurement of Creatinine Clearance

Clearance is the volume of plasma that is cleared of a drug per unit of time. The renal clearance of a drug depends on the glomerular filtration, tubular secretion and reabsorption. At the bedside of the patient, urinary creatinine clearance (CL_{CR}) can be obtained from a well timed urine collection and a corresponding blood sampling, after respective measurements of creatinine concentration. CL_{CR} can be calculated according to the following formula,

$$CL_{CR}\ (mL/min/1.73m^2) = [(CRT_U \times UFR) \div CRT_S] \times (1.73m^2 \div BSA) \qquad (formula\ 1)$$

where CRT_U is the urinary concentration of creatinine, UFR is the urine flow rate within a predetermined interval of time, CRT_S is the serum concentration of creatinine and BSA is the body surface area. There are two major biasses associated with the measurement of CL_{CR}. *First*, the under-estimation of true GFR in a situation where there is an incomplete urine collection. *Second*, the over-estimation of true GFR, due to increased creatinine tubular secretion, especially for low values of GFR [32].

Mathematical Estimations

In clinical practice, the most common used estimates are the Cockcroft and Gault (CG), Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations.

CG equation [33] was deducted from a cohort of 249 males with stable renal function, ranged between normal and moderately impaired, using two sequential measurements of 24h-CL_{CR} as reference method. Individuals with variable serum creatinine were excluded. The location of the patients was predominantly in medical wards. Besides serum creatinine covariates, age and actual weight were included. This formula over-estimates 24h-CL_{CR} and needs adjustment for sex and BSA [34]. MDRD Study equation [35] was deducted and validated from a cohort of 1628 patients with chronic kidney diseases, using renal clearance of ^{125}I-iothalamate as reference method. A simplified version of this equation was described afterwards, considering only 4 variables (instead of the original 6 variables): serum creatinine, age, sex and race. Both equations predict GFR with automatic adjustment for BSA. CKD-EPI equation [36] was deducted and validated from a cohort of 12.150 participants, with and without kidney disease, using predominantly renal clearance of ^{125}I-iothalamate as reference method. GFR prediction is

automatically adjusted for BSA. CKD-EPI creatinine equation is more accurate than MDRD especially for values of GFR greater than 60 mL/min/1.73 m^2 [36]

GFR estimates are fundamental clinical tools for the detection, monitoring and management of patients with stable chronic kidney disease (CKD). However, the main limitations of the use of estimates are related to their use in patients with extreme body habitus, unstable kidney function, acute kidney injury, and in patients displaying a normal renal function, since these formulas are not validated in these groups of individuals. More specifically, prolonged critical illness is associated with muscle mass loss, leading to a decrease in serum creatinine levels, confounding the real assessment of renal function [37,38].

Renal dosing adjustment of medications, with special focus on drugs with narrow therapeutic indices, kidney donors and patients involved in research protocols, such as the assessment of new antimicrobials with respective dosing, are examples of medical situations where it is paramount to have more precise calculation of GFR [34,39].

AUGMENTED RENAL CLEARANCE AND RENAL DYSFUNCTION IN THE CRITICALLY ILL PATIENT: A DISTINCT POINT OF VIEW

The concept of renal dysfunction in the critically ill patient leads us straightaway to the unidirectional misconception of decreased function of the kidneys (truly the most frequent observed clinical scenario) easily detected and with severe prognostic implications in critical care settings [31]. However, this perspective is fundamentally flawed and misleading, since physicians rather need to value the full spectrum of renal function. Of utmost importance is the fact that there is a group of acutely ill patients that shows a common (and frequently ignored) manifestation of renal dysfunction, characterized by an increased renal ability. The renal function, in this setting, is above the normal accepted physiological limits, corresponding to a physiologic response of kidneys to a variety of stimuli, recruiting the 'redundant' capacity of the normal kidney, also known as renal reserve. Patients with this particular pattern of renal dysfunction are difficult to identify particularly to the unwarned clinician. On the one hand, this condition cannot be considered a true disease with a specific constellation of signs and symptoms. On the other hand, its identification requires the use of specific clinical measurements not routinely used in clinical settings, albeit easily accessible at the bedside's patient. In recent years, this clinical condition has been denominated Augmented Renal Clearance and has been identified in acute adult and pediatric patients, whether in ICU or non-ICU settings [40-46]. As a new emerging concept, although recognized since 1978 by Loirat and co-workers [47], no standardized definition exists for ARC. However, most of researchers have used values of CL_{CR} higher than 130 mL/min/1.73 m^2 to define ARC [40,43,48-55].

In **chapter 2,** through a narrative and critical review of the medical literature, we collect, analyze and discuss the available evidence from original studies regarding ARC, gathering updated information related to definition, epidemiology, physiopathology, diagnostic, clinical and therapeutic implications in critically ill patients, with special emphasis on the effect of ARC on the elimination of hydrophilic antibiotics.

The incidence of ARC in the population of critically ill patients worldwide is largely unknown, as a result of two principal reasons. *Firstly*, ARC is clinically silent, only revealed after adequate measure of renal function. *Secondly*, although showing growing trend over the last few years, ARC in critically ill adults has received very little attention and is topic of scarce published research. However, after considering large-scale epidemiological data in critical care settings, available data show that the prevalence of ARC is relevant, varying between 28 and 65% of the studied patients [56]. In addition, the risk factors associated with ARC are poorly studied; the current available data come predominantly from studies not specially designed for this purpose.

Therefore, as a contribute to the epidemiology of ARC in critical care settings, in **chapter 3,** we carry out two studies: 1) a prospective, multicenter and observational study examining the frequency of ARC in critically ill patients with no evidence of renal impairment at admission; 2) a single-center retrospective study in a large multipurpose ICU, to analyze the prevalence of ARC and identify predictors of this condition in the critically ill.

Accurate evaluation of renal function is crucial in the critically ill patient for several reasons: it allows early clinical recognition of acute kidney injury (AKI), the implementation of therapeutic plans (such as adequate intravenous fluids or pharmacological dosing modification) and the elaboration of prognostic charts. As well as serum concentration of creatinine (CRT_S) can be an insensitive marker of kidney injury, ARC is hard to detect based only on its isolated measurement. Mathematical estimates based on the value of CRT_S have long been used for evaluation of renal function, in patients with or without renal dysfunction, and have been rapidly incorporated in hospital routine analysis. Since they are considered a surrogate of renal function, these estimates frequently provide the basis to establish an (presumed) adequate dosing of a vast range of medication bearing the effects of a predominant renal elimination. Although this rational applies reasonably well to the healthy person or to the patient with CKD and stable renal function, the same is not true for the critically ill patient. On the one hand, the critically ill have, by definition, an unstable renal function. On the other hand, CRT_S seldom reflects accurately the dynamics of the renal function, due to the delay of time needed for creatinine concentration in serum to equilibrate. Nevertheless, given the simplicity of the method, mathematical estimates are widely used to evaluate and categorize renal function in the critical ill patient, whether in clinical or research settings. Of note, common used mathematical formulae to estimate renal function are not validated in the critically ill patient neither in patients without CKD [31]. This leads to inaccurate evaluation of renal function, with serious implications in clinical decisions or research conclusions.

From a pragmatic point of view, the most important implication is related to the optimization of drug dosing usually based on these estimates. Frequently, patients in critical care settings show abnormal renal function, whether decreased or augmented. Both circumstances need dosing adjustment if the involved drug(s) have substantial renal participation in their pharmacokinetic process. In the particular scenario of critically ill patients with sepsis showing ARC, the insensitivity of mathematical estimates to identify accurately this condition puts the patient at risk of sub-therapeutic antimicrobial exposure, treatment failure and death. Hydrophilic antibiotics, acyclovir, valacyclovir, fluconazole, low-molecular-weight heparins, and levetiracetam constitute the single group of drugs that were studied regarding this issue [55,57-69]. Metformin, dabigatran,

rivaroxaban and apixaban show tendency to lower efficiency in non-critical patients exhibiting high levels of CL_{CR} [70,71].

In **chapter 4** we carry out two studies, one a *post hoc* analysis of prospectively collected data in two tertiary centers ICUs (Portugal and Australia), and another a prospective in a large multipurpose ICU, both evaluating the performance of mathematical estimates in the assessment of renal function in critical care patients, highlighting particularly patients showing ARC.

APPLICATION OF PHARMACOKINETIC/PHARMACODYNAMIC PRINCIPLES IN THE SEPTIC CRITICALLY ILL PATIENTS

In sepsis, time is life. Nowadays, clinicians are able to *"buy"* time by using supportive care, either by resuscitation maneuvers, vasoactive drugs, mechanical ventilation, or extracorporeal treatments. However, only two kinds of interventions are potentially curative in sepsis, despite the technological advances in critical care: source control and antibiotic treatment[72]. In their absence, the failure of treatment is inevitable.
Appropriate antimicrobial therapy is one of the cornerstones in the successful management of sepsis and constitutes the single most important factor influencing the survival of the septic patient[73]. Additionally, medical literature shows a strong association between adequate antibiotic exposure and positive clinical outcome within several classes of antibiotic [63,74-81].

Early achievement of target pharmacokinetic/pharmacodynamic (PK/PD) indices should be a priority when considering antimicrobial treatment in the critically ill patient, in order to provide adequate drug concentration at the site of infection [72,82]. Having in mind the technical limitations, plasma drug concentrations are considered a surrogate for the concentration at the site of infection[83]. PK describes the study of the modifications of the concentration of a drug over a given time period and PD refers to the relationship between PK exposure and pharmacological effect [82,84]. Dosing must be optimized since the very first administration of the antimicrobial, fulfilling the classical principles of empiric therapy - broad spectrum antimicrobials, synergistic association, adequate dosing and early administration: «*getting it right the first time*» [85,86].

The second most severe consequence of suboptimal administration of antimicrobials, beyond treatment failure, is that it carries an increased risk of developing multidrug resistance pathogens [87]. This association has been described for quinolones and beta-lactams [88-90], but extrapolation to other antibiotics seems logical. ICU patients are, by definition, a very heterogeneous group regarding the age, cause of admission, severity of illness, and outcomes. This large variability extends PK characteristics, whether inter-individual (from patient to patient) or intra-individual (in the same patient over time). PK understanding allows the estimate of the time course of antimicrobial concentrations in the different tissues/fluids. It is well established that PK showed by critically ill patients is usually altered, including absorption, volume of distribution, protein binding, tissue penetration and drug clearance [91]. Consequently, selection of drug dosing should be individualized, instead of using the traditional principle of «*one-size-fits-all*» dosing for antibiotics [92].

Regrettably, information regarding dosing adaptation of antimicrobials in critical care settings is lacking. Manufactures' recommended dosing is often grounded in studies performed in healthy volunteers, ignoring PK specificities of the critically ill patient. Therefore, extrapolation of these data to this population can be unsafe and potentially leading to drug dosing miscalculations and potential severe clinical consequences. It is worth noticing that the increment of dosing in patients showing ARC is seldom stated, in opposition to the common recommendation for reducing dosing in patients with AKI or decreased renal function.

Therapeutic drug monitoring (TDM) has been used primarily for the identification of patients with iatrogenic risk related to the use of drugs with narrow therapeutic indices, such as vancomycin, aminoglycosides, digoxin, immunosuppressive and anti-epileptic drugs [93,94]. Only recently, TDM emerged as a new tool enabling the evaluation of adequacy of antimicrobial exposure in the septic patient, including for drugs with wide therapeutic/toxic window, as it is the case of beta-lactams.
Early use of broad-spectrum antimicrobials, usually in combination, is one of the above described principles of empirical therapy in the critically ill patient with sepsis or septic shock. Indeed, when considering a hypotensive septic patient, for each hour delay of administration of appropriate antimicrobials, there is an average decrease in survival of 7.6% [95]. Additionally, combination therapy is associated with higher survival, particularly in the group of patients more severely ill [96]. These results have a sizeable impact on the decision to include coverage for Gram-positive when starting empiric treatment of bacterial septic patients in critical care settings, particularly in the suspicion of nosocomial infection, as strongly recommended by national and international guidelines [20,97-99]. Patients with hospital-acquired infection or those that show specific risk factors (immunocompromised, prosthetic devices, prior use of antibiotics or advanced lung structural disease) are prone to sepsis with methicillin-resistant *S. aureus*.

From a practical point of view, this means that vancomycin is a common initial prescription in the critically ill (which is the case of our ICU, with an average of 60 vancomycin treatments/year). Vancomycin, a glycopeptide antibacterial bactericidal agent, is one of the most widely used antibiotics for the treatment of different types of gram-positive bacterial infections, including serious MRSA infections, with reports demonstrating increasing use over time [100]. Vancomycin is a hydrophilic molecule, with a volume of distribution ranging from 0.4-1L/kg with up to 55% of protein binding [101]. Tissue penetration into solid organs is poor and is eliminated primarily via the renal route (>80% unchanged) [101]. The total body drug clearance and the volume of distribution of hydrophilic molecules may be deeply altered in patients with sepsis and septic shock, secondary to fluctuations in cardiac output, renal function, reduced albumin levels, altered vascular permeability, fluid resuscitation, indwelling surgical drains, mechanical ventilation, renal replacement therapy and extracorporeal membrane oxygenation [102-106].

Vancomycin shows both concentration- and time-dependent activity and the goal is to maximise the amount of drug administered daily. The recommended PK/PD target more predictive of clinical success for vancomycin is an area under the plasma concentration time curve to minimum inhibitory concentration ratio using broth microdilution method (AUC_{0-24h}/MIC) [107] between 400 and 600 mg.h/L, equivalent to serum level between 17 and 25mg/L on steady-state [108,109]. For severe infections in adults, plasma vancomycin concentrations up to 35mg/mL are recommended by some authors [110]. It has to be acknowledged that it is currently recommended that the optimal target (400-600 mg.h/L) should be reached within the first 24 to 48

hours [108]. Insufficient AUC_{0-24}/MIC target attainment in the first 2 days of therapy has been associated with treatment failure in patients with MRSA endocarditis and bloodstream infections [111,112]. Conversely, AUC_{0-24h}/MIC above 650 mg.h/L is associated with AKI [113]. Monitoring according to PK/PD parameters (AUC_{0-24h}/MIC) is possible but complex at the bedside of the patient, which is why vancomycin serum concentrations are considered a surrogate marker for predicting AUC_{0-24h}/MIC [114]. The optimal use of vancomycin is a priority and constitutes a key strategy to limit the development of resistance [82,108].

Despite apparent simplicity, the process of optimizing antibiotic therapy in the ICU can be an overwhelming challenge [110]. Implementation of a TDM program is a key factor to individualize and optimize drug therapy and should be incorporated in ICU antimicrobial stewardship programs. In practical terms the latter has been defined as *«the right drug at the right time and the right dose for the right bug for the right duration»* [19]. Or, as stated by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Antimicrobial Stewardship, the *«coherent set of actions which promote using antimicrobials in ways that ensure sustainable access to effective therapy for all who need them»* [115].

To evaluate the influence of ARC on the effective treatment of septic critically ill patients, in **chapter 5** we present the results of a monocentric prospective study, analyzing and discussing the impact of ARC on the attainment of adequate serum levels of vancomycin administered as continuous infusion (C_{inf}) in a group of critically ill patients. The results of this research lead us to the next study, presented in **chapter 6.** Herein, we show the results of a single-center, two parts study. *First*, we retrospectively developed an original dosing nomogram for the administration of vancomycin by means of C_{inf} . *Then*, we prospectively tested it in an independent cohort of critically ill patients.

Chapter 7 merges our current findings of this thesis and presents an integrated discussion concerning ARC in critical care settings, including clinical implications, problems and respective solutions, meaning of this study, and implications for practice.

In **Chapter 8** we present our conclusions.

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The global aim of this thesis is to clinically characterize the critically ill adult patient showing ARC, how to identify it, and to understand its therapeutic consequences.

1 – In the first stage, the background picture of patients with ARC is drawn, exposing the current concepts about it and describing its epidemiological, clinical, and pathophysiological features (chapter 2).

2 – In the second stage, we characterize the demographic features of the critically ill adult patient with ARC and identify independent risk factors for this condition (chapter 3).

3 – In the third stage, we clarify the utility and accuracy of common mathematical estimates of renal function in the critically ill adult patient showing ARC (chapter 4).

4 – In the fourth stage of this project, we demonstrate that patients exhibiting ARC have a lower probability to attain serum therapeutic levels of vancomycin (chapter 5).

5 – In the last stage, after a pharmacokinetic analysis, we develop a new nomogram for the treatment with vancomycin in critically ill adult patients showing a wide range of renal function (chapter 6).

PUBLICATIONS INCLUDED IN THIS THESIS

Table A – Framework of the original articles within this thesis.

ARTICLE COMPILATION (In order of appearance)	YEAR	STUDY METHODOLOGY	PUBLICATION	QUARTILE	IF	CITATIONS*
Augmented Renal Clearance	*2018*	Narrative review	*Book Chapter: Antibiotic PK/PD Considerations in the Critically Ill, Springer Nature*	-	-	6
Augmented renal clearance in the ICU: results of a multicenter observational study of renal function in critically ill patients with normal plasma creatinine concentrations	*2014*	Prospective Four-centers observational study (Portugal, Australia, Singapore and Hong Kong)	*Critical Care Medicine*	Q1	7.42	226
Prevalence and Risk Factors for Augmented Renal Clearance in a Population of Critically Ill Patients	*2020*	Retrospective Single-center observational study	*Journal of Intensive Care Medicine*	Q1	3.51	10
A comparison of estimates of glomerular filtration in critically ill patients with augmented renal clearance	*2011*	*Post hoc* analysis of prospectively collected data Two-centers observational study (Portugal and Australia)	*Critical Care*	Q1	4.72	185
Accuracy of the estimation of glomerular filtration rate within a population of critically ill patients	*2014*	Prospective Single-center observational study	*Journal of Nephrology*	Q2	1.35	46
Augmented renal clearance in septic patients and implications for vancomycin optimisation	*2012*	Prospective Single-center observational study	*International Journal of Antimicrobial Agents*	Q1	4.26	164
Decreasing the time to achieve therapeutic vancomycin concentrations in critically ill patients: developing and testing of a dosing nomogram	*2014*	Retrospective and prospective Single-center interventional study	*Critical Care*	Q1	4.95	48

* Accessed in 20/11/2021.

IF – Impact Factor; IF refers to the year following the year of the publication. Q- Quartile; the Q refers to the year following the year of the publication.

CHAPTER 2

AUGMENTED RENAL CLEARANCE

Baptista JP.
in the Book: A.A. Udy et al. (eds.), (2018) Antibiotic Pharmacokinetic/ Pharmacodynamic Considerations in the Critically Ill. Springer Nature, Singapore Pte.Ltd.

Augmented Renal Clearance

João Pedro Baptista

7.1 Introduction

Renal clearance is the process by which the kidneys eliminate circulating metabolites, toxins, waste products, and drugs. This involves filtration, secretion, and reabsorption. Along with the liver, the kidneys constitute a key organ in human body homeostasis. From a physiological point of view, renal clearance is the volume of plasma from which a substance is completely removed by the kidney in a given amount of time. This process affects predominantly hydrophilic substances, as is the case for most antibiotics.

These drugs are crucial to the successful treatment of sepsis and septic shock in the intensive care unit (ICU). However, critically ill patients are different from those encountered in a ward setting. Critical illness and its therapies often induce profound pathophysiological changes, contributing to inadequate antibiotic therapy. Hypoalbuminaemia, expansion of the volume of distribution (V_d), tissue hypoperfusion, organ dysfunction, use of vasoactive drugs, and the co-existence of renal replacement or extracorporeal membrane oxygenation therapies are among the most important factors. Renal dysfunction is common in critical care settings, and is often a focus for clinicians. Indeed, the converse—*supra-normal function of the kidneys* is infrequently considered.

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A.A. Udy et al. (eds.), *Antibiotic Pharmacokinetic/Pharmacodynamic Considerations in the Critically Ill*, DOI 10.1007/978-981-10-5336-8_7

This chapter will focus on the key aspects of the concept, diagnosis, pathophysiology, epidemiology, and clinical implications of augmented renal clearance (ARC) in the critically ill patient.

7.2 Definition of Augmented Renal Clearance

According to Udy et al. [1], ARC is defined as the enhanced renal elimination of circulating solutes as compared with an expected baseline. However, to date, there is no standard accepted definition of an accurate cut-off value to define ARC and there are several reasons for this. First, although the clinical recognition of ARC is by all means not recent [2], it was only in the last few years that a considerable amount of medical literature emerged reporting the features of ARC in the critically ill. Second, the "normal" values of glomerular filtration rate (GFR) physiologically decline with age, depend on sex, race, and body surface area, and show important variation within normal individuals. Third, different groups of investigators have used varying cut-offs to define ARC, between 120 and 160 mL/min/1.73 m^2. Finally, several methods have been used to measure or estimate the GFR, leading to significant heterogeneity in the results, and difficulties in interpretation and comparison.

The concept of ARC is likely more dynamic, representing the changeable physiology encountered when the body reacts to an acute severe disease or medical intervention (e.g., severe brain injury or intravenous fluid challenge, respectively), provided that renal reserve is preserved. The quantification of *renal function*, and its implications for antibiotic drug dosing is by far more important, that the restrictive qualitative classification based on the presence or absence of ARC (Fig. 7.1).

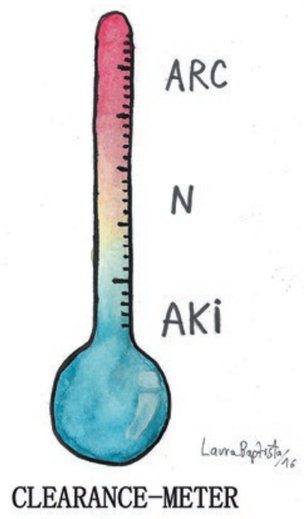

Fig. 7.1 The full spectrum of renal dysfunction—be aware of both under and *over*-function of kidneys

In this respect, GFR values at the upper limit of normal (120 mL/min/1.73 m^2) have also been associated to suboptimal levels of some antibiotics [3, 4], exposing patients to under-treatment, potentially poor outcomes and emergence of bacterial resistances.

From a practical point of view, the cut-off value of 130 mL/min/1.73 m^2 has several advantages, namely: (a) it represents, with reliability, the upper limit of normal renal physiology for the majority of healthy persons [5]; (b) renal clearance of creatinine greater than 130 mL/min/1.73 m^2 has been linked to sub-therapeutic serum concentrations of several antibiotics [6–11]; and (c) there is a growing amount of clinical studies which have used this cut-off, which provides good methodological consistency. This value should be adapted for the female gender, probably by the same factor used in several estimates—10% less, corresponding to 120 mL/min/1.73 m^2. However, some issues need clarification, such as the influence of race, the rate of decline with age, and the standardization of the method of measurement, as each may imply a different threshold value.

7.3 Identification of the Critically Ill Patient with ARC

The evaluation of renal function is essential in the critical setting, aiming to prevent and diagnose any deviation from "normality", and providing useful clinical information concerning specific treatments and drug dosing adjustments. GFR is the best overall measure of kidney function [12], and it is essential to identify patients with ARC.

The gold standard for determining GFR is the measurement of the renal clearance of inulin [13]. More convenient and simpler methods are available, such as the administration of iothalamate, iohexol, diethethylenetriaminopenta-acetic acid (DTPA), or ethylenediamine tetraacetic acid (EDTA); however, these tests are not suitable for use in daily clinical practice.

Serum creatinine concentrations are a commonly used surrogate of renal function; however, they are an insensitive marker of the GFR. Though some reliability lies in the stable patient, this is untrue within the context of the unstable patient, even outside the ICU. On the contrary, by definition the critically ill patient is not stable, and the information provided by isolated values of serum creatinine in these patients is poor and potentially dangerous: on the one hand, they are not always useful in the timely and accurate diagnosis of acute kidney injury, and on the other, are unable to identify ARC. Although elevated levels of serum creatinine identify patients with renal failure, the inverse is not true. The majority of patients with ARC show contemporaneous levels of serum creatinine within the normal range.

Some authors have described a "non-invasive" method for identifying ARC, through the biochemical analysis of urine, where the combination of creatininuria higher than 45 mg/L and patient's age below 65-years-old allows the identification of patients with ARC with significant accuracy (78%) and specificity (88%) [14]. Another group of researchers developed an ARC scoring system based on three risk

factors: age below 51 years, trauma as the ICU admission diagnosis, and a modified SOFA score below 5. The accuracy of this combined ARC score was 89% [15]. Both methods can be useful to screen patients with ARC in ICUs where the measurement of renal clearance is still not established. In addition, in theory they can be combined; however, a confirmatory diagnostic test is typically needed.

Several methods use mathematical equations based on the serum creatinine concentration to estimate GFR. These calculations are suitable and validated for the evaluation of renal function in patients with chronic but stable kidney diseases. Nonetheless, knowing that the serum creatinine level is not reliable in the critically ill patient, and that it does not accurately reflect renal function, estimation of GFR based on these equations e.g. Cockroft–Gault (CG), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), and Modification of Diet in Renal Disease Study (MDRD) formulae—is flawed, and is not recommended in the critical care setting with fluctuating renal function [16–21].

Despite this, the use of mathematical estimates continues to be the standard tool for evaluation of renal function and drug adjustment calculations in many ICUs around the world, and in addition they are frequently used in clinical research. In a point prevalence, single-day, prospective study of 919 patients in 42 ICUs in Spain, Herrera-Gutierrez et al. reported that the method used for estimating GFR was serum creatinine in 36.6%, measured creatinine clearance in 41.5% and equations in 22% [22].

Taking into account simplicity, availability, costs, and feasibility, a measured urinary creatinine clearance (CL_{CR}) should be considered the single most accessible bedside parameter providing information on the potential pharmacokinetic (PK) implications of dynamic changes in renal function in the critically ill. In addition, it is the best method to screen patients for ARC [17]. This can be easily accomplished in the ICU, using continuous urine collections (via an indwelling catheter) of 2, 6, 8, 12, or 24 h.

Nevertheless, some limitations should be observed regarding CL_{CR}. Firstly, it is not a "gold-standard" for the assessment of GFR [12]. Secondly, the assessment of GFR is difficult in non-steady states and frequently changing volume status in critically ill patients [23]. Thirdly, overestimation of true GFR can occur with this measure (10–20% higher), related to tubular secretion of creatinine, albeit this difference will be more significant at lower GFR values [24]. Finally, the bias can be introduced if the urinary collection is not performed accurately.

7.4 Physiopathology of ARC

The specific pathophysiology of ARC is far from being fully understood and multiple factors contribute to the development of this condition (Fig. 7.2). Based on current knowledge, we can divide contributing factors into two categories: endogenous and exogenous.

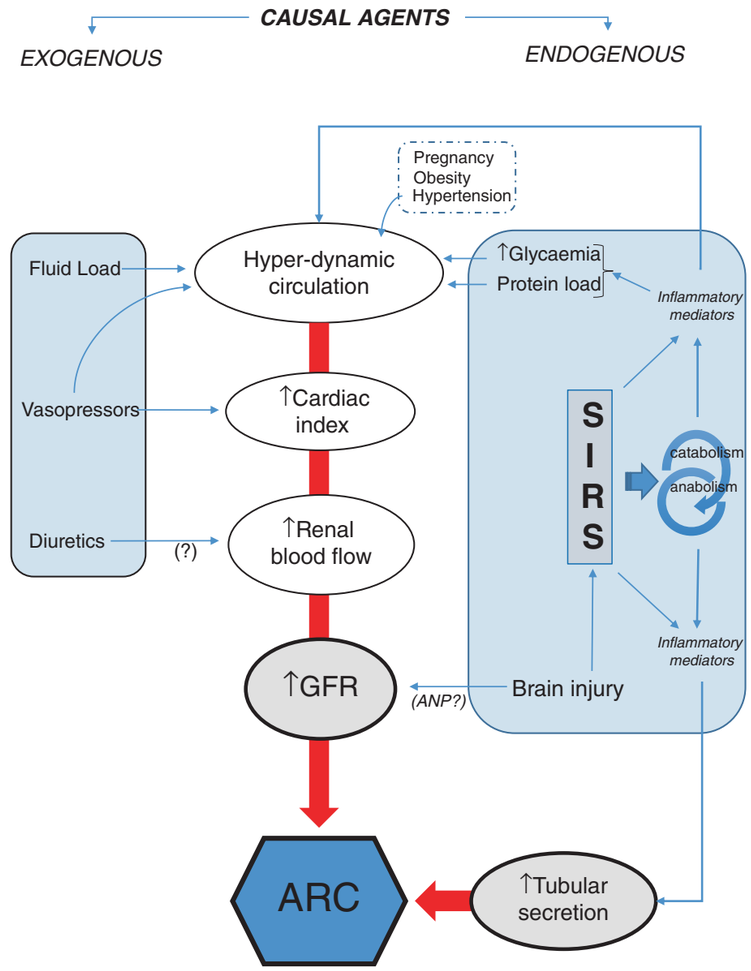

Fig. 7.2 A contextual framework for the pathogenesis of ARC, dividing causal agents of ARC in two categories: endogenous and exogenous. *ARC* augmented renal clearance, *SIRS* systemic inflammatory response syndrome, *GFR* glomerular filtration rate, *ANP* atrial natriuretic peptide

7.4.1 Endogenous Factors

In the critically ill, extreme physiological stress is applied, regardless of the underlying aetiology. Sepsis, trauma, burns, pancreatitis, autoimmune diseases, and major surgery, among others, are all prone to inciting an inflammatory and hypermetabolic state which, results in broad and profound changes in organ function, including the kidneys. This "storm of mediators" induces changes in the cardiovascular system,

namely a hyperdynamic state, characterized by increased cardiac output and diminished vascular resistance. Major organ blood flow is increased, including that of the kidneys, leading to a significant increase in GFR. These effects were demonstrated in an animal model of hyperdynamic sepsis [25] and are described in burns, post-surgical, and trauma critically ill patients [15, 26–28], although the correlation between cardiac index and CL_{CR} was greater in septic patients and absent in the trauma group [15]. Of note, Udy et al. demonstrated increased sinistrin clearance in a selected cohort of 20 critically ill patients considered at risk of ARC, with significant correlation with CL_{CR}, thus supporting the concept of hyperfiltration in these patients [27].

Additionally, they demonstrated elevated renal tubular anion secretion, which at least theoretically, could contribute to enhanced clearance of certain beta-lactams—known anionic antibiotics [27]. Moreover, it has been known for some time that hyperaminoacidemia, as a result of catabolism and/or inflammation, stimulates the secretion of several hormones that increase GFR and renal flow [29]. In addition, the high levels of CL_{CR} could be secondary to the renal response to a protein load. Finally, increased levels of GFR have been described in pregnant women, obesity, after nephrectomy, and among patients with essential hypertension and diabetes mellitus [30–34]. Taking all these factors into account, it seems plausible that the kidneys are able to recruit physiological reserve when exposed to systemic biological stress, such as hyperperfusion, a high protein load, or hyperglycaemia.

Recently, a significant correlation was described between cerebrovascular pressure reactivity index (as a measure of cerebrovascular reactivity) and estimated creatinine clearance, in a group of patients with severe traumatic brain injury. These results suggest there may be a physiological link between brain injury and kidney function, with the possible involvement of mediators, such as atrial natriuretic peptide (ANP) [35, 36].

7.4.2 Exogenous Factors

In the early stages of sepsis with hypotension, aggressive administration of crystalloid fluid (30 mL/kg) is recommended, and this strategy can be continued until haemodynamic improvement occurs [37]. Generalization of this practice in the critical care setting, including in the non-septic patient, conceivably contributes to producing a high cardiac index and increased renal blood flow, which in turn leads to an increase in GFR and urine output [38]. Similarly, the use of vasopressor support in sepsis is associated with an increase in cardiac output and CL_{CR} [39, 40]. Both therapeutic interventions induce these alterations in the absence of renal dysfunction.

Diuretics are still commonly used in the treatment critically ill patients; however, the influence of these drugs on renal function is controversial. Although mannitol does not seem to affect GFR in normal individuals [41], independent groups of researchers [42, 43] found that post-surgical patients and severely injured patients showed an increase in GFR, in the order of between 20 and 26%. Likewise, research

exploring the effects of frusemide on renal function in healthy volunteers are conflicting; data separately demonstrate no effect, a decrease in GFR, and an increase of GFR [44–46]. As such, the implications of diuretics in terms of ARC remain uncertain.

7.5 Epidemiology of ARC

Identification of patients at risk of ARC is likely to be helpful in optimizing treatment, particularly when renally eliminated drugs are being employed. However, data concerning the natural history, incidence, prevalence, risk factors, and implications of ARC are still scarce. Of note, over the past decade an increasing amount of epidemiological data has identified certain clinical characteristics associated with ARC. Currently, the absence of clear and well-defined criteria for ARC hampers the interpretation of these data.

7.5.1 Prevalence of ARC

Previous studies have shown that ARC is a frequent condition in the critical care setting; however, there are only few large-scale epidemiological data available (Table 7.1).

Table 7.1 Selected epidemiological data from recent studies investigating ARC (modified by author from "Baptista JP, Udy AA: Augmented renal clearance in critical illness: 'The Elephant in the ICU'? Minerva Anestesiol. 2015. 81(10):1050–2")

Year	First author	Country	ICU patients (*n*)	Measurements (*n*)	ARC criteria (mL/m)	Urine time collection (h)	ARC incidence (%)
2016	Baptista	Portugal	477	4271	≥130	8	33
2015	De Waele	Belgium	1081	4472	≥130	24	55.8
2015	Ruiz	France	360	360	≥130	24	33
2014	Campassi	Brazil	363	363	>120	24	28
2014	Baptista	Portugal	54	644	>130	8	55.6
2014	Udy	Australia, Portugal, Malaysia, Hong-Kong	281	1660	≥130	8	65.1
2013	Claus	Belgium	128	599	≥130	24	51.6
2013	Udy	Australia	71	213	≥130	2	57.7
2012	Lautrette	France	32	224	>140	24	47
2012	Grootaert	Belgium	1317	4019	≥120	24	41

ICU Intensive care unit, *ARC* augmented renal clearance; *h* hours

De Waele et al. performed a single-centre retrospective cohort study of 1081 ICU patients during a period of 15 months [47], generating 4472 ICU patient-days for evaluation. They found that more than 50% of the patients had at least one episode of ARC during their ICU stay, and the incidence per 100 patient-days was 36.6 episodes; in addition, 32.8% of these patients manifest ARC throughout their ICU stay [47]. Similarly, although primarily designed to evaluate the accuracy of mathematical estimates of renal function in critically ill patients, an observational, retrospective, single-centre study was performed by Grootaert et al. in a cohort of 1317 patients, providing 4019 measured 24 h–CL_{CR} [18], showing an ARC incidence of 41%. A prospective observational study by Ruiz et al. [48] described an incidence of 33% in a population of 360 consecutive critically ill patients, with normal serum creatinine concentrations. Recently, Baptista et al. conducted an observational retrospective single-centre study in a large population of critically ill patients with normal plasma creatinine concentrations—477 patients within the period of 1 year, corresponding to 4271 measurements [49]. This study concluded that ARC was a frequent condition, which was identified in 33% of the admission days. Udy et al. conducted a multicentre, multinational, prospective, observational study in 281 critically ill patients without evidence of renal impairment [50], and concluded that nearly 65% showed ARC on at least one occasion in the first week of ICU admission.

Smaller studies in different countries have reported a significant prevalence of ARC, with values of 17.9 and 25% on ICU admission [51, 52], 39, 51.6, 55.6, 57.7, and 85% over the ICU length of stay [15, 21, 53–55] and 30–47% during the first week in ICU [51, 52].

ARC is therefore common in the critically ill, with a not insignificant prevalence, and underlies why this phenomenon has been described as a “devil in disguise” [56] or the “elephant in the ICU” [57], particularly in that, despite its ubiquity, ARC is often overlooked by clinicians.

7.5.2 Gender and Age

Studies focusing on the influence of gender on ARC are scarce. Nevertheless, the current available data coherently shows that the incidence of this condition is higher in males [15, 49, 50, 53, 58]. Similarly, different groups of researchers conclude that younger patients exhibit more ARC more frequently [4, 15, 48–51, 53, 59–61].

Men have, physiologically, higher rates of GFR [5] and show higher renal vascular resistance; thus, this gender difference can persist even in hyperfiltration status. One possible explanation for this difference is the distinct production of and sensitivity to vasoactive substances that influence renal vascular resistance [62].

As mentioned earlier, the influence of age fits into the concept of “renal reserve”, which is higher in younger people by virtue of better glomerular preservation and function. It was only very recently that studies addressing the issue of ARC in children have been published. In 2015, De Cock et al. reported the augmented renal clearance of amoxicillin-clavulanic acid in 50 paediatric critically ill patients [63]. The authors

concluded that renal function was a significant covariate on amoxicillin-clavulanic acid clearance and that ARC could be the cause of the sub-therapeutic concentrations observed. More recently, another group of researchers [64] performed an observational study on 109 children (>1 year) who received vancomycin therapy. These authors found globally elevated values of (estimated) glomerular filtration, which were even higher in the group of 21 patients with febrile neutropenia, compared to the remainder (182.0 vs. 156.2 mL/min/1.73 m^2, $p < 0.05$), in addition to the increased renal clearance of vancomycin (0.151 vs. 0.119 L/h/kg, $p < 0.05$). It should be noted that febrile neutropenia was the unique independent risk factor for ARC (defined here as an estimated GFR ≥ 160 mL/min/1.73 m^2).

7.5.3 Patient Populations

Previous studies recognized ARC as a frequent condition in selected populations of critically ill patients.

Victims of severe multi-trauma, namely when associated with trauma brain injury (TBI), seem to be at increased risk of developing ARC. In an observational small cohort study [54], in patients receiving active treatment for the optimization of cerebral perfusion, Udy et al. reported that ARC was a very frequent occurrence (85%). Similarly, in an observational study aimed at investigating renal and cardiac performance in patients with isolated TBI [36], the authors founded very significant augmented CL_{CR} measures, with median values of 201 mL/min on the first day of the study. Minville et al. [58] retrospectively studied 284 patients in a mixed ICU, evaluating 24 h–CL_{CR} within two distinct groups: non-trauma and multi-trauma patients. Notably, despite the fact that no significant differences were found between serum creatinine concentrations between the groups, a significant difference existed in regard to measured 24 h–CL_{CR}: 85 vs. 131 mL/min/1.73 m^2, respectively. Other groups [15, 28, 49–51, 65, 66] found similar results, reporting increased measured CL_{CR} in primarily multi-trauma, post-surgical or TBI patients. An important fact is that in two of these studies [15, 49], trauma was identified as a risk factor for ARC in a multivariate analysis model, strengthening the validity of these epidemiological data.

Patients with non-traumatic sub-arachnoid haemorrhage (SAH) are another subgroup of critically ill patients who are likely to demonstrate ARC. Recently, a prospective single-centre study performed by May et al. [67] evaluated 20 consecutive patients with new aneurysmal SAH. They demonstrated that ARC was present in all 20 patients, with a mean 24 h–CL_{CR} value of 325 ± 135 mL/min/1.73 m^2. The cohort was predominately made up of women and was relatively young, which may partially explain the remarkable prevalence (100%) in this population, in addition to the proposed link between ARC and cerebrovascular autoregulation [35, 67]. Significantly, the authors did not find a difference in 24 h–CL_{CR} between patients receiving, or not receiving, hyperdynamic therapy to treat cerebral vasospasm [67]. High values of CL_{CR} were also frequently observed in 32 consecutive ICU patients admitted with community-acquired meningitis [52].

Patients with major burns are also at risk of manifesting ARC. Interestingly, probably the first clinical description of very high values of CL_{CR} was performed in 1978 by Loirat et al. in a group of 20 patients with burn injury [2]; the average CL_{CR} was 172 ± 48 mL/min/1.73 m^2 and 13 patients showed values above 200 mL/min/1.73 m^2. Recently, Conil et al. prospectively studied 36 adult patients with burn injury (all with normal serum creatinine concentrations) and found 42% (15 patients) had a CL_{CR} above 120 mL/min/1.73 m^2 [68]. Increased catabolism, a hyperdynamic circulation, frequent episodes of sepsis, vasopressor support, and a generally young population, all contribute to the high prevalence of ARC in this subgroup of patients.

Studies involving patients with sepsis illustrate the high prevalence of ARC in the critically ill. Although the majority of these reports were not designed as epidemiological studies, each included a diverse case-mix of medical, neurologic, trauma, non-trauma, and post-surgical critically ill patients. In these studies [6, 7, 10, 52, 53, 59, 60, 69, 70], ARC was noted to have a prevalence of between 40 and 79%.

Patients with haematological malignancies and febrile neutropenia are also at risk of manifesting ARC, as suboptimal levels of meropenem and glycopeptides have been described [64, 71–74]. However, each study included patients with severe sepsis, who were mostly young men, generating uncertainty in regard to the role of the malignancy in the genesis of ARC.

7.5.4 Severity of Disease

Patients in critical care settings with lower illness severity, as reflected by lower Acute Physiology and Chronic Health Evaluation (APACHE) II scores and/or lower Sequential Organ Failure Assessment (SOFA) scores, seem to be at greater risk of developing ARC [4, 15, 60, 61], although this has not been confirmed in all reports [53]. This interaction may be confounded by age being included in the APACHE score although the observation that lower SOFA scores are associated with ARC implies the absence of organ dysfunction as a key factor. Recently, an ARC risk score based in three factors (age, trauma, and SOFA) and used to define three distinct categories (low, medium, high) has been described [15]. A subsequent simplification (reclassification into two categories) was tested [75] and demonstrated a sensitivity of 100% and specificity of 71%, in accurately identifying patients with ARC.

7.5.5 ARC Outside the ICU

Until recently, ARC was almost exclusively reported in the critical care setting. In 2016, a prospective observational single-centre point prevalence study was conducted in 232 adult non-critically ill surgical patients [76]. This revealed that ARC was present in 30% of abdominal and 35% of trauma surgery patients, when

evaluated by means of 8 h–CL_{CR}. In addition, these researchers identified younger age and male gender (specifically in the trauma subgroup) as risk factors for ARC. In accordance with these results, Hites et al. found, in a pharmacokinetic study of beta-lactams, that over 25% of 56 non-critically ill septic and obese patients had a 24 h–CL_{CR} above 150 mL/min [9]. Another study [59] previously showed that ARC was present in 61% (11/18) of a small sample of non-critically ill patients. However, this was a retrospective study and the CG formulae was used for estimating renal function; notably, estimated clearance was remarkably high—median of 150.5 mL/min/1.73 m^2.

These findings are in keeping with the more representative results observed in the critically ill. More importantly, these studies underline that ARC is an underestimated diagnosis, even in non-critical care settings. The severity of a disease is a continuum; thus, it seems logical that severely ill patients, before having absolute criteria to warrant ICU admission or even those who have never been admitted at an ICU, can show similar pathophysiology, including an inflammatory systemic response, hyperdynamic circulation, augmented renal flow, and supra-normal glomerular filtration.

7.5.6 ARC and Outcome

Few studies have investigated the link between ARC and outcome. In a prospective, single-centre, observational study, the relationship between ARC and 30-day mortality was explored in a cohort of 36 critically ill patients without brain lesions or neurologic disease [77]. This pilot research showed that patients demonstrating ARC ($n = 23$; 63%), independently of their diagnosis or the presence of sepsis, had a significantly lower mortality (8.7% vs. 38.5%, $p < 0.05$). On the contrary, in another prospective observational study performed in patients in a mixed ICU receiving antimicrobial therapy, Claus et al. [53] reported that therapeutic failure was more frequent in the subgroup of ARC patients. Similarly, Falcone et al. [78] found that critically ill patients with severe sepsis caused by Gram-positive microorganisms and exhibiting augmented renal clearance of daptomycin presented higher in-hospital mortality (30.7% vs. 10.8%). However, this subset of 13 patients had higher SOFA scores, a much higher rate of MRSA bacteraemia, severe sepsis, and septic shock, when compared to the remaining 37 patients. In a prospective, double-blind, randomized trial involving 272 patients with late-onset ventilator-associated pneumonia (comparing 7-day doripenem with 10-day imipenem-cilastatin), Kollef et al. [79] found that clinical cure rates in the subgroup of 46 patients with a $CL_{CR} \geq 150$ mL/min, favoured imipenem (28 patients). Finally, another group of researchers was unable to find an association between ARC and clinical outcome, in a cohort of 100 critically ill patients [6].

These data suggest an urgent need to conduct additional outcome studies concerning ARC.

7.6 Clinical Implications of ARC

7.6.1 Assessing Renal Function: More Than Just Kidney Injury

Clinicians generally assess renal function from a conservative perspective, such that "normal" renal function is typically inferred from plasma biomarkers (such as creatinine or cystatin C), which are often flawed and/or misleading in the critically ill [16, 21]; while, the possibility of "supra-normal" clearance is infrequently considered.

In daily practice, clinicians frequently adjust medication on the basis of impaired renal function. However, rarely does the same clinicians consider dose adjustment in patients with ARC. This is principally because most practitioners unfamiliar with this condition, and routine daily measured CL_{CR} is usually not performed in the ICU. Instead, clinicians tend to prefer mathematical estimates of renal function, which are insensitive in identifying critically ill patients with ARC [17]. Taking into consideration emerging data which suggests a not insignificant prevalence of ARC in the critically ill, the daily measure of urinary CL_{CR} should arguably be more common in the ICU. Moreover, it is inexpensive, easy to apply, reliable, reproducible, and both clinically and scientifically useful. Finally, considering existing prevalence data for ARC (Sect. 7.5.1), at least one in four patients in the ICU without renal impairment are likely to manifest this phenomenon; and will be exposed to undertreatment when prescribed standard doses of renally eliminated antibiotics. Importantly, the pharmaceutical industry and regulators should consider this when new agents enter clinical practice.

7.6.2 Antibiotics: Drugs with Specific Characteristics

In severe sepsis, control of the primary focus, haemodynamic resuscitation, organ support, and initial empiric antibiotic therapy are paramount, and any delay will result in increased morbidity and mortality [80]. Applied to antibiotic therapy, the proverb indicating *"there is only one opportunity to make a first good impression",* means that an adequate dose of antibiotic must be delivered very early, ideally at first administration. In addition, in critical care settings, clinicians rely on clinical feedback to validate the efficacy of therapy. For the majority of drugs used in such cases, it is possible to perform a rapid, obvious, and easy assessment of the clinical response of the patient. The use of vasopressors, antihypertensive, diuretics, sedatives, antipyretics, and analgesia are classic examples. However, this is not the case with antibiotics: a favourable clinical response is difficult to assess in the first days of therapy, even if the treatment is adequate in terms of dosing, spectrum of bacterial cover, and penetration.

In addition, the emergence of antibiotic resistance correlates with selective pressure as a consequence of using these drugs [81–83], even after brief exposure in the ICU environment [84]. Plus, the prevalence of less susceptible bacteria is higher in the ICU setting [85]. Moreover, inadequate antibiotic therapy affects not only the "target" patient but also subsequent patients to be treated, jeopardizing the success of future treatments and increasing the ecological risk to the hospital and to the community. While waiting for new agents, the strategy of maximal optimization of antibiotics must be incorporated into daily clinical practice, in addition to reviving old antibiotics, such as in the case of fosfomycin and colistin [86]. Indeed, on June 26th 1945, Sir Alexander Fleming (1881–1955) pronounced the following wise words: "*the thoughtless person playing with penicillin is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. I hope this evil can be averted*" [87].

7.6.3 ARC and Beta-Lactams Antibiotics

The beta-lactams (penicillins, cephalosporins, carbapenems, monobactams) are the most commonly prescribed and studied class of antibiotics, including in the ICU setting. Most beta-lactam antibiotics show time-dependent pharmacokinetic/pharmacodynamics (PK/PD), with the duration the free drug concentration exceeds the minimum inhibitory concentration ($f\ T_{>MIC}$) being the optimal index associated with clinical efficacy. In addition, this family of antibiotics exhibit short half-lives, low volumes of distribution, low to moderate binding to serum proteins, poor or absent post-antibiotic effect (except for carbapenems) and are predominantly cleared by the kidney. More specifically, the clearance of this class of antibiotics directly correlates with renal clearance [60, 88–91] and inversely correlates with trough drug serum concentration [7, 92]. Importantly, increased drug elimination will predominantly affect the half-life of beta-lactam antibiotics.

Huttner and colleagues [6] performed a single-centre, prospective, observational study in 100 critically ill septic patients, treated with imipenem, meropenem, piperacillin/tazobactam, or cefepime. They concluded that patients with ARC were three times more likely to have one or more undetectable trough concentrations (odds ratio of 3.3; confidence interval: 1.1–9.9). In a selected group of 48 critically ill patients treated with six different beta-lactams, researchers showed that a significant proportion received inadequate dosing even though standard regimens were used [7]; furthermore, using multivariate analysis, a robust relationship was demonstrated between low trough concentrations and 8 h–CL_{CR}. In a prospective, observational, PK study [8], Carlier et al. analysed data from 61 ICU patients receiving treatment with meropenem or piperacillin-tazobactam administered by extended infusion. They demonstrated that, in the subset of ARC patients, 76% (22/29) did not reach 100% $f\ T_{>MIC}$ and 37% (7/19 patients) did not reach 50% $f\ T_{>MIC}$. In a recent single-centre

observational study [60], Udy et al. examined the impact of ARC in a convenience sample of 48 septic critically ill patients receiving piperacillin-tazobactam, 4.5 g four times a day. They found that a significant proportion of patients (~2/3rds) manifest inferior drug exposure, when using the MIC at the upper limit of susceptibility (16 mg/L). Besides low concentrations, these authors demonstrated that the study cohort had an increased clearance of piperacillin-tazobactam (1.5 × values in healthy volunteers). Similarly, a post hoc analysis of the DALI study—a prospective, multicentre PK point prevalence study performed across 68 ICUs [93]—found that 19% and 41% of patients did not reach 100% $fT_{>MIC}$ and 50% $fT_{>MIC}$, respectively. Of note, increased CL_{CR} (using mathematical estimates) was a significant co-factor associated with PK/PD target failure [94]. These results are consistent with other analyses [61], where higher estimated CL_{CR} significantly reduces the probability of the target attainment. Significantly, the probability of reaching 100% $fT_{>MIC}$ decreased by 3% with every 1 mL/min increase in the estimated CL_{CR}. Another group [95] performed a prospective randomized controlled study in 32 critically ill patients treated with piperacillin/tazobactam, investigating the added value of using therapeutic drug monitoring in achieving PK/PD targets. The authors observed that plasma piperacillin concentrations were significantly lower in patients with ARC when compared to those without this condition. Finally, Hites et al. demonstrated, in a cohort of 56 non-critically ill obese patients, that ARC (defined by a 24 h–CL_{CR} > 150 mL/min) was the only risk factor identified for insufficient serum concentrations of standard doses of ceftazidime, cefepime, piperacillin/tazobactam, and meropenem [9].

Studies exploring higher than normal doses of beta-lactams are scarce and largely from single centres [96], or are small case series and case reports [97–99]. Further studies are urgently needed specifically addressing the optimization of antibiotic dosing in patients with ARC. This new information should be quickly incorporated into the summary of product characteristics (SPC) by regulatory authorities and drug developers. Of note, this is the case for ceftobiprole—a recent new-generation cephalosporin—for which a recommendation exist in the SPC [100] in order to prolong the infusion time to 4 h in patients with a supra-normal creatinine clearance (above 150 mL/min). Similarly, the SPC for doripenem was updated and currently recommends that 1 g every 8 h, as a 4-h infusion, should be considered in patients with ARC [101]. A new combination product (ceftazidime with avibactam) has obtained initial authorization from the European Medicines Agency (EMA); within the assessment report of the product several, PK considerations are made regarding ARC and sepsis [102].

7.6.4 ARC and Glycopeptides Antibiotics

Vancomycin is the most commonly prescribed glycopeptide in the intensive care setting and is the most common first-line option for treating resistant Gram-positive bacteria. Briefly, vancomycin is a hydrophilic antibiotic, with moderate binding to serum proteins, is mainly excreted by the kidneys, with a low volume of distribution, long half-life, and a moderate post-antibiotic effect. The best PK/PD index

associated with clinical efficacy is the ratio between the area under the curve of drug concentrations over 24 h ($AUC_{0–24}$) and the MIC of the bacteria ($AUC_{0–24}$/MIC), ideally exceeding 400 [103, 104]. Like beta-lactams, vancomycin's body clearance correlates very well with creatinine clearance, both in critically ill and non-critically ill patients [105–111].

In the recent past, a growing body of evidence has emerged demonstrating that standard doses of vancomycin result in suboptimal serum or tissue concentrations in critically ill patients [4, 10, 26, 59, 64, 106, 112–118]. Of note, the authors of a secondary analysis from the DALI study [119] concluded that an important proportion of critically ill patients (43%) did not achieve adequate vancomycin exposure, defined as a trough concentration at least 15 mg/L. Although the reasons for this is multifactorial, ARC is likely to be a key driver. However, published studies specifically dedicated to this issue are relatively scarce.

Two contemporaneous studies investigated the relationship between ARC and vancomycin concentrations in the initial few days of therapy in ICU patients receiving continuous infusion. Ocampos-Martinez et al. [3] prospectively studied 261 critically ill patients, of which 16% (43 patients) had a 24 h–CL_{CR} higher than 120 mL/min/1.73 m^2. ARC was associated with suboptimal serum levels in 84% during the early phase of treatment with vancomycin (the first 2 days of drug administration). Consistent with these results, Baptista et al. [10], in a prospective single-centre study involving 93 ICU patients, demonstrated that the serum concentration of vancomycin on the first day of treatment had a moderate inverse correlation with 24 h–CL_{CR} and that, in those with ARC, significantly lower levels on the first three consecutive days of the study were noted. Equally, in another prospective study, Campassi et al. [4] recruited 363 patients in a general ICU over a 1-year period. They observed that none of the 103 patients with 24 h–CL_{CR} > 120 mL/min/1.73 m^2 reached the targeted trough level on the first day; in addition, these patients showed persistently lower levels over the first three days when compared to the patients without ARC, despite being exposed to increased doses of vancomycin.

Another group [59] performed a retrospective study evaluating the influence of ARC (estimated by CG method) on the exposure to vancomycin in a heterogeneous population (critical and non-critical care setting). They concluded that ARC cases had double the risk of sub-therapeutic vancomycin serum concentration. Shimamoto et al. [26] found significantly lower trough vancomycin levels in septic ICU patients with a greater systemic inflammatory response; of note the estimated renal function was "supra-normal" in this group (>120 mL/min, CG estimated). Very recently, Chu et al. [11] reached similar conclusions in a study involving 148 infected patients receiving empirical vancomycin therapy. The authors demonstrated that patients with ARC (>130 mL/min, CG estimated) treated with conventional dosage of vancomycin exhibited significantly lower steady-state trough serum concentrations. Equally, Spadaro et al. identified ARC (here defined as measured 24 h–CL_{CR} > 130 mL/min/1.73 m^2) as the main determinant of sub-therapeutic vancomycin serum concentrations, in a group of 348 critically ill patients treated with continuous infusion of vancomycin [120]. Similar results were also published recently in a retrospective study involving neurosurgical patients [121].

Teicoplanin is another glycopeptide used in ICU. It is hydrophilic, highly protein bound, and predominantly renally eliminated [122]. Recently, Nakano et al. [123] reported that septic patients manifesting a systemic inflammatory response syndrome (SIRS) had significantly lower plasma trough concentrations during the first 3 days of treatment, when compared to non-SIRS patients administered an equivalent loading dose. Similarly, distinct groups have reported an augmented rate of teicoplanin clearance in febrile, severely neutropenic patients and in critically ill patients [71, 125].

7.6.5 ARC and Other Antibiotic Drugs

From a theoretical point of view, the PK of any agent that is renally cleared, will potentially be altered by ARC. However, depending on the bacterial kill PK/PD profile, the magnitude of this effect will vary.

For hydrophilic antibiotics exhibiting a time-dependent profile, particularly with low protein binding, an effect similar to that with beta-lactams is expected. This is the case of oxazolidinones (e.g. linezolid, the first to be approved for clinical use) and fosfomycin. Although the level of renal clearance of linezolid is modest (less than 30%) higher values of glomerular filtration are documented as a risk factor for suboptimal serum concentrations in patients with severe sepsis [125]. On the contrary, fosfomycin is eliminated almost entirely by the kidneys [126]. Consequently, higher dosing, shortening of intervals and alternative ways of administration of these drugs—such as extended or continuous infusion—should be considered [127–129].

For hydrophilic antibiotics exhibiting a concentration-dependent profile, such as with aminoglycosides, the peak plasma concentration is less affected by ARC and more affected by the increased volume of distribution [130]. However, ARC has been described as a covariate leading to the requirement of higher than standard dosage in critically ill patients [131–133]. In addition, the shortening of dosing intervals to less than 24 h can be considered.

For levofloxacin, a moderately lipophilic drug with a high volume of distribution and almost totally cleared by the kidneys, recent work by Pai et al. [134] showed that in a population of morbidly obese septic patients, a standard dosage was insufficient to achieve the defined PK/PD target, and that CL_{CR} constituted the best predictor of levofloxacin renal clearance. In line with others [135], the final recommendation by these authors is that the dosage of levofloxacin should be increased in patients with higher CL_{CR} [134].

Daptomycin, a novel cyclic lipopeptide, is a hydrophilic antibiotic characterized by a low volume of distribution, predominant renal excretion, prolonged post-antibiotic effect, and a concentration-dependent PK/PD profile. Falcone et al. studied 50 critically ill patients treated with standard doses of this antibiotic and reported augmented daptomycin clearance and significantly lower drug exposures in a subset of 13 patients [78]. Similar results were observed in cancer patients with febrile neutropenia and in patients with burn injuries treated with daptomycin, suggesting the need for higher doses at the onset of treatment [136, 137].

7.6.6 My Septic Patient Has ARC: So What?

Based on growing literature, it seems rational to conclude that augmented CL_{CR} is a significant predictor of sub-therapeutic beta-lactam and vancomycin concentrations in critically ill patients, when standard doses are employed. Moreover, as discussed above, current data regarding other antibiotics are in keeping with this, reinforcing the clinical importance of ARC as a determinant of antibiotic exposure in the early phase of severe sepsis. Importantly, these data are highly generalizable, and suggest intensive care physicians, pharmacists, researchers, and pharmaceutical regulators should be cognizant of the implications of ARC. A "one-size-fits-all" approach to dosing is likely to be grossly flawed in the critically ill. It is imperative that all those involved in the treatment of critically ill patients move towards an individualized dosing approach.

Adequacy of antibiotic therapy is of paramount importance in achieving optimal outcomes in septic patients [138, 139]. The prescription of an antibiotic should always consider the "bug-drug-host" triad, with efficacy of therapy intimately linked to optimizing each of these factors. Although ARC is only one piece of this intricate chain, ignoring this phenomenon will significantly impact the success of antibiotic therapy. In this respect, three recent position papers—one from "Antimicrobials: A Global Alliance for Optimizing their Rational Use in Intra-Abdominal Infections" (AGORA), another by the most recent "Surviving Sepsis Campaign Guidelines" Committee, and the third from the "Infectious Diseases Society of America/American Thoracic Society 2016 Clinical Practice Guidelines"—underline the need to optimize antimicrobial exposure to obtain better clinical outcomes and reduce resistance, and make special mention of the clinical relevance of ARC [140–142].

From a practical point of view at the bedside of a severely ill patient with ARC, clinicians should strongly consider: (a) the use of the maximal recommended doses of antibiotics that are renally cleared; (b) optimization of the mode of administration with extended or continuous infusions (vancomycin, beta-lactams); and (c) the shortening of dosing intervals with intermittent schedules (aminoglycosides, beta-lactams). Often, larger "off-label" doses may be required. In this respect, a number of nomograms based on CL_{CR} values have been developed to assist prescribers [96, 106, 111, 112, 143]. Traditionally, therapeutic drug monitoring (TDM) is used to largely prevent toxic effects, particularly in older patients, patients with rapid changes in renal function and in the critical care setting. However, TDM can and should be used for dose titration where available, and is especially useful in patients with ARC, although this practice is still infrequently applied [144].

Of note, *over-dosing* of adequate antibiotic drugs at the beginning of the treatment of the severely ill septic patient is probably more advantageous and life-saving than *under-dosing*. Logically, when more aggressive antibiotic doses using agents with a narrow therapeutic window are applied, such as vancomycin and aminoglycosides, complications can also occur (such as nephrotoxicity) [145, 146]. However, in our experience, with tight monitoring any elevation of serum creatinine is usually transient and mild, and the frequency of severe AKI is low [111, 147–150].

7.7 Conclusions

Septic patients in the ICU are severely ill, with frequent organ dysfunction, and are often infected with more resistant microorganisms. Because of numerous physiological changes, the PK characteristics of antibiotics are grossly altered, and an individualized approach to the critically ill patient, must be considered when prescribing these agents.

Augmented renal clearance has emerged recently as a common feature in some subsets of critically ill patients and has been increasingly described in this setting. This condition is often overlooked by clinicians, albeit can have profound and severe consequences on the efficacy of drugs that are predominantly eliminated by the kidneys. The use of traditional antibiotic dosing strategies in patients showing persistent ARC may lead to suboptimal antibiotic exposure, increasing the risk of treatment failure, when standard doses are used. Consequently, this may contribute to an increase in bacterial resistance and the prevalence of (even more) difficult-to-treat infections. As such clinicians should be cognizant of this phenomenon, using simple and reliable methods (such as a measured CL_{CR}) to identify patients where dose adjustment is needed.

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CHAPTER 3

AUGMENTED RENAL CLEARANCE IN THE ICU: RESULTS OF A MULTICENTER OBSERVATIONAL STUDY OF RENAL FUNCTION IN CRITICALLY III PATIENTS WITH NORMAL PLASMA CREATININE CONCENTRATIONS

Udy AA, Baptista JP, Lim NL, Joynt GM, Jarrett P, Wockner L, Boots RJ, Lipman J. Crit Care Med. 2014 Mar;42(3):520-7.

PREVALENCE AND RISK FACTORS FOR AUGMENTED RENAL CLEARANCE IN A POPULATION OF CRITICALLY III PATIENTS

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Augmented Renal Clearance in the ICU: Results of a Multicenter Observational Study of Renal Function in Critically Ill Patients With Normal Plasma Creatinine Concentrations

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Objective: To describe the prevalence and natural history of augmented renal clearance in a cohort of recently admitted critically ill patients with normal plasma creatinine concentrations.
Design: Multicenter, prospective, observational study.
Setting: Four, tertiary-level, university-affiliated, ICUs in Australia, Singapore, Hong Kong, and Portugal.
Patients: Study participants had to have an expected ICU length of stay more than 24 hours, no evidence of absolute renal impairment (admission plasma creatinine < 120 µmol/L), and no history of prior renal replacement therapy or chronic kidney disease. Convenience sampling was used at each participating site.
Interventions: Eight-hour urinary creatinine clearances were collected daily, as the primary method of measuring renal function. Augmented renal clearance was defined by a creatinine clearance more than or equal to 130 mL/min/1.73 m^2. Additional demographic, physiological, therapeutic, and outcome data were recorded prospectively.
Measurements and Main Results: Nine hundred thirty-two patients were admitted to the participating ICUs over the study period, and 281 of which were recruited into the study, contributing 1,660 individual creatinine clearance measures. The mean age (95% CI) was 54.4 years (52.5–56.4 yr), Acute Physiology and Chronic Health Evaluation II score was 16 (15.2–16.7), and ICU mortality was 8.5%. Overall, 65.1% manifested augmented renal clearance on at least one occasion during the first seven study days; the majority (74%) of whom did so on more than or equal to 50% of their creatinine clearance measures. Using a mixed-effects model, the presence of augmented renal clearance on study day 1 strongly predicted ($p = 0.019$) sustained elevation of creatinine clearance in these patients over the first week in ICU.
Conclusions: Augmented renal clearance appears to be a common finding in this patient group, with sustained elevation of creatinine clearance throughout the first week in ICU. Future studies should focus on the implications for accurate dosing of renally eliminated pharmaceuticals in patients with augmented renal clearance, in addition to the potential impact on individual clinical outcomes. (*Crit Care Med* 2013; 42:00–00)

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Key Words: augmented renal clearance; creatinine clearance; critical illness

Accurate assessment of organ function in the critically ill remains uniquely challenging. Such patients routinely manifest an inflammatory response, which in combination with invasive interventions results in physiology that is infrequently encountered in other settings (1). Regular clinical examination and use of select biomarkers dominate modern critical care practice, being primarily employed to identify and monitor evolving organ dysfunction. Enhanced or augmented organ performance is often of less concern, based on the premise that this is unlikely to lead to adverse outcomes.

However, changes in renal function, and therefore drug handling, can significantly distort the normal pharmacokinetic profile of many commonly prescribed agents (2, 3). As a consequence, the clinician may adjust the dosing regimen. Usually, progressive acute kidney injury (AKI), often recognized by a rising plasma creatinine concentration, will impair the elimination of renally cleared agents, leading to drug accumulation. Consequently, dose reduction is generally appropriate to avoid drug toxicity.

The converse, dose escalation in the presence of augmented renal drug elimination, is infrequently reported in clinical practice (4). This largely results from the lack of "visibility" of this phenomenon, due to the poor discrimination of plasma creatinine concentrations, when reported within the "normal" reference range (5). There is, however, increasing evidence supporting the presence of augmented renal clearance (ARC) in critically ill patients (6). ARC is defined as the enhanced renal elimination of circulating solute (7). Specifically, elevated creatinine clearance (CL_{CR}), has been reported in burns (8), traumatic brain injury (9), polytrauma (10), sepsis (11), ventilator-associated pneumonia (12), and general intensive care practice (13, 14).

Although there is a paucity of specific data detailing renal drug clearance in the critically ill, CL_{CR} is a routinely used surrogate, representing a key covariate describing renal drug elimination (3). Mathematical estimates of CL_{CR} have been proposed; however, these were principally designed for use in an ambulatory or ward-based setting and are inaccurate in the critically ill (15, 16). As such, a directly measured urinary CL_{CR} is the most accurate and reproducible measure of renal function routinely available (17).

Currently little data exist that describe the epidemiology of ARC, particularly in respect to its prevalence and natural history. The impact of ARC on drug pharmacokinetics is not only relevant for daily practice but also the implementation and interpretation of clinical trials of new or emerging pharmaceuticals (4). As such, there is significant uncertainty regarding the design of robust investigations that account for this phenomenon. The aims of this multicenter prospective observational study were therefore to examine the prevalence and natural history of ARC in a cohort of critically ill patients with normal plasma creatinine concentrations, with a view to informing future clinical study and current prescribing practice.

MATERIALS AND METHODS

Setting

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

Study Population

Study participants had to have an expected ICU length of stay (LOS) more than 24 hours, no evidence of absolute renal impairment (admission plasma creatinine < 120 µmol/L), and no history of prior renal replacement therapy or chronic kidney disease. Patients were excluded if 1) either invasive hemodynamic monitoring (principally an intraarterial cannula) or an indwelling urinary catheter (IDC) was not used as part of standard management; 2) they were younger than 18 years; 3) they were pregnant; 4) rhabdomyolysis was clinically suspected or the admission plasma creatinine kinase was more than 5,000 IU/L; or 5) they were in the "risk" category or greater for AKI, as defined by the Risk, Injury, Failure, Loss, and End-stage criteria (18). Convenience sampling was used at each participating site. Patients undergoing an operative procedure within 24 hours prior to admission were classified as "surgical." Planned postoperative admissions were considered "elective."

Interventions

Demographic and outcome data, including age, gender, anthropometric measures, admission diagnosis, Acute Physiology and Chronic Health Evaluation (APACHE) II scores, ICU and hospital LOS, and ICU mortality, were recorded prospectively. Modified (excluding the neurological and renal components) Sequential Organ Failure Assessment (SOFA) scores, physiological variables, ventilation variables, 24-hour fluid balance, vasopressor/inotrope administration, diuretic use, and antibacterial administration were recorded daily. Data collection commenced within 48 hours of ICU admission and were discontinued at 1) ICU discharge; 2) death; 3) development of severe renal impairment (CL_{CR} < 30 mL/min/1.73 m^2); 4) institution of renal replacement therapy; 5) removal of invasive monitoring or IDC; 6) withdrawal of informed consent; or 7) day 28, whichever came first.

An 8-hour CL_{CR} was the primary method of measuring renal function. Urine was collected via the IDC between midnight and 08:00 AM daily, following which urinary volume and creatinine concentration were determined by laboratory analysis. Concurrent plasma creatinine concentrations were obtained, following which CL_{CR} was calculated using the standard formula. Creatinine measurement in plasma and urine used automated analyzers employing a modified Jaffe (alkaline picrate) technique, representing an isotope dilution mass spectrometry traceable assay. As per convention, CL_{CR} values were subsequently normalized to a body surface area (BSA) of 1.73 m^2. ARC was defined as an 8-hour CL_{CR} more than or equal to 130 mL/min/1.73 m^2, given the association with subtherapeutic antibacterial concentrations, when using standard doses (19).

Statistical Analysis

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

RESULTS

Demographic Data

During the study period, 932 patients were admitted to participating ICUs, of which 281 patients were recruited into the study, contributing 1,660 individual CL_{CR} measures. Demographic, admission, and illness severity data are presented in **Table 1**. The cohort was relatively young (54.4 yr [52.5–56.4 yr]), with most requiring admission to ICU on an emergent basis, with or without an antecedent operation. Routine admissions were scarce (< 10%). Illness severity scores were moderately low, despite the nonelective nature of the cohort. Data collection commenced on day 1 (1–2), with patients remaining in the ICU for a median of 4 days (2–10 d). As determined by protocol, admission plasma creatinine concentrations were within the normal range (mean, 72 µmol/L [69–75 µmol/L]). ICU mortality was 8.5%.

TABLE 1. Demographic, Admission, and Illness Severity Data

Variable	Summary Data
Age, yr, mean (95% CI)	54.4 (52.5–56.4)
Gender, male, *n* (%)	178 (63.3)
Weight, kg, mean (95% CI)	72.4 (70.1–74.6)
Height, m, mean (95% CI)	1.66 (1.65–1.68)
Body mass index, kg/m^2, mean (95% CI)	26.0 (25.3–26.6)
Body surface area, m^2, mean (95% CI)	1.80 (1.77–1.83)
Acute Physiology and Chronic Health Evaluation II score, mean (95% CI)	16.0 (15.2–16.7)
Modified Sequential Organ Failure Assessment score (max), median (IQR)	3 (2–6)
Mechanical ventilation (at any point), *n* (%)	206 (73.8)
Vasopressor/inotropes (at any point), *n* (%)	111 (39.5)
Participating site, *n* (%)	
Australia	116 (41.3)
Singapore	81 (28.8)
Hong Kong	59 (21.0)
Portugal	25 (8.9)
Admission category, *n* (%)	
Elective	26 (9.3)
Emergency	93 (33.1)
Surgical emergency	126 (44.8)
Trauma	36 (12.8)
ICU day of enrolment, median (IQR)	1 (1–2)
Plasma creatinine concentration (day 1), µmol/L, mean (95% CI)	72 (69–75)
Creatinine excretion rate, mg/kg/d, (day 1), mean (95% CI)	19.2 (17.8–20.5)
Creatinine clearance, mL/min/1.73 m^2 (day 1), mean (95% CI)	108 (102–115)
ICU length of stay (d), median (IQR)	4 (2–10)
ICU mortality, *n* (%)	24 (8.5)

IQR = interquartile range.

Prevalence of ARC

Overall, 65.1% (*n* = 183) of the cohort manifested ARC on at least one occasion during the first seven study days. On study day 1, ARC was evident in 108 patients (prevalence = 38.4%), with the majority of new cases occurring on study day 2 (*n* = 41) and day 3 (*n* = 13). The number of evaluable patients fell to 231 on study day 2, with the prevalence of ARC increasing to 49.4% (*n* = 114). Of the 50 patients not completing a second CL_{CR}, 64% (*n* = 32) did not manifest ARC. **Figure 1** demonstrates the prevalence of ARC, as a fraction of the patients

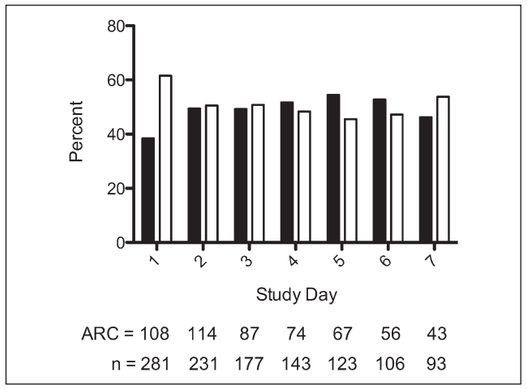

Figure 1. Daily prevalence of augmented renal clearance (ARC) to study day 7. Percentage of patients with ARC (*solid bars*) compared with no ARC (*open bars*) on each study day. The total number (*n*) of patients remaining in the study and those manifesting ARC are provided.

remaining in the study, through day 7. From day 2, the prevalence of ARC remained relatively constant (~50%) with the highest prevalence (54.5%, $n = 67$) recorded on study day 5. Of those patients who did not manifest ARC on day 1 and remained in the ICU, 43.4% did so at least once in the next 6 days. Thirty-four point nine percent (34.9%) of patients never displayed ARC on any CL_{CR} measure. Of those patients manifesting ARC, the majority (74%) did so on more than or equal to 50% of their CL_{CR} measures.

Characteristics of Patients Displaying ARC

Comparison of admission, demographic, and illness severity data between groups (ARC vs no ARC) are presented in **Table 2**. Differences in physiological and treatment variables on study days 1, 4, and 7 are provided in **Appendix A** (Supplemental Digital Content 1, http://links.lww.com/CCM/A755). Patients manifesting ARC (at any point in the first seven study days) tended to be younger, men, and multitrauma victims, receiving mechanical ventilation. On study day 1, the absence of ARC was associated with higher modified SOFA scores ($p = 0.007$), the application of vasopressor or inotropic support ($p = 0.015$), and a lower 24-hour urine output ($p = 0.004$). Frusemide use was more common in those not manifesting ARC. Differences in the minimum mean arterial pressure (study day 1) and body temperatures (study day 4) were also observed, although these deviations are unlikely to be clinically meaningful. No difference was observed in the provision of enteral nutrition between groups. Significantly lower plasma creatinine concentrations ($p < 0.01$) and high creatinine excretion rates ($p < 0.001$) were consistently noted in those manifesting ARC (Appendix A, Supplemental Digital Content 1, http://links.lww.com/CCM/A755).

TABLE 2. Demographic, Therapeutic, and Illness Severity Data in Those With and Without Augmented Renal Clearance at Any Time During the First Seven Study Days

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

ARC = augmented renal clearance, IQR = interquartile range.

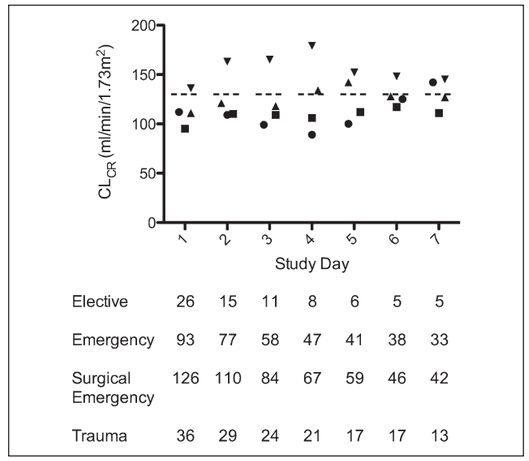

Figure 2. Daily creatinine clearance (CL_{CR}) measures by admission type to study day 7. Mean CL_{CR} in elective (*solid circle*), emergency (*solid square*), surgical emergency (*solid triangle*), and trauma (*inverted solid triangle*) patients to study day 7. The *dashed line* represents the cutoff for augmented renal clearance (130 mL/min/1.73 m^2). The number of patients of each admission type remaining in the study per day is provided.

Natural History of ARC and Comparison Between Admission Types

Figure 2 displays mean CL_{CR} as a function of admission type to study day 7. In the overall cohort, a significant rise is noted on study day 2 (day 2, 121 mL/min/1.73 m^2 [113–129 mL/min/1.73 m^2]; day 1, 108 mL/min/1.73 m^2 [102–115 mL/min/1.73 m^2]; $p = 0.001$). Significant differences in demographics, anthropometric measures, illness severity, and interventions exist between diagnostic groups (**Table 3**). In addition, CL_{CR} varies both between and within the groups. Of note, CL_{CR} on study day 2 rises significantly in trauma ($p = 0.013$) and surgical emergency admissions ($p = 0.015$), although no significant difference was identified in elective cases ($p = 0.916$) or emergency admissions ($p = 0.121$). Sustained increases in CL_{CR} appear to occur in trauma victims and surgical emergency admissions primarily (Fig. 2).

Variations in CL_{CR} as a function of ARC status on study day 1 are presented in **Figure 3**. Significant differences exist between groups on each study day, although greater within group variability is noted in those without ARC initially. Specifically, a significant increase in CL_{CR} is noted on study day 2 in those not previously manifesting ARC ($p < 0.001$), which is not the case in those with documented augmented clearances already. However, the presence of ARC initially is associated with a sustained elevation of CL_{CR}, over the first seven study days (Fig. 3).

TABLE 3. Comparison of Demographics, Anthropometric Measures, Illness Severity, and Interventions Between Admission Types

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

IQR = interquartile range.

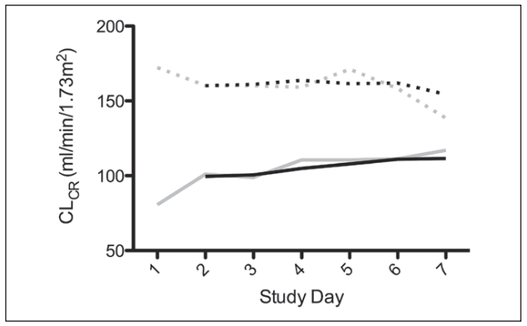

Figure 3. Mixed-effects model comparing those with and without augmented renal clearance (ARC) on study day 1. Mean creatinine clearance (CL_{CR}) (*gray lines*) and results from the model (*black lines*). The *solid lines* represent those without ARC on study day 1 and the *dotted lines* those with ARC on study day 1.

A mixed-effects model was generated to account for variable ICU LOS. Modeling occurred from study day 2, to mitigate the influence of factors outside ICU. Significant covariates included hospital location, age, ARC status on day 1, daily modified SOFA scores, and frusemide administration. Vasopressor use was not included, given the strong correlation with modified SOFA scores, while gender, mechanical ventilation, 24-hour fluid balance, and admission type were not predictive of daily CL_{CR}. As shown in Figure 3, ARC status on study day 1 significantly predicts CL_{CR} from day 2 to 7, with values being markedly lower in those without ARC initially ($p = 0.019$). Changes in modified daily SOFA scores are only significant in those without ARC, whereby increasing scores promote lower CL_{CR} values ($p < 0.001$). Age was highly significant, with patients 65 years old or older having log CL_{CR} values on average 0.46 units lower than those younger than 40 years ($p < 0.001$). Hospital location was included as an adjusting variable to account for differences in case-mix. Of note, frusemide administration was associated with lower CL_{CR} values ($p < 0.001$).

DISCUSSION

This article reports the findings of a multicenter observational study examining the frequency of ARC in critically ill patients with normal plasma renal indices at admission. Major observations include a high prevalence overall, with ~65% of patients manifesting ARC on at least one occasion in the first seven study days. ARC on day 1 is also strongly associated with higher clearances over the subsequent 6 days, a finding that is not simply related to ongoing fluid loading. Although plasma creatinine concentrations were consistently lower in those manifesting ARC, the sustained elevation in CL_{CR} and creatinine excretion rates, and the lack of any significant difference in 24-hour fluid balance, strongly suppots this assertion.

These data suggest that a significant proportion of patients will manifest sustained augmented renal solute elimination over the first week in ICU, a consideration not immediately obvious to the clinician or prescriber. Importantly, ARC will significantly impact drug pharmacokinetics for a variety of renally eliminated pharmaceuticals (such as low–molecular weight heparins, aminoglycosides, glycopeptides, and β-lactams) (2), leading to subtherapeutic concentrations and potentially adverse clinical outcomes (20–22).

Brown et al (13) reported similar data in their work examining creatinine, osmolar, and free water clearance in 50 critically ill postoperative patients. In those patients admitted to the surgical ICU with trauma, CL_{CR} values were elevated on day 1 (mean, 140 mL/min/1.73 m^2), peaked on day 4 (mean, 190 mL/min/1.73 m^2), and returned to initial levels by day 7. A strong inverse relationship was also demonstrated between age and CL_{CR}, as measured on the second postoperative day (13). Similar observations have been reported in more contemporary research (6, 9, 10, 14), whereas this study confirms these findings in a larger multicenter dataset.

The mechanisms driving such variation in renal function in the critically ill remain poorly understood. Increased major organ blood flow has been demonstrated in large animal models of Gram-negative sepsis (23), similar to changes observed in human pregnancy (24), which may promote enhanced renal solute elimination. Recent clinical investigation, however, has demonstrated at best only a weak correlation between pulse contour–derived cardiac index and CL_{CR} in critical illness (6). Of note, the high prevalence of ARC in this patient group suggests that this might represent the "expected" response to systemic inflammation, as an indicator of accessible physiological reserve. Whether the absence of ARC can be used as a useful diagnostic or prognostic indicator represents an important area for future clinical investigation.

The true biological influence of trauma and surgery in the pathogenesis of ARC remains uncertain, given the confounding influence of age (25). Specifically, age was identified as the most significant covariate in predicting the development of ARC in mixed-effects modeling, suggesting that the high prevalence in trauma may simply be a reflection of the underlying demographic. As illustrated, the trauma subgroup was almost exclusively young men, with greater body size, who were frequently ventilated. As such, systemic inflammation coupled with a greater physiological reserve may account for the higher clearances observed, rather than any unique mechanism. Although an increase in glomerular filtration in response to protein loading may also be implicated (26, 27), no difference in the provision of enteral nutrition was noted between patients with and without ARC.

Of note is the significant increase in CL_{CR} between day 1 and 2, which appears to drive some of the within subject variability, particularly in those not manifesting ARC initially. Interpreting this finding is complex, given the number of patients not completing a second CL_{CR} and the potential impact of pre-ICU care. Relatively poor renal function despite normal plasma creatinine concentrations at admission to the ICU has been previously reported (28) and may suggest the presence of "occult" AKI, in parallel with a greater disease burden. This is reflected in the higher modified SOFA scores, greater vasopressor requirements, and lower urine outputs in patients without ARC on day 1. In those remaining in the study, renal function appears to improve, possibly associated with ICU intervention or disease evolution.

Identifying a specific pattern of intrapatient variation, particularly in relation to ICU intervention, remains complex. Vasopressor administration increases renal blood flow and glomerular filtration in large animal models (29), although the relationship in critical illness is much more dynamic. The inverse association between vasopressor administration and CL_{CR} on day 1 illustrates this. Of interest, the majority of participants received norepinephrine, such that exploring the influence of differing vasoactive agents is limited in the current dataset. The true clinical significance of mechanical ventilation is also uncertain, and likely it reflects the ubiquitous nature of this intervention and longer LOS in patients with ARC. The association between frusemide administration and lower CL_{CR} is also unclear; although this may represent clinician directed diuretic therapy in the context of worsening azotemia, or overly aggressive attempts at fluid diuresis.

LIMITATIONS

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

Eight-hour collections were used as the primary outcome measure, as prior research has suggested that this time period provides the best balance between feasibility and accuracy (30). In addition, the observed creatinine excretion rates are within the range reported for the general populous (31). We acknowledge that CL_{CR} is not a "gold standard" measure of glomerular filtration (such as inulin clearance), although tubular creatinine secretion is unlikely to confound the results at higher filtration rates (32). Of note, we have not collected data on patient ethnicity, which represents an unexplored variable in this analysis.

The prevalence of ARC reported is consistent with recent data (22), although the exclusion of patients unlikely to remain in the ICU for more than 24 hours, and those with established or evolving AKI, has resulted in a select study population. This is reflected in the moderate overall APACHE II score and ICU mortality, although the majority of patients were mechanically ventilated and ~40% received vasopressor or inotrope therapy. As such, although the prevalence of ARC may be lower in the wider ICU population, this analysis provides a unique longitudinal view of CL_{CR} in a significant fraction of critically ill patients. We do not report on specific pharmacokinetic endpoints, therapeutic outcomes, or antibiotic resistance patterns; as such data were beyond the aims of this study. In addition, although ARC was associated with a longer ICU LOS, it should be recognized that this study was not designed to assess any specific clinical outcomes.

CONCLUSIONS

The findings from this prospective, multicenter, observational study suggest that a substantial group of patients will manifest significantly elevated renal solute elimination over the first 7 days in ICU, not overtly obvious to the clinician. In addition, the observation of relatively low CL_{CR} in some patients reinforces the concept that an assessment of "renal function," as opposed to simply identifying "kidney injury," is necessary. Recognition of patients at risk of ARC allows the targeted use of CL_{CR} measurement (not routine in most units) to monitor changes in renal function. Future studies should focus on expanding current knowledge regarding the implications for accurate dosing of renally eliminated pharmaceuticals in patients with ARC. In addition, given the high prevalence of ARC in this study (65.1%), further investigation to assess the potential impact on individual clinical outcomes is warranted.

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Prevalence and Risk Factors for Augmented Renal Clearance in a Population of Critically Ill Patients

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Abstract

Background: Critically ill patients show a high, albeit variable, prevalence of augmented renal clearance (ARC). This condition has relevant consequences on the elimination of hydrophilic drugs. Knowledge of risk factors for ARC helps in the early identification of ARC. The aims of this study were evaluation of (1) risk factors for ARC and (2) the prevalence of ARC in critically ill patients over a period of 1 year. **Methods:** A retrospective cohort study was performed for all consecutive patients admitted to our intensive care unit (ICU). Augmented renal clearance was defined by a creatinine clearance $\geq$130 mL/min/1.73 m^2. "Patient with ARC" was defined as a patient with a median of creatinine clearance $\geq$130 mL/min/1.73 m^2 over the period of admission. Four variables were tested, Simplified Acute Physiology Score II (SAPS II), male gender, age, and trauma as cause for ICU admission. An analysis (patient based and clearance based) was performed with logistic regression. **Results:** Of 475 patients, 446 were included in this study, contributing to 454 ICU admissions and 5586 8-hour creatinine clearance (8h-CL_{CR}). Overall, the prevalence of patients with ARC was 24.9% (n = 113). In a subset of patients with normal serum creatinine levels, the prevalence was 43.0% (n = 104). Of the set of all 8h-CL_{CR} measurements, 25.4% (1418) showed ARC. In the patient-based analysis, the adjusted odds ratio was: 2.0 (confidence interval [CI]:1.1-3.7; $P < .05$), 0.93 (CI: 0.91-0.94; $P < .01$), 2.7 (CI: 1.4-5.3; $P < .01$), and 0.98 (CI: 0.96 -1.01; $P = .15$), respectively, for trauma, age, male sex, and SAPS II. In the clearance-based analysis, the adjusted odds ratio were 1.7 (CI: 1.4-1.9; $P < .01$), 0.94 (CI: 0.932-0.942; $P < .01$), and 2.9 (CI: 2.4-3.4; $P < .01$), respectively, for trauma, age, and male sex. **Conclusions:** Trauma, young age, and male sex were independent risk factors for ARC. This condition occurs in a considerable proportion of critical care patients, which was particularly prevalent in patients without evidence of renal dysfunction.

Keywords
critical care, epidemiology, augmented renal clearance, risk, creatinine clearance, antibiotics

Introduction

In critical care setting, renal function is usually assessed based on a dichotomous point of view: Kidneys are working normally or have distinct levels of acute renal injury, eventually involving the initiation of renal replacement therapy. This classic understanding excludes, potentially, a large number of patients who show a functional state characterized by a renal enhanced capacity of elimination of circulating solutes.[1,2] This underidentified condition, named augmented renal clearance (ARC),[2] has been increasingly reported in the medical literature in recent years, where most representative studies in the critical care setting show prevalence between 28% and 65%.[3-10] The majority of antimicrobial drugs are subject to renal elimination which is the main excretion mechanism for the β-lactams (penicillins, cephalosporins, carbapenems, and monobactams), glycopeptides, and aminoglycosides. Although it does not need specific therapy, ARC has important pharmacokinetic implications in the treatment of critically ill patients. More specifically, considering the drugs that are predominantly eliminated by the kidneys, it is expected that in patients showing ARC, usual or even maximal recommended drug dosing will most probably not achieve the desired therapeutic levels. Indeed, these consequences have been described

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in several studies from different countries.[11-14] In practical terms, this means that critically ill patients with sepsis showing ARC are potentially exposed to undertreatment, jeopardizing one of the fundamental cornerstones of the treatment of sepsis—adequate antibiotherapy.[11,13,15-18] In addition, ARC is clinically silent and only an adequate measure of urinary clearance is able to accurately identify this particular group of patients, given the inadequacy and inaccuracy of the mathematical estimates of glomerular filtration rate (GFR).[19] Therefore, the identification of risk factors for ARC in the critically ill patient is of paramount importance, allowing early signaling of the potential patient requiring optimization of therapy, particularly in the scenario of antibiotic therapy. In recent medical literature, trauma, young age, and male sex are among the most frequent conditions associated with ARC. Other factors inconsistently associated with ARC include illness severity, mechanical ventilation, high blood pressure, vasopressor, diuretic treatment, and less positive fluid balance.[20,21] However, the studies presenting these results were not specifically designed for the evaluation of risk factors for ARC.

The aims of our study were to examine, during 1 year and in a large cohort of mixed intensive care unit (ICU) patients, (1) the prevalence of ARC and (2) the strength of the association between ARC condition and 4 hypothesized risk factors—Simplified Acute Physiology Score II (SAPS II), trauma as cause of ICU admission, age, and sex of the patient.

Materials and Methods

Study Design

This single-center observational study was conducted in a 20-bed mixed adult ICU at the Coimbra University Hospitals (CHUC, Coimbra, Portugal). Data were collected retrospectively over a 12-month period from all consecutive adult patients admitted to the ICU. Critically ill patients from coronary, heart surgery, and transplantation units were treated elsewhere in the hospital (files were not available), as they were not included in this cohort. This study was approved by the Human Research Ethics Committee of Coimbra University Hospitals (CHUC-112-13), which waived the need for informed consent.

Study Population

Patients were eligible for inclusion if the anthropomorphic data registry (height and weight) was available, if a urinary catheter with hourly quantified urine was present, and a daily measured urinary creatinine clearance (CL_{CR}) was performed. This measure involves a standard urinary collection via an indwelling catheter between 23:00 hours and 07:00 hours as part of our daily routine procedure, following evaluation of urine and blood creatinine concentrations. Patients with anuria were excluded. We performed 2 distinct but complementary types of analysis of the data: (1) a patient-based analysis, considering the average CL_{CR} present in every patient during the ICU admission period, and (2) a CL_{CR}-based analysis, corresponding to all the observed patient-days (herein designated as creatinine clearance days). In some subset of the study, urine samples with contemporaneous (ie, on the same day) serum creatinine (S_{CR}) $\geq$1.2mg/dL were excluded. The rationale was that elevated levels of S_{CR} are almost never associated with ARC[6,10,22,23]; therefore, with the exclusion of these patients with low probability of showing ARC, we intended to increase the specificity of risk assessment. Values of CL_{CR} <5 were rounded up to 5 mL/min/1.73 m^2. Values of CL_{CR} >600 mL/min/1.73 m^2 were excluded because they were considered severe outliers. Anthropomorphic, demographic, and clinical data were collected. In the patient-based risk analysis (odds ratio [OR] and adjusted OR [$_A$OR]), only patients with a length of stay (LOS) more than 48 hours were considered, to get a minimum of 3 CL_{CR} measurements per patient and to avoid bias related to early death occurrence or less severe patients. In the CL_{CR}-based risk analysis (OR and adjusted OR), the samples showing contemporaneous S_{CR} <1.2 mg/dL were taken into consideration only. The cause of ICU admission was grouped into 3 groups: trauma, medical, or surgical. The last category was considered if the patient had major surgery in the previous 72 hours, whether elective or urgent. All the patients who had major trauma were included in the "trauma" category, independent of the surgical procedure. For the study of age categories, the cutoff defined was 50 years old.

Definitions

The DuBois and DuBois formula was used to calculate body surface area (BSA) as follows: BSA = 0.007184 × (height [cm])$^{0.725}$× (weight [kg])$^{0.425}$. Body mass index (BMI) was calculated according to the formula: BMI = mass (kg)/height^2 (m^2). Obesity was defined as BMI $\geq$30 kg/m^2. A modified SAPS II was calculated without considering the age factor. Creatinine used in the study was isotope dilution mass spectrophotometry traceable. A daily 8-hour renal creatinine clearance (8h-CL_{CR}) was used throughout the ICU admission period. Calculation of the 8h-CL_{CR} was performed according to the formula: 8h-CL_{CR} = ($Urinary_{CR}$ × $Urinary_{8h\text{-}Output}$/$Serum_{CR}$ × 480) × 1.73/BSA mL/min/m^2. ARC was defined as an 8h-CL_{CR} $\geq$130 mL/min/1.73 m^2. If a patient had a median of the 8h-CL_{CR} during the ICU admission period above or equal to 130 mL/min/1.73 m^2, he would be classified as "patient with ARC."[6]

Statistical Analysis

Quantitative data are presented as the median and interquartile range (quartile 1 [Q1] and Q3, respectively, corresponding to the percentile 25th and 75th percentile), and qualitative data are presented as n (%). For comparative tests on continuous variables, the Mann-Whitney *U* test was used. Differences in categorical variables were calculated using Fisher exact test. Correlations were assessed with the Spearman correlation coefficient (rS). A logistic regression model was developed to evaluate the risk factors associated with ARC, in univariate and multivariate analyses. Odds ratio and $_A$OR were calculated for each factor. Hosmer-Lemeshow and Nagel R^2 statistic were used to assess good fit. The method used in logistic regression was the "Enter." The outcome variable values are "non-ARC patient" and "ARC patient." The predictor variable values are "Male" and "Female" for sex, "Trauma" and "No Trauma" for trauma, SAPS II, and age values "<50 years" and "≥50 years" for the age-group. All requirements for the application of logistic regression were verified.

Statistical significance was defined as a *P* value <.05, and statistical analysis was performed using SPSS (IBM Corp. SPSS Statistics for Macintosh, version 24.0) and MedCalc 9.3.8 for Windows (MedCalc, Mariakerke, Belgium).

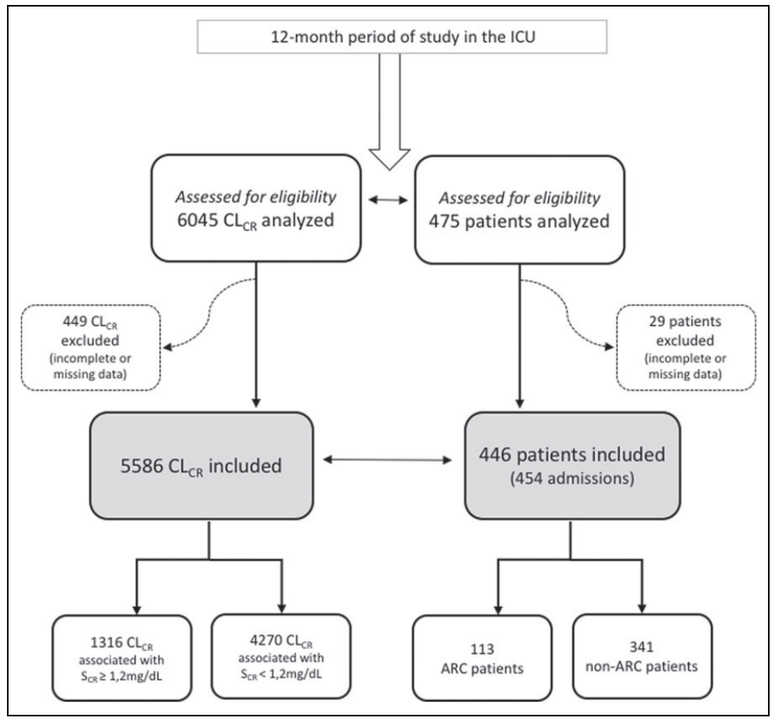

Figure 1. Diagram displaying study participant and 8-hour renal creatinine clearance (CL_{CR}) selection. ARC indicates augmented renal clearance; S_{CR}, serum creatinine.

Results

During this 1-year study period, 475 patients were admitted to our ICU (corresponding to 495 ICU admissions) contributing to 6045 8h-CL_{CR}. Of these, 446 patients (corresponding to 454 ICU admissions) were eligible for the study, contributing to 5586 evaluable 8h-CL_{CR} (Figure 1).

Patient-Based Analysis

The main characteristics and results of the patients corresponding to the 454 admissions are shown in Table 1. The medical cause was the main reason for ICU admission (n = 203, 44.7%). The median of ICU LOS was 12 (6.8-24), 9 (4-16.5), and 8 (4-13) days, respectively, for trauma, surgical, and medical group of patients ($P < .01$). We identified 120 (26%) of 454 obese patients.

The prevalence of patients with ARC (median value of 8h-CL_{CR} during the ICU admission period above or equal to 130 mL/min/1.73 m^2) was 24.9% (113/454) when considering all the studied population and was 43.0% (104/242) after exclusion of patients who showed $S_{CR} \geq$ 1.2 mg/dL at any point during the ICU stay. One hundred twenty-five patients (125/454; 27.5%) showed ARC in half of the admission days (number of ARC days in the ICU/number of days in the ICU). Comparison between patients with ARC and non-ARC patients is shown in Table 2, illustrating the distinct characteristics of both groups. The ICU mortality was significantly lower in patients with ARC (12.4 vs 25.5%, $P < .01$). The SAPS II was 37 (28-46) and 43 (36-52)for ARC and non-ARC patients, respectively ($P < .01$). Body mass index was similar in both

Table 1. Baseline Characteristics of the Studied Population (454 admissions).[a]

Demographics	Results
Patients, n	446
Readmissions, n	8
Male sex, n (%)	293 (64.5)
Age, years	66 (52-76)
Patients with age ≥50 years n (%)	359 (79.1)
Weight, kg	75 (65-85)
BMI, kg/m^2	26.7 (24.2-30.4)
BSA, m^2	1.82 (1.72-1.95)
Admission days	9 (4-17)
APACHE II	17 (14-22)
SAPS II	41 (34-51)
Mechanical Ventilation, n (%)	445 (98%)
ICU mortality, n (%)	101 (23)
Urine output on D_1, mL	2230 (1553-3085)
Fluid resuscitation on D_1, mL	2000 (1542-2600)
Diabetes, n (%)	82 (18.2)
8h-CL_{CR}, mL/min/1.73 m^2	86.4 (89.5)
Patients with $S_{CR} \geq$ 1.2 mg/dL, n (%)[b]	212 (46.7)
ARC patients (total), n (%)[c]	113 (24.9)
ARC patients (exclusion of those with $S_{CR} \geq$ 1.2 mg/dL), n (%)[b]	104 (43.0)
ICU Admission group diagnosis	
Trauma, n (%)	110 (24.2)
Surgical, n (%)	141 (31.1)
Medical, n (%)	203 (44.7)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ARC, augmented renal clearance; BMI, body mass index; BSA, body surface area; D_1, first 24 hours at the ICU; SAPS, Simplified Acute Physiology Score; S_{CR}, serum creatinine; ICU, intensive care unit; 8h-CL_{CR}, 8-hour measured urinary creatinine clearance.
[a]Quantitative variables were expressed as median (first quartile-third quartile).
[b]At any point during ICU stay.
[c]Patients with a median of 8h-CL_{CR} ≥130 mL/min/1.73 m^2 during ICU stay.

groups (27 vs 26 kg/m^2, respectively, for non-ARC and ARC group). Figures 2 to 4 show the difference in medians of 8h-CL_{CR} within sex, group of <50 or ≥50 years, and the presence of trauma (as a cause for ICU admission). Of the 113 patients with ARC, 90 (79.6%) were men (Table 2). The correlations between 8h-CL_{CR} and fluid volume resuscitation, urine output, and fluid overload in the first ICU day were rS = 0.17 ($P < .01$), rS = 0.31 ($P < .01$), and rS = −0.13 ($P < .01$), respectively. No correlation was present between modified SAPS II and 8h-CL_{CR} (rS =0.08, $P = .1$).

Of the total admissions, 403 (corresponding to 392 patients) patients had an LOS higher than 48 hours. In the univariate analysis, the OR for ARC of trauma, male, age-group < 50 years, SAPS II, and age were 4.2 (confidence interval [CI]: 2.6-6.8; $P < .01$), 2.5 (CI: 1.5-4.3; $P < .01$), 6.5 (CI: 3.8-10.9; $P < .01$), 0.96 (CI: 0.94-0.98; $P < .01$), and 0.92 (CI: 0.90-0.94; $P < .01$), respectively. A multivariate analysis was performed including 4 covariates (trauma, age, sex, and SAPS II). This analysis showed an $_A$OR for ARC of 2.0 (CI: 1.1-3.7; $P < .05$), 0.93 (CI: 0.91-0.94; $P < .01$), 2.7 (CI: 1.4-5.3; $P < .01$), and 0.98 (CI: 0.96 -1.01; $P = .15$) for trauma, age, male sex, and SAPS II, respectively. Using age categories instead of age, the $_A$OR was 4.5 (CI: 2.5-8.0; $P < .01$) for age <50 years. The obtained results of the Nagelkerke R^2 and of the Hosmer-Lemeshow test (0.42 and $P = .14$, respectively) indicate a good fit of the model. The SAPS II, age, sex, and trauma were slightly associated. Age and SAPS II were weakly correlated (rS < 0.4). However, no problems of multicollinearity were detected in the model.

When considered together, the group of patients (n = 35) presenting these 3 risk factors (trauma, male sex, and age younger than 50) showed a prevalence of ARC of 80% (28/35). The specificity of this combination of risk factors for ARC identification was 98% (334/341; 95% CI: 95.8%-99.2%). The differences in 8h-CL_{CR} between this group and the reminiscent patients (n = 419) were 171 versus 82 mL/min/1.73 m^2 ($P < .01$).

Creatinine Clearance–Based Analysis

A total of 5586 CL_{CR} measurements were gathered, originating an equivalent number of clearance days, of which 4270 (76%) had contemporaneous S_{CR} <1.2 mg/dL (Table 3). The most contributive patients were those belonging to the medical group, with 2117 (37.9%) urine samples corresponding to an equivalent number of 8h-CL_{CR} measurements. Values between 60 and 129 mL/min/1.73 m^2—group II—were the most frequently found (n = 2107, 37.7%). Group I (<60 mL/min/1.73 m^2) was present in 2060 measurements (36.9%) corresponding to 178 patients. Group III (>129 mL/min/1.73 m^2) was present in 1419 measurements, of which 1146 (81%) belonged to male patients. The median and IQR of 8h-CL_{CR} were 117.5 (81.3-167.2) for the group of trauma samples and 61.9 (28.2-108.7) mL/min/1.73 m^2 for the nontrauma samples—$P < .01$. When considering only the samples showing contemporaneous S_{CR} <1.2 mg/dL (n = 4270), the median and IQR CL_{CR} were 123.3 (87.6-170.9) and 86.9 (56.6-128.8) mL/min/1.73 m^2, respectively, for trauma and nontrauma samples ($P < .01$). Additional relevant results are shown in Table 3.

Age, sex, and trauma were slightly associated. However, no problems of multicollinearity were detected in the model. Multivariate analysis showed an $_A$OR for ARC of 1.7 (CI: 1.4-1.9; $P < .01$), 0.94 (CI: 0.932-0.942; $P < .01$), and 2.9 (CI: 2.4-3.4; $P < .01$) for trauma ICU admission, age, and male sex, respectively. The Hosmer-Lemeshow test showed a $P < .01$, which could be related to the large sample size, making the adjustment of the model more difficult. However, the Nagelkerke R^2 value of 0.34 indicated a good fit of the model.

Discussion

In this retrospective observational study performed in a large cohort of critically ill patients, corresponding to 454 patients and 5586 clearance days, ARC occurred very frequently: 24.9% of all studied ICU population showed an average 8h-CL_{CR} equal or higher than 130 mL/min/1.73 m^2 (patients with ARC) and 25.4% of all clearance days were higher than 130

Table 2. Comparison between 2 Groups of ICU Patients According to the Exhibition of ARC.[a]

	ARC, n = 113[b]	Non-ARC, n = 341	*P*
Male sex n (%)	90 (79.6)	203 (59.5)	<.001
Age, years	50 (36-69)	70 (50-79)	<.001
Patients with age ≥50 years n (%)	59 (52.2)	300 (88.0)	<.001
Weight, Kg	79 (70-90)	72 (65-82)	<.01
BMI, kg/m^2	26 (24-30)	27 (24-30)	ns
BSA, m^2	1.87 (1.80-2.0)	1.81 (1.71-1.91)	<.01
Admission days	9 (5-17)	9 (4-17)	ns
Fluid resuscitation on D_1, mL	2155 (1844-2789)	1998 (1496-2500)	<.05
Urine output on D_1, mL	2498 (1946-3448)	2113 (1465-2930)	<.05
Fluid overload on D_1, mL	−143 (−889 to +369)	56 (−967 to +988)	<.05
Diabetes, n (%)	10 (12.2)	72 (21.2)	<.01
ICU mortality, n (%)	14 (12.4)	87 (25.5)	<.01
8h-CL_{CR}, mL/min/1.73 m^2	160 (144-189)	61.5 (28.8-99.1)	<.001
Presence of $S_{CR} \geq$ 1.2 mg/dL, n (%)[c]	9 (8.0)	203 (59.5)	<0.001
ICU admission group diagnosis			
Trauma, n (%)	51 (45.1)	59 (17.3)	<.001
Surgical, n (%)	30 (26.5)	111 (32.6)	<.001
Medical, n (%)	32 (28.3)	171 (50.1)	<.001

Abbreviations: ARC, augmented renal clearance; BMI, body mass index; BSA, body surface area; ICU, intensive care unit; S_{CR}, serum creatinine; 8h-CL_{CR}, 8-hour measured urinary creatinine clearance; NS, nonsignificant.
[a]Quantitative variables were expressed as median (first quartile-third quartile).
[b]Patients with a median of 8h-CL_{CR} ≥130 mL/min/1.73 m^2 during ICU stay.
[c]At any point during ICU stay.

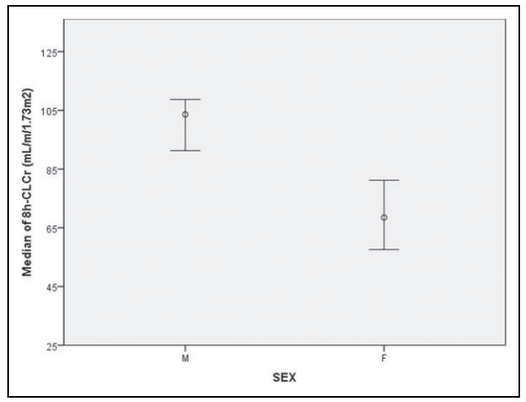

Figure 2. Median and 95% confidence interval of 8-hour measured urinary creatinine clearance (8h-CL_{CR}, mL/min/1.73 m^2) differences according to sex (M, male; F, female). $P < .01$.

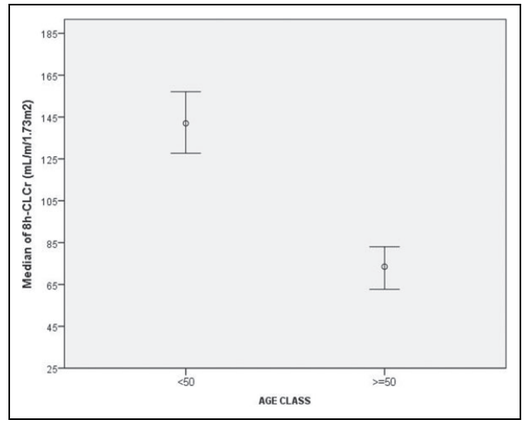

Figure 3. Median and 95% confidence interval of 8-hour measured urinary creatinine clearance (8h-CL_{CR}, mL/min/1.73 m^2) differences, according to the age-group (cutoff of 50 Years). $P < .01$.

mL/min/1.73 m^2 (group III; Table 1 and 3, respectively). In addition, we demonstrated, by the multivariate analysis, trauma as the cause for ICU admission, and age of the patient and male sex were significant independent risk factors for ARC.

Longitudinal investigations in mixed ICU studying a significant number of clearance days (n > 500) for the evaluation of prevalence of ARC are scarce in the medical literature. De Waele et al retrospectively analyzed the epidemiologic features of ARC in a mixed 1081 ICU patients, during a period of 15 months, and found that this condition was present in 36.6% of the 4472 clearance days. Of note, these authors identified a higher prevalence of patients showing ARC in half of the ICU admission days when compared to our data (60.9% vs 27.2%).[7] Three other studies analyzed 1660, 664, and 599 clearance days and observed a prevalence of ARC of 65.1%, 55.6%, and 51.6%, respectively.[5,6,9] Our results are in line with these studies, confirming the high prevalence of ARC in critically ill patients. These data reinforce the idea that ARC is probably ubiquitous in every ICU around the world and is often

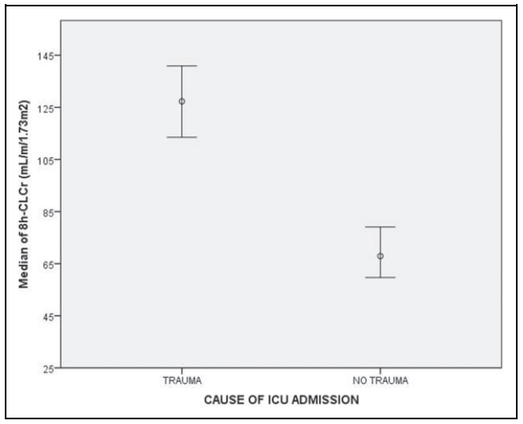

Figure 4. Median and 95% confidence interval of 8-hour measured urinary creatinine clearance (8h-CL_{CR}, mL/min/1.73 m^2) differences according to the cause of admission (trauma vs nontrauma). $P < .01$.

Table 3. Baseline Characteristics of the Studied Urine and Blood Samples Contributing to the Calculation of 8-h CL_{CR}.[a]

Variable	Results
Urine samples, n	5586
Urine samples from patients with trauma, n (%)	1769 (31.7)
Urine samples from surgical patients, n (%)	1700 (30.4)
Urine samples from medical patients, n (%)	2117 (37.9)
Urine samples with contemporaneous S_{CR} <1.2mg/dL, n (%)	4270 (76)
Urine samples form patients with trauma, n (%)	1631 (38.2)
Urine samples form surgical patients, n (%)	1193 (27.9)
Urine samples form medical patients, n (%)	1446 (33.9)
8h-CL_{CR}, mL/min/1.73 m^2 (all patients)	81.5 (39.1-130.1)
8h-CL_{CR}, mL/min/1.73 m^2 (trauma)	117.5 (81.3-167.2)
8h-CL_{CR}, mL/min/1.73 m^2 (surgical)	63.6 (27.8-116.8)
8h-CL_{CR}, mL/min/1.73 m^2 (medical)	61.2 (28.4-103.8)
S_{CR}, mg/dL	0.7 (0.7-1.13)
BUN, mg/dL	25.0 (16-41)
8h-Urine output, mL	770 (520-1070)
8h-CL_{CR} Groups	
Group I: <60 mL/min/1.73 m^2, n (%)	2060 (36.9)
Group II: 60 – 129 mL/min/1.73 m^2, n (%)	2107 (37.7)
Group III: ≥130 mL/min/1.73 m^2, n (%)	1419 (25.4)

Abbreviations: BUN, blood urea nitrogen; S_{CR}, serum creatinine; 8h-CL_{CR}, 8-hour measured urinary creatinine clearance.
[a]Quantitative variables were expressed as median (first quartile-third quartile).

overlooked. In addition, these data underline the importance of the measurement of CL_{CR} in the ICU (via urine output monitoring of a predetermined period of time), which constitutes a unique tool to identify patients with ARC, given that mathematical estimates of GFR lack sensitivity and accuracy to identify ARC.[19,24] Considering the predominant renal elimination of the most common antibiotics used in the ICU setting (β-lactams, glycopeptides, and aminoglycosides), ignoring the increased clearance of hydrophilic antibiotics will result in subtherapeutic levels after usual drug dosing, jeopardizing the efficient treatment of the septic critically ill patient.

Nowadays, physiopathology of ARC is poorly understood and probably has a multifactorial etiology, involving endogenous and exogenous causes. On the one hand, inflammatory activity, hyperdynamic status, and metabolic modifications all concur with the increase in GFR.[25-27] On the other hand, exogenous factors such as aggressive fluid therapy and some diuretics can contribute to the additional increase in GFR. One possible explanation is that ARC reflects the recruitment of the functional renal reserve of healthy persons when exposed to acute stress injury. Notably, the literature shows that pregnant women and living donors after nephrectomy can manifest ARC.[28-30] Young male patients are among the most frequently associated with ARC, which fits in the concept of renal reserve; indeed, from a physiological point of view, although of controversial magnitude, male sex exhibits higher values of GFR and renal flow.[31,32] In our study, the majority (79.6%) of patients with ARC were men, and as much as 81% of clearance days ≥130 mL/min/1.73 m^2 belonged to male patients.

The GFR declines with normal aging, mainly driven by a physiological process, the reason for which we will expect both lower CL_{CR} and renal reserve.[33,34] Accordingly, our study shows that patients with ARC were significantly younger than non-ARC patients: 50 (36-69) versus 70 (50-79) years old, respectively ($P < .001$). When the analysis was performed within age categories (cutoff: 50 years), the differences were much more significant, with only 12% of the non-ARC patients (n = 41) showing age below 50 years. Conversely, almost half of patients with ARC were <50 years old (n = 54, 47.8%).

Several studies recently reported that patients with multiple trauma, concurrently with traumatic brain injury (TBI), seem to be at increased risk of developing ARC, including studies with noncritically ill patients.[9,23,35-37] Such association seems logical for several reasons: (1) severe trauma, including TBI, typically is more frequent in men[38]; (2) patients admitted after severe trauma are usually younger than other groups of patients, thus with higher functional renal reserve; (3) trauma usually is a sudden and unforeseeable event (traffic accident, work, or ludic activity), affecting primarily previously healthy persons, therefore with a preserved renal (and other organs) physiology; (4) according to current guidelines,[39] patients with severe trauma and hypotension are frequently treated with significant amount of intravenous fluids, leading to an increase in the cardiovascular index, renal flow, and urine output; and (5) a direct correlation seems to exist between cerebrovascular pressure reactivity index and renal creatinine clearance, providing a link between brain and kidney.[35,40]

In our study, despite trauma being the less represented group (110 patients, 24%; Table 2), this subset of patients contributed to the majority (38.2%) of measured 8h-CL_{CR} (samples with contemporaneous S_{CR} <1.2 mg/dL; Table 3). In addition, samples from trauma patients showed significantly higher median 8h-CL_{CR} (117.5 mL/min/1.73 m^2) when compared to the other

2 groups (medical and surgical; Table 3). Remarkably, of the 113 patients with ARC, almost half (45.1%) originated from the trauma group. On the other hand, a significantly lower prevalence was reported within the surgical and medical groups (26.5% and 28.3%, respectively; Table 2).

While trauma, male, age, and SAPS II are naturally related, we performed a multivariate analysis showing that the adjusted risk for ARC was 2.7 times higher in male, 2 times higher in trauma patient, and was 0.93 for age (meaning that the risk of ARC decreased 7% for each more year of life). The SAPS II was not associated with ARC. After performing similar analysis but considering the total number of clearance days obtained (samples showing contemporaneous S_{CR} < 1.2 mg/dL), we observed adjusted risks for ARC of 2.9, 1.7, and 0.94 (6% less probable of showing ARC for each more year of life) for male, trauma, and age, respectively.

Although several studies have shown a significant association between trauma and ARC,[23,35,41] to the best of our knowledge, only 3 studies investigated the risk factors for ARC through multivariate analysis. Udy et al[8] identified trauma and age younger than 50 years as independent risk factors for ARC, with an $_{A}$OR of 16.1 (95% CI: 3.0-87.7) and of 28.6 (95% CI: 4.4 to 187.2), respectively; the described very high $_{A}$OR for age and trauma could probably be attributed to the characteristics of the study, using a convenience sample of multitrauma patients and critically ill patients with sepsis as part of another primary study.[8,42] Ruiz et al also showed that age ≤58 years and admission diagnosis of polytrauma were independent predictors of ARC, although their study was not primarily designed to study risk evaluation for ARC.[10] Third, in a retrospective and observational study, Minville et al[23] concluded that age and trauma were independently correlated with 24h-CL_{CR} above 120 mL/min/1.73 m^2 in a population of 284 critically ill stable patients.

Our results are in line with these studies, confirming that trauma and young age are independent risk factors for ARC. Additionally, we demonstrated, for the first time in a mixed nonselected cohort of medical, neurocritical, and surgical critically ill patients, that male sex was a strong and independent risk factor for this condition (ARC). Two other studies also observed an independent association between ARC and male sex; however, these investigations were conducted in specific groups of ICU individuals—trauma patients[36] or patients under antibiotic treatment.[5] In our study, the combination of these 3 risk factors (trauma, young age, and male sex) showed a very high specificity for ARC (98%). In other words, only 2% of patients without these 3 risk factors showed ARC.

The association between illness severity and ARC has been described inconsistently in the medical literature.[3,5,8,23,43-45] The SAPS II was not a risk factor for ARC in our study. This interaction may be misleading because of the inclusion of age in the definition of SAPS II score.

As shown in Table 2, ICU mortality was significantly lower in patients displaying ARC. This apparent "protective effect" of the ARC condition can likely be explained by the younger age and higher organ physiological reserve reported in patients with ARC.

There was a weakly positive correlation between 8h-CL_{CR} and fluid volume resuscitation and between 8h-CL_{CR} and urine output in the first day. Conversely, the correlation was negative (although equally weak) regarding the amount of fluid overload in the first ICU day. This is reflected by the modest differences in medians within the 2 groups (Table 2). Previous investigators found either a similar tendency or no significant differences between patients with ARC and non-ARC patients, suggesting further studies are needed to elucidate the role of fluids and urine output on the frequency of ARC manifestation.[3,9,46,47]

Several limitations need to be considered when evaluating this study. Firstly, this was a single-center study, and therefore, our results may not apply to other clinical settings. However, we underline that this was a longitudinal study over a 12-month period, in a multipurposed ICU of a tertiary hospital with a large case mix, and we included a very significant number of patients with 8h-CL_{CR} measurements; actually, to the best of our knowledge, our study involved the highest number of 8-hour clearance days reported (n = 5586). Secondly, the contribution of each patient to the study was unbalanced, potentially leading to the violation of the principle of independency. However, we used the median of the 8h-CL_{CR} during ICU admission and excluded patients with an LOS ≤48 hours, which presumably attenuated this effect. In addition, the risk evaluation that we performed included 2 different (but complementary) pathways: a "patient-based" and a "clearance day–based" analysis, both showing similar results, regarding $_{A}$OR for trauma, age, and sex. Thirdly, power analysis and sample size calculation were not calculated before the study was performed. However, we did not have ethics constraints imposing a minimum number of patients to be admitted to this investigation, given the observational nature of this study. In addition, the methodology of this study proposed a time-based analysis as a way to overcome the expected demographic variability of ICU admissions related to seasonality. Fourthly, we intentionally excluded from our analysis other factors that have been sporadically associated with ARC, such as mechanic ventilation, diuretic therapy, vasopressor therapy, sepsis, febrile neutropenia, hematological malignancies, and hepatic cirrhosis. However, at our ICU, the rate of nonventilated patients/year with an LOS >48 hour was very low (<3%), and the frequency of admission of patients with hepatic cirrhosis, febrile neutropenia, and/or hematological malignancies was under 1%, making inadequate such analysis of risk. On the other hand, the majority of our ICU patients were receiving diuretic and vasopressor therapy, making this specific analysis impossible, considering the design of our study. Regarding sepsis and ARC, considering its etiological, clinical, and diagnostic complexity, we believe that a primary prospective study specifically directed to this subject would be more appropriate. Finally, since data collection was retrospective, the quality of the information depends on the quality of the data collection. In addition, clinical files of critically ill patients from coronary, heart

surgery, and transplantation units were not available and were not included in this cohort, precluding the generalization of our findings to these particular groups of patients.

Conclusion

In the present study, we found a high prevalence of ARC (24.9%) in this cohort of critically ill patients. The prevalence was especially high in a subgroup of patients with normal values of S_{CR} during ICU admission (43.0%). In addition, this study demonstrated that 3 factors independently predicted ARC condition in critically ill patients: male sex, age (particularly if <50 years), and trauma (as the cause of ICU admission). These predictors, despite nonmodifiable, can be easily recognized and can help identify risk of ARC and anticipate decisions regarding antibiotic dosing intensification, namely, in ICUs where the measurement of the urine creatinine clearance is not performed on a daily basis.

Authors' Note

João Pedro Baptista and Paulo Jorge Martins conceived the study. João Pedro Baptista collected and structured data, performed statistical analyses, and drafted the manuscript. Margarida Marques advised on statistical analysis. João Pedro Baptista, Paulo Jorge Martins, and Jorge Manuel Pimentel revised the manuscript. All the authors read and approved the final manuscript. The results of this study were presented in part as a poster at the ESICM 29th Annual Congress in Milan (2016). All data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of Conflicting Interests

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CHAPTER 4

A COMPARISON OF ESTIMATES OF GLOMERULAR FILTRATION IN CRITICALLY ILL PATIENTS WITH AUGMENTED RENAL CLEARANCE

Baptista JP, Udy AA, Sousa E, Pimentel J, Wang L, Roberts JA, Lipman J.
Crit Care. 2011 Jun 8;15(3):R139.

ACCURACY OF THE ESTIMATION OF GLOMERULAR FILTRATION RATE WITHIN A POPULATION OF CRITICALLY ILL PATIENTS

Baptista JP, Neves M, Rodrigues L, Teixeira L, Pinho J, Pimentel J.
J Nephrol. Aug 2014;27(4):403-10.

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CRITICAL CARE

RESEARCH Open Access

A comparison of estimates of glomerular filtration in critically ill patients with augmented renal clearance

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Introduction: Increasingly, derived estimates of glomerular filtration, such as the modification of diet in renal disease (MDRD) equation and Cockcroft-Gault (CG) formula are being employed in the intensive care unit (ICU). To date, these estimates have not been rigorously validated in those with augmented clearances, resulting in potentially inaccurate drug prescription.

Methods: Post-hoc analysis of prospectively collected data in two tertiary level ICU's in Australia and Portugal. Patients with normal serum creatinine concentrations manifesting augmented renal clearance (ARC) (measured creatinine clearance (CL_{CR}) > 130 ml/min/1.73 m^2) were identified by chart review. Comparison between measured values and MDRD and CG estimates were then undertaken. Spearman correlation coefficients (r_s) were calculated to determine goodness of fit, and precision and bias were assessed using Bland-Altman plots.

Results: Eighty-six patients were included in analysis. The median [IQR] measured CL_{CR} was 162 [145-190] ml/min/1.73 m^2, as compared to 135 [116-171], 93 [83-110], 124[102-154], and 108 [87-135] ml/min/1.73 m^2 estimated by CG, modified CG, 4-variable MDRD and 6-variable MDRD formulae. All of the equations significantly underestimated the measured value, with CG displaying the smallest bias (39 ml/min/1.73 m^2). Although a moderate correlation was noted between CL_{CR} and CG (r_s = 0.26, P = 0.017) and 4-variable MDRD (r_s = 0.22, P = 0.047), neither had acceptable precision for clinical application in this setting. CG estimates had the highest sensitivity for correctly identifying patients with ARC (62%).

Conclusions: Derived estimates of GFR are inaccurate in the setting of ARC, and should be interpreted with caution by the physician. A measured CL_{CR} should be performed to accurately guide drug dosing.

Introduction

Accurate assessment of renal function in the critically ill is essential, not only to detect acute kidney injury, but also for the appropriate prescription of pharmaceuticals and timely application of therapeutic strategies. Although the kidneys have a range of functions in normal homeostasis, the glomerular filtration rate (GFR) remains the most widely accepted index of renal function in both health and disease [1]. Largely, any assessment of GFR in clinical practice focuses on identifying renal impairment, where serum creatinine concentrations are typically employed as a key biomarker for this purpose. In respect to drug prescription, elevated serum creatinine concentrations regularly trigger dose reduction for renally excreted drugs, although the converse-increasing drug dosing in response to low serum values-is infrequently considered in clinical practice.

To further improve the sensitivity of such measures to screen for and monitor chronic kidney disease (CKD), Levey and colleagues have developed a formula to estimate the glomerular filtration rate (eGFR) from serum creatinine concentrations and readily available demographic variables [2]. Although initially developed in a cohort of ambulatory out-patients with CKD, the modification of diet in renal disease (MDRD) equation has

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been widely adopted in clinical practice, and is now routinely reported by laboratories worldwide. In particular, there has been an increasing trend to use such measures to modify drug dosing, although concerns have been raised about such practice [3]. Perhaps a more familiar estimate of renal function in optimising drug dosing is that defined by the Cockcroft-Gault equation. Initially described in 1976 in a small cohort of male patients [4], this equation has been widely employed as a surrogate of GFR in both clinical and research practice, although its role in the critically ill remains uncertain.

Importantly, these mathematical estimates fail to consider the important effects of the underlying disease process and additional therapies provided, both of which may significantly alter renal function from baseline. Although ideal filtration markers (such as inulin) have been employed in a research setting, they are infrequently available in clinical practice. Similarly, radionucleotide measures of GFR are expensive and impractical in the ICU. As such, a measured renal creatinine clearance (CL_{CR}) is possibly the easiest and most accurate measure of GFR routinely available to the intensive care clinician.

Given the established concerns regarding the use of estimates of GFR in the critically ill [3], this *post-hoc* investigation was aimed at characterising the accuracy of four commonly used equations in comparison with a measured CL_{CR} in a sub-group of patients exhibiting augmented renal clearance (ARC) or 'supra-normal filtration'. The primary end-point was the precision and bias of these estimates compared with CL_{CR} measures.

Materials and methods

Study population

This study represents a *post-hoc* analysis of prospectively collected data from two multi-disciplinary tertiary level ICUs in Portugal (20 beds) and Australia (30 beds). The only major patient groups not represented include: paediatric, postoperative cardiac surgical patients and solid organ transplant recipients. Patients enrolled in prospective antibacterial pharmacokinetic studies undertaken between 2005 and 2009 at each centre were eligible for inclusion. All patients had to display normal renal function, determined by serum creatinine concentrations less than 1.4 mg/dl (124 μmol/l), without the requirement for renal replacement therapy. Informed consent was obtained from all participants or a surrogate decision maker, and institutional ethics approval was provided at each facility (Australia: Royal Brisbane and Women's Hospital Human Research Ethics Committee, References 2005/038, 2005/072, 2007/188, and Portugal: Innovation and Development Unit, Coimbra University Hospital, Reference 23/IDU/09/A). From this cohort, a sub-group of patients demonstrating ARC (measured CL_{CR} >130 ml/min/1.73 m^2) were identified. Standard definitions for SIRS, sepsis, severe sepsis or septic shock were employed [5]. Diagnostic groups included trauma, sepsis, respiratory failure without sepsis, post-operative patients without sepsis and others.

Measurement of CL_{CR} and calculation of mathematical estimates

An 8-hour renal creatinine clearance was utilised in Australia, while a 24-hour collection was employed in Portugal, representing differing practice at each institution. This technique involves a standard urinary collection (via an indwelling catheter) for the defined time period, following which the creatinine concentration is measured in both urine and blood. The measured CL_{CR} is then calculated according to the equations presented in Table 1. Both centres employ automated analysers using a modified Jaffe technique (alkaline picrate). Reported reference ranges for serum creatinine concentrations are 0.6-1.3 mg/dl (53-115 μmol/l) in Portugal, and 0.8-1.2 mg/dl (73-108 μmol/l) in Australia. The mathematical estimates of GFR chosen for comparison included: Cockcroft-Gault (CG), modified CG, 4-variable and 6-variable MDRD formulae (Table 1). As the studies were conducted prior to implementation of an isotope dilution mass spectrometry (IDMS) traceable assay, the original '186' 4-variable MDRD equation was employed (see Table 1).

Statistical analysis

Data are presented as the mean (SD) or median [IQR] as appropriate. Correlations were assessed using a scatter graph and Spearman correlation coefficient (r_s). A Wilcoxon Signed Rank test was used to compare paired data, where as one-way ANOVA, and Kruskal-Wallis were used for sub-group analysis. Precision and bias were assessed using a Bland-Altman plot, with the bias representing the mean difference between each variable, and precision being one SD from the mean. Statistical significance was defined as a p-value < 0.05, and all statistical analysis employed SPSS 13.0® (SPSS, Chicago, IL) and MedCalc 9.3.8 for Windows® (MedCalc, Mariakerke, Belgium).

Table 1 Calculations employed

Formulae
24 hour $CL_{CR} = (U_{CR} \times U_{Vol}/S_{CR} \times 1440) \times 1.73/BSA$
8 hour $CL_{CR} = (U_{CR} \times U_{Vol}/S_{CR} \times 480) \times 1.73/BSA$
$BSA = 0.007184 \times (Ht)^{0.725} \times (Wt)^{0.425}$
CG CL_{CR} = (140-Age) × Wt × 1.73/(S_{CR} × 72 × BSA) × 0.85 if female
Modified CG CL_{CR} = if S_{CR} <1, use 1
4-variable MDRD eGFR = $186 \times S_{CR}^{-1.154} \times age^{-0.203} \times 1.210$ if black × 0.742 if female
6-variable MDRD eGFR = $170 \times S_{CR}^{-0.999} \times BUN^{-0.17} \times S_{Alb}^{0.318} \times Age^{-0.176} \times 1.18$ if black × 0.762 if female

BSA, body surface area (m^2); BUN, blood urea nitrogen (mg/dl); CG CL_{CR}, Cockcroft-Gault creatinine clearance (ml/min/1.73 m^2); CL_{CR} , creatinine clearance (ml/min/1.73 m^2); eGFR, estimated glomerular filtration rate (ml/min/1.73 m^2); Ht, height (cm); MDRD, modification of diet in renal disease; S_{Alb}, serum albumin concentration (g/dl); S_{CR}, serum creatinine concentration (mg/dl); U_{CR}, urinary creatinine concentration (mg/dl); U_{Vol}, urinary volume (ml); Wt, weight (Kg).

Results

Two hundred and nine patients in total were enrolled in studies at each centre. Demographic details of these cohorts are provided in Table 2. Of these, 86 (Australia *n* = 43, Portugal *n* = 43) were identified as manifesting ARC (CL_{CR} > 130 ml/min/1.73 m^2). Demographic and therapy specific data for this sub-group are also presented. All patients manifesting ARC (*n* = 86) demonstrated a systemic inflammatory response syndrome (SIRS) or sepsis on the day of measurement, with a maximum serum creatinine concentration of 1.26 mg/dl (111 μmol/l) being recorded. Of the patients, 58% were admitted after a trauma, 27% with sepsis, 7% with respiratory failure without sepsis, 3.5% were post-surgical without sepsis and 4.7% had another diagnosis (see Table 2).

A direct comparison between each assessment technique is presented in Table 3 and graphically in Figure 1. As demonstrated, each mathematical estimate was significantly lower than the median measured CL_{CR} value. Although a statistically significant correlation was noted between CL_{CR} and CG (*P* = 0.017), modified CG (*P* = 0.044) and 4-variable MDRD (*P* = 0.047) estimates, the strength of these correlations was poor, with Spearman coefficients (r_s) less than 0.3. The modified CG estimates demonstrate better correlation in the Portugal cohort (*P* = 0.017), although this remains very weak (r_s = 0.36). Using a cut-off for ARC of more than 130 ml/min/1.73 m^2, CG estimates had the greatest sensitivity, correctly identifying 53 (62%) of the cohort. The 4-variable and 6-variable MDRD formulae were less accurate, with sensitivities of 47% and 29%, respectively (see Figure 1 andTable 3).

Bland-Altman plots are presented in Figures 2, 3, 4 and 5. Summary values for each equation overall and at each centre separately are presented in Table 4. As demonstrated, all of the formulae had poor clinical utility in terms of their precision and bias, although CG estimates appeared to perform better in the Australian setting. Examining the relation between the observed

Table 2 Demographic data

Variable	Portugal (*n* = 120)	Australia (*n* = 89)
Male/Female, n (%)	87 (72.5)/33 (27.5)	64 (71.9)/25 (28.1)
Age, years, mean (SD)	55.9 (21.1)	40.0 (18.9)
APACHE II, mean (SD)	17.2 (6.1)	18.2 (7.4)
Diagnosis, n (%)		
Trauma	56 (46.7)	40 (44.9)
Sepsis	38 (31.7)	39 (43.8)
Respiratory failure (without sepsis)	13 (10.8)	2 (2.2)
Post-operative (without sepsis)	7 (5.8)	3 (3.4)
Other	6 (5.0)	5 (5.6)
	ARC Subgroup (*n* = 86)	
Male/Female, n (%)	66 (76.7)/20 (23.3)	
Age, years, median (IQR)	35 (25-51.2)	
Weight, kg, median (IQR)	80 (70-90)	
Height, m, median (IQR)	1.7 (1.68-1.76)	
BSA, m^2, median (IQR)	1.93 (1.81-2.07)	
APACHE II, mean (SD)	14.8 (5.8)	
SIRS (on day of study), n (%)	86 (100)	
Septic (on day of study), n (%)	65 (75.6)	
Mechanical ventilation (on day of study), n (%)	83 (96.5)	
Vasoactive drugs (on day of study), n (%)	24 (27.9)	
Diuretic (on day of study), n (%)	35 (40.7)	
Fluid balance (on day of study), ml, mean (SD)	311 (1640)	
Serum creatinine, mg/dl (μmol/l), median (IQR)	0.7 (0.6-0.9) (62 (53-80))	
Measured CL_{CR}, ml/min/1.73 m^2, median (IQR)	162 (145-190)	

APACHE, acute physiology and chronic health evaluation; ARC, augmented renal clearance; BSA, body surface area; CL_{CR}, creatinine clearance; IQR, interquartile range; SD, standard deviation; SIRS, systemic inflammatory response syndrome.

Table 3 Correlation between different measures of glomerular filtration

	Median (IQR) (All, *n* = 86)	r_s (*P*-value) (All, *n* = 86)	r_s (*P*-value) (Portugal, *n* = 43)	r_s (*P*-value) (Australia, *n* = 43)
Measured CL_{CR}, ml/min/1.73 m^2	162 (145-190)			
CG, ml/min/1.73 m^2	135 (116-171)*	0.26 (0.017)	0.29 (0.059)	0.29 (0.056)
Modified CG, ml/min/1.73 m^2	93 (83-110)*	0.22 (0.044)	0.36 (0.017)	0.05 (0.732)
4-variable MDRD, ml/min/1.73 m^2	124 (102-154)*	0.22 (0.047)	0.22 (0.161)	0.24 (0.122)
6-variable MDRD, ml/min/1.73 m^2	108 (87-135)*	0.18 (0.097)	0.25 (0.105)	0.11 (0.490)

* *P*<0.01 when compared with measured CL_{CR}.
CG, Cockcroft Gault; CL_{CR}, creatinine clearance; IQR, interquartile range; MDRD, modification of diet in renal disease; r_s = Spearman correlation coefficient.

difference (as a percentage) and the average value, weak correlations were identified for CG (r_s = -0.34, *P* = 0.002), 4-variable MDRD (r_s = -0.31, *P* = 0.004), and 6-variable MDRD (r_s = -0.32, *P* = 0.003) estimates, suggesting a small negative proportional error. No correlation was identified with the modified CG formula (see Figures 2, 3, 4 and 5 and Table 4).

There was no significant correlation between fluid balance (r_s = 0.16, *P* = 0.13) or acute physiology and chronic health evaluation (APACHE) II score (r_s = 0.03, *P* = 0.776) and the measured CL_{CR}. Although the daily fluid balance was considerably more negative in those who received diuretics (-541 (1207) ml vs 895 (1651) ml, *P*<0.001), there was no significant difference in CL_{CR} (158 (141-179) vs 164 (147-208) ml/min/1.73 m^2, *P* = 0.20). Neither fluid balance (*P* = 0.31), nor CL_{CR} (*P* = 0.17) were significantly different between diagnostic categories, and there was no difference in CL_{CR} in those receiving vasoactive medications (159 (141-169) vs 166 (150-196) ml/min/1.73 m^2, *P* = 0.11).

Discussion

Our results demonstrate that in critically ill patients exhibiting ARC, mathematical estimates of GFR are insensitive in identifying this phenomenon. Clinicians will often consider renal function in both their choice and dose of pharmaceuticals, in particular antibacterial agents. For example, using a previously published population pharmacokinetic model of vancomycin in the critically ill [6], required daily dosing could vary by as much as 1000 mg when using estimated versus measured values. Significantly, lower dose selection could predispose to sub-therapeutic drug exposure, treatment failure or the selection of drug-resistant strains [7], and as such, clinicians should be cautious when employing such estimates of GFR in this setting.

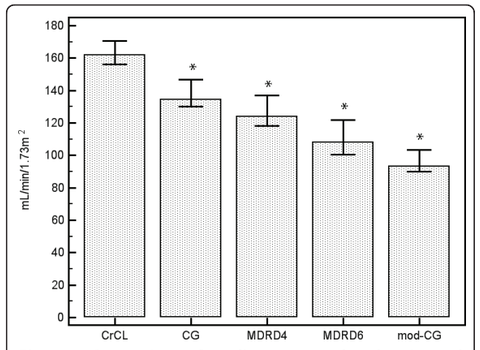

Figure 1 Comparison of median measured and estimated glomerular filtration rate. Median values (95% confidence interval) for measured and estimated glomerular filtration rate. All mathematical equations significantly underestimate the measured value,'star' indicates *P*<0.01 when compared with measured creatinine clearance (CL_{CR}). The modified Cockcroft-Gault (modCG) formula performs the most poorly in this setting. CG, Cockcroft-Gault; MDRD_4, 4-variable modification of diet in renal disease equation; MDRD_6, 6-variable modification of diet in renal disease equation.

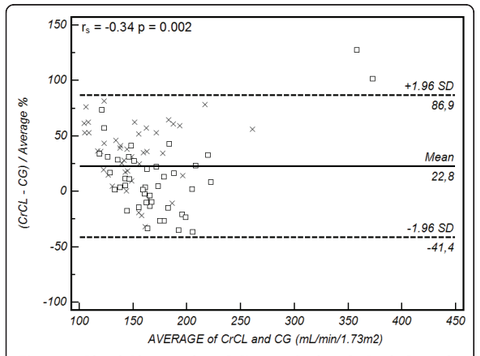

Figure 2 Bland-Altman plot of CL_{CR} vs Cockcroft Gault formula. Comparison of the difference between the measured creatinine clearance (CL_{CR}) and Cockcroft Gault (CG) formula (as a percentage) on the y-axis, versus the average value obtained on the x-axis. The solid line represents the bias (mean percentage difference obtained across the range of values), where as the dashed lines are the limits of agreement (+/- 1.96 × standard deviation (SD)). square, Australia cohort; cross, Portugal cohort. The Spearman correlation coefficient (r_s) for the percentage difference and average value is provided in the top left hand corner (outliers excluded).

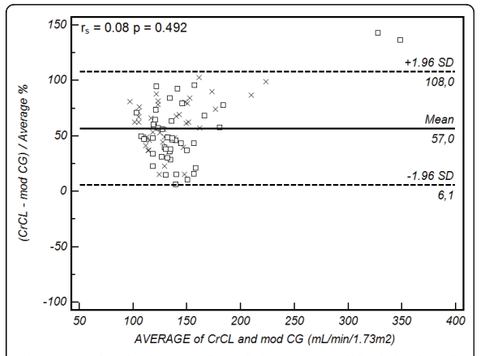

Figure 3 Bland-Altman plot of CL_{CR} vs modified Cockcroft Gault formula. Comparison of the difference between the measured creatinine clearance (CL_{CR}) and modified Cockcroft Gault (modCG) formula (as a percentage) on the y-axis, versus the average value obtained on the x-axis. The solid line represents the bias (mean percentage difference obtained across the range of values), where as the dashed lines are the limits of agreement (+/- 1.96 × standard deviation (SD)). square, Australia cohort; cross, Portugal cohort. The Spearman correlation coefficient (r_s) for the percentage difference and average value is provided in the top left hand corner (outliers excluded).

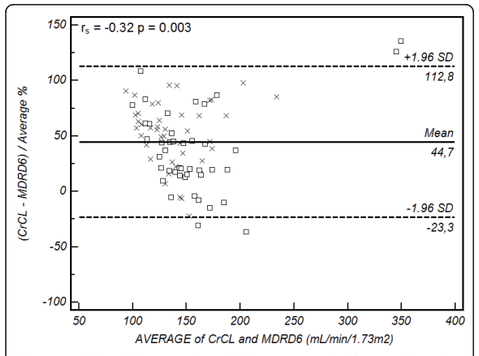

Figure 5 Bland-Altman plot of CL_{CR} vs 6-variable modification of diet in renal disease equation. Comparison of the difference between the measured creatinine clearance (CL_{CR}) and 6-variable modification of diet in renal disease equation (MDRD_6) (as a percentage) on the y-axis, versus the average value obtained on the x-axis. The solid line represents the bias (mean percentage difference obtained across the range of values), where as the dashed lines are the limits of agreement (+/- 1.96 × standard deviation (SD)). square, Australia cohort; cross, Portugal cohort. The Spearman correlation coefficient (r_s) for the percentage difference and average value is provided in the top left hand corner (outliers excluded).

Figure 4 land-Altman plot of CL_{CR} vs 4-variable modification of diet in renal disease equation. Comparison of the difference between the measured creatinine clearance (CL_{CR}) and 4-variable modification of diet in renal disease equation (MDRD_4) (as a percentage) on the y-axis, versus the average value obtained on the x-axis. The solid line represents the bias (mean percentage difference obtained across the range of values), where as the dashed lines are the limits of agreement (+/- 1.96 × standard deviation (SD)). square, Australia cohort; cross, Portugal cohort. The Spearman correlation coefficient (r_s) for the percentage difference and average value is provided in the top left hand corner (outliers excluded).

Ours is not the first study to raise concerns about the validity of these equations in the non-CKD population. Herrera-Gutierrez *et al.* in their work comparing 2-hour versus 24-hour CL_{CR} measurements in the ICU, also examined the accuracy of Cockcroft-Gault estimates [8]. In 359 recently admitted patients, the mean 24-hour CL_{CR} was 100.9 ± 4.21 ml/min/1.73 m^2, as compared with 87.4 ± 3.05 ml/min/1.73 m^2 when determined by Cockcroft-Gault [8]. The reported bias was 21.87 ml/min/1.73 m^2 with a precision of ± 58.27 ml/min/1.73 m^2. Importantly, this was largely generated by those patients with a CL_{CR} of more than 100 ml/min/1.73 m^2 [7], and compares favourably with our study. A similar result was also noted by Martin *et al.* in 109 critically ill patients, where only a weak correlation was demonstrated between 24-hour measured CL_{CR} and Cockcroft-Gault estimates [9].

Cherry *et al.* have also examined measured CL_{CR} versus mathematical estimates in a cohort of critically ill and traumatised patients. In 100 patients (45 trauma victims), Cockcroft-Gault estimates significantly underestimated the mean 24-hour CL_{CR} (CL_{CR} = 103.2 ± 5.7 ml/min vs CG CL_{CR} = 86.2 ml/min ± 4.2) [10], although separate investigators have suggested a modified Cockcroft-Gault equation is reliable in stable trauma patients [11]. In comparison, although approximately 60% of the

Table 4 Precision and bias between measured CL_{CR} and mathematical estimates

	All patients(n = 86)		Portugal patients (n = 43)		Australia patients (n = 43)	
	Bias	**Precision**	**Bias**	**Precision**	**Bias**	**Precision**
CG, ml/min/1.73 m^2, (%)	39 (23)	± 75 (33)	50 (34)	± 47 (28)	28 (12)	± 96 (34)
Modified CG, ml/min/1.73 m^2, (%)	84 (57)	± 70 (26)	83 (61)	± 42 (21)	85 (53)	± 93 (30)
4-variable MDRD, ml/min/1.73 m^2, (%)	48 (30)	± 76 (34)	56 (38)	± 52 (30)	41 (22)	± 97 (36)
6-variable MDRD, ml/min/1.73 m^2, (%)	68 (45)	± 76 (35)	73 (52)	± 48 (29)	63 (37)	± 99 (38)

CG, Cockcroft Gault; CL_{CR}, creatinine clearance; MDRD, modification of diet in renal disease.

patients in this study were victims of trauma, significant numbers required mechanical ventilation, vasoactive medications or were septic on the day of the study.

Hoste *et al.* examined the relation between a measured 1-hour CL_{CR} and Cockcroft-Gault, 6-variable and 4-variable MDRD estimates in recently admitted critically ill patients with normal serum creatinine concentrations [12]. Twenty-eight older (median age 58 years) moderately sick (median APACHE II 21) patients were included, with a measured CL_{CR} of 86 (62.6-121.6) ml/min/1.73 m^2 [12]. Of note, only the 6-variable MDRD equation had any degree of statistical correlation with the measured value (R = 0.466, P = 0.012), and biases were much lower than reported in our study (Cockcroft-Gault -6.2, 6-variable MDRD 11.2, 4-variable -9.4 ml/min/1.73 m^2) [12]. Importantly, a significant number of these patients (n = 13) had renal impairment (CL_{CR} <80 ml/min/1.73 m^2), despite a normal serum creatinine concentration. This is in agreement with data provided by Poggio *et al.* noting similar levels of bias in ill hospitalised patients with moderate renal dysfunction, as compared with iothalamate measures of GFR [13].

More recently, Martin *et al.* have examined the use of MDRD and Cockcroft-Gault estimates in a cohort of primarily head injured or burnt patients with normal serum creatinine concentrations. Measured 8-hour CL_{CR} values were significantly elevated (median 163 (124-199) ml/min), and substantial bias was reported with both mathematical formulae (-12 ml/min/1.73 m^2 4-variable MDRD, 17 ml/min Cockcroft-Gault CL_{CR}) [14]. Of note, significant improvement in MDRD performance was seen with correction for anthropomorphic measures [14]. Conil *et al.* have also noted the pitfalls of using such equations in patients with burn injuries, reporting a mean measured 24-hour CL_{CR} of 119 ± 53 ml/min/1.73 m^2, compared with 98 ± 38 ml/min/1.73 m^2, and 101 ± 52 ml/min/1.73 m^2 with 4-variable MDRD and Cockcroft-Gault estimates, respectively [15]. A significant negative bias was noted with both equations.

These data confirm that these commonly employed estimates of GFR are largely flawed in the critically ill, and should be viewed with caution in this setting. Our study extends this prior work, with analysis in a selected population of patients exhibiting ARC (CL_{CR} >130 ml/min/1.73 m^2). Although a relatively new term, ARC reflects supra-normal renal excretion of circulating solute [16], and is being increasingly recognised in the ICU environment [17,18], largely as a consequence of the underlying inflammatory state and therapeutic interventions provided [19]. Of note, the sub-group manifesting ARC in our analysis were primarily young male traumatised patients, and is in keeping with recent work by Minville *et al.*, demonstrating elevated CL_{CR} in polytrauma victims [20].

The implications of this phenomenon primarily relate to the potential for sub-therapeutic drug exposure, and treatment failure. This is reinforced by research demonstrating a close correlation between drug elimination and CL_{CR} [21,22], in addition to data provided by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), demonstrating that mathematical estimates of GFR can result in up to about 20% discordance in drug-dosing recommendations, depending on the equation employed [23]. This is likely to be even higher in those manifesting ARC, because the population reported had significantly lower measured GFRs (mean (standard deviation) GFR-75 (44) ml/min) [23], compared with those observed in this analysis.

This study has a number of potential limitations. Firstly, it represents a *post-hoc* analysis of prospectively collected data. Secondly, an 8-hour CL_{CR} was employed in Australia, while a 24-hour collection was performed in Portugal, although previous authors have demonstrated acceptable agreement when using either technique [10,24]. Importantly, our data demonstrate that mathematical estimates have poor clinical utility in comparison to either measure. Thirdly, calibration of creatinine assays can also introduce systematic bias, but as both laboratories use the same analytical process, this should be limited. Fourthly, it could be considered that our patients were not at 'steady-state' and as such, the serum creatinine concentrations are systematically lower than might be expected. However, there was no significant correlation between fluid balance and CL_{CR}, and vasoactive medications, diuretic administration, and admission diagnosis had no influence on the measured value. Finally, although CL_{CR} is not considered a gold standard measure of GFR (due to tubular secretion of creatinine at lower filtration rates) [25], in the population under study (CL_{CR} >130 ml/min/1.73 m^2), this is unlikely to be a major cause of error.

Examining our data closely, two patients appeared to have CL_{CR} values that were well outside the 'normal' range, and as such, lack biological plausibility (Figures 2, 3, 4 and 5). These 'outliers' likely represent a random error in measurement, although on repeated inspection, no specific fault could be identified. These results are reported in order to maintain the integrity of the dataset, but must be viewed with caution. Repeating the analysis after removing these values (n = 84), continued to demonstrate clinically unacceptable bias and precision (Cockcroft-Gault CL_{CR} 30 ± 47 ml/min/1.73 m^2, modified Cockcroft-Gault CL_{CR} 75 ± 39 ml/min/1.73 m^2, 4-variable MDRD 40 ± 52 ml/min/1.73 m^2, and 6-variable MDRD 59 ± 49 ml/min/1.73 m^2) as compared with the measured values.

Conclusions

In conclusion, this study has demonstrated that commonly employed estimates are inaccurate in quantifying GFR in a sub-group of critically ill patients with ARC. Both Cockcroft-Gault and MDRD derived values significantly underestimate the measured CL_{CR} and are insensitive in identifying this phenomenon. This has important ramifications for adequate dosing of various pharmaceuticals in this setting, particularly antibacterial agents. Clinicians should be cautious in altering prescriptions on the basis of mathematical estimates alone. Instead we recommend the routine use of measured CL_{CR} as a surrogate of GFR in the ICU.

Key messages

- A significant proportion of critically ill patients will have creatinine clearances well above the normal reference range, a phenomenon termed ARC.
- Creatinine clearance is closely correlated with renal drug elimination.
- Mathematical estimates of GFR and creatinine clearance are flawed in the critically ill, and will tend to significantly under-estimate renal function in those with ARC.
- Altering drug prescription on the basis of these estimates is likely to lead to sub-therapeutic drug concentrations, promoting the possibility of treatment failure.

Abbreviations

APACHE: acute physiology and chronic health evaluation; ARC: augmented renal clearance; CKD: chronic kidney disease; CL_{CR}: creatinine clearance; eGFR: estimated glomerular filtration rate; GFR: glomerular filtration rate; MDRD: modification of diet in renal disease equation; SIRS: systemic inflammatory response syndrome.

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Authors' contributions

JB, AU, LW, ES, JR and JP were involved in protocol development, ethics approval and implementation. JB, AU and LW were involved in data acquisition. JB and AU performed the statistical analysis. JB, AU, JR and JL wrote the manuscript. AU takes responsibility for archiving the data and guarantees the integrity of the paper form inception to publication. All of the authors have read and approved the article for publication.

Competing interests

Dr Baptista has previously acted as a consultant for AstraZeneca. Dr Udy has no conflicts of interest to disclose. Dr Sousa has no conflicts of interest to disclose. Professor Pimentel has no conflicts of interest to disclose. Miss Wang has no conflicts of interest to disclose. Dr Roberts has no conflicts of interest to disclose.
Professor Lipman is a consultant to AstraZeneca and Janssen-Cilag, and has received an honorarium from AstraZeneca, Janssen-Cilag and Wyeth Australia. AstraZeneca provides an annual donation to the Burns, Trauma and Critical Care Research Center (BTCCRC), University of Queensland.

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ORIGINAL ARTICLE

Accuracy of the estimation of glomerular filtration rate within a population of critically ill patients

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Abstract
Background Accuracy of glomerular filtration rate (GFR) estimates has been questioned and several authors recommend routine use of measured renal creatinine clearance (CL_{CR}) as a surrogate of GFR in the intensive care unit (ICU). Our purpose was to compare estimates of GFR using Cockroft–Gault (CG), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease Study (MDRD) equations with 8h-CL_{CR}, within a population of critically ill patients with a wide range of measured CL_{CR}.
Methods Through a prospective, observational study of 54 patients with normal serum creatinine (sCr) admitted to ICU, daily 8h-CL_{CR} (reference method) and GFR estimates (644 paired samples) were matched and compared. Augmented renal clearance (ARC) was defined as 8h-CL_{CR} >130 ml/min/1.73 m^2.
Results No significant difference was found between mean 8h-CL_{CR} (135.5 ml/min/1.73 m^2) and CG equation (135.7 ml/min/1.73 m^2), but significant differences ($p < 0.01$) were found for the MDRD (124.4 ml/min/1.73 m^2) and CKD-EPI (107.6 ml/min/1.73 m^2) equations. Correlation between 8h-CL_{CR} and all estimates was weak ($R = 0.2$, 0.19 and 0.34, respectively). We observed poor agreement in terms of precision (40.9, 39.8 and 33.4 %, respectively). Analysing subgroups, we observed that all equations significantly underestimated 8h-CL_{CR} >120 ml/min/1.73 m^2 and overestimated 8h-CL_{CR} <120 ml/min/1.73 m^2 ($p < 0.05$). The incidence of ARC patients was 55.6 %.
Conclusions Estimates of GFR using CG, CKD-EPI and MDRD formulae are flawed in the critically ill with normal sCr, significantly underestimating renal function in those with ARC and overestimating it in those with normal or decreased 8h-CL_{CR}. Globally, the population exhibited ARC on more than half of the ICU admission days.

Keywords Acute kidney injury · Critically ill · Augmented renal clearance · Prediction equations

Introduction

Glomerular filtration rate (GFR) is the best overall measure of kidney function [1]. It is essential to detect acute kidney injury (AKI) and to identify patients with augmented renal clearance (ARC)—defined as increased renal elimination of circulating solutes and drugs as compared with normal baseline [2]. Additionally, at-bedside GFR could be the single most accessible parameter allowing appraisal of pharmacokinetic characteristics of the critically ill patient by providing an estimate of renal drug elimination [3–7].

Use of mathematical estimates of renal function has become common in the critical care setting. However, the accuracy of GFR estimates has been questioned in the medical literature and several authors recommend routine use of measured renal creatinine clearance (CL_{CR}) as a surrogate of GFR in the intensive care unit (ICU) [8–12].

This study compares the performance of estimates of GFR using Cockroft–Gault (CG), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease Study (MDRD) equations [13–15]

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Table 1 Description of the formulae used

DuBois and DuBois	$0.007184 \times [\text{height (cm)}]^{0.725} \times [\text{weight (kg)}]^{0.425}$
8h-CL_{CR}	(uCr/sCr) × (8-h urinary output/480) × (1.73/BSA)
CG	(140 − age) × weight × 1.73/(sCr × 72 × BSA) (×0.85 if female)
4-variable MDRD[a]	$175 \times \text{sCr}^{-1.154} \times \text{age}^{-0.203} \times 1.210$ (if black) (×0.742 if female)
CKD-EPI	Female ≤0.7 mg/dl: $144 \times (\text{sCr}/0.7)^{-0.329} \times 0.993^{\text{age}}$ (×1.159 if black)
	Female >0.7 mg/dl :$144 \times (\text{sCr}/0.7)^{-1.209} \times 0.993^{\text{age}}$ (×1.159 if black)
	Male ≤0.9 mg/dl: $141 \times (\text{sCr}/0.9)^{-0.411} \times 0.993^{\text{age}}$ (×1.159 if black)
	Male >0.9 mg/dl: $141 \times (\text{sCr}/0.9)^{-1.209} \times 0.993^{\text{age}}$ (×1.159 if black)

8h-CL_{CR} 8-hour renal creatinine clearance, *CG* Cockroft–Gault, *MDRD* Modification of Diet in Renal Disease Study, *CKD-EPI* Chronic Kidney Disease Epidemiology Collaboration, *sCr* serum creatinine, *uCr* urine creatinine, *BSA* body surface area

[a] The study used "isotope dilution mass spectrometry" (IDMS) traceable creatinine

with measured CL_{CR}, in a population of critically ill patients with normal range serum creatinine (sCr). In addition, the incidence of ARC during the study period was evaluated and demographic characteristics of these patients analysed.

Subjects and methods

Study population

This observational single-centre study was conducted in a 20-bed multipurpose ICU at the 1,375-bed Coimbra University Hospitals (Portugal). Patients were prospectively enrolled over 4 months, and studied throughout the admission period.

Definitions

A daily 8-h renal creatinine clearance was used throughout the ICU admission period. This technique involves a standard urinary collection (via indwelling catheter) for the 8 h period following measurement of creatinine concentration (urine and blood). Creatinine used in the study was isotope dilution mass spectrophotometry (IDMS)-traceable. ARC was defined as 8h-CL_{CR} >130 ml/min/1.73 m^2 [1, 16]. A patient was defined as an "ARC patient" if ≥50 % of measurements during the admission period were >130 ml/min/1.73 m^2. Height, weight and body surface area (BSA) were measured. Exclusion criteria were the following: (i) need for renal replacement therapy, (ii) sCr >1.3 mg/ml, (iii) known chronic kidney disease, (iv) development of AKI during the study period, as defined by the AKI Network [17], (v) age under 18 years, (vi) pregnancy, and (vii) ICU stay of less than 48 h. The formulae used are described in Table 1.

Table 2 Baseline characteristics of the studied population (54 patients)

Characteristics	All patients	ARC patients	Non-ARC patients	p
Number of patients [n (%)]	54 (100)	30 (55.6)	24 (44.4)	–
Male gender [n (%)]	39 (72.2)	25 (64)	14 (36)	**0.04**
Age [years, mean (SD)]	54.2 (16.9)	49.4 (15)	60.2 (17.5)	**0.02**
Actual body weight [kg, mean (SD)]	78.4 (19.6)	77 (18.3)	79.5 (20)	0.62
Body surface area [m^2, mean (SD)]	1.86 (0.25)	1.88 (0.24)	1.84 (0.24)	0.56
APACHE II [mean (SD)]	15.3 (6.9)	15.5 (7.9)	15.1 (5.7)	0.84
Total SOFA [median (IQR)][a]	5.3 (4)	5.0 (3.6)	5.75 (4.1)	0.78
ICU length of stay [days, median (IQR)]	12.4 (9.3)	10.6 (7)	14.6 (11.3)	0.78
28-day mortality [n (%)]	14 (26)	6 (20)	8 (33)	0.21
8h-CL_{CR} [ml/min/m^2, mean (SD)][a]	136.1 (36.6)	161.2 (27.9)	104.6 (15.5)	**<0.001**

Bold values indicate statistical significance ($p < 0.05$)

ARC augmented renal clearance, *SD* standard deviation, *IQR* interquartile range, *APACHE* acute physiology and chronic health evaluation score, *SOFA* sequential organ failure assessment score, *ICU* intensive care unit, *8h-CL_{CR}* 8-hour renal creatinine clearance

[a] Calculations used the average value during ICU admission period for each of the 54 patients

Statistical analysis

Data are presented as mean and standard deviation (SD) or median and interquartile range (IQR). Correlations were assessed with Pearson correlation coefficient (R) or Spearman correlation coefficient (r_S). A t-test or Wilcoxon Signed Rank test was used to compare paired data. The Friedman test was used to detect differences across multiple comparisons. Accuracy was assessed using a Bland–Altman plot, with bias representing the mean difference between each variable, and precision being one SD from the mean difference between each variable. Differences in categorical variables were calculated using Fisher's exact test. Statistical significance was defined as a p value <0.05, and statistical analysis employed SPSS 19.0® (SPSS, Chicago, IL, USA) and MedCalc 9.3.8 for Windows® (MedCalc, Mariakerke, Belgium).

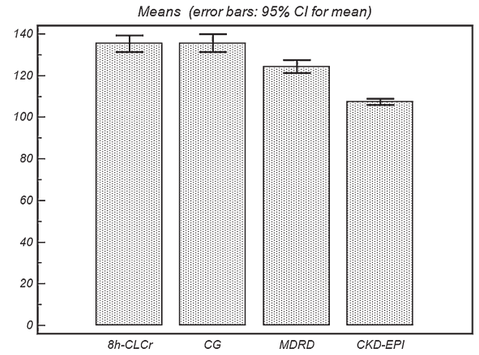

Fig. 1 Comparison of mean values and 95 % confidence interval (CI) of the glomerular filtration rate measured by 8-hour renal creatinine clearance (8h-CL_{CR}) vs. estimated by the Cockcroft–Gault (CG), Modification of Diet in Renal Disease Study (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations

Results

During the study period, 54 patients met the admission criteria, 30 of whom (55.6 %) were ARC patients. The main characteristics and results of these patients are shown in Table 2. Each patient contributed an average of 12 samples [2–47; 95 % confidence interval (CI) for the mean 9.5–14.4]. The ICU diagnostic category at admission was medical in half of the patients and trauma in 29.6 %. The total number of measured 8h-CL_{CR} was 644, ranging between 16.2 and 378.3 ml/min/1.73 m^2.

These 644 samples were matched with the respective estimates (Fig. 1) and showed no significant difference with regard to the mean values of CG (135.5 vs. 135.7 ml/min/1.73 m^2) but a significant difference regarding MDRD and CKD-EPI equations (124.4 and 107.6 ml/min/1.73 m^2, respectively; $p < 0.01$ for both). Although a statistically significant correlation was noted between 8h-CL_{CR} and all three estimates ($p < 0.05$), the strength of this correlation was poor ($R = 0.2$, 0.19 and 0.34, respectively). The Bland–Altman plot (Fig. 2) showed poor agreement between pairs of comparisons (precision of 40.9, 39.8 and 33.4 %, respectively). The difference between medians and the strength of association for each estimate according to trauma, gender, age-class and weight are presented in Tables 3 and 4.

In the 644 samples regarding the 54 patients, 320 (49.7 %) of all measured 8h-CL_{CR} showed values >130 ml/min/1.73 m^2, indicating that ARC was present on almost half of the studied admission days. All 54 patients had ARC present at least once.

We subsequently created 12 subgroups of paired measurements, according to different cut-offs of 8h-CL_{CR}. A progressive underestimation of 8h-CL_{CR} for values >120 ml/min/1.73 m^2 and a progressive overestimation for values <120 ml/min/1.73 m^2 was demonstrated, with all differences showing statistical significance ($p < 0.05$) (Fig. 3).

Considering each patient's contribution to the pool of 644 compared samples (between 2 and 47 samples of 8h-CL_{CR} per patient), we performed an equivalent data analysis considering the 54 results of 8h-CL_{CR} (the first ICU evaluation per patient). The mean 8h-CL_{CR} was 132.9, CG estimate was 116.0 ($p = 0.05$), MDRD was 105.3 ($p < 0.05$) and CKD-EPI was 100.6 ml/min/1.73 m^2 ($p < 0.05$). The correlation between the three pairs had values of $R < 0.3$, and Bland–Altman plots are shown in Fig. 4.

Discussion

This study shows that estimates of GFR are flawed in the critically ill, tending to significantly underestimate renal function in those with ARC and to overestimate renal function in those with normal or decreased renal function. Additionally, we showed that critically ill patients with normal sCr frequently exhibit ARC during ICU stay.

The evaluation of GFR in critically ill patients allows for the early identification of patients with undetected renal dysfunction or ARC, particularly for drug dosing adjustment. This information allows us to prevent, treat, or invert renal injury related to drug toxicity, and to optimise therapy regarding renally eliminated drugs, such as β-lactamic antibacterials, glycopeptides and aminoglycosides, by using alternative dosing strategies (increasing dosage, shortening intervals between drug administrations, extended or continuous infusion) that counterbalance the pharmacokinetic effects of ARC.

A recent study showed that mathematical estimates have become the standard tool for evaluation of renal function and drug adjustment calculations in 21.4 % of Spanish ICUs [18]. Despite not being the gold-standard, measurement of CL_{CR} constitutes the best method to evaluate renal function across its range, particularly in the critical care setting, where patients are non-stable by definition. Unlike

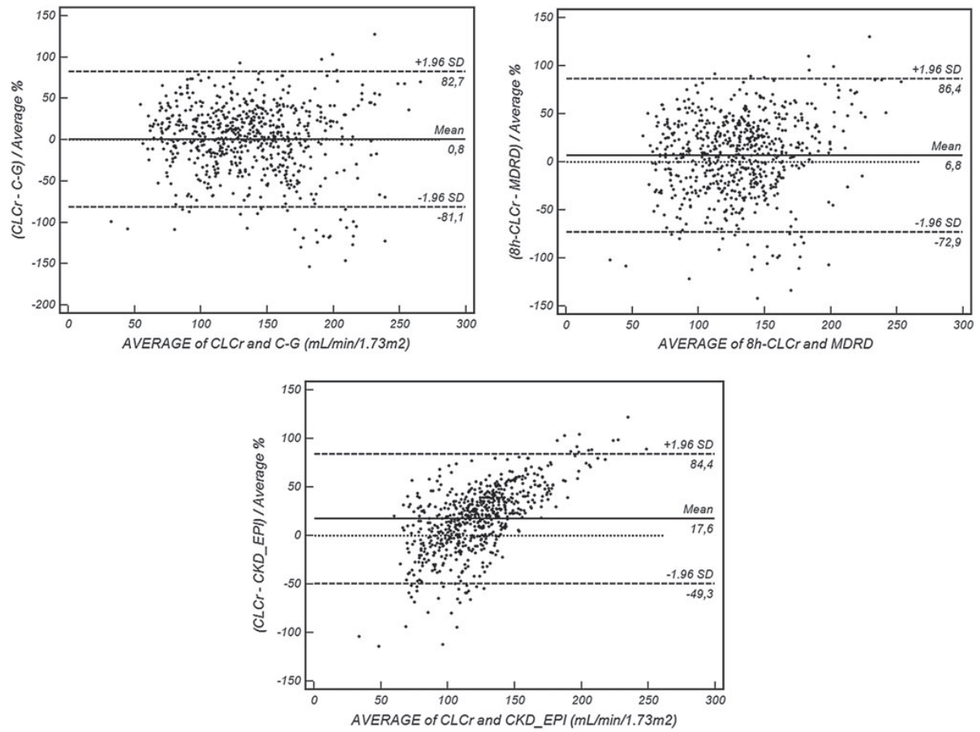

Fig. 2 Comparison as a percentage of the differences between 8-hour renal creatinine clearance (8h-CL_{CR}) and, respectively, CG, MDRD and CKD-EPI estimates. *Solid line* represents the bias (mean percentage difference). *Dashed lines* represent the limits of agreement [±1.96 × standard deviation (SD)]. *CG* Cockroft–Gault, *MDRD* Modification of Diet in Renal Disease Study, *CKD-EPI* Chronic Kidney Disease Epidemiology Collaboration

Table 3 Medians and interquartile range (IQR) for each estimate according to gender, classes of actual body weight, classes of age and trauma as cause of admission

Group	Subgroup (n)	8h-CL_{CR}	CG	MDRD	CKD-EPI
Gender	Male (503)	131.7 (101.5)	131.4 (33.5)	127.7 (50.0)*	108.8 (26.3)*
	Female (141)	121.5 (70.0)	105.1 (62.2)*	94.8 (42.3)*	99.8 (24.0)*
Actual weight	<80 kg (344)	129.5 (62.0)	118.7 (62.0)*	120.3 (60.6)*	105.7 (21.7)*
	≥80 kg (296)	129.6 (61.9)	134.3 (67.6)*	121.9 (51.8)*	105.9 (24.7)*
Age (years)	<41 (106)	157.7 (68.4)	169.1 (49.3)	151.2 (47.1)*	132.2 (14.5)*
	41–64 (302)	142.3 (45.5)	144.8 (55.9)	124.6 (48.9)*	112.4 (16.3)*
	>64 (236)	105.3 (49.0)	93.4 (45.1)*	103.1(48.9)	92.9 (14.1)*
Trauma as cause of admission	No (427)	123.5 (54.5)	119.5 (51.3)*	113.4 (49.7)*	102.7 (23.4)*
	Yes (217)	149.0 (70.0)	159.0 (70.3)	135.8 (50.1)*	119.2 (28.2)*

8h-CL_{CR} 8-hour renal creatinine clearance, *CG* Cockroft–Gault, *MDRD* Modification of Diet in Renal Disease Study, *CKD-EPI* Chronic Kidney Disease Epidemiology Collaboration

* $p < 0.05$ when compared with reference method (8h-CL_{CR})

direct measurement of GFR with inulin, nonradioactive contrast agents or radiolabelled compounds, CL_{CR} is easily performed, inexpensive and adequate for critically ill patients. In these patients, sCr is inaccurate for the detection of renal dysfunction [19]. In patients with normal sCr, a low CL_{CR} may be an early indicator of AKI. Furthermore, CG and other equations are widely employed as a surrogate of GFR in both clinical and research practice. Although estimates perform well in stable patients with or without chronic kidney disease [20], to our knowledge these formulae have not been validated in critically ill patients [8, 12, 21–25]. In a recently published observational study involving 1,317 critically ill patients and 4,019 measured 24 h-creatinine clearances (24h-CL_{CR}), Grootaert et al. [9] concluded that there is poor agreement between CG estimates and 24h-CL_{CR} >120 ml/min/1.73 m^2, with limits of agreement of −131 and +109 ml/min. Among critically ill patients with severe AKI, the CG equation tends to relatively overestimate kidney function [24, 25].

Table 4 Correlation between 8h-CL_{CR} and the tested equations (Spearman's rho)

Group	Subgroup (n)	CG	MDRD	CKD-EPI
Gender	Male (503)	0.30*	0.20*	0.35*
	Female (141)	0.55*	0.56*	0.57*
Actual weight	<80 kg (344)	0.52*	0.50*	0.51*
	≥80 kg (296)	−0.05	−0.01	0.12*
Age (years)	<41 (106)	0.24*	0.17	0.29*
	41–64 (302)	−0.20*	−0.03	−0.11
	>64 (236)	0.27*	0.32*	0.29*
Trauma as cause of admission	No (427)	0.45*	0.37*	0.49*
	Yes (217)	−0.13	−0.06	0.06
All patients	(644)	0.36*	0.28*	0.40*

8h-CL_{CR} 8-hour renal creatinine clearance, *CG* Cockroft–Gault, *MDRD* Modification of Diet in Renal Disease Study, *CKD-EPI* Chronic Kidney Disease Epidemiology Collaboration

* $p < 0.05$

The results of our study are in line with these data. The apparent equivalence of the means regarding two of the three used methods (Fig. 1)—mainly for the CG—constitutes a mathematical illusion, as a result of the balance of the over- and underestimations of GFR, when considering all 644 samples (Fig. 3). Ultimately, this illusion dissipates after analysis of correlation (weak association), and after Bland–Altman plot analysis, showing clinically unacceptable precision, thereby jeopardising the correct evaluation of GFR in a critical care setting. When considering subgroup analysis (Tables 3, 4 and additional supporting documents), we observed that CKD-EPI had the poorest performance of the three estimates and that correlation and

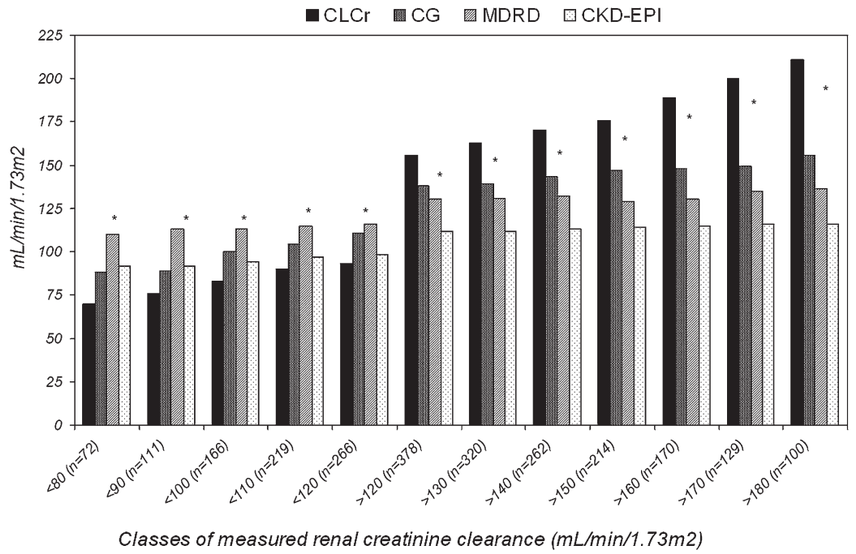

Fig. 3 Comparison of measured and estimated median values of glomerular filtration, displayed by 12 intervals of 8h-CL_{CR} (from <80 to >180 ml/min/1.73 m^2); *$p < 0.05$ vs. 8h-CL_{CR}. *CL_{CR}* renal creatinine clearance, *CG* Cockroft–Gault, *MDRD* Modification of Diet in Renal Disease Study, *CKD-EPI* Chronic Kidney Disease Epidemiology Collaboration

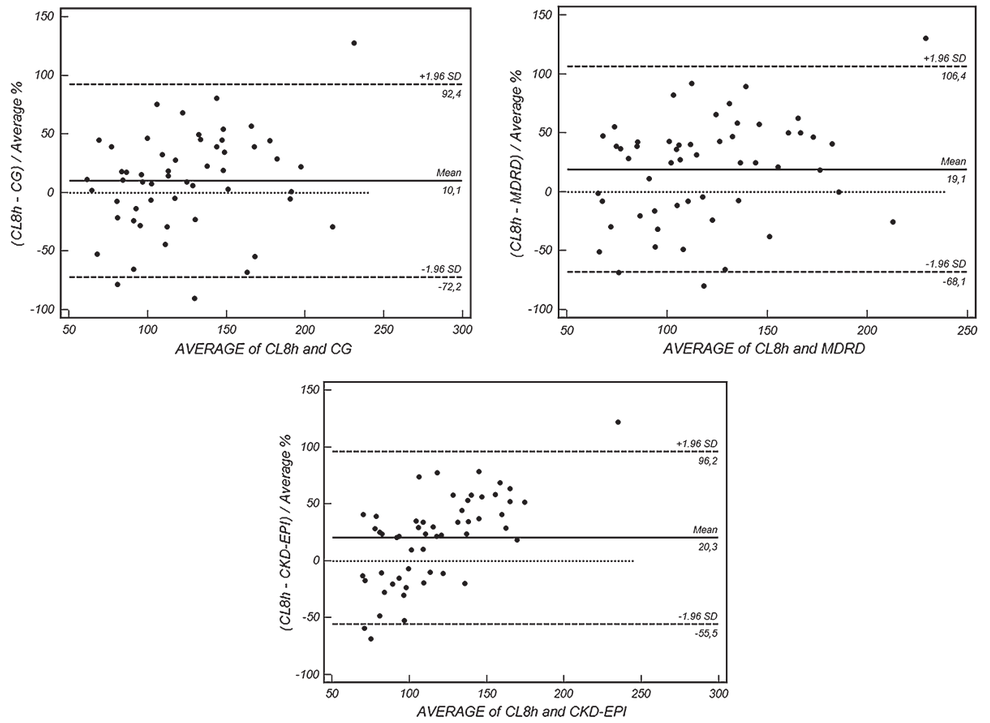

Fig. 4 Comparison as a percentage of the differences between 8-hour renal creatinine clearance (8h-CL_{CR}) and Cockcroft–Gault, MDRD and CKD-EPI estimates considering one sample per patient (n = 54). *Solid line* represents the bias (mean percentage difference). *Dashed lines* represent the limits of agreement [±1.96 × standard deviation (SD)]. *MDRD* Modification of Diet in Renal Disease Study, *CKD-EPI* Chronic Kidney Disease Epidemiology Collaboration

precision were slightly better for males, patients under 80 kg and with no trauma.

Although different authors use different cut-offs, ranging from 120 to 160 ml/min/1.73 m^2, ARC is increasingly described in the recent medical literature, with an incidence between 18 and 85 % in critically ill patients without renal dysfunction, although the extremely high latter value was found in a select group of young patients with sustained head injuries [5, 9, 26, 27]. Our study, with only 29.6 % trauma admissions, shows an ARC incidence of 49.7 % of all measured 8h-CL_{CR} (n = 644) and an incidence of 55.6 % (30/54) of "ARC patients". These patients were significantly younger (aged 49.4 vs. 60.2 years) and a significantly higher proportion were male (64 vs. 36 %) (Table 1).

The clinical relevance of correct identification of this subset of critically ill patients with ARC is related to the desirable dosing optimisation of renally eliminated drugs, such as hydrophilic antibiotics. A correlation between CL_{CR} and drug clearance has been reported for several agents [5, 26, 27] whereby ARC should be considered as a major cause of sub-therapeutic antibiotic levels, treatment failure and potential emergence of bacterial resistance in critically ill septic patients [28–30]. Nevertheless, GFR estimates by CG have low sensitivity for the identification of this group of patients (40 % for a cut-off ≥160 ml/min/1.73 m^2), compromising correct prescriptions and promoting treatment failure. The routine use of measured CL_{CR} is highly recommended as a surrogate of GFR in the ICU.

Our study has several limitations. Firstly, it was conducted in a single institution, limiting generalisation of our findings to other patient populations. Secondly, in the original description by Cockroft and Gault, the derived formula for estimation of GFR was validated for the means of two 24h-CL_{CR} measured in 236 patients. We used 8h-CL_{CR} for two reasons: it constitutes our daily practice and the 24h-CL_{CR} calculation is laborious. This factor could be a bias for imperfect urine collection, leading to clearance miscalculations. Previous authors have demonstrated acceptable agreement when using either technique [31, 32]. Thirdly, independent of the time period considered, measured CL_{CR} cannot be accepted as a gold-standard method to assess kidney function: its determination requires a steady-state situation, which is a rarely reached condition in critically ill patients. GFR can be overestimated in some patients with AKI, particularly at lower filtration rates, secondary to tubular secretion of creatinine. Finally, the contribution of each patient to the study was unbalanced, which could violate the principle of independency. However, performing the same analysis considering one sample per patient led to similar conclusions, thus conferring consistency and robustness to our data.

In conclusion, we demonstrate that in a population of patients with a large range of GFR values, the estimate equations have no clinical reliability, overestimating normal or decreased 8h-CL_{CR} values and underestimating 8h-CL_{CR} >120 ml/min/1.73 m^2. Additionally, ARC is a frequent occurrence in critically ill patients with normal sCr levels.

Conflict of interest The authors declare that they have no conflicts of interest.

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CHAPTER 5

AUGMENTED RENAL CLEARANCE IN SEPTIC PATIENTS AND IMPLICATIONS FOR VANCOMYCIN OPTIMISATION

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Augmented renal clearance in septic patients and implications for vancomycin optimisation

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ABSTRACT

The aim of this study was to evaluate the effect of augmented renal clearance (ARC) on vancomycin serum concentrations in critically ill patients. This prospective, single-centre, observational, cohort study included 93 consecutive, critically ill septic patients who started treatment that included vancomycin by continuous infusion, admitted over a 2-year period (March 2006 to February 2008). ARC was defined as 24-h creatinine clearance (CL_{Cr}) > 130 mL/min/1.73 m^2. Two groups were analysed: Group A, 56 patients with a $CL_{Cr} \leq 130$ mL/min/1.73 m^2; and Group B, 37 patients with a $CL_{Cr} > 130$ mL/min/1.73 m^2. Vancomycin therapeutic levels were assessed on the first 3 days of treatment (D_1, D_2 and D_3). Serum vancomycin levels on D_1, D_2 and D_3, respectively, were 13.1, 16.6 and 18.6 μmol/L for Group A and 9.7, 11.7 and 13.8 μmol/L for Group B ($P < 0.05$ per day). The correlation between CL_{Cr} and serum vancomycin on D_1 was −0.57 ($P < 0.001$). ARC was strongly associated with subtherapeutic vancomycin serum concentrations on the first 3 days of treatment.

1. Introduction

Achieving an adequate serum concentration of antibiotic has been a challenge through the years. This challenge is greater when it is related to septic patients admitted to the Intensive Care Unit (ICU). Affected tissues are exposed to great metabolic and haemodynamic variations and these can lead to lower efficacy of antibiotics. The early phase of sepsis is often a hypermetabolic condition leading to increased renal blood flow, glomerular filtration rate (GFR), renal creatinine clearance and clearance of renally eliminated drugs, namely antibiotics [1–4]. This situation is usually ignored by clinicians; however, even though this is underassessed, it should be considered a major cause of treatment failure and emergence of bacterial resistance in critically ill septic patients. Vancomycin has been widely used for many years as a first-choice antibiotic for nosocomial infections due to Gram-positive bacteria. Despite readily available therapeutic drug monitoring (TDM), achieving the correct serum level can be a difficult task, particularly in severely septic patients, even with repeated loading doses and daily increments in perfusion rate, usually with higher doses than normally recommended.

The aim of this study was to evaluate the influence of augmented renal clearance (ARC) on serum vancomycin levels in a population of critical septic patients.

2. Materials and methods

This study was conducted at a 1427-bed teaching hospital belonging to the University of Coimbra (Hospitais da Universidade de Coimbra, Coimbra, Portugal). In total, 93 consecutive, ventilated, adult patients with severe sepsis or septic shock, according to accepted definitions [5], who started empirical or directed treatment that included vancomycin were prospectively enrolled over the 2-year period March 2006 to February 2008. Serum levels were evaluated on the first 3 days of treatment (D_1, D_2 and D_3). Our vancomycin protocol starts with a loading dose, depending on the patient's actual weight, of 1000 mg (body weight ≤70 kg) or 1500 mg (body weight >70 kg) over 1 h, followed by continuous infusion (30 mg/kg/day) irrespective of the patient's 24-h creatinine clearance (CL_{Cr}). Thereafter, daily analysis of serum levels was performed, with 13.8–20.7 μmol/L considered the target level for adequate treatment for Gram-positive microorganisms, including lung infection [6]; if appropriate, dosage adjustment was performed on subsequent days. Vancomycin is stable for slow intravenous administration over a 24-h period [7]. At Hospitais da Universidade de Coimbra, *Staphylococcus aureus* show no resistance to vancomycin [minimum inhibitory concentration (MIC) ≤ 1 μg/mL].

ARC was defined as $CL_{Cr} > 130$ mL/min/1.73 m^2 [8–11]. Body surface area (BSA) was measured, and CL_{Cr} for the 93 patients and adjusted accordingly to create two groups, as follows: Group A (control group) with a $CL_{Cr} \leq 130$ mL/min/1.73 m^2 ($N = 56$ patients); and Group B (study group) with a $CL_{Cr} > 130$ mL/min/1.73 m^2 ($N = 37$ patients). Simplified Acute Physiology Score II and Acute Physiology

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and Chronic Health Evaluation (APACHE) II score were recorded. Diuretic and vasoactive drug use were recorded on the first day of the study. Exclusion criteria for study admission were as follows: (i) renal replacement therapy; (ii) serum creatinine concentration (S_{Cr}) > 115 μmol/L on the first day of the study; (iii) time interval between loading dose and TDM of vancomycin <12 h; and (iv) pregnant women.

2.1. Patient sampling and analytical assay

Single serum and urinary creatinine, single blood urea nitrogen (BUN) and total serum proteins, albumin and vancomycin determinations were determined each morning (7:00–7:30 am) as part of the routine procedure in this unit, as well as the urine collection over a 24-h period.

Serum vancomycin concentrations were measured using a colorimetric turbidimetric immunoassay (PETINIA; Siemens Laboratories, Deerfield, IL). The limit of detection (LOD) was 0.8 μg/mL and the intra-assay coefficient of variation (CV) was between 2.4% and 5.3%. S_{Cr} and urinary creatinine concentration (U_{Cr}) were automatically measured using alkaline picrate methodology. The normal S_{Cr} reference range for adult males and females is 62–115 μmol/L and 53–97 μmol/L, respectively. The LOD was 4.4 μmol/L for S_{Cr} and 119 μmol/L for U_{Cr}; the imprecision of the creatinine assay was <6% total CV for concentrations >88.4 μmol/L and the standard deviation (S.D.) was ≤8.8 μmol/L for concentrations ≤88.4 μmol/L. The BUN was determined automatically using urease methodology. The normal BUN reference range for adult males and females aged >50 years is 3–9.2 mmol/L and 3.5–7.2 mmol/L, respectively, and is 3.2–7.4 mmol/L and 2.5–6.7 mmol/L in the remaining ages. The LOD for BUN was 0.25 mmol/L; the imprecision of the BUN assay was <4.5% total CV. A photometric colour test for quantitative determination of total protein and albumin in human serum and plasma was performed on Hitachi chemistry analysers (Olympus Life and Material Science Europa GmbH, O'Callaghan's Mills, Ireland) according to the manufacturer's recommendations. The normal adult reference intervals are 66–83 g/L and 35–52 g/L for total protein and albumin, respectively.

2.2. Statistical analysis

Continuous variables are expressed as mean or median when applied, together with their dispersion coefficients (S.D. or interquartile range, respectively). Qualitative variables are presented as frequencies and percentages. For subgroup comparison, Student's *t*-test or Mann–Whitney *U*-test were used as indicated. The correlation between continuous variables was established using the Spearman coefficient (*rS*). Multiple regression analyses were performed in order to examine confounding effects or interactions with age and sex. A *P*-value of <0.05 was considered statistically significant.

The results were analysed with the SPSS software package v.13.0 (SPSS Inc., Chicago, IL) and with MedCalc software v.9.3.8 for Windows (MedCalc Software, Mariakerke, Belgium).

2.3. Formulae

CL_{Cr} was calculated according to formula: $CL_{Cr} = (U_{Cr}/S_{Cr}) \times (24\text{-h urinary output}/1440) \times (1.73/\text{BSA})$. The DuBois and DuBois formula was used to calculate BSA: $\text{BSA} = 0.007184 \times [\text{height (cm)}]^{0.725} \times [\text{weight (kg)}]^{0.425}$.

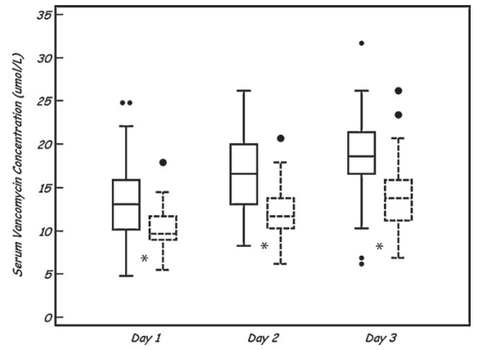

Fig. 1. Box and whisker plots showing the evolution of median (interquartile range) serum vancomycin concentrations on the studied days (Days 1–3) and comparison between Group A [control group without augmented renal clearance (ARC); continuous line] and Group B (study group with ARC; dashed line). * Indicates statistical significance for median differences ($P < 0.01$).

3. Results

The main characteristics and results of the 93 patients are shown in Table 1. In this study, 40% of the patients showed ARC. These patients were significantly younger, less severely ill, with trauma as the leading cause of admission, and with lower BUN on the first day of the study (Table 1).

In Group A, 16 patients (28.6%) were identified with $CL_{Cr} < 60$ mL/min/1.73 m^2. The total amount of vancomycin and the time interval between the loading dose and TDM of vancomycin on D_0 (the day before the first serum level analysis) was equivalent in both groups (Table 2). The serum vancomycin concentration in Group B was significantly lower than in the control group for the 3 days of the study: 13.1 vs. 9.7 μmol/L on D_1, 16.6 vs.11.7 μmol/L on D_2 and 18.6 vs.13.8 μmol/L on D_3 for Groups A and B, respectively (Fig. 1). Only four patients belonging to Group B reached therapeutic levels (>13.8 μmol/L) on D_1 (4/37; 10.8%), 11 patients on D_2 (11/35; 31.4%) and 16 patients on D_3 (16/31; 51.6%). When considering all patients, the correlation (*rS*) between age and serum vancomycin concentration on D_1 was 0.56 ($P < 0.001$) and between CL_{Cr} and D_1 serum vancomycin was −0.57 ($P < 0.001$) (Fig. 2). To assess the independence of CL_{Cr}, multiple regression analysis was performed, which showed that this effect was independent of the age and sex of the patient ($P < 0.01$).

4. Discussion

This study shows that ARC is strongly associated with subtherapeutic serum vancomycin levels in critically ill patients in the early hyperdynamic stage of severe sepsis, even in the presence of TDM. In addition, in patients with normal S_{Cr}, ARC is a frequent condition in the critical care setting (40% of septic patients in this study) and identifies a subgroup of younger and less severe critically ill patients.

Several pathological conditions, such as severe sepsis at early stage, burn injuries, acute leukaemia and severe trauma patients, exhibit hyperdynamic status, hypervolaemia and increased cardiac output, leading to augmented blood flow to major organs [2,12,13]. Subsequently, increased renal blood flow leads to raised glomerular filtration and raised clearance of renally eliminated drugs such as vancomycin. Some authors have described $CL_{Cr} > 120$ mL/min/1.73 m^2 as a frequent condition in recently

Table 1
Baseline characteristics of the studied population (93 patients) in Group A [control group without augmented renal clearance (ARC)] and Group B (study group with ARC).

	All patients (*N* = 93)	Group A (*N* = 56)	Group B (*N* = 37)	*P*-value
Males [*n* (%)]	69 (74.2)	40 (71.4)	29 (78.4)	N/S
Septic shock incidence [*n* (%)]	30 (32.3)	20 (35.7)	10 (27.0)	N/S
Urine output (mL/day) [mean (S.D.)]	2618 (826)	2459 (740)	2862 (899)	<0.05
Age (years) [median (IQR)]	58 (34–75)	70 (52–79)	41 (32–56)	<0.05
Use of diuretics [*n* (%)]	60 (64.5)	35 (62.5)	25 (67.6)	N/S
Actual body weight (kg) [median (IQR)]	73.5 (65–85)	74 (61–80)	77 (68.5–88.5)	N/S
APACHE II score [mean (S.D.)]	17.2 (6)	19.1 (6)	14.1 (5.7)	<0.05
SAPS II [mean (S.D.)]	42.2 (14.3)	45.9 (14)	36.3 (12.9)	<0.05
Serum creatinine (μmol/L) [median (IQR)]	70.7 (61.9–79.6)	70.7 (61.9–88.4)	61.9 (53–79.6)	N/S
BUN (μmol/L) [median (IQR)]	8 (5.6–10.4)	8.6 (6.6–11)	5.7 (4.8–8.6)	<0.05
Serum proteins (g/L) [median (IQR)]	53 (48–60)	52 (47–57)	57 (51–62)	<0.05
Serum albumin (g/L) [median (IQR)]	30 (25–34)	27 (24–31)	32 (29–36)	<0.05
CL_{Cr} (mL/min/m^2) [median (IQR)]	109.6 (68.1–152.5)	69.6 (57.8–104.2)	158.9 (140.9–193.6)	<0.05
Admission diagnosis [*n* (%)]				
Trauma	45 (48.4)	23 (41.1)	22 (59.5)	<0.05
Sepsis	28 (30.1)	22 (39.3)	6 (16.2)	<0.05
Respiratory failure without sepsis	11 (11.8)	8 (14.3)	3 (8.1)	N/S
Post surgery	5 (5.4)	2 (3.6)	3 (8.1)	N/S
Other	4 (4.3)	1 (1.8)	3 (8.1)	N/S

S.D., standard deviation; IQR, interquartile range; APACHE, Acute Physiology and Chronic Health Evaluation; SAPS, Simplified Acute Physiology Score; BUN, blood urea nitrogen; CL_{Cr}, 24-h creatinine clearance; N/S, not significant (at a level of 0.05).

Table 2
Median (interquartile range) vancomycin dose and time interval between loading dose and therapeutic drug monitoring (TDM) of vancomycin on the first treatment day (D_0) for Group A [control group without augmented renal clearance (ARC)] and Group B (study group with ARC).

	Group A	Group B	*P*-value
Loading dose (g)	1.0 (1.0–1.1)	1.0 (1.0–1.5)	N/S
Perfusion dose (g)	2.0 (1.9–2.4)	2.1 (2.0–2.4)	N/S
Total dose (g)	3.1 (2.9–3.8)	3.4 (3.0–3.9)	N/S
Loading dose/actual weight (mg/kg)	15.4 (12.5–18.2)	14.5 (12.5–18.2)	N/S
Perfusion dose/actual weight (mg/kg)	30 (26.7–34.4)	30 (25.0–32.3)	N/S
Total dose/actual weight (mg/kg)	47.7 (40.0–51.8)	45.4 (38.8–48.6)	N/S
Time interval between loading dose and TDM of vancomycin on D_0 (h)	17 (16–17)	17 (17–18)	N/S

N/S, not significant (at a level of 0.05).

admitted critically ill patients (17.9%), increasing to rates as high as 30% during the first week of admission [11]. Accordingly, serum and tissue subtherapeutic drug levels are the pharmacological consequences, contributing to treatment failure of severe infections. This condition, here defined as ARC, is unappreciated in the critical care setting and is under-reported in the medical literature, and can be a co-factor responsible for inadequate antibiotic prescription despite adequate recommended dosage and respective adjustment to body weight. One of the particularities of the current data was that a group of patients in which renal clearance was actually measured, and not estimated, was studied. A previous study has shown that in critically ill patients exhibiting ARC, estimates of GFR are insensitive in identifying this phenomenon [14].

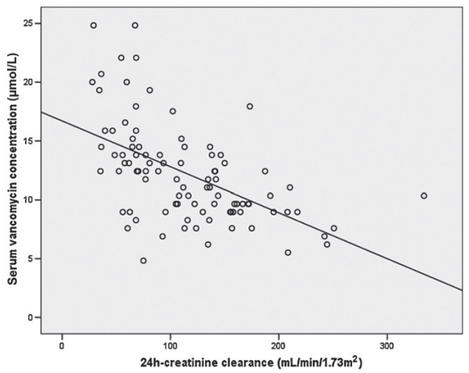

Fig. 2. Linear correlation between 24-h creatinine clearance (CL_{Cr}) and serum vancomycin concentration on Day 1. The serum vancomycin concentration displayed a significant direct correlation with CL_{Cr} in 93 septic critically ill patients ($rS = -0.57$; $P < 0.01$).

Vancomycin is a hydrophilic drug with predominantly renal excretion (80–90%), whose clearance correlates with CL_{Cr} [15,16]. It shows time-dependent activity that, in turn, is linked to the ratio of the 24-h area under the concentration–time curve (AUC_{24}) to MIC. As shown in Fig. 1, the serum vancomycin concentration in Group B just reached, on average, therapeutic levels on D3 (13.8 μmol/L). Actually, only 52% of patients (16/31) reached minimal therapeutic serum levels, meaning that approximately one-half of the patients have not yet started optimal treatment of infection on D3, in other words only 72 h after the vancomycin loading dose. These results are in agreement with another recent study in which the authors found that in critically ill patients a higher dose of vancomycin in continuous infusion than usual is needed, following an adequate loading dose, to achieve a target plateau concentration of 17.3 μmol/L (25 μg/mL) [17].

Patients in both groups, on average, were treated with an equivalent total amount of vancomycin (loading plus maintenance dose) during the 24 h of D_0 (Table 2). A very high rate of subtherapeutic serum vancomycin concentration was observed on D_1, mostly in Group B (89%) but also in Group A (53%). This last result was unexpected since Group A had 28.6% of patients (16/56) with $CL_{Cr} < 60$ mL/min/1.73 m^2. It is possible that, in these patients without ARC, other factors such as hypoalbuminaemia and increased volume of distribution (V_d), could contribute to this low therapeutic level on D_1. Serum albumin, a major determinant of V_d, was

significantly higher in patients with ARC (Group B), an event that is not surprising since this group was younger, less severely ill and with a higher potential physiological reserve. Moreover, vancomycin is not a highly albumin-bound drug (30–55%) so it should not greatly influence vancomycin availability; however, even for hydrophilic antibiotics with low albumin binding, increased V_d has been described [18,19].

Although we have analysed a considerable number of patients ($n = 93$), the main limitation of the present study lies in the fact that it is a single-centre study, reflecting the case mix of our ICU, namely with a significant trauma population. Furthermore, the CL_{Cr} measurement is laborious and this factor could be a bias for imperfect urine collection, thus leading to clearance miscalculations. Finally, V_d was not assessed in this study, thus the discussion around this issue is merely speculative.

In conclusion, amongst critically ill patients with normal S_{Cr}, ARC is strongly associated with subtherapeutic serum vancomycin levels and this study clearly shows the need to use a more aggressive initial loading dose as well as TDM in these particular patients. ARC appears to be a relatively frequent occurrence in this setting, namely in young males with trauma and less severe disease.

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Competing interests: None declared.

Ethical approval: This study was approved by the Institutional Review Board of the Committee of the Innovation and Development Unit, Coimbra University Hospital (Coimbra, Portugal) (Project Approval No. 42/IDU/10/D).

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CHAPTER 6

DECREASING THE TIME TO ACHIEVE THERAPEUTIC VANCOMYCIN CONCENTRATIONS IN CRITICALLY ILL PATIENTS: DEVELOPING AND TESTING OF A DOSING NOMOGRAM

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DOI 10.1186/s13054-014-0654-2

CRITICAL CARE

RESEARCH Open Access

Decreasing the time to achieve therapeutic vancomycin concentrations in critically ill patients: developing and testing of a dosing nomogram

João Pedro Baptista[1*], Jason A Roberts[2,3,4,5], Eduardo Sousa[1], Ricardo Freitas[1], Nuno Deveza[1] and Jorge Pimentel[1]

Abstract

Introduction: Achievement of optimal vancomycin exposure is crucial to improve the management of patients with life-threatening infections caused by susceptible Gram-positive bacteria and is of particular concern in patients with augmented renal clearance (ARC). The aim of this study was to develop a dosing nomogram for the administration of vancomycin by continuous infusion for the first 24 hours of therapy based on the measured urinary creatinine clearance (8 h CL_{CR}).

Methods: This single-center study included all critically ill patients treated with vancomycin over a 13-month period (group 1), in which we retrospectively assessed the correlation between vancomycin clearance and 8 h CL_{CR}. This data was used to develop a formula for optimised drug dosing. The efficiency of this formula was prospectively evaluated in a second cohort of 25 consecutive critically ill patients (group 2). Vancomycin serum concentrations between 20 to 30 mg/L were considered adequate. ARC was defined as 8 h CL_{CR} more than 130 ml/min/1.73 m^2.

Results: The incidence of ARC was 36% (n = 29/79) and 40% (10/25) in group 1 (n = 79) and 2 (n = 25), respectively. The mean serum vancomycin concentration on day 1 was 21.5 (6.4) and 24.5 (5.2) mg/L, for both groups respectively. On the treatment day, vancomycin plasma clearance was 5.12 (1.9) L/h in group 1 and correlated significantly with the 8 h CL_{CR} (r^2 = 0.66; P <0.001). The achievement of adequate vancomycin serum concentrations in group 2 was 84% (n = 21/25) versus 51% (n = 40/79) – P <0.005.

Conclusions: This new vancomycin nomogram enabled the achievement of adequate serum concentrations in 84% of the patients on the first day of treatment.

Introduction

The emergence of multidrug-resistant bacteria has been associated with the inappropriate use and the inadequate dosing of antibiotics [1]. The EPIC II study showed that 51% of the patients admitted to ICU had infections and that 71% of all patients were receiving antibiotics [2]. In addition, this study demonstrates that infection by methicillin-resistant *Staphylococcus aureus* (MRSA) is particularly problematic. Compared to methicillin-susceptible *S. aureus* (MSSA), MRSA is independently associated with an almost 50% higher likelihood of hospital death [3] and has been considered as a serious threat by the Centers for Disease Control and Prevention (CDC) [4]. Despite its widespread use, vancomycin remains the first-line agent in the treatment of patients with MRSA infection, including those in the critical-care setting. In Portugal, MRSA prevalence is one of the highest in Europe and the emergence of vancomycin-resistant enterococci and vancomycin-resistant *S. aureus* is an area of particular concern [5,6].

Though there are limited data to support its routine use in patient care [7], the administration of vancomycin by continuous infusion (CI) has been used for the treatment of critically ill septic patients, because of its practical advantages: 1) rapid achievement of steady-state target concentrations; 2) lower variability in drug exposure; 3) simplicity of interpretation of therapeutic drug monitoring

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(TDM) and dose adjustment; 4) ease of administration; 5) lower rates of nephrotoxicity, 6) lower costs and 7) lower mortality [8-11]. However, achieving the desired serum concentration can still be difficult in this group of patients [11-14]. Amongst the several factors that contribute to the difficulties in establishing adequate dosing regimens [15], augmented renal clearance (ARC) is emerging as a new and crucial factor, since vancomycin is predominantly eliminated by the kidneys [16,17]. ARC refers to an enhanced elimination of circulating solute including drugs and is defined as a creatinine clearance exceeding 130 ml/minute. ARC appears to be quite common in sub-populations of critically ill patients and can lead to very low concentrations of renally cleared drugs like vancomycin.

The aim of this study was to develop a dosing nomogram for the administration of vancomycin by CI for the first 24 h of therapy based on an 8-h measured urinary creatinine clearance (8 h CL_{CR}); and second, to evaluate its efficiency in a separate cohort of critically ill septic patients.

Material and methods

Study design

This single-center study was conducted in a 20-bed mixed ICU at the 1,375-bed Coimbra University Hospitals (Portugal). Data were collected retrospectively over a 13-month period from all consecutive, ventilated, adult patients with severe sepsis or septic shock who started empirical or directed treatment that included vancomycin (group 1). The intravenous treatment protocol started with a loading dose of vancomycin (Vancomicina Hikma®, Hikma Farmacêutica, Terrugem, Sintra, Portugal) based on the patient's actual weight, of 1,000 mg (body weight ≤70 kg) or 1,500 mg (body weight >70 kg) over 1 to 2 h, followed by CI (30 mg/kg/day). Daily TDM (between 7:00 and 7:30 am) of serum vancomycin concentrations was performed, starting the next day (day 1). Serum concentrations between 20 and 30 mg/L were considered adequate [16]. An increased serum creatinine concentration >0.3 mg/dL on two or more consecutive days and so-called red-man syndrome were considered adverse effects related to vancomycin administration. Ototoxicity evaluation was not feasible during the study period. At Coimbra University Hospitals, *S. aureus* shows no resistance to vancomycin (minimum inhibitory concentration (MIC) ≤1 mg/L - European Committee on Antimicrobial Susceptibility Testing (EUCAST)).

Height, weight, body mass index (BMI) and body surface area (BSA) were measured. The DuBois and DuBois formula was used to calculate BSA as follows:

$$\mathrm{BSA} = 0.007184 \times (\mathrm{Height\ (cm)})^{0.725} \times (\mathrm{weight\ (kg)})^{0.425}.$$

A daily 8 h CL_{CR} was collected during the patient's ICU admission, between 23:00 h and 07:00 h, as part of the daily routine procedure in our unit. This measurement used a standard urinary collection (via indwelling catheter) for the 8-h period following measurement of creatinine concentration in urine (u) and blood (s) for calculation of 8 h CL_{CR} (ml/minute/1.73 m^2), according to the formula:

$$8h\,CL_{CR} = (uCr/sCr) \times (8h\,urinary\,output/480) \times (1.73/BSA) \quad (1)$$

Augmented renal clearance was defined as 8 h CL_{CR} >130 ml/minute/1.73 m^2. Exclusion criteria were the following: 1) need for renal replacement therapy; 2) serum creatinine concentration >1.3 mg/dL; 3) known chronic kidney disease; 4) age under 18 years; 5) pregnancy, and 6) ICU stay of less than 48 h. Using a previously described methodology [17,18], we calculated the vancomycin plasma clearance (CL_{vanco}) according to the formula:

$$CL_{vanco}(L/h) = IR(mg/h) / C_{ss}(mg/L) \quad (2)$$

Where IR represents infusion rate of vancomycin by CI and and C_{ss} represents the vancomycin serum concentration at pseudo steady-state. Relationship between CL_{vanco} and 8 h CL_{CR} was used to define a dosing nomogram for vancomycin for different 8 h CL_{CR} that targets a target C_{ss} of 25 mg/L. The rationale behind the choice of 25 mg/L as the ideal target was based on current recommendations and on the pharmacokinetic/pharmacodynamic (PK/PD) characteristics of vancomycin [16,19]. The resultant dosing nomogram was then prospectively applied for vancomycin dosing by CI in the ICU (after adequate loading dose). Thereafter, we collected data on the serum drug concentration on day 1 on the first 25 treated critically ill septic patients (group 2). Vancomycin treatment was initiated at the discretion of the ICU physician. Inclusion criteria for the second cohort were as following: 1) evaluation of 8 h CL_{CR} the day of initiation of vancomycin; 2) stable renal function; 3) administration of loading and maintenance dose per protocol, and 4) interval between loading dose and TDM for vancomycin >12 h and <24 h.

This study was approved by the Human Research Ethics Committee of Coimbra University Hospitals (CHUC-114-13), which waived the need for informed consent.

Statistical analysis

The results were analyzed with the SPSS software package v.19.0 (SPSS Inc., Chicago, IL, USA) and with MedCalc software v.9.3.8 for Windows (MedCalc Software, Mariakerke, Belgium). Continuous variables are expressed as mean (standard deviation) or median (interquartile range) where applicable. Qualitative variables are presented as frequencies and percentages. Differences in categorical variables were calculated using Fisher's exact test. For subgroup comparison of continuous data, the Student *t*-test was used. Linear regression was employed for curve fitting. A *P*-value of <0.05 was considered statistically significant.

Results

The main demographic characteristics of the patients belonging to groups 1 and 2 (79 and 25 patients, respectively) are shown in Table 1 and the dosing characteristics and observed pharmacokinetics of vancomycin treatment are described in Table 2. The predominant foci of the infection were lung (63.2%), skin and soft tissues (7.5%), bloodstream (6.3%) and abdominal (6.3%). Globally, the frequency of achievement of adequate vancomycin serum concentrations (20 to 30 mg/L) was 51% (n = 40/79) in group 1 versus 84% (n = 21/25) in group 2 (*P* <0.005). Of note, the population of group 1 showed a wide range of renal function, between 25 and 335 ml/minute/1.73 m^2. The incidence of ARC in group 1 was 36% (n = 29/79) and the CL_{vanco} was 6.8 and 4.2 L/h in patients with and without ARC, respectively. Within these 29 patients showing ARC, only 28% achieved adequate vancomycin serum concentrations (20 to 30 mg/L); 74% of the remaining 50 patients achieved therapeutic concentrations. The 8 h CL_{CR} and CL_{vanco} on day 1 in group 1 was significantly linearly correlated ($r^2 = 0.66$; P <0.001) (Figure 1).

The equation from the linear regression was as follows:

$$CL_{vanco}(L/h) = 0.021\,x\,8h\,CL_{CR}(mL/min) + 2.3 \quad (3)$$

Using equation 3, a new equation was developed for calculating a continuous infusion vancomycin dose per day, considering 25 mg/L as the preferred target:

$$\begin{aligned} Vancomycin\,dose\,(g/d) &= (0.021\,x\,8h\,CL_{CR} + 2.3) \times 25(mg/L) \times 24/1000 \\ &= (0.021\,x\,8h\,CL_{CR} + 2.3) \times 0.6 \end{aligned} \quad (4)$$

We then used equation 4 to develop a dosing nomogram for vancomycin dosing in the first 24 h, after a loading dose (Figure 2). As a result of the application of this nomogram on group 2 (n = 25 patients), we observed that 21 (84%) achieved serum concentrations between 20 and 30 mg/L on day 1. Two patients (8%) exceeded these limits (34.3 and 33.7 mg/L) and another two patients did not meet the target interval (16.8 and 16.7 mg/L). Of note, all the patients with ARC belonging to group 2 were in the target concentration range (n = 10/10), meaning that all the

Table 1 Baseline characteristics of the studied population: group 1 (retrospective cohort) and group 2 (second cohort)

Demographics	Group 1 (79 patients)	Group 2 (25 patients)	*p*
Male, number (%)	52 (66.0)	17 (68.0)	ns
Age, years	57.8 (15.5)	59.9 (17.2)	ns
Body weight, kg	77 (70-86)	75 (67.5-87.5)	ns
Body surface area, m^2	1.87 (0.16)	1.86 (0.19)	ns
Body mass index, kg/m^2	28.1 (25.3-30.4)	25.7 (24.4-30.6)	ns
New simplified acute physiology score	39 (34-50)	43 (37-46)	ns
8 h CL_{CR} on day 1, mL/min/1.73 m^2	125.1 (66.5)	120.5 (54.2)	ns
Baseline serum creatinine, mg/mL	0.68 (0.30)	0.68 (0.31)	ns
Lowest serum creatinine, mg/mL*	0.57 (0.20)	0.60 (0.19)	ns
Highest serum creatinine, mg/mL*	0.73 (0.28)	0.81 (0.45)	ns
Patients with serum creatinine increase >0.3 mg/mL, number (%)*	5 (6.3)	1 (4.0)	ns
Patients with ARC on day 1, number (%)	29 (36.7)	10 (40.0)	ns
Mechanical ventilation on day 1, number (%)	79 (100)	25 (100)	ns
Admission days	19 (9-29)	23 (18-30)	ns
Admission group diagnosis, %			
Trauma admission	44.3	52.0	ns
Surgical admission	16.5	28.0	ns
Medical admission	39.2	20.0	ns

Quantitative variables were expressed as mean (standard deviation) or median (interquartile range) when applied. *During the vancomycin treatment. Augmented renal clearance (ARC) defined as 8 h CL_{CR} >130 mL/min/1.73 m^2; 8 h CL_{CR}, 8-hour measured urinary creatinine clearance; ns, non significant.

Table 2 Dosing information and pharmacokinetics of vancomycin in the retrospective cohort (group 1) and in the second cohort (group 2)

	Group 1 (79 patients)	Group 2 (25 patients)
Loading dose of vancomycin on day 0, mg	1000 (1000-1500)	1500 (1000-1500)
Loading dose of vancomycin on day 0, mg/kg	14.3 (12.8-17.6)	18.8 (16.7-21.4)
Perfusion dose of vancomycin on day 0, mg	1920 (1512-2400)	2072 (1750-2622)
Total dosing of vancomycin on day 0, mg	3160 (2520-3880)	3584 (2976-4138)
Time interval (h) between vancomycin perfusion and TDM	18 (17-27)	18 (17-19)
Serum vancomycin concentration on day 1, mg/L	20.6 (16.7-26)	24.5 (22.2-27.4)
Clearance of vancomycin on day 1, L/h	5.1 (1.9)	NC

Values are expressed as median and interquartile range [Q25-Q75] except for Clearance of vancomycin on day 1 (mean and standard deviation).
TDM, therapeutic drug monitoring; day 0, the day before day 1, corresponding to the day of the administration of vancomycin; NC, not calculated.

under- and over-treated patients were non-ARC patients (4/15, 26.6%). The observed vancomycin serum concentrations within the 25 patients, and the respective visual interrelation with the target interval (20 to 30 mg/L) and preferred target concentration (25 mg/L) is showed in the Figure 3. With the exception of one patient who had an increase of over 0.3 mg/dL of serum creatinine concentration in two consecutive days without needing treatment interruption (1/25, 4.0%), no clinical or laboratory vancomycin-related side effects were noted during the period of treatment at the ICU within group 2. On the other hand, the incidence of nephrotoxicity during vancomycin treatment in group 1 was 6.3% (5/79) (Table 1).

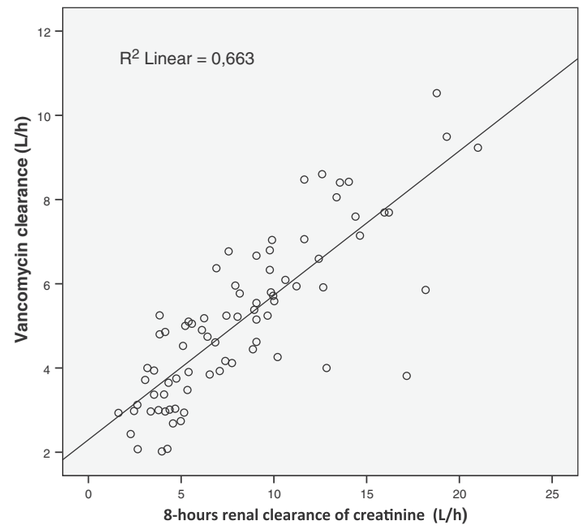

Figure 1 Linear correlation between 8-hour measured urinary creatinine clearance and vancomycin clearance on day 1 in group 1 (79 patients). $R^2 = 0.663$, $P < 0.001$.

Discussion

Our results show that in a broad population of adult ICU patients treated with continuously infused vancomycin, the use of a dosing nomogram significantly increased the achievement of therapeutic concentrations in the first 24 h of treatment, particularly in the patients exhibiting ARC. Application of this nomogram was found to be easy, user-friendly and effective. The nomogram requires the availability of an 8 h CL_{CR} and vancomycin serum concentration monitoring, which is not available in all ICUs, but these results demonstrate how beneficial such tests can be to ensure more accurate antibiotic dosing.

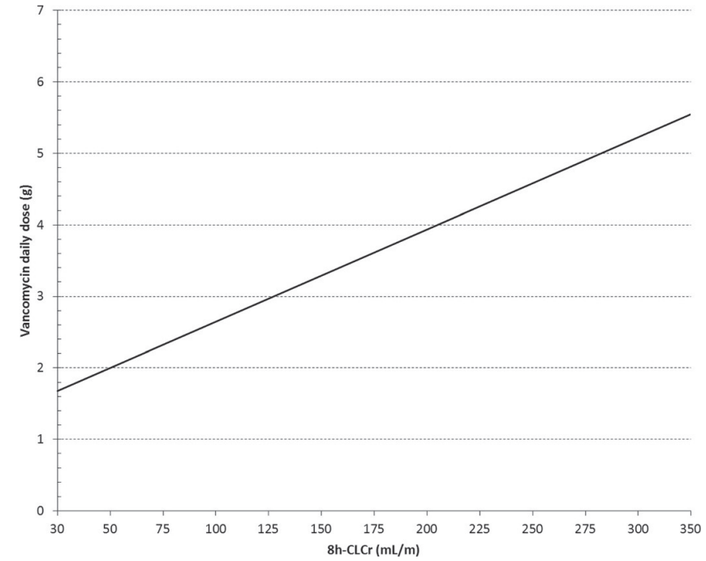

Figure 2 Nomogram for calculation of the daily vancomycin dosage (g/24 h) administered by continuous infusion required for achievement of target drug concentration (25 mg/L) based on 8-hour measured urinary creatinine clearance. 8 h CL_{CR} = 8-hour measured urinary creatinine clearance.

Vancomycin is a glycopeptide antibacterial agent that is predominantly excreted unchanged in urine by glomerular filtration and as such, kidney function is a determinant factor of vancomycin pharmacokinetics and dosing. The best measure of kidney function is the glomerular filtration rate (GFR). Urinary creatinine clearance seems to be the best clinical surrogate of renal function, taking into account its applicability at the bedside, its reliability and the negligible costs associated, provided that clinicians are aware of its limitations [20-22]. Estimates of GFR using equations based on serum creatinine concentrations are flawed in the critically ill patient [21,23]. Taking all of this information together, the measurement of the renal clearance of creatinine in this setting could be used, from a clinical point of view, as the single most accessible parameter allowing appraisal of pharmacokinetic characteristics of the critically ill patient.

Clinicians are used to adjusting the dosing of antibiotics according to acute or chronic renal failure, however the adjustment to elevated function of the kidneys is considered to be quite rare, and there are no recommendations on this clinical issue. Moreover, the incidence of ARC (here defined as CL_{CR} >130 ml/minute/1.73 m^2) is probably high and ubiquitous in every ICU with an underestimated incidence [24]. Indeed ARC is being increasingly described, with previously reported rates, varying widely between 18% to as high as 57% in critically ill patients without renal dysfunction [23,24].

In the context of severe infection, a major consequence of ARC is the high renal clearance of hydrophilic antibiotics leading to a risk of inducing sub-therapeutic concentrations, therapeutic failure, emergence of multi-resistant bacterial strains, and even potentially increased mortality [25]. To date, different antibiotics have been studied in the presence of ARC and these reports have shown a strong association between ARC and sub-therapeutic concentrations [12,26,27]. Importantly for vancomycin, low serum concentrations are associated with decreases in susceptibility and in treatment failure of patients with MRSA infections [28]. A recent large-scale multicentre point-prevalence study revealed that a substantial proportion of critically ill patients treated with vancomycin did not achieve the target vancomycin concentration and showed high variability in pharmacokinetics parameters, supporting a re-evaluation of vancomycin dosing recommendations in this particular setting [29]. Furthermore, a recent consensus review recommended more aggressive vancomycin dosing to ensure achievement of the pharmacodynamic index associated with efficacy [16]. Though vancomycin is widely used in the ICU, there are relatively few studies focused on the early optimization of serum concentrations where CI is the prescribed mode

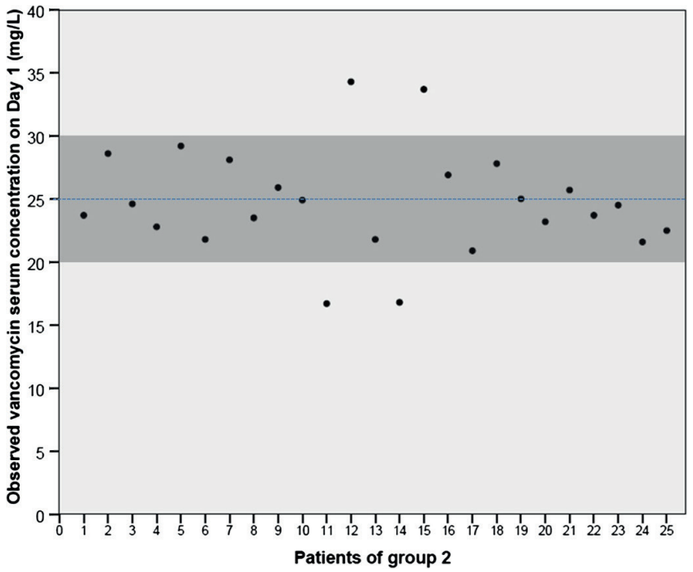

Figure 3 Distribution of the serum vancomycin concentrations within the 25 patients belonging to group 2. The grey area represents the target interval for serum vancomycin on the day 1 of treatment (serum concentrations between 20 and 30 mg/L).

of administration [18,30-35]. Surprisingly, only three studies among these used measured renal clearance of creatinine [32-34], three used mathematical estimates of renal function [18,31,35] and one study did not provide this information [30]. Among those studies evaluating the serum vancomycin concentration on day 1 or day 2, the achievement of target concentrations of 20 to 30 mg/L ranged between 48 and 52% [30,32].

A recent study described a new regimen for CI of vancomycin during continuous renal replacement therapy, which allowed the achievement of target drug concentrations in 63% of patients at 24 h [36]. Our study, using a dosing regimen guided by a dosing nomogram that is based on the 8 h CL_{CR} and after an adequate loading dose, permitted us to reach the target drug concentration in most patients on day 1 (n = 21/25, 84%), providing optimal and early antibiotic exposure in the septic patient, with negligible secondary effects (only one patient with a minor increase in serum creatinine concentration, without evolution to renal failure or need for interruption of the treatment). Roberts *et al.* conducted a population pharmacokinetic analysis of vancomycin CI in a large cohort of critically ill patients, using a Monte Carlo dose simulation for different total body weight, for different creatinine clearances and for different weight-based dosing vancomycin CI regimens [35]. The authors found that higher-than-recommended loading and daily doses of vancomycin seem to be necessary to rapidly achieve therapeutic serum concentrations in these patients. In addition, they state that a patient with a CL_{CR} of 100 ml/minute/1.73 m^2 would require at least 35 mg/kg per day by CI to maintain target concentrations. Curiously, when we use the average weight of our 25 patients belonging to group 2 (75 kg), we found very similar results: 2.625 mg versus 2.600 mg (according to Table 3) in a period of 24 h, respectively. Both approaches seem to exhibit some complementarity: a retrospective development of a model and, on the other hand, a clinical prospective validation of a nomogram, respectively.

To the best of our knowledge, the study by Pea *et al.* is the only to provide and validate two user-friendly dosing nomograms for the treatment of critical ill patients with vancomycin by CI [18]. They described a significant correlation between CL_{vanco} and creatinine clearance ($r^2 = 0.56$, $P < 0.001$) and between the observed and the predicted serum drug concentration ($r^2 = 0.64$, $P < 0.001$), confirming the dependency of vancomycin elimination on the renal function. However, as acknowledged by the authors, the renal performance was evaluated by the Cockroft-Gault formula, which is a limitation of the study [21,23]. Of interest and despite this, when we created a new dosing nomogram based on the formula described by

Table 3 Daily vancomycin dosage administered by continuous infusion for achievement of target drug concentration (25 mg/L) for different values of creatinine clearance using two different nomograms

Creatinine clearance, mL/minute	Vancomycin dosing, g/24 h	
	Baptista *et al.* (present study)	Pea *et al.* [18]
30	1.8	1.1
50	2.0	1.4
75	2.3	1.9
100	2.6	2.3
125	3.0	2.7
150	3.3	3.2
175	3.6	3.6
200	3.9	4.0
225	4.2	4.5
250	4.5	4.9
275	4.8	5.3
300	5.2	5.8
350	5.8	6.7

these authors, but using the same ideal target that we used in our study (25 mg/L), we obtained similar results for the calculation of the daily vancomycin dosage by CI to achieve target drug concentration (Table 3), confirming in two independent studies the need for a higher dosage to achieve adequate concentrations in the first 24 h of treatment with vancomycin by CI. The similar methodology applied in both studies, similar populations, exclusion of patients with prolonged ICU admission, and choice of the Cockroft-Gault formula by Pea and coworkers (showing higher accuracy when compared with other estimates of renal creatinine clearance [23]) may be possible explanations for the similarities between the two nomograms. On the other hand, the lower incidence of ARC in both cohorts (approximately 15%) when compared to those in our study (36.7 and 40.0% in group 1 and 2, respectively) and the recent literature describing lower accuracy of Cockroft-Gault estimates in both extremes of the normal range of 8 h CL_{CR} [23,37] may be possible explanations for the lower agreement between the two nomograms, particularly when considering low and very high values of 8 h CL_{CR}.

Altogether, our study shows that it is possible to increase the likelihood of target attainment in the first 24 h of treatment with vancomycin, with potential benefits including better outcome and reduction of the development of bacterial resistance. Our study strengths lie in the considerable number of patients included in the retrospective cohort, the significant correlation obtained between measured 8 h CL_{CR} and CL_{vanco} ($r^2 = 0.66$, $P < 0.001$), and the wide range of 8 h CL_{CR} exhibited by these patients (25 to 335 ml/minute/1.73 m^2). Therefore, this study is based on a representative cohort of septic critically ill patients, making it applicable in various levels of renal function, including patients with ARC - a sub-group with particular risk of under-treatment with vancomycin [12].

However, some limitations should be acknowledged. First, this was a single-center study, and therefore an extrapolation of the findings to other settings must be done with caution. Second, the second cohort (group 2) was smaller, giving less certainty to our conclusions. Third, 8 h CL_{CR} cannot be accepted as a gold-standard method to assess kidney function: its determination requires creatinine concentrations to be at steady-state, which is a rarely reached condition in critically ill patients. Finally, pharmacokinetic studies require a constant physiological status, leading us again to the absence of physiological stability in the critical-care setting. In addition, it is possible that not all patients were at actual steady-state, given that 11% of patients in group 1 had an interval between commencement of vancomycin infusion and sampling for TDM less than 16 h.

Conclusions

A novel and easy-to-use vancomycin dosing nomogram for the first 24 h of treatment, based on the 8-h renal clearance of creatinine has been developed and prospectively shown to be effective in septic and critically ill patients at a teaching hospital.

Key messages

- Augmented renal clearance appears to be quite common in sub-populations of critically ill patients and can lead to very low serum concentrations of vancomycin on the first day of treatment
- Clinicians are used to adjusting the dosing of antibiotics according to renal failure; however the adjustment to elevated function of the kidneys appears important to ensure target concentrations are achieved
- This study prospectively validated a new vancomycin dosing nomogram based on the 8-hours renal clearance of creatinine and demonstrated that it is possible to increase the likelihood of target attainment in the first 24 h of treatment, particularly in patients with augmented renal clearance
- Adequate serum concentrations of vancomycin should be confirmed with therapeutic drug monitoring, particularly in patients with extreme renal function alteration

Abbreviations

8 h CL_{CR}: 8-hour measured urinary creatinine clearance; APACHE II: Acute physiology and chronic health evaluation II score; ARC: augmented renal clearance; B: blood; BMI: body mass index; BSA: body surface area; CDC: Centers for Disease Control and Prevention; CI: continuous infusion;

CL_{vanco}: vancomycin plasma clearance; C_{ss}: vancomycin serum concentration at pseudo steady-state; EUCAST: European Committee on Antimicrobial Susceptibility Testing; GFR: glomerular filtration rate; IR: infusion rate of vancomycin by continuous infusion; MIC: minimum inhibitory concentration of the suspected bacteria; MRSA: methicillin-resistant *Staphylococcus aureus*; MSSA: methicillin-susceptible *Staphylococcus aureus*; PD: pharmacodynamics; PK: pharmacokinetics; sCr: serum creatinine; TDM: therapeutic drug monitoring; u: urine.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
JPB contributed to the conception and design, data collection, analysis, interpretation, manuscript writing and final approval of the manuscript. JAR contributed to the conception and design, interpretation, manuscript writing and final approval of the manuscript. ES contributed to the data collection, interpretation, manuscript writing and final approval of the manuscript. RF contributed to the data collection, interpretation, manuscript writing and final approval of the manuscript. ND contributed to the data collection, interpretation, manuscript writing and final approval of the manuscript. JP contributed to the interpretation, manuscript writing and final approval of the manuscript. All authors read and approved the final manuscript.

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CHAPTER 7. INTEGRATED DISCUSSION

INTEGRATED DISCUSSION

In brief, the results of this thesis compiled from six original studies and one narrative review demonstrate that, in critical care setting: ARC is an observed frequent condition; age, sex, and trauma are strong predictors of this condition; estimates of renal function based on common mathematical equations are inaccurate, when compared to CL_{CR}; ARC is associated to subtherapeutic vancomycin serum levels at the early phase of treatment of sepsis; a strong correlation exists between vancomycin plasma clearance and CL_{CR}; the development of an original vancomycin nomogram allows the likelihood of target attainment in the first day of treatment in critically ill patients, including those with augmented renal clearance.

THE PROBLEM

In **chapter 2**, we carried out a narrative review focused on ARC [1]. Briefly, to avoid redundancy, we observed that, although recognized early at the end of the seventies [2], only recently has special attention been given to this issue, following the growing interest in individualization of drug therapy and the rising number of PK/PD research in ICU settings. The most notable and interesting characteristic of ARC is that it does not constitute a pathological condition neither a disease. On the contrary, one of the prerequisites for the exhibition of ARC by a patient is that there is a normal renal function.

Clinicians are used to look at renal performance only through two dimensions: normal or decreased function. Particularly and regarding drug dosing optimization, clinicians are used to prescribe usual recommended dosing for normal renal function (commonly accepted as >60mL/min/1.73m^2) [3] or dosing reduction, according to the rate of decreased renal function. However, *"three-dimension glasses"* are needed, so that the full spectrum of renal function is perceived. This is the case of the patient with ARC showing a deviation to the right side of the physiologic spectrum, beyond the considered normal limits of renal function (Figure B). Ignoring this puts the patient at risk of under-exposure for several drugs, particularly those with significant hydrophilic component, whether antimicrobials or not, therefore more dependent of the renal filtration.

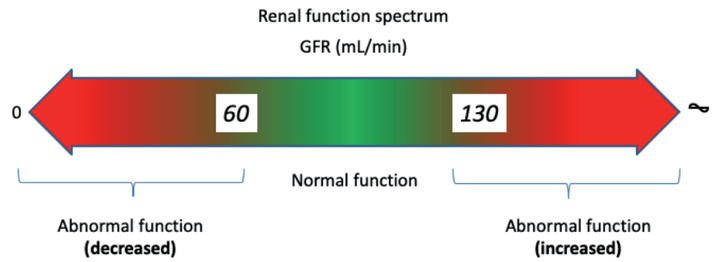

Figure B – Schematic illustration showing the theoretical full spectra of renal function

Specific recommendations for dosing strategies in patients with ARC are lacking. To our knowledge, and regarding antimicrobials, information concerning dosing adjustment to the critically ill is not usually included in guidelines or pharmaceutical product information. More often, PK information is obtained from studies performed with non-critically ill patients (sometimes in young healthy volunteers), and thereafter extrapolated to this population, introducing an error factor potentially leading to inadequate dosing of antimicrobials. This is particularly relevant in the initial stage of the treatment of the septic critically ill, period where the pathophysiological changes associated with critical illness are more common.

THE ORIGIN OF THE PROBLEM

The precise sequence of factors leading to ARC is poorly understood and under-studied. Multiple etiologic factors are accepted as contributors to the ARC status, as depicted in the Figure 7.2 presented in **chapter 2**. Although persistent hyperfiltration can be associated to susceptibility to renal injury in patients with hypertension, diabetes or high-protein diet, from a pragmatic point of view, hyperfiltration in the critically ill leading to ARC seems to be a clinical transient condition not conducing to any kind of acute or chronic renal injury. Although it remains unknown, pathophysiology of ARC is very likely related to the interconnection between fluid therapy (following adequate volume resuscitation) and cardiovascular hyperdynamic status, both often present in the initial stage of septic, neurologic or trauma critically ill patients, leading to increased cardiac index and renal blood flow [4,5]. Using a conventional piglet animal model, Dhondt *et al.* showed that prolonged intravenous fluid therapy was associated with ARC, increased total body iohexol and amikacin clearances [6]. These same authors explored the role of continuous infusion of lipopolysaccharides (LPS), a very well-known sepsis-like state-inducing endotoxin, in the genesis of ARC; however, the small sample used in this exploratory study as well as the presence of uncontrolled fluid administration of all subjects (five piglets) made it difficult to demonstrate the association between LPS/sepsis and ARC [7]. Recently, in a controlled and experimental study in twelve healthy male volunteers challenged with bacterial endotoxin, the systemic immune response was significantly associated with the increase of GFR measured by iohexol plasma clearance, and was independent of blood pressure variation [8]. This research seems to reinforce the primordial role of the systemic immune response in sepsis, as a pathophysiological frame leading to an increased renal function, whether through a direct (renal) or indirect (hemodynamic) effect.

In addition, the frequent use of diuretics and/or vasoactive drugs contributes to the manifestation of this condition in critical illness. More importantly, a preserved functional renal reserve (FRR) must be present, so that ARC can be expressed [9]. Theoretically, FRR is expected to be more expressive in young patients with normal renal function, since the capacity of recruitment is proportional to the amount of preserved renal nephrons and renal blood flow, as showed in a study by Bosch *et al* [10].

This concept fits nicely with our data presented in **chapter 3**, where we showed that age was a strong and independent risk to the exhibition of ARC [11], reinforcing the importance of a well preserved FRR of these patients in the genesis of this super-physiological condition. More specifically, the probability of a patient showing ARC in this cohort of 454 critically ill

patients (corresponding to 5586 clearance-days) decreased 7% for each more year of life. In other words, within the two age classes studied in our investigation [11], patients under 50 years-old had four-and-half-fold greater risk of showing ARC in comparison to older patients (≥ 50 years). The progressive decline of mean values of GFR from the age of 40, as stated in a recent meta-analysis of 12 original studies, gives support to these results [12].

We also identified male sex as an independent risk factor for ARC [11], similarly to works published afterwards [13-15], in which men seem to be three times more at risk than women. However, our study was the first to demonstrate it in a mixed non-selected cohort of medical, neurocritical, and surgical critically ill patients, instead of specific and smaller groups of critically ill [16,17]. Although it is commonly accepted that GFR is higher in men [18], recent studies did not found significant differences in total plasma clearance or GFR between normal adult males and females [19,20]. However, GFR decline seems to be faster in women, particularly from the age of 50 [12], which is possibly related to the fact that they no longer have hormonal protection in the post-menopausal period.

Trauma is consistently associated with patients showing ARC [13,16,21-28]. Our study showed that patients admitted in the ICU due to trauma was an independent risk factor of expressing ARC - adjusted odds ratio of 1.7, interval: 1.4-1.9; p <0.01 [11]. Four main reasons for this association can be articulate. *1)* Victims are frequently young patients, with male predominance and trauma patients show very often low rate of co-morbidity; consequently, they usually have preserved FRR. *2)* They are frequently submitted to aggressive initial fluid challenge. *3)* In the particular case of the neurocritically ill, plausible physiological link between brain injury, renal function and ARC [29,30]. *4)* Frequent use of osmotic therapy in the neurocritical patient.

Of note, although not investigated in our project, the increase in protein intake seems to be an additional and recent described risk factor to ARC. Dickerson *et al*. showed, in a multivariate model, an association between higher levels of protein intake and ARC, in a population of 203 critically ill patients (50% with 24h-CL_{CR} >149mL/min/1.73m^2). Previous investigation in critically and non-critically ill hospitalized patients, as well as in healthy subjects, showed that increased intake of protein, whatever the route of administration, was associated to an increase of the glomerular filtration, giving physiologic consistency to this conclusion [10,31-33].

THE DIMENSION OF THE PROBLEM

Prevalence of ARC in our single-center study was up to 43% after considering the sub-group of patients with normal values of CRT_s and it was 24,9% when all the patients were included [11]. On the other hand, our multicenter prospective study (performed in four ICUs in Australia, Singapore, Hong Kong, and Portugal) showed 65% of patients manifesting ARC on at least one occasion in the first week of the study [34].

This is in accordance with previous studies by our group and other researchers [17,35-41], where the described prevalence ranges between 28 and 57.7% in large-scale epidemiological studies. Udy *et al.* [21], when focusing on specific groups of patients such as traumatic brain injury, found that ARC, on one day at least, can be present in up to 85% of the cases.

More recently, additional epidemiological data have been described as consistent with our current results. Morbitzer *et al.* [42] prospectively studied 80 neurocritical patients with hemorrhagic stroke and showed that ARC was evident, on one day at least, in 50% of participants with intracerebral hemorrhage and in 94% with aneurysmal subarachnoid hemorrhage. In an epidemiological multicenter study performed in Spain, the prevalence of ARC was 38,5%, with a median measured 24h-CL_{CR} of 163mL/min; these patients were significantly younger, with a tendency to show male gender predominance [14]. In a single-center observational and prospective study in adult indigenous and non-Indigenous Australian ICU patients, after exclusion of anuric or patients under renal replacement treatment, researchers observed a prevalence of ARC between 21 and 32%, respectively [43]; notably, younger age was significantly associated to ARC [43]. Further important studies include a 2021 retrospective evaluation, by Johnston *et al.*[44], comprising the largest cohort of patients with ARC admitted to the ICU in the United Kingdom. The authors retrospectively evaluated 1328 patients, reporting an ARC prevalence of 47% and a significant association, in a logistic regression model, with younger age, male sex and diagnosis of sepsis. Recently, a first report from a Middle-Eastern country (Bahrain, 2020) showed that ARC was present in more than half of the studied critically ill patients [45]. Similar findings were observed in Jordan, in a 2021 prospective and observational study in critically ill patients with cancer, showing an ARC prevalence of 32% and identifying age as a significant risk factor for this condition [46].

It seems that ARC can be potentially present in any critically ill patient with cardiovascular hyperdynamic status due to sepsis, as showed in recent research regarding the pandemic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) termed coronavirus disease 2019 (COVID-19), describing the presence of ARC in this group of patients admitted to the ICU, with a prevalence between 25 and 55% [47-51]. In selected groups of ICU trauma patients, different researchers observed an ARC prevalence between 54 and 67%, on ICU admission [13,15]. Worthy of note, Chinese investigators very recently described an ARC prevalence of 47,1% in a population of 427 critically ill obstetric patients and a significant association, in a multivariate logistic regression analysis, with infection, weight, gestational age, albumin level, vasoactive drugs use, acute pancreatitis, hypertriglyceridemia and severe preeclampsia[52]. Finally, in a recent and first described prospective observational study performed in a large cohort of pediatric ICU patients, researchers found an ARC prevalence of 67%, confirming previous published data describing ARC in children [53]. Similarly to our results in adults[11], male gender was identified as an independent risk factor for the development of ARC in this group of children, a clinical setting where hormonal differences are less relevant [53].
Gathering these data together, we can presume that the prevalence of ARC should be significant throughout ICUs worldwide and for several reasons. *First*, previously healthy, young and male patients are very frequent in ICU setting, especially in units where trauma is a frequent cause of admission. *Secondly*, increased cardiovascular index, renal flow, and urine output are very often associated with fluid administration as part of the initial treatment of septic and/or trauma patient, as well as the use of cardio and vasoactive drugs. *Finally*, septic, trauma and neurocritically ill patients, as a whole, constitute the majority of patients treated in the ICU and correspond to the patients that most frequently show ARC. However, ARC is an understudied issue and its real prevalence is underestimated in the critically ill.

One of the major reasons for this is the overuse of estimates of renal function in the critically ill patient whether in clinical or research settings. Medical literature showing the inaccuracy of mathematical estimates for evaluation of renal function in the critical illness is overwhelming [13,16,28,36,39,41-43,54-60]. Despite this, clinicians persist in calculating estimates instead of measuring the CL_{CR} in a pre-determined period of time (from 2 to 24h).
In **Chapter 4** we present two original studies demonstrating how flawed these estimates are for the identification of patients with ARC [35,61]. Whether exclusively in a group of patients with ARC or in a larger sample of critically ill patients with more comprehensive stage of renal function, both our studies clearly showed how mathematical estimates of renal function are insensitive in identifying ARC. Using estimates of renal function for adjustment of dosing of antimicrobials may lead to major errors, up to 25% of discordance in drug dosing [59]. Particularly in the case of critically ill patients showing ARC, the expected clinical consequences are under dosing, treatment failure and risk of acquisition of bacterial resistances. The frequent use of estimates of renal function in the development of PK models as a way to know how to provide simplified approach to antimicrobial dosing in the critically ill patient is of major concern. Concretely, derivation of nomograms to customize dosing of antimicrobials in the critical illness based on inaccurate principles can have worrying consequences, amplifying the primary miscalculation. Whatever the scientific area is, an investigation chain is only as strong as its weakest link.

In ICU, any method of assessing kidney function that does not consider urine output should be considered an unreliable method. The exception can be the early evaluation of renal function upon ICU admission, a time period where the urine output is not available; in this setting, applying a specific cut-off to the identification of ARC is acceptable. Accordingly, and very recently, Gijsen *et al* proposed a «least worse» alternative to measure 24h-CL_{CR}, using CKD-EPI formula and applying a cut-off of 96.5mL/min/1.73m^2 for the detection of ARC, with a reasonable performance[58]. On the other hand, Dang *et al* used CG formula with a cut-off value of 95.69mL/min/1.73m^2, showing an area under the curve (AUC) >0.75 to detect ARC[28]. In addition, loss of muscle mass as a result of prolonged ICU admission leads to low levels of CRT_s overtime [62]. In a *post hoc* study concerning 248 critically ill patients, Volbeda *et al* recently showed a low accuracy of the mathematical estimates (particularly of CG and MDRD) when in comparison with measured 24h-CL_{CR}, which was related to the observed reduction of CRT_s during the first month of ICU admission [63]. Of note, The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock (2020) [64] advert to the potential flawed results related to the use of estimates of renal function in the critically ill, stating that *«the true GFR should be assumed to be smaller than the estimated GFR if CRT levels have a tendency to increase, and larger than the estimated GFR if CRT levels have a tendency to decrease».*

However, some limitations of the use of measured CL_{CR} have to be taken into account. *Firstly*, long time interval of measurement allows for errors in the accurate collection of urine. *Secondly,* the residual urine in the bladder can be significant when short intervals of time are considered. Both limitations are minimized when an indwelling urinary catheter is used, as it is the case for patients admitted to an ICU. *Thirdly,* the over-estimation of true GFR, due to increased creatinine tubular secretion.

CLINICAL IMPLICATIONS OF ARC ON THE CRITICAL ILLNESS: THE CASE OF VANCOMYCIN

Taken together, the 2 studies presented in **chapter 5 and 6** [65,66] constitute a framework encompassing an approach to overcome the common finding of underdosing of vancomycin in patients admitted in the ICU, particularly in those showing ARC.

Firstly, we showed that the treatment with vancomycin in our ICU was sub-optimal. More specifically, approximately one-half of the group of 37 critically ill septic patients with a 24h-CL_{CR} >130mL/min/1.73m^2 did not reach the target (serum concentrations between 20 and 30mg/L) 72 h after treatment initiation. In addition (after considering the whole studied sample, 93 patients with normal CRT_s), significant correlation was observed between 24h-CL_{CR} and serum vancomycin on the first day after initiation of vancomycin treatment. *In the second study,* we developed a nomogram based on 8h-CL_{CR} for the administration of vancomycin by continuous infusion (C_{Inf}) and we validated it prospectively in a distinct cohort of septic and critically ill patients.

Regarding the first study, similar results have been published afterwards, equally showing underexposure to vancomycin in critically ill patients, after prescription of dosing considered adequate [42,45,52,67-78], thus giving strength to our results. In a secondary analysis of the seminal multicenter point-prevalence (Defining Antibiotic Levels in Intensive Care Unit Patients - DALI) study, the first large-scale study investigating PK/PD target attainment of vancomycin in the critically ill, researchers showed that more than one quarter of the patients receiving vancomycin did not reach a $AUC_{0\text{-}24h}$/MIC ratio >400mg.h/L [79]. Interestingly, these authors suggest, in their final remarks, the *«reevaluation of vancomycin dosing recommendations in critically ill patients with new approaches to more rapidly and consistently achieve clinically relevant PK/PD targets»* [79]. Although TDM allows the correction of serum levels of antimicrobials, reaching optimal target can be time consuming and exposes the patient to a variable time window (hours to days) during which adequate antimicrobial exposure is not achieved and may amplify the selection of resistant bacterial strains [80,81]. The longer the concentration of the antibiotic remains within the mutant selection window (between the MIC of the susceptible pathogens and that of the least susceptible mutants), the greater the likelihood that resistant strains will emerge and amplify [82].

The delay of adequate initiation of antimicrobials is associated with treatment failure and mortality in patients with sepsis and septic shock [83,84], which is why the administration as soon as possible of intra-venous antimicrobials within one hour for both sepsis and particularly septic shock constitutes a strong recommendation of Surviving Sepsis Campaign and International Guidelines for Management of Sepsis and Septic Shock [85]. Specifically, researchers observed that, in a cohort of 122 patients with septic shock and *S. aureus* bacteremia, each hour delay in appropriate antibiotic administration after emergency admission was associated with an 11% increased risk of dying [84].

Since the start of use of vancomycin, a main concern has been its dosing and monitoring, given the narrow therapeutic-toxic window showed by this antimicrobial. In 2020, the Revised Consensus Guideline and Review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society and the Society of Infectious Diseases Pharmacists was published, [86,87] containing several recommendations for adults treated with vancomycin: *1)* $AUC_{0\text{-}24h}$/MIC should be considered the most accurate index for the management of vancomycin dosing. *2)* Daily $AUC_{0\text{-}24h}$/MIC should be maintained between 400 and 600mg.h/L (assuming a MIC of 1mg/L). *3)* This $AUC_{0\text{-}24h}$/MIC target should be achieved within the first 1-2 days. *4)* Loading doses should be used (15-20 to 25-35mg/kg, considering actual body weight) in order to achieve early optimal exposure, particularly in the case of critical illness, patients receiving C_{Inf} or patients under renal replacement therapy. Remarkably, in a 3-years survey in an adult ICU, average loading doses of 15mg/kg proved to be insufficient after 48h of administration by C_{Inf} [88]. Bearing in mind that vancomycin has time-dependent pharmacodynamics characteristics, administration of vancomycin by C_{Inf} constitutes a rational alternative to intermittent infusion[89], with several advantages that are depicted in Table B [78,87,90-96].

Ease of administration
Rapid achievement of steady-state $AUC_{0\text{-}24h}$/MIC guided target concentrations
Less variability in serum concentrations
Less variability in drug exposure
Simplicity of interpretation of therapeutic drug monitoring and dose adjustment
Requires minimal information about patients
Lower rates of nephrotoxicity
Lower mortality
Lower costs
Advantage in middle-income regions

Table B – Advantages of continuous infusion versus intermittent infusion in vancomycin treatment

These advantages are maximized in the ICU setting, where this way of administration is currently expanding, and is used in 31% of ICUs [97]. In fact, assuming that achievement of steady-state target concentrations is faster with C_{Inf}, $AUC_{0\text{-}24h}$/MIC calculation is a simple task: it lies in the multiplication of the vancomycin serum concentration at any time point at steady-state ($[V_{SS}]$) by 24 (corresponding to the hours within a day) allowing the calculation of $AUC_{0\text{-}24h}$:

$$AUC_{0\text{-}24h}\ (mg.h/L) = [V_{SS}]\ (mg/L) \times 24\ (h) \qquad (formula\ 2)$$

However, current accepted optimal PK/PD index for vancomycin (between 400 and 600mg.h/L) have been derived from retrospective, single-center and observational studies and validation for C_{Inf} mode of administration has not been performed [86,87,98]. In addition, although C_{Inf} of vancomycin is considered safe concerning it stability, special attention must be paid to incom-

patibilities with associated drugs, and the use of independent intravenous lines should be considered in specific situations[99,100].

Traditionally, clinicians use serum vancomycin trough levels as a surrogate of PK/PD index. However, recent current recommendations (2020) state that trough-only monitoring, targeting concentrations of 15-20mg/L, might not allow efficient vancomycin dosing and is associated with higher incidence of AKI [87]. For this reason, a transition to vancomycin $AUC_{0\text{-}24h}$/MIC monitoring is gradually recognized as a way to achieve precision dosing targeted through TDM and clinical efficacy [87,101,102]. In a study comprising 252 adults treated with vancomycin, researchers showed that achievement of therapeutic targets was more effective if dosing was guided by $AUC_{0\text{-}24h}$, instead of trough-guided dosing [103]. In addition, this change of paradigm leads to fewer collection of blood samples, higher proportion of adequate $AUC_{0\text{-}24h}$/MIC attainment, shorter durations of therapy, and reduced nephrotoxicity [103]. Worthy of note, these researchers observed that one third of AUC_s ≥400mg.h/L was associated with troughs less than 10mg/L and around two thirds were associated with troughs below 15mg/L [103].

Till recently, $AUC_{0\text{-}24h}$/MIC monitoring was laborious, requiring multiple blood samples within the dosing interval enabling the calculation of the area. Since then, calculations have become simpler, either by the use of Bayesian software programs or of estimates based in first-order PK equations, allowing vancomycin $AUC_{0\text{-}24h}$/MIC monitoring in real-time, based in much less number of drug serum concentrations. However, the handling of this software can be complex, and on the other hand, the estimates of the $AUC_{0\text{-}24h}$/MIC based on a unique point in time of blood collection are not validated in critically ill patients. Additionally, in patients under unstable physiological state, such as the critically ill patients, these calculations are proportionally less accurate, requiring the introduction of additional covariates, rendering calculations more complex [104].

The development of a nomogram inferred from PK data regarding a specific population under treatment with vancomycin, which is the case of the methodology applied in our study [66], allows for AUC/MIC drug monitoring in a simpler way. This methodology based on a derived nomogram - designed as "*a priori*", in opposition to "*a posteriori*" or "*a posteriori* and *a priori*" methods, such as estimations based on first-order PK equations or in Bayesian software [105], as described above – has several advantages, particularly if applied to C_{Inf} mode of administration of a drug. *Firstly,* the nomogram is of very easy interpretation as well as of bedside applicability. *Secondly,* it enables the calculation of the initial rate of C_{Inf} of vancomycin based on the renal clearance (after loading dose based on body weight). *Thirdly,* the first evaluation of the serum concentration of vancomycin (usually after 18-24h of starting therapy) serves as a starting point for the correction of dosing, aiming to the desired target. *Finally,* vancomycin $AUC_{0\text{-}24h}$/MIC monitoring is feasible at any point in time, by using the above mentioned calculations (formula 2). In our study, the chosen target V_{SS} was 25mg/L, corresponding to a $AUC_{0\text{-}24h}$/MIC of 600mg.h/L (25mg/L x 24h), which is within the target advocated by recent 2020 published guidelines [86]. Of note, two important conditions were present in our study providing robustness to our conclusions: *1)* a strong linear correlation was observed between 8h-CL_{CR} and vancomycin clearance (r^2 = 0.66; p <0.001 - Figure 1, chapter 6); *2)* similarity between baseline characteristics of retrospective deduction cohort and prospective validation cohort (Table 1, chapter 6).

After the publication of our study [66], a significant number of studies addressing this issue in the critically ill were published. A comprehensive review of the literature since 2014, gathering twenty articles, revealed that 9 of these were not comparable with ours, due to the distinct mode of administration of vancomycin investigated – intermittent as opposed to C_{Inf} [74,106-113]. Within the group of the remaining eleven studies concerning dosing strategies of vancomycin administered by C_{Inf}, several methodological limitations listed below were identified, making it difficult to carry out any comparisons with our study:

a) Studies using estimates of renal function instead of measured CL_{CR} [26,67,71,114-118];
b) Studies with inaccurate definition of PK/PD target (below 400mg.h/L) [26,116,119];
c) Studies addressing specific cohorts of ICU patients, such as obese or trauma patients, therefore making the extrapolation of the findings to other settings difficult [26,71];
d) Studies not considering ARC or using imprecise definitions such as "*out of range values*" of CL_{CR} [117,119];
e) Studies using population PK modeling with Monte Carlo or other software simulations [116,118];
f) Studies using the patient weight for the calculation of the dosing maintenance of vancomycin [26,115,118,120];
g) Studies using simplistic and binomial vancomycin dosing regimen, only based on the presence (or absence) of renal impairment, without measuring CL_{CR} or applying a unique cut-off (CL_{CR} >50mL/min) [26,120];
h) Studies deducting only the loading dosing without exploring the maintenance dosing of vancomycin [121].

Strictly speaking, comparisons between different studies with distinct methodology, distinct populations and distinct targets are always a difficult task. Even so, we expanded the original table presented in our work [66] adding the results obtained from two new nomograms published after our study [67,114], and we compared the daily vancomycin dosage administered by C_{Inf} for achievement of target drug concentration (25mg/L) for different levels of renal function (Table C).

Creatinine Clearance (mL/minute)	Vancomycin Dosing (g/24h)*			
	Baptista *et al.* (2014)	Pea *et al.* (2011)	Medellin-Garibay *et al.* (2017)	Vu *et al.* (2019)
30	1.8	1.1	– **	0.5
50	2.0	1.4	0.8	0.8
75	2.3	1.9	1.2	1.2
100	2.6	2.3	1.4	1.6
125	3.0	2.7	1.6	2.0
150	3.3	3.2	1.9	2.4
175	3.6	3.6	2.1	2.8
200	3.9	4.0	2.3	3.3
225	4.2	4.5	– **	3.7
250	4.5	4.9	– **	4.1
275	4.8	5.3	– **	4.5
300	5.2	5.8	– **	4.9

** Target drug concentration of 25mg/L*

*** Results not available in the nomogram*

Table C – Comparison of infusion rate of vancomycin between 4 different nomograms

Although not recent, the work by Pea *et al.* [122] still shows the best dosing equivalence, when compared to the results of our nomogram (Table C). It should be highlighted that the three comparators in table C used CG estimates. Nevertheless, we selected these studies, since this formula seems to have the best performance within most common estimates of renal function in critical care settings, when compared with measured CL_{CR} [35,61,123]. However, a measured CL_{CR} should be used to maximize accuracy of guided dosing. It is important to note that given the easiness of development of a nomogram in a cohort of critical patients under treatment with vancomycin by C_{Inf} and the expected specificities of different patients from different ICUs, it seems advisable that each ICU develops their own nomograms. The routine application of these customized and more efficient nomograms could improve the clinical outcome of the critically ill patient with MRSA infections treated with vancomycin.

Towards precise medicine, personalizing dosing of antibiotics allows maximal performance of the binomial efficacy/toxicity, benefiting special populations such as children, older adults, obese patients and critically ill patients, particularly those with ARC. Ideally, optimization of dosing in underrepresented groups, as is the case of ARC patients, should be clarified during the stage of drug development, preventing the consequences of imprecise dosing, such as poor outcomes and economic burden for the health care system[124,125].

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CHAPTER 8. CONCLUSIONS

CONCLUSIONS OF THIS THESIS

Overall, the results of this thesis show that:

1 – The prevalence of ARC (defined as CL_{CR} higher than 130 mL/min/1.73 m^2) is high in the critically ill adult patients, between 43.0 and 55.6% of patients with normal values of serum creatinine. This prevalence can reach 65% when considering patients manifesting ARC on at least one occasion in the first seven days of study. Our results give a non-negligible epidemiological burden to this clinical entity (ARC).

2 – Trauma, young age and male sex were independent risk factors for ARC in critically ill patients.

3 – Mathematical estimates based on CG, CKD-EPI and MDRD formulae are inaccurate for the correct evaluation of the renal function in critically ill patients, underestimating it in ARC patients and overestimating it in the remaining patients.

4 – Significant correlation was demonstrated between 8h-CL_{CR} and vancomycin clearance (r^2 =0.66), portraying the predominant renal elimination of this antimicrobial in critically ill patients.

5 – Within critically ill patients with normal values of serum creatinine, ARC is strongly associated with subtherapeutic levels of serum vancomycin, on the first three days of treatment.

6 – The development of a dosing nomogram for critically ill patients treated with vancomycin in continuous infusion, grounded in simple PK concepts, allows the achievement of adequate treatment in 84% of the studied patients, reaching a AUC_{0-24}/MIC around 600 mg.h/L.

MEANING OF THIS THESIS AND CURRENT IMPLICATIONS FOR PRACTICE

The acknowledgment of the importance of the accurate evaluation of renal function and of its consequences in the optimization of vancomycin in critical care settings led to the implementation of a protocol with the Clinical and Pathology Laboratory of the CHUC, for the standard urinary collection (for the 8h period, via indwelling catheter), following measurement of creatinine concentration (urine and blood) and respective calculation of 8h-CL_{CR}. Since 2011, the 8h-CL_{CR} is integrated in the daily routine of the complementary diagnosis exams of our patients. This innovation at the ICU allowed, on the one hand, the early diagnosis of renal dysfunction (whether diminished or augmented), and on the other hand, the dosing adaptation of predominantly renal excreted drugs. As a second consequence of our study, our original dosing nomogram for vancomycin in continuous infusion was implemented in our ICU in 2014, and it is currently being used as a tool to optimize vancomycin treatment.

FUTURE AREAS OF RESEARCH

Based on the results from this project, the following four general viewpoints for future research were established:

Firstly, with the exception of the recently admited patient, the use of mathematical estimates of renal function should be abandoned in ICUs, whether in clinical or research settings. Very frequently, ICUs still use formulae to estimate the renal function which are not validated in the ICU and can lead to severe inaccurate and flawed results. As a call for further research, a questionnaire assessing the level of knowledge of PK principles ruling antimicrobial dosing in Portuguese ICUs, with special focus on renal function and ARC evaluation could be a useful tool to answer several paramount issues.

Secondly, the rationale behind our thesis can be totally applied to beta-lactamics antimicrobials administered by continuous infusion - the current recommended mode of administration of these drugs. Thus, dosing nomograms can be developed and afterwards validated in critically ill patients, optimizing and customizing antibiotic treatment in severe septic patients. The development of programs for routine serum drug monitoring for beta-lactamics (nearly nonexistent in the national laboratorial panorama) is an essential tool to achieve this goal.

Thirdly, post-licensing studies of old and new antibiotics can provide a better understanding of the pharmacokinetic idiosyncrasies displayed by special patient populations as it is the case of the critically ill. This was the case of vancomycin, an old antimicrobial which was approved by the US Food and Drug Administration for clinical use in 1958, as the object of study in this thesis, more than 50 years after. Post-licensing reevaluation of antimicrobials pharmacokinetics in special patient populations, such as ARC patients, can provide opportunities to improve treatment of severe infection. Gathering these new data from "old" and "not so old" drugs as well as updating drug dosing in light of the most recent knowledge regarding pathophysiology, pharmacometrics and microbiology is imperative. Better dosing will mean better results, high rates of cure, less hospital admission days and less attributable mortality.

Fourthly, pathophysiologic mechanisms of ARC remain obscure, which is why this is an area that should be explored in a near future. Although the complete understanding of the pathophysiology of ARC is not essential, in clinical practice, to overcome the underexposure of critically ill patients to antimicrobials, the clarity of the mechanism underlying ARC can be an opportunity to deepen our knowledge of the interconnection between the kidney, the heart and the brain of the critically unwell patient.

Finally, the prognostic value of ARC in the critically ill patient is not known. By opposition, it is well know that diminished renal clearance or acute renal injury is strongly associated with high morbidity and mortality of critically ill patients admitted to the ICU. If the rationale for the presence of ARC is on the dependency of a previous and preserved optimal renal reserve, showing this propriety can add prognostic value. The balance between this pre-morbid condition (good renal reserve) and the potential risk of sub-optimal treatment with antibiotics of this type of patients will determine the direction of the prognostic value.