UNIVERSITAT DE BARCELONA

# Optimization of meropenem and piperacillin dosing in critically ill patients with septic shock and acute kidney injury requiring continuous renal replacement therapy: a pharmacokinetic and pharmacodynamic study

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# OPTIMIZATION OF MEROPENEM AND PIPERACILLIN DOSING IN CRITICALLY ILL PATIENTS WITH SEPTIC SHOCK AND ACUTE KIDNEY INJURY REQUIRING CONTINUOUS RENAL REPLACEMENT THERAPY:

# A PHARMACOKINETIC AND PHARMACODYNAMIC STUDY

**Tesi presentada per**

**Marta Ulldemolins Gómez**

per a optar al títol de Doctora en Medicina

**Directors:**

**Dra Dolors Soy Muner**
**Dr Ignacio Martín-Loeches Carrondo**

**Barcelona, 2017**

UNIVERSITAT DE BARCELONA

*“We know everything about antibiotics except how much to give”*

Prof Maxwell Finland

# AUTORITZACIÓ DELS DIRECTORS DE TESI

La Dra Dolors Soy i Muner, farmacèutica clínica, consultora sènior del Servei de Farmàcia de l'Hospital Universitari Clínic de Barcelona,

**CERTIFICA:**

Que la memòria de tesi titulada "*Optimization of meropenem and piperacillin dosing in critically ill patients with acute kidney injury requiring continuous renal replacement therapy: a pharmacokinetic and pharmacodynamic study*", presentada per la Marta Ulldemolins i Gómez per optar al títol de Doctora en Medicina, ha estat realitzada sota la meva direcció. Un cop finalitzada, n'autoritzo la seva presentació per tal que sigui avaluada pel tribunal corresponent.

I perquè en quedi constància a efectes oportuns, signo el present document a Barcelona, Març de 2017.

Dra Dolors Soy i Muner

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El Dr Ignacio Martín-Loeches Carrondo, metge intensivista, consultor sènior del Servei de Medicina Intensiva de l'Hospital Universitari Sant James de Dublín,

**CERTIFICA:**

Que la memòria de tesi titulada "*Optimization of meropenem and piperacillin dosing in critically ill patients with acute kidney injury requiring continuous renal replacement therapy: a pharmacokinetic and pharmacodynamic study*", presentada per la Marta Ulldemolins i Gómez per optar al títol de Doctora en Medicina, ha estat realitzada sota la meva direcció. Un cop finalitzada, n'autoritzo la seva presentació per tal que sigui avaluada pel tribunal corresponent.

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Dr Ignacio Martín-Loeches Carrondo

# AGRAÏMENTS

Ja fa uns quants anys des que vaig començar a treballar en els estudis que constitueixen aquesta tesi doctoral, anys que em van permetre conèixer i treballar amb moltes persones a les quals m'agradaria reconèixer i agrair la seva participació i suport.

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Amb la gosadia de prendre'ls els mots a dos dels teus artistes preferits, els grans Leonard Cohen i Federico García-Lorca,

*"Ay, Ay, Ay, Ay*
*Take this waltz, take this waltz*
*With its "I'll never forget you, you know!"'"*

Take this waltz- L. Cohen

*"¡Ay, ay, ay, ay!*
*Toma este vals*
*del "Te quiero siempre"."*

Pequeño vals vienés- F. García Lorca

Ballarem sempre aquest vals amb tu. T'estimarem sempre.

*Marta Ulldemolins i Gómez*

*Març de 2017*

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# ABSTRACT

***Background***

Early and appropriate antibiotic administration has been shown to be the most effective intervention for reducing mortality in critically ill patients with septic shock and multiple organ dysfunction syndrome (MODS). However, despite its relevance, antibiotic dosing in those patients with MODS including acute kidney injury (AKI) that require continuous renal replacement therapy (CRRT) still represents a major challenge for clinicians. In our environment, the broad-spectrum beta-lactams meropenem and piperacillin (in combination with tazobactam) are the antibiotics most frequently prescribed to these patients with very high levels of sickness severity. The impact of septic shock, AKI and CRRT on these antibiotics' dose requirements is vital, as medical interventions and the disease itself are likely to produce significant variations in their pharmacokinetics (PK), which may lead to alterations in drug concentrations over time and hence compromise the achievement of drug concentrations within the therapeutic range. However, it is still very complex to individualize piperacillin and meropenem dosing in patients with septic shock and AKI necessitating CRRT.

***Hypothesis***

Meropenem and piperacillin dosing is not optimal in critically ill patients with septic shock and AKI requiring CRRT due to disease and medical-driven variations in antibiotic PK and, therefore, in dose requirements, which may lead to failure in the achievement of therapeutic concentrations.

***Aims***

1. To evaluate the suitability of current meropenem and piperacillin dosing recommendations in critically ill patients with septic shock and AKI necessitating CRRT;
2. To identify the sources of variability that compromise optimal drug dosing in this patient population; and
3. To develop new recommendations that allow dose individualization considering these variability sources.

***Methods***

Three studies have been developed under the study hypothesis and aims.

Study 1: Literature review. A systematic literature review and critical evaluation of the available evidence on meropenem and piperacillin dosing in critically ill patients with septic shock and AKI necessitating CRRT has been performed.

Studies 2 and 3: Characterization of the PK of meropenem and piperacillin in critically ill patients with septic shock and AKI necessitating CRRT. Two observational, prospective, multicenter, open-label pharmacokinetic studies have been performed in the Intensive Care Units from three Spanish tertiary hospitals. Thirty patients with septic shock and CRRT receiving meropenem and 19 patients receiving piperacillin have been enrolled. Two population PK models have been developed and subsequently validated with data from these patients, and Monte Carlo simulations have been undertaken using NONMEM v.7.3®.

***Results***

The main finding of study 1 is that present *"one-size-fits-all"* dosing recommendations for meropenem and piperacillin in critically ill patients with septic shock and AKI requiring CRRT are based on studies with some drawbacks, such as: 1) different sickness severities and levels of renal function, 2) different admission diagnostics (medical *versus* surgical *versus* trauma), 3) different clinical managements mainly CRRT settings, 4) heterogeneous PK methodologies, and 5) different PD targets for dosing recommendations. This scenario limits extrapolation of their conclusions to our patient population.

Later on, studies 2 and 3 have identified important sources of meropenem and piperacillin PK variability that may assist in dose individualization. For meropenem, the main finding of the population PK analysis is the relationship existing between the 24h urine output and meropenem total clearance (CL). Patients with conserved diuresis (>500mL/24h) exhibit at least a 30% increase in meropenem total CL compared to those patients who are anuric (<100mL/24h), increase that is directly proportional to urine volume. Following Monte Carlo simulations based on this population PK model have shown that for maintaining unbound concentrations of meropenem above the minimum

inhibitory concentration (MIC) of the bacteria for a 100% of the dosing interval (100% $f_u T_{>MIC}$), oligoanuric patients (residual diuresis 0-500mL/24h) require 500mg/q8h over 30min for the treatment of susceptible bacteria (MIC<2mg/L), while patients with preserved diuresis (>500 mL/24h) require the same dose over a 3h-infusion. If bacteria with MIC close to the resistance breakpoint (2-4mg/L) are to be treated with meropenem, a dose of 500mg/q6h is necessary: over a 30min-bolus for oligoanuric patients and over a 3h-infusion for patients with preserved diuresis. For the attainment of more conservative PD targets (40% $f_u T_{>MIC}$), 500mg/q8h over a 30min-bolus is sufficient regardless of residual diuresis

With regards to piperacillin, the main finding of the population PK analysis is the relationship existing among the type of membrane used for CVVHDF, the patient's weight and piperacillin total CL; for a body weight of 80kg, piperacillin total CL is doubled when a 1.5$m^2$ AN69 acrylonitrile and sodium methallyl sulfonate copolymer filter pre-coated with heparin and polyethyleneimine (AN69ST) is used compared to the CL for a 0.9$m^2$ AN69 filter. Subsequent Monte Carlo simulations have shown that for a PD target of 100% $f_u T_{>MIC}$, patients receiving CVVHDF with 1.5$m^2$ AN69ST membranes require doses of 4000mg/q8h for the treatment of bacteria with a susceptibility to piperacillin close to the clinical breakpoint (MIC = 8-16mg/L). In contrast, 2000mg/q8h are sufficient for patients with CVVHDF using 0.9$m^2$AN69 membranes. For the treatment of bacteria with high susceptibility to piperacillin (MIC ≤ 4mg/L) or for the attainment of a more conservative PD target (50% $f_u T_{>MIC}$), 2000mg/q8h are sufficient in all cases.

***Conclusions***

Due to data heterogeneity, current meropenem and piperacillin dosing recommendations for patients with septic shock and CRRT follow a one-size-fits-all fashion, which often translates into a best-guess dosing at the bedside. In this context, we have shown that identification and consideration of clinical and demographic parameters that influence meropenem and piperacillin PK, such as 24h urine output, patient's weight and type of CRRT membrane, is advantageous for dose titration. As they are characteristics easy to be measured at the bedside, the implementation of our

research findings in the real clinical setting is easy and may be helpful in the complex process of optimization of antibiotic use in the Intensive Care Unit.

**Keywords:** septic shock, meropenem, piperacillin, population pharmacokinetics, pharmacodynamics, continuous renal replacement therapy, residual diuresis, AN69 membrane, surface-coated AN69ST membrane

# RESUM


***Introducció***

L'administració precoç d'antibioteràpia apropiada ha demostrat ser la intervenció més eficaç per reduir la mortalitat en pacients crítics amb xoc sèptic i síndrome de disfunció multiorgànica (SDMO). Malgrat la seva rellevància, però, la dosificació antibiòtica en els pacients amb SDMO incloent insuficiència renal aguda (IRA) que requereixen teràpia continua de suport renal (TCSR) encara representa un repte diari pels professionals de la salut. Al nostre medi, els antibiòtics beta-lactàmics d'ampli espectre meropenem i piperacil·lina (en combinació amb tazobactam) són els antibiòtics més prescrits a aquests pacients d'altíssima complexitat i gravetat. L'impacte del xoc sèptic, la IRA i la TCSR en els requeriments de dosis d'aquests fàrmacs és vital, ja que tant la pròpia malaltia com les intervencions mèdiques produeixen alteracions significatives en la seva farmacocinètica (FC), que duen a variacions en els perfils concentració-temps i, conseqüentment, comprometen l'assoliment de concentracions del fàrmac dins del rang terapèutic. No obstant això, individualitzar la dosificació de meropenem i piperacil·lina en pacients amb xoc sèptic, IRA i requeriment de TCSR és encara molt complex.

***Hipòtesi***

La dosificació de meropenem i piperacil·lina en pacients crítics amb xoc sèptic i IRA que requereixen TCSR és sub-òptima degut a les variacions en el comportament FC dels fàrmacs produïdes tant per la malaltia com pel maneig mèdic d'aquesta. Aquestes variacions FC poden comprometre l'assoliment de concentracions terapèutiques.

***Objectius***

1. Avaluar la idoneïtat de les recomanacions actuals sobre dosificació de meropenem i piperacil·lina en pacients crítics amb xoc sèptic i IRA que requereixen TCSR;
2. Identificar les fonts de variabilitat que comprometen l'exposició òptima a aquests antibiòtics en la nostra població de pacients; i
3. Desenvolupar noves recomanacions per individualitzar la dosificació d'aquests antibiòtics tenint en compte aquestes fonts de variabilitat.

***Metodologia***

En base a la hipòtesi i els objectius, s'han desenvolupat els tres estudis següents:

Estudi 1: Revisió de la literatura. S'ha realitzat una revisió sistemàtica i avaluació crítica de l'evidència disponible sobre la dosificació de meropenem i piperacil·lina en pacients crítics amb xoc sèptic, IRA i requeriment de TCSR.

Estudis 2 i 3: Caracterització de la FC de meropenem i piperacil·lina en pacients crítics amb xoc sèptic i IRA que requereixen TCSR. S'han realitzat dos estudis farmacocinètics multicèntrics, oberts, prospectius observacionals, a les Unitats de Medicina Intensiva de tres hospitals espanyols de tercer nivell. S'han inclòs a l'estudi 30 pacients amb xoc sèptic, IRA i TCSR que rebien meropenem i 19 pacients que rebien piperacil·lina. Amb les dades procedents d'aquests pacients, s'han desenvolupat i validat dos models FC poblacionals, a partir dels quals s'han realitzat simulacions de Monte Carlo de diferents esquemes terapèutics (mitjançant el software NONMEM v.7.3®).

***Resultats***

La principal troballa de l'estudi 1 és que les recomanacions actuals de dosificació de meropenem i piperacil·lina en pacients crítics amb xoc sèptic i IRA que requereixen TCSR es basen en estudis amb algunes limitacions, com ara: 1) diferents nivells de gravetat de la malaltia i de disfunció renal, 2) diferents diagnòstics d'ingrés (mèdic *versus* quirúrgic *versus* trauma), 3) diferents maneigs clínics, principalment referent a les característiques de la TCSR, 4) metodologies heterogènies d'anàlisi FC, i 5) diferents objectius farmacodinàmics (FD) en base als quals es fan les recomanacions de dosificació. Això compromet l'extrapolació dels resultats d'aquests estudis a la nostra població de pacients.

Posteriorment, els estudis 2 i 3 han identificat importants fonts de variabilitat en la FC de meropenem i piperacil·lina, que si es consideren en el moment de la dosificació poden ser útils per individualitzar el tractament antibiòtic. Pel que fa a meropenem, la principal conclusió de l'anàlisi FC poblacional és la relació existent entre la diüresi acumulada de 24h i l'aclariment total de meropenem (CL). Els pacients amb diüresi conservada (>500ml/24h) presenten un increment d'almenys el 30% sobre el CL total de meropenem en comparació amb aquells pacients anúrics (<100mL/24h), sent aquest augment en el

CL del fàrmac directament proporcional al volum d'orina. Posteriorment, les simulacions de Monte Carlo basades en aquest model FC poblacional han demostrat que per tal de mantenir les concentracions de meropenem per damunt de la concentració mínima inhibitòria (CMI) dels bacteris durant un 100% de l'interval de dosificació (100% $f_u T_{>CMI}$), els pacients oligo-anúrics (diüresi residual de 0-500mL/24h) requereixen 500mg/q8h administrats en un bolus de 30 minuts per al tractament de microorganismes susceptibles (CMI <2 mg/L), mentre que els pacients amb diüresi conservada (>500mL/24h) requereixen la mateixa dosi administrada mitjançant una perfusió de 3h. Pel tractament de microorganismes amb una CMI propera al límit de susceptibilitat (2-4mg/L) és necessària una dosi de 500mg/q6h: administrada en un bolus de 30 minuts de en pacients oligo-anúrics i mitjançant una perfusió de 3h en pacients amb una diüresi conservada. Si s'escull un objectiu FD més conservador, (40% $f_u T_{>CMI}$), una dosi de 500mg/q8h administrada en un bolus de 30 minuts és suficient amb independència de la diüresi residual.

Pel que fa a la piperacil·lina, la principal conclusió de l'anàlisi FC poblacional és la relació existent entre el tipus de membrana utilitzada per la TCSR, el pes del pacient i el CL total de piperacil·lina; per a un pes de 80 kg, el CL total de piperacil·lina es duplica quan es fa servir una membrana d'1,5$m^2$ de copolímer d'acrilonitril i sulfat sòdic de metal·lil amb un recobriment d'heparina i polietilenimina (AN69ST) en comparació amb el CL total observat quan es fa servir un filtre AN69 convencional de 0,9$m^2$. Posteriors simulacions de Monte Carlo han demostrat que per a un objectiu FD de 100% $f_u T_{>CMI}$, els pacients que reben TCSR amb membranes AN69ST d'1,5$m^2$ requereixen dosis de 4000mg/q8h per al tractament de microorganismes amb CMI properes al límit de susceptibilitat (CMI = 8-16mg/L). Per contra, 2000mg/q8h són suficients per als pacients que reben TCSR amb membranes AN69 de 0,9 $m^2$. Per al tractament de soques d'alta susceptibilitat a la piperacil·lina (CMI ≤ 4mg/L), o per l'assoliment d'un objectiu FD més conservador (50% $f_u T_{>CMI}$), 2000mg/q8h són suficients en tots els casos.

***Conclusions***

Com a conseqüència de l'heterogeneïtat dels estudis publicats, les recomanacions posològiques actuals de meropenem i piperacil·lina en pacients amb teràpia de suport renal són genèriques i no extrapolables a pacients d'alta gravetat com el pacient crític amb xoc sèptic, IRA i requeriment de TCSR. En aquest context, hem demostrat que la identificació i consideració de paràmetres clínics i demogràfics que modifiquen la FC de meropenem i piperacil·lina, els dos antibiòtics més freqüentment prescrits de forma empírica a aquests pacients, és avantatjós per individualitzar la posologia. A més, com que es tracta de paràmetres fàcils de mesurar a peu de llit, els resultats de la nostra recerca són aplicables directament a la pràctica clínica i poden ser útils en el complex procés de l'optimització de l'ús d'antibiòtics a la Unitat de Medicina Intensiva.

**Paraules clau:** xoc sèptic, meropenem, piperacil·lina, farmacocinètica poblacional, farmacodinàmica, teràpia continua de suport renal, diüresi residual, membrana de diàlisis AN69, membrana de diàlisis amb recobriment de superfície AN69ST.

# ABBREVIATIONS

## LIST OF ABBREVIATIONS USED IN THE TEXT, TABLES AND FIGURES

AKI: Acute kidney injury

AN69: Acrylonitrile and sodium methallyl sulfonate copolymer filter

AN69ST: Acrylonitrile and sodium methallyl sulfonate copolymer filter precoated with heparin and polyethyleneimine

APACHE II: Acute Physiology and Chronic Health Evaluation II

$AUC_{0\text{-}24h}$: Area Under the drug Concentration Curve over 0-24h

$AUC_{0\text{-}24h}$/MIC : Ratio between the Area Under the Concentration Curve over 0-24h and the MIC of the pathogen

BSAC: British Society for Antimicrobial Chemotherapy

CAVHD: Continuous arterio-venous hemodialysis

CCF: Cleveland clinic foundation

CI: Confidence interval

CL: Total drug clearance

$CL_{CRRT}$: Component of total drug CL related to the CRRT

$CL_{MEMB}$: Component of total drug CL related to the dialysis membrane

CLSI: Clinical and laboratory standards institute

CMI: Concentració mínima inhibitòria

$C_{max}$: peak drug concentration

$C_{min}$: trough drug concentration

$C_{max}$/MIC: Ratio between the peak concentration and the MIC of the pathogen

$C_{min}$/MIC: Ratio between the trough concentration and the MIC of the pathogen

COV: Covariate

CrCL: Creatinine clearance

CRRT: Continuous renal replacement therapy

CSUPT: Corporació Sanitària Universitària Parc Taulí of Sabadell

CV: Coefficient of variation.

CVVHD: Continuous veno-venous hemodialysis

CVVHDF: Continuous veno-venous hemodiafiltration

CVVHF: Continuous veno-venous hemofiltration

CWRES: Conditional weighted residuals

DV: Dependent variable

EBEs: Empirical Bayesian estimates

ECMO: Extracorporeal membrane oxygenation

EMA: European medicines agency

EUCAST: European committee on antimicrobial susceptibility testing

FD: Farmacodinàmica

FDA: Food and drug administration

FC: Farmacocinètica

FOCE-I: First order conditional estimation method with interaction

GAM: Generalized additive models

HCB: Hospital Clínic of Barcelona

HJ23: Hospital Joan XXIII of Tarragona

HPLC: High performance liquid chromatography

IAPE: Individual absolute prediction error

ICU: Intensive care unit

IIV: inter-individual variability

IL: interleukin

IPE: Individual prediction error

IPRED: Individual Bayesian predicted concentrations

IQR: Interquartile range

IRA: Insuficiència renal aguda

ISF: Interstitial fluid

IWRES: Individual weighted residuals

KDIGO: Kidney disease improving global outcomes

LADME: Processes of liberation, absorption, distribution, metabolism and elimination of a drug

LC-MS/MS: Liquid chromatography - mass spectrometry

MAP: Mean arterial blood pressure

MIC: Minimum inhibitory concentration

MEMB: type of membrane

MODS: Multiple organ dysfunction syndrome

MRM: Multiple reaction monitoring

N/A: Not applicable

N/R: Not reported

NCCLS: National committee of clinical laboratory standards

ND: Not determined

OBS: Observed concentrations

OFV: Objective function value

PAPE: Population absolute prediction error

PD: Pharmacodynamics

PK: Pharmacokinetics

qSOFA: quick SOFA score

Q: Intercompartmental CL

$Q_D$: Dialysis fluid flow rate

$Q_R$: Replacement fluid flow rate

PPE: Population prediction error

PRED: Population Bayesian predicted concentrations

PTA: Probability of target attainment

RRT: Renal replacement therapy

RSE: Relative standard error

S/R: Sensitive/resistant

SAPS: Simplified acute physiology score

$S_c$: Sieving coefficient

SCM: Stepwise covariate model building

$S_d$: Saturation coefficient

SD: Standard deviation

SDMO: Síndrome de disfunció multiorgànica

SOFA: Sequential organ failure assessment

$T_{1/2}$: drug elimination half-life

TCSR: Teràpia continua de suport renal

TDM: Therapeutic drug monitoring

TNF: Tumor necrosis factor

VAP: Ventilator-associated pneumonia

Vd: Apparent volume of distribution

$Vd_c$: Apparent volume of distribution of the central compartment

$Vd_p$: Apparent volume of distribution of the peripheral compartment

WT: body weight at admission

$f_u$: Drug unbound fraction

% $T_{>MIC}$: Percentage of dosing interval while total concentration of the antibiotic is above the MIC of the pathogen

% $f_u T_{>MIC}$: Percentage of dosing interval while unbound concentration of the antibiotic is above the MIC of the pathogen

# CHAPTER 1. INTRODUCTION

Optimization of antibiotic dosing in critically ill patients with severe infections admitted to the Intensive Care Unit (ICU) is still a controversial issue that clinicians face daily. Despite compelling evidence supports that early and appropriate antibiotic therapy is the most determinant intervention for improving patient survival[1], antibiotic selection and dosing is often challenging in critically ill patients because of disease complexity, resulting physiological alterations, and reduced antibiotic susceptibilities of nosocomial pathogens. Classically, the *in vitro* susceptibility of the causal pathogen has been the cornerstone of antibiotic prescription. However, selection according to susceptibility is only a component of the optimal antibiotic therapy, and many other factors must also be considered. In terms of posology, it is paramount to design dosing strategies that maximize the likelihood of attaining the pharmacodynamic (PD) target associated with therapy success in the biophase. This is complex in the critically ill patient since it is well known that critical sickness and clinical interventions can drive to physiological changes likely to alter drug pharmacokinetics (PK) and, therefore, likely to compromise the attainment of these PD targets[2].

Beta-lactam antibiotics are the most prescribed antibiotics in the ICU[3]. Significant and unpredictable PK variability of this pharmacological group has been well documented in critically ill patients: Volume of distribution (Vd) and Clearance (CL) of beta-lactams have been found to vary significantly depending on patient severity, protein concentrations in plasma, organ failure and medical interventions[4]. However, available clinical evidence supporting beta-lactams dosing is still limited and in many cases not applicable upfront to the currently accepted routine clinical management of these patients, being dosing recommendations mainly elucidated from healthy volunteers' data and simulation studies that do not take into account the pathophysiological changes occurring due to systemic inflammation, typically seen in critically ill patients.

Among beta-lactams, meropenem and piperacillin/tazobactam are two of the most frequently prescribed antibiotics for the empirical treatment of severe infections due to their extended spectrum, low profile of adverse events and price. In fact, piperacillin/tazobactam and meropenem (together with imipenem) account for a 27.9% (countries with low incidence of resistance) – 53.7% (countries with high incidence of

resistance) of the empirical prescriptions to septic patients according to a large worldwide multicenter study[5]. These percentages may be even higher for patients who are sicker, such as those with septic shock and acute kidney injury (AKI) necessitating continuous renal replacement therapy (CRRT). Also for this reason, optimization in the use of these antibiotics is especially relevant in such a challenging situation.

## 1.1 The critically ill patient with septic shock and acute kidney injury

Critically ill patients with septic shock and AKI represent an important sub-group of patients in the ICU: a recent worldwide cross-sectional study has estimated that 57% of the patients admitted to the ICU present some degree of AKI[6]. Of these patients, 23.5% require organ support in the form of renal replacement therapy (RRT)[6]. Infection is the most common cause of AKI in the ICU followed by hypovolemia[6, 7], and is associated with adverse outcomes such as increased ICU and hospital stay, development of chronic kidney disease and an unacceptably high (40-60%) in-hospital mortality[8].

A recent consensus document has been published by the European Society of Intensive Care Medicine and the Society of Critical Care Medicine task force with the aim to update the most used definitions of sepsis and septic shock in the medical community[9]. In this document, sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Following are some of the most relevant specifications about sepsis from this document:

- Organ dysfunction can be identified as an acute change in total Sequential Organ Failure Assessment score (SOFA score)[10] ≥ 2 points consequent to the infection. The baseline SOFA score can be assumed to be zero in patients not known to have preexisting organ dysfunction
- A SOFA score ≥ 2 reflects an overall mortality risk of approximately 10% in a general hospital population with suspected infection. Even patients presenting with modest dysfunction can deteriorate further, emphasizing the seriousness of

this condition and the need for prompt and appropriate intervention, if not already being instituted.

- In lay terms, sepsis is a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs.
- Patients with suspected infection that are likely to have a prolonged ICU stay or to die in the hospital can be promptly identified at the bedside with the quick SOFA score (qSOFA), defined as alteration in mental status, systolic blood pressure ≤ 100mmHg and/or respiratory rate ≥ 22/min.

The same document defines septic shock as a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality. Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressor drugs to maintain the mean arterial blood pressure (MAP) ≥ 65mmHg and having a serum lactate level > 18mg/dL despite adequate volume resuscitation. With these criteria, hospital mortality is in excess of 40%[9].

Regarding AKI, many definitions have been proposed to identify this condition in critically ill patients[11, 12] considering several clinical and analytic parameters such as urine output, serum creatinine and glomerular filtration rate (GFR). Nowadays, the latest consensus definition for AKI is the one provided by the Kidney Disease Improving Global Outcomes (KDIGO) international guidelines group, which defines an acute kidney insult as any of the following[13]:

- Increase in serum creatinine by ≥ 0.3 mg/dL within 48 hours; or
- Increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
- Urine volume < 0.5 mL/kg/h for 6 hours

Likewise, AKI is staged for severity according to the following criteria[13]:

<u>Stage 1</u>

- Serum creatinine: 1.5–1.9 times baseline or ≥ 0.3 mg/dL increase

- Urine output: < 0.5 mL/kg/h for 6–12 hours

Stage 2

- Serum creatinine: 2.0–2.9 times baseline
- Urine output: < 0.5 mL/kg/h for ≥ 12 hours

Stage 3

- Serum creatinine: 3.0 times baseline or increase in serum creatinine to ≥4.0mg/dL or initiation of RRT or, in patients < 18 years, decrease in estimated GFR to < 35 ml/min/1.73 $m^2$
- Urine output: < 0.3 mL/kg/h for ≥ 24 hours or anuria for ≥ 12 hours

The KDIGO international guidelines group also provides recommendations for the management of AKI, including considerations to when and how to start RRT. Whether or not to provide RRT, and when to start, are two of the fundamental questions facing clinicians in most cases of severe AKI. In current practice, the decision to start RRT is based most often on clinical features of volume overload and biochemical features of solute imbalance (mainly hyperkalemia and severe acidosis). The actual recommendation is that RRT should be started emergently when life-threatening changes in fluid, electrolyte, and acid-base balance exist. Consideration of the broader clinical context, the presence of conditions that can be modified with RRT, and trends of laboratory tests—rather than single blood urea nitrogen and creatinine thresholds alone—should be paramount when making the decision of starting RRT[13].

## 1.2 Principles of continuous renal replacement therapy

Different methods for extracorporeal renal support in patients with AKI have been used for years in the ICU with the objective of preserving life and allow organ recovery to occur. Despite they do not improve survival or other clinical outcomes such as duration of RRT or ICU or hospital length of stay[14-16], continuous techniques are the most used RRT techniques in the critical care setting; in fact, a large multicenter multinational study in critically ill patients with AKI showed that among the patients who were treated with RRT, continuous renal replacement therapy (CRRT) was the most common initial

modality used (80%), followed by intermittent RRT (16.8%), and peritoneal dialysis and slow continuous ultrafiltration (3.2%)[7]. This is because CRRT is preferred for the treatment of those patients who are unstable hemodynamically, as it can be accurately tailored to changes in the patient's clinical condition during critical illness and hence mimic the normal renal physiology and fluid homeostasis[13, 17]. Continuous techniques can be prescribed to remove solutes by convection (hemofiltration, CVVHF), diffusion (hemodialysis, CVVHD) or a combination of both (hemodiafiltration, CVVHDF). Few data are available on the differences in clinical outcome advantages among CRRT modalities[18] and therefore, there is significant heterogeneity in clinicians' choice of CRRT modality and settings. Briefly, CVVHD is based on the principle of diffusion of solutes across a semipermeable membrane driven by a concentration gradient. This gradient is created by a countercurrent flow, where the dialysate solution flows in the opposite direction to blood flow in the extracorporeal circuit. Both compartments (blood and dialysate) are separated by a semipermeable membrane filter. Dialysis is limited by the membrane pores size, therefore clearance efficiency is inversely proportional to molecular weight, for which small hydrophilic molecules such as urea, creatinine and small antibiotics will be easily cleared. Conversely, larger molecules or highly protein-bound molecules will not be able to pass across the filter membrane. On the other hand, CVVHF is driven mainly by convection removal, where a positive hydrostatic pressure drives water and solutes across the filter membrane from the blood compartment to the filtrate compartment, from which it is drained (ultrafiltrate). As compared to hemodialysis, convection overcomes the reduced removal rate of larger solutes by diffusion, so that drug molecular weight is a less relevant factor, and solutes with a broader range of molecular weights can cross the filter membrane. Despite this, CVVHD is a much more efficient solute removal than CVVHF. Again, only low protein bound hydrophilic molecules are those significantly eliminated by CVVHF. Finally, CVVHDF is the most efficient technique for solute removal and consists on the combination of the two-abovementioned techniques. It results in the joint removal of water and hydrophilic molecules with a broad range of molecular weights[19, 20].

The main settings that can be chosen in CRRT and determine solute and fluid removal are intensity and type of membrane. The CRRT intensity is defined as the effluent flow

rate (combined dialysate and ultrafiltrate flow rates) in mL per hour, or as mL/kg (ideal) body weight per hour. Several studies have evaluated the impact of using different CRRT intensities on mortality and recovery of renal function in critically ill patients, with different and, usually, debatable results[8, 21-24]. Due to this lack of definitive evidence, current clinical recommendations define the "area of best practice" for CRRT intensity laying between 20 and 35 mL/kg/h[17], being the clinician the responsible for individualizing the appropriate CRRT intensity for each particular patient.

Regarding dialysis membranes, many types can be found depending on the membrane surface, pore size and material. Filter permeability is influenced by pore size, the number of pores and the thickness of the membrane; solutes can pass through the membrane according to their size, for which small and mid sized molecules are able cross it without the loss of larger and valuable molecules such as proteins. The surface area of the membrane determines the available area for diffusion and ultrafiltration. Finally, the material of which the membrane has been built determines other characteristics such as adsorption, which is defined as the ability of larger solutes to adhere to its surface. Strong adsorption of mid sized molecules including inflammatory mediators has been shown in *in vivo* models of sepsis[25] and in septic patients[26] using synthetic membranes such as acrylonitrile and sodium methallyl sulfonate copolymer membranes (AN69). Further, AN69 membranes with a surface treatment consisting of the grafting of a first layer with polyethyleneimine and a second layer of heparin[27] (AN69ST membranes) have been recently launched with the aim of enhancing the adsorption of inflammatory molecules and waste products with molecular weights beyond the membrane cut-off[28]. This has been demonstrated with different inflammatory mediators including cytokines[29, 30].

## 1.3 Pharmacokinetic and pharmacodynamic principles for beta-lactams

Since the moment a dose of a drug is administered to a patient, it undergoes several actions that determine its concentrations both in plasma and in the biophase and,

hence, the clinical outcome. A number of phases occur once the drug enters into contact with the organism; these are described using the acronym LADME:

- (L) Liberation of the active substance from the delivery system,
- (A) Absorption of the active substance by the organism,
- (D) Distribution through the blood plasma and different body tissues,
- (M) Metabolism that is, inactivation of the exogenous substance, and finally
- (E) Excretion of the substance or the products of its metabolism.

These abovementioned processes determine the concentration-over-time profiles of a drug. Pharmacokinetics (PK) is the science that studies the interrelationship between drug dose and variations in drug concentrations in plasma and tissue over time due to these processes. PK typifies the effect of the body on a given drug after its administration considering the LADME phases. As meropenem and piperacillin are antibiotics administered intravenously, liberation and absorption phases are not present in the kinetic process, and distribution, metabolism and excretion are the main processes that determine their PK.

The most relevant measures and parameters for the study of meropenem and piperacillin PK are:

- $C_{max}$: peak concentration achieved after a single dose. Units: concentration (*e.g*. mg/L).
- Volume of distribution (Vd): apparent volume of fluid that homogeneously contains the total drug dose administered at the same concentration as in plasma. Units: volume (*e.g.* L).
- Clearance (CL): quantifies the irreversible loss of drug from the body by metabolism and/or excretion through time. Units: volume/time (*e.g.* mL/h).
- Elimination Half-Life ($t_{1/2}$): time required for the plasma concentration to fall by one-half. In linear PK, it depends on both drug CL and Vd. Units: time (*e.g.* h).
- Protein binding: extent to which the drug binds to plasma proteins. Units: percentage (*e.g.* %).

- $AUC_{0-24}$: total area under the concentration-time curve over 24-hours. It provides information about drug exposure and clearance. Units: amount x time/volume (*e.g.* mg x h/L).

Once the drug arrives to the site of action (biophase) at an adequate concentration, it produces its therapeutic effect through its mechanism of action. In our case, beta-lactams are bactericidal by inhibiting the synthesis of the peptidoglycan layer of bacterial cell walls.

Pharmacodynamics (PD) is the science that studies the relationship between drug concentrations and effect. In particular, beta-lactams are considered as time-dependent antibiotics, where optimal activity is achieved when unbound plasma concentrations are maintained above the Minimum Inhibitory Concentration (MIC) of the bacteria for a defined fraction of the dosing interval (% $f_u T_{>MIC}$) [31].

## 1.4 Beta-lactams physicochemistry

A simple drug chemical classification can be made from the affinity for water for each particular compound, classifying them as hydrophilic or lipophilic. Depending on this ability to dissolve in water and fat, drug molecules will distribute to one body compartment preferably over another. Therefore, *hydrophilic antibiotics* include those antibiotics that mainly distribute in the extracellular body water: they are not able to distribute inside the cells because they are unable to cross the lipid cell membrane, while *lipophilic antibiotics* distribute intracellularly and into the lipid tissues, such as adipose tissue and central nervous system. Due to these distribution proprieties, drug affinity for water will determine the total Vd of the drug. A paradigmatic example of a hydrophilic family of antibiotics is beta-lactams. Therefore, the Vd of beta-lactams is usually consistent with the extracellular body water (approximately 0.1-0.3L/kg in non-critically ill individuals). This feature makes Vd of beta-lactams very variable in critically ill patients due to the frequent fluid shifts that commonly occur in this special population.

Consideration of Vd is especially relevant in initial antibiotic doses, as a larger Vd supposes lower serum drug concentration and requires the administration of loading doses to properly saturate body tissues where the drug distributes whilst still achieving appropriate concentrations at the site of infection.

## 1.5 Impact of altered beta-lactam pharmacokinetics on dose requirements in patients with septic shock and CRRT requirement

As mentioned above, septic shock is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection such that underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality[9]. In this scenario, homeostasis cannot be maintained without intervention, and usually involves two or more organ systems, especially the renal system, as it is particularly sensitive to hypoperfusion due to the dependence of glomerular filtration on arteriolar blood pressure. Mechanistically, the pathogenesis of septic shock is not yet completely understood, but it is accepted that a key role in the development of severe sepsis is played by an immune and coagulation response to an infection. Infection mediators such as endotoxin or exotoxin act as an inflammatory insult that triggers a very complex, variable and prolonged host response, in which the production of pro-inflammatory and anti-inflammatory mediators like interleukin-1β (IL-1β) and tumor necrosis factor (TNF) can lead to a constellation of clinical manifestations. These cytokines cause neutrophil–endothelial cell adhesion, activate the clotting mechanism, and generate microthrombi. They also stimulate the release of numerous other mediators, including leukotrienes, lipoxygenase, histamine, bradykinin, serotonin, and IL-2[32]. Many of these endogenous molecules are active on the vascular endothelium, leading to vasodilatation and transcapillary leakage of water and proteins into the extracellular space[33]. Therefore, during the first stage of septic shock, there is a dilation of peripheral arteries; this decreases peripheral arterial resistance and causes a reflex increase in heart rate and cardiac output. Later, typical features of septic shock may appear, including a decrease in cardiac output and blood pressure. During the “warm shock” phase, hypoperfusion of vital organs (*e.g*. brain, kidneys or lung) occurs, while

peripheral tissues and non-vital organs still receive high blood flow as a consequence of peripheral vasodilation and increased cardiac output. Later on, hypoperfusion of the peripheral tissues can occur as a result of the body's attempt to maintain an adequate perfusion of the vital organs[34]. In this context of circulatory dysregulation, impaired tissue oxygenation has a crucial role in the pathogenesis of organ failure. Several factors, including hypotension, and microvascular thrombosis, contribute to impaired tissue oxygenation and organ damage. In addition, mitochondrial damage caused by oxidative stress and other mechanisms impairs cellular oxygen use. The most commonly affected organ systems are the cardiovascular, the respiratory, the renal and the central nervous systems[35]. With regards to the renal system, the mechanisms that trigger and develop AKI have yet to be completely understood. Hemodynamic factors have an important role in the loss of glomerular filtration rate, mainly due to low kidney perfusion, but it seems that this is not the sole component that leads to the AKI syndrome. Other non-hemodynamic systems of organ damage are likely to be involved, such as inflammatory, immunologic or toxic mechanisms[36].

Linking the pathophysiology of septic shock and organ dysfunction to beta-lactam dose requirements, one can distinguish between two important time periods that must be considered for dosing. The first period corresponds to the first 24-48h of therapy, where the main determinant for antibiotic dosing must be Vd since it determines the early attainment of antibiotic concentrations within the therapeutic range. Consideration of this issue is crucial as it has been extensively demonstrated that the therapeutic intervention that improves the most survival in critically ill patients with septic shock is early and appropriate antibiotic administration[1]. In general, an increased Vd for hydrophilic antibiotics should be expected in all critically ill patients with septic shock, as capillary leakage increases the amount of extracellular water, where these antibiotics distribute[4]. When the Vd is abnormally increased, distribution of hydrophilic antibiotics such as beta-lactams becomes more extensive for trying to compensate this larger space, with greater movement of the drug molecules from the central compartment (bloodstream) to the peripheral compartments (mainly extravascular fluid). Consequently, this decreases the drug amount in plasma and, therefore, the plasma concentration. Consequently, given a particular MIC, shorter % $f_u T_{>MIC}$ in plasma should

be anticipated, which compromises beta-lactams pharmacodynamic target attainment[37]. This effect may be magnified in the occurrence of hypoalbuminemia for highly-and moderately protein-bound beta-lactams, as lower albumin concentrations translate into a higher proportion of unbound fraction, that will in turn distribute to the increased extracellular space and thus decrease plasma concentrations[38]. Regarding beta-lactams PK and PD at the biophase, as peripheral tissues are frequently the source of infection, fluid shifts, capillary leak and edema can also lead to a failure to attain therapeutic concentrations at the site of infection[12]. In this case, despite the increased movement of plasma and drugs to the extravascular compartment, drug concentrations at the target site can be decrease due to a dilution effect. The effect of peripheral hypoperfusion in the second phase of shock will also contribute to compromise the attainment of therapeutic concentrations in the biophase. It follows that critically ill patients may require front-loaded doses of beta-lactam antibiotics during the first 24-48h regardless of organ function in order to compensate the increased Vd and to reach concentrations within the therapeutic range on the first day of therapy[37].

The second period starts from day 2 and thereafter. During this period, the estimated drug CL is the main determinant of dosing, with the objective of maintaining the equilibrium between input and output as the tissues should already exhibit therapeutic antibiotic concentrations. In this context, CRRT represents a particular challenge in terms of beta-lactam dosing, as concentrations may vary depending on the degree of extraction, that in turn depends on drug physicochemistry and CRRT modality and settings[20]. With regards to CRRT modality, there is discordance in the literature on whether a specific modality makes a difference or not in terms of dosing. While some studies support that there is a difference[39, 40], some others suggest that there are no substantial variations between modalities[41]. Theoretically, convective and diffusive methods eliminate molecules from the bloodstream using different processes, and therefore total drug CL should differ between CRRT modalities as has been shown with piperacillin and meropenem[39, 40], but the majority of dosing recommendations for CRRT are still broad and generic.

Regardless of the modality prescribed, a common determinant of drug clearance by CRRT is protein binding. Due to protein size and electrical charge, protein-bound molecules are unable to pass through the filter membranes and only unbound molecules will be available for elimination by CRRT. This is such critical that both sieving ($S_c$) and saturation coefficients ($S_d$) are usually simplified as the unbound drug fraction. However, antibiotic protein-binding alterations have been broadly observed in ICU patients[38] due to the altered plasmatic proteins homeostasis associated to critical illness and to the presence of other highly protein-bound exogenous drugs and endogenous molecules in plasma. This may translate, consequently, in alterations in the extent to which an antibiotic is cleared by CRRT. However, whereas the effect of hypoalbuminemia on antibiotic pharmacokinetics in critically ill patients with preserved renal function has been documented in previous studies[38], there are no available studies regarding its combined impact with CRRT.

Other potential factors likely to affect the extent to which beta-lactams are cleared by CRRT are CRRT settings such as intensity or the type of membrane prescribed. Regarding CRRT intensity, there are a number of studies that document that total flow rate may affect the CL of meropenem and piperacillin binding[39, 40, 42, 43], where others suggest that low intensities may be enough to maximize the CL of these antibiotics by CRRT and that higher intensities may add little to total CL[44]. Interpretation of these results and consequent dose adjustment based upon intensity is controversial and challenging. Regarding type of membrane, there are limited data on the impact of different materials and surface areas on total and CRRT antibiotic CL. In particular, a small study with colistin[27] suggests that heparin and polyethyleneimine surface-coated AN69ST may increase the CL of polar antibiotics by means of surface absorption compared to conventional AN69 filters. However, no extensive work has been performed yet under this hypothesis, which is clearly insufficient for providing dose recommendations depending on the type of membrane used.

Further, residual renal function is usually variable, difficult to assess and rarely considered when dosing, despite that its relevant contribution to beta-lactam CL in patients undergoing CRRT has been described with meropenem and piperacillin, among

other antibiotics[45-47]. Finally, the patient's condition evolves throughout the ICU stay, so that the influence of the previously mentioned factors may vary over time, making it difficult to generalize recommendations only based on CRRT modality and settings. Dosing should ideally be titrated daily depending on the CRRT characteristics and the evolution of the patient's clinical condition. However, there is a dearth of data guiding dose adjustment at the bedside based on easily available (*i.e.* non-invasive) clinical and biological parameters.

## 1.6 Population PK and Monte Carlo Simulations

As stated above, antibiotic dosing optimization is considered an essential step for the achievement of the best possible outcomes in the treatment of patients with severe infections. It is well known, though, that administration of standard doses does not always guarantee the achievement of therapeutic concentrations due to the broad variability in PK encountered among patients, in particular critically ill patients, who exhibit very important variations in their physiology that have a direct effect in the achievement of therapeutic drug concentrations in plasma and biophase. To overcome these variations and administer an individualized posology to each patient, it is important to identify the sources of PK variability. In this context, population PK analysis can be a very powerful tool to assist clinicians in the complex task of antimicrobial use optimization.

Population PK is a mathematical-statistical methodology introduced by Sheiner and Beal[48] which introduces a different approach to drug PK; it is based in the estimation of the PK parameters encountered in a whole population, while classical PK are based in the estimation of individual PK parameters. Basically, population PK studies inter- and intra-individual variability in a group of patients with defined clinical and patho-physiological characteristics. This methodology is broadly used in both academic research and pharmaceutical drug development, and has the following aims:

- to describe the PK of a drug in a group of patients that are representative of the target population,

- to identify the principal sources of the PK variability encountered in this population (*e.g.* clinical and demographic characteristics, concomitant medication, …), and
- to evaluate the inter- and intra-individual variability that has not been explained by those identified sources of PK variability (residual variability).

There are different approaches to perform population PK analysis, mainly the naïve-pooled analysis and the standard two-stage analysis, but the most frequently used approach is the non-linear mixed effects modeling because it exhibits important advantages over the other methodologies, mainly less biased parameter estimation[49].

### *1.6.a Non-linear mixed effects modeling*

Sheiner *et al.* performed the first attempt at estimating interindividual pharmacokinetic variability without neglecting the difficulties (*e.g.*, data imbalance, sparse data, subject-specific dosing history) associated with data from real patients undergoing drug therapy by using the nonlinear mixed-effects model approach. This approach analyzes the data of all individuals at once, but considering the interindividual random effects structure. This ensures that confounding correlations and imbalance that may occur in observational data are properly accounted for[49].

Non-linear mixed effects modeling is based in two principal components:

1) A structural model, defined by fixed effect parameters that inter-relate dependent (concentrations) and independent (time, dose, ..) variables. Fixed effect parameters are the population values of the PK parameters and their relations with the covariates evaluated in the study.
2) A statistical or variance model, defined by random effect parameters, which evaluates the existing variability in the fixed effects parameters and in the dependent variable. Random effect parameters are representatives of inter- and intra-individual (residual) variability, and are expressed by the variances $\omega^2$ and $\sigma^2$ from the distributions $\eta_i$ and $\varepsilon_j$ that come, respectively, from the variance-covariance matrixes Ω and Σ.

Data for the development of non-linear mixed effects modeling consists on an independent sample of *n* subjects with the *i*th subject having $n_j$ observations (drug concentrations) measured at different time points. Non-linear mixed effects modeling establishes that variability in the measured response (*i.e*. plasma concentrations) in a sample composed of *n* individuals is due to 1) residual error, which includes intra-individual variability, variability in the analytical technique, errors in the process of sample collection, … and 2) inter-individual variability on fixed effect parameters. Therefore, the dependent variable y (plasma concentration) can be described by equation 1:

Eq. 1: $$y_{ij} = f(\theta_i, x_{ij}) + \varepsilon_j$$

,where $y_{ij}$ are the individual observations for a *i* subject collected at each time $x_{ij}$ for a *j*=1,…*n*, $\theta_i$ is the vector of parameters corresponding to the *i* subject, $f$ is a non-linear function that establishes the relationship between predictions and population PK parameters for each individual, and $\varepsilon_j$ is the difference between the observed and the predicted value of the dependent variable at a time *j*[50].

It is generally assumed that the values of $\varepsilon_j$, that represent residual variability, are independent and follow a normal distribution with a mean = 0 and a variance = $\sigma^2$. Regarding the population PK parameters, they are constant for the population, but their magnitudes can vary from one individual to another as per equation 2:

Eq. 2: $$\theta_i = g(\bar{\theta}, z_{ij}) + \eta_j$$

, where $g$ is the structural model that best defines $\theta_i$ (vector of the individual PK parameters) as a function of a series of specific covariates $z_{ij}$ for each individual *i*, $\overline{\theta}$ is the vector of the population PK parameters and $\eta_j$ is the associated inter-individual variability.

### *1.6.b Structural model*

The fist step in the development of a population PK model is to identify the base or structural model, which is the model that best describes the data in absence of covariates. The structural model, therefore, defines the evolution of concentrations (dependent variable) over time (independent variable) using integrated or differential equations that inter-relate with the fixed effect parameters (Vd, CL, …). The structural model tends to be compartmental. From the structural model, a covariates model will be developed that includes those covariates that may have an influence over the PK parameters. The regression parameters that define the influence of the covariates on the structural model are also fixed effect parameters.

### *1.6.c Statistical model*

In a population PK analysis, there are usually two forms of variability: inter-individual variability and intra-individual variability (residual error). Inter-individual variability refers to the variation of a parameter across different individuals in the population, whereas residual variability refers to the unexplained variability in the observed data after controlling for other sources of variability.

#### *1.6.c.1 Inter-individual variability*

Assuming a normal distribution, inter-individual variability can be modeled using different mathematical models. Some of the more frequently used models are the following:

| | | |
|---|---|---|
| *Additive model* | Eq. 3: | $\theta_i = \bar{\theta} + \eta_j$ |
| *Proportional model* | Eq. 4: | $\theta_i = \bar{\theta} \times (1 + \eta_j)$ |
| *Exponential model* | Eq. 5: | $\theta_i = \bar{\theta} \times (e^{\eta_j})$ |

#### *1.6.c.1 Residual error*

With regards to residual error, the most frequently used models, that assume a normal distribution of $\varepsilon_j$, are the following:

| | | |
|---|---|---|
| *Additive error* | Eq. 6: | $y_{ij} = f(\theta_i, D_i, x_{ij}) + \varepsilon_j$ |
| *Proportional error* | Eq. 7: | $y_{ij} = f(\theta_i, D_i, x_{ij}) \times (1 + \varepsilon_j)$ |
| *Mixed error* | Eq. 8: | $y_{ij} = f(\theta_i, D_i, x_{ij}) \times (1 + \varepsilon_{j1}) + \varepsilon_{j2}$ |

, where $f(\theta_i, D_i, x_{ij})$ represents the individual predicted concentration using the structural model $f$, depending on the values of the individual parameters $\theta_i$, the time $x_{ij}$ at which samples were collected and the administered dose $D_i$.

### *1.6.d Covariate analysis*

In a population PK model, covariates can be prognostic factors that explain part of the variability associated to the parameters. Therefore, identification of covariates that modify the PK parameters is essential in population PK, as it is useful for 1) explaining part of the observed variability, 2) increment the predictive performance of the model and, 3) facilitate individualization of dosing schemes. The fist step in building a covariate model is to identify the covariates that are to be examined. The covariates selected should have some physiological rationale for their inclusion in the model, and should result in a model improvement. Previous literature on the study drug PK can be helpful in the identification of potential covariates to be tested. The covariates can be introduced in the population PK model using different mathematical equations that depend on the covariate nature (continuous *versus* categorical). The most frequently used equations, as well as the specific steps of the covariate analysis, are detailed in the methodology section.

### *1.6.e Model validation*

Model validation is a key step in population PK analysis, and has the main aim of evaluating whether the final model describes the data properly, to ultimately demonstrate the predictive performance of the model. Model validation can be performed as internal or external validation depending on the aim of the validation and the nature of the data used for the validation. As such, internal validation endeavors to evaluate whether the model adequately describes the data, for which it is performed using the same data that was used for its development. There are several graphical and

mathematical methods for performing the internal validation of a population PK model, being visual predictive checks[51] and resampling techniques (such as bootstrap[52], cross-validation[53] or jackknife) some of the most frequently used.

Regarding external validation, its main aim is to demonstrate the predictive performance of the model in front of new data, and it is performed by comparing observed data from new subjects with data that the model predicts using the characteristics of these new subjects[54]. External validation is, ultimately, the most precise and accurate way to evaluate the verisimilitude of a model and its suitability to be used in clinical practice.

### *1.6.f Monte Carlo Simulations*

Monte Carlo simulations are essentially the use of computer software via simulation platforms for data generation. This has the aim of incrementing the sample size of a study considering both the variability of the population PK parameters and the identified covariates to provide predictions of the likely result of different therapeutic approaches on the achievement of therapeutic targets. For the specific case of antimicrobial dosing, Roberts *et al*. described the principal requirements to perform Monte Carlo simulations in this context, that are: 1) a well-evaluated and robust population PK model with defined distribution and covariance of PK parameters, 2) a covariate model that provides information about how the population PK parameters change with respect to observable clinical characteristics, and 3) a defined target that inter-relates PK and PD, that for beta-lactams is the % $f_u T_{>MIC}$[55]. From this simulation data, it can be calculated the probability of target attainment (PTA), that is defined as the probability that a PD index, in the beta-lactams case the attainment of a certain % $f_u T_{>MIC}$, is achieved for a specific MIC. In other words, for each evaluated dosing regimen, it is possible to calculate the percentage of individuals that will achieve the PD target associated with success for a certain MIC and depending on certain covariates. Consequently, for a subgroup of patients such as the critically ill patients, that exhibit high variability on their physiology that alters drug PK and ultimately dose requirements, this methodology is potentially useful for individualizing dosing.

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# CHAPTER 2. HYPOTHESIS AND AIMS

Despite decades of clinical experience with antibiotic use, treatment of severe infections remains a challenge for clinicians. From a clinical perspective, optimization of antibiotic use is crucial in critically ill patients with septic shock, where early and appropriate antibiotic prescription has been shown to be the most effective intervention for reducing mortality.

In our environment, patients with septic shock and AKI necessitating CRRT are especially likely to receive antibiotic therapy with broad-spectrum beta-lactams, mainly meropenem and piperacillin (in combination with tazobactam). The impact of septic shock, AKI and CRRT implementation on these antibiotics' dose requirements is vital, as medical interventions and the disease itself are likely to produce significant variations in their PK, which will lead to alterations in drug concentrations over time and hence compromise the achievement of optimal therapeutic concentrations. However, despite the PK derangements in these antibiotics have been previously described for patients with septic shock, there is still an absence of a general guidance to individualize piperacillin and meropenem dosing in those patients with septic shock and AKI necessitating CRRT, who have higher levels of sickness severity and whereby effective antibiotic therapy may even have a bigger impact on clinical outcome. *Ergo,* it is essential to understand well the PK of these antimicrobials and the factors that influence the PK processes in our patients. In this context, population PK analysis and Monte Carlo simulations enable the characterization of drug PK and the identification of those factors that influence PK. Later on, this knowledge can be applied in the clinical setting in order to design dosing strategies that are individualized to the particular characteristics of each patient and enhance the probabilities of therapy success.

Therefore, the present thesis was developed under the **hypothesis** that dosing of the most prescribed beta-lactams in the ICU, meropenem and piperacillin, is not optimal in critically ill patients with septic shock and AKI requiring CRRT due to disease and medical-driven variations in antibiotic PK and, therefore, in dose requirements.

Consequently, the **aims** of this thesis were:

1) to evaluate the suitability of current meropenem and piperacillin dosing recommendations in critically ill patients with septic shock and AKI necessitating CRRT,

2) to identify the sources of variability that compromise optimal dosing in this population, and

3) to develop new recommendations taking into account these variability sources.

To fulfill these aims, the present work was divided into three main studies:

**STUDY 1:** Systematic review and critical evaluation of the available evidence on meropenem and piperacillin dosing in critically ill patients with septic shock and AKI necessitating CRRT. Specifically,

a. Description of the current clinical scenario for meropenem and piperacillin dosing in these patients;
b. Identification of the sources of variability among the different studies that compromise generalization to clinical practice;
c. Identification of the opportunities for future research and improvement in this field.

**STUDY 2:** Characterization of meropenem PK in critically ill patients with septic shock and AKI necessitating CRRT by developing and validating a population PK model to further provide dosing recommendations. For that purpose, the following concrete objectives were set:

d. Identification of the sources of meropenem PK variability in these patients;
e. Validation of the final model to investigate the feasibility and performance of the obtained population PK model;
f. Development of different dosing simulations to assess their PTA by MIC, in order to provide individualized dosing recommendations based on clinical characteristics that maximize the attainment of the pharmacodynamic target associated with therapy success for carbapenems (% $f_u T_{>MIC}$).

**STUDY 3:** Characterization of of piperacillin PK in critically ill patients with septic shock and AKI necessitating CRRT by developing and validating a population PK model to further provide dosing recommendations. For that purpose, the following concrete objectives were set:

g. Identification of the sources of piperacillin PK variability in these patients;
h. Validation of the final model to investigate the feasibility and performance of the obtained population PK model;
i. Development of different dosing simulations to assess their PTA by MIC, in order to provide individualized dosing recommendations based on clinical characteristics that maximize the attainment of the pharmacodynamic target associated with therapy success for penicillins (% $f_u T_{>MIC}$).

# CHAPTER 3. PATIENTS AND METHODS

## 3.1 Study 1

**Systematic review and critical evaluation of the available evidence on meropenem and piperacillin dosing in critically ill patients with septic shock and AKI necessitating CRRT.**

With the aim of thoroughly compile and analytically evaluate the available evidence on meropenem and piperacillin dosing in critically ill patients with septic shock and AKI requiring CRRT, a systematic review of the published evidence was performed. Data for this review were identified by systematic searches of PubMed (1966 to November 2013), as well as references cited by relevant articles. Search terms included were “meropenem” or “piperacillin”, “critically ill patient” or “intensive care unit” or “critical illness”, “continuous veno-venous hemodiafiltration” or “continuous veno-venous hemodialysis” or “continuous veno-venous hemofiltration” or “continuous renal replacement therapy” and “pharmacokinetics” or “pharmacodynamics”. Relevant articles written in English, Spanish and Catalan where considered for this review. Those describing the pharmacokinetics of meropenem and piperacillin/tazobactam in adult critically ill patients receiving CRRT were included.

## 3.2 Studies 2 and 3

**Characterization of the PK of meropenem and piperacillin in critically ill patients with septic shock and AKI necessitating CRRT; identification of the sources of PK variability in these patients; and development of individualized dosing recommendations based on clinical characteristics**

An observational, prospective, multicenter, open-label PK study was performed in the Intensive Care Units of the Hospitals Corporació Sanitària Universitària Parc Taulí of Sabadell (CSUPT), Clínic of Barcelona (HCB) and JoanXXIII (HJ23) of Tarragona. Authorization for the study was granted by the Spanish Regulatory Medicines Agency (code IEM-ANT-2012-1) and ethical approval was obtained from the local Ethics Committees **(appendices 1 and 2)**. The study was conducted following the

Declaration of Helsinki guidelines. Consent to participate was obtained from the patient's legal representative **(appendix 3)**.

Inclusion criteria were age ≥ 18 years, septic shock diagnosed by the Surviving Sepsis Campaign guidelines criteria[1], CRRT requirement and clinical indication for meropenem or piperacillin/tazobactam. The major exclusion criterion was severe chronic renal failure requiring intermittent hemodialysis. In accordance with usual practice, all patients had an indwelling arterial cannula and a urinary catheter.

### *3.2.a Demographic and Clinical Data*

Patients' demographic and clinical data were collected. Age, weight, height, sex, site of infection, routine serum biochemistry, residual diuresis (defined as the volume of urine collected over the 24h of the natural day of the study), severity scores at admission (Acute Physiology and Chronic Health Evaluation II score (APACHE II)[2]) and on the day of study (SOFA[3]), vasopressors requirement, CRRT settings (mainly CRRT modality, intensity, blood flow and type of dialysis membrane), isolated microorganisms and MICs to meropenem/piperacillin, days of antibiotic therapy and hospital survival were recorded **(appendix 4).** These data came from clinical routine and were registered in a database specially designed for this study and only available to the researchers.

### *3.2.b Continuous Renal Replacement Therapy (CRRT)*

Patients prescribed either CVVHDF or CVVHF were considered for inclusion. The CRRT systems used were Prisma® (Hospal, France). According to *in-house* guidelines, filters used were 1.5$m^2$ AN69ST acrylonitrile and sodium methallyl sulfonate copolymer filter (PrismaFlex® ST150, Hospal, France) at HJ23 and 0.9 $m^2$ AN69 acrylonitrile and sodium methallyl sulfonate copolymer filter (PrismaFlex® M100, Gambro Hospal, Switzerland) at CSPT and HCB. Dialysate and ultrafiltrate flow rate and blood flow were at the discretion of the treating physician.

### *3.2.c Antibiotic administration and dosage*

All patients received meropenem or piperacillin/tazobactam as their standard of care. Dose and infusion time were at the discretion of the treating physician, ranging from 500mg every 12h (q12h) to 2000mg/q8h for meropenem and from 2000mg/q8h to 4000mg/q6h for piperacillin. In all patients, antibiotics were administered through a separate lumen of a venous catheter using free-fall bolus systems or volumetric infusion pump controllers as required, depending on the rate of infusion.

### *3.2.d Blood sampling*

Per sample, 5mL of blood were collected at apparent steady state of meropenem or piperacillin. For bolus sampling, 6 samples were collected at pre-defined times. For extended antibiotic infusion sampling, 5 samples were collected at different times (table 1):

**Table 1:** samples collection times

| Sample | Time (Bolus) | Time (Extended infusion) |
|---|---|---|
| 1 | 10 min pre-dose | 10 min pre-dose |
| 2 | 0 min (end of the infusion) | 0 min (end of the infusion) |
| 3 | 15 min | 60 min |
| 4 | 60 min | 120 min |
| 5 | Between 3-6h | Pre-dose |
| 6 | Pre-dose | |

Blood samples were kept in ice and, within one hour of collection, were centrifuged at 3000rpm at 4$^{o}$C for 10min. Immediately after, plasma was frozen at -80$^{o}$C for posterior analysis.

### *3.2.e Liquid Chromatography-Mass Spectrometry (LC-MS/MS) analysis*

Meropenem and piperacillin plasmatic concentrations were analyzed in an external laboratory (Dr F. Echevarne, Análisis S.A., Barcelona, Spain) using a validated method. Briefly, a 50 µL aliquot of plasma with buffered internal standard (cefotaxime sodium salt, Santa Cruz Biotechnology, Texas, USA) was precipitated with methanol, centrifuged thereafter, mixed with Milli-Q® grade water and injected into the chromatographic system. Injection volume was 3 µL. Total meropenem and piperacillin in plasma were measured using liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) (1200 HPLC binary pump, Agilent Technologies and API 4000 AB SCIEX mass spectrometer). The autosampler temperature was set to 4°C. The stationary phase was an Atlantis T3 50 x 2.1mm x 3µm column maintained at 40°C. The mobile phase was composed of (A) 10mM ammonium formiate buffer pH = 2.5 and (B) 0.1% formic acid in acetonitrile with a gradient flow at a rate of 0.5mL/min. Meropenem, piperacillin and the internal standard (cefotaxime) were detected by multiple reaction monitoring (MRM). The method was linear over a range of meropenem and piperacillin concentrations of 0.4-300mg/L and 1.5-400mg/L, respectively. Analysis of independently prepared quality control samples indicated good within-run and between-run precision (coefficients of variation ≤10%) and accuracy (measured concentrations ≤10.0% from target concentrations) according to the European Medicine Agency Guidelines[4].

Similarly, short term stability (4h), long term stability (1.5 years), freeze and thaw stability and processed samples conditions stability were assessed in order to ensure that every step taken during sample preparation and sample analysis, as well as the storage conditions used do not affect the concentration of the analyte[4]. In all cases, measured concentrations were ≤10.0% from target concentrations.

### *3.2.f Statistical analysis*

Statistical analysis was performed using SPSS v.20 for Macintosh (IBM®SPSS®Statistics, USA) or R for Macintosh v3.0.2 (The R Foundation for Statistical Computing). Results are expressed as absolute and relative frequencies for categorical variables and as medians with percentiles 25-75 (IQR) for continuous

variables. A two-tailed Student t-test was used for comparing normally distributed variables, U-Mann Whitney test for non-normally distributed variables and chi-square ($\chi^2$) test for categorical variables. The significance level for all analyses was defined as $p \leq 0.05$.

### *3.2.g Population pharmacokinetic modeling*

Population PK analysis was performed using NONMEM v.7.3 (Icon Development Solutions, USA)[5] following a three-step strategy: 1) development of the basic population PK model, 2) covariate selection and set-up the final population PK model, and 3) validation of the final population PK model[6, 7].

#### *3.2.g.1 Development of the basic population PK model*

In both cases (meropenem and piperacillin), models of one and two compartments with first-order elimination were evaluated. Interindividual variability on PK parameters was modeled as log-normal after being tested for log-normality. Additive, proportional and combined error models were tested for residual variance on drug concentrations. The first-order conditional estimation method with interaction (FOCE-I) was used for parameter estimation.

Goodness-of-fit for a model was assessed by:

- biological plausibility of the estimated population PK parameters;
- changes in the NONMEM minimum objective function value (OFV): -2log-likelihood;
- plots of population and individual Bayesian predicted (PRED and IPRED, respectively) *versus* observed antibiotic concentrations (DV); and conditional weighted residuals (CWRES) *versus* observed antibiotic concentrations (DV) and time[6, 8]; and
- changes in the standard error of parameter estimates (precision).

The difference in the -2log-likelihood between two hierarchical models was assumed to follow an asymptotical $\chi^2$ distribution with degrees of freedom equal to the difference in number of model parameters. A significance level of 0.05 denoted a

significant improvement of fit for a one-parameter difference. The following table summarizes the association between changes in the OFV and the *p*-value.

**Table 2:** equivalence between decreases in the OFV and the significance level (*p*-value), assuming that the difference in the -2log-likelihood between two hierarchical models follows an asymptotical $\chi^2$ distribution with degrees of freedom equal to the difference in the number of model parameters.

| **Decrease in the OFV** | ***p*-value** |
|---|---|
| >3.84 | <0.05 |
| >6.63 | <0.01 |
| >7.88 | <0.005 |
| >10.83 | <0.001 |

The Xpose® program, version 4.0, was used to guide the model building process[9].

*3.2.g.2 Covariate selection and set-up the final population PK model*

In a second step, all reasonable demographic and biological factors were tested for inclusion as covariates in the basic population PK model. The relationship between individual PK parameters and covariates was graphically examined. The generalized additive models (GAM) procedure (on Xpose®) was also used to investigate the effects of the covariates on model parameters. They were further tested in NONMEM using the stepwise covariate model building (SCM) approach. Continuous covariates were assessed as a proportional or a power function (Equations 9 and 10):

Eq 9*:* $$P_j = \theta_{POP} \times (1 + \theta_{COV} \times \frac{COV_i}{Median(COV_i)})$$

Eq 10*:* $$P_j = \theta_{POP} \times (\theta_{COV}^{\frac{COV_i}{Median(COV_i)}})$$

,where $P_j$ is the PK parameter for the $j^{th}$ patient, $\theta_{POP}$ is the typical value of the PK parameter in the population, $\theta_{COV}$ is the multiplicative factor for the influence of a particular continuous covariate on the PK parameter, $COV_i$ is the individual value of

this covariate for the $j^{th}$ patient, and $Median(COV_i)$ is the median value for this covariate in the study subjects.

Categorical variables were included in the model as equation 11:

$$\text{Eq. 11:} \qquad P_j = \theta_{POP} + \theta_{COV} \times (1 - COV_i)$$

,where $P_j$ is the PK parameter for the $j^{th}$ patient, $COV_i$ is a numeric index value (1 for the reference category or 0 for the comparative category), $\theta_{POP}$ is the typical value of a PK parameter for the reference covariate values (*i.e.*: $Cov_i$ equals 1) and $\theta_{COV}$ is the multiplicative factor for the influence of this covariate on the PK parameter. Covariates were first entered individually into the basic population PK model and then by cumulative forward inclusion/backward elimination procedures. Each covariate investigated was retained if it led to a significant improved fit evaluated by: biological plausibility, graphical displays based on the agreement between the observed (OBS) and predicted drug concentrations (PRED and IPRED), uniformity of the distribution of the CWRES, improvement of the precision in parameter estimates, and log-likelihood ratio test. The difference in minus twice the log likelihood - the NONMEM OFV - between a full model (including a covariate) and a reduced model (without the covariate) was assumed to be asymptotically $\chi^2$ distributed with degrees of freedom equal to the difference in the number of parameters between the models. Covariates were included in the model if they yielded $p$ <0.05 according to this test. A significance level of $p$ <0.001 was required during the backward elimination step. In addition, a decrease of at least 10% in inter-individual variability associated with a specific PK parameter was considered clinically relevant for the inclusion of that specific covariate. The extent of Bayesian shrinkage, as a measure of model over-parameterization, was evaluated for each PK parameter in the final model using PsN[10].

#### *3.2.g.3 Model evaluation*

Internal validation of the final PK model was performed by graphical and statistical methods, including visual predictive checks[11]. Bootstrap resampling technique was

used to build confidence intervals (CI) of PK parameters to assess their stability and evaluate the robustness of the final model[12].

When possible, the external predictive performance of the PK model was assessed by analyzing data from new individuals (20-30% of the study population) following the Food and Drug Administration (FDA) guidelines[13]. Empirical Bayesian estimates (EBEs) of antibiotic concentrations for all sampling times were obtained by Bayesian estimation using the PK parameter values from the final population PK model as prior information. The performance of the Bayesian analysis was evaluated by comparison of the OBS concentrations with the PRED AND IPRED concentration values. Bias was assessed in terms of individual and population prediction error (IPE% and PPE% respectively). Precision was assessed as absolute individual and population prediction error (IAPE% and PAPE% respectively)[14], as follows:

Bias:

Eq. 12: $$IPE(\%) = \left[\frac{|OBS - IPRED|}{OBS}\right] \times 100$$

Eq. 13: $$PPE(\%) = \left[\frac{|OBS - PRED|}{OBS}\right] \times 100$$

Precision:

Eq. 14: $$IAPE(\%) = \left[\frac{|OBS - IPRED|}{IPRED}\right] \times 100$$

Eq. 15: $$PAPE(\%) = \left[\frac{|OBS - PRED|}{PRED}\right] \times 100$$

### *3.2.h Dosing simulations*

Stochastic simulations for different dosing regimens were performed using the Monte Carlo approach. Population mean and inter-individual variability of the PK parameters were used to simulate 1000 PK responses to different meropenem and piperacillin dosing regimens, considering those covariates included in the final population PK models. From these data the percentages of patients with 40% $f_u T_{>MIC}$, 50% $f_u T_{>MIC}$, 100% $f_u T_{>MIC}$ and/or 5x100% $f_u T_{>MIC}$ according to meropenem and piperacillin clinical susceptibility breakpoints[15] were calculated as appropriated (PTA). A PTA ≥ 90% was considered satisfactory[16].

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# CHAPTER 4. SUMMARY OF THE ARTICLES

The present doctoral thesis is composed by three articles that focus on the optimization of meropenem and piperacillin dosing in critically ill patients with septic shock and AKI requiring CRRT.

These articles are the following:

1. Ulldemolins M, Vaquer S, Llauradó-Serra M, Pontes C, Calvo G, Soy D, Martín-Loeches I. Beta-lactam dosing in critically ill patients with septic shock and continuous renal replacement therapy. [Review]. *Crit Care* 2014; **18:** 227-243. doi: 10.1186/cc13938.

   *Critical Care* is a journal included in the Journal Citation Report of the Web of Science®, with an impact factor in 2014 of **4.476** (ranked 5/27 under the category *Critical Care Medicine*, first quartile).

2. Ulldemolins M, Soy D, Llauradó-Serra M, Vaquer S, Castro P, Rodríguez AH, Pontes C, Calvo G, Torres A, Martín-Loeches I. Meropenem population pharmacokinetics in critically ill patients with septic shock and continuous renal replacement therapy: influence of residual diuresis on dose requirements. *Antimicrob Agents Chemother* 2015; **59:** 5520-8. doi: 10.1128/AAC.00712-15.

   *Antimicrobial Agents and Chemotherapy* is a journal included in the Journal Citation Report of the Web of Science®, with an impact factor in 2015 of **4.415** (ranked 22/123 under the category *Microbiology* and 34/253 under the category *Pharmacology & Pharmacy,* first quartile).

*3.* Ulldemolins M, Martín-Loeches I, Llauradó-Serra M, Fernández J, Vaquer S, Rodríguez AH, Pontes C, Calvo G, Torres A, Soy D. Piperacillin population pharmacokinetics in critically ill patients with multiple organ dysfunction syndrome receiving continuous veno-venous hemodiafiltration: effect of type of dialysis membrane on dosing requirements*. J Antimicrob Chemother* 2016; **71**: 1651-9. doi: 10.1093/jac/dkv503.

*The Journal of Antimicrobials and Chemotherapy* is a journal included in the Journal Citation Report of the Web of Science®, with an impact factor in 2015 of **4.919** (ranked 9/83 under the category *Infectious Diseases*, 19/123 under the category of *Microbiology* and 29/253 under the category *Pharmacology & Pharmacy,* first quartile).

The global impact factor of the three publications that conform this doctoral thesis is **13.810 points**.

**ARTICLE 1:**

**Beta-lactam dosing in critically ill patients with septic shock and continuous renal replacement therapy.** [Review].

Ulldemolins M, Vaquer S, Llauradó-Serra M, Pontes C, Calvo G, Soy D, Martín-Loeches I. *Crit Care* 2014; **18:** 227-243. doi: 10.1186/cc13938.

***Background:*** Although early and appropriate antibiotic therapy remains the most important intervention for a successful treatment of septic shock, data guiding optimization of beta-lactam prescription in critically ill patients with septic shock and AKI necessitating CRRT are still limited. Being small hydrophilic molecules, beta-lactams are likely to be cleared by CRRT to a significant extent. As a result, additional variability may be introduced to the *per se* variable antibiotic concentrations in critically ill patients.

***Aims:*** To outline the existing clinical scenario of beta-lactam dosing in critically ill patients with septic shock and CRRT, to highlight the sources of variability among the different studies that reduce extrapolation to clinical practice and to identify the opportunities for future research and improvement in this field.

***Methods:*** Three frequently prescribed beta-lactams (meropenem, piperacillin and ceftriaxone) were chosen for review. Systematic searches in PubMed were performed for the period January 1966 - November 2013. Many articles were identified through reviews of the references of the identified papers.

*Study selection:* Search terms included were “meropenem” or “piperacillin” or “ceftriaxone”, “critically ill patient” or “intensive care unit” or “critical illness”, “continuous veno-venous hemodiafiltration” or “continuous veno-venous hemodialysis” or “continuous veno-venous hemofiltration” or “continuous renal replacement therapy“, and “pharmacokinetics” or “pharmacodynamics”. In total, 26 articles met the inclusion criteria.

***Results and Conclusions:*** Our findings showed that present dosing recommendations are based on studies with drawbacks that limit their applicability in the clinical

setting. In general, current antibiotic dosing regimens for CRRT follow a “one-size-fits-all” approach despite emerging clinical data that suggests that drug total CL may be partially dependent on CRRT settings. Moreover, some studies pool data from heterogeneous populations with CRRT that may exhibit different pharmacokinetics (*e.g*. admission diagnoses different to septic shock, such as trauma), which also limit their extrapolation to critically ill patients with septic shock. Finally, there is still no consensus regarding the % $f_u T_{>MIC}$ that should be chosen as the pharmacokinetic/pharmacodynamic target for antibiotic therapy in patients with septic shock and CRRT.

For an empirically optimized dosing, at the first day a loading dose is required for compensating the increased Vd, typically seen in critically ill patients, regardless of impaired organ function. It is noteworthy to consider that an additional loading dose may be required when CRRT is initiated due to steady-state equilibrium breakage driven by antibiotic CL variation. From day two after CRRT initiation and thereafter, dosing must be adjusted to CRRT settings and residual renal function. Further research on dose adjustment of beta-lactam antibiotics in critically ill patients with septic shock and AKI necessitating CRRT is required in order to establish reliable and up-to-date recommendations that ensure optimal exposure and thus increase the likelihood of optimal outcomes in this special population.

**ARTICLE 2:**

**Meropenem population pharmacokinetics in critically ill patients with septic shock and continuous renal replacement therapy: influence of residual diuresis on dose requirements.**

Ulldemolins M, Soy D, Llauradó-Serra M, Vaquer S, Castro P, Rodríguez AH, Pontes C, Calvo G, Torres A, Martín-Loeches I. *Antimicrob Agents Chemother* 2015; **59:** 5520-8. doi: 10.1128/AAC.00712-15.

***Background:*** Meropenem dosing in critically ill patients with septic shock and CRRT is complex, with the recommended maintenance doses being 500mg-1000mg/q8-12h.

***Aims:*** This multicenter, prospective, observational study aimed to describe the PK of meropenem in this population, to identify the sources of PK variability and to evaluate different dosing regimens for developing optimal recommendations based on demographic variables and clinical parameters.

***Patients and Methods:*** Observational, prospective, multicenter, open-label pharmacokinetic study performed in the Intensive Care Units from three Spanish tertiary hospitals. Authorization for the study was granted by the Spanish Regulatory Medicines Agency (code IEM-ANT-2012-1). Thirty patients with septic shock and CRRT receiving meropenem were enrolled (153 plasma samples in total). Ethical approval was obtained from the local ethics committees, and the study was conducted following the Declaration of Helsinki guidelines. Consent to participate was obtained from the patient's legal representative. A population PK model was developed with data from 24 patients, and subsequently validated with data from 6 patients using NONMEM v.7.3®.

***Results:*** Patients median age was 66.5 years (range [34-85]), median weight was 72.8kg ([49-126]), median APACHE II score at admission was 24 ([5-44]) and median SOFA score on the day of study was 12 ([4-19]). The final population PK model was characterized by:

$$V(L) = 33.00(CV\ 10\%) \times (\frac{Weight(Kg)}{73})^{2.07(24\%)}$$

$$CL(L/h) = 3.68(11\%) + 0.22(47\%) \times (\frac{Residual\ diuresis(mL)}{100})$$

Neither CRRT intensity nor filter type were identified as drug CL modifiers. Monte Carlo simulations based on the final population PK model and assuming a 2% protein binding showed that for maintaining unbound concentrations of meropenem above the MIC of the bacteria for a 40% of the dosing interval (40% $f_u T_{>MIC}$), 500mg/q8h over a 30min-bolus would be sufficient regardless of residual diuresis. If a 100% $f_u T_{>MIC}$ was chosen as the PD target, oligoanuric patients (residual diuresis 0-500 mL/24h) would require 500mg/q8h over 30min for the treatment of susceptible bacteria (MIC<2mg/L), while patients with preserved diuresis (>500mL/24h) would require the same dose over a 3h-infusion. If bacteria with MIC close to the resistance breakpoint (2-4mg/L), according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) 2015 Clinical breakpoints, were to be treated with meropenem, a dose of 500mg/q6h would be necessary: over a 30min-bolus for oligoanuric patients and over a 3h-infusion for patients with preserved diuresis.

***Conclusions:*** Our results suggest that residual diuresis may be an easy and inexpensive tool to help titrating meropenem dose and infusion time in critically ill patients with septic shock and CRRT requirement.

**ARTICLE 3:**

**Piperacillin population pharmacokinetics in critically ill patients with multiple organ dysfunction syndrome receiving continuous veno-venous hemodiafiltration: effect of type of dialysis membrane on dosing requirements.**

Ulldemolins M, Martín-Loeches I, Llauradó-Serra M, Fernández J, Vaquer S, Rodríguez AH, Pontes C, Calvo G, Torres A, Soy D*. J Antimicrob Chemother* 2016; **71**: 1651-9. doi: 10.1093/jac/dkv503.

***Background**:* Piperacillin dosing in critically ill patients with septic shock and CRRT is complex and dosing recommendations are wide, with the recommended maintenance doses being 2000-4000mg/q6-12h.

***Aims:*** This observational, prospective, multicenter study aimed to describe the PK of piperacillin in critically ill patients with MODS receiving CVVHDF, to identify the sources of PK variability and to evaluate different dosing regimens to develop optimal recommendations based on clinical parameters.

***Patients and methods*****:** Observational, prospective, multicenter, open-label pharmacokinetic study performed in the Intensive Care Units from three Spanish tertiary hospitals. Authorization for the study was granted by the Spanish Regulatory Medicines Agency (code IEM-ANT-2012-1). Nineteen patients with MODS and CVVHDF receiving piperacillin/tazobactam were enrolled (95 plasma samples). Ethical approval was obtained from the local ethics committees, and the study was conducted following the Declaration of Helsinki guidelines. Consent to participate was obtained from the patient's legal representative. Population PK modeling and Monte Carlo simulations were performed using NONMEM v.7.3®.

***Results:*** Patients median age was 70 years (range [39-82]), median weight was 80kg ([45-129]), median APACHE II score at admission was 21 ([13-33]) and median SOFA score on the day of study was 11 ([8-21]). The final population PK model was characterized by:

Central Vd ($Vd_c$) (L) = 19.4 (CV 14.2%)

Peripheral Vd ($Vd_p$) (L) = 12.9 (90.7%)

Intercompartmental CL (Q) (L/h) = 9.5 (41.8%)

$$CL(L/h) = 6.11(8.2\%) \times (\frac{Weight(kg)}{80})^{1.39(19.9\%)} \times CL_{MEMB}$$

Regarding CL, if membrane = 1.5$m^2$ AN69ST then the value of $CL_{MEMB}$ = 1, if membrane = 0.9$m^2$ AN69, $CL_{MEMB}$ was estimated to be 0.51 (13.3%). Monte Carlo simulations assuming a 20% protein binding showed that, to maintain unbound piperacillin concentrations above the MIC of the bacteria for 100% of dosing interval (100% $f_u T_{>MIC}$), patients receiving CVVHDF with 1.5$m^2$ AN69ST membranes required doses of 4000mg/q8h for the treatment of bacteria with a susceptibility to piperacillin close to the clinical breakpoint (MIC = 8-16mg/L). In contrast, 2000mg/q8h were sufficient for patients with CVVHDF using 0.9$m^2$ AN69 membranes. For the treatment of bacteria with high susceptibility to piperacillin (MIC ≤ 4mg/L) or for the attainment of a more traditional PD target (50% $f_u T_{>MIC}$), 2000mg/q8h sufficed regardless of type of membrane and patient's total body weight.

***Conclusions:*** Our results suggest that type of membrane and total body weight should be considered for piperacillin dose titration in critically ill patients with MODS and CVVHDF requirement.

# CHAPTER 5. STUDY 1: LITERATURE REVIEW

## Published manuscript entitled "BETA-LACTAM DOSING IN CRITICALLY ILL PATIENTS WITH SEPTIC SHOCK AND CONTINUOUS RENAL REPLACEMENT THERAPY"

The manuscript entitled "Beta-lactam dosing in critically ill patients with septic shock and continuous renal replacement therapy" has been published by *Critical Care* (*Crit Care* 2014; **18**: 227-243. doi: 10.1186/cc13938).

*Critical Care* is a journal included in the Journal Citation Report of the Web of Science®, with an impact factor in 2014 of **4.476** (ranked 5/27 under the category *Critical Care Medicine*, first quartile).

The co-authors contributed to the manuscript as follows: All literature reviews and analyses were performed by the PhD candidate, Marta Ulldemolins, under the supervision of Dr Dolors Soy and Dr Ignacio Martín-Loeches. The PhD candidate, Marta Ulldemolins, took the leading role in manuscript preparation and writing. All the co-authors participated in the manuscript drafting, and reviewed and approved the final version of the article.

The manuscript is presented as published; except tables have been inserted into the text at slightly different positions. Also, the numbering of pages and tables has been adjusted to fit the overall style of the thesis. The references are found at the end of the chapter.

# BETA-LACTAM DOSING IN CRITICALLY ILL PATIENTS WITH SEPTIC SHOCK AND CONTINUOUS RENAL REPLACEMENT THERAPY

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## 5.1 Abstract

Although early and appropriate antibiotic therapy remains the most important intervention for a successful treatment of septic shock, data guiding optimization of beta-lactam prescription in critically ill patients prescribed with CRRT are still limited. Being small hydrophilic molecules, beta-lactams are likely to be cleared by CRRT to a significant extent. As a result, additional variability may be introduced to the per se variable antibiotic concentrations in critically ill patients.

The aims of this article are to describe the current clinical scenario of beta-lactam dosing in critically ill patients with septic shock and CRRT, to highlight the sources of variability among the different studies that reduce extrapolation to clinical practice and to identify the opportunities for future research and improvement in this field. For this purpose, three frequently prescribed beta-lactams (meropenem, piperacillin and ceftriaxone) were chosen for review.

Our findings showed that present dosing recommendations are based on studies with drawbacks that limit their applicability in the clinical setting. In general, current antibiotic dosing regimens for CRRT follow a "*one-size-fits-all*" fashion despite emerging clinical data suggesting that drug CL is partially dependent on CRRT modality and intensity. Moreover, some studies pool data from heterogeneous populations with CRRT that may exhibit different pharmacokinetics (*e.g.* admission diagnoses different to septic shock, such as trauma), which also limit their extrapolation to critically ill patients with septic shock. Finally, there is still no consensus regarding the % $T_{>MIC}$ that should be chosen as the pharmacodynamic target for antibiotic therapy in patients with septic shock and CRRT. For an empirically optimized dosing during the first day a loading dose is required for compensating the increased Vd, regardless of impaired organ function. An additional loading dose may be required when CRRT is initiated due to steady-state equilibrium breakage driven by CL variation. From day two and thereafter, dosing must be adjusted to CRRT settings and residual renal function. Therapeutic drug monitoring

of beta-lactams may be regarded as a useful tool to daily individualize dosing and to ensure optimal antibiotic exposure.

**Key Words:** beta-lactams, meropenem, piperacillin, ceftriaxone, septic shock, intensive care unit, critically ill patients, pharmacokinetics, pharmacodynamics, continuous renal replacement therapy, volume of distribution, clearance, therapeutic drug monitoring.

## 5.2 Introduction

Optimal antibiotic dosing in the Intensive Care Unit (ICU) is still a controversial issue that clinicians face daily. Despite compelling evidence supporting that early and appropriate antibiotic therapy is one of the most effective interventions for improving patient outcome[1], antibiotic selection and dosing are often challenging in critically ill patients because of disease complexity, resulting physiological alterations, and reduced antibiotic susceptibilities of nosocomial pathogens. Besides, selecting an antimicrobial to which the causal agent is susceptible is not sufficient to achieve the best clinical outcomes, and factors such as an adequate tissue penetration and achievement of the pharmacodynamic target associated with therapeutic success according to the antibiotic class are crucial for improving infection cure and patient morbi-mortality[2-4].

Beta-lactam antibiotics are time-dependent antibiotics, meaning that they exhibit optimal killing activity when plasma concentrations are maintained above the Minimum Inhibitory Concentration (MIC) of the bacteria during a percentage of the dosing interval (% $T_{>MIC}$). Beta-lactams are also the most prescribed antibiotics in the ICU[5]. Significant and unpredictable pharmacokinetic variability of this pharmacological group has been well documented in critically ill patients: Volume of distribution (Vd) and Clearance (CL) of beta-lactams have been found to vary significantly depending on patient severity, plasmatic proteins concentrations and organ failure among other factors[3, 6]. Acute kidney injury (AKI) and the requirement of continuous renal replacement therapy (CRRT) add further variability on beta-lactams CL. However, available clinical evidence supporting beta-lactam dosing in critically ill patients with septic shock and CRRT is not optimal yet, since recommendations are mainly elucidated from healthy volunteers' data and clinical studies with important patient variability and limited sample sizes.

The aims of this article are to describe the current clinical scenario of beta-lactam dosing in critically ill patients with septic shock and CRRT, to highlight the sources of

variability among the different studies that reduce extrapolation to clinical practice and to identify the opportunities for future research and improvement in this field. For this purpose, two of the most frequently prescribed beta-lactams for nosocomial infections (meropenem and piperacillin) and a highly protein-bound antibiotic usually prescribed for community-acquired infections (ceftriaxone) were chosen for a thorough review. A systematic review of all available data on beta-lactam antibiotic pharmacokinetics in critically ill patients with CRRT was beyond the scope of this article, as this has been done elsewhere[7-9].

## 5.3 Review

### *5.3.a Search strategy and selection criteria*

Data for this review were identified by systematic searches of PubMed (1966 to November 2013), as well as references cited by relevant articles. Search terms included were “meropenem” or “piperacillin” or “ceftriaxone”, “critically ill patient” or “intensive care unit” or “critical illness”, “continuous veno-venous hemodiafiltration” or “continuous veno-venous hemodialysis” or “continuous veno-venous hemofiltration” or “continuous renal replacement therapy” and “pharmacokinetics” or “pharmacodynamics”. Relevant articles written in English, Spanish and Catalan where considered for this review. Those describing the pharmacokinetics of meropenem, piperacillin/tazobactam and ceftriaxone in adult critically ill patients receiving CRRT were included.

### *5.3.b Effect of septic shock and CRRT in antibiotic dosing optimization*

Classically, the *in vitro* susceptibility of the causal pathogen has been the cornerstone of antibiotic prescription. However, selection according to susceptibility is only a component of the optimal antibiotic therapy, and many other factors must also be considered. In terms of posology, it is paramount to design dosing strategies that maximize the likelihood of attaining the pharmacodynamic target associated with therapy success in the biophase. This is complex in the critically ill patient with

septic shock and CRRT since it is well known that critical sickness and clinical interventions can drive to physiological changes likely to alter drug pharmacokinetics[3] and, therefore, likely to compromise the attainment of these pharmacodynamic targets.

There are two important time periods that must be considered for antibiotic dosing. The first period corresponds to the first day of therapy, where the main determinant for dosing must be Vd since it determines the early attainment of antibiotic concentrations within the therapeutic range. In critically ill patients with sepsis, increased Vd must be expected for hydrophilic antibiotics such as beta-lactams, aminoglycosides and glycopeptides[10-38]. This increase may be due to the presence of bacterial endotoxins in the bloodstream, which has a cascade effect on the production of endogenous molecules that act on the vascular endothelium, leading to vasodilation and transcapillary leakage of fluid and proteins into the extracellular space, where these antibiotics distribute. When the Vd is abnormally increased, distribution of hydrophilic antibiotics such as beta-lactams becomes more extensive for trying to compensate this larger space, with greater movement of the drug molecules from the central compartment (bloodstream) to the peripheral compartments (mainly extravascular fluid). The amount of the drug in plasma consequently decreases, and therefore the plasma concentration decreases. Consequently, given a particular MIC, shorter % $T_{>MIC}$ can be expected, which in turn may compromise beta-lactams pharmacodynamic target attainment.[39] Critically ill patients may therefore require front-loaded doses of beta-lactam antibiotics during the first 24 to 48 hours, regardless of organ function, in order to compensate the increased Vd and to reach concentrations within the therapeutic range on the first day of therapy[39].

The particular case of CRRT requirement poses another scenario where loading doses may be considered. At the time of CRRT initiation, antibiotic concentrations-over-time are at steady-state equilibrium (if the antibiotic was initiated before CRRT commencement), but one can hypothesize that the change in drug CL induced by CRRT initiation may lead to the breakage of this equilibrium and, consequently, to a

decrease in drug concentrations. A new steady-state will follow after 5-7 half-lives since the introduction of the foreign source of drug CL. However, during this time period, concentrations may fall below the therapeutic range. At this point, an additional loading dose may help in the maintenance of therapeutic levels. This phenomenon of steady-state breakage follows the theoretical pharmacokinetics principles but there are no studies yet that describe it in critically ill patients and hence concrete loading dose recommendations cannot be provided. Certainly this is a very interesting area that deserves further research to be properly understood.

The second period starts from day 2 and thereafter. During this period, the estimated drug CL is the main determinant of dosing, with the objective of maintaining the equilibrium between input and output as the tissues should already hold therapeutic antibiotic concentrations. In this context, CRRT represents a particular challenge in terms of dosing, especially for hydrophilic antibiotics, as concentrations may vary depending on the degree of extraction, that in turn depends on the CRRT modality, on drug physicochemistry and, presumably, on CRRT intensity[7]. Moreover, residual renal function is usually variable, difficult to assess and rarely considered when dosing, despite its relevant contribution to antibiotic CL in patients undergoing CRRT that has been described for meropenem and piperacillin among others[26, 29, 32]. Finally, the patient's condition evolves throughout the ICU stay, so that the influence of the previously mentioned factors may vary over time, making it difficult to generalize recommendations only based on CRRT modality and intensity. Dosing should ideally be titrated daily depending on the CRRT settings and the evolution of the patient's renal function. With this aim, therapeutic drug monitoring (TDM) of trough levels might be a useful tool for refining dosing decisions during the maintenance phase of therapy, as it is routinely performed with aminoglycosides and glycopeptides. However, despite emerging data that suggests that beta-lactams TDM might improve the attainment of pharmacodynamic targets associated with therapeutic success[40], the impact of systematic TDM on clinical outcomes and resources use is still to be prospectively validated. Due to the variable pharmacokinetics of these drugs in critically ill patients with CRRT, TDM certainly deserves further investigation.

### *5.3.c Determinants of drug clearance by CRRT*

Among the many options for renal replacement, CRRT is the most used in the critical care setting due to its advantages in hemodynamically unstable patients compared with intermittent techniques[41]. Drug clearance through CRRT is multifactorial and depends on both drug characteristics and CRRT modality and intensity. Continuous veno-venous hemodialysis (CVVHD) is based on the principle of diffusion of solutes across a semipermeable membrane driven by a concentration gradient, while continuous veno-venous hemofiltration (CVVHF) clearance is driven mainly by convection removal, where a positive hydrostatic pressure drives water and solutes across the filter membrane from the blood compartment to the filtrate compartment, from which it is drained. Continuous veno-venous hemodiafiltration is the most efficient technique for solute removal, consisting of a combination between the two abovementioned techniques and resulting in the removal of hydrophilic solutes with simultaneous water elimination[7].

Regardless of the modality prescribed, a common determinant of drug clearance in CRRT is protein binding. Due to protein size and electrical charge, protein-bound molecules are unable to pass through the filter membranes and only unbound molecules will be available for elimination by CRRT. This is such critical that both sieving ($S_c$) and saturation coefficients ($S_d$) are usually simplified as the unbound drug fraction. However, antibiotic protein-binding alterations have been broadly observed in ICU patients[6] due to the altered plasmatic proteins homeostasis associated to critical illness (the SAFE study reported that 40-50% of the ICU patients had albumins < 25 g/L)[42] and to the presence of other highly protein-bound exogenous drugs and endogenous molecules (such as bilirubin) in plasma. This may translate, consequently, in alterations in the extent to which an antibiotic is cleared by CRRT. However, whereas the effect of hypoalbuminemia on antibiotic pharmacokinetics in critically ill patients with preserved renal function has been documented in previous studies[6], there are no available studies regarding its combined impact with CRRT.

Another factor likely to affect the extent to which drugs are cleared by CRRT is CRRT intensity. Which is the optimal CRRT intensity has been a controversial issue since its

first implantation. Several studies have evaluated the impact of using different CRRT intensities on mortality and recovery of renal function in critically ill patients, with different and, usually, debatable results[43-48]. Due to this lack of definitive evidence, current clinical recommendations define the "area of best practice" for CRRT intensity laying between 20 and 40 mL/kg/h[41], being the clinician the responsible for individualizing the appropriate CRRT intensity for each particular patient. However, the impact of different CRRT intensities on antibiotic dosing requirements has not yet been sufficiently evaluated.

Additional to the abovementioned points, more variability in drug CL by CRRT may be introduced by medical devices that may coexist with CRRT in patients with septic shock, such as polymyxin B fiber columns (to reduce endotoxin levels in sepsis) or extra-corporeal membrane oxygenation (ECMO). Other factors such as filter lifespan, filter anticoagulants such as citrate and drug recirculation may also have an effect on drug CL. However, their potential for antibiotic adsorption and removal has not yet been estimated.

### *5.3.d Main limitations of available pharmacokinetic studies*

With aim to discuss the current scenario of beta-lactam dosing in patients with septic shock and CRRT, we performed a thorough review of the existing clinical data on three of the most frequently used (and studied) beta-lactam antibiotics in the ICU. The following tables summarize the available evidence on meropenem, piperacillin/tazobactam and ceftriaxone pharmacokinetics in critically ill patients with CRRT[15-38, 49, 50].

**Table 3:** Describes available data on meropenem pharmacokinetics in CRRT. The table includes healthy volunteers' data with comparative purpose.

| Study | n | Population and score (Mean ± SD) (Median (IQR)) | Site of infection | Pathogen (MIC) | Antibiotic | Type of filter | Type of CRRT | RRT dose (Mean ± SD) (Median (IQR)) |
|---|---|---|---|---|---|---|---|---|
| Spanish product information | N/R | Healthy volunteers | N/A | N/A | Meropenem 2g | N/A | N/A | N/A |
| | | | | | | | | |
| Ververs *et al.*[16] | 5 | Critically ill patients with septic shock and AKI. Severity score N/R | Several | Target: 100% $T_{>MIC90}$ of sensitive trains (*Serratia sp* 0.06mg/L and *Pseudomonas aeruginosa* 2mg/L) | Meropenem 500mg q12h | PAN 06 polyacrylonitrile filter | CVVHF | $Q_R$: 1.60 L/h |
| | | | | | | | | |
| Bilgrami *et al.*[15] | 10 | Critically ill patients with septic shock and AKI. APACHE II score 25 (22-28) | Several | Target: 100% $T_{>MIC90}$ of *Burkholderia pseudomallei* (MIC 4mg/L) | Meropenem 1g q8h | AN 69 HF, 2.15 $m^2$ polyacrylonitrile fiber membrane | CVVHF | $Q_R$: 4.40 L/h |
| | | | | | | | | |
| Krueger *et al.* [24] | 8 | Critically ill patients with sepsis and MODS or cardiogenic shock and AKI. APACHE II score 29.90 ± 6.64 | Several | Target: 40% $T_{>MIC}$ of susceptibility and intermediate-susceptibility breakpoint (4 mg/L and 8mg/L, NCCLS) | Meropenem 500mg q12h | AN 69 HF, 0.9$m^2$ polyacrylonitrile fiber membrane | CVVHF | $Q_R$: 1.60 L/h |
| | | | | | | | | |
| Thalhammer *et al.* [18] | 9 | Critically ill patients with sepsis and AKI. Severity score N/R | Several | Target: 40-50% $T_{>MIC90}$ of *Pseudomonas aeruginosa* susceptibility and intermediate-susceptibility | Meropenem 1g single dose | 0.43 $m^2$ polysulphone fiber membrane | CVVHF | $Q_R$: 2.75 L/h |

| Study | n | Population and score (Mean ± SD) (Median (IQR)) | Site of infection | Pathogen (MIC) | Antibiotic | Type of filter | Type of CRRT | RRT dose (Mean ± SD) (Median (IQR)) |
|---|---|---|---|---|---|---|---|---|
| | | | | breakpoint (4 mg/L and 8mg/L, NCCLS) | | | | |
| | | | | | | | | |
| Tegeder *et al.* [19] | 9 | Critically ill patients with septic shock and AKI. Severity score N/R | Several (66.6% abdominal) | Target: 100% $T_{>MIC90}$ of *Pseudomonas aeruginosa* intermediate-susceptibility breakpoint (8 mg/L) | Meropenem 500mg q8-12h | AN 69 HF type of membrane N/R | CVVHF | $Q_R$: 1 L/h |
| | | | | | | | | |
| Valtonen *et al.* [49] | 6 | Infected patients with AKI. Severity score N/R | N/R | Target: 100% $T_{>MIC90}$ of *Pseudomonas aeruginosa and Enterococcus faecalis* susceptibility breakpoint (4 and 8 mg/L, BSAC) | Meropenem 1g single dose | AV 400S, 0.7$m^2$ polysulphone fiber membrane | CVVHDF | $Q_D$: 1L/h<br>$Q_R$: N/R |
| | | | | | | | CVVHDF | $Q_D$: 2L/h<br>$Q_R$: N/R |
| | | | | | | | CVVHF | $Q_R$: N/R |
| | | | | | | | | |
| Robatel *et al.* [20] | 13 | Critically ill patients with septic shock and AKI. Severity score N/R | Several | Target: ≥75% $T_{>MIC90}$ of susceptibility breakpoint (4mg/L) | Meropenem 0.5-1g q8-12h | AN 69 HF, 0.9$m^2$ polyacrylonitrile fiber membrane | CVVHDF | $Q_D$: 0.60-1.50 L/h<br>$Q_R$: 0-1L/h |
| | | | | | | | | |
| Langgartner *et al.* [21] | 6 | Critically ill patients with sepsis and AKI. Severity score N/R | Several (50% pneumonia) | Target: 100% $T_{>MIC}$ *Pseudomonas aeruginosa* intermediate-susceptibility breakpoint (MIC 8mg/L) | Meropenem 1g q12h (bolus or CI) | AV 600S, 1.4$m^2$ polysulphone fiber membrane | CVVHDF | Total flow rate ($Q_D$+$Q_R$): 2 L/h |
| | | | | | | | | |

| Study | n | Population and score (Mean ± SD) (Median (IQR)) | Site of infection | Pathogen (MIC) | Antibiotic | Type of filter | Type of CRRT | RRT dose (Mean ± SD) (Median (IQR)) |
|---|---|---|---|---|---|---|---|---|
| Seyler *et al.* [22] | 17 | Critically ill patients with severe sepsis/septic shock and AKI. Severity score N/R | N/R | Target: 40% $T_{>4xMIC}$ of *Pseudomonas aeruginosa* susceptibility breakpoint (≤2mg/L, EUCAST) (8mg/L) | Meropenem 1g q12h | AN 69 HF type of membrane N/R | CVVHDF/ CVVHF | $Q_D$: 1.61 ± 0.63<br>$Q_R$: 1.54 ± 0.84<br>(for a 70 kg adult, weight N/R) |
| | | | | | | | | |
| Giles *et al.* [23] | 5 | Critically ill patients with septic shock and AKI. APACHE II | N/R | Target: 100% $T_{>MIC90}$ of *Pseudomonas aeruginosa* susceptibility breakpoint (4 mg/L) | Meropenem 1g q12h | AN 69 HF, 0.9$m^2$ Polyacrylonitrile fiber membrane | CVVHF | $Q_D$: 1.20 L/h<br>$Q_R$: 1.45 L/h |
| | 5 | Critically ill patients with septic shock and AKI. APACHE II | N/R | Target: 100% $T_{>MIC90}$ of *Pseudomonas aeruginosa* susceptibility breakpoint (4 mg/L) | Meropenem 1g q12h | AN 69 HF, 0.9$m^2$ Polyacrylonitrile fiber membrane | CVVHDF | |
| | | | | | | | | |
| Krueger *et al.* [17] | 9 | Critically ill patients with septic shock/cardiogenic shock and AKI. APACHE II 28.6 ± 9.1 | Several (66.7% pneumonia) | Target: 100% $T_{>MIC}$ of susceptibility and intermediate-susceptibility breakpoint (4 mg/L and 8mg/L) | Meropenem 1g q12h | AN 69 HF, 0.9$m^2$ Polyacrylonitrile fiber membrane | CVVHDF | $Q_D$: 1.60 L/h<br>$Q_R$: Variable |
| | | | | | | | | |
| Isla *et al.* [26] | 7 | Critically ill patients with sepsis and CrCL <10 mL/min. SOFA 13 ± 4.12 | N/R | Target: 100% $T_{>MIC90}$ of *Pseudomonas aeruginosa and Enterobacteriaceae sp* susceptibility breakpoint (4 mg/L, NCCLS) | Meropenem 500mg q6h (5 cases), 500mg q8h (1), 1g q8h (1) | AN 69 HF 0.9$m^2$ Polyacrylonitrile fiber/ AV600S 1.4$m^2$ polysulphone fiber membrane | CVVHDF | $Q_D$: 0.93 L/h<br>$Q_R$: 1.20 L/h |

| Study | n | Population and score (Mean ± SD) (Median (IQR)) | Site of infection | Pathogen (MIC) | Antibiotic | Type of filter | Type of CRRT | RRT dose (Mean ± SD) (Median (IQR)) |
|---|---|---|---|---|---|---|---|---|
| | 7 | Critically ill patients with sepsis and CrCL10-50 mL/min. SOFA 12.3 ± 3.2 | N/R | Target: 100% $T_{>MIC90}$ of *Pseudomonas aeruginosa and Enterobacteriaceae sp* susceptibility breakpoint (4 mg/L, NCCLS) | Meropenem 500mg q6h (6 cases), 1g q8h (1) | AN 69 HF 0.9$m^2$ Polyacrylonitrile fiber/ AV600S 1.4$m^2$ polysulphone fiber membrane | CVVHF (4 cases) / CVVHDF (3 cases) | $Q_D$: 0.43 L/h $Q_R$: 1.84 L/h |
| | 6 | Critically ill patients (mostly trauma patients) with sepsis and CrCL>50 mL/min. SOFA 14.0 ± 5.2 | N/R | Target: 100% $T_{>MIC90}$ of *Pseudomonas aeruginosa and Enterobacteriaceae sp* susceptibility breakpoint (4 mg/L, NCCLS) | Meropenem 2g q8h (5 cases), 1g q6h (1) | AN 69 HF, 0.9$m^2$ Polyacrylonitrile fiber membrane | CVVHF | $Q_R$: 1.25 L/h |
| | | | | | | | | |
| Isla *et al*. [25] | 13 | Critically ill patients with sepsis and AKI. SOFA 11.9 ± 2.8 | N/R | Target: 100% $T_{>MIC9}$ of *Enterobacteriaceae sp, Pseudomonas aeruginosa and Staphylococcus aureus* susceptibility and intermediate-.susceptibility breakpoints (4 mg/L and 8mg/L respectively, NCCLS) | Meropenem 500mg- 1g-2g q6-8h | AN 69 HF, 0.9$m^2$ Polyacrylonitrile fiber membrane or AV 600S, 1.4$m^2$ polysulphone fiber membrane | CVVHF/CVVHDF | Total flow rate ($Q_D$+$Q_R$): 2.28 L/h |
| | | | | | | | | |
| Meyer *et al.* [27] | 1 | Critically ill patient with septic shock and AKI | Meningitis | Target: 100% $T_{>MIC90}$ of *Neisseria meningitidis* susceptibility breakpoint (0.016 mg/L) | Meropenem 1g q12h for 3 doses then 1g q8h | AN 69 HF, type of membrane N/R | CVVHDF | $Q_D$: 0.75 L/h $Q_R$: 1.25 L/h |

**Table 3 continuation:**

| Reference | Sieving coefficient (mean ± SD/ mean(25-75% range)) | Type of PK analysis | Total CL (L/h) (mean ± SD/ mean(range)) | Vd (L/kg) (mean ± SD) | Residual diuresis (mL/24h) (mean ± SD) | Clinical Outcome | Authors dose recommendation | Study limitations |
|---|---|---|---|---|---|---|---|---|
| Spanish product information | N/A | N/R | 12.3 | 0.25 | Normal renal function | N/A | N/A | N/A |
| | | | | | | | | |
| Ververs *et al.* [16] | 0.63 ± 0.252 | Non-compartmental | 4.57 ± 0.89 | 0.37 ± 0.15 | Anuric (range 0-19mL/24h) | 20% survival. 100% target attainment | 500mg q12h for sensible strains, shorter dosage interval for intermediate strains | Severity score N/R; small sample size |
| | | | | | | | | |
| Bilgrami *et al.* [15] | 0.74 (0.71-0.77) | Non-compartmental | 6 (5.2-6.2) | 0.37 (0.32-0.46) | Oligoanuric | 70% survival. 100% target attainment | 1000mg q8h | High flow rate used, not applicable to patients with standard CVVHF settings |
| | | | | | | | | |
| Krueger *et al.* [24] | 0.91 ± 0.1 | Two-compartments modeling | 4.98 ± 1.29 | 0.28 ± 0.07 | < 500 | 62.5% survival. 100% target attainment for MIC= 4mg/L, 75% target attainment for MIC=8mg/L | 500mg q12h for susceptible bacteria | Heterogenic group with patients with cardiogenic shock |
| | | | | | | | | |

| Reference | Sieving coefficient (mean ± SD/ mean(25-75% range)) | Type of PK analysis | Total CL (L/h) (mean ± SD/ mean(range)) | Vd (L/kg) (mean ± SD) | Residual diuresis (mL/24h) (mean ± SD) | Clinical Outcome | Authors dose recommendation | Study limitations |
|---|---|---|---|---|---|---|---|---|
| Thalhammer *et al.* [18] | N/R | Non-compartmental | 8.62 ± 1.12 | 0.34 ± 0.03 | Anuric | 33.3% survival. 100% target attainment for MIC=8mg/L | 1g q8h | First-dose pharmacokinetics; severity score N/R; no septic shock |
| | | | | | | | | |
| Tegeder *et al.* [19] | 1.17 ± 0.11 | Non-compartmental | 3.12 ± 0.50 | 0.18 ± 0.03 (for a 70kg adult, weight N/R) | 5 anuric, 4 with urine output < 300mL/24h | Survival N/R. 100% target attainment | 500mg q12h or 250mg q6h | Severity score N/R |
| | | | | | | | | |
| Valtonen *et al.* [49] | N/R | Non-compartmental | 4.72 ± 2.69 | N/R | 111.8 ± 201.7 | Survival N/R, 83.3% target attainment | 1g q12h | Vd N/R; First-dose pharmacokinetics; No septic shock, not applicable to critically ill patients |
| | N/R | Non-compartmental | 5.71 ± 3.58 | N/R | 120.9 ± 204.7 | Survival N/R, 83.3% target attainment | 1g q12h | Vd N/R; First-dose pharmacokinetics; No septic shock, not applicable to critically ill patients |
| | N/R | Non-compartmental | 3.27 ± 2.30 | N/R | 120.9 ± 204.7 | Survival N/R, 83.3% target attainment | 500mg q8h | Vd N/R; First-dose pharmacokinetics; No septic shock, not applicable to critically ill patients |
| | | | | | | | | |

| Reference | Sieving coefficient (mean ± SD/ mean(25-75% range)) | Type of PK analysis | Total CL (L/h) (mean ± SD/ mean(range)) | Vd (L/kg) (mean ± SD) | Residual diuresis (mL/24h) (mean ± SD) | Clinical Outcome | Authors dose recommendation | Study limitations |
|---|---|---|---|---|---|---|---|---|
| Robatel *et al.* [20] | 0.65 (39% CV) | Four-compartments modeling | 5.5 (38% CV) | 0.52 | Anuric | 46.7% survival. Target attainment N/R | 750mg q8h or 1500mg q12h | Severity score and average total CRRT dose N/R |
| | | | | | | | | |
| Langgartner *et al.* [21] | 0.97 (0.87-1.05) bolus 0.89 (0.79-0.93) CI | Non-compartmental | 4.32 (3.93-4.96) bolus 4.40 (3.58-5.58) CI | 0.43 (0.38-0.54) | N/R | 66.7% survival. 83.3% target attainment in CI, 66.6% target attainment in bolus | 0.5g loading dose, 2g q24h CI | Severity score and residual renal function N/R; no septic shock |
| | | | | | | | | |
| Seyler *et al.* [22] | N/R | Non-compartmental | 4.9 (2.1-14) (for a 70kg adult, weight N/R) | 0.45 (0.20-3.03) | N/R | Survival N/R, 81% target attainment | 1g q8h loading dose (first 48h), dose reduction thereafter | CVVHDF and CVVHF data analyzed altogether; severity score and residual renal function N/R |
| | | | | | | | | |
| Giles *et al.* [23] | 0.95 ± 0.03 | Two-compartments modeling | 3.63 ± 0.95 | 0.38 ± 0.12 | N/R | 60% survival. 60% target attainment | 1g q12h | Small sample size; residual renal function N/R |
| | 0.91 ± 0.09 | Two-compartments modeling | 4.72 ± 1.69 | 0.31 ± 0.08 | N/R | 60% survival. 60% target attainment | 1g q12h | Small sample size; residual renal function N/R |
| | | | | | | | | |
| Krueger *et al.* [17] | 1.06 | Two-compartments modeling | 3.28 ± 1.02 | 0.26 ± 0.09 | Anuric | 66.7% survival. 100% target attainment | 1g q12h | Heterogenic group with patients with cardiogenic shock; $Q_D$ N/R |

| Reference | Sieving coefficient (mean ± SD/ mean(25-75% range)) | Type of PK analysis | Total CL (L/h) (mean ± SD/ mean(range)) | Vd (L/kg) (mean ± SD) | Residual diuresis (mL/24h) (mean ± SD) | Clinical Outcome | Authors dose recommendation | Study limitations |
|---|---|---|---|---|---|---|---|---|
| Isla *et al.* [26] | 0.76 ± 0.10 | Non-compartmental | 9.0 ± 4.55 | 0.57 ± 0.29 | N/R, mean CrCL = 1.1 mL/min | Survival N/R, 85.7% target attainment | 500mg q6h | No septic shock; the study compares three groups with different CRRT modalities; residual diuresis and CrCL estimation method N/R |
| | 0.85 ± 0.13 | Non-compartmental | 8.16 ± 3.43 | 0.37 ± 0.10 | N/R, mean CrCL = 23.5 mL/min | Survival N/R, 57.1% target attainment | 500mg q6h | No septic shock; the study compares three groups with different CRRT modalities; residual diuresis and CrCL estimation method N/R |
| | N/R | Non-compartmental | 63.90 ± 39.74 | 1.31 ± 0.9 | N/R, mean CrCL = 95.9 mL/min | Survival N/R, 16.7% target attainment | Doses >2g q8h | No septic shock; the study compares three groups with different CRRT modalities; residual diuresis and CrCL estimation method N/R |
| | | | | | | | | |
| Isla *et al.* [25] | 0.72 (6.3% CV) | Two-compartments modeling | 8.04 (13% CV) | 0.50 (10% CV) | N/R, mean CrCL = 22 mL/min | Survival N/R, target attainment N/R | Continuous infusion of 700mg/24h (MIC=4mg/L) or 1400mg/24h | No septic shock; CVVHDF and CVVHF data analyzed altogether; different filters used; residual |

| Reference | Sieving coefficient (mean ± SD/ mean(25-75% range)) | Type of PK analysis | Total CL (L/h) (mean ± SD/ mean(range)) | Vd (L/kg) (mean ± SD) | Residual diuresis (mL/24h) (mean ± SD) | Clinical Outcome | Authors dose recommendation | Study limitations |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | (MIC=8) in CrCL<10mL/min, higher doses when >10mL/min | diuresis and CrCL estimation method N/R |
| | | | | | | | | |
| Meyer *et al.* [27] | 1.02 ± 0.26 | Non-compartmental | 7.76 | 0.54 | Anuric | Survived but with significant sequels. Pharmacodynamic target was attained. | 1g q12h | Case report with limited comparability to other studies |

Table legend: CRRT: continuous renal replacement therapy; SD: standard deviation; IQR: interquartile range; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; MIC: minimum inhibitory concentration; Vd: volume of distribution; CL: Clearance; % $T_{>MIC}$: percentage of dosing interval while concentration of the antibiotic is above the MIC of the pathogen; CrCL: creatinine clearance; N/R: not reported, N/A: not applicable, CVVHF: continuous veno-venous hemofiltration, CVVHD: continuous veno-venous hemodialysis; CAVHD: continuous arterio-venous hemodialysis; CVVHDF: continuous veno-venous hemodiafiltration; $Q_R$: replacement fluid flow rate, $Q_D$: dialysis fluid flow rate; AKI: Acute kidney injury; MODS: multiple organ dysfunction syndrome; S/R: sensitive/resistant; CLSI: clinical and laboratory standards institute; NCCLS: National Committee of Clinical Laboratory Standards; EUCAST: European Committee on Antimicrobial Susceptibility Testing; CI: continuous infusion; CV: coefficient of variation.

**Table 4:** Describes the available data on piperacillin pharmacokinetics in CRRT. The table includes healthy volunteers' data with comparative purpose.

| Study | n | Population and score (Mean ± SD) (Median (IQR)) | Site of infection | Pathogen (MIC) | Antibiotic | Type of filter | Type of CRRT | RRT dose (Mean ± SD) (Median (IQR)) |
|---|---|---|---|---|---|---|---|---|
| Occhipinti *et al.* [28] | 12 | Healthy volunteers | N/A | N/A | Piperacillin 4.5g q8h | N/A | N/A | N/A |
| | | | | | | | | |
| Arzuaga *et al.* [29] | 4 | Critically ill patients with sepsis and CrCL < 10mL/min. SOFA 13.5 **±** 3.1 | Several | Target: 100% $T_{>MIC}$ for susceptibility and intermediate-susceptibility breakpoints (<32 mg/L and >64mg/L) | Piperacillin/Tazobactam 4.5g q6-8h | AN 69 HF, 0.9$m^2$ copolymer filter | CVVHF | $Q_R$: 1.63 **±** 0.47 L/h |
| | 5 | Critically ill patients with sepsis and CrCL 10-50mL/min. SOFA 11 **±** 2.1 | Several (60% peritonitis) | Target: 100% $T_{>MIC}$ for susceptibility and intermediate-susceptibility breakpoints (<32 mg/L and >64mg/L) | Piperacillin/Tazobactam 4.5g q6-8h | AN 69 HF, 0.9$m^2$ copolymer filter | CVVHF | $Q_R$: 1.82 **±** 0.26 L/h |
| | 5 | Critically ill patients with sepsis and CrCL > 50m/min. SOFA 9 **±** 1.4 | Several (60% VAP) | Target: 100% $T_{>MIC}$ for susceptibility and intermediate-susceptibility breakpoints (<32 mg/L and >64mg/L) | Piperacillin/Tazobactam 4.5g q6-8h | AN 69 HF, 0.9$m^2$ copolymer filter | CVVHF | $Q_R$: 1.20 **±** 0.45 L/h |
| | | | | | | | | |

| Study | n | Population and score (Mean ± SD) (Median (IQR)) | Site of infection | Pathogen (MIC) | Antibiotic | Type of filter | Type of CRRT | RRT dose (Mean ± SD) (Median (IQR)) |
|---|---|---|---|---|---|---|---|---|
| van der Werf *et al.* [30] | 9 | Critically ill patients with septic shock and MODS. APACHE II 30.1 ± 4.2 | Several | Target: 100% $T_{>MIC}$ of the *in vitro* sensitivity of microbial isolates recovered from the infection site | Piperacillin/Tazobactam 4.5g q8h | N/R | CVVHF | $Q_R$: 1.55 ± 0.59 L/h |
| | | | | | | | | |
| Capellier *et al.* [31] | 10 | Critically ill patients with septic shock (7) or cardiogenic shock (3) and AKI. SAPS II score 74 ± 6 | N/R | N/R | Piperacillin 4g q8h (6 cases first-dose, 4 cases steady state) | 0.5 $m^2$ polysulphone filter | CVVHF | N/R |
| | | | | | | | | |
| Asín-Prieto *et al.* [32] | 16 | Critically ill patients with sepsis/polytrauma and different degrees of renal function (CrCL 1.3-110mL/min) SOFA 11 ± 3 | N/R | Target: 100% $T_{>MIC}$ for the susceptibility breakpoint (16 mg/L) (CLSI) | Piperacillin/Tazobactam 4.5g q 4-6-8h (2, 7 and 7 cases respectively) | AN 69 HF, 0.9$m^2$ copolymer filter | CVVHF | $Q_R$: 1.54 ± 0.43 L/h |
| | | | | | | | | |
| Bauer *et al.* [33] | 42 | Critically ill patients with sepsis and AKI/end-stage renal disease, CCF score 7.9 ± 2.8 | N/R | Target: 50% $T_{>MIC}$ for the susceptibility and intermediate-susceptibility breakpoint (16 and 64 mg/L) | Piperacillin/Tazobactam 2.25g-3.375g q 6-8-12h | M60-M100 HF, 0.6-0.9 $m^2$ acrylonitrile filter or NxStage System One, 1.5$m^2$ polyethersulphone filter | CVVHD/ CVVHDF | $Q_T$: 2.4 (for mean weight of 95kg) |
| | | | | | | | | |

| Study | n | Population and score (Mean ± SD) (Median (IQR)) | Site of infection | Pathogen (MIC) | Antibiotic | Type of filter | Type of CRRT | RRT dose (Mean ± SD) (Median (IQR)) |
|---|---|---|---|---|---|---|---|---|
| Mueller *et al.* [34] | 8 | Critically ill patients with sepsis and AKI. Severity score N/R | Pneumonia | Target: 50% $T_{>MIC}$ for the susceptibility and intermediate-susceptibility breakpoint (16 and 32 mg/L) | Piperacillin/Tazobactam 4.5g q8-12-24h (3, 4 and 1 cases respectively) | AN 69 HF, 0.6$m^2$ filter | CVVHD | $Q_D$: 1.5 L/h<br>$Q_R$: 0.08-0.20 L/h |
| | | | | | | | | |
| Keller *et al.* [35] | 12 | Critically ill patients with sepsis and AKI. Severity score N/R. | Several | N/R | Piperacillin 4g single dose (10 cases), 4g q8h (2 cases) | AN 69 HF, 0.43$m^2$ copolymer filter | CAVHD | $Q_D$: 1.22 ± 0.09 L/h |
| | | | | | | | | |
| Valtonen *et al*. [50] | 6 | Septic patients with AKI. Severity score N/R. | Several | Target: 100% $T_{>MIC}$ *Pseudomonas spp and Enterobacteriaceae spp* susceptibility breakpoint (16 mg/L, BSAC) | Piperacillin/Tazobactam 4.5g q12h | AV 400S, 0.7$m^2$ polysulphone membrane | CVVHDF | $Q_D$: 1L/h<br>$Q_{R:}$ N/R |
| | | | | | | | CVVHDF | $Q_D$: 2L/h<br>$Q_{R:}$ N/R |
| | | | | | | | CVVHF | $Q_{R:}$ N/R |
| | | | | | | | | |
| Seyler *et al.* [22] | 16 | Critically ill patients with severe sepsis/septic shock and AKI. Severity N/R. | N/R | Target: 50% $T_{>4xMIC}$ *Pseudomonas aeruginosa* susceptibility breakpoint (≤16 mg/L, EUCAST) (64 mg/L) | Piperacillin/Tazobactam 4.5g q6h | AN 69 HF, type of membrane N/R | CVVHDF/ CVVHF | $Q_D$: 0.023 ± 0.009 L/kg/h (1.61 L/h for a 70kg adult)<br>$Q_R$: 0.022 ± 0.012 L/kg/h<br>(1.54 L/h for a 70kg adult) |

| Study | n | Population and score (Mean ± SD) (Median (IQR)) | Site of infection | Pathogen (MIC) | Antibiotic | Type of filter | Type of CRRT | RRT dose (Mean ± SD) (Median (IQR)) |
|---|---|---|---|---|---|---|---|---|
| Varghese *et al*.[38] | 10 | Critically ill patients with severe sepsis/septic shock and AKI. APACHE II 33 (31-36), SOFA 12 (10-15) | N/R | Target: 50% $T_{>MIC}$ for clinically relevant MIC (2, 4, 8,16, 32 and 64 mg/L) in plasma and subcutaneous tissue | Piperacillin/Tazobac-tam 4.5g q8h | AN 69 HF, 1.05$m^2$ polyacrylonitrile filter | CVVHDF | $Q_D$: 1-1.5 L/h<br>$Q_{R:}$ 1.5-2 L/h<br>$Q_T$: 3.0 - 3.9 L/h |

**Table 4 continuation:**

| Reference | Sieving coefficient (mean ± SD/ mean(25-75% range)) | Type of PK analysis | Total CL (L/h) (mean ± SD/ mean(range)) | Vd (L/kg) (mean ± SD) | Residual diuresis (mL/24h) (mean ± SD) | Clinical Outcome | Authors dose recommendation | Study limitations |
|---|---|---|---|---|---|---|---|---|
| Occhipinti *et al.* [28] | N/A | Non-compartmental | 10.90 ± 1.17L/h/1.73m$^2$ | 0.15 ± 0.02 | N/A | N/A | N/A | N/A |
| | | | | | | | | |
| Arzuaga *et al.* [29] | 0.42 ± 0.25 | Non-compartmental | 3.00 ± 3.22 | 0.28 ± 0.16 | N/R, CrCL <10mL/min | Survival N/R, 100% target attainment | Dose reduction | Small sample size, residual diuresis and CRCL estimation method N/R |
| | 0.38 ± 0.37 | Non-compartmental | 5.44 ± 1.80 | 0.36 ± 0.27 | N/R, CrCL 10-50mL/min | Survival N/R, 100% target attainment for MIC<32, 50% target attainment for MIC >64 | Dose reduction | Small sample size, residual diuresis and CRCL estimation method N/R |
| | 0.23 ± 0.07 | Non-compartmental | 15.91 ± 9.13 | 0.56 ± 0.25 | N/R, CrCL >50mL/min | Survival N/R, 55.5% target attainment for MIC<32, 16.6% target attainment for MIC >64 | 4.5g q4h | Small sample size, residual diuresis and CRCL estimation method N/R |
| | | | | | | | | |
| van der Werf *et al.* [30] | N/R | Two-compartments | 2.52 ± 1.38 | 0.30 ± 0.21 | Anuric | 77.8% survival, 100% target attainment | Dose as for patients with slightly impaired renal function | Sieving and MIC N/R (MIC classified as S/R) |
| | | | | | | | | |

| Reference | Sieving coefficient (mean ± SD/ mean(25-75% range)) | Type of PK analysis | Total CL (L/h) (mean ± SD/ mean(range)) | Vd (L/kg) (mean ± SD) | Residual diuresis (mL/24h) (mean ± SD) | Clinical Outcome | Authors dose recommendation | Study limitations |
|---|---|---|---|---|---|---|---|---|
| Capellier *et al.* [31] | N/R | Non-compartmental | First dose: 4.75 ± 1.42<br>Steady state: 1.49 ± 0.79 | First dose: 0.48 ± 0.24<br>Steady state: 0.14 ± 0.07 | Mainly anuric, 3 with residual diuresis between 220 and 400 mL/24h | N/R | 4.5 g q 12h | CRRT dose, MIC target and outcome N/R; some patients with cardiogenic shock |
| | | | | | | | | |
| Asín-Prieto *et al.* [32] | 0.37 ± 0.25 | Two-compartments | 7.32 (4.21-10.86) (Bootstrap) | 0.59 (0.38-0.82) (Bootstrap) | Different degrees of renal function, residual diuresis N/R, CrCL 43 ± 34 mL/min | Survival N/R, target attainment (MIC=16) after simulations:<br><br>When CrCL > 100mL/min, 60% target attainment with high doses (4g q4h)<br><br>When CrCL = 50mL/min, 93% target attainment with 4g q4h, 62% PTA with 4g q6h<br><br>When CrCL = 10mL/min, 96% target attainment with 4g q8h | After simulations:<br><br>When CrCL = 100mL/min, CI 16g q24h<br><br>When CrCL = 50 mL/min, CI 12g q24h | Number of patients by renal function group and residual diuresis N/R; CrCL estimated using Cockroft-Gault method (not validated for critically ill patients) |

| Reference | Sieving coefficient (mean ± SD/ mean(25-75% range)) | Type of PK analysis | Total CL (L/h) (mean ± SD/ mean(range)) | Vd (L/kg) (mean ± SD) | Residual diuresis (mL/24h) (mean ± SD) | Clinical Outcome | Authors dose recommendation | Study limitations |
|---|---|---|---|---|---|---|---|---|
| Bauer *et al.* [33] | N/R | One-compartment | 3.87 L/h (IQR: 3.56) | 0.38 L/kg (IQR: 0.20) | Oligoanuric (Median 38 mL/24h, IQR: 157mL) | 50% survival; 100% target attainment for MIC=16 (total and unbound piperacillin), for MIC=64 83% (total), 77% (unbound) | > 9g piperacillin/24h | Sparse sampling; CVVHDF and CVVHD data analyzed altogether |
| | | | | | | | | |
| Mueller *et al.* [34] | 0.84 ± 0.21 | Non-compartmental | 2.82 (1.56-13.2) | 0.31 ± 0.07 | Anuric | Survival N/R, 87.5% target attainment with 4.5g/q12h/2.25g q8h | 4.5g q12h or 2.25g q8h | Severity score and outcomes N/R; no septic shock |
| | | | | | | | | |
| Keller *et al.* [35] | 0.71 ± 0.21 | One-compartment | 2.83 ± 1.34 | 0.37 ± 0.05(for a 70kg adult, weight N/R) | Anuric | 16.7% survival. | 150% of dose for anuric patients | First-dose kinetics; severity score, MIC target and outcomes N/R |
| | | | | | | | | |
| Valtonen *et al*. [50] | N/R | Non-compartmental | 5.06 ± 1.68 | N/R | 133 ± 199 | Survival N/R, 33.3% target attainment | 4.5g q8h | Severity score and Vd N/R; no septic shock, not applicable to critically ill patients |
| | N/R | Non-compartmental | 5.48 ± 2.11 | N/R | 151 ± 224 | Survival N/R, 33.3% target | 4.5g q8h | Severity score and Vd N/R; no septic |

| Reference | Sieving coefficient (mean ± SD/ mean(25-75% range)) | Type of PK analysis | Total CL (L/h) (mean ± SD/ mean(range)) | Vd (L/kg) (mean ± SD) | Residual diuresis (mL/24h) (mean ± SD) | Clinical Outcome | Authors dose recommendation | Study limitations |
|---|---|---|---|---|---|---|---|---|
| | | | | | | attainment | | shock, not applicable to critically ill patients |
| | N/R | Non-compartmental | 3.89 ± 1.23 | N/R | 109 ± 182 | Survival N/R, 33.3% target attainment | 4.5g q8h | Severity score and Vd N/R; no septic shock, not applicable to critically ill patients |
| | | | | | | | | |
| Seyler *et al.* [22] | N/R | Non-compartmental | 4.9 (0.14-26.6) (for a 70kg adult, weight N/R) | 0.44 (0.22-1.72) | N/R | Survival N/R, 71% target attainment | 4.5g q6h loading dose (first 48h), dose reduction thereafter | CVVHDF and CVVHF data analyzed altogether; severity score, weight and residual renal function N/R |
| | | | | | | | | |
| Varghese *et al*. [38] | 0.67 (0.53–0.78) | Non-compartmental | 5.1 (4.2–6.2) | 0.42 (0.29–0.49) | 5 anuric, 5 oliguric (<0.5mL/kg/h for ≥ 6h) | Survival N/R, 100% target attainment for MIC ≤ 32mg/L | 4.5g q8h for susceptible microorganisms (MIC ≤ 32mg/L) | Site of infection and survival N/R |

Table legend: CRRT: continuous renal replacement therapy; SD: standard deviation; CV: coefficient of variation; IQR: interquartile range; MIC: Minimum Inhibitory Concentration; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; CCF: Cleveland Clinic Foundation; SAPS: Simplified Acute Physiology Score; Vd: volume of distribution, CL: Clearance; % $T_{>MIC}$: percentage of dosing interval while concentration of the antibiotic is above the MIC of the pathogen; CrCL: creatinine clearance; N/R: not reported, N/A: not applicable, CVVHF: continuous veno-venous hemofiltration, CVVHD: continuous veno-venous hemodialysis; CAVHD: continuous arterio-venous hemodialysis; CVVHDF: continuous veno-venous hemodiafiltration; $Q_R$: replacement fluid flow rate, $Q_D$: dialysis fluid flow rate; AKI: acute kidney injury; VAP: ventilator-associated pneumonia; MODS: multiple organ dysfunction syndrome; S/R: sensitive/resistant; CLSI: clinical and laboratory standards institute; BSAC: British Society for Antimicrobial Chemotherapy, CI: continuous infusion

**Table 5:** Describes the available data on ceftriaxone pharmacokinetics in hemofiltration. The table includes healthy volunteers' data with comparative purpose.

| Study | n | Population and score (Mean ± SD) (Median (IQR)) | Site of infection | Pathogen (MIC) | Antibiotic | Type of filter | Type of CRRT | RRT dose (Mean ± SD) (Median (IQR)) |
|---|---|---|---|---|---|---|---|---|
| Spanish product information | N/R | Healthy volunteers | N/A | N/A | Ceftriaxone 1g | N/A | N/A | N/A |
| | | | | | | | | |
| Garot *et al.* [36] | 54 | Critically ill patients with sepsis, severe sepsis or septic shock with various degrees of renal function, 12 with CVVHF. SAPS II 50 (9-87) | Several (61% pneumonia) | 100% $T_{>MIC}$ for MIC values ranging from 0.016 mg/L (*Streptococcus pneumoniae*) to 8 mg/L (*Staphylococcus aureus*) | Ceftriaxone 2g q24h (41 cases), 1g q24h (1), 2g q12h (1) and 2g q8h (1) | N/R | CVVHF | N/R |
| | | | | | | | | |
| Kroh *et al.* [37] | 6 | Critically ill patients with sepsis and AKI | Several | N/R | Ceftriaxone 2g q24h | Polyamide filter | CVVHF | $Q_R$: 1.2-1.8 L/h |

**Table 5 continuation:**

| Reference | Sieving coefficient (mean ± SD /mean(25-75% range)) | Type of PK analysis | Total CL (L/h) (mean ± SD/ mean(range)) | Vd (L/kg) (mean ± SD) | Residual diuresis (mL/24h) (mean ± SD) | Clinical Outcome | Authors dose recommendation | Study limitations |
|---|---|---|---|---|---|---|---|---|
| Spanish product information | N/A | N/R | 0.6-1.2 | 0.10- 0.17 | N/A | N/A | N/A | N/A |
| | | | | | | | | |
| Garot *et al.* [36] | N/R | Two-compartments | 0.97 (for the low CrCL=5.5mL/min) | 0.26 (for a 70kg adult, weight N/R) | N/R, CrCL range 5.5-.214 mL/min | 100% attainment of 100% $T_{>MIC}$ | No dose adjustment | Severity scores, RRT settings, residual diuresis and CrCL estimation method N/R; unbound concentration calculated using a formula; heterogenic population |
| | | | | | | | | |
| Kroh *et al.* [37] | 0.69 ± 0.39 | Non-compartmental | 2.36 | 0.42 ± 0.19 | N/R, CrCL range 0-10 mL/min | N/R | No dose adjustment | Residual diuresis and CrCL estimation method N/R; no outcomes study performed; no septic shock; no albumin concentrations considered |

Table legend: CRRT: continuous renal replacement therapy; SD: standard deviation; SAPS: Simplified Acute Physiology Score; MIC: minimum inhibitory concentration; Vd: volume of distribution; CL: Clearance; % $T_{>MIC}$: percentage of dosing interval while concentration of the antibiotic is above the MIC of the pathogen; N/R: not reported, N/A: not applicable, CVVHF: continuous veno-venous hemofiltration, CVVHD: continuous veno-venous hemodialysis; CVVHDF: continuous veno-venous hemodiafiltration; $Q_R$: replacement fluid flow rate; AKI: acute kidney injury.

Critical review of these studies has lead to identification of the following points that limit applicability of dose recommendations to critically ill patients with septic shock and CRRT.

#### *5.3.d.1 Patient population*

The identified studies handle a highly heterogeneous patient population, which may jeopardize the generalizability of the results. For example, there are studies that pool together patients with septic shock and cardiogenic shock[17, 31]. The physiopathology of these two types of shock, however, is very different: septic shock is caused by peripheral vasodilation, systemic inflammation and, consequently, increased Vd; while cardiogenic shock involves peripheral vasoconstriction, which should have no effect on the Vd. Other studies include septic and polytrauma patients requiring CRRT[25, 32]. Of note, one of these studies overcame the admission diagnosis-driven variability by developing a population pharmacokinetics model. The investigators found that admission diagnosis significantly influenced pharmacokinetic parameters: trauma patients exhibited higher Vd and CL than septic patients (V1=69.5L and 15.7L in trauma and septic patients respectively, CL= 54.15L/h and 8.04L/h in trauma and septic patients respectively)[25]. Also, patients with sepsis/severe sepsis may substantially differ from patients with septic shock: septic shock patients may exhibit higher Vd due to capillary leakage and aggressive fluid resuscitation as compared to critically ill patients without septic shock. In spite of this, some of the available studies include patients with sepsis/severe sepsis and AKI[21, 33-35, 37, 49, 50] but not those with septic shock. Furthermore, a significant number of the articles do not report clinical severity scores of the studied population. In particular, increasing APACHE II scores have been shown to correlate with increased Vd for hydrophilic antibiotics such as aminoglycosides[12]. However, Tables 3 and 4 show variations in Vd among the studies of meropenem and piperacillin; it cannot be ascertained whether these are partially related to the differences in disease severity, since severity scores have not been reported. Similarly, CRRT may be prescribed in patients who still present a significant residual renal function. The influence of residual renal function on piperacillin pharmacokinetics in patients receiving CVVHF has been assessed by Arzuaga and colleagues, and significant differences in

piperacillin CL have been reported, for example total drug CL in patients with CrCL > 50mL/min was tripled as compared with patients with CrCL < 10mL/min[51]. These points suggest that the "one-size-fits-all" dosing recommendations based only on CRRT prescription may not apply to all different types of critically ill patients, as they are a highly heterogeneous population that may require different doses.

#### *5.3.d.2 CRRT modality and flow rate*

Regarding CRRT modalities, there is discordance in the literature on whether a specific modality makes a difference or not in terms of dosing. While some studies support a difference in modalities[49, 50], some others suggest that there are no substantial variations between modalities[22]. Theoretically, convective and diffusive methods eliminate molecules from the bloodstream using different processes, and therefore the total drug CL should differ between CRRT modalities as has been shown with piperacillin and meropenem[49, 50], but a significant volume of dosing recommendations are still generic for CRRT.

Regarding CRRT intensity, emerging evidence suggests that total flow rate affects the CL of hydrophilic drugs with low protein binding. For example, Beumier *et al*. developed a population pharmacokinetics model for vancomycin administered as a continuous infusion in critically ill patients with sepsis and septic shock and found that inclusion of CRRT intensity as a covariate on CL significantly improved the model[52]. Similarly, a study by Bilgrami and colleagues specifically targeted patients with high intensity CRRT (> 4L/h) receiving meropenem[15] and found that total drug CL was higher compared with previous studies with lower intensity CRRT, intensity being the main parameter that accounted for the differences in meropenem CL ($R^2$ = 0.89). The high CRRT intensity was such a determinant of meropenem CL that the doses required for the coverage of less susceptible bacteria (MIC= 4mg/L) were similar to those used in patients without renal failure (1000mg q8h). These data may suggest that different CRRT intensities may translate into different drug CL and, therefore, into different dose requirements. Importantly, one must also highlight that most of the published studies use CRRT intensities in the lower range of the "area of best practice" (1L/h-2L/h: 14.3-28.5 mL/kg/h for a 70kg-adult)[16, 17, 19-21, 27, 29,

[30, 32, 34, 35, 49, 50], while the actual tendency in the clinical setting may be using CRRT intensities in the higher range (>30 mL/kg/h), especially for septic patients[41, 46]. In fact, a recent study by Varghese and colleagues[38] studied the pharmacokinetics of piperacillin/tazobactam in critically ill patients with anuria/oliguria and CRRT at a median intensity of 38.5 mL/kg/h and reported higher drug CL (5.1 (4.2–6.2) L/h) compared with other studies that used lower CRRT intensities (see table 4).

Moreover, the methodology for the calculation of CRRT intensity is not defined in most of the studies. Some of the studies report that an absolute CRRT intensity (L/h) was prescribed to all patients, without being normalized to body weight. This leads to inherently variable CRRT doses (mL/kg/h), inversely proportional to the actual patient's weight. For instance, an absolute CRRT intensity of 2L/h for a 100kg patient results in a relative flow rate of 20 mL/kg/h, whereas for a 50kg patient the rate is 40mL/kg/h. When relative flow rate is prescribed, clinicians usually use body weight previous to admission or ideal body weight, and calculate flow rate using the following formula (equation 16:

Eq. 16: $$Flow\ rate = \frac{(Q_D + Q_R)}{WT}$$

; where $Q_D$: dialysis fluid flow rate (mL/h)

$Q_R$: replacement fluid flow rate (mL/h)

WT: weight (kg)

The rationale of this methodology is to avoid variations in the calculated flow rate over time as the patient real weight fluctuates during the ICU stay (for example, due to fluid therapy or edema)[53], notwithstanding the fact that most of the studies do not report how body weight was considered and in spite of the fact that it is essential to know which CRRT intensity was prescribed[43]. When real body weight is used, calculated flow rate may be falsely low, as the denominator in the equation usually increases during the ICU stay. Recommendations include application of body weight previous to admission or ideal body weight[43]. However, considering the

increasing prevalence of obesity in developed countries, it should be discussed whether ideal body weight or body weight previous to admission should be used.

#### *5.3.d.3 Pharmacodynamic target for dosing recommendations*

Antibiotic dosing recommendations intend to achieve a pharmacodynamic target that, for beta-lactams, is defined by the $T_{>MIC}$ value[54]. Classical studies report that penicillins and monobactams require at least a 50-60% $T_{>MIC}$ for maximal bactericidal activity, cephalosporins a 60-70% $T_{>MIC}$ and carbapenems a 40% $T_{>MIC}$[54]. However, most of these recommendations are based on *in vitro* studies and on animal models of bacteremia, where penetration into the site of infection is not considered. *In vivo*, higher % $T_{>MIC}$ in plasma may be needed for achieving the abovementioned targets in biophases other than bloodstream, since penetration to the target site follows diffusion kinetics and depends on the physicochemistry of each particular tissue. For instance, Roberts *et al*. reported that full doses of meropenem administered by continuous infusion (for a PD target of 100% $T_{>MIC}$ in plasma) were required for achieving 40% $T_{>MIC}$ for less susceptible pathogens in subcutaneous tissue[11]. Also, the attainment of a particular percentage of $T_{>MIC}$ may be modified by the susceptibility cut-offs for the different bacteria, that vary depending on the country where the study is performed (*e.g*. EUCAST *versus* CLSI breakpoints). Therefore, the recommendations based upon a particular MIC in Europe may not apply to the United States of America and vice versa.

Critical review of clinical pharmacokinetics data leads to the final consideration that there are multiple missed opportunities in the available literature. Further studies should be more focused on the study population of critically ill patients with septic shock in order to avoid variability derived from pathophysiological conditions other than septic shock. Therefore, inclusion and exclusion criteria should carefully evaluate the admission diagnosis and the patient condition during the study period. Also, a population pharmacokinetics approach would be preferred to the non-compartmental approach, since non-compartmental approach draws inaccurate conclusions because covariates that have an effect on parameter variability cannot

be identified. Finally, consensus regarding clinical pharmacodynamic targets for beta-lactams would be helpful in the unification of dosing recommendations.

## 5.4 Conclusions

Optimization of beta-lactam therapy in critically ill patients with septic shock and CRRT requirement is complex and dependent on several drug, CRRT and patient-related factors. Consideration of drug physicochemistry and protein binding, CRRT settings and disease-related pharmacokinetic alterations is essential for individualizing dose regiments with the purpose of attaining pharmacodynamic targets associated with success.

During the first day, an initial loading dose is required to achieve drug concentrations within the therapeutic range early in time, regardless of impaired organ function. This principle may also apply to the moment of CRRT commencement, where a loading dose may be required to maintain concentrations within the therapeutic range. From day two and thereafter, dosing must be adjusted to CRRT settings and residual renal function. The complexity of dosing is due to the great variability encountered. As such, TDM of trough levels of beta-lactams may be regarded as a promising and key tool to daily individualize dosing and ensure optimal exposure to the antibiotic.

Current dose recommendations are based on studies with some drawbacks that limit their applicability to the current clinical scenario. Mainly, dosing recommendations in CRRT follow a "*one-size-fits-all*" fashion, despite emerging clinical data suggests that beta-lactams CL is partially dependent on CRRT modality and intensity. Moreover, heterogeneous populations have been pooled in the studies, limiting extrapolation to critically ill patients with septic shock and CRRT. Finally, there is still some controversy on the % $T_{>MIC}$ that must be chosen as the pharmacodynamic target associated with success for tailoring dosing recommendations.

Further research on dose adjustment of beta-lactam antibiotics in critically ill patients with septic shock and CRRT is required in order to establish reliable and up-to-date recommendations that ensure optimal therapy and, thus, increase the likelihood of optimal outcomes in this population.

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## 5.6 Transparency Declarations

The authors do not have any competing interest to declare.

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# CHAPTER 6. STUDY 2: MEROPENEM

## Published manuscript entitled "MEROPENEM POPULATION PHARMACOKINETICS IN CRITICALLY ILL PATIENTS WITH SEPTIC SHOCK AND CONTINUOUS RENAL REPLACEMENT THERAPY: INFLUENCE OF RESIDUAL DIURESIS ON DOSE REQUIREMENTS"

The manuscript entitled "Meropenem population pharmacokinetics in critically ill patients with septic shock and continuous renal replacement therapy: influence of residual diuresis on dose requirements" has been published by Antimicrobial Agents and Chemotherapy (*Antimicrob Agents Chemother* 2015; **59**:5520-8. doi: 10.1128/AAC.00712-15).

*Antimicrobial Agents and Chemotherapy* is a journal included in the Journal Citation Report of the Web of Science®, with an impact factor in 2015 of **4.415** (ranked 22/123 under the category *Microbiology* and 34/253 under the category *Pharmacology & Pharmacy,* first quartile).

The co-authors contributed to the manuscript as follows: Study design was performed by the PhD candidate, Marta Ulldemolins, under the supervision of Dr Dolors Soy, Dr Ignacio Martín-Loeches, Dr Caridad Pontes, Dr Gonzalo Calvo and Dr Antoni Torres. Along with the PhD candidate, Marta Ulldemolins, Dr Dolors Soy, Dr Mireia Llauradó-Serra, Dr Alejandro H Rodríguez, Dr Pedro Castro and Dr Sergi Vaquer coordinated patient enrolment and collection of clinical samples in each hospital. Data collection, analysis and interpretation were undertaken by the PhD candidate, Marta Ulldemolins, under the supervision of Dr Dolors Soy and Dr Ignacio Martín-Loeches. The PhD candidate, Marta Ulldemolins, took the leading role in manuscript preparation and writing. All the co-authors participated in the manuscript drafting, and reviewed and approved the final version of the article.

The manuscript is presented as published; except figures and tables have been inserted into the text at slightly different positions. Also, the numbering of pages,

figures and tables has been adjusted to fit the overall style of the thesis. The references are found at the end of the chapter.

# MEROPENEM POPULATION PHARMACOKINETICS IN CRITICALLY ILL PATIENTS WITH SEPTIC SHOCK AND CONTINUOUS RENAL REPLACEMENT THERAPY: INFLUENCE OF RESIDUAL DIURESIS ON DOSE REQUIREMENTS

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## 6.1 Abstract

Meropenem dosing in critically ill patients with septic shock and continuous renal replacement therapy (CRRT) is complex, with the recommended maintenance doses being 500 mg to 1000 mg every 8h (q8h) to every 12h. This multicenter study aimed to describe the pharmacokinetics (PK) of meropenem in this population to identify the sources of PK variability and to evaluate different dosing regimens to develop recommendations based on clinical parameters. Thirty patients with septic shock and CRRT receiving meropenem were enrolled (153 plasma samples were tested). A population PK model was developed with data from 24 patients and subsequently validated with data from 6 patients using NONMEM software (v.7.3). The final model was characterized by $CL = 3.68 + 0.22\times(\frac{Residual\ diuresis}{100})$ and $V = 33.00\times(\frac{Weight}{73})^{2.07}$, where CL is total body clearance (in liters per hour), residual diuresis is the volume of residual diuresis (in milliliters per 24h), and V is the apparent volume of distribution (in liters). CRRT intensity was not identified to be a CL modifier. Monte Carlo simulations showed that to maintain concentrations of the unbound fraction ($f_u$) of drug above the MIC of the bacteria for 40% of dosing interval T (referred to as 40% of the $f_uT_{>MIC}$), a meropenem dose of 500 mg/q8h as a bolus over 30 min would be sufficient regardless of the residual diuresis. If 100% of the $f_uT_{>MIC}$ was chosen as the target, oligoanuric patients would require 500 mg/q8h as a bolus over 30 min for the treatment of susceptible bacteria (MIC<2 mg/liter), while patients with preserved diuresis would require the same dose given as an infusion over 3 h. If bacteria with MICs close to the resistance breakpoint (2 to 4 mg/liter) were to be treated with meropenem, a dose of 500 mg/q6h would be necessary: a bolus over 30 min for oligoanuric patients and an infusion over 3h for patients with preserved diuresis. Our results suggest that residual diuresis may be an easy and inexpensive tool to help with titration of the meropenem dose and infusion time in this challenging population.

**Keywords:** septic shock, meropenem, population pharmacokinetics, continuous renal replacement therapy, residual diuresis.

## 6.2 Introduction

Meropenem is a broad-spectrum carbapenem with high activity against Gram-positive and Gram-negative pathogens including *Pseudomonas aeruginosa, Acinetobacter sp* and anaerobes[1], and is one of the most prescribed antibiotics for the empirical treatment of severe infections[2]. It exhibits optimal killing activity when plasma unbound concentrations are maintained above the Minimum Inhibitory Concentration (MIC) of the bacteria during a percentage of the dosing interval (%$f_u T_{>MIC}$), that *in vitro* and *in vivo* animal studies have defined to be around 40%[3]. However, some clinical data suggest that critically ill patients may require longer %$f_u T_{>MIC}$, even 100%[4, 5].

Meropenem is a hydrophilic, small molecule, with a low volume of distribution (Vd) (0.3L/Kg) and very low protein binding (<2%). These characteristics make meropenem a drug mainly eliminated by the kidneys, as only the unbound fraction is available for glomerular filtration (major elimination pathway)[1]. This also makes meropenem a dialyzable drug because the main determinants of drug RRT clearance ($CL_{CRRT}$) are low molecular size, high affinity for water, low Vd and high unbound fraction[6]. Thus there is a potential combined impact of RRT and residual renal function on meropenem total clearance (CL), which may be particularly important for critically ill patients with septic shock and continuous renal replacement therapy (CRRT) requirement. For these patients, available guidelines recommend to prescribe 500-1000mg of meropenem q8-12h[7], which is a considerably broad dose range. However, this population is subject to conditions such as hypoproteinemia, variable urine output or diverse CRRT settings that may significantly influence meropenem pharmacokinetics (PK) and, consequently, modify dosing requirements[6]. It follows that while several studies have described meropenem PK in critically ill patients with continuous veno-venous hemofiltration (CVVHF) and hemodiafiltration (CVVHDF)[8-19], empirical dosing at the bedside is still challenging in this scenario.

## 6.3 Aims

The aims of this study were: to describe the PK of meropenem in critically ill patients with septic shock and CRRT, to identify the sources of PK variability in these patients, and to perform different dosing simulations to assess their probability of target attainment by MIC, in order to provide empirical dosing recommendations based on clinical characteristics.

## 6.4 Patients and Methods

### *6.4.a Patients*

We performed a multicenter, prospective, open-label PK study in the Intensive Care Units of the Hospitals Corporació Sanitària Universitària Parc Taulí of Sabadell (CSUPT), Clínic of Barcelona (HCB) and Joan XXIII (HJ23) of Tarragona. Patients were enrolled between December 2011 and May 2014. Authorization for the study was granted by the Spanish Regulatory Medicines Agency (code IEM-ANT-2012-1). Ethical approval was obtained from the local Ethical Committees, and the study was conducted following the Declaration of Helsinki guidelines. Consent to participate was obtained from the patient's legal representative. Inclusion criteria were age ≥ 18 years, septic shock diagnosed by the Surviving Sepsis Campaign guidelines criteria[20], CRRT requirement and indication for meropenem. The major exclusion criterion was severe chronic kidney disease requiring RRT. Meropenem dose and infusion time were at the discretion of the treating physician. The drug was administered through a separate lumen of a venous catheter using free-fall bolus systems or volumetric infusion pump controllers as required.

Patients' demographic and clinical data were collected. Age, weight, height, sex, site of infection, serum biochemistry, vasopressors requirement, CRRT settings, filter down-time, residual diuresis (defined as the volume of urine collected over the 24h of the natural day of the study), severity scores at admission (Acute Physiology and Chronic Health Evaluation II score (APACHE II))[21] and on the day of study (Sequential

Organ Failure Assessment score (SOFA))[22], isolated microorganisms and meropenem MICs, days of antibiotic therapy and hospital survival were recorded[23]. These data came from clinical routine and were registered in a database only available to the researchers.

### *6.4.b Continuous Renal Replacement Therapy*

Patients prescribed either CVVHDF or CVVHF were considered for inclusion. The CRRT systems used were Prisma®(Hospal, France). Filters used were 1.5$m^2$ surface-treated acrylonitrile and sodium methallyl sulfonate copolymer filter (AN69ST, PrismaFlex® ST150, Hospal, France) (HJ23) and 0.9 $m^2$ acrylonitrile and sodium methallyl sulfonate copolymer filter (AN69, PrismaFlex® M100, Gambro Hospal, Switzerland) (CSUPT and HCB). All CRRT settings were prescribed at the discretion of the treating physician.

### *6.4.c Blood sampling*

Per sample, 5mL of arterial blood were collected after at least 24h of CRRT and meropenem therapy. For bolus sampling, 6 samples were collected at 10min-predose, 0min, 15min, 60min, between 3-6h after the end of the infusion and just before the next dose. For extended infusion sampling, 5 samples were collected at 10min-predose, 0 min, 60min, 120min after the end of the infusion and just before the next dose. Within one hour of collection, samples were centrifuged at 3000rpm at 4$^{o}$C for 10min and plasma was frozen at -80$^{o}$C for posterior analysis.

### *6.4.d Liquid Chromatography-Mass Spectrometry analysis*

Total meropenem concentration in plasma was measured using liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) (1200HPLC binary pump, Agilent Technologies/API 4000 AB SCIEX MS) in an external laboratory using a validated method. The method was linear over a range of meropenem concentrations of 0.4-300 mg/L. Within-run and between-run precision and accuracy (coefficients of variation ≤ 10%) showed adequate results, according to EMA guidelines[24].

### *6.4.e Statistical analysis*

Statistical analysis was performed using SPSS v20 for Macintosh (IBM®SPSS®Statistics, USA). Results are expressed as absolute and relative frequencies for categorical variables and as medians [range] for continuous variables. A two-tailed Student t-test was used for comparing normally distributed variables, U-Mann Whitney test for non-normally distributed variables and Chi-square or Fisher's exact tests for categorical variables as appropriated. The significance level for all analyses was defined as $p \leq 0.05$.

### *6.4.f PK modeling*

Non-linear effects modeling was performed using NONMEM v7.3[25] and XPose v4.0 [26] following a three-step strategy: 1) basic population model selection, 2) covariate selection, and 3) validation[27, 28]. The first-order conditional estimation method with interaction was used for parameter estimation. Interindividual variability (IIV) was modeled as log-normal after being tested for log-normality. Additive, proportional and combined error models were tested for residual variance. Goodness-of-fit for a model was assessed by: 1) significant decreases in -2log-likelihood of the objective function value; 2) plots of population and individual predicted *versus* observed concentrations; and conditional weighted residuals (CWRES) *versus* observed concentrations and time[29, 30]; and 3) changes in the standard error of parameter estimates (precision).

In a second step, all reasonable demographic and clinical variables were tested for inclusion as covariates in the basic population PK model. Graphical examination and the generalized additive models procedure[26] were used to investigate their effects on model parameters. Continuous covariates were assessed as a proportional or a power function. Categorical variables were included in the model as: $P_j = \theta_{POP} + \theta_{COV} \times (1 - COV_i)$; where $P_j$ is the PK parameter for the j$^{th}$ patient, $COV_i$ is a numeric index value, $\theta_{POP}$ is the typical value of a PK parameter for the reference covariate values and $\theta_{COV}$ is the multiplicative factor for the influence of this covariate on the PK parameter. Each covariate investigated was retained if it led to an improved fit

evaluated by: biological plausibility, graphical displays based on the agreement between the observed (OBS) and predicted drug concentrations, uniformity of the distribution of the CWRES, improvement of the precision in parameter estimates, and log-likelihood ratio test. The extent of Bayesian shrinkage, as a measure of model over-parameterization, was evaluated for each PK parameter[31].

### *6.4.g Model evaluation*

Internal validation of the PK model was performed by graphical and statistical methods, including visual predictive checks[32]. Bootstrap resampling technique (200 replicated datasets) was used to build confidence intervals (CI) of PK parameters to assess their stability and evaluate the robustness of the final model[33].

External predictive performance of the PK model was assessed by analyzing data from new individuals (20-30% of the enrolled subjects)[34, 35], following the Food and Drug Administration guidelines[36]. Individual predicted meropenem concentrations for all sampling times were obtained by Bayesian estimation. Bias was assessed in terms of individual and population prediction error (IPE% and PPE%). Precision was assessed as absolute individual and population prediction error (IAPE% and PAPE%)[37].

### *6.4.h Dosing simulations*

Monte Carlo dosing simulations were performed. Each simulation generated concentration-time profiles for 1000 subjects per dosing regimen using the final estimated population PK parameters. Three bolus (500mg/q8h, 500mg/q6h and 1000mg/q8h over 30min) and three extended infusion (500mg/q8h, 500mg/q6h and 1000mg/q8h over 3h) regimens were simulated using a mean patient body weight of 70 kg and three categories of residual diuresis (50 mL, 300 mL and 700 mL) accounting for the definitions of anuria (<100mL/24h), oliguria (100-500mL/24h) and conserved urine output (>500mL/24h) respectively[38]. From these data the percentages of patients with 40%$f_u$$T_{>MIC}$, 100%$f_u$$T_{>MIC}$ and trough concentration ($C_{min}$)/MIC ratio equal to 5 according to meropenem clinical susceptibility breakpoints[39] were calculated (Probability of Target Attainment (PTA)).

## 6.5 Results

### *6.5.a Subjects and samples*

Thirty patients with septic shock and CRRT receiving meropenem were enrolled. Table 6 summarizes patients' demographic and clinical characteristics.

**Table 6**: Demographics and clinical characteristics of the subjects included in the index dataset, in the validation dataset and overall. Data is expressed as median [range] or as count (%). CRRT intensity was defined as (filtrate + dialysate flow rate)/(ideal body weight) for CVVHDF and as (filtrate flow rate)/(ideal body weight) for CVVHF, using 24 kg/m$^2$ as ideal body mass index. Hepatic impairment was defined as liver function tests > 2 x upper limit of normality.

| Variable | Model development (n=24) | Model Validation (n=6) | *p* value | Overall (n=30) |
|---|---|---|---|---|
| **Age (years)** | 68.5 [50-81] | 56 [34-85] | 0.40 | 66.5 [34-85] |
| **Females (%)** | 12 (50%) | 2 (33.3%) | 0.66 | 14 (46.7%) |
| **Weight[$] (kg)** | 72.8 [49-95] | 75 [68-126] | 0.24 | 72.8 [49-126] |
| **APACHE score[$]** | 26 [5-44] | 20 [15-33] | 0.18 | 24 [5-44] |
| **SOFA score[#]** | 12 [4-19] | 9 [5-19] | 0.67 | 12 [4-19] |
| **Hepatic impairment** | 5/24 (20.8%) | 1/5 (20%) | 0.88 | 6/30 (20%) |
| **Vasopressors[#]** | 24 (100%) | 4 (66.7%) | 0.034* | 28 (93.3%) |
| **Mechanical Ventilation[#]** | 23 (95.8%) | 6 (100%) | 1 | 29 (96.7%) |
| **CRRT Modality (CVVHDF/CVVHF)** | 21/3 | 5/1 | 1 | 26/4 |
| **Accumulated days of meropenem[#]** | 4 [2-22] | 2.5 [2-4] | 0.2 | 3 [2-22] |
| **CRRT Intensity[#] (mL/kg/h)** | 34.5 [18.7-60.1] | 39.2 [30.6-49.5] | 0.36 | 34.7 [18.7-60.1] |
| **Dialysate flow rate[#] (mL/h)** | 1000 [500-1600] | 900 [800-1350] | 0.73 | 1000 [500-1600] |
| **Ultrafiltrate flow rate[#] (mL/h)** | 1200 [750-2000] | 1800 [1000-2500] | 0.06 | 1550 [750-2500] |

| Variable | Model development (n=24) | Model Validation (n=6) | *p* value | Overall (n=30) |
|---|---|---|---|---|
| **Blood Flow[#] (mL/min)** | 200 [130-250] | 200 [200-250] | 0.38 | 200 [130-250] |
| **Albumin[#] (g/L)** | 21.3 [12.4-38] | 24.6 [18.1-32.6] | 0.61 | 23.4 [12.4-38] |
| **Urea[#] (mg/dL)** | 64.3 [22-168] | 52 [29-98] | 0.34 | 61.7 [22-168] |
| **Creatinine[#] (mg/dL)** | 1.6 [0.7-2.6] | 0.99 [0.4-2.3] | 0.14 | 1.4 [0.4-2.6] |
| **Diuresis[#] (mL/24h)** | 76.5 [<10-880] | 282.5 [82-2050] | 0.11 | 137.5 [<10-2050] |
| **Survival** | 14 (58.3%) | 3 (50%) | 1 | 56.7% |

Table legend: (*): Statistical significance (p<0.05), ([S]): on admission, ([#]): day of the study.

Median age was 66.5 years [range 34-85], median APACHE score on admission was 24 [range 5-44] and median SOFA score on the day of the study was 12 [range 4-19]. Sources of infection were intra-abdominal (13 patients), respiratory (7), bloodstream (4), urinary tract (2) and central nervous system (2). It could not be determined in 2 patients. Twenty-six patients were prescribed CVVHDF and 4 CVVHF. Regarding CRRT settings, median intensity on the day of the study was 34.7 mL/kg/h [range 18.7-60.1], and median blood flow was 200 mL/min [range 130-250]. In 4 patients the filters were non-functional during a fraction of the sampling interval due to filter clotting and exchange: one of them during the antibiotic administration (30 min), 2 during 1 h and 1 during 2.5h. Visual inspection did not identify alterations in the meropenem concentration-over-time profiles of these individuals that could be attributed to these incidences. With regards to urine output on the day of the study, 14 patients were anuric (<100mL/24h), 11 patients were oliguric (100-500mL/24h) and 5 patients had preserved diuresis (>500mL/24h). Median urine output was 137.5mL/24h (range 0-2050mL/24h). Respecting index and validation dataset, subjects were comparable in all characteristics except for vasopressors use at the time of the study: 2 of the patients in the validation dataset were not on vasopressors when samples were collected. Concerning microbiology, positive cultures were obtained from 23 patients (76.7%). Most frequently isolated microorganisms were *Escherichia coli* (21.4%) and *Pseudomonas aeruginosa* (14.3%). Table 7 shows meropenem MIC values for the 28 isolated strains.

**Table 7:** Isolated microorganisms and meropenem susceptibility by MIC.

| Microorganism | Number of isolates | MIC (mg/L) |
|---|---|---|
| *Burkholderia cepacia* | 1 | 1 |
| *Clostridium intestinale* | 1 | 2 |
| *Enterobacter cloacae* | 1 | 1 |
| *Enterococcus faecalis* | 2 | 2 |
| *Enterococcus faecalis* | 1 | Not determined |
| *Enterococcus faecium* | 1 | 8 |
| *Enterococcus faecium* | 1 | Not determined |
| *Escherichia coli* | 6 | 2 |
| *Klebsiella pneumoniae* | 1 | 32 |
| *Listeria monocytogenes* | 1 | Not determined |
| *Moraxella catarrhalis* | 1 | 1 |
| *Pseudomonas aeruginosa* | 1 | 1 |
| *Pseudomonas aeruginosa* | 1 | 2 |
| *Pseudomonas aeruginosa* | 1 | 4 |
| *Pseudomonas aeruginosa* | 1 | 8 |
| *Salmonella enteritidis* | 1 | 2 |
| *Serratia marcescens* | 1 | 2 |
| *Staphylococcus aureus* | 1 | 2 |
| *Staphylococcus epidermidis* | 3 | Not determined |
| *Stenotrophomonas maltophilia* | 1 | Not determined |

Patients were prescribed meropenem 500mg/q12h over 30min (1 subject), 500mg/q8h over 30min (2) or 3h-infusion (3), 500mg/q6h over 3h-infusion (1), 1000mg/q12h over 30min (6), 3h-infusion (1) or 4h-infusion (1), 1000mg/q8h over 30min (8), 3h-infusion (5) or 4h-infusion (1) or 2000mg/q8h over 30min (1). Median duration of meropenem therapy was 10 days [range 4-28].

### *6.5.b Population PK analysis*

The population PK modeling was developed using data from 24 subjects (124 samples). Data were better described by a one-compartment linear model

characterized by population CL and Vd at steady-state, with interindividual variability incorporated in both PK parameters. Residual variability consisted of additive and proportional error. Goodness-of-fit plots showed good accordance between observed (OBS) and predicted (PRED) and individual predicted (IPRED) concentrations (Figure 1). The mean (±SD) of the CWRES was close to zero, and residual error plots did not show systematic deviations over time. The magnitude of ε-shrinkage was 14.5%. The model parameters had moderate levels of η-shrinkage for CL (33.3%) and V (20.9%).

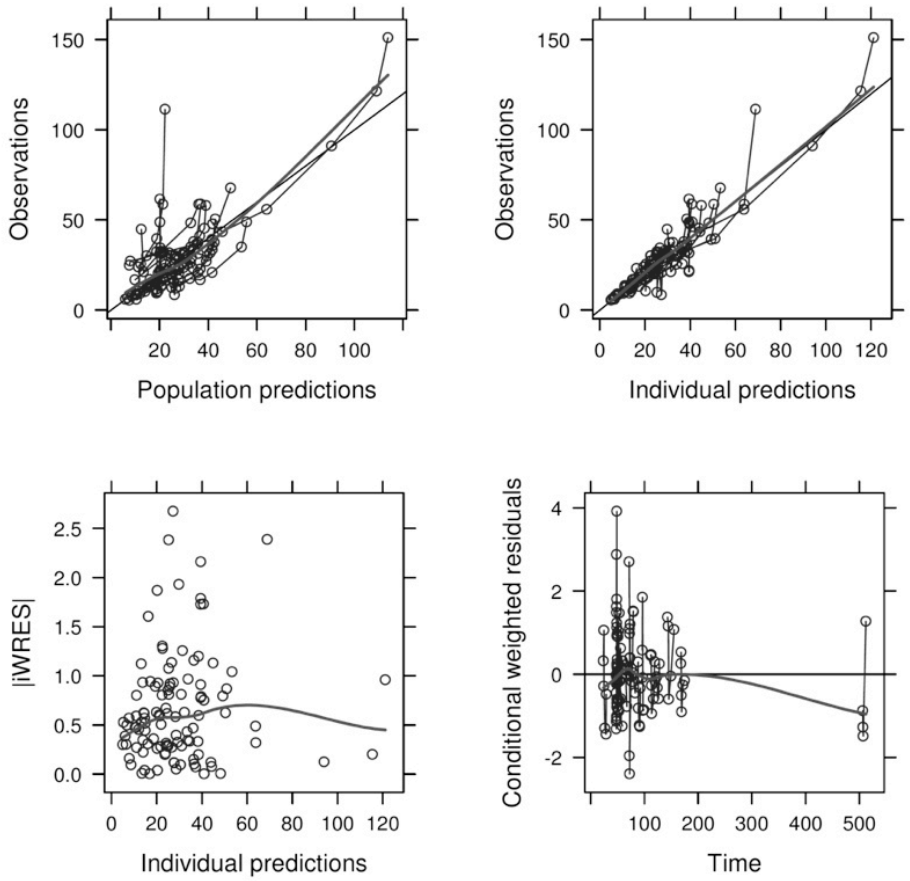
Concerning the covariate analysis, residual diuresis significantly influenced meropenem CL, whereas CRRT intensity, filter down-time, blood flow, type of membrane and albumin did not. Concerning Vd, only total body weight on admission showed a significant impact on the parameter, whereas severity scores, age and albumin did not. The final model is displayed in Table 8 and summarized as follows:

$$CL\ (L/h) = 3.68 + 0.22 \times \left(\frac{Residual\ diuresis\ (mL)}{100}\right)$$

$$V(L) = 33.00 \times \left(\frac{Weight(kg)}{73}\right)^{2.07},$$

, where residual diuresis is normalized to the defined cut-off for anuria[38] and weight to the median weight of our patient population.

**Figure 1:** Goodness-of-fit plots for the final population PK model. Left upper panel: plot of observed meropenem concentrations *versus* population predictions; solid thin line: line of identity; solid thick line: data smooth. Right upper panel: plot of observations *versus* individual predictions; solid thin line: line of identity; solid thick line: data smooth. Left bottom panel: plot of individual weighted residuals (iWRES) *versus* individual predictions; thick line: smooth. Right bottom panel: plot of conditional weighted residuals *versus* time; thick line: smooth. Concentrations are in mg/L; time is in hours.




### *6.5.c Validation*

The results from the visual predictive check plot showed that practically all observations dropped into the 95% CI. The statistical distributions of the parameter estimates obtained from the bootstrap analyses are shown in Table 8.

**Table 8:** Population PK estimates for the final model and bootstrap results.

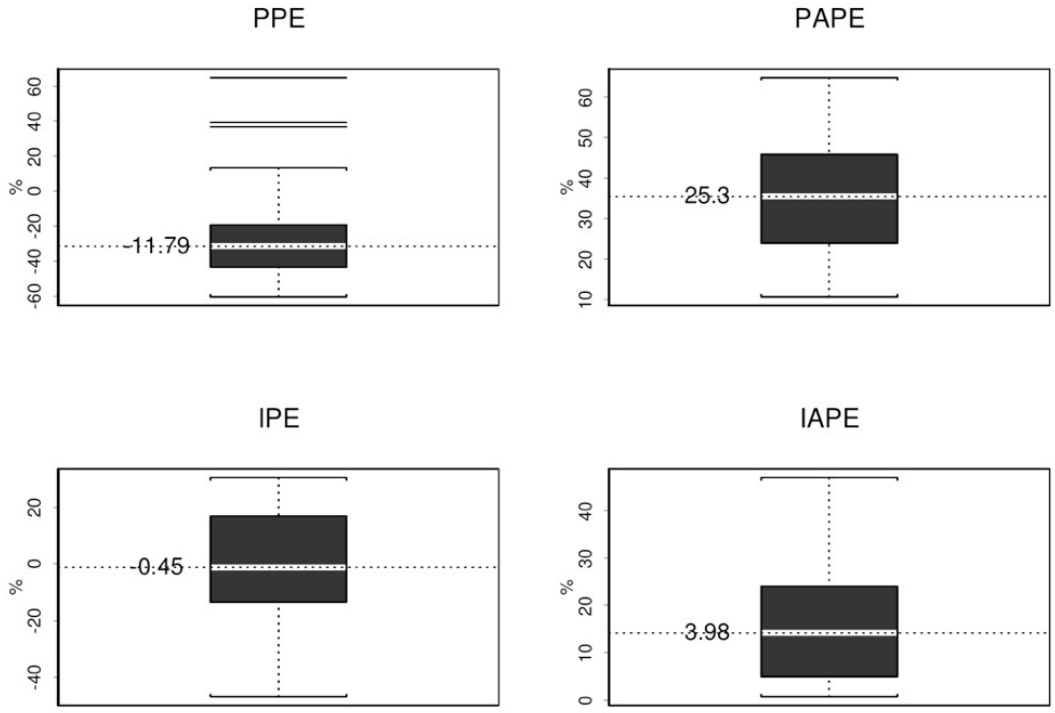
| **Parameter** | **Estimate (RSE %)** | **Bootstrap, median [95% confidence interval]** |
|---|---|---|
| **CL (L/h)** | | |
| $\theta_{CL}$ | 3.68 (11) | 3.59 [2.90 – 4.46] |
| $\theta_{DIUR}$ | 0.22 (47) | 0.22 [0.003 – 0.44] |
| **Vd (L)** | | |
| $\theta_{Vd}$ | 33.00 (10) | 31.94 [26.65 – 39.35] |
| $\theta_{WT}$ | 2.07 (24) | 2.27 [0.82 – 3.32] |

| Parameter | Estimate (RSE %) | Bootstrap, median [95% confidence interval] |
|---|---|---|
| **IIV_CL (CV %)** | 37 (27) | 37.15 [24.35 – 46.12] |
| **IIV_Vd (CV %)** | 45 (61) | 47.89 [12.25 – 65.04] |
| **Additive Residual Error (mg/L)** | 0.0002 (42.76) | 0.0002 [0.0001 – 0.001] |
| **Proportional Residual Error** | -0.258 (10) | -0.25 [(-0.35) – (-0.17)] |

Table legend: CL: total body clearance; Vd: apparent volume of distribution; $\theta_{CL}$: typical value for CL in the population; $\theta_{DIUR}$: multiplicative factor for the influence of residual diuresis on CL; $\theta_{Vd}$ : typical value for Vd in the population; $\theta_{WT:}$ power factor for the influence of weight on V; IIV_CL: interindividual variability associated with CL; IIV_Vd: interindividual variability associated with V; RSE: relative standard error

Median values of the parameters estimated from the bootstrap were in good agreement with the NONMEM point estimates, and the 95% CI were reasonably narrow, demonstrating satisfactory precision. With respect to external validation, mean bias and precision for the maximum a posterior Bayesian estimates (IPRED) were -0.45% and 3.98% respectively, much better than those values obtained from the population PK model-based estimates (PRED), which were -11.79% and 25.3% respectively (Figure 2).

**Figure 2:** Bias and precision for model estimates as regards to the external validation. Top line: left panel: box-plot of the population prediction error (PPE); right panel: population absolute prediction error (PAPE); Bottom line: left panel: box-plot of the individual prediction error (IPE); right panel: individual absolute prediction error (IAPE). The white band in each error box marks the $50^{th}$ percentile; the box boundaries are at the $25^{th}$ and $75^{th}$ percentiles, and the limits of the whiskers are at the $10^{th}$ and $90^{th}$ percentiles.




### *6.5.d Simulations*

PTA *versus* MIC profiles for simulations of different dosing regimens by residual diuresis and $f_u T_{>MIC}$ target are presented in Table 9. A PTA>90% was considered satisfactory.

**Table 9:** Probability of target attainment (PTA) by MIC for simulations of different dosing regimens of meropenem and stratified by residual diuresis (anuria, oliguria and preserved diuresis) and pharmacodynamic target (PTA40: 40%$f_u T_{>MIC}$, PTA100: 100% $f_u T_{>MIC}$ and PTA500: 5 x 100%$f_u T_{>MIC}$). MIC are expressed in mg/L, PTA are expressed in (%). Shadowed areas correspond to PTA≥ 90 %.

| **RESIDUAL DIURESIS** | **Dose: 500mg/q8h** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **30min bolus** | | | | **3h infusion** | | | |
| | **MIC (mg/L)** | **PTA40** | **PTA100** | **PTA500** | **MIC (mg/L)** | **PTA40** | **PTA100** | **PTA500** |
| **Anuria (< 100 mL/24h)** | 0.5 | 100 | 99.3 | 92.9 | 0.5 | 100 | 99.9 | 97.9 |
| | 1 | 100 | 98.4 | 66.1 | 1 | 100 | 99.9 | 80.4 |
| | 2 | 99.9 | 94.4 | 6.6 | 2 | 100 | 97.5 | 15.1 |
| | 4 | 98.4 | 74.0 | 0.2 | 4 | 99.3 | 85.8 | 0.2 |
| **Oliguria (100-500 mL/24h)** | 0.5 | 100 | 98.6 | 88.2 | 0.5 | 100 | 99.9 | 93.7 |
| | 1 | 100 | 96.1 | 50.2 | 1 | 100 | 99.2 | 68.5 |
| | 2 | 100 | 89.9 | 4.1 | 2 | 100 | 94.5 | 8.2 |
| | 4 | 98.1 | 62.0 | 0.9 | 4 | 99.5 | 76.3 | 0.2 |
| **Preserved diuresis (> 500 mL/24h)** | 0.5 | 100 | 96.9 | 76.1 | 0.5 | 100 | 98.5 | 88.5 |
| | 1 | 100 | 92.1 | 34.3 | 1 | 100 | 97.3 | 51.2 |
| | 2 | 99.9 | 79.9 | 1.8 | 2 | 100 | 90.8 | 3.4 |
| | 4 | 99.3 | 46.5 | 0 | 4 | 100 | 64.2 | 0 |

**Table 9 continuation:**

| RESIDUAL DIURESIS | Dose: 500mg/q6h | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 30min bolus | | | | 3h infusion | | | |
| | MIC (mg/L) | PTA40 | PTA100 | PTA500 | MIC (mg/L) | PTA40 | PTA100 | PTA500 |
| Anuria (< 100 mL/24h) | | 100 | 99.9 | 98.9 | 0.5 | 100 | 100 | 99.8 |
| | 1 | 100 | 99.6 | 87.0 | 1 | 100 | 100 | 95.5 |
| | 2 | 100 | 99.2 | 23.2 | 2 | 100 | 99.9 | 37.5 |
| | 4 | 100 | 95.1 | 0.3 | 4 | 100 | 98.8 | 1.2 |
| Oliguria (100-500 mL/24h) | 0.5 | 100 | 99.7 | 97.4 | 0.5 | 100 | 100 | 98.7 |
| | 1 | 100 | 99.2 | 80.4 | 1 | 100 | 99.7 | 92.6 |
| | 2 | 99.9 | 98.7 | 14.4 | 2 | 100 | 99.2 | 26.2 |
| | 4 | 99.8 | 90.9 | 0.2 | 4 | 100 | 97.0 | 0.6 |
| Preserved diuresis (> 500 mL/24h) | 0.5 | 100 | 99.5 | 93.2 | 0.5 | 100 | 100 | 98.0 |
| | 1 | 100 | 98.7 | 62.5 | 1 | 100 | 99.7 | 83.9 |
| | 2 | 99.9 | 95.7 | 6.0 | 2 | 100 | 98.8 | 15.2 |
| | 4 | 99.7 | 77.3 | 0 | 4 | 100 | 93.5 | 0 |

**Table 9 continuation:**

| RESIDUAL DIURESIS | Dose: 1000mg/q8h | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 30min bolus | | | | 3h infusion | | | |
| | MIC (mg/L) | PTA40 | PTA100 | PTA500 | MIC (mg/L) | PTA40 | PTA100 | PTA500 |
| Anuria (< 100 mL/24h) | | 100 | 99.7 | 97.7 | 0.5 | 100 | 99.9 | 99.0 |
| | 1 | 100 | 99.5 | 93.1 | 1 | 100 | 99.9 | 96.8 |
| | 2 | 100 | 98.5 | 64.5 | 2 | 100 | 99.3 | 80.7 |
| | 4 | 99.9 | 93.3 | 7.4 | 4 | 100 | 97.4 | 13.4 |
| Oliguria (100-500 mL/24h) | 0.5 | 100 | 99.9 | 97.6 | 0.5 | 100 | 100 | 98.8 |
| | 1 | 100 | 99.1 | 88.6 | 1 | 100 | 99.8 | 94.9 |
| | 2 | 100 | 97.8 | 51.1 | 2 | 100 | 98.9 | 69.9 |
| | 4 | 99.9 | 90.1 | 3.4 | 4 | 100 | 95.2 | 9.9 |
| Preserved diuresis (> 500 mL/24h) | 0.5 | 100 | 98.6 | 90.9 | 0.5 | 100 | 99.6 | 97.2 |
| | 1 | 100 | 97.1 | 75.6 | 1 | 100 | 99.1 | 88.3 |
| | 2 | 100 | 92.4 | 32.6 | 2 | 100 | 97.6 | 50.8 |
| | 4 | 99.8 | 80.7 | 1.4 | 4 | 100 | 90.3 | 3 |

For the attainment of the classical pharmacodynamic (PD) target for carbapenems, (40% $f_u T_{>MIC}$), 500mg/q8h over a 30min-bolus would be sufficient for the treatment of bacteria with MIC even close to the susceptibility breakpoint (MIC ≤ 4mg/L), regardless of urine output. If a 100% $f_u T_{>MIC}$ was chosen as PD target, oligoanuric patients would require dose of 500mg/q8h over 30min for the treatment of susceptible bacteria (MIC < 2mg/L), while patients with diuresis >500mL/24h may require the same dose over a 3h-infusion. If bacteria with MIC close to the resistance breakpoint (2-4mg/L) were to be treated with meropenem, a dose of 500mg/q6h would be necessary, administered as a 30min-bolus for oligoanuric patients and as a 3h-infusion for patients with preserved diuresis. For the attainment of more aggressive PD targets, such as five times the ratio $C_{min}$/MIC described by Li *et al*.[5], doses of 1000mg/q8h over a 3h infusion or higher would be required regardless of urine output. Table 10 summarizes the recommendations developed from these simulated data.

**Table 10:** Summary of meropenem maintenance dosing recommendations based on the results of the present study.

| **Pharmacodynamic Target** | **Pathogen MIC (mg/L)** | **Dose recommendation** |
|---|---|---|
| 40% $f_u T_{>MIC}$ | ≤ 4mg/L | 500mg/q8h as a 30min-bolus (all urine outputs) |
| | | |
| 100% $f_u T_{>MIC}$ | ≤ 2mg/L | Oligoanuria:<br>500mg/q8h as a 30min-bolus<br>Preserved diuresis:<br>500mg/q8h as a 3h-infusion |
| | 2-4mg/L | Oligoanuria:<br>500mg/q6h as a 30min-bolus<br>Preserved diuresis:<br>500mg/q6h as a 3h-infusion |
| | | |
| $C_{min}$/MIC = 5 | ≤ 1mg/L | 1000mg/q8h as a 3h-infusión<br>(all urine outputs) |

## 6.6 Discussion

To our knowledge, this is the largest multicenter study that characterizes the PK of meropenem in critically ill patients with septic shock and CRRT requirement. Our PK parameter estimates were in agreement with previous studies with a comparable population[15, 18].

Our main finding is the relationship existing among the 24h urine output, the pathogen MIC and meropenem dosing requirements for the maintenance phase of therapy, i.*e.* after 24h of meropenem therapy and CRRT commencement. In general, antibiotic dose adjustments in critically ill patients are very challenging for the clinician because, unlike other drugs like vasopressors or sedatives among others, their pharmacological effect is not immediately evident but requires a certain period of time, even days, to be visible. For critically ill patients with septic shock and CRRT requirement, these are even more challenging due to all the PK changes driven by critical illness and the use of extracorporeal devices[6]. In spite of this difficulty, attainment and maintenance of therapeutic concentrations are crucial, as they have an impact in both clinical outcomes and development of bacterial resistances. In this context, we have identified that consideration of residual diuresis might be advantageous for meropenem maintenance dose and infusion time adjustment based on the MIC of the pathogen. For the attainment of a PD target of 100% $f_u T_{>MIC}$, fixed doses would be required depending on the bacteria MIC, but infusion time would depend on residual diuresis: oligoanuric patients would benefit from a 30min bolus while a 3h-extended infusion would be more appropriated for those patients with preserved diuresis. One may hypothesize that residual diuresis may influence meropenem requirements because a given percentage of the administered dose is eliminated with the urine. Conversely, for the attainment of the classical PD target for carbapenems, *i.e.* 40% $f_u T_{>MIC}$, a standard dose of 500mg/q8h over a 30min-bolus would be sufficient for all cases. Further, for the attainment of a more aggressive target such as a $C_{min}$/MIC ratio = 5, doses of 1000mg/q8h over a 3h-infusion or higher would be required. Of note, empirical dosing on the first day still

would need to be made based on predicted Vd and local antibiogram data, as the use of the 24h urine output measure can only have meaningful impact on empirical dosing after 24h, *i.e.* during the maintenance phase of the therapy.

It is important to highlight that we have principally based our empirical dosing recommendations targeting a 100% $f_u T_{>MIC}$ rather than the 40% $f_u T_{>MIC}$ described in the classical studies[3]. We believe that such a thoughtful PD target is more recommendable for our patient population for several reasons. Firstly, emerging evidence has associated higher % $f_u T_{>MIC}$ with better outcomes[4, 5]. For instance, Li *et al.* reported that trough concentrations higher than 5 times the MIC of the pathogen ($C_{min}$/MIC ratio = 5) were associated with better clinical and microbiological success rates[5]. Also, Roberts *et al.* found that a higher % $T_{>MIC}$ had a tendency to better survival odds compared to lower % $T_{>MIC}$ (Odds Ratio 1.02 [95% CI, 1.01–1.04] for 50%$T_{>MIC}$ and 1.56 [95% CI, 1.15–2.13] for 100%$T_{>MIC}$), despite these odds data were not statistically compared [4]. Further, all this evidence is based on plasmatic concentrations, but it is well known that critically ill patients with severe infections exhibit microcirculatory alterations that impair tissue distribution and lead to lower % $f_u T_{>MIC}$ at the target site. This was shown in a nice study by Varghese *et al.,* who reported that tissue concentrations of meropenem in critically ill patients with CVVHDF accounted for a median of 60-70% of plasma concentrations[18], which may be even lower in patients with septic shock. Due to sickness severity of patients with septic shock we believe that more aggressive pharmacodynamic targets should be preferred for ensuring and early and adequate antibiotic antimicrobial therapy. We also report the dosing recommendations for the attainment of a more ambitious target that has been associated with better outcomes in patients treated with meropenem ($C_{min}$/MIC ratio=5)[5]. However, we believe that such an ambitious target is probably too aggressive and the risks of such high concentrations may outweigh the potential benefits. Also, we arbitrarily accepted a ~ 90% PTA as satisfactory for our dose recommendations, as to our knowledge the optimal PTA breakpoint is still a matter of debate[40].

Interestingly, our model failed to identify CRRT intensity as a significant modifier of meropenem CL. We initially expected that intensity would have a significant effect on meropenem CL by CRRT according to available literature that report differential meropenem CL when different intensities were used[12, 41]. However, exploratory and regression analysis on the covariates effect on individual CL did not show any visual or statistical trend between intensity and the estimates of individual CL, which may lead to the hypothesis that even the lowest intensities studied may be enough to maximize meropenem clearance by CRRT and that higher intensities may add little to total meropenem CL. This explanation is consistent with data from Roberts *et al*., who also failed in the identification of intensity as a meropenem CL modifier[42]. Similarly, we did not observe differences between CRRT techniques, likely because of the under-representation of CVVHF (4 out of 30 patients) in our study population. Controversy exists on the impact of CRRT modality in drug CL, as different meropenem CL between CRRT methods have been reported by some researchers[12], while others have not found any difference[15]. Also, we did not find differences in CL between types of membrane, albeit they where different among hospitals (1.5$m^2$ AN69ST in HJ23, 0.9$m^2$ AN69 in CSUPT and HCB). Importantly, the presence of polyethylenimine and heparin in the membrane surface (AN69ST) did not significantly influence CL, suggesting that meropenem adsorption to the surface-treated filter may not be a major elimination pathway, unlike for other molecules like colistin[43].

A strong point of our population PK model is that it has been externally validated with new subjects. Before carrying out Monte Carlo simulations to assist in recommending any dosage regimen for a specific patient population, it should be previously established that the population PK model is predictive[34]. However, despite the paramount importance of this step, it has been estimated that only 7% of the population PK models are externally validated[44]. External validation showed that, by means of bias and precision, our population PK model had mean values within good limits, which supported its utility for undertaking dosing simulations.

Our main limitation was not measuring meropenem urinary and ultrafiltrate concentrations, for which we could estimate neither the sieving coefficient, which has been already well described to be around 1 for meropenem using AN69 membranes[8, 9, 19, 45]; nor truly quantify the degree of $CL_{CRRT}$. Furthermore, we only included patients with septic shock and renal failure requiring CRRT, therefore our conclusions cannot be extrapolated to other patient populations like those without septic shock, without renal failure, with intermittent RRT or with other extracorporeal blood purification therapies. Also, due to the low representation of CVVHF in the patient cohort, our conclusions may only be applied to patients receiving CVVHDF. Finally, the measurement of residual diuresis was performed by the nursing staff as part of their clinical routine, which might not be optimal for obtaining the exact volume of urine but is certainly sufficient for classifying the patients as oligoanuric or with preserved diuresis. Conversely, the major strengths of this study are its multicenter nature, its large sample size (30 patients) and the fact that the population PK model has been externally validated. Moreover, our recommendations are based on an easy-to-measure and inexpensive clinical parameter such as residual diuresis; hence our results can be easily implemented in daily care.

## 6.7 Conclusions

In conclusion, we present the results of the largest multicenter pharmacokinetic study of meropenem prescribed to critically ill patients with septic shock and CRRT. Our population PK model successfully identified residual diuresis as a modifier of total meropenem CL. Continuous renal replacement therapy intensity did not significantly modify meropenem CL, for which dose adjustments based on intensity seem to be unnecessary. Given a certain MIC, simulations showed that meropenem dose titration considering residual diuresis was advantageous for the attainment of a 100% $f_u T_{>MIC}$ as a PD target. If classical PD targets (40% $f_u T_{>MIC}$ ) were targeted, a standard dose of 500mg/q8h over a 30min bolus would be sufficient regardless of urine output.

## 6.8 Acknowledgments

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## 6.9 Transparency Declarations

All authors: none to declare.

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# CHAPTER 7. STUDY 3: PIPERACILLIN

## Published manuscript entitled "PIPERACILLIN POPULATION PHARMACOKINETICS IN CRITICALLY ILL PATIENTS WITH MULTIPLE ORGAN DYSFUNCTION SYNDROME RECEIVING CONTINUOUS VENO-VENOUS HEMODIAFILTRATION: EFFECT OF TYPE OF DIALYSIS MEMBRANE ON DOSING REQUIREMENTS"

The manuscript entitled "Piperacillin Population Pharmacokinetics in Critically Ill Patients with Multiple Organ Dysfunction Syndrome receiving Continuous Veno-Venous Hemodiafiltration: Effect of Type of Dialysis Membrane on Dosing Requirements" has been published by The Journal of Antimicrobials and Chemotherapy (*J Antimicrob Chemother* 2016; **71**: 1651-9. doi: 10.1093/jac/dkv503).

*The Journal of Antimicrobials and Chemotherapy* is a journal included in the Journal Citation Report of the Web of Science®, with an impact factor in 2015 of **4.919** (ranked 9/83 under the category *Infectious Diseases*, 19/123 under the category of *Microbiology* and 29/253 under the category *Pharmacology & Pharmacy,* first quartile).

The co-authors contributed to the manuscript as follows: Study design was performed by the PhD candidate, Marta Ulldemolins, under the supervision of Dr Dolors Soy, Dr Ignacio Martín-Loeches, Dr Caridad Pontes, Dr Gonzalo Calvo and Dr Antoni Torres. Along with the PhD candidate, Marta Ulldemolins, Dr Dolors Soy, Dr Mireia Llauradó-Serra, Dr Alejandro H Rodríguez, Dr Javier Fernández and Dr Sergi Vaquer coordinated patient enrolment and collection of clinical samples in each hospital. Data collection, analysis and interpretation were undertaken by the PhD candidate, Marta Ulldemolins, under the supervision of Dr Dolors Soy and Dr Ignacio Martín-Loeches. The PhD candidate, Marta Ulldemolins, took the leading role in manuscript preparation and writing. All the co-authors participated in the manuscript drafting, and reviewed and approved the final version of the article.

The manuscript is presented as published; except figures and tables have been inserted into the text at slightly different positions. Also, the numbering of pages, figures and tables has been adjusted to fit the overall style of the thesis. The references are found at the end of the chapter.

# PIPERACILLIN POPULATION PHARMACOKINETICS IN CRITICALLY ILL PATIENTS WITH MULTIPLE ORGAN DYSFUNCTION SYNDROME RECEIVING CONTINUOUS VENO-VENOUS HEMODIAFILTRATION: EFFECT OF TYPE OF DIALYSIS MEMBRANE ON DOSING REQUIREMENTS

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## 7.1 Abstract

**Objectives:** To describe the pharmacokinetics (PK) of piperacillin in critically ill patients with multiple organ dysfunction syndrome (MODS) and continuous veno-venous hemodiafiltration (CVVHDF) requirement by using a population PK model, to identify the factors associated with PK variability and to evaluate different dosing regimens for developing recommendations based on clinical characteristics.

**Patients and methods:** Nineteen patients with MODS and CVVHDF receiving piperacillin/tazobactam were enrolled from three tertiary hospitals (95 plasma samples). Population PK modeling and Monte Carlo simulations were performed using NONMEMv.7.3®.

**Results:** Patients median age was 70 years (range [39-82]), median weight was 80kg ([45-129]), median APACHE II score at admission was 21 ([13-33]) and median SOFA score on the day of study was 11 ([8-21]). The final population PK model was characterized by $CL = 6.11\times(\frac{Weight}{80})^{1.39}\times CL_{MEMB}$. If membrane=1.5m$^2$ AN69ST, $CL_{MEMB}$=1, if membrane=0.9m$^2$ AN69, $CL_{MEMB}$=0.51. Monte Carlo simulations showed that: 1) to maintain unbound piperacillin concentrations above the MIC of the bacteria for 100% of dosing interval T (100% $f_u T_{>MIC}$), patients receiving CVVHDF with 1.5m$^2$AN69ST membranes required doses of 4000mg/q8h for the treatment of bacteria with a susceptibility to piperacillin close to the clinical breakpoint (MIC = 8-16mg/L) (2000mg/q8h was sufficient for patients with CVVHDF using 0.9m$^2$AN69 membranes) and 2) for the treatment of bacteria with high susceptibility to piperacillin (MIC ≤ 4mg/L) or for the attainment of a more traditional pharmacodynamic target (50% $f_u T_{>MIC}$), 2000mg/q8h sufficed regardless of type of membrane and body weight.

**Conclusions:** Our results suggest that type of membrane and body weight should be considered for piperacillin dose titration in critically ill patients with MODS and CVVHDF requirement.

**Keywords:** piperacillin, population pharmacokinetics, pharmacodynamics, septic shock, acute kidney injury, AN69 membrane, surface-coated AN69ST membrane.

## 7.2 Introduction

Piperacillin is an extended-spectrum beta-lactam antibiotic belonging to the family of the penicillins. Combined with the beta-lactamase inhibitor tazobactam, it exhibits broad activity against several species of Gram-positive and Gram-negative pathogens, including *Pseudomonas aeruginosa* and anaerobes. For this reason, piperacillin is one of the most used antipseudomonal agents in the empirical therapy of patients with severe infections[1]. Piperacillin is a hydrophilic antibiotic, with low molecular weight (517.5g/mol) and moderate protein binding (20-30%). These characteristics make piperacillin a drug cleared mainly by renal excretion as unchanged drug (68%), being biliary excretion a secondary elimination pathway[2]. Likewise, piperacillin is a drug cleared by renal replacement therapies (RRT), as low molecular weight, hydrophilicity and low protein binding are the main determinants of RRT elimination[3]. Regarding its pharmacodynamics (PD), piperacillin exhibits maximal killing activity when its unbound concentration at the site of infection is maintained over the MIC of the pathogen during a certain period of the dosing interval (% $f_u T_{>MIC}$), that for penicillins has been defined to be around 50% in *in vitro* and *in vivo* animal studies[4].

In critically ill patients, the presence of multiple organ dysfunction syndrome (MODS) including septic shock and acute kidney injury (AKI) requiring RRT has been shown to dramatically decrease survival, leading to inacceptable mortality rates (~60%)[5]. In this subgroup of patients with very high levels of sickness severity, effective antibiotic therapy may be even more important to clinical outcome. However, they represent one of the most complex patients to correctly dose. This is due to the observed variations in antibiotic pharmacokinetics (PK) caused by the pathophysiology of MODS and medical management, including technical factors relating to the RRT modality itself[6]. Particularly, continuous veno-venous hemodiafiltration (CVVHDF) is one the most frequently used modalities of RRT in the early phases of AKI in the context of MODS, mainly due to patient's hemodynamic

instability. This modality has the characteristic of using convective and diffusive methods for solute and fluid elimination.

Due to its clinical relevance, previous studies have documented piperacillin PK in critically ill patients with MODS and CVVHDF requirement[7-10]. These data have lead to different dose recommendations (ranging between 8mg and 16g/day)[3] due to the variability observed in piperacillin PK, especially in CL. However, the causes of variability reported in those studies have not been sufficiently investigated yet. The hypothesis of this study was that this variability observed in piperacillin PK could be explained by clinical and demographic characteristics.

Consequently, our aims were: 1) to describe the PK of piperacillin in critically ill patients with MODS receiving CVVHDF; 2) to identify the sources of PK variability in this population; and 3) to perform dose simulations for providing dosing recommendations that maximize piperacillin exposure (% $f_u$ $T_{>MIC}$).

## 7.3 Patients and Methods

### *7.3.a Patients*

We conducted a prospective, multicenter, open-label PK study in the multidisciplinary Intensive Care Units of the tertiary Hospitals Corporació Sanitària Universitària Parc Taulí of Sabadell (CSUPT), Clínic of Barcelona (HCB) and Joan XXIII (HJ23) of Tarragona during the period January 2012 - May 2014. Authorization for the study was granted by the Spanish Regulatory Medicines Agency (code IEM-ANT-2012-1) and ethical approval was obtained from the local Ethics Committees. Written informed consent was obtained from each patient's legally authorized representative. Inclusion criteria were age ≥ 18 years, MODS including septic shock diagnosed by the Surviving Sepsis Campaign guidelines criteria[11] and AKI requiring CVVHDF, and clinical indication for piperacillin. The major exclusion criterion was chronic renal disease requiring dialysis.

Patients' demographic and clinical data were collected and registered in a database only available to the study investigators. Age, weight, height, sex, site of infection, serum biochemistry, organ support requirement, CVVHDF settings[12], filter down-time, residual diuresis, severity scores at admission (APACHE II)[13] and on the day of study (SOFA)[14], clinically significant bacterial isolates and MICs to piperacillin, days of antibiotic therapy and hospital survival were the main variables recorded.

### *7.3.b Continuous Renal Replacement Therapy*

The CVVHDF systems used were Prisma®(Hospal, France). Filters used were 0.9 $m^2$ AN69 acrylonitrile and sodium methallyl sulfonate copolymer filter (PrismaFlex®M100, Gambro Hospal, Switzerland) (CSUPT and HCB) and 1.5$m^2$ AN69ST acrylonitrile and sodium methallyl sulfonate copolymer filter precoated with heparin and polyethyleneimine (PrismaFlex®ST150, Hospal, France) (HJ23). All CVVHDF settings were prescribed at the discretion of the treating physician.

### *7.3.c Drug dosing*

Piperacillin/tazobactam dose and infusion time were at the discretion of the treating physician. It was administered through a separate lumen of a venous catheter using free-fall bolus systems or volumetric infusion pump controllers as required.

### *7.3.d Blood sampling*

Five milliliters of arterial blood per sample were collected after at least 24h of CVVHDF and piperacillin/tazobactam therapy. For bolus sampling, 6 samples were collected at 10min-predose, 0min, 15min, 60min, between 3-6h after the end of the infusion and just before the next dose. For extended infusion (3h or 4h) sampling, 5 samples were collected at 10min-predose, 0 min, 60min, 120min after the end of the infusion and just before the next dose. After being drawn, blood samples were immediately put into an ice bath at 0-4$^{o}$C. Then, within one hour of collection, plasma was obtained by centrifugation at 3000rpm at 0-4$^{o}$C for 10min and frozen at -80$^{o}$C for its posterior analysis.

### *7.3.e Liquid Chromatography-Mass Spectrometry analysis*

Total piperacillin concentration in plasma was measured using liquid chromatography coupled to tandem mass spectrometry (1200HPLC binary pump, Agilent Technologies/API 4000 AB SCIEX MS) in an external laboratory using a validated method. The method was linear over a range of piperacillin concentrations of 1.5-400mg/L. Within-run and between-run precision and accuracy showed adequate results (coefficients of variation ≤ 10%), according to EMA guidelines[15].

### *7.3.f Statistical analysis*

Statistical analysis was performed using R for Macintosh v3.0.2 (The R Foundation for Statistical Computing®). Results are expressed as absolute and relative frequencies for categorical variables and as median [range] for continuous variables.

### *7.3.g Population PK modeling*

Non-linear effects modeling was performed using NONMEM v7.3 (Icon Development Solutions, USA)[16] and guided using XPose v4.0 following a three-step strategy: 1) basic model selection; 2) covariate selection; and 3) validation[17, 18]. The first-order conditional estimation method with interaction was used for parameter estimation. Interindividual variability (IIV) was modeled as log-normal after being tested for log-normality. Additive, proportional and combined error models were tested for residual variance. Goodness-of-fit for a model was assessed by: 1) significant decreases in -2log-likelihood of the objective function value (OFV); 2) plots of population (PRED) and individual (IPRED) Bayesian predicted *versus* observed concentrations (OBS), and conditional weighted residuals (CWRES) *versus* OBS and time[19]; and 3) improvements in the precision of parameters estimation (% of standard error).

Afterwards, several demographic and clinical variables were tested for inclusion as covariates in the basic population PK model. Each covariate was retained if it led to an improved fit evaluated by: biological plausibility, visual inspection of the abovementioned graphs, improvement of the precision in parameter estimates and changes in the OFV. The extent of Bayesian shrinkage, as a measure of model over-

parameterization, was calculated for each PK parameter with associated IIV variability[20].

### *7.3.h Model evaluation*

Internal validation of the PK model was performed by graphical and statistical methods, including prediction-corrected visual predictive checks[21]. Bootstrap resampling technique (500 replicated datasets) was used to build confidence intervals (CI) of PK parameters to assess their stability and evaluate the robustness of the final model[22].

### *7.3.i Dosing simulations*

We used Monte Carlo simulations for simulating two bolus (4000mg and 2000mg/q8h over 30min) and two extended infusion (4000mg and 2000mg/q8h over 4h) regimens. The covariates included in the final population PK model were considered in these simulations. Each simulation generated concentration-time profiles for 1000 subjects per dosing regimen using the final estimated population PK parameters. We applied a 20% protein binding to the simulated concentrations to estimate unbound concentrations following the results shown by Wong *et al*.[23], who described a 17.5% protein binding of piperacillin at the trough time in patients receiving CRRT. Then, we calculated the percentages of patients with 50% and 100% $f_u T_{>MIC}$ from total and unbound concentrations according to the European Clinical Susceptibility Breakpoints for piperacillin[24] (Probability of Target Attainment (PTA)).

## 7.4 Results

### *7.4.a Patients*

Nineteen patients treated with CVVHDF and piperacillin/tazobactam were enrolled. Table 11 summarizes patients' demographic and clinical characteristics.

**Table 11**: Demographics and clinical characteristics of the enrolled subjects. Data are expressed as median [range] or as count (%). CVVHDF intensity was defined as (filtrate + dialysate flow rate)/(ideal body weight), using 24 kg/m$^2$ as ideal body mass index. Hepatic impairment was defined as liver function tests > 2 x upper limit of normality.

| Variable | Values (n=19) |
|---|---|
| **Age (years)** | 70 [39-82] |
| **Females** | 4 (21.1%) |
| **Weight (kg)**[$] | 80 [45-129] |
| **Hospital (HCB/ CSUPT/HJ23)** | 2/7/10 |
| **APACHE score**[$] | 21 [13-33] |
| **SOFA score**[#] | 11 [8-21] |
| **Hepatic impairment** | 2 (10.5%) |
| **Vasopressors**[#] | 19 (100%) |
| **Mechanical Ventilation**[#] | 19 (100%) |
| **Ultrafiltrate Flow Rate (mL/h)**[#] | 1600 [850-2000] |
| **Dialysate Flow Rate (mL/h)**[#] | 1000 [500-1600] |
| **CVVHDF Intensity**[#] **(mL/kg/h)** | 32.8 [20.2-45.9] |
| **Blood Flow**[#] **(mL/min)** | 200 [120-280] |
| **Type of filter (AN69/AN69ST)** | 9/10 |
| **Albumin**[#] **(g/L)** | 21.1 [14.2-36] |
| **Urea**[#] **(mg/dL)** | 70 [19.5-182] |
| **Creatinine**[#] **(mg/dL)** | 1.2 [0.2-3.5] |
| **Diuresis**[#] **(mL/24h))** | 90 [0-1350] |
| **Survival** | 4 (21.1%) |

Table legend: ([$]): measured on admission, ([#]): measured on the day of the study.

Patients' median age was 70 years [range 39-82], and 21.1% were females. At admission, median APACHE II score was 21 [13-33] and, on the day of sampling, median SOFA score was 11 [8-21]. Sources of infection were intra-abdominal (n=7), respiratory (n=6), urinary tract (n=2), skin and soft tissue (n=2), bloodstream

14/19(n=1) and joint (n=1). All patients presented MODS and required vasoactive and respiratory support at admission and on the day of sampling. Regarding CVVHDF settings, median intensity was 32.8mL/kg/h [20.2-45.9] and median blood flow was 200mL/min [120-280]. As for types of membrane, 9 patients received CVVHDF using 0.9$m^2$ AN69 filters, while the other 10 used 1.5$m^2$ AN69ST filters. Samples were drawn between 1 and 4 days after the initiation of CVVHDF therapy (median 2 days). All patients received piperacillin(tazobactam) at the following doses: 2000(250)mg/q8h over a 3h extended infusion (n=1), 2000(250)mg/q6h over a 30min bolus (n=2) or 3h extended infusion (n=1), 3000(375)/q8h over a 30min bolus (n=1), 4000(500)mg/q8h over 30min (n=3) or 4h-infusion (n=5) and 4000(500)mg/q6h over a 30min bolus (n=3), 3h-infusion (n=2) or 4h-infusion (n=1). Median duration of piperacillin therapy was 10 days [range 3-27]. Concerning microbiology, clinically relevant positive cultures were obtained from 14 patients (73.7%), accounting for 20 isolated strains (Table 12).

**Table 12:** Isolated microorganisms and piperacillin susceptibility by MIC.

| Microorganism | Number of isolates | MIC (mg/L) |
|---|---|---|
| *Bacillus sp* | 1 | 8 |
| *Burkholderia cepacia* | 2 | 8 |
| *Enterobacter cloacae* | 1 | Not determined |
| *Enterobacter cloacae* | 2 | 8 |
| *Enterococcus faecium* | 1 | 64 |
| *Escherichia coli* | 5 | 8 |
| *Klebsiella pneumoniae* | 1 | 64 |
| *Pseudomonas aeruginosa* | 2 | 8 |
| *Pseudomonas aeruginosa* | 2 | 16 |
| *Pseudomonas aeruginosa* | 1 | 64 |
| *Staphylococcus aureus* | 1 | 8 |
| *Staphylococcus epidermidis* | 1 | 64 |

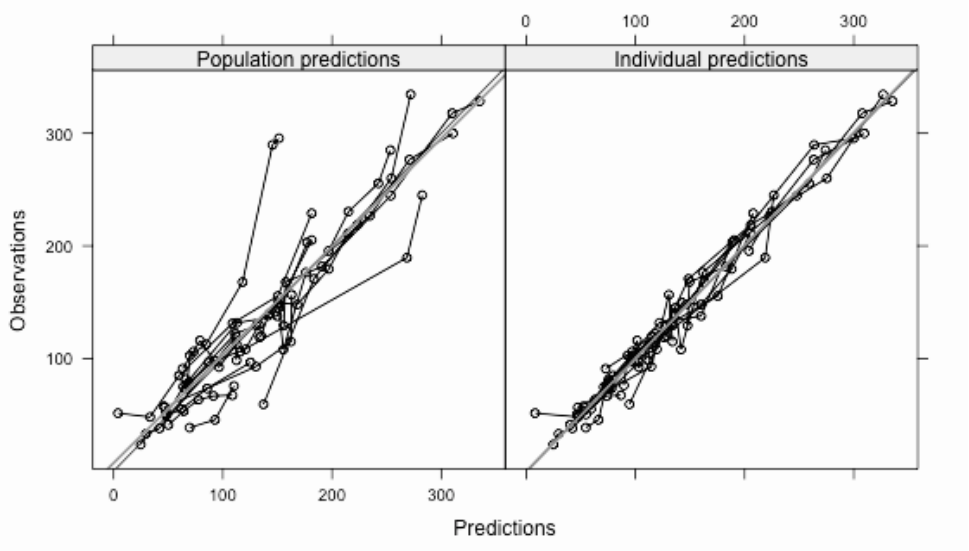
The most frequent pathogen was *Pseudomonas aeruginosa* (n=6, 30%), followed by *Escherichia coli* (n=5, 25%) and *Enterobacter cloacae* (n=3, 15%). Bacteria MIC were

≥8mg/L in all cases where MIC was determined, which is close to the susceptibility breakpoint to piperacillin established by the EUCAST (8-16mg/L)[24].

### *7.4.b Population PK analysis*

We used the concentration points obtained from the 95 plasma samples to build the population PK model. The model that described better the data was a two-compartment linear model characterized by population CL, $Vd_c$ (central volume), $Vd_p$ (peripheral volume) and Q (intercompartmental CL) at steady state, with IIV incorporated in CL and $Vd_c$. Residual variability was modeled as a combination of additive and proportional error. Figure 3 depicts the goodness-of-fit plots of the final model.

**Figure 3:** Goodness-of-fit plots for the final population PK model. Left panel: plot of observed piperacillin concentrations *versus* population predictions; solid black line: line of identity; solid grey line: data smooth. Right panel: plot of observations *versus* individual predictions; solid black line: line of identity; solid grey line: data smooth.




The mean and standard deviation of the CWRES was close to zero, and did not show systematic deviations over time. The value of ε-shrinkage was 18.4%, and the PK parameters had reasonably low levels of η-shrinkage for CL (3.6%) and $Vd_c$ (15.5%).

The covariate analysis identified type of membrane (MEMB) and total body weight at admission (WT) as significant modifiers of CL. Other variables such as CVVHDF intensity (defined as (filtrate + dialysate flow rate)/(ideal body weight), using 24 kg/m$^2$ as ideal body mass index), blood flow, residual diuresis and albumin were also tested but did not have a significant impact on IIV of this parameter. Regarding $Vd_c$, several covariates were tested, including SOFA and APACHE scores and albumin, but none of them improved the parameter variability. The final model is displayed in Table 13 and summarized as follows:

$$CL(L/h) = 6.11 \times (\frac{Weight(kg)}{80})^{1.39} \times CL_{MEMB}$$

If MEMB = 1.5m$^2$ AN69ST, $CL_{MEMB}$ = 1

If MEMB = 0.9m$^2$ AN69, $CL_{MEMB}$ = 1 - 0.49 = 0.51

, where weight is normalized to the median weight of our patient population (80 kg), and $CL_{MEMB}$ is a multiplicative factor that depends on the type of dialysis membrane used.

### *7.4.c Validation*

The prediction-corrected visual predictive check plot shows that practically all observations dropped into the 95% CI, which suggests that the model has a good predictive performance (Figure 4).

The statistical distributions of the parameter estimates obtained from the bootstrap analyses are shown in Table 13. It can be observed that median parameter estimations (95% CI) obtained by bootstrap are in accordance with NONMEM point parameter estimations.

**Figure 4:** Prediction-corrected visual predictive check for the final population PK model. Fifth percentile and 95$^{th}$ percentile, dashed lines; 50$^{th}$ percentile, continuous line. Raw data are shown as empty circles.

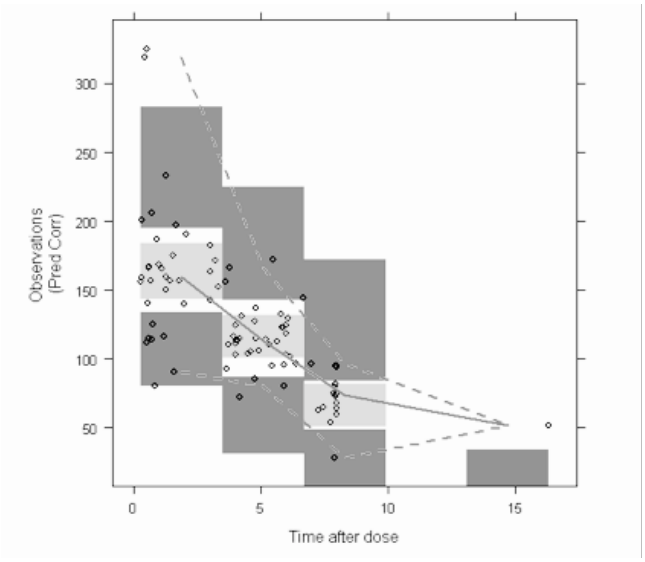



**Table 13:** Population pharmacokinetic estimates for the final model and bootstrap results.

| **Parameter** | **Estimate (RSE %)** | **Bootstrap median [5-95% percentile]** |
|---|---|---|
| **CL (L/h)** | | |
| $\theta_{CL}$ | 6.11 (8.2) | 6.19 [4.92 – 7.36] |
| $\theta_{MEMB}$ | -0.49 (13.3) | -0.52 [(-0.62) - (-0.37)] |
| $\theta_{WT}$ | 1.39 (19.9) | 1.50 [1.15 – 1.95] |
| | | |
| **Vd (L)** | | |
| $\theta_{Vd\_c}$ | 19.4 (14.2) | 19.0 [16.84 – 27.36] |
| $\theta_{Vd\_p}$ | 12.9 (90.7) | 14.0 [(-24.63) – 55.23] |
| | | |
| **Q (L/h)** | | |
| $\theta_{Q}$ | 9.5 (41.8) | 12.6 [5.01 – 19.4] |
| | | |
| **IIV_CL (%) (CV %)** | 17.54 (52.4) | 19.15 [5.2 – 24.9] |

| Parameter | Estimate (RSE %) | Bootstrap median [5-95% percentile] |
|---|---|---|
| **IIV_$Vd_c$ (%) (CV %)** | 52.2 (120) | 56.7 [16.9– 65.3] |
| | | |
| **Additive Residual Error (mg/L)** | 13.3 (66) | 8.34 [2.72 – 22.48] |
| | | |
| **Proportional Residual Error** | 0.06 (46) | 0.08 [0.03-0.12] |

Table legend: RSE: relative standard error; CV: coefficient of variation; CL: total body clearance; $\theta_{CL}$: typical value for CL in the population; $\theta_{MEMB}$: additive factor for the influence of the AN69 membrane on CL; $\theta_{WT:}$ power factor for the influence of weight on CL; Vd: apparent volume of distribution; $\theta_{Vd\_c}$: typical value for Vd in the central compartment in the population; $\theta_{Vd\_p}$: typical value for Vd in the peripheral compartment in the population; Q: intercompartmental CL; $\theta_Q$: typical value for Q in the population; IIV_CL: interindividual variability associated with CL; IIV_$Vd_c$: interindividual variability associated with $Vd_c$.

### *7.4.d Simulations*

After applying a 20% protein binding on the simulated concentrations, we calculated the PTA by MIC profiles for Monte Carlo simulations for four dosing regimens stratified by WT and MEMB (Table 14). We also calculated the PTA by MIC for total piperacillin concentrations (data not shown). A PTA ≥ 90% was considered satisfactory.

**Table 14:** PTA by MIC for a 50% and 100% $T_{>MIC}$ (PTA50 and PTA100 respectively) for simulations of different dosing regimens of piperacillin and stratified by weight and type of membrane. MIC are expressed in mg/L, PTA are expressed in (%). Shadowed areas = PTA ~90% or higher.

| WEIGHT | Dose: 2000mg q8h | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 30min bolus | | | | | | 4h extended infusion | | | | | |
| | AN69 | | | AN69ST | | | AN69 | | | AN69ST | | |
| | MIC (mg/L) | PTA50 | PTA100 | MIC (mg/L) | PTA50 | PTA100 | MIC (mg/L) | PTA50 | PTA100 | MIC (mg/L) | PTA50 | PTA100 |
| 60kg | 2 | 100 | 100 | 2 | 100 | 100 | 2 | 100 | 100 | 2 | 100 | 100 |
| | 4 | 100 | 100 | 4 | 100 | 100 | 4 | 100 | 100 | 4 | 100 | 100 |
| | 8 | 100 | 100 | 8 | 100 | 99.9 | 8 | 100 | 100 | 8 | 100 | 100 |
| | 16 | 100 | 99.9 | 16 | 99.9 | 58.0 | 16 | 100 | 100 | 16 | 100 | 93.1 |
| | 32 | 96.7 | 50.5 | 32 | 10.8 | 0 | 32 | 99.7 | 78.2 | 32 | 85.8 | 0.1 |
| 80kg | 2 | 100 | 100 | 2 | 100 | 100 | 2 | 100 | 100 | 2 | 100 | 100 |
| | 4 | 100 | 100 | 4 | 100 | 99.2 | 4 | 100 | 100 | 4 | 100 | 100 |
| | 8 | 100 | 100 | 8 | 100 | 79.4 | 8 | 100 | 100 | 8 | 100 | 98.5 |
| | 16 | 100 | 96.1 | 16 | 90.5 | 2.2 | 16 | 100 | 100 | 16 | 99.9 | 25.3 |
| | 32 | 52.4 | 1.5 | 32 | 0 | 0 | 32 | 93.7 | 8.4 | 32 | 67.5 | 0.1 |
| 100kg | 2 | 100 | 100 | 2 | 100 | 99.3 | 2 | 100 | 100 | 2 | 100 | 100 |
| | 4 | 100 | 100 | 4 | 100 | 83.2 | 4 | 100 | 100 | 4 | 100 | 98.6 |
| | 8 | 100 | 99.6 | 8 | 99.2 | 25.7 | 8 | 100 | 100 | 8 | 100 | 76.3 |
| | 16 | 99.8 | 51.9 | 16 | 35.9 | 0 | 16 | 100 | 90.5 | 16 | 99.5 | 1 |
| | 32 | 7.6 | 0 | 32 | 0 | 0 | 32 | 85.5 | 0 | 32 | 39.3 | 0 |

**Table 14 continuation:**

| WEIGHT | Dose: 4000mg q8h | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 30min bolus | | | | | | 4h extended infusion | | | | | |
| | AN69 | | | AN69ST | | | AN69 | | | AN69ST | | |
| | MIC (mg/L) | PTA50 | PTA100 | MIC (mg/L) | PTA50 | PTA100 | MIC (mg/L) | PTA50 | PTA100 | MIC (mg/L) | PTA50 | PTA100 |
| 60kg | 2 | 100 | 100 | 2 | 100 | 100 | 2 | 100 | 100 | 2 | 100 | 100 |
| | 4 | 100 | 100 | 4 | 100 | 100 | 4 | 100 | 100 | 4 | 100 | 100 |
| | 8 | 100 | 100 | 8 | 100 | 100 | 8 | 100 | 100 | 8 | 100 | 100 |
| | 16 | 100 | 100 | 16 | 100 | 99.9 | 16 | 100 | 100 | 16 | 100 | 100 |
| | 32 | 100 | 100 | 32 | 99.8 | 60.1 | 32 | 100 | 100 | 32 | 100 | 93.3 |
| 80kg | 2 | 100 | 100 | 2 | 100 | 100 | 2 | 100 | 100 | 2 | 100 | 100 |
| | 4 | 100 | 100 | 4 | 100 | 100 | 4 | 100 | 100 | 4 | 100 | 100 |
| | 8 | 100 | 100 | 8 | 100 | 99.3 | 8 | 100 | 100 | 8 | 100 | 100 |
| | 16 | 100 | 100 | 16 | 100 | 80.3 | 16 | 100 | 100 | 16 | 100 | 98.1 |
| | 32 | 100 | 95.4 | 32 | 90.4 | 2.4 | 32 | 100 | 99.7 | 32 | 99.9 | 23.8 |
| 100kg | 2 | 100 | 100 | 2 | 100 | 100 | 2 | 100 | 100 | 2 | 100 | 100 |
| | 4 | 100 | 100 | 4 | 100 | 98.8 | 4 | 100 | 100 | 4 | 100 | 100 |
| | 8 | 100 | 100 | 8 | 100 | 85.7 | 8 | 100 | 100 | 8 | 100 | 98.9 |
| | 16 | 100 | 99.4 | 16 | 98.9 | 27.2 | 16 | 100 | 100 | 16 | 100 | 71.5 |
| | 32 | 100 | 52.8 | 32 | 38.4 | 0 | 32 | 100 | 90.3 | 32 | 99.1 | 0.6 |

For a pharmacodynamic target of 100% $f_u$ $T_{>MIC}$, patients receiving CVVHDF using 1.5$m^2$ AN69ST membranes required piperacillin doses of 4000mg/q8h for the empirical treatment of bacterial strains with a susceptibility to piperacillin close to the clinical breakpoint (MIC = 8-16mg/L, most of our clinical isolates), whereas 2000mg/q8h were sufficient for patients with CVVHDF using 0.9$m^2$ AN69 membranes. For the treatment of bacteria with high susceptibility to piperacillin (MIC ≤ 4mg/L) or for the attainment of a more traditional pharmacodynamic target (*i.e.* 50% $f_u T_{>MIC}$), 2000mg/q8h of piperacillin sufficed regardless of the type of membrane and the patient's weight. We obtained the same conclusions when we calculated the PTA by MIC using total piperacillin concentrations, for which measurement of unbound concentrations seems unnecessary for piperacillin in this patient population. Table 15 summarizes dose recommendations by pharmacodynamic target, pathogen MIC, type of membrane used and patient's weight.

**Table 15:** Summary of piperacillin maintenance dosing recommendations based on the results of the present study.

| Pharmacodynamic Target | Pathogen MIC | Dose recommendation |
|---|---|---|
| 50% $f_u T_{>MIC}$ | ≤8 mg/L | AN69 membrane: 2000mg q8h over a 30min bolus.<br>AN69ST membrane: 2000mg q8h over a 30min bolus. |
| | 8-16 mg/L | AN69 membrane: 2000mg q8h over a 30min bolus.<br>AN69ST membrane: 2000mg q8h over a 30min bolus. A 4h extended infusion is required for weights >80kg*. |
| | | |
| 100% $f_u T_{>MIC}$ | ≤4 mg/L | AN69 membrane: 2000mg q8h over a 30min bolus.<br>AN69ST membrane: 2000mg q8h over a 30min bolus. |
| | 4-8 mg/L | AN69 membrane: 2000mg q8h over a 30min bolus.<br>AN69ST membrane: 2000mg q8h over a 4h extended infusion. A dose of 4000mg q8h over a 30min bolus is required for weights >80kg*. |

| Pharmacodynamic Target | Pathogen MIC | Dose recommendation |
|---|---|---|
| | 8-16 mg/L | AN69 membrane: 2000mg q8h over a 30min bolus. Consider 4h extended infusion for weights > 80 kg*.<br>AN69ST membrane: 4000mg q8h over a 30min bolus for weights ≤ 60kg. A 4h extended infusion is required for weights > 60 kg*. |

Table legend: (*) The heaviest patient enrolled in the present study weighted 129kg.

## 7.5 Discussion

With this manuscript we present the results of the largest multicenter population PK study of piperacillin performed in critically ill patients with MODS requiring CVVHDF. The main finding of this study is the relationship existing among the type of membrane used for CVVHDF, the patient's weight and the pathogen's MIC on piperacillin dose requirements during the maintenance phase of therapy. The results of the simulations based on the population PK model show that consideration of type of membrane (0.9m$^2$ AN69 *versus* 1.5m$^2$ AN69ST) and patient's weight in piperacillin dose titration and infusion time is advantageous for the attainment of the PD target of 100% $f_u T_{>MIC}$ for a certain MIC (Table 14). To our knowledge, this is the first study that reports differential CL with the use of 1.5m$^2$ AN69 filters surface-coated with heparin and polyethyleneimine (AN69ST) compared to non surface-treated 0.9m$^2$ AN69 filters. Our data show that, for a body weight of 80kg (the median of our patient population), piperacillin CL is doubled when a 1.5m$^2$ AN69ST filter is used compared to the CL for a 0.9m$^2$ AN69 filter (6.11L/h *versus* 3.12L/h respectively). This finding is important because no available sepsis guidelines make distinctions yet in piperacillin dosing depending on the type of dialysis membrane used for CVVHDF[11].

The recently launched AN69ST membranes are acrylonitrile and sodium methallyl sulfonate copolymer membranes with a surface treatment consisting of the grafting of a first layer with polyethyleneimine (positively charged) and a second layer of

heparin (negatively charged) coated during manufacturing[25]. This coating enhances the adsorption properties of acrylonitrile because it makes the membrane surface polarity variable, with the main objective of adsorbing inflammatory molecules and waste products with molecular weights beyond the membrane cut-off.[25] This has been demonstrated with different inflammatory mediators including cytokines[26, 27]. However, AN69ST membranes are non-selective for the adsorption of these inflammatory mediators and may also affect other circulating molecules such as drugs or oligoelements among others. This effect has been shown in small studies with polar antibiotics like colistin[28], but no extensive work has been performed yet under this hypothesis. Our results show that piperacillin CL is augmented when AN69ST filters are used for CVVHDF compared to non-coated AN69 filters. Based on the physicochemical proprieties of piperacillin, a molecule with both hydrogen bond donor and acceptor positions[29], one could hypothesize that piperacillin CL is augmented when AN69ST filters are used due to partial adsorption to the polar coating. Nevertheless, it has to be highlighted that we studied two dialysis membranes with different surface area; *i.e*. 1.5$m^2$ for AN69ST membranes *versus* 0.9$m^2$ for AN69 membranes. Therefore, membrane surface might partially account for the differences in CL observed between the two membranes. However, similar values of CL (Keller *et al.* 2.83L/h, Mueller *et al*. 2.82L/h and Arzuaga *et al.* 3L/h)[30-32] have been reported in studies that included similar populations that received continuous renal replacement therapy (CRRT) with AN69 filters that had different membrane surfaces (0.43, 0.6 and 0.9$m^2$ respectively). These piperacillin CL estimates are in accordance with our estimated CL using 0.9$m^2$ AN69 membranes (3.12L/h), and suggest that membrane surface may be a minor component of piperacillin CL.

Some other clinical variables were hypothesized to influence piperacillin PK according to the available literature[8, 32, 33] and hence were tested in the population PK model with unsuccessful results. With regards to residual diuresis, we expected it to be a significant modifier of piperacillin CL according to the results of previous studies[32, 33]. For instance, Asín-Prieto *et al.* performed a population PK study of piperacillin in a cohort of critically ill patients with AKI requiring CRRT and found that

the baseline creatinine CL (CrCL) was a modifier of renal drug CL[33]. In this case, we believe that the presence of two patient populations (septic and traumatic) accounted for the important effect of CrCL. Further, unlike other drugs that are mainly eliminated by glomerular filtration like meropenem[34], piperacillin has secondary elimination pathways such as biliary excretion that may be enhanced when renal function is impaired[2], which make renal CL less important. Unfortunately, these alternative routes of elimination could not be confirmed in our study since it was not designed to evaluate this issue. Similarly, CVVHDF intensity was *a priori* expected to have an impact on piperacillin CL but neither graphical nor population PK analysis showed any trend between intensity and the estimates of individual CL. This leads to the hypothesis that even the lowest intensities studied (20-25mL/kg/h) were sufficient for the maximization of piperacillin CL by CVVHDF and higher intensities (40-45mL/kg/h) added little to total drug CL. This explanation is consistent with recent data from Roberts *et al*.[35]

It is relevant to mention that our empirical dosing recommendations are mainly based on a quite aggressive PD target (100% $f_u T_{>MIC}$) rather than the 50% $f_u T_{>MIC}$ described in the classical studies[4]. Our proposal of such a thoughtful pharmacodynamic target for our patient population is based on the fact that, despite all the available evidence in septic critically ill patients is based on plasmatic concentrations, it is well known that microcirculatory alterations associated to MODS impair tissue distribution and lead to lower % $f_u T_{>MIC}$ at the target site. As an example, Varghese *et al.* described a 100% piperacillin penetration ratio in the interstitial fluid (ISF) in critically ill patients with sepsis and CVVHDF[10], whereas Joukhadar *et al.* reported a much lower tissue penetration ratio of 10% in patients with septic shock[36]. Due to sickness severity of patients with septic shock we believe that more aggressive PD targets should be preferred for ensuring an early and effective arrival of therapeutic antibiotic concentrations at the target site. Having said that, more aggressive PD targets require higher piperacillin doses and hence increment the risk of suffering from drug adverse effects. In our cohort of patients, we did not observe any case of neurological or hematological toxicity, despite they

were patients receiving high doses, even 16g/24h. However, toxicity may happen using these high doses and close monitoring of the most frequent adverse events is advisable in those patients prescribed with higher doses of piperacillin.

The main limitation of this study is that we did measure neither ultrafiltrate concentrations nor filter adsorption of piperacillin. For this reason, we cannot truly quantify the extent of antibiotic CL through the filter. In fact, this effect was not expected and hence no anticipation was done in that sense at the initial study design. However, the very significant difference in CL between the two membranes, AN69 and AN69ST, which are made of the same material and have the same pore size, suggests that one of the underlying mechanisms of differential elimination might be surface adsorption. We believe that these results should encourage further research with piperacillin and other antibiotics under this hypothesis. Further, we could not measure urine concentrations of piperacillin, for which we are unable to difference CL by CVVHDF from renal and non-renal CL. However, as almost all our patients were oligoanuric, we would not expect to see big differences in piperacillin CL in our patient population of critically ill patients with MODS and AKI. Also, our recommendations are based on data from critically ill patients with MODS including septic shock and CVVHDF requirement; therefore our conclusions may not be applicable in patients with a lower level of sickness severity. Conversely, the major strengths of this study are its large sample size (19 patients), patients' homogeneity (all of them with MODS and AKI receiving CVVHDF) and the rich sampling scheme adopted.

## 7.6 Conclusions

In conclusion, we present the results of this multicenter PK study of piperacillin prescribed to critically ill patients with MODS and CVVHDF requirement. Our population PK model has successfully identified that type of membrane ($0.9m^2$ AN69 *versus* $1.5m^2$ AN69ST) and body weight at admission are modifiers of piperacillin CL. Other CVVHDF settings or physiological characteristics did not significantly modify

piperacillin CL, for which dose adjustments based on these parameters seem to be unnecessary. Given a certain MIC, simulations showed that piperacillin dose titration considering surface-treatment of AN69 filters and body weight was advantageous for the attainment of a 100% $f_u T_{>MIC}$ as a pharmacodynamic target. If classical pharmacodynamic targets (50% $f_u T_{>MIC}$) were aimed, a dose of 2000mg/q8h would be sufficient in all cases.

## 7.7 Acknowledgements

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## 7.8 Transparency Declarations

All authors: none to declare.

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# CHAPTER 8. DISCUSSION

Optimization of antibiotic therapy is a priority in the critical care setting due to its impact in patient outcomes[1]. This measure is especially important for the subgroup of patients who exhibit the highest level of sickness severity, *i.e.* patients with septic shock and multiple organ failure including kidney dysfunction that require extracorporeal support. For the management of this patient population, broad-spectrum beta-lactam antibiotics such as piperacillin and meropenem are frequently selected due to their *in vitro* effectiveness against likely pathogens and excellent tolerability. However, meropenem and piperacillin dosing is unlikely to be optimal for these patients; the well-described changes in antibiotic pharmacokinetics driven by sickness severity and medical interventions can lead to potential therapeutic failure and later on, to the development of antibiotic resistance[2].

This thesis compiles the results of three studies that ultimately aim to assist clinicians in the optimization of meropenem and piperacillin dosing in critically ill patients with septic shock and AKI requiring CRRT.

## 8.1. Literature Review

As a first step to approach optimization of meropenem and piperacillin dosing in critically ill patients with septic shock and CRRT requirement, we preformed a critical review of the available literature on this topic in 2014. Study 1 has evidenced that the main recommendations for empirical dosing of meropenem and piperacillin are based on studies with important limitations that hamper their applicability to our clinical scenario.

### *8.1.a Patient population*

Regarding patient population, the identified studies deal with a highly heterogeneous pool of subjects, which jeopardizes generalization of the results. Mainly, many of the studies focus on patients with sepsis/severe sepsis and AKI, which are completely different from patients with septic shock. *e.g.* patients with septic shock exhibit increased Vd due to capillary leakage and aggressive fluid resuscitation. Therefore, higher antibiotic doses may be required to achieve

therapeutic concentrations as compared to critically ill patients without septic shock. In spite of this, many of the available studies are performed with patients with sepsis/severe sepsis and AKI,[3-9] not with septic shock, for which dose recommendations elucidated from this literature are not applicable to our patient population.

Similarly, CRRT may be prescribed to patients who still present significant residual renal function. The influence of residual renal function on piperacillin pharmacokinetics in patients receiving CVVHF has been assessed by Arzuaga *et al*., and significant differences in CL of piperacillin have been reported, *e.g.* total drug CL was triplicated in patients with CrCL > 50mL/min as compared to patients with CrCL < 10mL/min[10].

Further, inclusion of patients with different admission diagnostics (medical *versus* surgical *versus* trauma) limits the extrapolation of the results to critically ill patients with septic shock and CRRT requirement. It is well known that admission diagnosis makes a difference in patient pathophysiology and, consequently, in beta-lactam PK. For instance, it has been shown that trauma patients exhibit almost a 4-times increase in meropenem Vd and a 6-times increase in meropenem CL compared to septic patients ($Vd_c$ = 69.5 L and 15.7 L; CL = 54.22 L/h and 8.04 L/h in trauma and septic patients, respectively), which obviously greatly modifies dose requirements[11].

In summary, data from patient populations which are not critically ill patients with septic shock and CRRT requirement is not applicable to our patient population due to significant variations in meropenem and piperacillin PK that compromise optimal drug exposure.

### *8.1.b CRRT settings*

Regarding CRRT settings, literature has discordant views on whether modality and intensity do make a difference or not in terms of dosing. While some studies support that these parameters make a difference in CL[6, 7], some others suggest that no substantial variations are attributable to modality or intensity[12]. From a theoretical point of view, convective and diffusive methods eliminate molecules from the bloodstream using different processes; at the same time, velocity of elimination of solutes partially depends on CRRT intensity. It follows that total drug CL should at

least partially depend on these CRRT settings, as it has been suggested in some studies[6, 7, 13]. However, one could also hypothesize that the impact of modality and CRRT intensity on total drug CL is small and therefore has little relevance on drug dosing requirements[12, 14]. The lack of large population PK studies that analyze PK variability and try to identify the sources of this variability is probably one reason for which data regarding this issue is still controversial.

### *8.1.c Data analysis*

Regarding type of pharmacokinetic analysis, most of the studies use a simple non-compartmental methodology; however, in the case of critically ill patients that exhibit very high variability in beta-lactam PK, non-compartmental analysis does not have the capacity to identify the sources of this variability. Therefore, this type of analysis cannot fully identify the patient characteristics that determine different dose requirements and thus its conclusions lead to *"one-size-fits-all"* recommendations in most of the cases.

### *8.1.d Pharmacodynamic target*

Finally, regarding PD target, classical knowledge describes that penicillins require at least a 50-60% $f_u T_{>MIC}$ for maximal bactericidal activity, while carbapenems require a 40% $f_u T_{>MIC}$[15]. However, most of these recommendations are based on *in vitro* studies and on animal models of bacteremia, where penetration into the site of infection is not considered. *In vivo*, higher $f_u T_{>MIC}$ in plasma may be needed for achieving the abovementioned targets in biophases other than bloodstream, since penetration to the target site follows diffusion kinetics and depends on the physicochemistry of each particular tissue. In the available literature, there is also heterogeneity in the chosen PD target; however, the majority of the studies have chosen a PD target of 100% $f_u T_{>MIC}$[6-8, 11, 13, 16-24] following current scientific belief that more aggressive PD targets should be targeted for patients with high levels of sickness such as patients with septic shock and MODS.

In summary, critical analysis of published data has showed that despite there are several studies that describe the pharmacokinetics of meropenem and piperacillin in critically ill patients with AKI and CRRT requirement, there is an important heterogeneity among the studies that hampers extrapolation to daily practice and often translates into a best-guess dosing at the bedside, which is not optimal in such a fragile patient population. Hence, it is imperative to develop dose recommendations that consider bacterial susceptibilities and clinical characteristics of the patient to adjust antibiotic dosing in order to maximize the chances of optimal exposure.

## 8.2 Population PK studies

As a second step, we performed two clinical pharmacokinetic studies aiming to: 1) describe the pharmacokinetics of meropenem and piperacillin in critically ill patients with septic shock and AKI that require CRRT, and most importantly, 2) identify the sources of PK variability in this population in order to, 3) provide practical dose recommendations based on clinical parameters easy to be measured at the bedside.

### *8.2.a STUDY 2: Meropenem population pharmacokinetics in critically ill patients with septic shock and continuous renal replacement therapy: impact of residual diuresis on dose requirements.*

This study is, to our knowledge, the largest multicenter study that characterizes the PK of meropenem in critically ill patients with septic shock and AKI requiring CRRT. Meropenem data were better described by a one-compartment linear model characterized by population CL and Vd at steady-state, with interindividual variability incorporated in both PK parameters. The PK parameter estimates were in agreement with previous studies with a comparable population[14, 25]. Concerning the covariate analysis, residual diuresis significantly influenced meropenem CL, whereas total body weight on admission showed a significant impact on Vd. Internal validation evaluated suitability of the final model, and external validation with data from new individuals evaluated model predictability. Afterwards, Monte Carlo dosing

simulations were performed using three categories of residual diuresis accounting for the definitions of anuria (<100mL/24h), oliguria (100-500mL/24h) and conserved urine output (>500mL/24h) respectively[26]. From these data the percentages of patients with 40% $f_u T_{>MIC}$ and 100% $f_u T_{>MIC}$ (optimal PD targets) according to meropenem clinical susceptibility breakpoints[27] were calculated (PTA).

The main finding of the study is the relationship existing among the 24h urine output and meropenem dosing requirements for the maintenance phase of therapy, taking into account the pathogen's MIC. In our special patient population, consideration of residual diuresis is advantageous for meropenem maintenance dose and infusion time adjustment based on the MIC of the pathogen. For the attainment of a PD target of 100% $f_u T_{>MIC}$, fixed doses depend on the bacteria MIC, but infusion time depends on patient's residual diuresis. And so, oligoanuric patients benefit from a 30min bolus while a 3h-extended infusion is more appropriated for those patients with preserved diuresis. Concrete dosing recommendations are displayed in table 16.

**Table 16:** Summary of meropenem maintenance dosing recommendations based on the results of Study 2.

| **Pharmacodynamic Target** | **Pathogen MIC (mg/L)** | **Dose recommendation** |
|---|---|---|
| 40% $f_u T_{>MIC}$ | ≤ 4mg/L | 500mg/q8h as a 30min-bolus<br>(all urine outputs) |
| | | |
| 100% $f_u T_{>MIC}$ | ≤ 2mg/L | <u>Oligoanuria:</u><br>500mg/q8h as a 30min-bolus<br><u>Preserved diuresis:</u><br>500mg/q8h as a 3h-infusion |
| | 2-4mg/L | <u>Oligoanuria:</u><br>500mg/q6h as a 30min-bolus<br><u>Preserved diuresis:</u><br>500mg/q6h as a 3h-infusion |

| Pharmacodynamic Target | Pathogen MIC (mg/L) | Dose recommendation |
|---|---|---|
| $C_{min}$/MIC = 5 | ≤ 1mg/L | 1000mg/q8h as a 3h-infusión<br>(all urine outputs) |

***8.2.b. STUDY 3: Piperacillin population pharmacokinetics in critically ill patients with multiple organ dysfunction syndrome receiving continuous veno-venous hemodiafiltration: effect of the type of dialysis membrane on dosing requirements.***

This study presents the results of the largest multicenter population PK study of piperacillin performed in critically ill patients with MODS requiring CVVHDF. Piperacillin data were best described by a two-compartment linear model characterized by population CL, $Vd_c$, $Vd_p$ and Q at steady state, with interindividual variability incorporated in CL and $Vd_c$. The PK parameter estimates were also in agreement with previous studies with a comparable population[28]. Concerning the covariate analysis, total body weight and type of dialysis membrane (AN69 *versus* AN69ST) significantly influenced piperacillin CL. Internal validation evaluated suitability of the final model, and external validation with data from new individuals evaluated model predictability. Additionally, and due to the limited number of subjects in this study, we pooled together the data from index and external validation datasets and developed the population PK analysis again, obtaining similar results. After applying a 20% protein binding, as described in the literature for piperacillin[29], we used Monte Carlo simulations for simulating two bolus (4000mg and 2000mg/q8h over 30min) and two extended infusion (4000mg and 2000mg/q8h over 4h) regimens. The covariates included in the final population PK model were considered in these simulations. From these data the percentages of patients with 50% $f_u T_{>MIC}$ and 100% $f_u T_{>MIC}$ according to piperacillin clinical susceptibility breakpoints[27] were calculated (PTA).

The main finding of this study is the relationship existing among the type of membrane used for CVVHDF and the patient's total body weight on piperacillin dose requirements during the maintenance phase of therapy, considering the pathogen's MIC. The results of the simulations based on the population PK model show that

consideration of type of membrane (0.9 $m^2$ AN69 *versus* 1.5 $m^2$ AN69ST) and patient's total body weight in piperacillin dose titration and infusion time is advantageous for the attainment of the PD target of 100% $f_u T_{>MIC}$ for a certain MIC. To our knowledge, this is the first study that reports differential CL with the use of 1.5$m^2$ AN69 filters surface-coated with heparin and polyethyleneimine (AN69ST) compared to non surface-treated 0.9 $m^2$ AN69 filters. Our data show that, for a body weight of 80 kg (the median of our patient population), piperacillin CL is doubled when a 1.5 $m^2$ AN69ST filter is used compared to the CL for a 0.9 $m^2$ AN69 filter (6.11 L/h *versus* 3.12 L/h respectively). The recently launched AN69ST membranes are acrylonitrile and sodium methallyl sulfonate copolymer membranes with a surface treatment consisting of the grafting of a first layer with polyethyleneimine (positively charged) and a second layer of heparin (negatively charged) coated during manufacturing.[30] This coating enhances the adsorption properties of acrylonitrile because it makes the membrane surface polarity variable, with the main objective of adsorbing inflammatory molecules and waste products with molecular weights beyond the membrane cut-off.[30] This has been demonstrated with different inflammatory mediators including cytokines.[31, 32] However, AN69ST membranes are non-selective for the adsorption of these inflammatory mediators and may also affect other circulating molecules such as drugs or oligoelements among others. This effect has been shown in small studies with polar antibiotics like colistin[33], but no extensive work has been performed yet under this hypothesis. This finding is important because it is the first time that it has been shown that piperacillin dosing depends on the type of dialysis membrane used for CVVHDF[34]. Concrete dosing recommendations are displayed in table 17.

**Table 17:** Summary of piperacillin maintenance dosing recommendations based on the results of Study 3.

| Pharmacodynamic Target | Pathogen MIC | Dose recommendation |
|---|---|---|
| 50% $f_u T_{>MIC}$ | ≤8 mg/L | AN69 membrane: 2000mg q8h over a 30min bolus.<br>AN69ST membrane: 2000mg q8h over a 30min bolus. |

| Pharmacodynamic Target | Pathogen MIC | Dose recommendation |
|---|---|---|
| | 8-16 mg/L | AN69 membrane: 2000mg q8h over a 30min bolus.<br>AN69ST membrane: 2000mg q8h over a 30min bolus. A 4h extended infusion is required for weights >80kg. |
| | | |
| 100% $f_u T_{>MIC}$ | ≤4 mg/L | AN69 membrane: 2000mg q8h over a 30min bolus.<br>AN69ST membrane: 2000mg q8h over a 30min bolus. |
| | 4-8 mg/L | AN69 membrane: 2000mg q8h over a 30min bolus.<br>AN69ST membrane: 2000mg q8h over a 4h extended infusion. A dose of 4000mg q8h over a 30min bolus is required for weights >80kg. |
| | 8-16 mg/L | AN69 membrane: 2000mg q8h over a 30min bolus. Consider 4h extended infusion for weights > 80 kg.<br>AN69ST membrane: 4000mg q8h over a 30min bolus for weights ≤ 60kg. A 4h extended infusion is required for weights > 60 kg. |

It is important to highlight that meropenem and piperacillin dosing recommendations that we principally support are based on a rather exigent PD a 100% $f_u T_{>MIC}$ compared to the more conservative $f_u T_{>MIC}$ described in the classical studies (40% $f_u T_{>MIC}$ for carbapenems and 50% $f_u T_{>MIC}$ for penicillins). We believe that such a thoughtful pharmacodynamic target is more recommendable for critically ill patients with septic shock and AKI requiring extracorporeal renal support for several reasons. Firstly, emerging evidence has associated higher % $f_u T_{>MIC}$ with better outcomes[35, 36]. Further, all this evidence is based on plasmatic concentrations, but it is well known that critically ill patients with severe infections exhibit microcirculatory alterations that impair tissue distribution and lead to lower % $f_u T_{>MIC}$ at the target site[25, 28, 37]. For instance, Varghese *et al.* described a 100% piperacillin penetration ratio in the interstitial fluid in critically ill patients with sepsis and CVVHDF[28], whereas Joukhadar *et al.* reported a much lower tissue penetration

ratio of 10% in patients with septic shock[37]. Due to sickness severity of patients with septic shock we believe that more aggressive pharmacodynamic targets should be preferred for ensuring an early and adequate antibiotic antimicrobial therapy.

## 8.3. Impact of this research in bedside clinical practice

Meropenem and piperacillin are two of the most frequently prescribed antibiotics in the critical care setting for its extended spectrum, low profile of adverse events and price. In fact, according to a large worldwide multicenter study, meropenem plus imipenem account for a 17.3% (countries with low incidence of resistance) - 30.7% (countries with high incidence of resistance) of the empirical prescriptions to septic patients while piperacillin represents a 10.6% and a 23% of the empirical choices in countries of low and high incidence of resistance respectively. Altogether, these two antibiotics account for 27.9%- 53.7% of the empirical choices in the ICU[38], which are considerably high and relevant percentages. For this reason, dosing optimization of these drugs is mandatory for improving the management of critically ill patients with severe infections and septic shock and AKI receiving CRRT.

With these studies we have identified clinical characteristics easy to be measured at the bedside (*i.e.* residual renal function for meropenem and total body weight and type of CRRT membrane used for piperacillin) that are able to help in the complex process of empirical dose optimization early in time. Further, inappropriate antibiotic dosing has also been linked to the emergence of bacterial resistance, for which posology individualization based on patient's clinical characteristics may have a positive impact not only on the particular patient but also on hospital epidemiology[39]. Finally, individualization of dosing and avoidance of "one-size-fits-all" strategies may help in the rationalization of the use of healthcare resources, which in turn will contribute to contain sanitary expenses. Hence, the results of this research are directly applicable to patient care and likely to have tangible benefits in the short term.

## 8.4. Limitations and strengths of the present studies

The main limitation of Studies 2 and 3 is that all the analysis is performed with meropenem and piperacillin plasma concentrations. Urinary and ultrafiltrate concentrations were not measured, for which we could estimate neither the sieving coefficient, nor truly quantify the degree of CL attributable to CRRT. Furthermore, the studies of this thesis are focused on critically ill patients with septic shock and renal failure requiring CRRT, therefore our conclusions cannot be extrapolated to other patient populations like those without septic shock, without renal failure, with intermittent RRT or with other extracorporeal blood purification therapies. Finally, the measurement of residual diuresis was performed by the nursing staff as part of their clinical routine, which might not be optimal for obtaining the exact volume of urine but is certainly sufficient for classifying the patients as oligoanuric or with preserved diuresis.

Conversely, the major strengths of these studies are their multicenter nature, their large sample size and the robust methodology used for data analysis. Moreover, our recommendations are based on an easy-to-measure and inexpensive clinical parameter such as residual diuresis or type of CRRT filter; hence our results can be easily implemented in daily care.

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# CHAPTER 9. CONCLUSIONS

## CONCLUSIONS

1. Based on the findings of Study 1, we can conclude that current dose recommendations for meropenem and piperacillin in critically ill patients with septic shock and CRRT requirement are based on studies with some drawbacks, such as: 1) different sickness severities (sepsis *versus* severe sepsis *versus* septic shock) and levels of renal function; 2) different admission diagnostics (medical *versus* surgical *versus* trauma); 3) different clinical managements, mainly CRRT settings; 4) heterogeneous PK methodologies; and 5) different PD targets for dosing recommendations. This scenario limits extrapolation of their conclusions to our patient population.

2. Due to study heterogeneity, current meropenem and piperacillin dosing recommendations for patients with septic shock and CRRT follow a "*one-size-fits-all"* fashion despite that emerging clinical data suggest that PK and therefore dosing are partially dependent on patient's characteristics, CRRT settings and the chosen PD target for beta-lactams (% $f_u T_{>MIC}$). These broad and unspecific recommendations often translate into a best-guess dosing at the bedside, which is sub-optimal for optimizing antibiotic use in the critical care setting.

3. The PK of meropenem in critically ill patients with septic shock and CRRT substantially differed from the PK of this drug in patients with lower sickness severity (mainly sepsis/severe sepsis). This is probably due to the particular characteristics of patients with septic shock. This finding evidences that dosing recommendations derived from studies that include patients with lower sickness severity can not be implemented to critically ill patients with septic shock, AKI and CRRT requirement.

4. In our cohort of patients, the main finding from our population PK analysis is the relationship existing among the 24h urine output and the pathogen's MIC

on meropenem dose requirements during the maintenance phase of therapy; patients with conserved diuresis (>500mL/24h) exhibit at least a 30% increase in meropenem total CL compared to those patients who are anuric, increase that augments with the diuresis volume.

5. For meropenem, Monte Carlo simulations have shown that for a PD target of 100% $f_u T_{>MIC}$ in plasma, oligoanuric patients require a meropenem dose of 500mg/q8h over 30min for the treatment of susceptible bacteria (MIC <2mg/L), while patients with diuresis >500mL/24h require the same dose over a 3h-infusion. If bacteria with a MIC to meropenem close to the resistance breakpoint (2-4mg/L) were to be treated with this antibiotic, a dose of 500mg/q6h would be necessary, administered as a 30min-bolus for oligoanuric patients and as a 3h-infusion for patients with preserved diuresis. For the attainment of the classical PD target for carbapenems in plasma (40%$f_u T_{>MIC}$), a meropenem dose of 500mg/q8h over a 30min-bolus would be sufficient for the treatment of bacteria with MIC even close to the susceptibility breakpoint (MIC ≤ 4mg/L), regardless of urine output.

6. Similarly, the PK of piperacillin in critically ill patients with septic shock, AKI and CVVHDF requirement notably differed from the PK of this drug in patients with lower sickness severity (mainly sepsis/severe sepsis). This fact compromises extrapolation of the results of studies performed with patients who are less sick to our study population.

**7.** The main finding of our population PK analysis is the relationship existing among the type of membrane used for CVVHDF, the patient's weight and the pathogen's MIC on piperacillin dose requirements during the maintenance phase of therapy; for a body weight of 80kg, piperacillin CL is doubled when a 1.5$m^2$ AN69ST filter is used compared to drug CL with a 0.9$m^2$ AN69 filter.

8. For piperacillin, Monte Carlo simulations have shown that for a PD target of 100% $f_u T_{>MIC}$ in plasma, patients receiving CVVHDF using 1.5m$^2$ AN69ST membranes require piperacillin doses of 4000mg/q8h for the empirical treatment of bacterial strains with a susceptibility to piperacillin close to the clinical breakpoint (MIC = 8-16mg/L), whereas 2000mg/q8h are sufficient for patients with CVVHDF using 0.9m$^2$ AN69 membranes. For the attainment of the classical PD target for penicillins in plasma (*i.e.* 50% $f_u T_{>MIC}$) or for the treatment of bacteria with high susceptibility to piperacillin (MIC ≤ 4mg/L), 2000mg/q8h suffice regardless of the type of membrane and the patient's weight.

As a **final conclusion** for this thesis, we have shown that identification and consideration of clinical and demographic parameters that influence meropenem and piperacillin PK, such as 24h-residual diuresis, patient's weight and type of CRRT membrane, is advantageous for dose titration. As they are characteristics easy to be measured at the bedside, the implementation of our research findings in the real clinical setting is feasible and may be helpful in the complex process of optimization of antibiotic use in the Intensive Care Unit.

## CONCLUSIONS

1. En funció de les troballes de l'Estudi 1, podem concloure que les recomanacions posològiques actuals de meropenem i piperacil·lina per als pacients crítics amb xoc septic, IRA i requeriment de TCSR estan basades en estudis amb alguns elements que en limiten l'extrapolació, com ara: 1) diferents nivells de gravetat de la malaltia (sèpsia *versus* sèpsia greu *versus* xoc sèptic) i grau de disfunció renal 2) diferents diagnòstics d'ingrés (mèdic *versus* quirúrgic *versus* trauma), 3) diferències importants en el maneig clínic, principalment pel que fa a les característiques de la TCSR, 4) heterogeneïtat respecte a les metodologies d'anàlisi FC utilitzades, i 5) diferents objectius FD en els quals es basen les recomanacions posològiques. Degut a això, es limita l'extrapolació de les conclusions d'aquests estudis a la nostra població de pacients d'alta complexitat.

2. Com a conseqüència de l'heterogeneïtat de l'evidència disponible, les recomanacions posològiques actuals de meropenem i piperacil·lina per als pacients amb xoc sèptic i IRA que requereixen TCSR segueixen sent àmplies i genèriques. Tot i això, els resultats de diferents estudis emergents suggereixen que la FC d'aquests antibiòtics i, per tant, els requeriments posològics, són parcialment dependents de les característiques del pacient, de les característiques de la TCSR i de i l'objectiu FD escollit ($\%f_u$ $T_{>CMI}$). D'aquesta manera, aquestes recomanacions àmplies i genèriques sovint es tradueixen en una dosificació sub-òptima a peu de llit, comprometent l'optimització de l'ús d'antibiòtics a la Unitat de Medicina Intensiva.

3. La FC de meropenem en pacients crítics amb xoc sèptic, IRA i TCSR difereix substancialment de la FC d'aquest fàrmac en pacients menys greus (amb sèpsia/sèpsia greu). Probablement, aquest fenomen és degut a les característiques particulars dels pacients amb xoc sèptic. Per aquest motiu, les recomanacions posològiques obtingudes a partir d'estudis que inclouen

pacients menys greus no són aplicables als pacients amb un major grau gravetat.

4. La principal conclusió de l'estudi de FC poblacional realitzat amb les dades procedents de la nostra cohort de pacients que rebien meropenem és la relació existent entre la diüresi residual de 24h i la CMI del patogen en els requeriments de meropenem; els pacients amb diüresi conservada (>500 ml/24h) presenten un increment d'almenys el 30% en el CL total de meropenem respecte als pacients amb oligo-anúria, increment que resulta directament proporcional al volum d'orina en 24h.

5. Les simulacions de Monte Carlo basades en el model FC poblacional de meropenem han demostrat que per tal de mantenir les concentracions del fàrmac per damunt de la CMI dels microorganismes durant un 100% de l'interval posològic (100% $f_u T_{>CMI}$), els pacients oligo-anúrics (diüresi residual de 100-500 ml/24h) requereix 500 mg/8h administrats en un bolus de 30 minuts per al tractament de soques susceptibles (CMI <2 mg/L), mentre que els pacients amb diüresi conservada (>500 ml/24h) requereixen la mateixa dosi administrada mitjançant una perfusió de 3h. Pel tractament de microorganismes amb una CMI propera al límit de susceptibilitat (2-4mg/L) és necessària una dosi de 500 mg/q6h: administrada en un bolus de 30 minuts en pacients oligo-anúrics i mitjançant una perfusió de 3h en pacients amb una diüresi conservada. Si s'escull un objectiu FD més conservador, (40% $f_u T_{>CMI}$), una dosi de 500 mg/q8h administrada en un bolus de 30 minuts és suficient amb independència de la diüresi residual.

6. De manera similar a meropenem, la FC de la piperacil·lina en pacients crítics amb xoc sèptic, IRA i TCSR difereix substancialment de la FC d'aquest fàrmac en malalts menys greus (sèpsia/sèpsia greu). Pe aquest motiu, les recomanacions posològiques de piperacil·lina obtingudes a partir d'estudis que inclouen pacients menys greus no són aplicables als pacients amb un

grau més elevat de gravetat, com els malalts amb xoc sèptic, IRA i requeriment de TCSR.

7. La principal conclusió de l'anàlisi FC poblacional de piperacil·lina és la relació existent entre el tipus de membrana utilitzada per la TCSR, el pes del pacient i la CMI del patogen en els requeriments de piperacil·lina; per un pes de 80 kg, el CL total de piperacil·lina es duplica quan es fa servir una membrana d'1,5$m^2$ de copolímer d'acrilonitril i sulfat sòdic de metal·lil amb un recobriment d'heparina i polietilenimina (AN69ST) en comparació amb el CL total observat del fàrmac quan es fa servir un filtre AN69 convencional de 0,9$m^2$.

8. Les simulacions de Monte Carlo basades en el model FC poblacional de piperacil·lina han demostrat que per a un objectiu PD de 100% $f_u T_{>CMI}$, els pacients que reben TCSR amb membranes AN69ST d'1,5$m^2$ requereixen dosis de 4000mg/q8h per al tractament de microorganismes amb CMI a la piperacil·lina properes al límit de susceptibilitat (CMI = 8-16mg/L). D'altra banda, 2000 mg/q8h són suficients per als pacients que reben TCSR amb membranes AN69 de 0,9 $m^2$. Per al tractament de soques amb alta susceptibilitat a la piperacil·lina (CMI ≤ 4 mg/L), o per l'assoliment d'un objectiu FD més conservador (50% $f_u T_{>CMI}$), 2000 mg/q8h són suficients en tots els casos.

Com a **conclusió final** d'aquesta tesi, hem demostrat que la identificació i consideració de paràmetres clínics i demogràfics que modifiquen la FC de meropenem i piperacil·lina, els dos antibiòtics més freqüentment prescrits de forma empírica a aquests pacients, és avantatjós per la individualització de la dosificació. A més, com que es tracta de paràmetres fàcils de mesurar a peu de llit, els resultats de la nostra recerca són aplicables directament a la pràctica clínica i poden ser útils en el complex procés de l'optimització de l'ús d'antibiòtics a la Unitat de Medicina Intensiva.

# CHAPTER 10. BIBLIOGRAPHY

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# APPENDICES

# Appendix 1: Study authorization by the Spanish Regulatory Medicines agency

20121507

MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD

agencia española de medicamentos y productos sanitarios

DIRECCION DE LA AGENCIA ESPAÑOLA DE MEDICAMENTOS Y PRODUCTOS SANITARIOS

**DESTINATARIO:**

**DRA. COLOMA MORENO QUIROGA**
**RESPONSABLE OFICINA**
**INVESTIGACION**
**FUNDACIO PARC TAULI**
**PARC TAULI 1**
**EDIF. SANTA FE, IZD 2ª PLANTA**
**08208 SABADELL -BARCELONA**

**Fecha: 3 de agosto de 2012**

**REFERENCIA: ESTUDIO DEPURACION**

**ASUNTO: RESOLUCION DE AUTORIZACIÓN DE ESTUDIO FINANCIADO CON FONDOS PÚBLICOS**

Adjunto se remite la resolución sobre el estudio posautorización titulado **"Estudio farmacocinético y farmacodinámico de los antibióticos de amplio espectro de utilización más frecuente en la unidad de cuidados intensivos (piperacilina/tazobactam, meropenem, ceftriaxona) en pacientes con shock séptico sometidos a depuración renal de alto flujo"**, con código **IEM-ANT-2012-01**

El promotor o solicitante nombrado por éste deberá remitir la información pertinente o solicitar autorización a la AEMPS -según proceda- de las modificaciones relevantes a la documentación del estudio, informes de seguimiento, sospechas de reacciones adversas graves, finalización del estudio y demás circunstancias que establezca la legislación vigente.

Registre entrada F-76/2012
Registre sortida
Data 23-8-12

MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD
REGISTRO AUXILIAR
AGENCIA E. DE MEDICAMENTOS Y PRODUCTOS SANITARIOS
SALIDA
N. de Registro: 23917 / RG 42407
Fecha: 09/08/2012 13:05:11

CORREO ELECTRÓNICO
farmacoepi@aemps.es

C/ CAMPEZO, 1 – EDIFICIO 8
28022 MADRID

## Appendix 2: Ethical approval from the local Ethics Committees

**COMITÈ ÈTIC D'INVESTIGACIÓ CLÍNICA**
**Oficina de Recerca – Fundació Parc Taulí**

**A:** **Dr. Ignacio Martín-Loeches**
**Servei de Medicina Intensiva**

**De:** **Dra. Coloma Moreno**
**Secretaria Tècnica del CEIC**

**Assumpte:** Avaluació d'un projecte nou

**2012/507**
Estudio farmacocinético y farmacodinámico de los antibióticos de amplio espectro de utilización más frecuente en la unidad de cuidados intensivos (piperacilina/tazobactam, meropenem, ceftriaxona) en pacientes con shock séptico sometidos a depuración renal de alto flujo
**IP:** I. Martin-Loeches
**Codi:** CIR2011/072
**Promotor:** Beca Ministerio Sanidad, Políticas Sociales e Igualdad

Benvolgut,

El Comitè Ètic d'Investigació Clínica, en la seva sessió amb data 4 de gener de 2012, va avaluar el projecte a dalt esmentat, del qual n'ets investigadora principal, i va decidir donar la seva aprovació.

Nota: Es recorda que, sempre que el disseny de l'estudi ho permeti, les dades clíniques recollides en l'estudi han de ser totalment anònimes. En cas de no anonimització, les dades identificatives del pacient (nom i cognoms o les inicials, el número d'història clínica i el NIF) s'han de dissociar de les dades clíniques, tant en el quadern de recollida de dades com en els fitxers informàtics o base de dades que se'n derivin, atorgant un codi identificatiu als pacients.

Cordialment,

Coloma Moreno

Sabadell, 4 de gener de 2012

CLÍNIC
BARCELONA
Hospital Universitari

**Dña. Begoña Gómez Pérez**, Secretaria del Comité Ético de Investigación Clínica del Hospital Clínic de Barcelona,

CERTIFICA:

Que este Comité, con fecha de 29/12/2011, ha evaluado la propuesta del promotor para que se realice el estudio postautorización tipo observacional código de protocolo UCI-DRAF-2012 titulado **Estudio farmacocinético y farmacodinámico de los antibióticos de amplio espectro de utilización más frecuente en la unidad de cuidados intensivos (piperacilina/tazobactam, meropenem, ceftriaxona) en pacientes con shock séptico sometidos a depuración renal de alto flujo. Versión 3 de 20 Diciembre 2011; CI: versión 3 de 20 Diciembre 2011**, y considera que:

. Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles para el sujeto.

. La capacidad del investigador y los medios disponibles son apropiados para llevar a cabo el estudio.

. Son adecuados tanto el procedimiento para obtener el consentimiento informado como la compensación prevista para los sujetos por daños que pudieran derivarse de su participación en el estudio.

. El alcance de las compensaciones económicas previstas no interfiere con el respeto a los postulados éticos.

Que este Comité acepta que dicho estudio sea realizado en el Hospital Clínico de Barcelona por la **Dra. Soy Muner, Dolors** como investigador principal, debiendo ser comunicado a dicho Comité Ético todo cambio en el protocolo o acontecimiento adverso grave.

Lo que firmo en Barcelona, a 2 de enero de 2012

CLÍNIC
BARCELONA
Hospital Universitari
COMITÈ ÈTIC
INVESTIGACIÓ CLÍNICA

CIF - G-08431173

Cod. 852

Generalitat de Catalunya
Departament de Salut

HOSPITAL CLÍNIC DE BARCELONA
Villarroel, 170 - 08036 Barcelona (España)
Tel. 93 227 54 00 Fax 93 227 54 54
www.hospitalclinic.org

UNIVERSITAT DE BARCELONA

HOSPITAL UNIVERSITARI
DE TARRAGONA
JOAN XXIII

Carrer del Doctor Mallafrè Guasch, 4
43007 Tarragona
Telèfon 977 29 58 00

## INFORME DEL COMITÉ ÉTICO DE INVESTIGACIÓN CLÍNICA

Doña María De la Coba Navarrete, Secretaria del Comité Ético de Investigación Clínica del Hospital Universitari de Tarragona Joan XXIII,

**C E R T I F I C A**

Que este Comité ha evaluado la propuesta del promotor **Servei de Medicina Intensiva, Hospital de Sabadell, Corporació Sanitària Parc Taulí,** para que se realice el estudio código de protocolo **IEM-ANT-2012-01,** titulado "**Estudio farmacocinético y farmacodinámico de los antibióticos de amplio espectro de utilización más frecuente en la unidad de cuidados intensivos (piperacilina/tazobactam, meropenem, ceftriaxona) en pacientes con shock séptico sometidos a depuración renal de alto flujo"**, y que considera que:

Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles para el sujeto.

La capacidad del investigador y los medios disponibles son apropiados para llevar a cabo el estudio.

Es adecuado el procedimiento para obtener el consentimiento informado del sujeto participante en el estudio.

El alcance de las compensaciones económicas previstas no interfiere con el respeto a los postulados éticos.

Y que este Comité acepta que dicho estudio postautorización, sea realizado en el **"HOSPITAL UNIVERSITARI DE TARRAGONA JOAN XXIII"**, por el Dr. Alejandro Rodríguez Oviedo.

Lo que firmo en Tarragona, a 04 de diciembre de 2012

Generalitat de Catalunya
Hospital de Tarragona
Joan XXIII
Comitè Ètic
d'Investigació Clínica

Sra. María De la Coba Navarrete
Secretaria del Comité Ético de Investigación Clínica

XXIII-HA037 — 304863— jun.03



Institut Català
de la Salut

## Appendix 3: Informed Consents

HOJA DE INFORMACIÓN AL PACIENTE

**Título: Estudio observacional farmacocinético y farmacodinámico de los antibióticos de amplio espectro de utilización más frecuente en la unidad de cuidados intensivos (piperacilina/tazobactam, meropenem, ceftriaxona) en pacientes con shock séptico sometidos a depuración renal continua de alto flujo.**

**Código protocolo:** ---

**Promotor:** Servei de Medicina Intensiva. Hospital de Sabadell. Corporació Sanitària Parc Taulí.

**Investigador Principal:** Dr. Alejandro Rodriguez. Servicio Medicina Intensiva. 977 295818

**Centro:** Hospital Universitario Joan XXIII

### Introducción

Nos dirigimos a usted para informarle sobre un estudio de investigación en el que se le invita a participar. Este estudio ha sido aprobado por el Comité Ético de Investigación Clínica de nuestro Centro.

Nuestra intención es tan solo que usted reciba la información correcta y suficiente para que pueda evaluar y juzgar si quiere o no participar en este estudio. Para ello lea esta hoja informativa con atención y nosotros le aclararemos las dudas que le puedan surgir después de la explicación. Además, puede consultar con las personas que considere oportuno.

### Participación voluntaria

Debe saber que su participación en este estudio es voluntaria y que puede decidir no participar o cambiar su decisión y retirar el consentimiento en cualquier momento, sin que por ello se altere la relación con su médico ni se produzca perjuicio alguno en su tratamiento.

### Descripción general del estudio

Las infecciones graves son causadas por diferentes microorganismos, generalmente bacterias, y requieren un tratamiento antibiótico correcto. En los pacientes que tienen una infección generalizada puede encontrarse con frecuencia una mala función de diferentes órganos y sistemas corporales, entre ellos el riñón. Dicho fallo, obliga la utilización de dispositivos que depuren su sangre, filtrándola para extraer de ella las substancias tóxicas que de otro modo

se podrían acumular. Estás maquinas podrían filtrar no sólo las toxinas acumuladas, sino también parte de los antibióticos que se le están administrando, de modo que se podría aumentar la rapidez con que se eliminan, lo que teóricamente podría dar lugar a que no tuviesen el efecto deseado. Esto nunca se ha estudiado para los antibióticos que usted recibe. Para conocer de qué manera afectan los dispositivos depuradores la eliminación de los antibióticos de la sangre de los pacientes, nos proponemos medir los niveles de antibióticos en sangre antes y después de iniciar la diálisis, para comprobar si se están administrando a las dosis adecuadas y, si fuese necesario, cómo habría que ajustar las dosis en este tipo de pacientes. Esto nos permitiría a los médicos actuar en consecuencia con rapidez y efectividad para el control posterior de evolución y gravedad de la infección.
Su participación en este estudio es completamente voluntaria y no afectará en ningún modo a la atención médica que usted reciba.

Las Unidades de Medicina Intensiva estamos llevando a cabo un estudio en el que se analizarán los niveles de antibióticos de pacientes críticamente enfermos con terapias de sustitución renal para asegurar que son correctos. El objetivo del estudio es comprobar si las dosis de antibióticos administradas son adecuadas y, si no lo fuesen, cómo habría que modificarlas para asegurar un adecuado tratamiento de la infección causante del cuadro clínico. La realización de este estudio permitirá conocer mejor cómo deben utilizarse los antibióticos en las situaciones de infecciones muy graves y críticas, y esto puede redundar en el beneficio de pacientes que se encuentren en la misma situación que usted en el futuro.

Para este tipo de estudios se comparará los datos obtenidos en diferentes pacientes que presenten la enfermedad a estudio. Se estima incluir en este estudio a 60 pacientes en 1 año. Se tomarán muestras de su sangre para analizar los niveles de antibióticos durante un día solamente (6 muestras, de 8 ml cada una, representando 48ml en total). Su participación en el estudio no conllevará ninguna modificación del tratamiento médico habitual para su enfermedad. Las muestras de sangre se obtendrán a partir de uno de los accesos vasculares (catéteres) que usted lleva, sin que ello suponga pinchazos adicionales.

**Beneficios y riesgos derivados de su participación en el estudio**

Para este estudio únicamente se le extraerán muestras de sangre que serán analizadas en el Laboratorio, por lo tanto no se prevé que su participación en el estudio pueda resultar perjudicial para su salud.
A excepción de lo anterior, no variará la asistencia habitual que recibe en la unidad por el simple hecho de participar en este estudio. No se realizarán determinaciones de muestras de contenido genético.
El conocimiento de los marcadores asociados al desarrollo y/o evolución de las infecciones graves podrá redundar en el futuro en un mejor conocimiento de la enfermedad y en consecuencia poder manejar mejor los tratamientos antibióticos de que disponemos para combatir estas infecciones y las complicaciones asociadas.

No obstante, y dado que los datos de cada uno de los pacientes sólo se conocerán con posterioridad a la finalización del estudio, no se espera que usted obtenga ningún beneficio directo durante su participación en el mismo.

**Confidencialidad**

El tratamiento, la comunicación y la cesión de los datos de carácter personal de todos los sujetos participantes se ajustará a lo dispuesto en la Ley Orgánica 15/1999, de 13 de diciembre de Protección de Datos de Carácter Personal. De acuerdo a lo que establece la legislación mencionada, usted puede ejercer los derechos de acceso, modificación, oposición y cancelación de datos, para lo cual deberá dirigirse a su médico del estudio.

Los datos recogidos para el estudio estarán identificados mediante un código y sólo su médico del estudio / colaboradores podrán relacionar dichos datos con usted. Por lo tanto, su identidad no será revelada a persona alguna salvo excepciones, en caso de urgencia médica o requerimiento legal.

Las muestras de sangre estarán codificadas, y no constará ningún dato que permita la identificación directa del paciente; únicamente el equipo investigador del H. U. de Tarragona Joan XXIII podrá relacionar las muestras con sus datos personales. Estas muestras se guardaran en el Servicio de Medicina Intensiva, donde sólo el equipo investigador del Centro tendrá acceso a las mismas. Posteriormente serán enviadas a la Unidad de Bioanálisis-Farmacocinética de Laboratorios Echevarne, donde se realizarán los análisis del estudio. Una vez hayan sido analizadas, se procederá a su destrucción.

El acceso a su información personal quedará restringido al médico del estudio / colaboradores, autoridades sanitarias, al Comité Ético de Investigación Clínica y personal autorizado por el Promotor, cuando lo precisen para comprobar los datos y procedimientos del estudio, pero siempre manteniendo la confidencialidad de los mismos de acuerdo a la legislación vigente.

**Otra información relevante**

Si usted decide retirar el consentimiento para participar en este estudio, ningún dato nuevo será añadido a la base de datos, y puede exigir la destrucción de todas las muestras identificables previamente retenidas para evitar la realización de nuevos análisis.

También debe saber que puede ser excluido del estudio si el Promotor o los investigadores del estudio lo consideran oportuno, ya sea por motivos de seguridad o porque consideren que no está cumpliendo con los procedimientos establecidos. En cualquiera de los casos, usted recibirá una explicación adecuada del motivo que ha ocasionado su retirada.

Al firmar la hoja de consentimiento adjunta se compromete a cumplir con los procedimientos del estudio que se le han expuesto.

CONSENTIMIENTO INFORMADO

Yo (nombre y apellidos)
……..

He leído la hoja de información que se me ha entregado.
He podido hacer preguntas sobre el estudio.
He recibido suficiente información sobre el estudio.
He hablado con:
……
(nombre el investigador)

Comprendo que mi participación es voluntaria.
Comprendo que puedo retirarme del estudio:

1. Cuando quiera.
2. Sin tener que dar explicaciones.
3. Sin que esto repercuta en mis cuidados médicos.

- Presto libremente mi conformidad para participar en el estudio y doy mi consentimiento para el acceso y utilización de mis datos en las condiciones detalladas en la hoja de información.

Firma del paciente: Firma del investigador:

Nombre: Nombre:
Fecha: Fecha:

CONSENTIMIENTO INFORMADO REPRESENTANTE LEGAL

Yo (nombre y apellidos) ……en calidad de ……(relación con el participante) de …….. (nombre y apellidos del participante)

He leído la hoja de información que se me ha entregado.
He podido hacer preguntas sobre el estudio.
He recibido suficiente información sobre el estudio.
He hablado con:
……
(nombre el investigador)

Comprendo que la participación del paciente es voluntaria.
Comprendo que puede retirarse del estudio:

1. Cuando quiera.
2. Sin tener que dar explicaciones.
3. Sin que esto repercuta en sus cuidados médicos.

- En mi presencia se ha dado a …….. (nombre del participante) toda la información pertinente adaptada a su entendimiento y está de acuerdo en participar. Presto mi conformidad para que …….. (nombre del participante) participe en este estudio y doy mi consentimiento para el acceso y utilización de sus datos en las condiciones detalladas en la hoja de información.

Firma del representante: Firma del investigador:

Nombre: Nombre:
Fecha: Fecha:

Yo ……(nombre del paciente), una vez recuperada la capacidad, y habiendo sido informado de mi participación en este estudio, confirmo que quiero continuar participando en el mismo.

Si ☐ No ☐

_____ _____

Fecha y hora Firma del paciente

_____ _____

Fecha y hora Firma del investigador

# Hoja de información al paciente/ representante y de consentimiento informado

Corporació Parc Taulí

CLÍNIC BARCELONA Hospital Universitari

***Consentimiento informado para participación en el estudio:***

***Estudio observacional farmacocinético y farmacodinámico de los antibióticos de amplio espectro de utilización más frecuente en la unidad de cuidados intensivos (piperacilina/tazobactam, meropenem, ceftriaxona) en pacientes con shock séptico sometidos a depuración renal continua de alto flujo.***

***Investigador principal:*** *Dr. Ignacio Martín-Loeches.*

Su médico le ha solicitado de palabra participar en este estudio, ahora y en cumplimiento de la Ley de Investigación Biomédica, reiteramos la explicación por escrito con objeto de que nos autorice a incluirl sus datos en este estudio. Es importante que usted conozca la finalidad y los procedimientos llevados a cabo en este estudio, lea atentamente esta información y no dude en comentar con su médico, al investigador o a cualquiera de sus colaboradores todas aquellas cuestiones que no le queden claras.

## ANTECEDENTES

Las infecciones graves son causadas por diferentes microorganismos, generalmente bacterias, y requieren un tratamiento antibiótico correcto. En los pacientes que tienen una infección generalizada puede encontrarse con frecuencia un mal función de diferentes órganos y sistemas corporales, entre ellos el riñón. Dicho fallo, obliga la utilización de dispositivos que depuren su sangre, filtrándola para extraer de ella las substancias tóxicas que de otro modo se podrían acumular. Estás maquinas podrían filtrar no sólo las toxinas acumuladas, sino también parte de los antibióticos que se le están administrando, de modo que se podría aumentar la rapidez con que se eliminan, lo que teóricamente podría dar lugar a que no tuviesen el efecto deseado. Esto nunca se ha estudiado para los antibióticos que usted recibe.

Para conocer de qué manera afectan los dispositivos depuradores la eliminación de los antibióticos de la sangre de los pacientes, nos proponemos medir los niveles de antibióticos en sangre antes y después de iniciar la diálisis, para comprobar si se están administrando a las dosis adecuadas y, si fuese necesario, cómo habría que ajustar las dosis en este tipo de pacientes.Esto nos permitiría a los médicos actuar en consecuencia con rapidez y efectividad para el control posterior de evolución y gravedad de la infección.

Su participación en este estudio es completamente voluntaria y no afectará en ningún modo a la atención médica que usted reciba.

## OBJETIVO DEL ESTUDIO

Las Unidades de Medicina Intensiva estamos llevando a cabo un estudio en el que se analizarán los niveles de antibióticos de pacientes críticamente enfermos con terapias de sustitución renal para asegurar que son correctos. El objetivo del estudio es comprobar si las dosis de antibióticos administradas son adecuadas y, si no lo fuesen, cómo habría que modificarlas para asegurar un adecuado tratamiento de la infección causante del cuadro clínico.

## DESCRIPCION DEL ESTUDIO

Para este tipo de estudios se comparará los datos obtenidos en diferentes pacientes que presenten la enfermedad a estudio. Se estima incluir en este estudio a 60 pacientes en 1 año. Se

tomarán muestras de su sangre para analizar los niveles de antibióticos. Su participación en el estudio no conllevará ninguna modificación del tratamiento médico habitual para su enfermedad. Las muestras de sangre se obtendrán a partir de uno de los accesos vasculares (catéteres) que usted lleva, sin que ello suponga pinchazos adicionales.

## RIESGOS DEL ESTUDIO

Para este estudio únicamente se le extraerá una pequeña muestra de sangre que será analizada en el Laboratorio, por lo tanto no se prevé que su participación en el estudio pueda resultar perjudicial para su salud.

A excepción de lo anterior, no variará la asistencia habitual que recibe en la unidad por el simple hecho de participar en este estudio. No se realizarán determinaciones de muestras de contenido genético.

## BENEFICIOS DE PARTICIPAR EN EL ESTUDIO

El conocimiento de los marcadores asociados al desarrollo y/o evolución de las infecciones graves podrá redundar en el futuro en un mejor conocimiento de la enfermedad y en consecuencia poder manejar mejor los tratamientos antibióticos de que disponemos para combatir estas infecciones y las complicaciones asociadas.

No obstante, y dado que los datos de cada uno de los pacientes sólo se conocerán con posterioridad a la finalización del estudio, no se espera que usted obtenga ningún beneficio directo durante su participación en el mismo.

## OBLIGACIONES

Su participación en el estudio es completamente voluntaria. Usted puede negarse a participar o retirar su consentimiento cualquier momento sin que de ello se derive ningún perjuicio ni pérdida de los beneficios sanitarios a los que Usted tiene derecho.

## AVANCES EN EL CONOCIMIENTO

La realización de este estudio permitirá conocer mejor cómo deben utilizarse los antibióticos en las situaciones de infecciones muy graves y críticas, y esto puede redundar en el beneficio de pacientes que se encuentren en la misma situación que usted en el futuro.

## CONFIDENCIALIDAD Y ALMACENAMIENTO DE MUESTRAS

Siguiendo la Ley Orgánica 15/1999, de 13 de Diciembre, de Protección de datos de carácter personal, todos los datos recogidos en el transcurso del estudio serán tratados de forma estrictamente confidencial, por medio de un sistema de codificación numérica, al cual sólo tendrá acceso el equipo investigador y serán utilizados para la valoración del estudio sin desvelar en ningún momento su nombre ni apellidos. Todas las personas que forman parte del equipo investigador están obligadas a mantener el secreto profesional.

Sus muestras de sangre se mantendrán conservadas en frío en las instalaciones de los centros participantes, con controles de seguridad técnicos. Finalmente, serán remitidas a un centro de análisis acreditado para proceder a la determinación de las concentraciones de antibióticos en sangre. Las muestras analizadas y remanentes serán conservadas durante 1 año tras la finalización del análisis de los resultados. Las muestras sólo serán utilizadas para el presente estudio y posteriormente cualquier remanente de muestra será destruido.

## HOJA DE CONSENTIMIENTO

**Persona de contacto: _____ Teléfono _____**

**D/DÑA:_____**

Mediante el presente documento **DOY MI AUTORIZACION** para participar en este estudio

- He leído la información y he podido hacer preguntas sobre el mismo
- Considero que la información recibida es suficiente.
- He hablado con el Dr_____( investigador)
- Comprendo que mi participación es voluntaria y que puedo retirarme del estudio cuando quiera sin tener que dar explicaciones y sin que repercuta en mis cuidados médicos

Y para que así conste, firmo el presente documento, después de haberlo leído y comprendido, y por mi propia voluntad.

En _____, a_____de_____de_____

**Firma del Participante:_____**

---

**Declaración del familiar, persona allegada o representante legal, en su caso, de que han recibido la información por incapacidad temporal o incompetencia del paciente.**

Nombre_____

Firma: _____ Fecha: _____

## REVOCACIÓN DE CONSENTIMIENTO

**Revoco el consentimiento prestado en fecha……y no deseo que mis datos y las muestras extraídas sigan siendo utilizadas para el presente proyecto.**

**Nombre del Paciente:_____**

**Firma del Paciente_____Fecha:_____**

---

**Familiar, persona allegada o Representante legal (si procede)**
**Nombre:_____**

**Firma del familiar, persona allegada o Representante legal (si procede)**

**Firma _____Fecha:_____**

---

**Nombre del Médico:_____**

**Firma del Médico _____Fecha:_____**

**Appendix 4: Case report form**

Corporació Parc Taulí

CLÍNIC BARCELONA Hospital Universitari

IDIBAPS

# Cuaderno de recogida de datos

Estudio farmacocinético y farmacodinámico de los antibióticos de amplio espectro de utilización más frecuente en la unidad de cuidados intensivos (piperacilina/tazobactam, meropenem, ceftriaxona) en pacientes con shock séptico sometidos a depuración renal de alto flujo

UCI DRAF 2012

Centro

- ☐ Hospital de Sabadell
- ☐ Hospital Clínic
- ☐ Hospital Joan XXIII

Numero del paciente

| | | |
|---|---|---|
| | | |

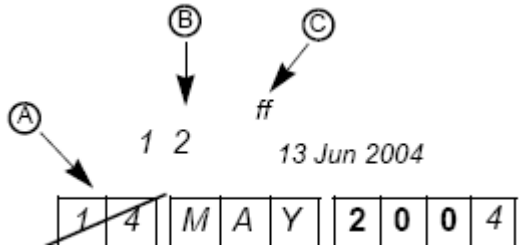
He leído y comprobado la información recogida en el CRD, y confirmo que es correcta y está completa.

Investigador (nombre): _____

Firma_____ Fecha _ _ /_ _ _/_ _ _ _

# INSTRUCCIONES GENERALES

- Usar un bolígrafo preferentemente negro.
- Las fechas deben registrarse como DD MMM AAAA (ejemplo 29 OCT 2012).o como dd/mm/aa (ejemplo 29/10/12), según se indique.
- Si solo se conoce una parte de la fecha, escribir la parte conocida y trazar guiones en los datos desconocidos (ejemplo -- --- 2012).
- Las horas deben recogerse en formato de 24 horas, por ejemplo: 14:00 no 02:00 p.m. La medianoche debe recogerse como 00:00, no como 24:00.
- Para identificar al paciente deben recogerse solo 3 iniciales, correspondientes a la primera letra de los dos apellidos y del nombre, sin tener en cuenta nombres o apellidos compuestos. Deben coincidir tanto en la portada como en los encabezados de las hojas del CRD.
- El número del paciente debe recogerse en todas las hojas del CRD
- Los errores deben tacharse con una línea diagonal (A) que permita su lectura posterior, y la corrección debe escribirse al lado (B), no encima. Deben ponerse iniciales y fecha al lado de la corrección (C). NO USAR TIPPEX.




- Las páginas que no sean necesarias deben dejarse en blanco pero deben tener el número de paciente y sus iniciales, y debe trazarse una línea diagonal tachando toda la página.
- Cuando un procedimiento no se realice y por tanto no haya datos, debe indicarse con las siguientes notaciones:

"NH" indicando "No Hecho".

"UK" indicando "Desconocido"

"NA" indicando "No Aplicable".

(Después de indicar cualquiera de estas notaciones, cruzar los espacios no empleados con una línea diagonal)

- Todos los campos del cuaderno deben escribirse, salvo que se indique lo contrario mediante instrucciones del CRD.
- Fecha de visita o procedimiento: Recoger la fecha real de la visita o procedimiento, no la prevista por el protocolo.
- El investigador principal en el centro debe revisar el CRD y firmar y fechar la hoja de fin de estudio.

| ☐ Hospital de Sabadell<br>☐ Hospital Clínic<br>☐ Hospital JoanXXIII | Numero del paciente<br>☐☐☐ | | UCI-DRAF-2012 |
|---|---|---|---|

## CONSENTIMIENTO

Se ha obtenido el consentimiento informado del paciente Si ☐ No ☐

## DATOS DEMOGRÁFICOS Y CLÍNICOS DEL PACIENTE

Día de ingreso en el Hospital ☐☐ (D D) ☐☐☐ (M M M) ☐☐☐☐ (A A A A)

Día de ingreso en la UCI ☐☐ (D D) ☐☐☐ (M M M) ☐☐☐☐ (A A A A)

Sexo: ☐ Hombre ☐ Mujer

Edad: ☐☐ años
(al ingreso en UCI)

Peso ☐☐☐ , ☐ Kg
(al ingreso en UCI)

Altura ☐☐☐ cm

IMC ☐☐ , ☐☐ $Kg/m^2$

**Diagnóstico de ingreso en el hospital**

**Diagnóstico de ingreso en intensivos**

## ANTIBIÓTICO PRESCRITO

| | Antibiótico | Dosis (mg) | Intérvalo (horas) | Tiempo infusión | Fecha inicio |
|---|---|---|---|---|---|
| ☐ | Piperacilina/Tazobactam | | | | _ _ /_ _ /_ _ (dd mm aa) |
| ☐ | Meropenem | | | | _ _ /_ _ /_ _ (dd mm aa) |
| ☐ | Ceftriaxona | | | | _ _ /_ _ /_ _ (dd mm aa) |

| ☐ Hospital de Sabadell<br>☐ Hospital Clínic<br>☐ Hospital JoanXXIII | Numero del paciente<br>\| \| \| \| | | UCI-DRAF-2012 |
|---|---|---|---|

## COMORBILIDADES

Fallo hepático moderado (tests de función hepática ≥ 2 x LSN) ☐

Fallo hepático severo (tests de función hepática ≥ 5 x LSN) ☐

Insuficiencia renal previa ☐

Insuficiencia cardíaca previa ☐

Inmunosupresión ☐

*LSN = LÍMITE SUPERIOR DE LA NORMALIDAD*

## EPISODIO SÉPTICO

Día de inicio del episodio séptico | | | | | | | | | |
D D M M M A A A A

Foco de la infección (describir)

| |
|---|
| |

Puntuación SOFA ☐

Puntuación APACHE II ☐

Puntuación SAPS II ☐

| | **Fecha inicio** | **Hora inicio** |
|---|---|---|
| Fármacos vasoactivos | _ _ /_ _ /_ _<br>dd mm aa | _ _:_ _<br>h h :mm |
| Ventilación mecánica | _ _ /_ _ /_ _<br>dd mm aa | _ _:_ _<br>h h :mm |

| ☐ Hospital de Sabadell<br>☐ Hospital Clínic<br>☐ Hospital JoanXXIII | Numero del paciente<br>\| \| \| \| | | UCI-DRAF-2012 |
|---|---|---|---|

## TERAPIA DE REEMPLAZO RENAL CONTINUO (TRRC)

### Motivo del establecimiento de la TRRC

| |
|---|
| |

### Parámetros analíticos en el momento de instauración de la TRRC

| Parámetro | Valor | Unidades | Fecha muestra | Hora muestra |
|---|---|---|---|---|
| Creatinina | | mg/dL | _ _ /_ _ /_ _ (dd mm aa) | _ _:_ _ (h h :mm) |
| Urea / BUN | | mg/dL | _ _ /_ _ /_ _ (dd mm aa) | _ _:_ _ (h h :mm) |
| Albúmina | | g/dL | _ _ /_ _ /_ _ (dd mm aa) | _ _:_ _ (h h :mm) |

### Parámetros analíticos en el momento del 1er muestreo para PK:

| Parámetro | Valor | Unidades | Fecha muestra | Hora muestra |
|---|---|---|---|---|
| Creatinina | | mg/dL | _ _ /_ _ /_ _ (dd mm aa) | _ _:_ _ (h h :mm) |
| Urea / BUN | | mg/dL | _ _ /_ _ /_ _ (dd mm aa) | _ _:_ _ (h h :mm) |
| Albúmina | | g/dL | _ _ /_ _ /_ _ (dd mm aa) | _ _:_ _ (h h :mm) |

### Parámetros de la TRRC en el momento del 1er muestreo:

| Modalidad | | | | | | | | Fecha inicio | Hora |
|---|---|---|---|---|---|---|---|---|---|
| ☐ | HFVVC | ☐ | HDFVVC | ☐ | HDVVC | ☐ | | _ _ /_ _ /_ _ (dd mm aa) | _ _:_ _ (h h :mm) |

Dosis o tasa de hemofiltración | | | , | | mL/kg/h

Flujo sanguíneo | | | , | | mL/min

Diuresis residual el día del muestreo | | | | | mL/24 h

Balance hídrico de la TRRC el día del muestreo | | Positivo | | Negativo | | | | | mL

| | | | |
|---|---|---|---|
| ☐ Hospital de Sabadell<br>☐ Hospital Clínic<br>☐ Hospital JoanXXIII | Numero del paciente<br>_ _ _ | | UCI-DRAF-2012 |

## MUESTREO PARA FARMACOCINÉTICA

### Datos de la administración de antibiótico (DOSIS DE ESTUDIO)

Inicio de la administración de la dosis de estudio _ _/_ _/_ _ - _ _:_ _ (dd mm aa hh:mm)

Final de la administración de la dosis de estudio _ _/_ _/_ _ - _ _:_ _ (dd mm aa hh:mm)

### Extracción de muestras

| Num | Tipo | Tiempo desde administración | Hora exacta de la recolección | Comentarios |
|---|---|---|---|---|
| 1 | Pre-dosis | - 5 minutos | _ _/_ _/_ _ - _ _:_ _ (dd mm aa hh:mm) | |
| 2 | Final administración | 0 | _ _/_ _/_ _ - _ _:_ _ (dd mm aa hh:mm) | |
| 3 | Post-dosis 1 | 15’ | _ _/_ _/_ _ - _ _:_ _ (dd mm aa hh:mm) | |
| 4 | Post-dosis 2 | 60’ (P/T o M)<br>90’ (CFTX) | _ _/_ _/_ _ - _ _:_ _ (dd mm aa hh:mm) | |
| 5 | Post-dosis 3 | entre 3 y 6h (P/T o M)<br>entre 4 y 8h (CFTX) | _ _/_ _/_ _ - _ _:_ _ (dd mm aa hh:mm) | |
| 6 | Valle, pre-dosis | 8h (P/T o M)<br>12h (CFTX) | _ _/_ _/_ _ - _ _:_ _ (dd mm aa hh:mm) | |

** Recoger el día, mes y año sólo en la casilla inicial y si hay cambio de fecha durante el muestreo*

### Incidencias en la TRRC durante el muestreo

| Tipo | Inicio incidencia | Fin incidencia | Comentarios |
|---|---|---|---|
| | _ _/_ _/_ _ - _ _:_ _ (dd mm aa hh:mm) | _ _/_ _/_ _ - _ _:_ _ (dd mm aa hh:mm) | |
| | _ _/_ _/_ _ - _ _:_ _ (dd mm aa hh:mm) | _ _/_ _/_ _ - _ _:_ _ (dd mm aa hh:mm) | |
| | _ _/_ _/_ _ - _ _:_ _ (dd mm aa hh:mm) | _ _/_ _/_ _ - _ _:_ _ (dd mm aa hh:mm) | |

| ☐ Hospital de Sabadell<br>☐ Hospital Clínic<br>☐ Hospital JoanXXIII | Numero del paciente<br>\| \| \| \| | | UCI-DRAF-2012 |
|---|---|---|---|

## SEGUIMIENTO Y EVOLUCIÓN DEL PACIENTE

| Fecha de alta de UCI | _ _ /_ _ /_ _<br>dd mm aa | Fecha de alta hospitalaria | _ _ /_ _ /_ _<br>dd mm aa |
|---|---|---|---|

Defunción? Si ☐ No ☐

En caso afirmativo,

Fecha de defunción: _ _ /_ _ /_ _<br>dd mm aa

extrahospitalaria? ☐
intrahospitalaria? ☐

Servicio en el que se produce Intensivos ☐ Otro (Especificar)_____

Motivo principal de la defunción _____

**Finalización de procedimientos**

| | **Fecha final** | **Hora final** | | |
|---|---|---|---|---|
| TRRC de alto flujo | _ _ /_ _ /_ _<br>dd mm aa | _ _:_ _<br>h h :mm | Días de TRRC | |
| | **Fecha final** | **Hora final** | | |
| Terapia antibiótica* | _ _ /_ _ /_ _<br>dd mm aa | _ _:_ _<br>h h :mm | Días de ATB | |
| | **Fecha final** | **Hora final** | | |
| Drogas vasoactivas* | _ _ /_ _ /_ _<br>dd mm aa | _ _:_ _<br>h h :mm | Días de drogas vasoactivas | |
| | **Fecha final** | **Hora final** | | |
| Ventilación mecánica | _ _ /_ _ /_ _<br>dd mm aa | _ _:_ _<br>h h :mm | Días de ventilación mecánica | |
| | **Fecha final** | **Hora final** | | |

** Si no se dispone de las fechas, estimar la duración en días*

¿Ha tenido alguna reacción adversa al antibiótico estudiado? Si ☐ No ☐

¿Ha habido fracaso del tratamiento antibiótico estudiado? Si ☐ No ☐

¿Se han obtenido todas las muestras PK previstas? Si ☐ No ☐

¿Se han podido completar todas las evaluaciones? Si ☐ No ☐

| | | | |
|---|---|---|---|
| ☐ Hospital de Sabadell<br>☐ Hospital Clínic<br>☐ Hospital JoanXXIII | Numero del paciente | | UCI-DRAF-2012 |

## Datos microbiológicos (1)

**Muestra positiva numero 1**

**Sangre** ☐ **Orina** ☐ **BAL** ☐ **Esputo** ☐ **Peritoneal** ☐ **Otro** ☐ **Si otro: especificar** _____

Fecha de obtención: _ _/_ _/_ _ - _ _:_ _ (dd mm aa h h:mm)

Germen aislado:

Sensibilidad antibiótica (*S= sensible, I= intermedio, R= resistente)

| Antibiótico | S/I/R* | CMI | Antibiótico | S/I/R* | CMI |
|---|---|---|---|---|---|
| 1 | | | 9 | | |
| 2 | | | 10 | | |
| 3 | | | 11 | | |
| 4 | | | 12 | | |
| 5 | | | 13 | | |
| 6 | | | 14 | | |
| 7 | | | 15 | | |
| 8 | | | 16 | | |

**Muestra positiva numero 2**

Sangre ☐ Orina ☐ BAL ☐ Esputo ☐ Peritoneal ☐ Otro ☐ Si otro: especificar _____

Fecha de obtención: _ _/_ _/_ _ - _ _:_ _ (dd mm aa h h:mm)

Germen aislado:

Sensibilidad antibiótica (*S= sensible, I= intermedio, R= resistente)

| Antibiótico | S/I/R* | CMI | Antibiótico | S/I/R* | CMI |
|---|---|---|---|---|---|
| 1 | | | 9 | | |
| 2 | | | 10 | | |
| 3 | | | 11 | | |
| 4 | | | 12 | | |
| 5 | | | 13 | | |
| 6 | | | 14 | | |
| 7 | | | 15 | | |
| 8 | | | | | |

| | | | |
|---|---|---|---|
| ☐ Hospital de Sabadell<br>☐ Hospital Clínic<br>☐ Hospital JoanXXIII | Numero del paciente | | UCI-DRAF-2012 |

## Datos microbiológicos (2)

### Muestra positiva numero 3

Sangre ☐ Orina ☐ BAL ☐ Esputo ☐ Peritoneal ☐ Otro ☐ Si otro: especificar _____

Fecha de obtención: _ _/_ _/_ _ - _ _:_ _ (dd mm aa hh:mm) Germen aislado:

Sensibilidad antibiótica (*S= sensible, I= intermedio, R= resistente)

| Antibiótico | S/I/R* | CMI | Antibiótico | S/I/R* | CMI |
|---|---|---|---|---|---|
| 1 | | | 9 | | |
| 2 | | | 10 | | |
| 3 | | | 11 | | |
| 4 | | | 12 | | |
| 5 | | | 13 | | |
| 6 | | | 14 | | |
| 7 | | | 15 | | |
| 8 | | | 16 | | |

### Muestra positiva numero 4

Sangre ☐ Orina ☐ BAL ☐ Esputo ☐ Peritoneal ☐ Otro ☐ Si otro: especificar _____

Fecha de obtención: _ _/_ _/_ _ - _ _:_ _ (dd mm aa hh:mm) Germen aislado:

Sensibilidad antibiótica (*S= sensible, I= intermedio, R= resistente)

| Antibiótico | S/I/R* | CMI | Antibiótico | S/I/R* | CMI |
|---|---|---|---|---|---|
| 1 | | | 9 | | |
| 2 | | | 10 | | |
| 3 | | | 11 | | |
| 4 | | | 12 | | |
| 5 | | | 13 | | |
| 6 | | | 14 | | |
| 7 | | | 15 | | |
| 8 | | | 16 | | |

| | | | |
|---|---|---|---|
| ☐ Hospital de Sabadell<br>☐ Hospital Clínic<br>☐ Hospital JoanXXIII | Numero del paciente<br>_ _ _ | | UCI-DRAF-2012 |

## MEDICACIÓN DURANTE EL DÍA DEL MUESTREO PK

| Numero | Nombre de la Medicación | Vía | Dosis | Frecuencia diaria* | Fecha & hora de comienzo | fecha/ hora finalización | Indicación | Comentarios |
|---|---|---|---|---|---|---|---|---|
| 1 | | | | | _ _/_ _/_ _ - _ _:_ _<br>dd mm aa hh:mm | _ _/_ _/_ _ - _ _:_ _<br>dd mm aa hh:mm | | |
| 2 | | | | | _ _/_ _/_ _ - _ _:_ _<br>dd mm aa hh:mm | _ _/_ _/_ _ - _ _:_ _<br>dd mm aa hh:mm | | |
| 3 | | | | | _ _/_ _/_ _ - _ _:_ _<br>dd mm aa hh:mm | _ _/_ _/_ _ - _ _:_ _<br>dd mm aa hh:mm | | |
| 4 | | | | | _ _/_ _/_ _ - _ _:_ _<br>dd mm aa hh:mm | _ _/_ _/_ _ - _ _:_ _<br>dd mm aa hh:mm | | |
| 5 | | | | | _ _/_ _/_ _ - _ _:_ _<br>dd mm aa hh:mm | _ _/_ _/_ _ - _ _:_ _<br>dd mm aa hh:mm | | |
| 6 | | | | | _ _/_ _/_ _ - _ _:_ _<br>dd mm aa hh:mm | _ _/_ _/_ _ - _ _:_ _<br>dd mm aa hh:mm | | |
| 7 | | | | | _ _/_ _/_ _ - _ _:_ _<br>dd mm aa hh:mm | _ _/_ _/_ _ - _ _:_ _<br>dd mm aa hh:mm | | |
| 8 | | | | | _ _/_ _/_ _ - _ _:_ _<br>dd mm aa hh:mm | _ _/_ _/_ _ - _ _:_ _<br>dd mm aa hh:mm | | |

* Frecuencia diaria debe estar en el siguiente formato: cada X horas

## Sospechas de reacciones adversas al antibiótico estudiado

| **SAR 1** | **Fármaco sospechoso** | **Inicio** | **Final**<br>O ☐ continua |
|---|---|---|---|
| | | _ _/_ _/_ _ - _ _:_ _<br>dd mm aa hh:mm | _ _/_ _/_ _ - _ _:_ _ dd<br>mm aa hh:mm |
| **Descripción** | | | |
| **¿Se trata de una reacción grave?**<br>☐ No<br>☐ Si. Señale el motivo:<br>☐1. Mortal<br>☐2. Pone en peligro la vida<br>☐3 Requiere hospitalización<br>☐4 Prolonga hospitalización<br>☐5 Causa incapacidad persistente o significativa<br>☐6 Defecto congénito<br>☐7 Es médicamente significativa | | **Intensidad**<br>☐ 1 Leve<br>☐ 2 Moderada<br>☐ 3 Muy intensa | **Relación causal**<br>☐ 1 No evaluable<br>☐ 2 No relacionada<br>☐ 3 Posible<br>☐ 4 Probable |
| **Desenlace**<br>☐ 1 Recuperación<br>☐ 2 Recuperación con secuelas<br>☐ 3 No recuperada aún<br>☐ 4 Muerte<br>☐ 5 Desconocido | | **Acción tomada**<br>☐ 1 Ninguna<br>☐ 2 Tratamiento médico<br>☐ 3 Suspensión de algún medicamento<br>☐ 4 Otra | |
| **Comentarios** | | | |

| **SAR 2** | **Fármaco sospechoso** | **Inicio** | **Final**<br>O ☐ continua |
|---|---|---|---|
| | | _ _/_ _/_ _ - _ _:_ _<br>dd mm aa hh:mm | _ _/_ _/_ _ - _ _:_ _ dd<br>mm aa hh:mm |
| **Descripción** | | | |
| **¿Se trata de una reacción grave?**<br>☐ No<br>☐ Si. Señale el motivo:<br>☐1. Mortal<br>☐2. Pone en peligro la vida<br>☐3 Requiere hospitalización<br>☐4 Prolonga hospitalización<br>☐5 Causa incapacidad persistente o significativa<br>☐6 Defecto congénito<br>☐7 Es médicamente significativa | | **Intensidad**<br>☐ 1 Leve<br>☐ 2 Moderada<br>☐ 3 Muy intensa | **Relación causal**<br>☐ 1 No evaluable<br>☐ 2 No relacionada<br>☐ 3 Posible<br>☐ 4 Probable |
| **Desenlace**<br>☐ 1 Recuperación<br>☐ 2 Recuperación con secuelas<br>☐ 3 No recuperada aún<br>☐ 4 Muerte<br>☐ 5 Desconocido | | **Acción tomada**<br>☐ 1 Ninguna<br>☐ 2 Tratamiento médico<br>☐ 3 Suspensión de algún medicamento<br>☐ 4 Otra | |
| **Comentarios** | | | |

## Appendix 5: Published articles

CRITICAL CARE

REVIEW

# Beta-lactam dosing in critically ill patients with septic shock and continuous renal replacement therapy

Marta Ulldemolins[1,2,3*], Sergi Vaquer[2], Mireia Llauradó-Serra[4,5], Caridad Pontes[6,7], Gonzalo Calvo[3,8,9], Dolors Soy[3,9,10,11] and Ignacio Martín-Loeches[2,11]

See related research by Roberts and Roberts, http://ccforum.com/content/18/3/156

## Abstract

Although early and appropriate antibiotic therapy remains the most important intervention for successful treatment of septic shock, data guiding optimization of beta-lactam prescription in critically ill patients prescribed with continuous renal replacement therapy (CRRT) are still limited. Being small hydrophilic molecules, beta-lactams are likely to be cleared by CRRT to a significant extent. As a result, additional variability may be introduced to the *per se* variable antibiotic concentrations in critically ill patients. This article aims to describe the current clinical scenario for beta-lactam dosing in critically ill patients with septic shock and CRRT, to highlight the sources of variability among the different studies that reduce extrapolation to clinical practice, and to identify the opportunities for future research and improvement in this field. Three frequently prescribed beta-lactams (meropenem, piperacillin and ceftriaxone) were chosen for review. Our findings showed that present dosing recommendations are based on studies with drawbacks limiting their applicability in the clinical setting. In general, current antibiotic dosing regimens for CRRT follow a one-size-fits-all fashion despite emerging clinical data suggesting that drug clearance is partially dependent on CRRT modality and intensity. Moreover, some studies pool data from heterogeneous populations with CRRT that may exhibit different pharmacokinetics (for example, admission diagnoses different to septic shock, such as trauma), which also limit their extrapolation to critically ill patients with septic shock. Finally, there is still no consensus regarding the $\%T_{>MIC}$ (percentage of dosing interval when concentration of the antibiotic is above the minimum inhibitory concentration of the pathogen) value that should be chosen as the pharmacodynamic target for antibiotic therapy in patients with septic shock and CRRT. For empirically optimized dosing, during the first day a loading dose is required to compensate the increased volume of distribution, regardless of impaired organ function. An additional loading dose may be required when CRRT is initiated due to steady-state equilibrium breakage driven by clearance variation. From day 2, dosing must be adjusted to CRRT settings and residual renal function. Therapeutic drug monitoring of beta-lactams may be regarded as a useful tool to daily individualize dosing and to ensure optimal antibiotic exposure.

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Full list of author information is available at the end of the article

## Introduction

Optimal antibiotic dosing in the ICU is still a controversial issue that clinicians face daily. Despite compelling evidence supporting early and appropriate antibiotic therapy as one of the most effective interventions for improving patient outcome [1], antibiotic selection and dosing is often challenging in critically ill patients because of disease complexity, resulting physiological alterations, and reduced antibiotic susceptibilities of nosocomial pathogens. Besides, selecting an antimicrobial to which the causal agent is susceptible is not sufficient to achieve the best clinical outcomes, and factors such as adequate tissue penetration and achievement of a pharmacodynamic target associated with therapeutic success according to the antibiotic class are crucial for improving infection cure and patient morbi-mortality [2-4].

Beta-lactam antibiotics are time-dependent antibiotics, meaning that they exhibit optimal killing activity when plasma concentrations are maintained above the minimum inhibitory concentration of the bacteria during a percentage of the dosing interval ($\%T_{>MIC}$). Beta-lactams are also the most prescribed antibiotics in the ICU [5]. Significant and unpredictable pharmacokinetic variability of this pharmacological group has been well documented in critically ill patients: the volume of distribution (Vd) and the clearance (CL) of beta-lactams have been found to vary significantly depending on patient severity, proteinemia and organ failure, among other factors [3,6]. Acute kidney injury and the requirement of continuous renal replacement therapy (CRRT) add further variability to beta-lactam CL. However, available clinical evidence supporting beta-lactam dosing in critically ill patients with septic shock and CRRT is not yet optimal, since recommendations are mainly elucidated from healthy volunteers' data and from clinical studies with important patient variability and limited sample sizes.

The aims of this article are to describe the current clinical scenario of beta-lactam dosing in critically ill patients with septic shock and CRRT, to highlight the sources of variability among the different studies that reduce extrapolation to clinical practice, and to identify the opportunities for future research and improvement in this field. For this purpose, two of the most frequently prescribed beta-lactams for nosocomial infections (meropenem and piperacillin) and a highly protein-bound antibiotic usually prescribed for community-acquired infections (ceftriaxone) were chosen for a thorough review. A systematic review of all available data on beta-lactam antibiotic pharmacokinetics in critically ill patients with CRRT was beyond the scope of this article, as this has been done elsewhere [7-9].

## Search strategy and selection criteria

Data for this review were identified by systematic searches of PubMed (1966 to November 2013), as well as references cited by relevant articles. Search terms included were 'meropenem' or 'piperacillin' or 'ceftriaxone','critically ill patient' or 'intensive care unit' or 'critical illness', 'continuous veno-venous hemodiafiltration' or 'continuous veno-venous hemodialysis' or 'continuous veno-venous hemofiltration' or 'continuous renal replacement therapy', and 'pharmacokinetics' or 'pharmacodynamics'. Relevant articles written in English, Spanish and Catalan where considered for this review. Those articles describing the pharmacokinetics of meropenem, piperacillin/tazobactam and ceftriaxone in adult critically ill patients receiving CRRT were included.

## Effect of septic shock and CRRT in antibiotic dosing optimization

Classically, the *in vitro* susceptibility of the causal pathogen has been the cornerstone of antibiotic prescription. However, selection according to susceptibility is only a component of the optimal antibiotic therapy, and many other factors must also be considered. In terms of posology, it is paramount to design dosing strategies that maximize the likelihood of attaining the pharmacodynamic target associated with therapy success in the biophase. This is complex in the critically ill patient with septic shock and CRRT since it is well known that critical sickness and clinical interventions can drive to physiological changes likely to alter drug pharmacokinetics [3] and therefore likely to compromise the attainment of these pharmacodynamic targets.

There are two important time periods that must be considered for antibiotic dosing. The first period corresponds to the first day of therapy, where the main determinant for dosing must be the Vd since this determines the early attainment of antibiotic concentrations within the therapeutic range. In critically ill patients with sepsis, increased Vd must be expected for hydrophilic antibiotics such as beta-lactams (see Tables 1, 2, 3, 4, 5 and 6), aminoglycosides and glycopeptides [10-38]. This increase may be due to the presence of bacterial endotoxins in the bloodstream, which has a cascade effect on the production of endogenous molecules that act on the vascular endothelium, leading to vasodilation and transcapillary leakage of fluid and proteins into the extracellular space, where these antibiotics distribute. When the Vd is abnormally increased, distribution of hydrophilic antibiotics such as beta-lactams becomes more extensive for trying to compensate this larger space, with greater movement of the drug molecules from the central compartment (bloodstream) to the peripheral compartments (mainly extravascular fluid). The amount of the drug in plasma consequently decreases, and therefore the plasma concentration decreases. Consequently, given a particular minimum inhibitory concentration, shorter $\%T_{>MIC}$ values can be expected, which in turn may compromise beta-lactams' pharmacodynamic target attainment [39]. Critically ill

**Table 1 Available data on meropenem pharmacokinetics in continuous renal replacement therapy**

| Study | *n* | Population and score[a] | Site of infection | Pathogen (MIC) | Antibiotic | Type of filter | Type of CRRT | RRT dose[a] |
|---|---|---|---|---|---|---|---|---|
| Spanish product information | N/R | Healthy volunteers | N/A | N/A | Meropenem 2 g | N/A | N/A | N/A |
| Ververs and colleagues [16] | 5 | Critically ill patients with septic shock and AKI. No severity score reported | Several | Target: 100 % $T_{>MIC90}$ of sensitive trains (*Serratia* sp. 0.06 mg/l and *Pseudomonas aeruginosa* 2 mg/l) | Meropenem 500 mg every 12 hours | PAN 06 polyacrylonitrile fiber membrane | CVVHF | $Q_R$: 1.60 l/hour |
| Bilgrami and colleagues [15] | 10 | Critically ill patients with septic shock and AKI. APACHE II score 25 (22 to 28) | Several | Target: 100 % $T_{>MIC90}$ of *Burkholderia pseudomallei* (MIC 4 mg/l) | Meropenem 1 g every 8 hours | AN 69 HF, 2.15 $m^2$ polyacrylonitrile fiber membrane | CVVHF | $Q_R$: 4.40 l/hour |
| Krueger and colleagues [24] | 8 | Critically ill patients with sepsis and MODS or cardiogenic shock and AKI. APACHE II score 29.90 ± 6.64 | Several | Target: 40 % $T_{>MIC}$ of susceptibility and intermediate-susceptibility breakpoint (4 and 8 mg/l, NCCLS) | Meropenem 500 mg every 12 hours | AN 69 HF, 0.9 $m^2$ polyacrylonitrile fiber membrane | CVVHF | $Q_R$: 1.60 l/hour |
| Thalhammer and colleagues [18] | 9 | Critically ill patients with sepsis and AKI. No severity score reported | Several | Target: 40 to 50 % $T_{>MIC90}$ of *P. aeruginosa* susceptibility and intermediate-susceptibility breakpoint (4 and 8 mg/l, NCCLS) | Meropenem 1 g single dose | 0.43 $m^2$ polysulphone fiber membrane | CVVHF | $Q_R$: 2.75 l/hour |
| Tegeder and colleagues [19] | 9 | Critically ill patients with septic shock and AKI. No severity score reported | Several (66.6 % abdominal) | Target: 100 % $T_{>MIC90}$ of *P. aeruginosa* intermediate-susceptibility breakpoint (8 mg/l) | Meropenem 500 mg every 8 to 12 hours | AN 69 HF type of membrane N/R | CVVHF | $Q_R$: 1 l/hour |
| Valtonen and colleagues [49] | 6 | Infected patients with AKI. No severity score reported | N/R | Target: 100 % $T_{>MIC90}$ of *P. aeruginosa* and *Enterococcus faecalis* susceptibility breakpoint (4 and 8 mg/l, BSAC) | Meropenem 1 g single dose | AV 400S, 0.7 $m^2$ polysulphone fiber membrane | CVVHDF | $Q_D$: 1 l/hour, $Q_R$: N/R |
| | | | | | | | CVVHDF | $Q_D$: 2 l/hour, $Q_R$: N/R |
| | | | | | | | CVVHF | $Q_R$: N/R |
| Robatel and colleagues [20] | 13 | Critically ill patients with septic shock and AKI. No severity score reported | Several | Target: ≥75 % $T_{>MIC90}$ of susceptibility breakpoint (4 mg/l) | Meropenem 0.5 to 1 g every 8 to 12 hours | AN 69 HF, 0.9 $m^2$ polyacrylonitrile fiber membrane | CVVHDF | $Q_D$: 0.60 to 1.50 l/hour, $Q_R$: 0 to 1 l/hour |
| Langgartner and colleagues [21] | 6 | Critically ill patients with sepsis and AKI. No severity score reported | Several (50 % pneumonia) | Target: 100 % $T_{>MIC}$ *P. aeruginosa* intermediate-susceptibility breakpoint (MIC 8 mg/l) | Meropenem 1 g every 12 hours (bolus or CI) | AV 600S, 1.4 $m^2$ polysulphone fiber membrane | CVVHDF | Total flow rate ($Q_D$ + $Q_R$): 2 l/hour |
| Seyler and colleagues [22] | 17 | Critically ill patients with severe sepsis/septic shock and AKI. No severity score reported | N/R | Target: 40 % $T_{>4xMIC}$ of *P. aeruginosa* susceptibility breakpoint (≤2 mg/l, EUCAST) (8 mg/l) | Meropenem 1 g every 12 hours | AN 69 HF type of membrane N/R | CVVHDF / CVVHF | $Q_D$: 1.61 ± 0.63, $Q_R$: 1.54 ± 0.84 (for a 70 kg adult, weight not reported) |
| Giles and colleagues [23] | 5 | Critically ill patients with septic shock and AKI | N/R | Target: 100 % $T_{>MIC90}$ of *P. aeruginosa* susceptibility breakpoint (4 mg/l) | Meropenem 1 g every 12 hours | AN 69 HF, 0.9 $m^2$ polyacrylonitrile fiber membrane | CVVHF | $Q_D$: 1.20 l/hour, $Q_R$: 1.45 l/hour |

**Table 1 Available data on meropenem pharmacokinetics in continuous renal replacement therapy** *(Continued)*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 5 | Critically ill patients with septic shock and AKI | N/R | Target: 100 % $T_{>MIC90}$ of *P. aeruginosa* susceptibility breakpoint (4 mg/l) | Meropenem 1 g every 12 hours | AN 69 HF, 0.9 $m^2$ polyacrylonitrile fiber membrane | CVVHDF | |
| Krueger and colleagues [17] | 9 | Critically ill patients with septic shock/ cardiogenic shock and AKI. APACHE II 28.6 ± 9.1 | Several (66.7 % pneumonia) | Target: 100 % $T_{>MIC}$ of susceptibility and intermediate-susceptibility breakpoint (4 and 8 mg/l) | Meropenem 1 g every 12 hours | AN 69 HF, 0.9 $m^2$ polyacrylonitrile fiber membrane | CVVHDF | $Q_D$: 1.60 l/ hour, $Q_R$: variable |
| Isla and colleagues [26] | 7 | Critically ill patients with sepsis and CrCL <10 ml/minute. SOFA 13 ± 4.12 | N/R | Target: 100 % $T_{>MIC90}$ of *P. aeruginosa* and *Enterobacteriaceae* spp. susceptibility breakpoint (4 mg/l, NCCLS) | Meropenem 500 mg every 6 hours (5 cases), 500 mg every 8 hours (1 case), 1 g every 8 hours (1 case) | AN 69 HF 0.9 $m^2$ polyacrylonitrile fiber/AV600S 1.4 $m^2$ polysulphone fiber membrane | CVVHDF | $Q_D$: 0.93 l/ hour, $Q_R$: 1.20 l/hour |
| | 7 | Critically ill patients with sepsis and CrCL 10 to 50 ml/minute. SOFA 12.3 ± 3.2 | N/R | Target: 100 % $T_{>MIC90}$ of *P. aeruginosa* and *Enterobacteriaceae* spp. susceptibility breakpoint (4 mg/l, NCCLS) | Meropenem 500 mg every 6 hours (6 cases), 1 g every 8 hours (1 case) | AN 69 HF 0.9 $m^2$ polyacrylonitrile fiber/AV600S 1.4 $m^2$ polysulphone fiber membrane | CVVHF (4 cases) / CVVHDF (3 cases) | $Q_D$: 0.43 l/ hour, $Q_R$: 1.84 l/hour |
| | 6 | Critically ill patients (mostly trauma patients) with sepsis and CrCL >50 ml/ minute. SOFA 14.0 ± 5.2 | N/R | Target: 100 % $T_{>MIC90}$ of *P. aeruginosa* and *Enterobacteriaceae* spp. susceptibility breakpoint (4 mg/l, NCCLS) | Meropenem 2 g every 8 hours (5 cases), 1 g every 6 hours (1 case) | AN 69 HF, 0.9 $m^2$ polyacrylonitrile fiber membrane | CVVHF | $Q_R$: 1.25 l/ hour |
| Isla and colleagues [25] | 13 | Critically ill patients with sepsis and AKI. SOFA 11.9 ± 2.8 | N/R | Target: 100 % $T_{>MIC90}$ of *Enterobacteriaceae* spp., *P. aeruginosa* and *Staphylococcus aureus* susceptibility and intermediate-susceptibility breakpoints (4 and 8 mg/l respectively, NCCLS) | Meropenem 500 mg, 1 to 2 g every 6 to 8 hours | AN 69 HF, 0.9 $m^2$ polyacrylonitrile fiber membrane or AV 600S, 1.4 $m^2$ polysulphone fiber membrane | CVVHF / CVVHDF | Total flow rate ($Q_D$ + $Q_R$): 2.28 l/ hour |
| Meyer and colleagues [27] | 1 | Critically ill patient with septic shock and AKI | Meningitis | Target: 100 % $T_{>MIC90}$ of *Neisseria meningitidis* susceptibility breakpoint (0.016 mg/l) | Meropenem 1 g every 12 hours for three doses then 1 g every 8 hours | AN 69 HF, type of membrane N/R | CVVHDF | $Q_D$: 0.75 l/ hour, $Q_R$: 1.25 l/hour |

The table includes healthy volunteers' data with comparative purpose. AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; BSAC, British Society for Antimicrobial Chemotherapy; CI, continuous infusion; CrCL, creatinine clearance; CRRT, continuous renal replacement therapy; CVVHDF, continuous venovenous hemodiafiltration; CVVHF, continuous venovenous hemofiltration; EUCAST, European Committee on Antimicrobial Susceptibility Testing; MIC, minimum inhibitory concentration; MODS, multiple organ dysfunction syndrome; N/A, not applicable; NCCLS, National Committee of Clinical Laboratory Standards; N/R, not reported; $Q_D$, dialysis fluid flow rate; $Q_R$, replacement fluid flow rate; RRT, renal replacement therapy; SOFA, Sequential Organ Failure Assessment; $\%T_{>MIC}$, percentage of dosing interval while concentration of the antibiotic is above the minimum inhibitory concentration of the pathogen. [a]Data presented as mean ± standard deviation or median (interquartile range).

patients may therefore require front-loaded doses of beta-lactam antibiotics during the first 24 to 48 hours, regardless of organ function, in order to compensate the increased Vd and to reach concentrations within the therapeutic range on the first day of therapy [39].

The particular case of CRRT requirement poses another scenario where loading doses may be considered. At the time of CRRT initiation, antibiotic concentrations over time are in steady-state equilibrium (if the antibiotic was initiated before CRRT commencement), but one can hypothesize that the change in drug CL induced by CRRT initiation may lead to the breakage of this equilibrium and, consequently, to a decrease in drug concentrations. A new steady state will follow after seven half-lives since the introduction of the foreign source of drug CL. During this time period, however, concentrations may fall below the therapeutic range. At this point, an additional loading dose may help in the maintenance of therapeutic levels. This phenomenon of steady-state breakage follows the theoretical pharmacokinetics principles but there are no studies yet that describe it in critically ill patients and hence concrete loading dose recommendations cannot be provided. Certainly this is a very interesting area that deserves further research to be properly understood.

**Table 2 Available data on meropenem pharmacokinetics in continuous renal replacement therapy**

| Study | Sieving coefficient[a] | Type of pharmacokinetic analysis | Total CL (l/hour)[a] | Vd (l/kg)[a] | Residual diuresis (ml/24 hours)[a] | Clinical outcome | Authors' dose recommendation | Study limitations |
|---|---|---|---|---|---|---|---|---|
| Spanish product information | N/A | N/R | 12.3 | 0.25 | Normal renal function | N/A | N/A | N/A |
| Ververs and colleagues [16] | 0.63 ± 0.252 | Noncompartmental | 4.57 ± 0.89 | 0.37 ± 0.15 | Anuric (range 0 to 19 ml/24 hours) | 20 % survival. 100 % target attainment | 500 mg every 12 hours for sensible strains, shorter dosage interval for intermediate strains | No severity score reported, small sample size |
| Bilgrami and colleagues [15] | 0.74 (0.71 to 0.77) | Noncompartmental | 6 (5.2-6.2) | 0.37 (0.32-0.46) | Oligoanuric | 70 % survival. 100 % target attainment | 1 g every 8 hours | High intensity used, not applicable to patients with standard CVVHF settings |
| Krueger and colleagues [24] | 0.91 ± 0.1 | Two-compartment modeling | 4.98 ± 1.29 | 0.28 ± 0.07 | <500 | 62.5 % survival. 100 % target attainment for MIC = 4 mg/l, 75 % target attainment for MIC = 8 mg/l | 500 mg every 12 hours for susceptible bacteria | Heterogenic group with patients with cardiogenic shock |
| Thalhammer and colleagues [18] | N/R | Noncompartmental | 8.62 ± 1.12 | 0.34 ± 0.03 | Anuric | 33.3 % survival. 100 % target attainment for MIC = 8 mg/l | 1 g every 8 hours | First-dose pharmacokinetics, no severity score reported, no septic shock |
| Tegeder and colleagues [19] | 1.17 ± 0.11 | Noncompartmental | 3.12 ± 0.50 | 0.18 ± 0.03 (for a 70 kg adult, weight not reported) | Five anuric, four with urine output <300 ml/24 hours | Survival N/R, 100 % target attainment | 500 mg every 12 hours or 250 mg every 6 hours | No severity score reported |
| Valtonen and colleagues [49] | N/R | Noncompartmental | 4.72 ± 2.69 | N/R | 111.8 ± 201.7 | Survival N/R, 83.3 % target attainment | 1 g every 12 hours | No report of Vd. First-dose pharmacokinetics. No septic shock, not applicable to critically ill patients |
| | N/R | Noncompartmental | 5.71 ± 3.58 | N/R | 120.9 ± 204.7 | Survival N/R, 83.3 % target attainment | 1 g every 12 hours | No report of Vd. First-dose pharmacokinetics. No septic shock, not applicable to critically ill patients |
| | N/R | Noncompartmental | 3.27 ± 2.30 | N/R | 120.9 ± 204.7 | Survival N/R, 83.3 % target attainment | 500 mg every 8 hours | No report of Vd. First-dose pharmacokinetics. No septic shock, not applicable to critically ill patients |
| Robatel and colleagues [20] | 0.65 (39 % CV) | Four-compartment modeling | 5.5 (38 % CV) | 0.52 | Anuric | 46.7 % survival. Pharmacokinetic target attainment N/R | 750 mg every 8 hours or 1.5 g every 12 hours | No severity score reported, no average total CRRT dose reported |
| Langgartner and colleagues [21] | 0.97 (0.87 to 1.05), bolus 0.89 (0.79 to 0.93), CI | Noncompartmental | 4.32 (3.93 to 4.96), bolus 4.40 (3.58 to 5.58), CI | 0.43 (0.38 to 0.54) | N/R | 66.7 % survival. 83.3 % target attainment in CI, 66.6 % target attainment in bolus | 500 mg loading dose, 2 g every 24 hours CI | No severity score and residual renal function reported, no septic shock |
| | N/R | Noncompartmental | | | N/R | | | |

**Table 2 Available data on meropenem pharmacokinetics in continuous renal replacement therapy** *(Continued)*

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Seyler and colleagues [22] | | | 4.9 (2.1 to 14) (for a 70 kg adult, weight N/R) | 0.45 (0.20 to 3.03) | Survival N/R, 81 % target attainment | 1 g every 8 hours loading dose (first 48 hours), dose reduction thereafter | CVVHDF and CVVHF data analyzed altogether. No severity score and residual renal function reported |
| Giles and colleagues [23] | 0.95 ± 0.03 | Two-compartment modeling | 3.63 ± 0.95 | 0.38 ± 0.12 | N/R | 60 % survival, 60 % target attainment | 1 g every 12 hours | Small sample size. No residual renal function reported. |
| | 0.91 ± 0.09 | Two-compartment modeling | 4.72 ± 1.69 | 0.31 ± 0.08 | N/R | 60 % survival, 60 % target attainment | 1 g every 12 hours | Small sample size. No residual renal function reported. |
| Krueger and colleagues [17] | 1.06 | Two-compartment modeling | 3.28 ± 1.02 | 0.26 ± 0.09 | Anuric | 66.7 % survival, 100 % target attainment | 1 g every 12 hours | Heterogenic group with patients with cardiogenic shock. $Q_D$ not reported |
| Isla and colleagues [26] | 0.76 ± 0.10 | Noncompartmental | 9.0 ± 4.55 | 0.57 ± 0.29 | N/R, mean CrCL = 1.1 ml/minute | Survival N/R, 85.7 % target attainment | 500 mg every 6 hours | No septic shock. The study compares three groups with different CRRT modalities. No residual diuresis and CrCL estimation method reported |
| | 0.85 ± 0.13 | Noncompartmental | 8.16 ± 3.43 | 0.37 ± 0.10 | N/R, mean CrCL = 23.5 ml/minute | Survival N/R, 57.1 % target attainment | 500 mg every 6 hours | No septic shock. CVVHDF and CVVHF data analyzed altogether. The study compares three groups with different CRRT modalities. No residual diuresis and CrCL estimation method reported |
| | N/R | Noncompartmental | 63.90 ± 39.74 | 1.31 ± 0.9 | N/R, mean CrCL = 95.9 ml/minute | Survival N/R, 16.7 % target attainment | Doses >2 g every 8 hours | No septic shock. Mainly trauma patients. The study compares three groups with different CRRT modalities. No residual diuresis and CrCL estimation method reported |
| Isla and colleagues [25] | 0.72 (6.3 % CV) | Two-compartment modeling | 8.04 (13 % CV) | 0.50 (10 % CV) | N/R, mean CrCL = 22 ml/minute | Survival N/R, target attainment N/R | CI of 700 mg/24 hours (MIC = 4 mg/l) or 1,400 mg/24 hours (MIC = 8 mg/l) in CrCL <10 ml/minute, higher doses when >10 ml/minute | No septic shock. CVVHDF and CVVHF data analyzed altogether. Different filters used. No residual diuresis and CrCL estimation method reported |
| Meyer and colleagues [27] | 1.02 ± 0.26 | Noncompartmental | 7.76 | 0.54 | Anuric | Survived but with significant sequels. Pharmacodynamic target was attained | 1 g every 12 hours | Case report with limited comparability to other studies |

The table includes healthy volunteers' data with comparative purpose. CI, continuous infusion; CL, clearance; CrCL, creatinine clearance; CRRT, continuous renal replacement therapy; CV, coefficient of variation; CVVHDF, continuous venovenous hemodiafiltration; CVVHF, continuous venovenous hemofiltration; MIC, minimum inhibitory concentration; N/A, not applicable; N/R, not reported; $Q_D$, dialysis fluid flow rate; Vd, volume of distribution. [a]Data presented as mean ± standard deviation or median (25 to 75 % range).

**Table 3 Available data on piperacillin pharmacokinetics in continuous renal replacement therapy**

| Study | *n* | Population and score[a] | Site of infection | Pathogen (MIC) | Antibiotic | Type of filter | Type of CRRT | RRT dose[a] |
|---|---|---|---|---|---|---|---|---|
| Occhipinti and colleagues [28] | 12 | Healthy volunteers | N/A | N/A | Piperacillin 4.5 g every 8 hours | N/A | N/A | N/A |
| Arzuaga and colleagues [29] | 4 | Critically ill patients with sepsis and CrCL <10 ml/minute. SOFA 13.5 ± 3.1 | Several | Target: 100 % $T_{>MIC}$ for susceptibility and intermediate-susceptibility breakpoints (<32 mg/l and >64 mg/l) | Piperacillin/tazobactam 4.5 g every 6 to 8 hours | AN 69 HF, 0.9 $m^2$ copolymer filter | CVVHF | $Q_R$: 1.63 ± 0.47 l/hour |
| | 5 | Critically ill patients with sepsis and CrCL 10 to 50 ml/minute. SOFA 11 ± 2.1 | Several (60 % peritonitis) | Target: 100 % $T_{>MIC}$ for susceptibility and intermediate-susceptibility breakpoints (<32 and >64 mg/l) | Piperacillin/tazobactam 4.5 g every 6 to 8 hours | AN 69 HF, 0.9 $m^2$ copolymer filter | CVVHF | $Q_R$: 1.82 ± 0.26 l/hour |
| | 5 | Critically ill patients with sepsis and CrCL >50 ml/minute. SOFA 9 ± 1.4 | Several (60 % VAP) | Target: 100 % $T_{>MIC}$ for susceptibility and intermediate-susceptibility breakpoints (<32 and >64 mg/l) | Piperacillin/tazobactam 4.5 g every 6 to 8 hours | AN 69 HF, 0.9 $m^2$ copolymer filter | CVVHF | $Q_R$: 1.20 ± 0.45 l/hour |
| van der Werf and colleagues [30] | 9 | Critically ill patients with septic shock and MODS. APACHE II 30.1 ± 4.2 | Several | Target: 100 % $T_{>MIC}$ of the *in vitro* sensitivity of microbial isolates recovered from the infection site | Piperacillin/tazobactam 4.5 g every 8 hours | N/R | CVVHF | $Q_R$: 1.55 ± 0.59 l/hour |
| Capellier and colleagues [31] | 10 | Critically ill patients with septic shock (seven cases) or cardiogenic shock (three cases) and AKI. SAPS II score 74 ± 6 | N/R | N/R | Piperacillin 4 g every 8 hours (six cases first dose, four cases steady state) | 0.5 $m^2$ polysulphone filter | CVVHF | N/R |
| Asín-Prieto and colleagues [32] | Total: 16, N/R by degree of renal function | Critically ill patients with sepsis/polytrauma and different degrees of renal function (CrCL 1.3 to 110 ml/minute). SOFA 11 ± 3 | N/R | Target: 100 % $T_{>MIC}$ for the susceptibility breakpoint (16 mg/dl) (CLSI) | Piperacillin/tazobactam 4.5 g every 4, 6 and 8 hours (two, seven and seven cases, respectively) | AN 69 HF, 0.9 $m^2$ copolymer filter | CVVHF | $Q_R$: 1.54 ± 0.43 l/hour |
| Bauer and colleagues [33] | 42 | Critically ill patients with sepsis and AKI/end-stage renal disease. CCF score 7.9 ± 2.8 | N/R | Target: 50 % $T_{>MIC}$ for the susceptibility and intermediate-susceptibility breakpoint (16 and 64 mg/dl) | Piperacillin/tazobactam 2.25 to 3.375 g every 6, 8 and 12 hours | M60 to M100 HF, 0.6 to 0.9 $m^2$ acrylonitrile filter or NxStage System One, 1.5 $m^2$ polyethersulphone filter | CVVHD / CVVHDF | $Q_T$: 2.4 (for mean weight of 95 kg) |
| Mueller and colleagues [34] | 8 | Critically ill patients with sepsis and AKI. No severity score reported | Pneumonia | Target: 50 % $T_{>MIC}$ for the susceptibility and intermediate-susceptibility breakpoint (16 and 32 mg/dl) | Piperacillin/tazobactam 4.5 g every 8, 12 and 24 hours (three, four and one cases, respectively) | AN 69 HF, 0.6 $m^2$ filter | CVVHD | $Q_D$: 1.5 l/hour, $Q_R$: 0.08 to 0.20 l/hour |

**Table 3 Available data on piperacillin pharmacokinetics in continuous renal replacement therapy** *(Continued)*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Keller and colleagues [35] | 12 | Critically ill patients with sepsis and AKI. No severity score reported | Several | N/R | Piperacillin 4 g single dose (10 cases), 4 g every 8 hours (two cases) | AN 69 HF, 0.43 $m^2$ copolymer filter | CAVHD | $Q_D$: 1.22 ± 0.09 l/hour |
| Valtonen and colleagues [50] | 6 | Septic patients with AKI. No severity score reported | Several | Target: 100 % $T_{>MIC}$ *Pseudomonas* spp. and *Enterobacteriaceae* spp. susceptibility breakpoint (16 mg/dl, BSAC) | Piperacillin/ tazobactam 4.5 g every 12 hours | AV 400S, 0.7 $m^2$ polysulphone membrane | CVVHDF | $Q_D$: 1 l/hour, $Q_R$: N/R |
| | | | | | | | CVVHDF | $Q_D$: 2 l/hour, $Q_R$: N/R |
| | | | | | | | CVVHF | $Q_R$: N/R |
| Seyler and colleagues [22] | 16 | Critically ill patients with severe sepsis/ septic shock and AKI. No severity score reported | N/R | Target: 50 % $T_{>4xMIC}$ *Pseudomonas aeruginosa* susceptibility breakpoint (≤16 mg/l, EUCAST) (64 mg/l) | Piperacillin/ tazobactam 4.5 g every 6 hours | AN 69 HF, type of membrane N/R | CVVHDF/ CVVHF | $Q_D$: 0.023 ± 0.009 l/kg/ hour (1.61 l/hour for a 70 kg adult, weight N/R), $Q_R$: 0.022 ± 0.012 l/kg/hour (1.54 l/hour for a 70 kg adult, weight N/R) |
| Varghese and colleagues [38] | 10 | Critically ill patients with severe sepsis/ septic shock and AKI. APACHE II 33 (31 to 36), SOFA 12 (10 to 15) | N/R | Target: 50 % $T_{>MIC}$ for clinically relevant MIC (2, 4, 8, 16, 32 and 64 mg/l) in plasma and subcutaneous tissue | Piperacillin/ tazobactam 4.5 g every 8 hours | AN 69 HF, 1.05 $m^2$ polyacrylonitrile filter | CVVHDF | $Q_D$: 1 to 1.5 l/hour, $Q_R$: 1.5 to 2 l/hour, $Q_T$: 3.0 to 3.9 l/hour |

The table includes healthy volunteers' data with comparative purpose. AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; BSAC, British Society for Antimicrobial Chemotherapy; CAVHD, continuous arteriovenous hemodialysis; CCF, Cleveland Clinic Foundation; CI, continuous infusion; CLSI: Clinical and Laboratory Standards Institute; CrCL, creatinine clearance; CRRT, continuous renal replacement therapy; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; CVVHF, continuous venovenous hemofiltration; EUCAST, European Committee on Antimicrobial Susceptibility Testing; MIC, minimum inhibitory concentration; MODS, multiple organ dysfunction syndrome; N/A, not applicable; N/R, not reported; $Q_D$, dialysis fluid flow rate; $Q_R$, replacement fluid flow rate; $Q_T$, total flow rate; RRT, renal replacement therapy; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; $\%T_{>MIC}$, percentage of dosing interval while concentration of the antibiotic is above the minimum inhibitory concentration of the pathogen; VAP, ventilator-associated pneumonia. [a]Data presented as mean ± standard deviation or median (interquartile range).

The second period starts from day 2. During this period, the estimated drug CL is the main determinant of dosing, with the objective of maintaining the equilibrium between input and output as the tissues should already hold therapeutic antibiotic concentrations. In this context, CRRT represents a particular challenge in terms of dosing, especially for hydrophilic antibiotics, as concentrations may vary depending on the degree of extraction, which in turn depends on the CRRT modality, on drug physicochemistry and, presumably, on CRRT intensity [7]. Moreover, residual renal function is usually variable, difficult to assess and rarely considered when dosing, despite its relevant contribution to antibiotic CL in patients undergoing CRRT that has been described for meropenem and piperacillin among others [26,29,32]. Finally, the patient's condition evolves throughout the ICU stay so the influence of the previously mentioned factors may vary over time, making it difficult to generalize recommendations only based on CRRT modality and intensity. Dosing should ideally be titrated daily depending on the CRRT settings and the evolution of the patient's renal function. With this aim, therapeutic drug monitoring (TDM) of trough levels might be a useful tool for refining dosing decisions during the maintenance phase of therapy, as it is routinely performed with aminoglycosides and glycopeptides. However, despite emerging data suggesting that beta-lactam TDM might improve the attainment of pharmacodynamic targets associated with therapeutic success [40], the impact of systematic TDM on clinical outcomes and resource use is still to be prospectively validated. Due to the variable pharmacokinetics of these drugs in critically ill patients with CRRT, TDM certainly deserves further investigation.

## Determinants of drug clearance by CRRT

Among the many options for renal replacement, CRRT is the most used in the critical care setting due to its advantages in hemodynamically unstable patients compared with intermittent techniques [41]. Drug clearance

**Table 4 Available data on piperacillin pharmacokinetics in continuous renal replacement therapy**

| Study | Sieving coefficient[a] | Type of pharmacokinetic analysis | Total CL (l/hour)[a] | Vd (L/kg)[a] | Residual diuresis (ml/ 24 hours)[a] | Clinical outcome | Authors dose recommendation | Study limitations |
|---|---|---|---|---|---|---|---|---|
| Occhipinti and colleagues [28] | N/A | Noncompartmental | 10.90 ± 1.17 l/ hour/ 1.73 $m^2$ | 0.15 ± 0.02 | N/A | N/A | N/A | N/A |
| Arzuaga and colleagues [29] | 0.42 ± 0.25 | Noncompartmental | 3.00 ± 3.22 | 0.28 ± 0.16 | N/R, CrCL <10 ml/ minute | Survival N/R, 100 % target attainment | Dose reduction | Small sample size, no residual diuresis and CrCL estimation method reported |
| | 0.38 ± 0.37 | Noncompartmental | 5.44 ± 1.80 | 0.36 ± 0.27 | N/R, CrCL 10 to 50 ml/ minute | Survival N/R, 100 % target attainment for MIC < 32 mg/l, 50 % target attainment for MIC > 64 mg/l | Dose reduction | Small sample size, no residual diuresis and CrCL estimation method reported |
| | 0.23 ± 0.07 | Noncompartmental | 15.91 ± 9.13 | 0.56 ± 0.25 | N/R, CrCL >50 ml/ minute | Survival N/R, 55.5 % target attainment for MIC < 32 mg/l, 16.6 % target attainment for MIC > 64 mg/l | 4.5 g every 4 hours | Small sample size, no residual diuresis and CrCL estimation method reported |
| van der Werf and colleagues [30] | N/R | Two compartments | 2.52 ± 1.38 | 0.30 ± 0.21 | Anuric | 77.8 % survival, 100 % target attainment | Dose as for patients with slightly impaired renal function | No report of sieving, no report of MIC (classified as S/R) |
| Capellier and colleagues [31] | N/R | Noncompartmental | First dose: 4.75 ± 1.42, steady state: 1.49 ± 0.79 | First dose: 0.48 ± 0.24, steady state: 0.14 ± 0.07 | Mainly anuric, three with residual diuresis between 220 and 400 ml/ 24 hours | N/R | 4.5 g every 12 hours | No CRRT dose, MIC target and outcome reported, some patients with cardiogenic shock |
| Asín-Prieto and colleagues [32] | 0.37 ± 0.25 | Two compartments | 7.32 (4.21 to 10.86) (bootstrap) | 0.59 (0.38 to 0.82) (bootstrap) | Different degrees of renal function, residual diuresis N/ R, CrCL 43 ± 34 ml/ minute | Survival N/R, target attainment (MIC = 16 mg/l) after simulations: when CrCL >100 ml/ minute, 60 % target attainment with high doses (4 g every 4 hours); when CrCL = 50 ml/minute, 93 % target attainment with 4 g every 4 hours, 62 % PTA with 4 g every 6 hours; when CrCL = 10 ml/ minute, 96 % target attainment with 4 g every 8 hours | After simulations: when CrCL = 100 ml/minute, CI 16 g every 24 hours; when CrCL = 50 ml/ minute, CI 12 g every 24 hours | No report of number of patients by renal function group, no report of residual diuresis, CrCL estimated using Cockroft–Gault method (not validated for critically ill patients) |
| Bauer and colleagues [33] | N/R | One compartment | 3.87 l/hour (IQR: 3.56) | 0.38 l/kg (IQR: 0.20) | Oligoanuric (median 38 ml/ 24 hours, IQR: 157 ml) | 50 % survival, 100 % target attainment for MIC = 16 mg/l (total and unbound piperacillin), 83 % target attainment | >9 g piperacillin/ day | Sparse sampling, CVVHDF and CVVHD data analyzed altogether |

**Table 4 Available data on piperacillin pharmacokinetics in continuous renal replacement therapy** *(Continued)*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | for MIC = 64 mg/l (total piperacillin), and 77 % target attainment (unbound) | | |
| Mueller and colleagues [34] | 0.84 ± 0.21 | Noncompartmental | 2.82 (1.56 to 13.2) | 0.31 ± 0.07 | Anuric | Survival N/R, simulations show 87.5 % target attainment with 4.5 g every 12 hours/2.25 g every 8 hours | 4.5 g every 12 hours or 2.25 g every 8 hours | No severity score and outcomes reported, no septic shock |
| Keller and colleagues [35] | 0.71 ± 0.21 | One compartment | 2.83 ± 1.34 | 0.37 ± 0.05 (for a 70 kg adult, weight N/R) | Anuric | 16.7 % survival. | 150 % of dose for anuric patients | First-dose kinetics, no severity score, MIC target and outcomes reported |
| Valtonen and colleagues [50] | N/R | Noncompartmental | 5.06 ± 1.68 | N/R | 133 ± 199 | Survival N/R, 33.3 % target attainment | 4.5 g every 8 hours | No severity score and Vd reported. No septic shock, not applicable to critically ill patients |
| | N/R | Noncompartmental | 5.48 ± 2.11 | N/R | 151 ± 224 | Survival N/R, 33.3 % target attainment | 4.5 g every 8 hours | No severity score and Vd reported. No septic shock, not applicable to critically ill patients |
| | N/R | Noncompartmental | 3.89 ± 1.23 | N/R | 109 ± 182 | Survival N/R, 33.3 % target attainment | 4.5 g every 8 hours | No severity score and Vd reported. No septic shock, not applicable to critically ill patients |
| Seyler and colleagues [22] | N/R | Noncompartmental | 4.9 (0.14 to 26.6) (for a 70 kg adult, weight N/R) | 0.44 (0.22 to 1.72) | N/R | Survival N/R, 71 % target attainment | 4.5 g every 6 hours loading dose (first 48 hours), dose reduction thereafter | CVVHDF and CVVHF data analyzed altogether. No severity score, weight and residual renal function reported |
| Varghese and colleagues [38] | 0.67 (0.53 to 0.78) | Noncompartmental | 5.1 (4.2 to 6.2) | 0.42 (0.29 to 0.49) | Five anuric, five oliguric (<0.5 ml/kg/hour for ≥6 hours) | Survival N/R, 100 % target attainment for MIC ≤32 mg/l | 4.5 g every 8 hours for susceptible microorganisms (MIC ≤32 mg/l) | No site of infection and survival reported |

The table includes healthy volunteers' data with comparative purpose. CI, continuous infusion; CL, clearance; CrCL, creatinine clearance; CRRT, continuous renal replacement therapy; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; CVVHF, continuous venovenous hemofiltration; IQR, interquartile range; MIC, minimum inhibitory concentration; N/A, not applicable; N/R, not reported; PTA, probability of target attainment; S/R, sensitive/resistant; Vd, volume of distribution. [a]Data presented as mean ± standard deviation or median (25 to 75 % range).

through CRRT is multifactorial and depends on both drug characteristics and CRRT modality and intensity. Continuous venovenous hemodialysis is based on the principle of diffusion of solutes across a semipermeable membrane driven by a concentration gradient, while continuous venovenous hemofiltration clearance is driven mainly by convection removal, where a positive hydrostatic pressure drives water and solutes across the filter membrane from the blood compartment to the filtrate compartment, from which it is drained. Continuous venovenous hemodiafiltration is the most efficient technique for solute removal, consisting of a combination between the two abovementioned techniques and resulting in the removal of hydrophilic solutes with simultaneous water elimination [7].

Regardless of the modality prescribed, a common determinant of drug clearance in CRRT is protein binding. Due to protein size and electrical charge, protein-bound molecules are unable to pass through the filter membranes and only unbound molecules will be available for elimination by CRRT. This is so critical that both sieving coefficients and saturation coefficients are usually

**Table 5 Available data on ceftriaxone pharmacokinetics in hemofiltration**

| Study | *n* | Population and score[a] | Site of infection | Pathogen (MIC) | Antibiotic | Type of filter | Type of CRRT | RRT dose[a] |
|---|---|---|---|---|---|---|---|---|
| Spanish product information | N/R | Healthy volunteers | N/A | N/A | Ceftriaxone 1 g | N/A | N/A | N/A |
| Garot and colleagues [36] | 54 | Critically ill patients with sepsis, severe sepsis or septic shock with various degrees of renal function, 12 with CVVHF. SAPS II 50 (9 to 87) | Several (61 % pneumonia) | 100 % $T_{>MIC}$ for MIC values ranging from 0.016 mg/dl (*Streptococcus pneumoniae*) to 8 mg/dl (*Staphylococcus aureus*) | Ceftriaxone 2 g every 24 hours (41 cases), 1 g every 24 hours (one case), 2 g every 12 hours (one case) and 2 g every 8 hours (one case) | N/R | CVVHF | N/R |
| Kroh and colleagues [37] | 6 | Critically ill patients with sepsis and AKI | Several | N/R | Ceftriaxone 2 g every 24 hours | Polyamide filter | CVVHF | $Q_R$: 1.2 to 1.8 l/hour |

The table includes healthy volunteers' data with comparative purpose. AKI, acute kidney injury; CRRT, continuous renal replacement therapy; CVVHF, continuous venovenous hemofiltration; MIC, minimum inhibitory concentration; N/A, not applicable; N/R, not reported; $Q_R$, replacement fluid flow rate; RRT, renal replacement therapy; SAPS, Simplified Acute Physiology Score; $\%T_{>MIC}$, percentage of dosing interval while concentration of the antibiotic is above the minimum inhibitory concentration of the pathogen. [a]Data presented as mean ± standard deviation or median (interquartile range).

simplified as the unbound drug fraction. However, antibiotic protein-binding alterations have been broadly observed in ICU patients [6] due to the altered plasmatic protein homeostasis associated with critical illness (the SAFE study reported that 40 to 50 % of the ICU patients had albumins <25 g/l) [42] and due to the presence of other highly protein-bound exogenous drugs and endogenous molecules (such as bilirubin) in plasma. This may consequently translate into alterations in the extent to which an antibiotic is cleared by CRRT. However, whereas the effect of hypoalbuminemia on antibiotic pharmacokinetics in critically ill patients with preserved renal function has been documented in previous studies [6], there are no available studies regarding its combined impact with CRRT.

Another factor likely to affect the extent to which drugs are cleared by CRRT is the CRRT intensity. The question of what is the optimal CRRT intensity has been a controversial issue since its first implantation. Several studies have evaluated the impact of using different CRRT intensities on mortality and recovery of renal function in critically ill patients, with different, usually debatable, results [43-48]. Due to this lack of definitive evidence, current clinical recommendations define the area of best practice for CRRT intensity as lying between 20 and 40 ml/kg/hour [41], the clinician being responsible for individualizing the appropriate CRRT intensity for each particular patient. However, the impact of different CRRT intensities on antibiotic dosing requirements has not yet been sufficiently evaluated.

**Table 6 Available data on ceftriaxone pharmacokinetics in hemofiltration**

| | Sieving coefficient[a] | Type of pharmacokinetic analysis | Total CL (l/hour)[a] | Vd (l/kg)[a] | Residual diuresis (ml/24 hours)[a] | Clinical outcome | Authors' dose recommendation | Study limitations |
|---|---|---|---|---|---|---|---|---|
| Spanish product information | N/A | N/R | 0.6 to 1.2 | 0.10 to 0.17 | N/A | N/A | N/A | N/A |
| Garot and colleagues [36] | N/R | Two compartments | 0.97 (for low CrCL = 5.5 ml/minute) | 0.26 (for a 70 kg adult, weight N/R) | N/R, CrCL range 5.5 to 214 ml/minute | 100 % attainment of 100 % $T_{>MIC}$ | No dose adjustment | No report of severity scores, RRT settings, residual diuresis and CrCL estimation method, unbound concentration calculated using a formula, heterogenic population |
| Kroh and colleagues [37] | 0.69 ± 0.39 | Noncompartmental | 2.36 | 0.42 ± 0.19 | N/R, CrCL range 0 to 10 ml/minute | N/R | No dose adjustment | No residual diuresis and CrCL estimation method reported. No outcomes study performed, no septic shock, no albumin concentrations considered |

The table includes healthy volunteers' data with comparative purpose. CL, clearance; CrCL, creatinine clearance; N/A, not applicable; N/R, not reported; RRT, renal replacement therapy; $\%T_{>MIC}$, percentage of dosing interval while concentration of the antibiotic is above the minimum inhibitory concentration of the pathogen; Vd, volume of distribution. [a]Data presented as mean ± standard deviation or median (25 to 75 % range).

Additional to the abovementioned points, more variability in drug CL by CRRT may be introduced by medical devices that may coexist with CRRT in patients with septic shock, such as polymyxin B fiber columns (to reduce endotoxin levels in sepsis) or extracorporeal membrane oxygenation. Other factors such as filter lifespan, filter anticoagulants such as citrate and drug recirculation may also have an effect on drug CL. However, their potential for antibiotic adsorption and removal has not yet been estimated.

## Main limitations of available pharmacokinetic studies

To discuss the current scenario of beta-lactam dosing in patients with septic shock and CRRT, we performed a thorough review of the existing clinical data for three of the most frequently used (and studied) beta-lactam antibiotics in the ICU. Tables 1, 2, 3, 4, 5 and 6 summarize the available evidence on meropenem, piperacillin/tazobactam and ceftriaxone pharmacokinetics in critically ill patients with CRRT [15-38,49,50].

Critical review of these studies has lead to identification of the following points that limit applicability of dose recommendations to critically ill patients with septic shock and CRRT.

### Patient population

The identified studies handle a highly heterogeneous patient population, which may jeopardize the generalizability of the results. For example, there are studies that pool together patients with septic shock and cardiogenic shock [17,31]. The physiopathology of these two types of shock, however, is very different: septic shock is caused by peripheral vasodilation, systemic inflammation and, consequently, increased Vd; while cardiogenic shock involves peripheral vasoconstriction, which should have no effect on the Vd.

Other studies include septic and polytrauma patients requiring CRRT [25,32]. Of note, one of these studies overcame the admission diagnosis-driven variability by developing a population pharmacokinetics model. The investigators found that admission diagnosis significantly influenced pharmacokinetic parameters: trauma patients exhibited higher Vd and CL than septic patients (d = 69.5 and 15.7 l in trauma patients and septic patients, respectively; CL = 54.15 and 8.04 l/hour in trauma patients and septic patients, respectively) [25]. Patients with sepsis/severe sepsis may also substantially differ from patients with septic shock: septic shock patients may exhibit higher Vd due to capillary leakage and aggressive fluid resuscitation as compared with critically ill patients without septic shock. In spite of this, some of the available studies include patients with sepsis/severe sepsis and acute kidney injury [21,33-35,37,49,50] but not those with septic shock.

Furthermore, a significant number of the articles do not report clinical severity scores for the studied population. In particular, increasing Acute Physiology and Chronic Health Evaluation II scores have been shown to correlate with increased Vd for hydrophilic antibiotics such as aminoglycosides [12]. However, variations in the Vd of meropenem and piperacillin have been reported in the literature (see Tables 1, 2, 3, 4 and 5). Similarly, CRRT may be prescribed in patients who still present a significant residual renal function. The influence of residual renal function on piperacillin pharmacokinetics in patients receiving continuous venovenous hemofiltration has been assessed by Arzuaga and colleagues, and significant differences in piperacillin CL have been reported; for example, total drug CL in patients with creatinine CL > 50 ml/minute was tripled as compared with patients with creatinine CL < 10 ml/minute [51]. These points suggest that the one-size-fits-all dosing recommendations based only on CRRT prescription may not apply to all different types of critically ill patients, as they are a highly heterogeneous population that may require different doses.

### Continuous renal replacement therapy modality and flow rate

Regarding CRRT modalities, there is discordance in the literature on whether a specific modality makes a difference or not in terms of dosing. While some studies support a difference in CL partially due to CRRT modality [49,50], some others suggest that there are no substantial variations between modalities [22]. Theoretically, convective and diffusive methods eliminate molecules from the bloodstream using different processes, and therefore the total drug CL should differ between CRRT modalities, as has been shown with piperacillin and meropenem [49,50], but a significant volume of dosing recommendations are still generic for CRRT.

Regarding CRRT intensity, emerging evidence suggests that the total flow rate affects the CL of hydrophilic drugs with low protein binding. For example, Beumier and colleagues developed a population pharmacokinetics model for vancomycin administered as a continuous infusion in critically ill patients with sepsis and septic shock, and found that inclusion of CRRT intensity as a covariate on CL significantly improved the model [52]. Similarly, a study by Bilgrami and colleagues specifically targeted patients with high-intensity CRRT (>4 l/hour) receiving meropenem and found that total drug CL was higher compared with previous studies with lower intensity CRRT, intensity being the main parameter that accounted for the differences in meropenem CL ($R^2$ = 0.89) [15]. The high CRRT intensity was such a determinant of meropenem CL that the doses required for the coverage of less susceptible bacteria (minimum

inhibitory concentration = 4 mg/l) were similar to those used in patients without renal failure (1,000 mg every 8 hours). These data suggest that different CRRT intensities may translate into different drug CL and therefore into different dose requirements. Importantly, one must also highlight that most of the published studies use CRRT intensities in the lower range of the area of best practice (1 to 2 l/hour; 14.3 to 28.5 ml/kg/hour for a 70 kg adult) [16,17,19-21,27,29,30,32,34,35,49,50], while the actual tendency in the clinical setting may be using CRRT intensities in the higher range (>30 ml/kg/hour), especially for septic patients [41,46]. In fact, a recent study by Varghese and colleagues studied the pharmacokinetics of piperacillin/tazobactam in critically ill patients with anuria/oliguria and CRRT at a median intensity of 38.5 ml/kg/hour, and reported higher drug CL (median 5.1 (interquartile range 4.2 to 6.2) l/hour) compared with other studies that used lower CRRT intensities (see Table 3 and 4) [38].

Moreover, the methodology for the calculation of CRRT intensity is not defined in most of the studies. Some of the studies report that an absolute CRRT intensity was prescribed to all patients, without being normalized to body weight. This leads to inherently variable CRRT doses, inversely proportional to the actual patient's weight. For instance, an absolute CRRT intensity of 2 l/hour for a 100 kg patient results in a relative flow rate of 20 ml/kg/hour, whereas for a 50 kg patient the rate is 40 ml/kg/hour. When relative flow rate is prescribed, clinicians usually use body weight previous to admission or ideal body weight, and calculate the flow rate using the following formula:

$$Flow\ rate = (Q_D + Q_R)/weight\ (kg)$$

where $Q_D$ is the dialysis fluid flow rate (ml/hour) and $Q_R$ is the replacement fluid flow rate (ml/hour).

The rationale of this methodology is to avoid variations in the calculated flow rate over time as the patient real weight fluctuates during the ICU stay (for example, due to fluid therapy or edema) [53]. However, most of the studies do not report how body weight was considered in spite of the fact that it is essential to know which CRRT intensity was prescribed [43]. When real body weight is used, the calculated flow rate may be falsely low, as the denominator in the equation usually increases during the ICU stay. Recommendations include application of body weight previous to admission or ideal body weight [43]. However, considering the increasing prevalence of obesity in developed countries, one should discuss whether ideal body weight or body weight previous to admission should be used.

### Pharmacodynamic target for dosing recommendations

Antibiotic dosing recommendations intend to achieve a pharmacodynamic target that, for beta-lactams, is defined by the $\%T_{>MIC}$ value [54]. Classical studies report that penicillins and monobactams require at least a 50 to 60 % $T_{>MIC}$ for maximal bactericidal activity, cephalosporins require a 60 to 70 % $T_{>MIC}$ and carbapenems require a 40 % $T_{>MIC}$ [54]. However, most of these recommendations are based on *in vitro* studies and on animal models of bacteremia, where penetration into the site of infection is not considered. *In vivo*, higher % $T_{>MIC}$ values in plasma may be needed for achieving the abovementioned targets in biophases other than the bloodstream, since penetration into the target site follows diffusion kinetics and depends on the physicochemistry of each particular tissue. For instance, Roberts and colleagues reported that continuous infusion of full doses of meropenem (that is, 100 % $T_{>MIC}$ in plasma) was required for achieving 40 % $T_{>MIC}$ for less susceptible pathogens in subcutaneous tissue [11]. Also, the attainment of a particular percentage of $T_{>MIC}$ may be modified by the susceptibility cutoff values for the different bacteria, which vary depending on the country where the study is performed (for example, European Committee on Antimicrobial Susceptibility Testing vs Clinical and Laboratory Standards Institute breakpoints). The recommendations based upon a particular minimum inhibitory concentration in Europe may therefore not apply to the United States of America and *vice versa*.

Critical review of clinical pharmacokinetics data leads to the final consideration that there are multiple missed opportunities in the available literature. Further studies should be more focused on the study population of critically ill patients with septic shock in order to avoid variability derived from pathophysiological conditions other than septic shock. Inclusion and exclusion criteria should therefore carefully evaluate the admission diagnosis and the patient condition during the study period. Also, a population pharmacokinetics approach would be preferred to the noncompartmental approach, since the noncompartmental approach draws inaccurate conclusions because covariates that have an effect on parameter variability cannot be identified. Finally, consensus regarding clinical pharmacodynamic targets for beta-lactams would be helpful in the unification of dosing recommendations.

## Conclusions

Optimization of beta-lactam therapy in CRRT is complex and is dependent on several drug, CRRT and patient-related factors. Consideration of drug physicochemistry and protein binding, CRRT settings and disease-related pharmacokinetic alterations is essential for individualizing dose regimens with the purpose of

attaining pharmacodynamic targets associated with success.

During the first day, an initial loading dose is required to achieve drug concentrations within the therapeutic range early in time, regardless of impaired organ function. This principle may also apply to the moment of CRRT commencement, where a loading dose may be required to maintain concentrations within the therapeutic range. From day 2, dosing must be adjusted to CRRT settings and residual renal function. The complexity of dosing occurs due to the great variability encountered. As such, TDM of trough levels of beta-lactams may be regarded as a promising and key tool to individualize dosing daily and to ensure optimal exposure to the antibiotic.

Current dose recommendations are based on studies with some drawbacks that limit their applicability to the current clinical scenario. Mainly, dosing recommendations in CRRT follow a one-size-fits-all fashion, despite emerging clinical data suggesting that beta-lactam CL is partially dependent on CRRT modality and intensity. Moreover, heterogeneous populations have been pooled in the studies, limiting extrapolation to critically ill patients with septic shock and CRRT. Finally, there is still some controversy on the $\%T_{>MIC}$ value that must be chosen as the pharmacodynamic target associated with success for tailoring dosing recommendations.

Further research on dose adjustment of beta-lactam antibiotics in critically ill patients with septic shock and CRRT is required in order to establish reliable and up-to-date recommendations that ensure optimal therapy and thus increase the likelihood of optimal outcomes in this population.

#### Abbreviations

CL: Clearance; CRRT: Continuous renal replacement therapy; $Q_D$: Dialysis fluid flow rate; $Q_R$: Replacement fluid flow rate; $\%T_{>MIC}$: Percentage of dosing interval when concentration of the antibiotic is above the minimum inhibitory concentration of the pathogen; TDM: Therapeutic drug monitoring; Vd: Volume of distribution.

#### Competing interests

The authors declare that they have no competing interests.

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# Meropenem Population Pharmacokinetics in Critically Ill Patients with Septic Shock and Continuous Renal Replacement Therapy: Influence of Residual Diuresis on Dose Requirements

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**Meropenem dosing in critically ill patients with septic shock and continuous renal replacement therapy (CRRT) is complex, with the recommended maintenance doses being 500 mg to 1,000 mg every 8 h (q8h) to every 12 h. This multicenter study aimed to describe the pharmacokinetics (PKs) of meropenem in this population to identify the sources of PK variability and to evaluate different dosing regimens to develop recommendations based on clinical parameters. Thirty patients with septic shock and CRRT receiving meropenem were enrolled (153 plasma samples were tested). A population PK model was developed with data from 24 patients and subsequently validated with data from 6 patients using NONMEM software (v.7.3). The final model was characterized by CL = 3.68 + 0.22 · (residual diuresis/100) and $V = 33.00 \cdot (\text{weight}/73)^{2.07}$, where CL is total body clearance (in liters per hour), residual diuresis is the volume of residual diuresis (in milliliters per 24 h), and *V* is the apparent volume of distribution (in liters). CRRT intensity was not identified to be a CL modifier. Monte Carlo simulations showed that to maintain concentrations of the unbound fraction ($f_u$) of drug above the MIC of the bacteria for 40% of dosing interval *T* (referred to as 40% of the $f_uT_{>\text{MIC}}$), a meropenem dose of 500 mg q8h as a bolus over 30 min would be sufficient regardless of the residual diuresis. If 100% of the $f_uT_{>\text{MIC}}$ was chosen as the target, oligoanuric patients would require 500 mg q8h as a bolus over 30 min for the treatment of susceptible bacteria (MIC < 2 mg/liter), while patients with preserved diuresis would require the same dose given as an infusion over 3 h. If bacteria with MICs close to the resistance breakpoint (2 to 4 mg/liter) were to be treated with meropenem, a dose of 500 mg every 6 h would be necessary: a bolus over 30 min for oligoanuric patients and an infusion over 3 h for patients with preserved diuresis. Our results suggest that residual diuresis may be an easy and inexpensive tool to help with titration of the meropenem dose and infusion time in this challenging population.**

Meropenem is a broad-spectrum carbapenem with high levels of activity against Gram-positive and Gram-negative pathogens, including *Pseudomonas aeruginosa*, *Acinetobacter* spp., and anaerobes (1), and is one of the most prescribed antibiotics for the empirical treatment of severe infections (2). It exhibits optimal killing activity when the concentrations of the unbound fraction ($f_u$) of drug in plasma are maintained above the MIC of the bacteria for a certain percentage of dosing interval *T* (referred to as the percentage of the $f_uT_{>\text{MIC}}$), which in *in vitro* and *in vivo* animal studies has been defined to be about 40% (3). However, some clinical data suggest that critically ill patients may require a higher percentage of the $f_uT_{>\text{MIC}}$, even 100% (4, 5).

Meropenem is a hydrophilic, small molecule with a low volume of distribution (*V*; 0.3 liter/kg) and a very low level of protein binding (<2%). These characteristics make meropenem a drug mainly eliminated by the kidneys, as only the unbound fraction is available for glomerular filtration (major elimination pathway) (1). This also makes meropenem a dialyzable drug because the main determinants of drug clearance (CL) while a patient is receiving renal replacement therapy (RRT) are a low molecular size, a high affinity for water, a low *V*, and a large unbound fraction (6). Thus, there is a potential combined impact of RRT and residual renal function on meropenem total CL, which may be particularly important for critically ill patients with septic shock and a requirement for continuous renal replacement therapy (CRRT). For these patients, available guidelines recommend that 500 to 1,000 mg of meropenem every 8 h (q8h) to every 12 h (q12h) be prescribed (7), which is a considerably broad dose range. However,

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this population is subject to conditions that may significantly influence meropenem pharmacokinetics (PKs) and, consequently, modify the dosing requirements, such as hypoproteinemia, variable urine output, or diverse CRRT settings (6). It follows that while several studies have described meropenem PKs in critically ill patients with continuous venovenous hemofiltration (CVVHF) and continuous venovenous hemodiafiltration (CVVHDF) (8–19), empirical dosing at the bedside is still challenging in this scenario.

**Aims.** The aims of this study were to describe the PKs of meropenem in critically ill patients with septic shock and CRRT, to identify the sources of PK variability in these patients, and to perform different dosing simulations to assess their probability of target attainment by MIC, in order to provide empirical dosing recommendations based on clinical characteristics.

## MATERIALS AND METHODS

**Patients.** We performed a multicenter, prospective, open-label PK study in the intensive care units of the Hospitals Corporació Sanitària Universitària Parc Taulí of Sabadell (CSUPT), Clínic of Barcelona (HCB), and Joan XXIII (HJ23) of Tarragona, Spain. Patients were enrolled between January 2012 and May 2014. Authorization for the study was granted by the Spanish Regulatory Medicines Agency (code IEM-ANT-2012-1). Ethical approval was obtained from the local ethical committees, and the study was conducted following the Declaration of Helsinki guidelines. Consent to participate was obtained from the patient's legal representative. Inclusion criteria were an age of ≥18 years, a diagnosis of septic shock by the criteria of the Surviving Sepsis Campaign guidelines (20), CRRT, and an indication for treatment with meropenem. The major exclusion criterion was severe chronic kidney disease requiring RRT. The meropenem dose and infusion time were at the discretion of the treating physician. The drug was administered through a separate lumen of a venous catheter using free-fall bolus systems or volumetric infusion pump controllers, as required.

**Demographic and clinical data.** The patients' demographic and clinical data were collected. Age, weight, height, sex, site of infection, serum biochemistry, a requirement for vasopressors, CRRT settings, filter downtime, the level of residual diuresis (defined as the volume of urine collected over the 24 h of the natural day of the study), severity scores at admission (acute physiology and chronic health evaluation II [APACHE II] score) (21) and on the day of study (sequential organ failure assessment [SOFA] score) (22), the isolated microorganisms and the meropenem MICs for those microorganisms, the number of days of antibiotic therapy, and hospital survival were recorded (23). These data came from the clinical routine and were registered in a database available only to the researchers.

**Continuous renal replacement therapy.** Patients prescribed either CVVHDF or CVVHF were considered for inclusion. Prisma CRRT systems (Hospal, France) were used. A 1.5-$m^2$ surface-treated acrylonitrile and sodium methallyl sulfonate copolymer filter (AN69ST; PrismaFlex ST150; Hospal, France) was used at HJ23, and a 0.9-$m^2$ acrylonitrile and sodium methallyl sulfonate copolymer filter (AN69; PrismaFlex M100; Gambro Hospal, Switzerland) was used at CSUPT and HCB. All CRRT settings were prescribed at the discretion of the treating physician.

**Blood sampling.** For each sample, 5 ml of arterial blood was collected after at least 24 h of CRRT and meropenem therapy. For bolus sampling, 6 samples were collected at 10 min predose; at 0 min, 15 min, 60 min, and between 3 and 6 h after the end of the infusion; and just before the next dose. For extended infusion sampling, 5 samples were collected at 10 min predose; at 0 min, 60 min, and 120 min after the end of the infusion; and just before the next dose. Within 1 h of collection, samples were centrifuged at 3,000 rpm at 4°C for 10 min and plasma was frozen at −80°C for posterior analysis.

**LC-MS analysis.** The total meropenem concentration in plasma was measured using liquid chromatography (LC) coupled to tandem mass spectrometry (MS/MS) (1200 HPLC binary pump [Agilent Technologies], API 4000 AB Sciex MS) in an external laboratory using a validated method. The method was linear over the range of meropenem concentrations of 0.4 to 300 mg/liter. Within-run and between-run precision and accuracy (coefficients of variation, ≤10%) showed adequate results, according to the guidelines of the European Medicines Agency (24).

**Statistical analysis.** Statistical analysis was performed using SPSS software (v20) for Macintosh (IBM SPSS Statistics, USA). Results are expressed as absolute and relative frequencies for categorical variables and as medians (ranges) for continuous variables. A two-tailed Student *t* test was used to compare normally distributed variables, the Mann-Whitney U test was used to compare nonnormally distributed variables, and the chi-square or Fisher's exact test was used to compare categorical variables, as appropriate. The significance level for all analyses was defined as a *P* value of ≤0.05.

**PK modeling.** Nonlinear effects modeling was performed using NONMEM (v7.3) (25) and XPose (v4.0) (26) software following a three-step strategy: (i) basic population model selection, (ii) covariate selection, and (iii) validation (27, 28). The first-order conditional estimation method with interaction was used for parameter estimation. Interindividual variability (IIV) was modeled as log normal after being tested for log normality. Additive, proportional, and combined error models were tested for residual variance. The goodness of fit for a model was assessed by (i) significant decreases in the −2 log likelihood of the objective function value, (ii) plots of population and individual predicted versus observed concentrations and conditional weighted residuals (CWRES) versus observed concentrations and time (29, 30), and (iii) changes in the standard error of parameter estimates (precision).

In a second step, all reasonable demographic and clinical variables were tested for inclusion as covariates in the basic population PK model. Graphical examination and the generalized additive models procedure (26) were used to investigate their effects on model parameters. Continuous covariates were assessed as a proportional or a power function. Categorical variables were included in the model as $P_j = P_{POP} + \theta_{COV} \cdot (1 - Cov_i)$, where $P_j$ is the PK parameter for the *j*th patient, $Cov_i$ is a numeric index value, $P_{POP}$ is the typical value of a PK parameter for the reference covariate values, and $\theta_{COV}$ is the multiplicative factor for the influence of this covariate on the PK parameter. Each covariate investigated was retained if it led to an improved fit, as evaluated by biological plausibility, graphical displays based on the agreement between the observed and predicted drug concentrations, the uniformity of the distribution of the CWRES, improvement of the precision in parameter estimates, and the log likelihood ratio test. The extent of Bayesian shrinkage, as a measure of model overparameterization, was evaluated for each PK parameter (31).

**Model evaluation.** Internal validation of the PK model was performed by graphical and statistical methods, including visual predictive checks (32). The bootstrap resampling technique (200 replicated data sets) was used to build the confidence intervals (CIs) of the PK parameters to assess their stability and evaluate the robustness of the final model (33).

The external predictive performance of the PK model was assessed by analyzing data from new individuals (20 to 30% of the enrolled subjects) (34, 35), following the Food and Drug Administration guidelines (36). Individual predicted meropenem concentrations for all sampling times were obtained by Bayesian estimation. Bias was assessed in terms of individual and population prediction error (IPE and PPE, respectively; in percent). Precision was assessed as absolute individual and population prediction error (IAPE and PAPE, respectively; in percent) (37).

**Dosing simulations.** Monte Carlo dosing simulations were performed. Each simulation generated concentration-time profiles for 1,000 subjects per dosing regimen using the final estimated population PK parameters. Three bolus regimens (500 mg q8h, 500 mg every 6 h [q6h], and 1,000 mg q8h over 30 min) and three extended infusion regimens (500 mg q8h, 500 mg q6h, and 1,000 mg q8h over 3 h) were simulated using a mean patient body weight of 70 kg and three categories of residual diuresis (50 ml, 300 ml, and 700 ml), accounting for the definitions of anuria (<100

**TABLE 1** Demographics and clinical characteristics of subjects included in index data set, validation data set, and overall

| Variable | Model development data set ($n = 24$) | Validation data set ($n = 6$) | *P* value | All data ($n = 30$) |
|---|---|---|---|---|
| Median (range) age (yr) | 68.5 (50–81) | 56 (34–85) | 0.40 | 66.5 (34–85) |
| No. (%) female | 12 (50) | 2 (33.3) | 0.66 | 14 (46.7) |
| Median (range) wt[a] (kg) | 72.8 (49–95) | 75 (68–126) | 0.24 | 72.8 (49–126) |
| Median (range) APACHE score[a] | 26 (5–44) | 20 (15–33) | 0.18 | 24 (5–44) |
| Median (range) SOFA score[b] | 12 (4–19) | 9 (5–19) | 0.67 | 12 (4–19) |
| No. (%) of patients with hepatic impairment[c] | 5 (20.8) | 1 (20) | 0.88 | 6 (20) |
| No. (%) of patients receiving: | | | | |
| Vasopressors[b] | 24 (100) | 4 (66.7) | 0.034[d] | 28 (93.3) |
| Mechanical ventilation[b] | 23 (95.8) | 6 (100) | 1 | (29) 96.7 |
| No. of patients receiving CVVHDF/no. of patients receiving CVVHF | 21/3 | 5/1 | 1 | 26/4 |
| Median (range) no. of accumulated days of meropenem[b] | 4 (2–22) | 2.5 (2–4) | 0.2 | 3 (2–22) |
| Median (range) total CRRT intensity[b,e] (ml/kg/h) | 34.5 (18.7–60.1) | 39.2 (30.6–49.5) | 0.36 | 34.7 (18.7–60.1) |
| Median (range) dialysate flow rate[b] (ml/h) | 1,000 (500–1,600) | 900 (800–1,350) | 0.73 | 1,000 (500–1,600) |
| Median (range) ultrafiltrate flow rate[b] (ml/h) | 1,200 (750–2,000) | 1,800 (1,000–2,500) | 0.06 | 1,550 (750–2,500) |
| Median (range) blood flow[b] (ml/min) | 200 (130–250) | 200 (200–250) | 0.38 | 200 (130–250) |
| Median (range) albumin concn[b] (g/liter) | 21.3 (12.4–38) | 24.6 (18.1–32.6) | 0.61 | 23.4 (12.4–38) |
| Median (range) urea concn[b] (mg/dl) | 64.3 (22–168) | 52 (29–98) | 0.34 | 61.7 (22–168) |
| Median (range) creatinine concn[b] (mg/dl) | 1.6 (0.7–2.6) | 0.99 (0.4–2.3) | 0.14 | 1.4 (0.4–2.6) |
| Median (range) vol of diuresis[b] (ml/24 h) | 76.5 (<10–880) | 282.5 (82–2,050) | 0.11 | 137.5 (<10–2,050) |
| % (no.) of patients surviving | 58.3 (14) | 50 (3) | 1 | 56.7 |

[a] On admission.
[b] On the day of the study.
[c] Hepatic impairment was defined as liver function test results with values >2 times the upper limit of normality.
[d] Statistically significant difference ($P < 0.05$).
[e] CRRT intensity was defined as (filtrate + dialysate flow rate)/(ideal body weight) for CVVHDF and as (filtrate flow rate)/(ideal body weight) for CVVHF, using 24 kg/m$^2$ as the ideal body mass index.

ml/24 h), oliguria (100 to 500 ml/24 h), and conserved urine output (>500 ml/24 h), respectively (38). From these data, the percentages of patients with 40% of the $f_uT_{>MIC}$, 100% of the $f_uT_{>MIC}$, and a trough (minimum) concentration ($C_{min}$)/MIC ratio equal to 5, according to meropenem clinical susceptibility breakpoints (39) (probability of target attainment [PTA]), were calculated.

## RESULTS

**Subjects and samples.** Thirty patients with septic shock and CRRT receiving meropenem were enrolled. Table 1 summarizes the patients' demographic and clinical characteristics. The median age was 66.5 years (range, 34 to 85 years), the median APACHE score on admission was 24 (range, 5 to 44), and the median SOFA score on the day of the study was 12 (range, 4 to 19). Sources of infection were intra-abdominal ($n = 13$ patients), respiratory ($n = 7$), bloodstream ($n = 4$), urinary tract ($n = 2$), and central nervous system ($n = 2$). It could not be determined in 2 patients. Twenty-six patients were prescribed CVVHDF, and 4 were prescribed CVVHF. Regarding the CRRT settings, the median intensity on the day of the study was 34.7 ml/kg/h (range, 18.7 to 60.1 ml/kg/h), and the median blood flow was 200 ml/min (range, 130 to 250 ml/min). In four patients, the filters were nonfunctional during a fraction of the sampling interval due to filter clotting and exchange: in one patient during antibiotic administration (30 min), in two patients for 1 h, and in one patient for 2.5 h. Visual inspection did not identify alterations in the meropenem concentration-over-time profiles of these individuals that could be attributed to these incidences. With regard to urine output on the day of the study, 14 patients were anuric (<100 ml/24 h), 11 patients were oliguric (100 to 500 ml/24 h), and 5 patients had preserved diuresis (>500 ml/24 h). The median urine output was 137.5 ml/24 h (range, 0 to 2,050 ml/24 h). For the index and validation data set, subjects were comparable in all characteristics except for vasopressor use at the time of the study: two of the patients in the validation data set were not on vasopressors when samples were collected. Concerning microbiology, positive cultures were obtained from 23 patients (76.7%). The most frequently isolated microorganisms were *Escherichia coli* (21.4%) and *Pseudomonas aeruginosa* (14.3%). Table 2 shows the meropenem MIC values for the 28 isolated strains.

Patients were prescribed meropenem at 500 mg q12h over 30 min ($n = 1$ subject); 500 mg q8h over 30 min ($n = 2$) or as a 3-h infusion ($n = 3$); 500 mg q6h as a 3-h infusion ($n = 1$); 1,000 mg q12h over 30 min ($n = 6$), as a 3-h infusion ($n = 1$), or as a 4-h infusion ($n = 1$); 1,000 mg q8h over 30 min ($n = 8$), as a 3-h infusion ($n = 5$), or as a 4 h-infusion ($n = 1$); or 2,000 mg q8h over 30 min ($n = 1$). The median duration of meropenem therapy was 10 days (range, 4 to 28 days).

**Population PK analysis.** The population PK model was developed using data from 24 subjects (124 samples). Data were better described by a one-compartment linear model characterized by population CL and *V* at steady state, with interindividual variability being incorporated into both PK parameters. Residual variability consisted of additive and proportional error. Goodness-of-fit plots showed good accordance between observed (OBS), predicted (PRED), and individual predicted (IPRED) concentrations (Fig. 1). The mean ± standard deviation of the CWRES was close to 0, and residual error plots did not show systematic deviations over time. The magnitude of ε shrinkage was 14.5%. The model

**TABLE 2** Isolated microorganisms and meropenem susceptibility by MIC

| Microorganism | No. of isolates | MIC (mg/liter) |
|---|---|---|
| *Burkholderia cepacia* | 1 | 1 |
| *Clostridium intestinale* | 1 | 2 |
| *Enterobacter cloacae* | 1 | 1 |
| *Enterococcus faecalis* | 2 | 2 |
| *Enterococcus faecalis* | 1 | ND[a] |
| *Enterococcus faecium* | 1 | 8 |
| *Enterococcus faecium* | 1 | ND |
| *Escherichia coli* | 6 | 2 |
| *Klebsiella pneumoniae* | 1 | 32 |
| *Listeria monocytogenes* | 1 | ND |
| *Moraxella catarrhalis* | 1 | 1 |
| *Pseudomonas aeruginosa* | 1 | 1 |
| *Pseudomonas aeruginosa* | 1 | 2 |
| *Pseudomonas aeruginosa* | 1 | 4 |
| *Pseudomonas aeruginosa* | 1 | 8 |
| *Salmonella enterica* serovar Enteritidis | 1 | 2 |
| *Serratia marcescens* | 1 | 2 |
| *Staphylococcus aureus* | 1 | 2 |
| *Staphylococcus epidermidis* | 3 | ND |
| *Stenotrophomonas maltophilia* | 1 | ND |

[a] ND, not determined.

parameters had moderate levels of η shrinkage for CL (33.3%) and *V* (20.9%).

Concerning the covariate analysis, residual diuresis significantly influenced meropenem CL, whereas CRRT intensity, filter downtime, blood flow, type of membrane, and albumin concentration did not. Concerning *V*, only total body weight on admission showed a significant impact on the parameter, whereas severity scores, age, and albumin concentration did not. The final model is displayed in Table 3 and summarized as follows: $CL = 3.68 + 0.22 \cdot (\text{residual diuresis}/100)$, and $V = 33.00 \cdot (\text{weight}/73)^{2.07}$, where CL is in liters per hour, residual diuresis is in milliliters and is normalized to the defined cutoff for anuria (38), *V* is in liters, and weight is normalized to the median weight of our patient population.

**Validation.** The results from the visual predictive check plot showed that practically all observations dropped into the 95% CI. The statistical distributions of the parameter estimates obtained from the bootstrap analyses are shown in Table 3. The median values of the parameters estimated from the bootstrap analyses were in good agreement with the NONMEM point estimates, and the 95% CIs were reasonably narrow, demonstrating satisfactory precision. With respect to external validation, mean bias and precision for the maximum *a posterior* Bayesian estimates (IPRED) were −0.45% and 3.98%, respectively, much better than those values obtained from the population PK model-based estimates (PRED), which were −11.79% and 25.3%, respectively (Fig. 2).

**Simulations.** PTA versus MIC profiles for simulations of different dosing regimens by residual diuresis and the percentage of the $f_u T_{>\text{MIC}}$ target are presented in Table 4. A PTA of >90% was considered satisfactory. For the attainment of the classical pharmacodynamic (PD) target for carbapenems, i.e., 40% of the

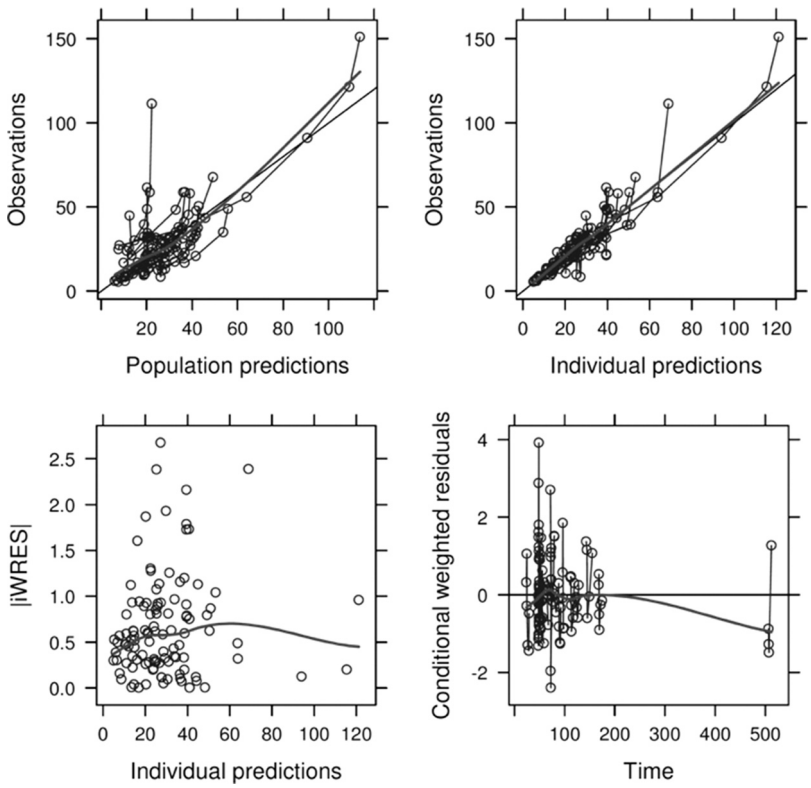


**FIG 1** Goodness-of-fit plots for the final population PK model. (Top left) Plot of observed meropenem concentrations versus population predictions. Solid thin line, line of identity; solid thick line, data smoother. (Top right) Plot of observations versus individual predictions. Solid thin line, line of identity; solid thick line, data smoother. (Bottom left) Plot of individual weighted residuals (iWRES) versus individual predictions. Thick line, data smoother. (Bottom right) Plot of conditional weighted residuals versus time. Solid thin line, zero slope line; solid thick line, data smoother. Predicted concentrations are in milligrams per liter; time is in hours.

**TABLE 3** Population pharmacokinetic estimates for the final model and bootstrap results[a]

| Parameter | Estimate (% RSE) | Median bootstrap value (95% CI) |
|---|---|---|
| CL (liters/h) | | |
| $\theta_{CL}$ | 3.68 (11) | 3.59 (2.90 to 4.46) |
| $\theta_{DIUR}$ | 0.22 (47) | 0.22 (0.003 to 0.44) |
| *V* (liters) | | |
| $\theta_V$ | 33.00 (10) | 31.94 (26.65 to 39.35) |
| $\theta_{WT}$ | 2.07 (24) | 2.27 (0.82 to 3.32) |
| IIV_CL (% CV) | 37 (27) | 37.15 (24.35 to 46.12) |
| IIV_V (% CV) | 45 (61) | 47.89 (12.25 to 65.04) |
| Additive residual error (mg/liter) | 0.0002 (42.76) | 0.0002 (0.0001 to 0.001) |
| Proportional residual error | −0.258 (10) | −0.25 (−0.35 to −0.17) |

[a] RSE, relative standard error; CL, total body clearance; *V*, apparent volume of distribution; $\theta_{CL}$, typical value for CL in the population; $\theta_{DIUR}$, multiplicative factor for the influence of residual diuresis on CL; $\theta_V$, typical value for *V* in the population; $\theta_{WT}$, power factor for the influence of weight on *V*; IIV_CL, interindividual variability associated with CL; IIV_V, interindividual variability associated with *V*; CV, coefficient of variation.

$f_uT_{>MIC}$, 500 mg q8h as a 30-min bolus would be sufficient for the treatment of bacteria with MICs even close to the susceptibility breakpoint (MICs ≤ 4 mg/liter), regardless of urine output. If 100% of the $f_uT_{>MIC}$ was chosen as the PD target, oligoanuric patients would require a dose of 500 mg q8h over 30 min for the treatment of susceptible bacteria (MICs < 2 mg/liter), while patients with diuresis of >500 ml/24 h may require the same dose given as a 3-h infusion. If bacteria with MICs close to the resistance breakpoint (MICs, 2 to 4 mg/liter) were to be treated with meropenem, a dose of 500 mg q6h would be necessary and would need to be administered as a 30-min bolus for oligoanuric patients and as a 3-h infusion for patients with preserved diuresis. For the attainment of more aggressive PD targets, such as five times the $C_{min}$/MIC ratio described by Li et al. (5), doses of 1,000 mg q8h as a 3-h infusion or higher would be required regardless of urine output. Table 5 summarizes the recommendations developed from these simulated data.

## DISCUSSION

To our knowledge, this is the largest multicenter study to have characterized the PKs of meropenem in critically ill patients with septic shock and CRRT. Our PK parameter estimates were in agreement with those from previous studies with a comparable population (15, 18).

Our main finding is the relationship existing among the 24-h urine output, the pathogen MIC, and meropenem dosing requirements for the maintenance phase of therapy, i.e., after 24 h of meropenem therapy and CRRT commencement. In general, antibiotic dose adjustments in critically ill patients are very challenging for the clinician because, unlike other drugs, such as vasopressors or sedatives, among others, the pharmacological effect of antibiotics is not immediately evident but requires a certain period of time, even days, to be visible. For critically ill patients with septic shock and a CRRT requirement, detection of the pharmacological effect of antibiotics is even more challenging due to all the PK changes driven by critical illness and the use of extracorporeal devices (6). In spite of this difficulty, the attainment and maintenance of therapeutic concentrations are crucial, as they have an impact on both clinical outcomes and the development of bacterial resistances. In this context, we have identified that consideration of residual diuresis might be advantageous for meropenem maintenance dose and infusion time adjustment on the basis of the MIC of the pathogen. For the attainment of a PD target of 100% of the $f_uT_{>MIC}$, fixed doses would be required, depending on the MIC of the bacteria, but the infusion time would depend on residual diuresis: oligoanuric patients would benefit from a 30-min bolus, while a 3-h extended infusion would be more appropriate for those patients with preserved diuresis. One may hypothesize that residual diuresis may influence meropenem re-

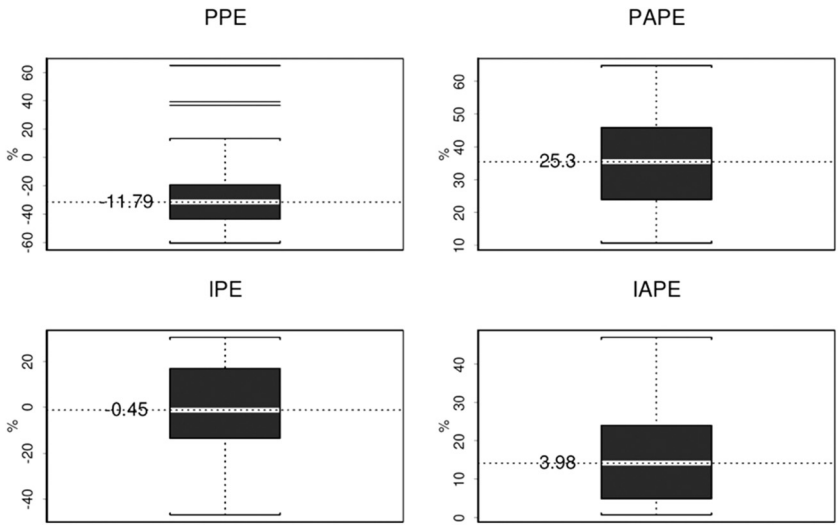


**FIG 2** Bias and precision for model estimates for external validation. Box plots of the population prediction error (PPE), population absolute prediction error (PAPE), individual prediction error (IPE), and individual absolute prediction error (IAPE) are shown. The white band in each error box marks the 50th percentile, and the value is presented; the box boundaries are at the 25th and 75th percentiles, and the limits of the whiskers are at the 10th and 90th percentiles. In the top left panel, lines outside the 10th and 90th percentiles represent the outliers from the model estimates for external validation.

**TABLE 4** PTA by MIC for simulations of different dosing regimens of meropenem stratified by residual diuresis and pharmacodynamic target[a]

| Dose and residual diuresis | 30-min bolus | | | | 3-h infusion | | | |
|---|---|---|---|---|---|---|---|---|
| | | PTA (%) | | | | PTA (%) | | |
| | MIC (mg/liter) | 40% of the $f_uT_{>MIC}$ | 100% of the $f_uT_{>MIC}$ | 5 × 100% of the $f_uT_{>MIC}$ | MIC (mg/liter) | 40% of the $f_uT_{>MIC}$ | 100% of the $f_uT_{>MIC}$ | 5 × 100% of the $f_uT_{>MIC}$ |
| 500 mg q8h | | | | | | | | |
| Anuria (<100 ml/24 h) | 0.5 | 100 | 99.3 | 92.9 | 0.5 | 100 | 99.9 | 97.9 |
| | 1 | 100 | 98.4 | 66.1 | 1 | 100 | 99.9 | 80.4 |
| | 2 | 99.9 | 94.4 | 6.6 | 2 | 100 | 97.5 | 15.1 |
| | 4 | 98.4 | 74.0 | 0.2 | 4 | 99.3 | 85.8 | 0.2 |
| Oliguria (100–500 ml/24 h) | 0.5 | 100 | 98.6 | 88.2 | 0.5 | 100 | 99.9 | 93.7 |
| | 1 | 100 | 96.1 | 50.2 | 1 | 100 | 99.2 | 68.5 |
| | 2 | 100 | 89.9 | 4.1 | 2 | 100 | 94.5 | 8.2 |
| | 4 | 98.1 | 62.0 | 0.9 | 4 | 99.5 | 76.3 | 0.2 |
| Preserved diuresis (>500 ml/24 h) | 0.5 | 100 | 96.9 | 76.1 | 0.5 | 100 | 98.5 | 88.5 |
| | 1 | 100 | 92.1 | 34.3 | 1 | 100 | 97.3 | 51.2 |
| | 2 | 99.9 | 79.9 | 1.8 | 2 | 100 | 90.8 | 3.4 |
| | 4 | 99.3 | 46.5 | 0 | 4 | 100 | 64.2 | 0 |
| 500 mg q6h | | | | | | | | |
| Anuria (<100 ml/24 h) | 0.5 | 100 | 99.9 | 98.9 | 0.5 | 100 | 100 | 99.8 |
| | 1 | 100 | 99.6 | 87.0 | 1 | 100 | 100 | 95.5 |
| | 2 | 100 | 99.2 | 23.2 | 2 | 100 | 99.9 | 37.5 |
| | 4 | 100 | 95.1 | 0.3 | 4 | 100 | 98.8 | 1.2 |
| Oliguria (100–500 ml/24 h) | 0.5 | 100 | 99.7 | 97.4 | 0.5 | 100 | 100 | 98.7 |
| | 1 | 100 | 99.2 | 80.4 | 1 | 100 | 99.7 | 92.6 |
| | 2 | 99.9 | 98.7 | 14.4 | 2 | 100 | 99.2 | 26.2 |
| | 4 | 99.8 | 90.9 | 0.2 | 4 | 100 | 97.0 | 0.6 |
| Preserved diuresis (>500 ml/24 h) | 0.5 | 100 | 99.5 | 93.2 | 0.5 | 100 | 100 | 98.0 |
| | 1 | 100 | 98.7 | 62.5 | 1 | 100 | 99.7 | 83.9 |
| | 2 | 99.9 | 95.7 | 6.0 | 2 | 100 | 98.8 | 15.2 |
| | 4 | 99.7 | 77.3 | 0 | 4 | 100 | 93.5 | 0 |
| 1,000 mg q8h | | | | | | | | |
| Anuria (<100 ml/24 h) | 0.5 | 100 | 99.7 | 97.7 | 0.5 | 100 | 99.9 | 99.0 |
| | 1 | 100 | 99.5 | 93.1 | 1 | 100 | 99.9 | 96.8 |
| | 2 | 100 | 98.5 | 64.5 | 2 | 100 | 99.3 | 80.7 |
| | 4 | 99.9 | 93.3 | 7.4 | 4 | 100 | 97.4 | 13.4 |
| Oliguria (100–500 ml/24 h) | 0.5 | 100 | 99.9 | 97.6 | 0.5 | 100 | 100 | 98.8 |
| | 1 | 100 | 99.1 | 88.6 | 1 | 100 | 99.8 | 94.9 |
| | 2 | 100 | 97.8 | 51.1 | 2 | 100 | 98.9 | 69.9 |
| | 4 | 99.9 | 90.1 | 3.4 | 4 | 100 | 95.2 | 9.9 |
| Preserved diuresis (>500 ml/24 h) | 0.5 | 100 | 98.6 | 90.9 | 0.5 | 100 | 99.6 | 97.2 |
| | 1 | 100 | 97.1 | 75.6 | 1 | 100 | 99.1 | 88.3 |
| | 2 | 100 | 92.4 | 32.6 | 2 | 100 | 97.6 | 50.8 |
| | 4 | 99.8 | 80.7 | 1.4 | 4 | 100 | 90.3 | 3 |

[a] Shaded areas correspond to a PTA of ≥90%.

quirements because a given percentage of the administered dose is eliminated with the urine. Conversely, for the attainment of the classical PD target for carbapenems (40% of the $f_uT_{>MIC}$), a standard dose of 500 mg q8h as a bolus over 30 min would be sufficient for all cases. Further, for the attainment of a more aggressive target, such as a $C_{min}$/MIC ratio of 5, doses of 1,000 mg q8h as a 3-h infusion or higher would be required. Of note, empirical dosing on the first day would still need to be made on the basis of the

**TABLE 5** Summary of meropenem maintenance dosing recommendations based on the results of the present study

| PD target | Pathogen MIC (mg/liter) | Dose recommendation |
|---|---|---|
| 40% of the $f_uT_{>MIC}$ | ≤4 | 500 mg q8h as a 30 min-bolus for all urine outputs |
| 100% of the $f_uT_{>MIC}$ | ≤2 | 500 mg q8h as a 30-min bolus for oligoanuria, 500 mg q8h as a 3-h infusion for preserved diuresis |
| | 2–4 | 500 mg q6h as a 30-min bolus for oligoanuria, 500 mg q6h as a 3-h infusion for preserved diuresis |
| $C_{min}$/MIC = 5 | ≤1 | 1,000 mg q8h as a 3-h infusion for all urine outputs |

predicted $V$ and local antibiogram data, as the use of the 24-h urine output measure can have a meaningful impact only with empirical dosing after 24 h, i.e., during the maintenance phase of therapy.

It is important to highlight that we have principally based our empirical dosing recommendations on targeting of the 100% of the $f_uT_{>MIC}$ rather than 40% of the $f_uT_{>MIC}$ described in the classical studies (3). We believe that such a thoughtful pharmacodynamic target is more recommendable for our patient population for several reasons. First, emerging evidence has associated a higher percentage of the $f_uT_{>MIC}$ with better outcomes (4, 5). For instance, Li et al. reported that trough concentrations higher than 5 times the MIC of the pathogen ($C_{min}$/MIC ratio = 5) were associated with better clinical and microbiological success rates (5). Also, Roberts et al. found that a higher percentage of the time that the concentration is greater than the MIC ($T_{>MIC}$) had a tendency to better the odds of survival compared to those with a lower percentage of the $T_{>MIC}$ (odds ratios, 1.02 [95% CI, 1.01 to 1.04] for a $T_{>MIC}$ of 50% and 1.56 [95% CI, 1.15 to 2.13] for a $T_{>MIC}$ of 100%), even though these odds data were not statistically compared (4). Further, all this evidence is based on plasma concentrations, but it is well-known that critically ill patients with severe infections exhibit microcirculatory alterations that impair the tissue distribution and lead to a lower percentage of the $f_uT_{>MIC}$ at the target site. This was shown in a nice study by Varghese et al., who reported that the tissue concentrations of meropenem in critically ill patients with CVVHDF accounted for a median of 60 to 70% of the plasma concentrations (18), which may be even lower in patients with septic shock. Due to the severity of the sickness in patients with septic shock, we believe that more aggressive pharmacodynamic targets should be preferred for ensuring early and adequate antimicrobial therapy. We also report the dosing recommendations for the attainment of a more ambitious target that has been associated with better outcomes in patients treated with meropenem ($C_{min}$/MIC ratio = 5) (5). However, we believe that such an ambitious target is probably too aggressive, and the risks of such high concentrations may outweigh the potential benefits. Also, we arbitrarily accepted a ~90% PTA to be satisfactory for our dose recommendations, as to our knowledge the optimal PTA breakpoint is still a matter of debate (40).

Interestingly, our model failed to identify CRRT intensity to be a significant modifier of meropenem CL. We initially expected that CRRT intensity would have a significant effect on meropenem CL according to the available literature, which reports differential meropenem CLs when different intensities are used (12, 41). However, exploratory and regression analyses on the effects of covariates on individual CL did not show any visual or statistical trend between intensity and the estimates of individual CL, which may lead to the hypothesis that even the lowest CRRT intensities studied may be enough to maximize meropenem clearance and that higher intensities may add little to total meropenem CL. This explanation is consistent with data from Roberts et al., who also failed in the identification of intensity as a meropenem CL modifier (42). Similarly, we did not observe differences between CRRT techniques, likely because of the underrepresentation of CVVHF (4 out of 30 patients) in our study population. Controversy exists on the impact of CRRT modality on drug CL, as different meropenem CLs between CRRT methods have been reported by some researchers (12), while others have not found any difference (15). Also, we did not find differences in CL between patients according to the different types of membranes used in the various hospitals (1.5-$m^2$ AN69ST in HJ23, 0.9-$m^2$ AN69 in CSUPT and HCB). Importantly, the presence of polyethylenimine and heparin on the membrane surface (AN69ST) did not significantly influence CL, suggesting that meropenem adsorption to the surface-treated filter may not be a major elimination pathway, unlike for other molecules, like colistin (43).

A strong point of our population PK model is that it has been externally validated with new subjects. Before carrying out Monte Carlo simulations to assist with recommending any dosage regimen for a specific patient population, it should be previously established that the population PK model is predictive (34). However, despite the paramount importance of this step, it has been estimated that only 7% of the population PK models are externally validated (44). External validation showed that, by means of bias and precision, our population PK model had mean values within good limits, which supported its utility for undertaking dosing simulations.

Our main limitation was not measuring meropenem urinary and ultrafiltrate concentrations, and so we could not estimate either the sieving coefficient, which has already been well described to be about 1 for meropenem using AN69 membranes (8, 9, 19, 45), or truly quantify the degree of CL during CRRT. Furthermore, we included only patients with septic shock and renal failure requiring CRRT; therefore, our conclusions cannot be extrapolated to other patient populations, like patients without septic shock, without renal failure, with intermittent RRT, or with other extracorporeal blood purification therapies. Also, due to the low level of representation of CVVHF in the patient cohort, our conclusions may be applied only to patients receiving CVVHDF. Finally, the measurement of residual diuresis was performed by the nursing staff as part of their clinical routine, which might not be optimal for obtaining the exact volume of urine but is certainly sufficient for classifying the patients as oligoanuric or as having preserved diuresis. Conversely, the major strengths of this study are its multicenter nature, its large sample size (30 patients), and the fact that the population PK model has been externally validated. Moreover, our recommendations are based on an easy-to-measure and inexpensive clinical parameter such as residual diuresis; hence, our results can easily be implemented in daily care.

**Conclusions.** In conclusion, we present the results of the largest multicenter pharmacokinetic study of meropenem prescribed to critically ill patients with septic shock and CRRT. Our population PK model successfully identified residual diuresis to be a modifier of total meropenem CL. CRRT intensity did not significantly modify meropenem CL, for which dose adjustments based on intensity seem to be unnecessary. Given a certain MIC, simulations showed that meropenem dose titration considering residual diuresis was advantageous for the attainment of 100% of the $f_uT_{>MIC}$ as a PD target. If classical PD targets (40% of the $f_uT_{>MIC}$) were targeted, a standard dose of 500 mg q8h as a 30-min bolus would be sufficient, regardless of urine output.

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We have no conflicts of interest to declare.

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# Piperacillin population pharmacokinetics in critically ill patients with multiple organ dysfunction syndrome receiving continuous venovenous haemodiafiltration: effect of type of dialysis membrane on dosing requirements

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**Objectives:** This multicentre study aimed to describe the pharmacokinetics (PK) of piperacillin in critically ill patients with multiple organ dysfunction syndrome (MODS) receiving continuous venovenous haemodiafiltration (CVVHDF), to identify the sources of PK variability and evaluate different dosing regimens to develop recommendations based on clinical parameters.

**Patients and methods:** Nineteen patients with MODS and CVVHDF receiving piperacillin/tazobactam were enrolled from three tertiary hospitals (95 plasma samples). Population PK modelling and Monte Carlo simulations were performed using NONMEM v7.3®.

**Results:** Patients' median age was 70 years (range 39–82), median weight was 80 kg (45–129), median APACHE II score at admission was 21 (13–33) and median SOFA score on the day of study was 11 (8–21). The final population PK model was characterized by CL (L/h) = 6.11 * [weight (kg)/80]$^{1.39}$ * $CL_{MEMB}$. If membrane = 1.5 $m^2$ AN69ST, $CL_{MEMB}$ = 1; if membrane = 0.9 $m^2$ AN69, $CL_{MEMB}$ = 0.51. Monte Carlo simulations showed that: (i) to maintain unbound piperacillin concentrations above the MIC for the bacteria for 100% of dosing interval *T* (100%$f_uT_{>MIC}$), patients receiving CVVHDF with 1.5 $m^2$ AN69ST membranes required doses of 4000 mg q8h for the treatment of bacteria with a susceptibility to piperacillin close to the clinical breakpoint (MIC = 8–16 mg/L) (2000 mg q8h was sufficient for patients with CVVHDF using 0.9 $m^2$ AN69 membranes); and (ii) for the treatment of bacteria with high susceptibility to piperacillin (MIC <4 mg/L) or for the attainment of a more traditional pharmacodynamic target (50%$f_uT_{>MIC}$), 2000 mg q8h sufficed regardless of type of membrane and body weight.

**Conclusions:** Our results suggest that type of membrane and body weight should be considered for piperacillin dose titration in critically ill patients with MODS and CVVHDF requirement.

## Introduction

Piperacillin is an extended-spectrum β-lactam antibiotic belonging to the penicillin family. Combined with the β-lactamase inhibitor tazobactam, it exhibits broad activity against several species of Gram-positive and -negative pathogens, including *Pseudomonas aeruginosa* and anaerobes. For this reason, piperacillin is one of the most used antipseudomonal agents in the

empirical therapy of patients with severe infections.[1] Piperacillin is a hydrophilic antibiotic, with low molecular weight (517.5 g/mol) and moderate protein binding (20%–30%). These characteristics make piperacillin a drug cleared mainly by renal excretion as unchanged drug (68%), with biliary excretion as a secondary elimination pathway.[2] Likewise, piperacillin is a drug cleared by renal replacement therapies (RRTs), as low molecular weight, hydrophilicity and low protein binding are the main determinants of RRT elimination.[3] Regarding its pharmacodynamics, piperacillin exhibits maximal killing activity when its unbound concentration at the site of infection is maintained above the MIC for the pathogen during a certain period of the dosing interval ($\%f_uT_{>MIC}$), which for penicillins has been defined to be ~50% in *in vitro* and *in vivo* animal studies.[4]

In critically ill patients, the presence of multiple organ dysfunction syndrome (MODS) including septic shock and acute kidney injury (AKI) requiring RRT has been shown to dramatically decrease survival, leading to unacceptable mortality rates (~60%).[5] In this subgroup of patients with very high levels of sickness severity, effective antibiotic therapy may be even more important to clinical outcome. However, they represent one of the most complex patient groups to correctly dose. This is due to the observed variations in antibiotic pharmacokinetics (PK) caused by the pathophysiology of MODS and medical management, including technical factors relating to the RRT modality itself.[6] Particularly, continuous venovenous haemodiafiltration (CVVHDF) is one the most frequently used modalities of RRT in the early phases of AKI in the context of MODS, mainly due to patients' haemodynamic instability. This modality has the characteristic of using convective and diffusive methods for solute and fluid elimination.

Owing to its clinical relevance, previous studies have documented piperacillin PK in critically ill patients with MODS and CVVHDF requirement.[7–10] These data have led to different dose recommendations (ranging between 8 g and 16 g/day)[3] due to the variability observed in piperacillin PK, especially in CL. However, the causes of variability reported in those studies have not been sufficiently investigated. The hypothesis of this study was that this variability observed in piperacillin PK could be explained by clinical and demographic characteristics.

Consequently, our aims were: (i) to describe the PK of piperacillin in critically ill patients with MODS receiving CVVHDF; (ii) to identify the sources of PK variability in this population; and (iii) to evaluate different dosing regimens to develop recommendations that maximize piperacillin exposure based on clinical parameters.

## Patients and methods

### Patients

We conducted a prospective, multicentre, open-label PK study in the multidisciplinary ICUs of the tertiary hospitals Corporació Sanitària Universitària Parc Taulí of Sabadell (CSUPT), Clínic of Barcelona (HCB) and Joan XXIII (HJ23) of Tarragona during the period January 2012–May 2014. Authorization for the study was granted by the Spanish Regulatory Medicines Agency (code IEM-ANT-2012-1) and ethics approval was obtained from the local ethics committees. Written informed consent was obtained from each patient's legally authorized representative. Inclusion criteria were age ≥18 years, MODS including septic shock diagnosed by the Surviving Sepsis Campaign guidelines criteria,[11] AKI requiring CVVHDF and clinical indication for piperacillin. The major exclusion criterion was chronic renal disease requiring dialysis.

### Demographic and clinical data

Patients' demographic and clinical data were collected and registered in a database only available to the study investigators. Age, weight, height, sex, site of infection, serum biochemistry, organ support requirement, CVVHDF settings,[12] filter downtime, residual diuresis, severity scores at admission (APACHE II)[13] and on the day of study (SOFA),[14] clinically significant bacterial isolates and MICs of piperacillin, days of antibiotic therapy and hospital survival were the main variables recorded.

### Continuous RRT (CRRT)

The CVVHDF systems used were from Prisma® (Hospal, France). The filters used were 0.9 $m^2$ AN69 acrylonitrile and sodium methallyl sulfonate copolymer filter (PrismaFlex® M100, Gambro Hospal, Switzerland) (CSUPT and HCB) and 1.5 $m^2$ AN69ST acrylonitrile and sodium methallyl sulfonate copolymer filter precoated with heparin and polyethyleneimine (PrismaFlex® ST150, Hospal, France) (HJ23). All CVVHDF settings were prescribed at the discretion of the treating physician.

### Drug dosing

Piperacillin/tazobactam dose and infusion time were at the discretion of the treating physician. It was administered through a separate lumen of a venous catheter using free-fall bolus systems or volumetric infusion pump controllers as required.

### Blood sampling

Five millilitres of arterial blood per sample were collected after ≥24 h of CVVHDF and piperacillin/tazobactam therapy. For bolus sampling, six samples were collected at 10 min predose, at 0 min, 15 min, 60 min and between 3 and 6 h after the end of the infusion and just before the next dose. For extended infusion (3 or 4 h) sampling, five samples were collected at 10 min predose, at 0, 60 and 120 min after the end of the infusion and just before the next dose. After being drawn, blood samples were immediately put into an ice bath at 0–4°C. Then, within 1 h of collection, plasma was obtained by centrifugation at 3000 rpm at 0–4°C for 10 min and frozen at −80°C for its posterior analysis.

### LC-MS analysis

Total piperacillin concentration in plasma was measured using LC coupled to tandem MS (1200 HPLC binary pump, Agilent Technologies/API 4000 AB SCIEX MS) in an external laboratory using a validated method. The method was linear over a range of piperacillin concentrations (1.5–400 mg/L). Within- and between-run precision and accuracy showed adequate results (coefficients of variation ≤10%) according to EMA guidelines.[15]

### Statistical analysis

Statistical analysis was performed using R for Macintosh v3.0.2 (R Foundation for Statistical Computing). Results are expressed as absolute and relative frequencies for categorical variables and as median (range) for continuous variables.

### PK modelling

Non-linear effects modelling was performed using NONMEM v7.3 (Icon Development Solutions, USA)[16] and guided using XPose v4.0 following a three-step strategy: (i) basic model selection; (ii) covariate selection; and (iii) validation.[17,18] The first-order conditional estimation method with interaction was used for parameter estimation. Interindividual variability (IIV) was modelled as log-normal after being tested for log-normality. Additive, proportional and combined error models were tested for residual variance. Goodness of fit for a model was assessed by: (i) significant

decreases in −2 log-likelihood of the objective function value (OFV); (ii) plots of population and individual Bayesian predicted versus observed concentrations (OBS) and of conditional weighted residuals (CWRES) versus OBS and time;[19] and (iii) improvements in the precision of parameters estimation (% of standard error).

Afterwards, several demographic and clinical variables were tested for inclusion as covariates in the basic population PK model. Each covariate was retained if it led to an improved fit evaluated by: biological plausibility; visual inspection of the above-mentioned graphs; improvement of the precision in parameter estimates; and changes in the OFV. The extent of Bayesian shrinkage, as a measure of model overparameterization, was calculated for each PK parameter with associated IIV variability.[20]

### Model evaluation

Internal validation of the PK model was performed by graphical and statistical methods, including prediction-corrected visual predictive checks.[21] The bootstrap resampling technique (500 replicated datasets) was used to build CIs of PK parameters to assess their stability and evaluate the robustness of the final model.[22]

### Dosing simulations

We used Monte Carlo simulations for simulating two bolus (4000 mg and 2000 mg q8h over 30 min) and two extended infusion (4000 mg and 2000 mg q8h over 4 h) regimens. The covariates included in the final population PK model were considered in these simulations. Each simulation generated concentration–time profiles for 1000 subjects per dosing regimen using the final estimated population PK parameters. We applied 20% protein binding to the simulated concentrations to estimate unbound concentrations following the results shown by Wong *et al.*,[23] who described 17.5% protein binding of piperacillin at the trough time in patients receiving CRRT. Then, we calculated the percentages of patients with 50% and 100% $f_uT_{>MIC}$ from total and unbound concentrations according to the European clinical susceptibility breakpoints for piperacillin (PTA).[24]

## Results

Nineteen patients treated with CVVHDF and piperacillin/tazobactam were enrolled. Table 1 summarizes patients' demographic and clinical characteristics. Patients' median age was 70 years (range 39–82) and 21.1% were females. At admission, median APACHE II score was 21 (13–33) and, on the day of sampling, median SOFA score was 11 (8–21). Sources of infection were intra-abdominal ($n=7$), respiratory ($n=6$), urinary tract ($n=2$), skin and soft tissue ($n=2$), bloodstream ($n=1$) and joint ($n=1$). All patients presented MODS and required vasoactive and respiratory support at admission and on the day of sampling. Regarding CVVHDF settings, median intensity was 32.8 mL/kg/h (20.2–45.9) and median blood flow was 200 mL/min (120–280). Regarding membrane type, 9 patients received CVVHDF using 0.9 $m^2$ AN69 filters, while the other 10 used 1.5 $m^2$ AN69ST filters. Samples were drawn between 1 and 4 days after the initiation of CVVHDF therapy (median 2 days). All patients received piperacillin (tazobactam) at the following doses: 2000 (250) mg q8h over a 3 h extended infusion ($n=1$); 2000 (250) mg q6h over a 30 min bolus ($n=2$); 2000 (250) mg q6h over a 3 h extended infusion ($n=1$); 3000 (375) q8h over a 30 min bolus ($n=1$); 4000 (500) mg q8h over a 30 min bolus ($n=3$); 4000 (500) mg q8h over a 4 h infusion ($n=5$); 4000 (500) mg q6h over a 30 min bolus ($n=3$); 4000 (500) mg q6h over a 3 h infusion ($n=2$) and 4000 (500) mg q6h over a 4 h infusion ($n=1$). Median duration of piperacillin therapy was 10 days (range 3–27). Concerning microbiology, clinically relevant positive cultures were obtained from 14 patients (73.7%), accounting for 20 isolated strains (Table 2). The most frequent pathogens were *Pseudomonas aeruginosa* ($n=5$, 30%) and *Escherichia coli* ($n=5$, 25%) followed by *Enterobacter cloacae* ($n=3$, 15%). MICs were ≥8 mg/L for all bacteria for which MIC was determined, which is close to the susceptibility breakpoint of piperacillin established by EUCAST (8–16 mg/L).[24]

**Table 1.** Demographics and clinical characteristics of the enrolled subjects

| Variable | Values ($n=19$) |
|---|---|
| Age (years) | 70 (39–82) |
| Females | 4 (21.1%) |
| Weight (kg) | 80 (45–129) |
| Patients (HCB/CSUPT/HJ23) | 2/7/10 |
| APACHE score[a] | 21 (13–33) |
| SOFA score[b] | 11 (8–21) |
| Hepatic impairment | 2 (10.5%) |
| Vasopressors[b] | 19 (100%) |
| Mechanical ventilation[b] | 19 (100%) |
| Ultrafiltrate flow rate (mL/h)[b] | 1600 (850–2000) |
| Dialysate flow rate (mL/h)[b] | 1000 (500–1600) |
| CVVHDF intensity[b] (mL/kg/h) | 32.8 (20.2–45.9) |
| Blood flow[b] (mL/min) | 200 (120–280) |
| Type of filter (AN69/AN69ST) | 9/10 |
| Albumin[b] (g/L) | 21.1 (14.2–36) |
| Urea[b] (mg/dL) | 70 (19.5–182) |
| Creatinine[b] (mg/dL) | 1.2 (0.2–3.5) |
| Diuresis[b] (mL/24 h) | 90 (0–1350) |
| Survival | 4 (21.1%) |

Data are expressed as median (range) or as count (%). CVVHDF intensity was defined as (filtrate + dialysate flow rate)/(ideal body weight), using 24 kg/$m^2$ as ideal BMI. Hepatic impairment was defined as liver function tests >2× upper limit of normal.
[a]Measured on admission.
[b]Measured on the day of the study.

**Table 2.** Isolated microorganisms and piperacillin susceptibility by MIC

| Microorganism | Number of isolates | MIC (mg/L) |
|---|---|---|
| *Bacillus* sp. | 1 | 8 |
| *Burkholderia cepacia* | 2 | 8 |
| *Enterobacter cloacae* | 1 | ND |
| *Enterobacter cloacae* | 2 | 8 |
| *Enterococcus faecium* | 1 | 64 |
| *Escherichia coli* | 5 | 8 |
| *Klebsiella pneumoniae* | 1 | 64 |
| *Pseudomonas aeruginosa* | 2 | 8 |
| *Pseudomonas aeruginosa* | 2 | 16 |
| *Pseudomonas aeruginosa* | 1 | 64 |
| *Staphylococcus aureus* | 1 | 8 |
| *Staphylococcus epidermidis* | 1 | 64 |

ND, not determined.

### *Population PK analysis*

We used the concentration points obtained from the 95 plasma samples to build the population PK model. The model that described the data best was a two-compartment linear model characterized by population CL, $V_1$ (central volume), $V_2$ (peripheral volume) and Q (intercompartmental CL) at steady-state, with IIV incorporated into CL and $V_1$. Residual variability was modelled as a combination of additive and proportional error. Figure 1 depicts the goodness-of-fit plots of the final model. The mean and standard deviation of the CWRES was close to zero and did not show systematic deviations over time. The value of ε-shrinkage was 18.4% and the PK parameters had reasonably low levels of η-shrinkage for CL (3.6%) and $V_1$ (15.5%).

The covariate analysis identified type of membrane (MEMB) and total body weight (WT) as significant modifiers of CL. Other variables such as CVVHDF intensity [defined as (filtrate + dialysate flow rate)/(ideal body weight), using 24 kg/m$^2$ as ideal BMI], blood flow, residual diuresis and albumin were also tested, but did not have a significant impact on the IIV of this parameter. Regarding $V_1$, several covariates were tested, including SOFA and APACHE scores and albumin, but none of them improved the parameter variability. The final model is displayed in Table 3 and summarized as follows:

$$\mathrm{CL(L/h)} = 6.11 * \left(\frac{\mathrm{WT(kg)}}{80}\right)^{1.39} * (\mathrm{CL_{MEMB}})$$

$$\text{If MEMB} = 1.5\,\mathrm{m^2}\ \text{AN69ST},\ \mathrm{CL_{MEMB}} = 1$$

$$\text{If MEMB} = 0.9\,\mathrm{m^2}\ \text{AN69}, \mathrm{CL_{MEMB}} = 1 - 0.49 = 0.51$$

where WT is normalized to the median WT of our patient population (80 kg) and $\mathrm{CL_{MEMB}}$ is a multiplicative factor that depends on the type of dialysis membrane used.

### *Validation*

The prediction-corrected visual predictive check plot shows that practically all observations fell within the 95% CI, which suggests that the model has a good predictive performance (Figure 2). The statistical distributions of the parameter estimates obtained from the bootstrap analyses are shown in Table 3. It can be observed that median parameter estimations (95% CI) obtained by bootstrap are in accordance with NONMEM point parameter estimations.

### *Simulations*

After applying a 20% protein binding on the simulated concentrations, we calculated the PTA by MIC profiles for Monte Carlo simulations of four dosing regimens stratified by WT and MEMB (Table 4). We also calculated the PTA by MIC of total piperacillin concentrations (data not shown). A PTA of ≥90% was considered satisfactory. For a pharmacodynamic target of 100%$f_uT_{>\mathrm{MIC}}$, patients receiving CVVHDF using 1.5 m$^2$ AN69ST membranes required piperacillin doses of 4000 mg q8h for the empirical treatment of bacterial strains with a susceptibility to piperacillin close to the clinical breakpoint (MIC = 8–16 mg/L; most of our clinical isolates), whereas 2000 mg q8h was sufficient for patients with CVVHDF using 0.9 m$^2$ AN69 membranes. For the treatment of bacteria with high susceptibility to piperacillin (MIC <4 mg/L) or for the attainment of a more traditional pharmacodynamic target (i.e. 50%$f_uT_{>\mathrm{MIC}}$), 2000 mg q8h of piperacillin sufficed regardless of the type of membrane and patient weight. We obtained the same conclusions when we calculated the PTA by MIC using total piperacillin concentrations, therefore measurement of unbound concentrations seems unnecessary for piperacillin in this patient population. Table 5 summarizes dose recommendations by pharmacodynamic target, pathogen MIC, type of membrane used and patient weight.

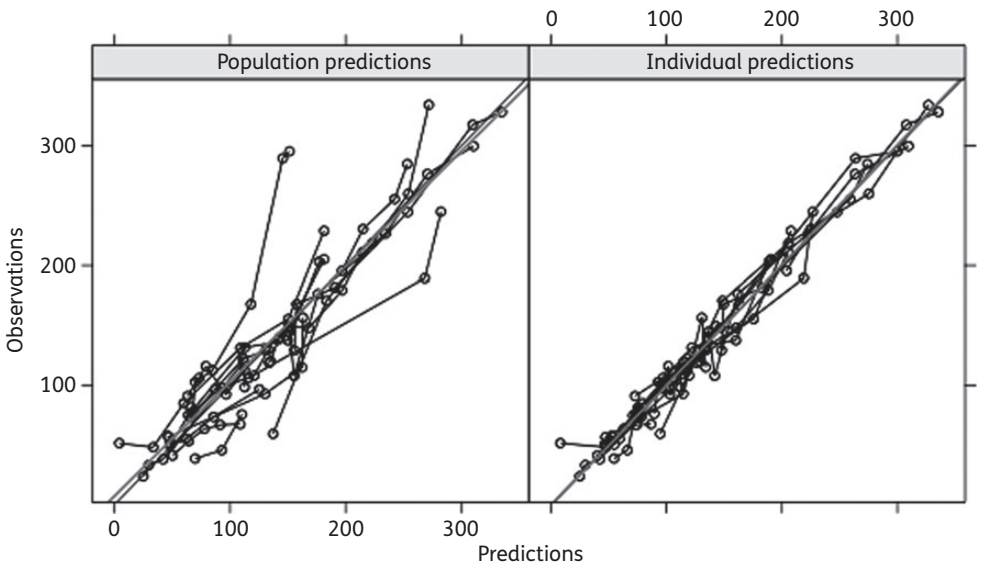


**Figure 1.** Goodness-of-fit plots for the final population PK model. Left panel, plot of observed piperacillin concentrations versus population predictions; solid black line, line of identity; solid grey line, smoothed data. Right panel, plot of observations versus individual predictions; solid black line, line of identity; solid grey line, smoothed data.

**Table 3.** Population PK estimates for the final model and bootstrap results

| Parameter | Estimate (RSE %) | Bootstrap median (5%–95% percentile) |
|---|---|---|
| CL (L/h) | | |
| $\theta_{CL}$ | 6.11 (8.2) | 6.19 (4.92–7.36) |
| $\theta_{MEMB}$ | −0.49 (13.3) | −0.52 (−0.62 to −0.37) |
| $\theta_{WT}$ | 1.39 (19.9) | 1.50 (1.15–1.95) |
| V (L) | | |
| $\theta_{V1}$ | 19.4 (14.2) | 19.0 (16.84–27.36) |
| $\theta_{V2}$ | 12.9 (90.7) | 14.0 (−24.63–55.23) |
| Q (L/h) | | |
| $\theta_{Q}$ | 9.5 (41.8) | 12.6 (5.01–19.4) |
| IIV_CL (%) (CV%) | 17.54 (52.4) | 19.15 (5.2–24.9) |
| IIV_$V_1$ (%) (CV%) | 52.2 (120) | 56.7 (16.9–65.3) |
| Additive residual error (mg/L) | 13.3 (66) | 8.34 (2.72–22.48) |
| Proportional residual error | 0.06 (46) | 0.08 (0.03–0.12) |

RSE, relative standard error; CV, coefficient of variation; CL, total body clearance; $\theta_{CL}$, typical value for CL in the population; $\theta_{MEMB}$, additive factor for the influence of the AN69 membrane on CL; $\theta_{WT}$, power factor for the influence of weight on CL; V, apparent volume of distribution; $\theta_{V1}$, typical value for V in the central compartment in the population; $\theta_{V2}$, typical value for V in the peripheral compartment in the population; Q, intercompartmental CL; $\theta_{Q}$, typical value for Q in the population; IIV_CL, interindividual variability associated with CL; IIV_$V_1$, interindividual variability associated with $V_1$.

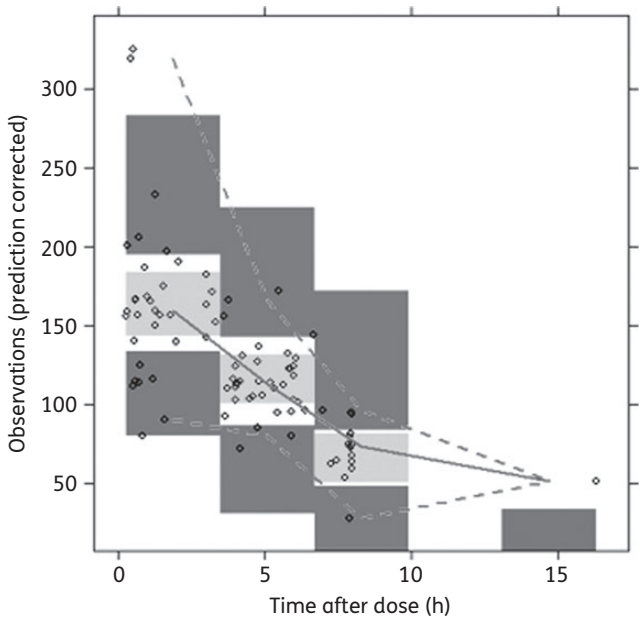


**Figure 2.** Prediction-corrected visual predictive check for the final population PK model. Fifth percentile and ninety-fifth percentile, dashed lines; fiftieth percentile, continuous line. Raw data are shown as empty circles.

## Discussion

Here, we present the results of the largest multicentre population PK study of piperacillin performed in critically ill patients with MODS requiring CVVHDF. The main finding of this study is the relationship existing between the type of membrane used for CVVHDF, the patient's weight and the pathogen's MIC on piperacillin dose requirements during the maintenance phase of therapy. The results of the simulations based on the population PK model show that consideration of the type of membrane (0.9 $m^2$ AN69 versus 1.5 $m^2$ AN69ST) and the patient's weight in piperacillin dose titration and infusion time is advantageous for the attainment of the pharmacodynamic target of 100%$f_uT_{>MIC}$ for a certain MIC (Table 5). To our knowledge, this is the first study that reports differential CL with the use of 1.5 $m^2$ AN69 filters surface-coated with heparin and polyethyleneimine (AN69ST) compared with non-surface-treated 0.9 $m^2$ AN69 filters. Our data show that, for a body weight of 80 kg (the median of our patient population), piperacillin CL is doubled when a 1.5 $m^2$ AN69ST filter is used compared with the CL for a 0.9 $m^2$ AN69 filter (6.11 versus 3.12 L/h, respectively). This finding is important because, to date, no available sepsis guidelines make distinctions in piperacillin dosing depending on the type of dialysis membrane used for CVVHDF.[11]

The recently launched AN69ST membranes are acrylonitrile and sodium methallyl sulfonate copolymer membranes with a surface treatment consisting of the grafting of a first layer with polyethyleneimine (positively charged) and a second layer of heparin (negatively charged) coated during manufacturing.[25] This coating enhances the adsorption properties of acrylonitrile because it makes the membrane surface polarity variable, with the main objective of adsorbing inflammatory molecules and waste products with molecular weights beyond the membrane cut-off.[25] This has been demonstrated with different inflammatory mediators including cytokines.[26,27] However, AN69ST membranes are non-selective for the adsorption of these inflammatory mediators and may also affect other circulating molecules such as drugs or oligoelements among others. This effect has been shown in small studies with polar antibiotics such as colistin,[28] but no extensive work has yet been performed under this hypothesis. Our results show that piperacillin CL is augmented when AN69ST filters are used for CVVHDF compared with non-coated AN69 filters. Based on the physicochemical proprieties of piperacillin, a molecule with both hydrogen bond donor and acceptor positions,[29] one could hypothesize that piperacillin CL is augmented when AN69ST filters are used due to partial adsorption to the polar coating. Nevertheless, it has to be highlighted that we studied two dialysis membranes with different surface area, i.e. 1.5 $m^2$ for AN69ST membranes versus 0.9 $m^2$ for AN69 membranes. Therefore, the membrane surface area might partially account for the differences in CL observed between the two membranes. However, similar values of CL (Keller *et al.* 2.83 L/h, Mueller *et al.* 2.82 L/h and Arzuaga *et al.* 3 L/h[30–32]) have been reported in studies that included similar populations that received CRRT with AN69 filters that had different membrane surface areas (0.43, 0.6 and 0.9 $m^2$, respectively). These piperacillin CL estimates are in accordance with our estimated CL using 0.9 $m^2$ AN69 membranes (3.12 L/h) and suggest that the membrane surface area may be a minor component of piperacillin CL.

Some other clinical variables were hypothesized to influence piperacillin PK according to the available literature[8,32,33] and hence were tested in the population PK model with unsuccessful results. Regarding residual diuresis, we expected it to be a significant modifier of piperacillin CL according to the results of previous studies.[32,33] For example, Asín-Prieto *et al.*[33] performed a

**Table 4.** PTA by MIC for a 50% and 100% $f_uT_{>MIC}$ ($PTA_{50}$ and $PTA_{100}$, respectively) for simulations of different dosing regimens of piperacillin and stratified by weight and type of membrane

| | 30 min bolus | | | | | | 4 h extended infusion | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | AN69 | | | AN69ST | | | AN69 | | | AN69ST | | |
| Weight | MIC (mg/L) | $PTA_{50}$ (%) | $PTA_{100}$ (%) | MIC (mg/L) | $PTA_{50}$ (%) | $PTA_{100}$ (%) | MIC (mg/L) | $PTA_{50}$ (%) | $PTA_{100}$ (%) | MIC (mg/L) | $PTA_{50}$ (%) | $PTA_{100}$ (%) |
| 2000 mg q8h | | | | | | | | | | | | |
| 60 kg | 2 | 100 | 100 | 2 | 100 | 100 | 2 | 100 | 100 | 2 | 100 | 100 |
| | 4 | 100 | 100 | 4 | 100 | 100 | 4 | 100 | 100 | 4 | 100 | 100 |
| | 8 | 100 | 100 | 8 | 100 | 99.9 | 8 | 100 | 100 | 8 | 100 | 100 |
| | 16 | 100 | 99.9 | 16 | 99.9 | 58.0 | 16 | 100 | 100 | 16 | 100 | 93.1 |
| | 32 | 96.7 | 50.5 | 32 | 10.8 | 0 | 32 | 99.7 | 78.2 | 32 | 85.8 | 0.1 |
| 80 kg | 2 | 100 | 100 | 2 | 100 | 100 | 2 | 100 | 100 | 2 | 100 | 100 |
| | 4 | 100 | 100 | 4 | 100 | 99.2 | 4 | 100 | 100 | 4 | 100 | 100 |
| | 8 | 100 | 100 | 8 | 100 | 79.4 | 8 | 100 | 100 | 8 | 100 | 98.5 |
| | 16 | 100 | 96.1 | 16 | 90.5 | 2.2 | 16 | 100 | 100 | 16 | 99.9 | 25.3 |
| | 32 | 52.4 | 1.5 | 32 | 0 | 0 | 32 | 93.7 | 8.4 | 32 | 67.5 | 0.1 |
| 100 kg | 2 | 100 | 100 | 2 | 100 | 99.3 | 2 | 100 | 100 | 2 | 100 | 100 |
| | 4 | 100 | 100 | 4 | 100 | 83.2 | 4 | 100 | 100 | 4 | 100 | 98.6 |
| | 8 | 100 | 99.6 | 8 | 99.2 | 25.7 | 8 | 100 | 100 | 8 | 100 | 76.3 |
| | 16 | 99.8 | 51.9 | 16 | 35.9 | 0 | 16 | 100 | 90.5 | 16 | 99.5 | 1 |
| | 32 | 7.6 | 0 | 32 | 0 | 0 | 32 | 85.5 | 0 | 32 | 39.3 | 0 |
| 4000 mg q8h | | | | | | | | | | | | |
| 60 kg | 2 | 100 | 100 | 2 | 100 | 100 | 2 | 100 | 100 | 2 | 100 | 100 |
| | 4 | 100 | 100 | 4 | 100 | 100 | 4 | 100 | 100 | 4 | 100 | 100 |
| | 8 | 100 | 100 | 8 | 100 | 100 | 8 | 100 | 100 | 8 | 100 | 100 |
| | 16 | 100 | 100 | 16 | 100 | 99.9 | 16 | 100 | 100 | 16 | 100 | 100 |
| | 32 | 100 | 100 | 32 | 99.8 | 60.1 | 32 | 100 | 100 | 32 | 100 | 93.3 |
| 80 kg | 2 | 100 | 100 | 2 | 100 | 100 | 2 | 100 | 100 | 2 | 100 | 100 |
| | 4 | 100 | 100 | 4 | 100 | 100 | 4 | 100 | 100 | 4 | 100 | 100 |
| | 8 | 100 | 100 | 8 | 100 | 99.3 | 8 | 100 | 100 | 8 | 100 | 100 |
| | 16 | 100 | 100 | 16 | 100 | 80.3 | 16 | 100 | 100 | 16 | 100 | 98.1 |
| | 32 | 100 | 95.4 | 32 | 90.4 | 2.4 | 32 | 100 | 99.7 | 32 | 99.9 | 23.8 |
| 100 kg | 2 | 100 | 100 | 2 | 100 | 100 | 2 | 100 | 100 | 2 | 100 | 100 |
| | 4 | 100 | 100 | 4 | 100 | 98.8 | 4 | 100 | 100 | 4 | 100 | 100 |
| | 8 | 100 | 100 | 8 | 100 | 85.7 | 8 | 100 | 100 | 8 | 100 | 98.9 |
| | 16 | 100 | 99.4 | 16 | 98.9 | 27.2 | 16 | 100 | 100 | 16 | 100 | 71.5 |
| | 32 | 100 | 52.8 | 32 | 38.4 | 0 | 32 | 100 | 90.3 | 32 | 99.1 | 0.6 |

MICs are expressed in mg/L and PTA in %. Shaded areas correspond to PTA ≥90%.

**Table 5.** Summary of piperacillin maintenance dosing recommendations based on the results of the present study

| Pharmacodynamic target | Pathogen MIC (mg/L) | Membrane | Dose recommendation |
|---|---|---|---|
| 50%$f_uT_{>MIC}$ | <8 | AN69 | 2000 mg q8h over a 30 min bolus |
| | | AN69ST | 2000 mg q8h over a 30 min bolus |
| | 8–16 | AN69 | 2000 mg q8h over a 30 min bolus |
| | | AN69ST | 2000 mg q8h over a 30 min bolus; a 4 h extended infusion is required for weights >80 kg[a] |
| 100%$f_uT_{>MIC}$ | <4 | AN69 | 2000 mg q8h over a 30 min bolus |
| | | AN69ST | 2000 mg q8h over a 30 min bolus |
| | 4–8 | AN69 | 2000 mg q8h over a 30 min bolus |
| | | AN69ST | 2000 mg q8h over a 4 h extended infusion; a dose of 4000 mg q8h over a 30 min bolus is required for weights >80 kg[a] |
| | >8 | AN69 | 2000 mg q8h over a 30 min bolus; consider 4 h extended infusion for weights >80 kg[a] |
| | | AN69ST | 4000 mg q8h over a 30 min bolus for weights ≤60 kg; a 4 h extended infusion is required for weights >60 kg[a] |

[a]The heaviest patient enrolled in the present study weighed 129 kg.

population PK study of piperacillin in a cohort of critically ill patients with AKI requiring CRRT and found that the baseline creatinine CL (CrCL) was a modifier of renal drug CL. In this case, we believe that the presence of two patient populations (septic and traumatic) accounted for the important effect of CrCL. Further, unlike other drugs that are mainly eliminated by glomerular filtration such as meropenem,[34] piperacillin has secondary elimination pathways such as biliary excretion that may be enhanced when renal function is impaired,[2] which make renal CL less important. Unfortunately, these alternative routes of elimination could not be confirmed in our study since it was not designed to evaluate this issue. Similarly, CVVHDF intensity was *a priori* expected to have an impact on piperacillin CL, but neither graphical nor population PK analysis showed any trend between intensity and the estimates of individual CL. This leads to the hypothesis that even the lowest intensities studied (20–25 mL/kg/h) were sufficient for the maximization of piperacillin CL by CVVHDF and higher intensities (40–45 mL/kg/h) added little to total drug CL. This explanation is consistent with recent data from Roberts *et al.*[35]

It is relevant to mention that our empirical dosing recommendations are mainly based on a quite aggressive pharmacodynamic target (100%$f_uT_{>MIC}$) rather than the 50%$f_uT_{>MIC}$ described in the classical studies.[4] Our proposal of such an ambitious pharmacodynamic target for our patient population is based on the fact that, despite all the available evidence in septic critically ill patients being based on plasma concentrations, it is well known that microcirculatory alterations associated with MODS impair tissue distribution and lead to lower %$f_uT_{>MIC}$ at the target site. As an example, Varghese *et al.*[10] described a 100% piperacillin penetration ratio in the interstitial fluid in critically ill patients with sepsis and CVVHDF, whereas Joukhadar *et al.*[36] reported a much lower tissue penetration ratio of 10% in patients with septic shock. Due to the sickness severity of patients with septic shock, we believe that more aggressive pharmacodynamic targets should be preferred for ensuring an early and effective arrival of therapeutic antibiotic concentrations at the target site. Nevertheless, more aggressive pharmacodynamic targets require higher piperacillin doses and hence increase the risk of suffering from drug adverse effects. In our cohort of patients, we did not observe any case of neurological or haematological toxicity, despite the fact that they were patients receiving high doses, even 16 g/24 h. However, toxicity may happen using these high doses and close monitoring of the most frequent adverse events is advisable in those patients prescribed with higher doses of piperacillin.

The main limitation of this study is that we measured neither ultrafiltrate concentrations nor filter adsorption of piperacillin. For this reason, we cannot truly quantify the extent of antibiotic CL through the filter. In fact, this effect was not expected and hence was not incorporated into the initial study design. However, the very significant difference in CL between the two membranes, AN69 and AN69ST, which are made of the same material and have the same pore size, suggests that one of the underlying mechanisms of differential elimination might be surface adsorption. We believe that these results should encourage further research with piperacillin and other antibiotics under this hypothesis. Further, we could not measure urine concentrations of piperacillin, and therefore we are unable to differentiate CVVHDF CL from renal and non-renal CL. However, as almost all our patients were oligoanuric, we would not expect to see big differences in piperacillin CL in our patient population of critically ill patients with MODS and AKI. Also, our recommendations are based on data from critically ill patients with MODS including septic shock and CVVHDF requirement; therefore, our conclusions may not be applicable in patients with a lower level of sickness severity. Conversely, the major strengths of this study are its large sample size (19 patients), patient homogeneity (all of them with MODS and AKI receiving CVVHDF) and the rich sampling scheme adopted.

## Conclusions

In conclusion, we present the results of a multicentre PK study of piperacillin prescribed to critically ill patients with MODS and CVVHDF requirement. Our population PK model has successfully identified that type of membrane (0.9 $m^2$ AN69 versus 1.5 $m^2$ AN69ST) and body weight at admission are modifiers of

piperacillin CL. Other CVVHDF settings or physiological characteristics did not significantly modify piperacillin CL, and therefore dose adjustments based on these parameters seem to be unnecessary. Given a certain MIC, simulations showed that piperacillin dose titration considering surface treatment of AN69 filters and body weight was advantageous for the attainment of 100%$f_uT_{>MIC}$ as a pharmacodynamic target. If classical pharmacodynamic targets (50%$f_uT_{>MIC}$) were aimed for, a dose of 2000 mg q8h would be sufficient in all cases.

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## Transparency declarations

None to declare.

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