Population Pharmacokinetics/Pharmacodynamics and Clinical Outcomes of Carbapenems in Critically ill patients

Apinya Boonpeng

A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Pharmaceutical Care

Prince of Songkla University

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Author	Miss Apinya Boonpeng
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ชื่อวิทยานิพนธ์ การศึกษาเภสัชจลนศาสตร์ประชากร/เภสัชพลศาสตร์ และผลลัพธ์ทางคลินิกของยา carbapenems ในผู้ป่วยวิกฤต

ผู้เขียน นางสาวอภิญญา บุญเป็ง

สาขาวิชา การบริบาลทางเภสัชกรรม

ปีการศึกษา 2563

บทคัดย่อ

ผู้ป่วยวิกฤตเป็นกลุ่มผู้ป่วยที่มีความรุนแรงของการเจ็บป่วยและพยาธิสรีรวิทยาที่แตกต่างจากกลุ่มผู้ป่วยทั่วไป พยาธิสรีวิทยาดังกล่าวส่งผลเปลี่ยนแปลงค่าเภสัชจลนศาสตร์ของยาปฏิชีวนะหลายประการ ซึ่งอาจลดประสิทธิภาพของยาได้ การศึกษานี้มีวัตถุประสงค์เพื่อ (1) ศึกษาลักษณะและหาค่าเภสัชจลนศาสตร์ประชากรของยากลุ่ม carbapenem ในผู้ป่วยวิกฤต (2) หาขนาดการใช้ยา carbapenem ที่เหมาะสมสำหรับรักษาโรคติดเชื้อในผู้ป่วยวิกฤต (3) ศึกษาความสัมพันธ์ระหว่างค่าเภสัชจลนศาสตร์/เภสัชพลศาสตร์ของยา carbapenem และผลลัพธ์ทางคลินิก โดยผู้ป่วยวิกฤตที่มีภาวะติดเชื้อแบคทีเรียและได้รับการรักษาด้วยยาฉีด meropenem หรือ imipenem ถูกคัดเลือกเข้าการศึกษา ผู้ป่วยแต่ละรายถูกเก็บตัวอย่างเลือดจำนวน 5 ครั้ง เพื่อนำไปวิเคราะห์หาระดับยาในเลือด จากนั้นระดับยาทั้งหมดถูกนำมาหาค่าเภสัชจลนศาสตร์ประชากรโดยใช้หลักการของ nonlinear mixed-effects modeling ผลการวิเคราะห์คุณลักษณะทางเภสัชจลนศาสตร์จากข้อมูลระดับยา meropenem ทั้งหมด 248 จุด จากผู้ป่วย 52 ราย และระดับยา imipenem 103 จุด จากผู้ป่วย 21 ราย พบว่า แบบจำลองทางเภสัชจลนศาสตร์แบบสองห้องที่การขจัดยาแปรผันตรงกับความเข้มข้น เป็นแบบจำลองที่อธิบายเภสัชจลนศาสตร์ของยาได้ดีที่สุด ค่าอัตราการขจัดยา ปริมาตรการกระจายยาส่วนกลาง ปริมาตรกระจายยาส่วนรอบนอก และอัตราการแลกเปลี่ยนสารระหว่างส่วนต่างๆ ของยา meropenem มีค่าเท่ากับ 4.27 ลิตรต่อชั่วโมง 9.85 ลิตร 12.5 ลิตร และ 15.4 ลิตรต่อชั่วโมง และสำหรับยา imipenem มีค่าเท่ากับ 8.99 ลิตรต่อชั่วโมง 15.2 ลิตร 23.4 ลิตร และ 15.9 ลิตรต่อชั่วโมง ตามลำดับ ปัจจัยที่มีผลต่ออัตราการขจัดยา carbapenem ได้แก่ อัตราการกรองของไต ส่วนภาวะอัลบูมินในเลือดต่ำและการใช้ยา dopamine มีผลเพิ่มปริมาตรการกระจายยา meropenem อย่างมีนัยสำคัญทางสถิติ สำหรับผลลัพธ์ทางคลินิก พบว่าในกลุ่มผู้ป่วยวิกฤติที่มีค่า $fT_{>MIC}$ ของยามากกว่าหรือเท่ากับร้อยละ 75 มีอัตราการหายจากโรคติดเชื้อและอัตราการรอดชีวิตที่สูงกว่ากลุ่มที่ $fT_{>MIC}$ น้อยกว่าร้อยละ 75 แต่ไม่มีนัยสำคัญทางคลินิก ส่วนการประเมินหาขนาดยาที่เหมาะสมพบว่า การให้ยา meropenem

และ imipenem ในขนาดมาตรฐานในผู้ป่วยวิกฤตที่มีอัตราการกรองของไตน้อยกว่า 90 มิลลิลิตรต่อนาที เพียงพอต่อการฆ่าเชื้อแบคทีเรียที่ไวต่อยา (MIC $\leq$ 2 mg/L) สำหรับผู้ป่วยที่มีอัตราการกรองของไตในช่วง 90 – 130 มิลลิลิตรต่อนาที ขนาดยามาตรฐานของ imipenem ยังคงเพียงพอต่อการฆ่าเชื้อ แต่สำหรับยา meropenem ควรให้ยาอย่างน้อย 3 กรัมต่อวัน และบริหารยาแบบหยดเข้าหลอดเลือดดำอย่างต่อเนื่อง

จากผลการศึกษาข้างต้น มีปัจจัยหลายประการที่ส่งผลกระทบต่อค่าเภสัชจลนศาสตร์ของยาในผู้ป่วยวิกฤต โดยทั่วไปการให้ยาในขนาดมาตรฐานยังคงเพียงพอต่อการฆ่าเชื้อแบคทีเรียที่ไวต่อยา แต่ในกรณีที่ผู้ป่วยมีอัตราการกรองของไตที่สูง หรือมีการติดเชื้อแบคทีเรียที่มีค่า MIC สูง อาจจำเป็นต้องทำการเพิ่มขนาดยา และ/หรือ บริหารยาแบบหยดเข้าหลอดเลือดดำอย่างต่อเนื่อง

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Major Program Pharmaceutical care
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ABSTRACT

Several pathophysiological changes in critically ill patients with severe infection can dramatically alter pharmacokinetic patterns of carbapenems. The objectives of this study were to (i) characterize and estimate the population pharmacokinetic parameters (PPK) of carbapenems (ii) determine the optimal carbapenem dosage regimens (iii) evaluate the relationship between pharmacokinetic/pharmacodynamic index of carbapenems and treatment outcome. Adult critically ill patients with bacterial infections receiving standard dosing of meropenem or imipenem were eligible for inclusion. Five blood samples were collected from each patient during the first 24 to 48 hours after intensive care unit admission. The population pharmacokinetic models were developed using a nonlinear mixed-effects modeling approach, and the final PPK model was subsequently used for Monte Carlo simulations to propose the optimal dosage regimens. A total of 248 unbound meropenem concentrations from 52 patients and 103 unbound imipenem concentrations from 21 patients were available for analysis. A two-compartment model with linear elimination best described the data. The mean PPK parameters of meropenem were: clearance (CL) 4.27 L/h, central volume of distribution (V_C) 9.85 L, peripheral volume of distribution (V_P) 12.5 L, and inter-compartment clearance (Q) 15.4 L/h. The mean PPK parameters of imipenem were: CL 8.99 L/h, V_C 15.2 L, V_P 23.4 L, and Q 15.9 L/h. The glomerular filtration rate (GFR) was a significant covariate affecting carbapenem clearance. Dopamine used and serum albumin level were the significant factors influencing meropenem V_C. For clinical outcome evaluations, the treatment success and survival rate in patients who achieved $fT_{>MIC} \geq$ 75% target were higher than those who did not but statistically insignificant. The

simulation results showed that the current standard dosing of meropenem and imipenem consistently achieved the 75%$fT_{>MIC}$ target against susceptible pathogens with MIC ≤ 2 mg/L in patients with GFR ≤ 90 mL/min. For patients with GFR 90 – 130 mL/min, the standard dose of imipenem provided sufficient coverage for susceptible pathogens, while a continuous infusion of at least 3 gm daily was required for meropenem.

In conclusion, the current study contributes a better understanding of carbapenem pharmacokinetics in critically ill patients. The current standard dosing of carbapenems provides sufficient coverage for susceptible pathogens in almost all patients. However, for patients with a high GFR level or treating pathogens with high MICs, dose increment and/or administered as continuous infusion might be needed.

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Throughout my doctoral researches, I have received a great deal of support and assistance. I would like to express my sincere thanks to all contributions.

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Apinya Boonpeng

LIST OF ABBREVIATIONS

ABW	Adjusted body weight
AIC	Alkaike's Information Criterion
AKI	Acute kidney injury
AKIN	Acute kidney injury network
ALB	Serum albumin
ALT	Alanine aminotransferase
APACHE	Acute Physiologic and Chronic Health Evaluation II
ARC	Augmented renal clearance
ARC	Augmented renal clearance
AST	Aspartate aminotransferase
BMI	Body mass index
BSI	Blood stream infection
BW	Body weight
CG	Cockcroft-Gault formula
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	Clearance
CL_{CR}	Creatinine clearance
CL_{CRCG}	Creatinine clearance calculated using the Cockcroft-Gault equation
C_{max}	Peak plasma concentration
Cov	Covariance
CV	Coefficient of variation
CV	Coefficient of variation
df	degree of freedom
DHP-1	Enzyme dehydropeptidase 1
EBE	empirical-Bayes estimate of individual parameter
ESBL	Extended-spectrum β-lactamase
$fAUC_{0-24}$	The area under the unbound plasma concentration curve over 24 hours
FOCE-I	A first-order conditional estimation method with η-ε interaction

LIST OF ABBREVIATIONS (CONTNUED)

$fT_{>MIC}$	Percentage of the dosing interval for which the unbound or free plasma concentrations remains above MIC value of the pathogens
GFR	Glomerular filtration rate
GFR_{EPI}	Glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration equation
GFR_{MDRD}	Glomerular filtration rate calculated using the Modification of Diet in Renal Disease equation
GOF	The goodness-of-fit plots
HAP	Hospital-acquired pneumonia
IAI	Intra-abdominal infection
IBW	Ideal body weight
IIV	Interindividual variability
IPRED	Individual predicted concentration
JEL	Jellife
K_{CP}	Transfer rate constant from central to the peripheral compartment
K_e	Elimination rate constant
K_{PC}	Transfer rate constant from peripheral to the central compartment
LD	Loading dose
LLOQ	Lower limit of quantification
LOD	Limit of detection
MCS	Monte Carlo simulations
MDRD	Modification of Diet in Renal Disease
MIC	Minimum inhibitory concentration (mg/L)
MICU	Medical Intensive Care Unit
mJEL	Modified Jellife
OFV	Objective function value
PBP	Penicillin-binding proteins
pcVPC	Prediction-corrected visual predictive check

LIST OF ABBREVIATIONS (CONTNUED)

PD	Pharmacodynamics
PI	Prolong infusion
PK	Pharmacokinetics
PPK	Population pharmacokinetic analysis
PRED	Population predicted concentration
PTA	Probability of target attainment
Q	Inter-compartmental clearance
RSE	Relative standard error
RUV	Residual unexplained variability
SAEM	Stochastic approximation expectation maximization estimation method
Scr	Serum creatinine
Shr	Shrinkage
SICU	Surgical Intensive Care Unit
SOFA	Sequential Organ Failure Assessment
VAP	Ventilator-associated pneumonia
V_C	Central volume of distribution
V_d	Volume of distribution
V_P	Peripheral volume of distribution
V_{ss}	Volume of distribution at steady-state

CONTENTS

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CHAPTER 1

INTRODUCTION

1.1 Background and rationale

Infections and related sepsis is a common problem for patients in intensive care units (ICUs) worldwide. In a large multicenter epidemiologic study across 75 countries, 51% of critically ill patients were classified as infected on the study day. [1] The estimates of sepsis associated with mortality remain high at 25-30%, and therefore it became one of the most significant health concerns in ICU. [1, 2] In septic patients, early initiation of an appropriate activity spectrum antimicrobial agents has been demonstrated to be an effective intervention in reducing mortality. [3, 4]

Carbapenems (imipenem, meropenem) is the broad-spectrum β-lactam antibiotic that is frequently prescribed to treat severe bacterial infections in critically ill patients. Imipenem and meropenem is a hydrophilic molecule with low plasma protein binding of 20% and 2%. [5] They are predominantly extracellular distribution with a volume of distribution at steady-state (V_{ss}) of 0.23 – 0.35 liters/kg. [5-8] Both drugs are mainly excreted as the unchanged form through the kidney. In patients with normal renal function, the elimination half-lives of meropenem and imipenem are approximately 1 hour. [5, 7] In patients with renal impairment, the elimination half-lives of both drugs are prolonged, and therefore the dosage adjustment is required to prevent excessive accumulation of drugs. [9, 10]

Similar to other β-lactam antibiotics, carbapenems display a time-dependent bacterial killing characteristic, that is, its antibacterial activity relied upon the percentage of the dosing interval for which the unbound or free plasma concentrations remains above the minimum inhibitory concentration (MIC) value of the pathogens ($fT_{>MIC}$). [11, 12] Generally, an $fT_{>MIC}$ of at least 40-50% of dosing interval is considered to be sufficient for carbapenems. However, a more aggressive target of 75 -100%$fT_{>MIC}$ was proposed to be more appropriate for the immunocompromised host or critically ill patients. [13, 14]

Pathophysiologic changes, particularly in patients with severe infections, have several significant impacts on carbapenems pharmacokinetics. Severe infection such as sepsis can cause endothelial damage and increase capillary leakage with subsequent fluid extravasation and tissue edema. The aggressive fluid therapy and the use of vasopressor/ inotropic agents in patients with septic shock will significantly increase the volume of distribution (V_d) of a hydrophilic antibiotic such as carbapenems. Moreover, the hyperdynamic state during the early phase of infection could increase renal blood flow and increase drug clearance. As a consequence of these alterations, it may result in low plasma concentrations of carbapenem antibiotics. [15-17]

Although the pharmacokinetics of meropenem and imipenem in critically ill patients have been widely studied, most studies were conducted on small patient populations ranging from 9 to 34 subjects. [18-26] The small cohort may impact the accuracy of pharmacokinetic parameters estimated, and the interindividual variability in critically ill patients could be poorly captured. Moreover, the clinical evidence of the relationship between PK/PD index and carbapenem treatment outcome was limited.

Therefore, this study aimed to estimate the population PK parameters of imipenem and meropenem in a large cohort of critically ill, investigate the factors that significantly affect these parameters and used this information to determine optimal carbapenem dosing regimens for critically ill patients across various ranges of renal function.

1.2 Objectives

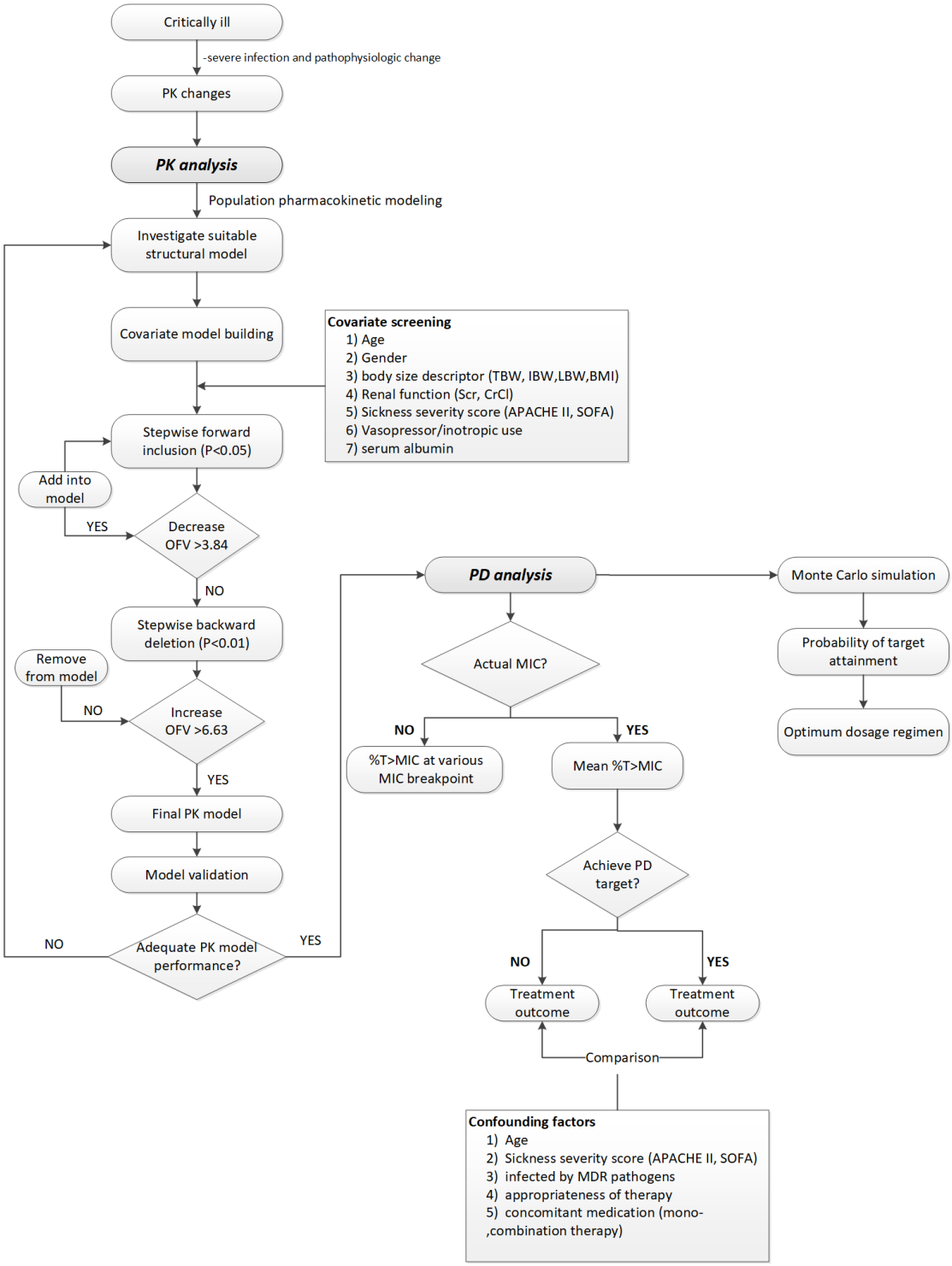
1.2.1 Primary objectives

- To characterized and estimated the population pharmacokinetic parameters of imipenem and meropenem in critically ill patients
- To investigate patient factors that account for sources of variability in imipenem and meropenem pharmacokinetic parameters
- Perform Monte Carlo simulations to assess the probability of target attainment (PTA) and identify the best regimen of imipenem and meropenem for achieving appropriate PK/PD targets.

1.2.2 Secondary objectives

- To evaluate the association between pharmacokinetic/pharmacodynamic index of carbapenem and treatment outcome in critically ill patients

1.3 Conceptual framework



CHAPTER 2

LITERATURE REVIEW

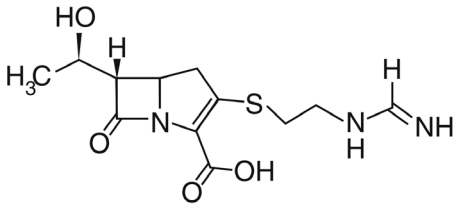
2.1 Clinical pharmacology of carbapenems

Carbapenems are members of β-lactam antimicrobial agents with a potent and broad-spectrum bactericidal activity against numerous Gram-negative and Gram-positive bacterial, including several drug-resistant pathogens. They are considered as one of the most crucial antibiotic classes for treating complicated or severe bacterial infections in critically ill patients. Of all available carbapenems in Thailand, imipenem/cilastatin and meropenem are the most frequently prescribed agents in the intensive care unit (ICU). Therefore, the scope of this literature review was focusing on these two agents.

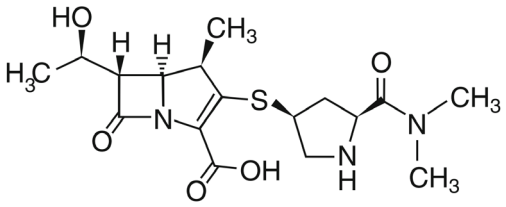
2.1.1 Chemistry

Carbapenems share a typical structure of the four-membered β-lactam ring, like penicillins and other β-lactam antibiotics. Their structure differs from penicillins in having a carbon instead of sulfur atom at C1 and an unsaturated bond between C2 and C3 in the five-membered ring structure (Figure 1). [27] The unique side chains of the trans-α-1-hydroxyethyl substituent at the 6th position on the β-lactam ring also plays a role in resistance to hydrolysis by β-lactamase. These differences are essential for their potency, broad spectrum of activity, and stability against β-lactamases. [28]

The early developed carbapenem, such as imipenem, is susceptible to hydrolysis by the enzyme dehydropeptidase (DHP-1) in the renal brush border. Therefore, it must be administered with cilastatin to inhibit the DHP-1 enzyme. Meropenem was stable to DHP-1 degradation and could be administered alone because it has a 1-β methyl group in the structure to prevents DHP-1 hydrolysis. [5, 28]



Imipenem



Meropenem

Figure 1 Chemical structures of imipenem and meropenem [5]

2.1.2 Mechanism of action

Carbapenems inhibit the bacterial cell wall synthesis by penetrating the bacterial cell wall and binding to the penicillin-binding proteins (PBPs). The complexing of the carbapenem molecule and PBPs inhibits the transpeptidation of peptidoglycan strands, therefore preventing the synthesis of an intact bacterial cell wall. In Gram-negative bacteria, carbapenems cause rapid cell lysis and reach a bactericidal activity by binding to PBPs 1a, 1b, and 2 rather than PBP3.[5, 27, 29]

2.1.3 Microbiological activity

Meropenem and imipenem have been shown to be active against the most commonly isolated species of both Gram-positives and Gram-negatives aerobic as well as anaerobic species such as *Pseudomonas aeruginosa, Acinetobacter* spp*, Enterococcus faecalis, Streptococcus pneumoniae, Klebsiella* spp, *Clostridium* spp. Carbapenems are also active against numerous drug-resistant Gram-negative bacteria, including AmpC β-lactamase and extended-

spectrum β-lactamase (ESBLs) producing strains. However, none of the carbapenem show clinically useful activity against methicillin-resistant *staphylococcus aureus (MRSA), Enterococcus faecium,* and *Stenotrophomonas maltophillia*. [5, 9, 10]

2.1.4 Pharmacokinetics properties

All of the currently available carbapenems are water-soluble drugs and are formulated as parenteral agents as they are not absorbed from the gastrointestinal tract. The pharmacokinetic profiles of single-dose intravenous imipenem and meropenem in healthy adult volunteers are described in Table 1.

Table 1 Pharmacokinetic parameters of carbapenems in healthy adult [5, 9, 10]

Parameter[§]	**Meropenem**	**Imipenem**
C_{max} (0.5 g infusion), mg/L	23 (range 14 – 26)	33 (range 31 – 49)
C_{max} (1 g infusion), mg/L	49 (range 39 – 58)	52 (range 56 – 88)
V_d (litre/kg)	0.23 – 0.35	0.23 – 0.31
Elimination half-life (hour)	1	1
Renal excretion (unchanged)	70%	70%
Plasma protein binding	2%	20%

[§]C_{max}, peak plasma concentration; Vd, the volume of distribution

2.1.5 Pharmacodynamics properties

Like other β-lactam antibiotics, carbapenems exhibit a time-dependent bactericidal activity. The pharmacodynamic index that best correlates with bacteriological and clinical efficacy is the percentage of time that unbound plasma drug concentration remains higher than MIC against the infecting organism ($fT_{>MIC}$). [11, 12] For carbapenems, an $fT_{>MIC}$ of approximately 20% is required for bacteriostatic activity, while an $fT_{>MIC}$ of at least 40% is needed to achieve bactericidal effects. [30]

2.1.6 Dosage and administration

Carbapenems are effective in treating severe infections at various sites. The U.S. Food Drug Administration (FDA) approved indications and dosage regimen are as follows:

2.1.6.1 Meropenem

FDA approved indications [9]

- Complicated skin and skin structure infection
- Complicated intra-abdominal infections
- Bacterial meningitis

Dosage for adult patients [9]

The usual dosage of meropenem is ranges from 0.5 to 1 gm every eight hours in adult patients with normal renal function, except for patients with bacterial meningitis, in whom the dose is 2 gm every 8 hours.

Dosage for adult patients with renal impairment [9]

Dosage of meropenem should be adjusted in patients with creatinine clearance less than 50 mL/min. The manufacturer's dosage recommendations for these patients are given in Table 2.

Table 2 Dosage adjustment of meropenem in adult patients with renal dysfunction [9]

CL_{CR}[§] (mL/min)	**Dose**	**Dosing interval**
>50	Recommended dose	every 8 hours
26-50	Recommended dose	every 12 hours
10-25	50% of recommended dose	every 12 hours
<10	50% of recommended dose	every 24 hours

[§] CL_{CR}, creatinine clearance calculated by Cockcroft and Gault equation

Preparation and administrations [9]

For the intravenous bolus preparation, dilute the meropenem 500 – 1000 mg with sterile water for injection to a concentration of 50 mg/mL and given over 3 -5 minutes. For intermittent infusion, directly dilute meropenem 500-1000 mg with a compatible solution such as 0.9% NaCl or 5% dextrose in water to a final concentration of 20 mg/mL and infusion over 15 – 30 minutes.

2.1.6.2 Imipenem

FDA approved indications [10]

- Lower respiratory tract infections
- Urinary tract infections
- Intra-abdominal infections
- Gynecologic infections
- Bacterial septicemia
- Bone and joint infections
- Skin and skin structure infections
- Endocarditis

Dosage for adult patients [10]

In adult patients with normal renal function, the dosage of imipenem/cilastatin is 0.5 gm every 6 hours or 1 gm every 8 hours for susceptible bacteria and 1 gm every 6 hours for intermediate susceptible bacteria.

Dosage for adult patients with renal impairment [10]

Adult patients with a creatinine clearance (calculated using Cockcroft-Gault equation) of 90 mL/min or less require dosage reduction as indicated in Table 3.

Table 3 Dosage adjustment of imipenem in renal impairment [10]

Imipenem dosage	**CL_{CR}[§] (mL/min)**			
	≥ 90	**60-90**	**30-59**	**15-29**
For susceptible bacterial	0.5 g q 6 h	0.4 g q 6 h	0.3 g q 6 h	0.2 g q 6 h
	OR			
	1 g q 8 h	0.5 g q 6 h	0.5 g q 8 h	0.5 g q 12 h
For intermediate susceptibility bacterial	1 g q 6 h	0.75 g q 8 h	0.5 g q 6 h	0.5 g q 12 h

[§] CL_{CR}, creatinine clearance calculated by Cockcroft and Gault equation

Preparation and administration [10]

Infuse a dose of 500 mg or less over 20 – 30 minutes. For a dose greater than 500 mg, it should be infused over 40-60 minutes.

2.1.7 Safety and tolerability

The safety profiles of imipenem and meropenem are similar. The mild, self-limiting drugs-related adverse events reported are nausea, vomiting, diarrhea, headache, constipation, pruritus, rash, injection-site reaction. [5, 9, 10]

Adverse events requiring drug withdrawal occurred in 1.4 – 1.8% of patients treated with carbapenems. Development of seizure and other adverse CNS side effects such as confusional states and myoclonic activity has been reported during treatment with carbapenems. [9, 10] The risk factors for seizure include pre-existing neurologic condition (such as stroke, brain injury, seizure), drug accumulation in renal impairment, high-dose carbapenems. Meropenem has

a lower potential to cause seizures than imipenem. Therefore it may be preferred for certain indications. [5, 31]

2.2 Pharmacokinetics and pharmacodynamics considerations in critically ill patients

The pharmacokinetics (PK) /pharmacodynamics (PD) index refers to the relationship between pharmacokinetics exposure and the observed pharmacologic effect. This relationship is often described by linking the PK parameters of antibiotics with minimum inhibitory concentration (MIC) of the infecting pathogens. Antibiotics are broadly classified into the following categories [12, 16]:

1) The time-dependent pattern of bactericidal activity

   Antibiotic agents showing this killing pattern are best described by the duration of time over a 24 hours period that the unbound concentration exceeds the MIC ($fT_{>MIC}$). The class of β-lactam antibiotics is an example of time-dependent agents. Prolonging the effective exposure duration should be the priority when used this antibiotic class.

2) The concentration-dependent pattern of bactericidal activity

   The difference between the maximum and minimum effects of this antibiotic class is large, and increasing drug concentrations resulted in increasing bactericidal activity. For these antibiotics, the ratio of the unbound maximum concentration divided by the MIC (fC_{max}/MIC) describes their antimicrobial effect best. An example of this class is aminoglycosides.

3) The Concentration-dependent with the time-dependent pattern of bactericidal activity

   Some antibiotics such as ac quinolones, glycopeptides display both concentration- and time-dependent kill characteristics. The area under the unbound plasma concentration curve over a 24-h period

divided by the MIC ($fAUC_{0\text{-}24}$/MIC) best correlate with their antimicrobial activity.

PK/PD properties of carbapenems

Carbapenems have similar PK/PD properties when compared with other β-lactams. They display a time-dependent bacterial killing characteristic, and $fT_{>MIC}$ is PK/PD index that best correlates with their antimicrobial efficacy. [11, 12] Unlike other β-lactam antibiotics, carbapenems have been reported to possess a postantibiotic effect (PAE) against Gram-negative and Gram-positive bacteria. [32, 33] This PAE effect could explain a shorter $fT_{>MIC}$ target of carbapenems compared with other β-lactams. An $fT_{>MIC}$ of approximately 20% is required for bacteriostatic activity, while an $fT_{>MIC}$ of at least 40% is needed to achieve bactericidal effects. [30] Therefore, it has been suggested that the $fT>MIC$ of carbapenem should be maintained at least 40-50% of the dosing interval. However, clinical data from severely ill patients did not consistently support this target. A higher $fT_{>MIC}$ target of 75 -100% was proposed to be more appropriate for an immunocompromised host or critically ill patients. [13, 14]

2.3 The impact of pathophysiological alteration during critical illness on pharmacokinetic parameters

Critically ill patients are a special population. These patients have a high level of sickness severity and are at high risk of developing a life-threatening infection. There are several factors that alter the pharmacokinetic parameters of antibiotics in critically ill patients. The presence of systemic inflammatory response syndrome in severe infections, such as severe sepsis and particularly septic shock, increases capillary permeability with subsequent fluid extravasation into interstitial space. This extravasation resulted in intravascular volume loss and hypotension. The initial management for hypotension is administering large volumes of fluid resuscitation to maintain sufficient pressure to perfuse organs. This process can lead to a volume expansion in the interstitial space and increase the V_d of hydrophilic drugs, which may decrease their plasma concentrations. The V_d of hydrophilic drugs such as carbapenems, aminoglycosides are also affected by serum albumin. Albumin,

the predominant plasma protein that binds to many drugs, is often low in critically ill patients. Low plasma albumin levels could result in a higher unbound proportion of drugs, leading to an increase in tissue distribution and elimination. This effect is associated with an increase in V_d and drug clearance (CL). [15, 16, 34, 35]

The initial hyperdynamic state of severe infection is associated with high cardiac output and, thus, enhanced blood flow to the kidney resulting in substantially raises the CL of renally cleared antibiotics such as β-lactams, carbapenems. The administration of fluid and inotropic agents during sepsis can also increase cardiac output and glomerular filtration rate (GFR). Some critically ill patients can develop augmented renal clearance (ARC). It is a clinical phenomenon of enhanced renal excretion with GFR greater than 130 mL/min/1.73 m^2. [36] ARC is often seen in critically ill patients, particularly in surgical and trauma patients and in young septic patients (age < 55 years). [37, 38] The use of a regular unadjusted dose of renally eliminated antimicrobial in these patients might lead to subtherapeutic concentration and treatment failure. [36, 39]

In contrast, a decrease in organ perfusion during sepsis, particularly septic shock, can lead to organ dysfunction. Renal impairment results in the accumulation of drugs and increases the risk of toxicity. The dose reduction of renally elimination antimicrobials needs to be considered. The flow diagram summarizing these effects on PK parameters is displayed in Figure 2.

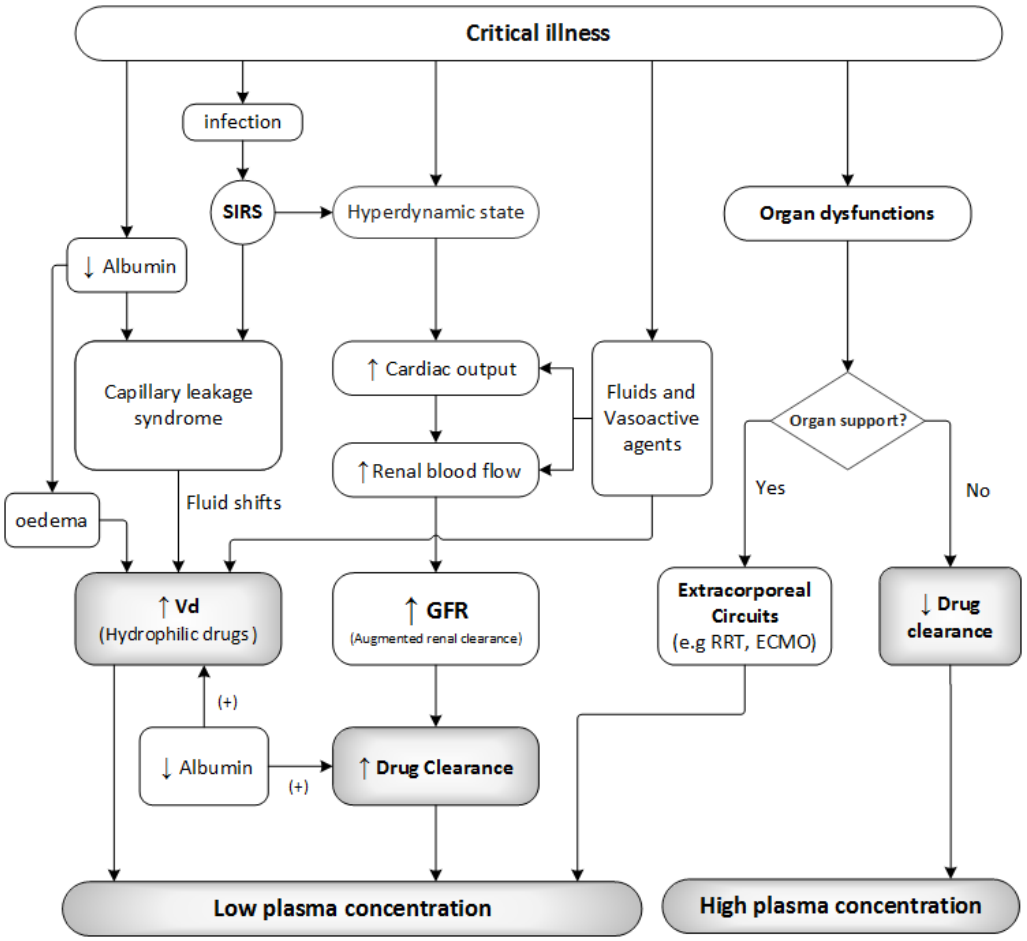


Figure 2 Flow diagram summarizing the effect of pathophysiologic alteration during critical illness on pharmacokinetic parameters of hydrophilic antimicrobials.

2.4 Population pharmacokinetics of carbapenems in critically ill patients

2.4.1 Meropenem

The population pharmacokinetic analysis (PPK) using a nonlinear mixed-effect model approach has dramatically improved the understating of the PK/PD characteristic of antimicrobial drugs. In the past ten years, there were several published PPK studies of meropenem in severely ill patients. The detail of each study is shown in Table 4.

Robert JA et al. [26] conducted the PPK study in 10 septic patients to compare the meropenem plasma and subcutaneous tissue concentration-time profiles between intermittent bolus (over 3 minutes) and continuous infusion (over 24 hours). The extensive blood sampling (15 samples per subject) was taken on the first and second days after therapy. All subjects included in their study had normal renal function with serum creatinine less than 120 μmol/L. A total of 222 plasma concentrations from ten septic patients were used for pharmacokinetic modeling. A two-compartmental linear elimination model and a combined residual error best described the data. The creatinine clearance calculated using the Cockcroft-Gault formula (CL_{CRCG}) was the only significant factor associated with meropenem clearance. The two-compartment model was parameterized in terms of central volume of distribution (V_C), peripheral volume of distribution (V_C), inter-compartment clearance (Q), and clearance (CL). The mean PK parameters of meropenem were: CL 13.6 L/h, Q 56.3 L/h, V_C 7.9 L, and V_P 14.8 L. The relatively small cohort could be considered a limitation of this study. Moreover, all subjects included in this study had a normal renal function with CL_{CRCG} range from 98 - 127 mL/min. Therefore, the generalizability of these results should be restricted to patients without renal impairment.

Crandon JL et al. [25] developed a meropenem PPK model using the data from 21 critically ill patients. After receiving at least three doses of meropenem, 1-3 blood samples were collected from each patient. A total of 55 concentrations from 21 subjects were included for the initial model building, and the additional 12 samples from 5 subjects were used for an external validation process. The mean age and weight were 60 years and 88.9 kg. Their median

CL_{CRCG} was 70 mL/min (range, 35-201). The median PK parameter estimates for V_C, transfer rate constant from central to the peripheral compartment (K_{CP}), and transfer rate constant from peripheral to the central compartment (K_{PC}) were 0.24 L/kg (16.8 L for 70 kg patients), 0.49 $h^{-1,}$ and 0.65 h^{-1}, respectively. This study was conducted in a larger cohort compare to Robert JA et al. However, only 55 total drug concentrations (bound+unboud) were used to estimate the two-compartment PK parameters, and the study populations were also included in non-critically ill patients. Therefore the results of this study should be used with caution in a critical care setting.

Jaruratanasirikul et al. [24] performed the PPK analysis to characterize meropenem pharmacokinetics during the early phase of sepsis. The analyzed dataset consisted of 171 unbound meropenem concentrations obtained from 9 septic patients. A one-compartment model with combined proportion and additive residual variability was selected to describe data, and the mean PK parameter estimates for CL and Vd in this population were 7.82 L/h and 23.7 L, respectively. Only one significant covariate relationship between the glomerular filtration rate calculated using the Modification of Diet in Renal Disease (GFR_{MDRD}) and clearance was identified during the model building process. The relatively small sample size could be considered a limitation of this study for exploring the other potential covariates affecting PK parameters.

Mattioli F et al. [21] were investigated the PPK parameters of meropenem in severely ill patients with *Klebsiella pneumoniae* infections (n=27). Five blood samples per subject were collected on the second day of meropenem therapy. A total of 118 blood samples were used for PPK analysis. The final model was a one-compartment model with a mixed error model. The mean values of CL and Vd_{ss} obtained from the final model were 9.38 L/h and 26.2 L, respectively. Gender, age, serum albumin, and the severity of infection (sepsis, severe sepsis, or septic shock) were identified as significant covariates for meropenem pharmacokinetics in this study. This study was conducted in a larger cohort of critically ill patients compared to previous studies. However, the total plasma (unbound + bound) concentrations of meropenem were used to derived PK parameters, while free plasma concentrations were used in other

studies. Moreover, meropenem is mainly excreted through renal, but renal function markers such as creatinine clearance have not been identified as a significant covariate for meropenem clearance in this study.

Mathew SK et al. [22] performed the PPK study among adult patients who were admitted to an intensive care setting (n=37). The PPK model was developed to compare the PTA between 3-hours and 0.5-hours infusion regimens of meropenem. Nine blood specimens were collected from each subject after at least five doses of meropenem had been administered. A 2-compartment multiplicative gamma error model with first-order elimination best described the data. CL_{CRCG} and body weight significantly affected the elimination rate constant (K_e) and V_C, respectively. The final PK parameters were: K_e 0.54 h^{-1}, V_C 9.36 L, K_{CP} 1.85 h^{-1}, K_{PC} 1.53 h^{-1}. The limitation of this study was that the total plasma concentrations of meropenem were used to derived PK parameters.

Tsai et al. [20] performed a study to compared the PPK parameters of meropenem between Australian indigenous and Caucasian critically ill patients. The 216 total drugs (bound+unbound) concentrations from only 11 patients were used to perform the PPK modeling. A two-compartment linear elimination model was chosen to describe the time-course of total meropenem concentrations. CL_{CRCG} and total body weight were the only tested covariates that significantly improved the model fit. The median final PK parameter estimates for CL, V_C, K_{CP}, and K_{PC} were 14.1 L/h, 13.6 L, 1.49 h^{-1}, and 2.38 h^{-1}. The total drug concentrations and the small sample size were also a limitation of this study. A small cohort of populations may limit the power to detect other potential covariates affecting meropenem pharmacokinetics.

Table 4 Summary of previously published population pharmacokinetics of meropenem in critically ill patients

Study (no. of patients)	Covariate tested[a]	PPK parameter[b]	Final model[c]
Robert et al. [26] (n=10)	Age, WT*, BMI, LBW, SOFA, Scr, CL_{CRCG}*	2-CMT: CL=13.6 Vc=7.9 Vp=14.8 Q=56.3 Vd_{ss}= 22.7	TVCL=CL×(CL_{CRCG}/100) TVVc=Vc× $(WT/80)^{0.75}$ TVVp=14.8
Crandon et al.[25] (n=21)	Age, Gender, Ethnicity, ABW*, APACHE, CL_{CRCG}*	2-CMT: Vc=0.24 L/kg K_{CP}=0.48 K_{PC}=0.65	K_e=0.392+0.003×(CL_{CRCG}) V_C=0.239×ABW For WT 62; Vd_{ss}=27.5 L
Jaruratanasirikul et al.[24] (n=9)	Age, WT, BMI, SBP, DBP, Fl_intake, Fl_output, pH, BUN, SOFA, APACHE, Scr ,CL_{CRCG}, GFR_{MDRD}*	1-CMT; CL=7.82 V=23.7	TVCL=3.01+0.07×GFR_{MDRD}

Table 4 Summary of previously published population pharmacokinetics of meropenem in critically ill patients (continued)

Study (no. of patients)	Covariate tested[a]	PPK parameter[b]	Final model[c]
Mattioli et al.[21] (n=27)	Gender*, age, height, WT, BMI, Scr, CL_{CRCG}, ALB*, septic shock	1-CMT: CL=9.38 V=26.2	TVCL = 2.2× [1 + 1.76 if female] × [1 + 0.427 if sepsis] TVV = 8.3 × [(ALB/22) × exp(0.521)] × [(AGE/61) × exp(0.517)]
Tsai et al.[20] (n=11)	Age, ethnicity, gender, WT*, SOFA, ALB, Scr, Vasopressor, CL_{CRCG}*	2-CMT; CL=14.1 Vc=13.6 K_{CP}=1.49 K_{PC}=2.38 Vdss=22.1	TVCL=14.1 × (CL_{CRCG}/100) TVVc=13.6 × $(WT/80)^{0.75}$

Table 4 Summary of previously published population pharmacokinetics of meropenem in critically ill patients (continued)

Study (no. of patients)	Covariate tested[a]	PPK parameter[b]	Final model[c]
Mathew et al.[22] (n=34)	Age, gender, WT*, CL_{CRCG}*	2-CMT; Vc=9.36 K_{CP}=1.85 K_{PC}=1.53 CL=5.1 Vd_{ss}=20.7	$Ke = 1.9 \times 10^{-5} \times CL_{CRCG}^{2.5}$ $Vc = 1.15 \times WT^{0.5}$

[a]WT; total body weight; BMI, body mass index; LBW, lean body weight; ABW, adjusted body weight; IBW, ideal body weight; ALB, serum albumin; SOFA, sepsis organ failure assessment score; APACHE, Acute Physiology and Chronic Health Evaluation; SBP, systolic blood pressure; DBP, diastolic blood pressure; Scr, serum creatinine; pH, arterial pH; BUN, blood urea nitrogen; CL_{CRCG}; creatinine clearance estimated with Cockcroft-Gault equation; GFR_{MDRD}, glomerular filtration rate estimate using the Modification of Diet in Renal Disease (MDRD)

[b]PPK parameters, population pharmacokinetic parameters (mean); 2-CMT, 2-compartment model; 1-CMT; 1-compartment model; CL, clearance (L/h); Vc, central volume of distribution; Vp, peripheral volume of distribution; Vd_{ss}, volume of distribution at steady state (V_c+V_p); Q, intercompartment clearance (L/h); K_{cp}, transfer rate constant from central to peripheral compartment; Kpc, transfer rate constant from peripheral to central compartment

[c]TVCL, typical value for clearance; TVVc, typical value for Vc, TVVp, typical value for V_p; K_e, elimination rate constant (h^{-1}); O, scaling factor for obesity

2.4.2 Imipenem/cilastatin

There were two previously published population pharmacokinetic studies of imipenem in critically ill patients.

Sakka SG et al.[19] developed the population pharmacokinetics of imipenem using 140 imipenem (bound+unbound) concentrations obtained from 20 critically ill patients. A two-compartment open model with zero-order input and first-order eliminations was selected to describe the data. Age, body weight, height, and body surface area significantly influenced imipenem clearance. Thus, all of these covariates were retained in the final model. The main limitations of this study were the small number of subjects and were not measuring the unbound concentrations of imipenem.

Couffignal C et al.[18] performed a PPK analysis of imipenem in 51 critically ill patients with ventilator-associated bacterial pneumonia. A total of 297 unbound imipenem concentrations were available for model building. A two-compartment linear model best characterized the data. The CL_{CR} has significantly affected the imipenem clearance, while body weight and serum albumin were significant covariates explaining the volume of distribution. The final PK parameters of imipenem were reliably estimated with acceptable precision. The detail of each study is summarized in Table 5.

Table 5 Summary of previously published population pharmacokinetics of imipenem/cilastatin in critically ill patients

Study (no. of patients)	Covariate tested[a]	PPK parameter[b]	Final model[c]
Sakka SG et al.[19] (n=20)	Age*, weight*, height*, BSA*, CL_{CRCG}	2-CMT; CL=11.1 Vc=12.2 K_{CP}=3.89 K_{PC}=5.63 Vdss=22.9	Not report
Couffignal et al. (n=51)[18]	Age, gender, WT, ALB*, SAPII, SOFA,ES, CL_{CR4h}*, PEEP, P/F ratio, septic shock	2-CMT; CL=13.2 Vc=22.4 Vp=9.9 Q=10.1 Vd_{ss}=32.3	$TVCL=13.2\times (CL_{CR4h}/86.4)^{0.2}$ $TVVc=20.4 \times (WT/77)^{1.3} \times(ALB/18)^{-1.1}$

[a]WT; total body weight; ALB, serum albumin; ES, odema score; CrCL4h, 4 hours urine creatinine clearance; SAPII, Simplified Acute Physiology Score; SOFA, sepsis organ failure assessment score; PEEP, positive end-expiratory pressure; P/F ratio, arterial partial pressure of oxygen/fraction inspired oxygen

[b]PPK parameters, population pharmacokinetic parameters (mean); 2-CMT, 2-compartment model; CL, clearance (L/h); Vc, central volume of distribution; Vp, peripheral volume of distribution; Vd_{ss}, volume of distribution at steady state (V_c+V_p); Q, intercompartment clearance (L/h); K_{cp}, transfer rate constant from central to peripheral compartment; Kpc, transfer rate constant from peripheral to central compartment

[c]TVCL, typical value for clearance; TVVc, typical value for Vc

*significant covariate

CHAPTER 3

MATERIALS AND METHODS

3.1 Study design

A single-center, prospective population pharmacokinetic study

3.2 Study setting

Medical and surgical intensive care unit at Songklanagarind Hospital, Hat Yai, Thailand

3.3 Study population

Adults patients who admitted to medical or surgical intensive care unit between June 2018 and July 2020

3.4 Eligible criteria

Inclusion criteria

1. Patients age greater or equal than 18 years who admitted to the medical or surgical intensive care unit and received intravenous meropenem or imipenem/cilastatin

Exclusion criteria

1. Patients undergoing renal replacement therapy during meropenem or imipenem/cilastatin therapy
2. Patients who had APACHE II score greater than 35
3. Pregnancy or lactation
4. Patients having known allergy to carbapenems

3.5 Sample size

In order to obtain accurate and precise population pharmacokinetic parameters, a PFIM interface 4.0 program [40] was used to calculate the number of subjects and the total number of drug concentrations need for PK estimation.

Meropenem sample size

The meropenem PPK parameters in severely ill patients reported by Robert JA et al.[26] were used as the reference parameters to investigate the optimal PK design. These parameters are as follows:

Fix-effect parameters :

CL=14.6 L/h, V_C=10.8 L, Q=18.6 L/h, Vp=12.6 L

Interindividual variability (exponential model):

ω^2_{CL}=0.118, ω^2_{V1}=0.143, ω^2_{Q}=0.290, ω^2_{V2}=0.102

Residual error (combine proportional and additive):

σ^2_{prop} = 0.0352, σ^2_{add} = 0.220

The result suggested that a total of 52 patients with at least five meropenem concentrations for each subject were sufficient for fixed- and random-effect parameter estimated.

Imipenem sample size

A pooled population pharmacokinetic analysis of imipenem/cilastatin in critically ill, febrile neutropenia and burn patients reported by Van Hasselt JC et al.[41] was used as the reference parameters. These parameters are as follows:

Fixed-effect parameters :

CL=11.5 L/h, V_C=9.37 L, Q=13.7 L/h, V_P=6.41 L

Interindividual variability:

ω^2_{CL}=0.025, ω^2_{V1}=0.1082, ω^2_{V2}=0.0404

Residual error (combine proportional and additive):

σ^2_{prop}=0.024, σ^2_{add}=0.30

The result suggested that a total of 50 patients with at least five imipenem concentrations for each subject were required for fixed- and random-effect parameter estimated.

3.6 Doses and drug administration

Meropenem and imipenem dosage regimens were prescribed according to the standard routine practice of Songklanakarind hospital. Each intravenous admixture was prepared by diluting the meropenem or imipenem in 0.9% NaCl or 5% dextrose in water to a volume of 50-100 mL. Then it was intravenously administered through standard intermittent infusion (30-60 min) via a venous catheter, according to the physician's prescription.

3.7 Blood sampling

This study was carried out during the ICU admission, and the blood sample were collected during the first 24 to 48 hours after meropenem or imipenem administration. Three milliliters (3 mL) of blood were obtained via an indwelling arterial catheter, and a total of 5 blood samples per patient was randomly collected from the following sampling windows.

Meropenem sampling window

Sample 1: shortly before meropenem administration (time zero)

Sample 2: 0 – 0.5 hours after meropenem administration

Sample 3: 0.5 – 2.5 hours after meropenem administration

Sample 4: 2.5 – 4.0 hours after meropenem administration

Sample 5: 4.0 – 8.0 or 4 -12 hours after meropenem administration

Imipenem sampling window

Sample 1: shortly before imipenem administration (time zero)

Sample 2: 0 – 0.5 hours after imipenem administration

Sample 3: 0.5 – 2 hours after imipenem administration

Sample 4: 2 – 4 hours after imipenem administration

Sample 5: 4 – 8 or 4 – 12 hours after imipenem administration

Sample handling and storage

All blood samples were collected in heparinized tubes, immediately placed on an ice bath, and rapidly separated by centrifugation within 15 minutes after collection. Meropenem and imipenem blood samples were centrifuged at 2000 ×g under 4 ˚C for 10 minutes and 1000 ×g under 4 ˚C for 15 minutes, respectively. For imipenem samples, an equal volume of stabilizing solution (0.5 M MOPS/water/ethylene glycol, 2:1:1, v/v/v) was added to each sample and vortex before storage. All samples were frozen at -80 ˚C until assayed within four weeks.

3.8 Unbound carbapenems concentration determination

3.8.1 Unbound meropenem assay

Unbound plasma meropenem concentrations were measured by reverse-phase HPLC based on a validated assay reported Ozkan et al.[42] The unbound fraction of meropenem was extracted by transfer 500 µl of sample to an ultrafiltration device (Nanosep 10K device, Pall Corp., Northborough, MA) and centrifuged 13,000 rpm at 4 °C for 30 minutes. Fifty microliters of the filtrates were injected into HPLC system for analysis and chromatographically separated on a reversed-phase column (µBondapak C_{18} column, 3.9 by 300 mm; Waters Associates). The mobile phase consisted of 15 mM KH_2PO_4, acetonitrile, and methanol (94:4:2 (v/v/v), adjusted pH to 4.6), which was flowed through the column at a rate of 1 mL/min. The transitional masses were monitored by a photodiode array detector (Waters 2996; Waters Associates, Milford, MA) at wavelength 296 nm. The chromatograms were evaluated and integrated with a Waters 746 data module (Waters Associates). The lower limit of quantitation (LOQ) for this analytical method was 0.5 µg/ml with intra-and inter-assay coefficients of variation (CVs) consistently less than 5%. The accuracy values range from 102.91% to 108.08%, and the recovery values ranged from 103.37% to 117.85%. Three meropenem concentrations (2, 32, and 128 µg/ml) with five replication were used for this validation method.

3.8.2 Unbound imipenem assay

The free imipenem concentrations were quantified using a previously published validated HLPC assay reported by Garcia-Capdevila et al.[43] To ensure the stability of imipenem, 250 μL of plasma samples were mixed with an equal volume of stabilizing solution (0.5 M MOPS/water/ethylene glycol, 2:1:1, v/v/v). The mixture was then subjected to an ultrafiltration device (Ultrafree®-MC Centrifugal Filter Unit) and centrifuged at 6000 g for 10 minutes to extract an unbound fraction of imipenem. A 50 μL was injected into HPLC system for analysis and separated by a reverse-phase HPLC column (Nova-Pak C_{18} column, Waters Associates, Milford, MA, USA). A 0.2 M borate buffer adjusted to pH 7.2 was used as the mobile phase, and the flow rate was set at 1 mL/min. The photodiode array detector (Waters 2996; Waters Associates) was performed at wavelength 300 nm. The limit of quantitation (LOQ) and limit of detection (LOD) for plasma imipenem were 0.25 and 0.075 μg/mL, respectively. The intra- and inter-assay coefficients of variation were consistently less than 5% for all three imipenem concentrations (0.75, 20, and 75 μg/mL). The short-term stability test results of samples containing imipenem 0.75 and 75 μg/mL showed that imipenem losses were less than 1% at room temperature for at least 1 hour. For the long-term stability test, imipenem losses were less than 5% at − 80 °C for at least 14 days.

3.9 Minimum inhibitory concentration (MICs) determination

All antimicrobial susceptibility testing was conducted in the microbiology laboratory at Songklanagarind hospital, Hat Yai, Thailand. MICs for meropenem and imipenem were evaluated using the Epsilometer test methodology **(**Liofilchem® MIC test Strips, Envimed, Thailand**)** for each patient in whom the microorganism was identified.

3.10 Population pharmacokinetic model building

3.10.1 Methods for handling data below the limit of quantification (BLOQ)

The lower limit of quantification (LLOQ) is the lowest concentration in a sample that can be quantified with suitable precision and accuracy. The U.S. Food and Drug Administration (FDA) guideline on bioanalytical method validation had specified that an interassay and intraassay coefficients of variation must be consistently less than or equal to 20%. In most of the laboratoires, concentrations that fall below the LLOQ are typically reported textually as "BLOQ" rather than an actual numeric value. Although the BLOQ data is potentially measured with less precision compared to a concentration higher than LLOQ, this data is still valuable information for pharmacokinetics analysis. Moreover, ignoring it can contribute to bias and imprecision in the PPK parameter estimated. Therefore, in this study, the following methods were tested to utilize BLOQ data in the modeling.

1) Discard all concentrations that fall below the LLOQ value
2) Below LLOQ concentrations were substituted with LLOQ/2 value and the subsequent BLOQ data from the same subjects were discard
3) Keep the below LLOQ data in the model and estimate the values using the likelihood-based method as summarized by Beal et al. (Beal M3 method) [44]
4) All detectable concentrations were included in the data set as continuous data, including data below the LLOQ. Concentrations below the limit of detection (LOD) were discarded. [45]

3.10.2 Structural model

The concentration-time profiles of meropenem and imipenem were analyzed by a nonlinear mixed-effects model approach using NONMEM® software version 7.4 (ICON Development Solution, Ellicott City, MD, USA) along with Perl-Speaks-NONMEM version 4.9.0 (Uppsala University, Uppsala, Sweden) and Pirana version 2.9.9 (Certara, Princeton, NJ, USA). Data visualization, post-processing of the NONMEM output, and graphical evaluation

were performed in R version 3.6.0 and RStudio version 1.2.1335 (R Foundation for Statistical Computing, Vienna, Austria).

A first-order conditional estimation method with η-ε interaction (FOCE-I) and stochastic approximation expectation maximization (SAEM) estimation methods were examined to estimate the PK parameters. If the FOCE-I method provides substantially the same results to SAEM, it will be used for parameter estimation throughout the analysis.

Structural model

One-, two- and three-compartment models with zero-order input and first-order elimination were compared to find the optimal fit for the meropenem and imipenem concentration-time data.

Stochastic models for random effects

Level 1 random-effects or interindividual variability (IIV) describe the magnitude of difference in parameter values between subjects. The interindividual variance terms were implemented using an exponential function on all PK parameters for which the estimation of variability can be supported by the data. Therefore, the parameter for the individual *i*th (θ_i) is written as:

$$\theta_i = \theta_{pop} \times exp\ (\eta_i)$$

Where θ_{pop} is the typical value (mean) and η_i is the deviation from mean, which is assumed to be normally distributed with a mean of 0 and variance ω^2.

The distribution of the IIV and correlation between them were examined graphically to assess the normality and independence assumption, respectively. The inclusion of covariance terms between random effect parameters was tested for any parameter displaying significant correlations. If implementing a correlation significantly improved the model fit, the covariance terms were then retained in the model.

Level 2 random-effects or residual variability (RV) is the variability that remains unexplained after controlling other sources of variability. The RV

was modeled by considering additive, proportional, exponential, or combined additive plus proportional error model.

Additive variance model

$Y = f(\theta, time) + \varepsilon$

Proportional variance model

$Y = f(\theta, time) \times (1+\varepsilon)$

Exponential variance model

$Y = f(\theta, time) \times exp(\varepsilon)$

Combined variance model

$Y = f(\theta, time) \times (1+\varepsilon_1) + \varepsilon_2$

The ε value in the models mentioned above is assumed to be normally distributed with zero mean and variance σ^2.

The most appropriate structural model was selected based on the smaller value of objective function value (OFV) and Akaike information criterion (AIC), an acceptable parameter precision, and adequate goodness-of-fit plots.

3.10.3 Covariate analysis

After the appropriate structural model was established, candidate covariates were investigated for their impact on parameters using a stepwise covariate modeling approach. A list of potential covariates was shown in Table 6.

The correlation analysis between covariates was first performed before covariate screening to avoid the simultaneous incorporation of colinear variables into the model. If a correlation coefficient between two covariates exceeded 0.5 and both covariates had statistically significant influence on a parameter, only one variable was chosen. In case where both covariates were important predictors on the PK parameter, the covariate was categorized, and the categorized variable was used in the model instead of the original value.

The first covariate screening step was done through graphical assessment. The plots between the empirical Bayesian estimates (EBEs) of PK parameter versus the covariates of interest were generated. If a trend in any of

these plots was visibly evident, then it was considered for inclusion in the structural model. Various function forms were used to relate the effects of covariates to PK parameters, as described bellowed:

For categorical covariates

$$\theta_i = \theta_{pop} \times \left(1 + \theta_{cov} \cdot (Cov - Cov_{median})\right)$$

For continuous covariates

Linear relation

$$\theta_i = \theta_{pop} + \theta_{cov} \cdot (Cov - Cov_{median})$$

Power relation

$$\theta_i = \theta_{pop} \times \left(\frac{Cov}{Cov_{median}}\right)^{\theta_{cov}}$$

Exponential relation

$$\theta_i = \theta_{pop} \cdot e^{\theta_{cov} \times (cov - cov_{median})}$$

where θ_i is the individual PK parameter for subject *i*th

θ_{pop} is the typical value or population mean of the PK parameter

θ_{cov} is the covariate coefficient

Cov is the specific covariate value

Cov_{median} is the median or mean value of covariate

The potential covariates were statistically tested for their impact on the PK parameter using a stepwise covariate modeling approach. The covariates were kept in the model if they were biologically plausible and their inclusion led to the significant improvement of model fit, as evaluated by a decrease of at least 3.84 units of OFV ($P<0.05$ for 1 degree of freedom [*df*]) for forward inclusion and an increase of at least 6.64 units of OFV ($P<0.01$ for 1 *df*) for backward-elimination.

Table 6 Summary of potential covariates to be evaluated on PK parameter [a]

No.	Covariates and descriptions	Model parameters
1	Age (years)	CL, V_C, V_P
2	Gender	CL, V_C, V_P
3	Body weight (BW, kg)	V_C, V_P
4	Ideal body weight (IBW, kg)	V_C, V_P
5	Lean body weight (LBW, kg) [46]	V_C, V_P
6	Adjusted body weight (ABW, kg) [47]	V_C, V_P
7	Body mass index (BMI, kg/m^2)	V_C, V_P
8	Obesity (defined as BMI greater or equal than 30 kg/m^2)	V_C, V_P
9	CL_{CRCG} using BW (CL_{CRCG_BW}, mL/min)	CL
10	CL_{CRCG} using IBW (CL_{CRCG_IBW}, mL/min)	CL
11	CL_{CRCG} using LBW (CL_{CRCG_LBW}, mL/min)	CL
12	CL_{CRCG} using ABW (CL_{CRCG_ABW}, mL/min)	CL
13	CL_{CRCG_IBW} using Scr rounding to 1 mg/dL instead of actual Scr when Scr was less than 1 mg/dL (CL_{CRCG_round}, mL/min)	CL
14	CL_{CR} estimated by JEL equation ($CL_{CR\text{-}JEL}$) without BSA[48] (CL_{CRJEL_noBSA}, mL/min)	CL

Table 6 Summary of potential covariates to be evaluated on PK parameter (cont.)

No.	Covariates and descriptions	Model parameters
16	CL_{CR} estimated by mJEL equation (CL_{CRmJEL_noBSA}, mL/min)[49]	CL
18	GFR estimated using the 4-variables MDRD equation (GFR_{MDRD_BSA}, mL/min/1.73 m^2) [50]	CL
19	GFR_{MDRD} without BSA (GFR_{MDRD4_noBSA}, mL/min)[50]	CL
22	GFR estimated by CKD-EPI equation (GFR_{EPI_BSA}, mL/min/1.73 m^2)[51]	CL
23	GFR_{EPI} without BSA (GFR_{EPI_noBSA}, mL/min)[51]	CL
24	Acute kidney injury (AKI) Definition and staging of AKI was based on AKIN criteria[52]	CL
25	Inotropics or vasopressors used (mg/kg/min)	CL, V_C, V_P
26	High dose vasopressors/inotropic used (yes/no)#	CL, V_C, V_P
27	Septic shock The definition was based on sepsis-3 criteria	CL, V_C, V_P
28	Corticosteroid used (yes/no)	CL, V_C, V_P
29	Total bilirubin (mg/dL)	CL
30	Direct bilirubin (mg/dL)	CL
31	Aspartate aminotransferase (AST, unit/L)	CL
32	Alanine amionotransferase (ALT, unit/L)	CL

Table 6 Summary of potential covariates to be evaluated on PK parameter (cont.)

No.	Covariates and descriptions	Model parameters
33	Alkaline phosphatase (ALP, unit/L)	CL
34	Serum albumin (ALB, g/dL)	CL, V_C, V_P
35	Hypoalbuminemia (ALB < 2.5 g/dL)	CL, V_C, V_P
36	APACHE II score	CL, V_C, V_P
37	SOFA score	CL, V_C, V_P
38	Mechanical ventilation used (MCV)	CL, V_C, V_P
39	Cumulative fluid balance (L/day)	V_C, V_P
40	Cumulative fluid balance per kg (L/kg/day)	V_C, V_P
41	24-h fluid balance (L/day)	V_C, V_P
42	48-h fluid balance (L/day)	V_C, V_P

[a] BSA, an individual's body surface area estimated by Gehan and George formula[53]; CL_{CR}, creatinine clearance; MDRD, the Modification of Diet in Renal Disease study equation; CKD-EPI, the Chronic Kidney Disease Epidemiology Collaboration study equation; CG, Cockcroft-Gault equation; JEL, Jelliffe equation; mJEL, Modified Jelliffe equation

High dose vasopressors/inotropic is defined as use norepinephrine or epinephrine > 0.5 mcg/kg/min or dopamine >25 mcg/kg/min [54]

3.10.4 Model evaluation

The minimum objective function value (OFV), parameter precision, and visual inspection of various goodness-of-fit plots were considered for model selection. A non-parametric bootstrap (n=2000) was performed to evaluate the robustness of the final model and to obtain confidence intervals of all parameter estimates. The predictive performance of the final model was also examined by using a prediction-corrected visual predictive check (pcVPC) to compare the 5^{th}, 50^{th}, and 95^{th} percentiles of the observed and simulated concentrations (n=2000).

3.11 Dosing optimization using Monte Carlo simulations (MCS)

The final PPK model along with the significant covariates, were used to generate the unbound concentration-time profiles of various carbapenem dosing regimens over the first 48 hours of the treatment course (n=5,000). The model simulations were conducted using NONMEM® version 7.4 (ICON Development Solution, Ellicott City, MD, USA) and R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria). The IIV of each PK parameter and residual variability was also included in each simulation. From the simulated concentration-time profiles, the $fT_{>MIC}$ was determined for each virtual patient over a range of doubling MICs from 0.0156 to 32 mg/L. Then the probability of target attainment (PTA) was calculated as the percentage of patients who achieved 40%$fT_{>MIC}$, 75%$fT_{>MIC}$, and 100%$fT_{>MIC}$ target. Regimens with PTAs of a least 90% were considered optimal.

3.12 Calculation of individual PK/PD index

The individual PK parameters from the final population PK model were used to calculated PK/PD index. The %$fT_{>MIC}$ of meropenem and imipenem was determined for each individual patient whose MIC was available using NONMEM® software version 7.4 (ICON Development Solution, Ellicott City, MD, USA) and R program version 3.6.0. If patients were infected with more than one strain/pathogen, the pathogen with the highest MIC was chosen to calculate the %$fT_{>MIC}$.

3.13 Clinical outcome assessment

The clinical outcomes of the study were the clinical response, microbiological success, and 28-day all-cause mortality.

Clinical response

The clinical responses were assessed by comparing the baseline clinical signs/symptoms of infection with those at the end of therapy. Clinical outcomes were categorized as either clinical success or failure. Clinical success was defined as completed or partial resolution of signs and symptoms caused by the infection, completion of treatment course without change or requirement for additional systemic antimicrobial therapy, and no additional antibiotic resumption within 48 h of cessation.

Clinical failure was defined as the persistence, worsening, development of any new clinical signs and symptoms of infection or death during the treatment course.

Microbiological response

The microbiological outcome was evaluated in patients whose baseline pathogen was identified by repeat culture of a suspected site of infection obtained between 3 days before through 7 days after clinical response. It was categorized as either success (including bacterial eradication and presumed eradication) or failure (including persistence and presumed persistence).

28-day all-cause mortality

It was defined as death from any cause within 28 days after the onset of infection.

3.14 Operational definitions

- Critically ill patients

  Patients who were admitted to medical or surgical intensive care units

- Cumulative fluid balance

  The sum of daily fluid balance (daily fluid intake – daily fluid output) from the first day of intensive care unit admission until the day of blood sample collection for pharmacokinetic analysis.

- Minimum inhibitory concentration (MIC)

  The lowest concentration (mg/L) of antimicrobial agents that prevents the visible growth of bacteria.

- Time above MIC ($fT_{>MIC}$)[55]

  The cumulative percentage of time over a 24 or 48 hours period that the free drug concentration exceeds the MIC value. In this study, the 24-hour period was used for the actual individual $fT_{>MIC}$ calculation, and the 48-hour period was used for dosing optimization.

- 40% of time above MIC ($40\%fT_{>MIC}$)

  The cumulative percentage of time over a 24 or 48 hours period that the free drug concentration exceeds the MIC value for at least 40% of the dosing interval. In this study, the 24-hour period was used for the actual individual $fT_{>MIC}$ calculation, and the 48-hour period was used for dosing optimization.

- 75% of time above MIC ($75\%fT_{>MIC}$)

  The cumulative percentage of time over a 24 or 48 hours period that the free drug concentration exceeds the MIC value for at least 75% of the dosing interval. In this study, the 24-hour period was used for the actual individual $fT_{>MIC}$ calculation, and the 48-hour period was used for dosing optimization.

- 100% of time above MIC ($100\%fT_{>MIC}$)

  The cumulative percentage of time over a 24 or 48 hours period that the free drug concentration exceeds the MIC value for 100% of the dosing interval. In this study, the 24-hour period was used for the actual individual $fT_{>MIC}$ calculation, and the 48-hour period was used for dosing optimization.

- Probability of target attainment (PTA) [55]

  The probability that at least the time above MIC ($fT_{>MIC}$) is achieved the predefine PK/PD targets at a specific MIC.

3.15 Ethical considerations

The ethical approval of the study protocol was granted by the Human Research Ethic Committee (HREC), Faculty of Medicine, Prince of Songkla University, Thailand (REC.61-061-14-1; 22 June 2018, Appendix E). The protocol was also registered at www.clinicaltrial.gov under identifier NCT03858387.

The protocol amendment for expanding the study site to the surgical intensive care unit at Songklanagarind Hospital, Thailand, was also approved by HREC (01 Jan 2020, Appendix E).

All participants or their legal representatives gave written informed consent before enrollment.

CHAPTER 4

RESULTS

This chapter describes the result of data analysis methods that have been mention in chapter three, in which all of the results will be used to support and answer the research objectives.

4.1 Population pharmacokinetics of meropenem

4.1.1 Demographic and clinical data

Two hundred and thirty-six critically ill patients who received intravenous meropenem between June 2018 and July 2020 were considered for study inclusion, of whom 184 patients failed to meet eligibility criteria. The remaining 52 patients were enrolled in the study, and the baseline characteristics were reported in Table 7. Most patients were admitted to the medical ICU (92%) and were male (60%) with a median age of 63. The median of the acute physiology and chronic health evaluation (APACHE) II score was 20 (range, 3 - 34). The median cumulative fluid balance, which is the sum of daily fluid balance from the first day of ICU admission until the PK day, was 3.6 liters (range, -2 to 11 liters). Approximately 30% of all patients exhibited moderate to severe renal impairment with GFR_{EPI} of less than 30 mL/min.

According to sepsis-3 criteria, only 15% of the included patients had septic shock. The primary infection source was respiratory (63.5%) and intra-abdominal (15.4%), respectively. Meropenem dosage regimens prescribed in this study ranged from 0.5 g every 12 hours to 2 g every 8 hours, and the standard infusion duration of 30-60 minutes was used to administer meropenem to all patients.

Table 7 Demographics and clinical characteristics of 52 critically ill patients receiving intravenous meropenem therapy[a]

Characteristic	All patients (n=52)
Male, *n* (%)	31 (59.6)
Age (years), median (IQR)	63 (48.0 – 74.0)
Body weight (kg), median (IQR)	61.5 (53.4 – 69.8)
Ideal body weight (kg), median (IQR)	57.1 (51.0 – 61.7)
Body mass index (kg/m^2), median (IQR)	22.9 (20.6 – 25.4)
Underlying disease, *n* (%)	
Hypertension	24 (46.2)
Diabetes	11 (21.2)
Ischemic heart disease	10 (19.2)
Hematologic malignancy	9 (17.3)
Solid malignancy	13 (25.0)
Pulmonary disease	7 (13.5)
Liver disease	6 (11.5)
Immunocompromised	7 (13.5)
Intensive care unit (ICU), *n* (%)	
Medical-ICU	48 (92.3)
Surgical-ICU	4 (7.7)
Disease severity score, median (IQR)	
APACHE II score	20 (14 – 23)
SOFA score	8 (6 – 11)
Inotropic/vasopressor used, *n* (%)	
Norepinephrine	17 (32.7)
Dopamine	6 (11.5)
Total bilirubin (mg/dL), median (IQR)	1.3 (0.5 – 3.9)
GFR_{EPI} (mL/min), median (IQR)	49.8 (25.1 – 86.3)
$CL_{CR\text{-}CG}$ (mL/min), median (IQR)	44.6 (24.2 – 80.7)
Acute kidney injury, *n* (%)	9 (17.3)
Septic shock, *n* (%)	8 (15.4)

Table 7 Demographics and clinical characteristics of 52 critically ill patients receiving intravenous meropenem therapy (continue)[a]

Characteristic	**All patients (n=52)**
Serum lactate (mmol/L), median (IQR)	3.4 (1.7 – 5.7)
Serum albumin (g/dL), median (IQR)	2.4 (2.0 – 2.9)
Hypoalbuminemia, *n* (%)	28 (53.8)
Mechanical ventilator, *n* (%)	46 (88.5)
Cumulative fluid balance (liters), median (IQR)	3.6 (1.7 – 5.9)
ICU length of stay (days), median (IQR)	9 (4 – 14)
Hospital length of stay (days), median (IQR)	24 (14 – 40)
Primary infection site, *n* (%)	
Respiratory	33 (63.5)
Intra-abdominal	8 (15.4)
Genitourinary	6 (11.5)
Bloodstream	2 (3.8)
Others	3 (5.8)
Nosocomial infection, *n* (%)	38 (73.1)
Meropenem dosage regimens, *n* (%)	
LD 2 g, 1 g q 8 h	24 (46.2)
LD 2 g, 1 g q 12 h	10 (19.2)
LD 2 g, 0.5 g q 12 h	6 (11.5)
2 g q 8 h (first day) then maintenance dose	4 (7.7)
2 g q 8 h	3 (5.8)
Others	5 (9.6)

[a]Data reported on the day of blood collection for pharmacokinetic analysis; IQR, interquartile range; GFR_{EPI}, estimated glomerular filtration rate (GFR) using the Chronic Kidney Disease Epidemiology Collaboration equation and was multiplied by each individual body surface area/1.73 m^2; CL_{CR-CG}, CL_{CR} estimated using standard Cockcroft-Gault formula based on total body weight; APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment score; LD, loading dose.

4.1.2 Structural model of meropenem

A total of 256 unbound meropenem concentrations from 52 critically ill patients were obtained for population pharmacokinetic (PPK) analysis. There were 16 drug concentrations (6%) that were reported as below the lower limit of quantification (LLOQ). Several methods include: discarding all of the below LLOQ value, replacing the below LLOQ value by LLOQ/2, Beal M3 method, and 'all data' approach had been evaluated to deal with these left-censored values. The parameter estimates were very similar for all four methods, as summarized in Table B1 (Appendix B). Based on the results of this analysis, the 'all data' approach was selected to handling the below LLOQ data.

All detectable concentrations, including points below the LLOQ, were included as continuous data, and the concentrations below the limit of detection (LOD), which presented only 8 out of 256 (3%) in the current dataset, were discarded. Therefore, the remaining 248 concentrations ranging from 0.12 to 127.7 mg/L were available for PPK analysis.

The comparisons of the PK parameter estimated obtained from SAEM and FOCE-I algorithm are presented in Table B2 (Appendix B). Both algorithms provided similar parameter estimations, but the runtimes were significantly shorter with FOCE-I compared to the SAEM method. This indicate that the FOCE-I algorithm reduced the estimation time without compromising the quality of parameter estimates in the current analysis. Therefore, the FOCE-I method was used for parameter estimation throughout the model-building process.

Based on the minimum objective function (OFV), Akaike information criterion (AIC), and the goodness-of-fit (GOF) plots, a two-compartment model with first-order elimination from the central compartment was chosen as the best-fit model. The combined proportional and additive error model provided the lowest AIC. However, the additive term of the combined error model was small and its standard error was large. This indicated that an additive structure could not be reliably estimated. Further model simplification by removing the additive error term did not change the overall model fit (ΔAIC=3.06), as shown in Figure B1 (Appendix B). Therefore, the proportional error model was selected to describe the residual variability of meropenem concentration-time profiles.

The two-compartment model was parameterized in terms of clearance (CL), central volume of distribution (V_C), the peripheral volume of distribution (V_P), and intercompartment clearance (Q). The interindividual variability (IIV) was implemented on all PK parameters. However, the IIV on Q was small; therefore, it was not estimated and was fixed to zero. Based on overall basic GOF plots (Figure 3), a sufficient structural model was obtained.

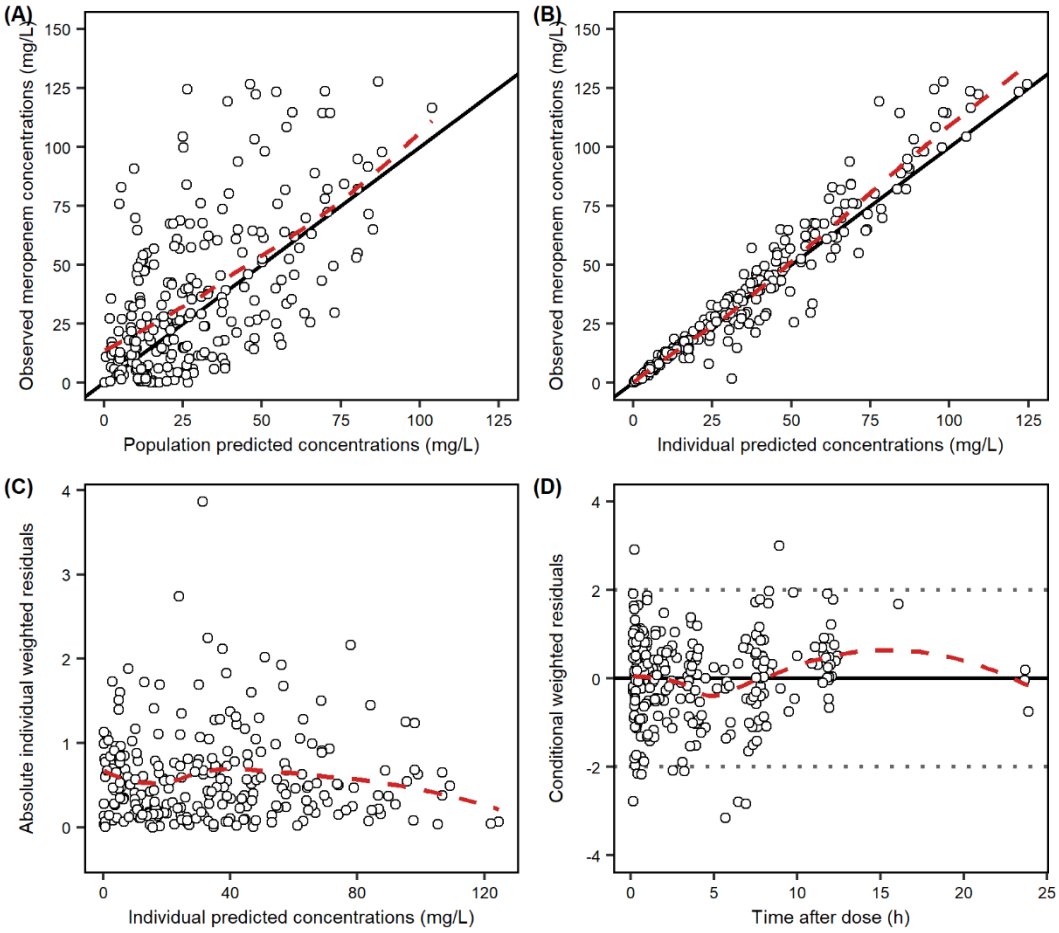


Figure 3 The goodness-of-fit plots of the meropenem structural pharmacokinetic model. Solid lines represent the line of identity, and the dashed line is the locally weighted smoothing (LOESS) line to indicate trends.

4.1.1 Covariate and final model of meropenem

The correlation analysis between covariates was performed before the covariate model building to avoid the simultaneous incorporation of colinear variables into the model. Figure B2 (Appendix B) showed that most of the tested covariates were not highly correlated. There were only two pairs of covariates with a correlation coefficient greater than 0.5 (GFR_{EPI} vs. Age, APACHE vs. SOFA). The scatterplots and boxplots of PK parameters versus the covariates of interest were provided in Figure 4.

All renal function markers from five different equations implemented as a covariate on clearance significantly improved the model fit Table B3 (Appendix B). The formulas that considered the patients' body surface area (BSA) or used the raw estimated glomerular filtration rate (GFR) giving units in mL/min were slightly superior to the GFR with BSA normalization (mL/min/1.73 m^2). Among all renal function markers and other covariate tested, the creatinine clearance calculated by the Cockcroft-Gault equation based on lean body weight (CL_{CRCG_LBW}) provided the lowest OFV. However, it was not statistically significant difference from the GFR using the Chronic Kidney Disease Epidemiology Collaboration equation (GFR_{EPI}). Since GFR_{EPI} are widely used for staging chronic kidney disease and are routinely reported without the need for additional calculations, it was selected and brought forward for further model development. The detail of the first step of forward addition was described in Table B4.

After including the GFR_{EPI} into the model, the remaining covariates were tested. The use of dopamine and serum albumin exhibited a significant effect on the volume of distribution of meropenem. The effect of dopamine on V_P was selected on this step because it provided the lowest reduction in OFV (Table B5, Appendix B). After accounting for the first two covariates effect, the relationship between serum albumin and V_P was still evident (Table B6, Appendix B). Therefore, it was further added to the reference model. When combining GFR_{EPI}, dopamine used, and serum albumin effect, no other covariates were found to significantly affect the PK of meropenem (Table B7, Appendix B).

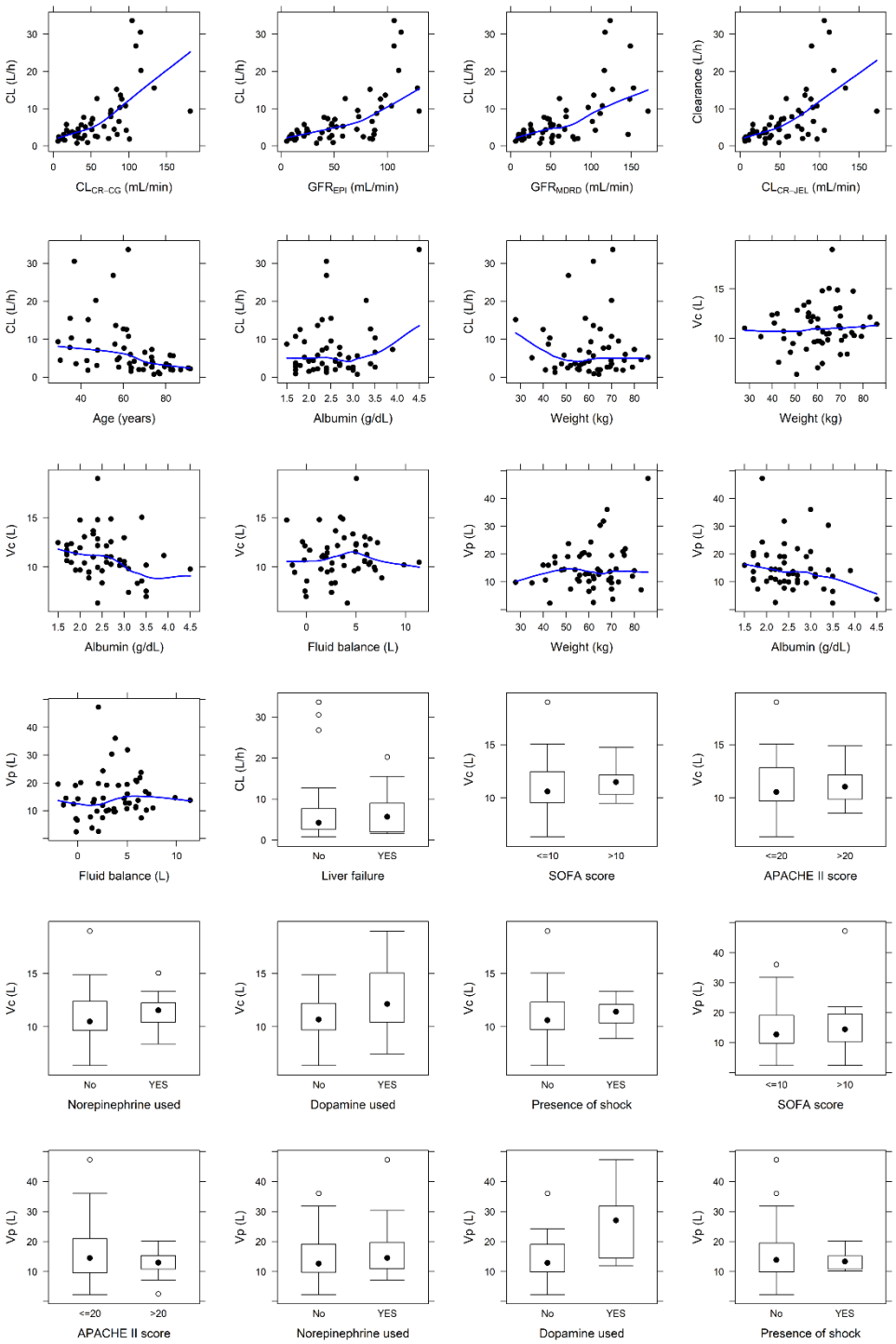


Figure 4 Graphical assessment of the relationship between some potential covariates and meropenem pharmacokinetic parameters. CL, Vc and Vp are total clearance, central volume of distribution, and peripheral volume of distribution, respectively.

After completion of forward selection step, the full multivariable model was evaluated. The pair-wise scatterplots of ETA terms and a correlation coefficient were generated to guide the development of a parsimonious omega-structure (Figure 5). According to the ETA pair-plots, there was a weak correlation between the ETA of CL and V_C. However, the estimation of the covariance term between the ETA on CL and V_C resulted in a reduction in the OFV of 6.7 units and improved in overall goodness-of-fit plots. Therefore, it was retained in the model.

In the backward deletion process, removal of GFR_{EPI}, dopamine used, or serum albumin resulted in an increase of OFV greater than 6.64. Therefore, these covariates were retained in the final model. The details of backward deletion step are displayed in Table B8 (Appendix B).

The final model is as follows:

$$CL\ (L/h) = 4.27 \times exp\ (0.018 \times (GFR_{EPI} - 50)) \times exp\ (\eta CL)$$

$$V_C\ (L) = 9.85 \times exp\ (\eta V_C)$$

$$V_P\ (L) = 12.5 \times (1 + 2 \times DA) \times (1 + -0.395 \times (ALB - 2.5)) \times exp\ (\eta V_P)$$

$$Q\ (L/h) = 15.4$$

where

CL is the individual clearance

GFR_{EPI} is estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation (mL/min)

V_C is the individual central volume of distribution

V_P is the peripheral volume of distribution

Q is the intercompartment clearance

DA is equal to 1 if patient use dopamine, otherwise it was set to 0

ALB is the serum albumin (g/dL)

The population pharmacokinetic parameter estimated in the final model is summarized in Table 8. All parameters estimated were identified with acceptable precision.

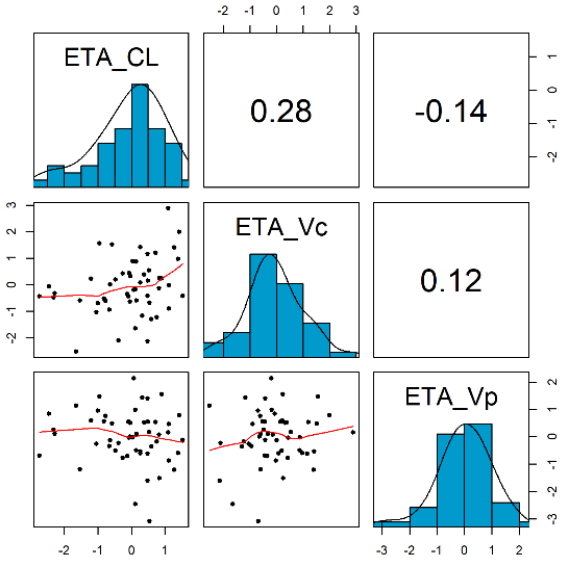


Figure 5 A pair-wise plots and histogram of extended empirical Bayes estimated. The correlation coefficient between ETAs was reported in upper right panel.

Table 8 Population pharmacokinetic parameters of meropenem from the base and final model[a]

Parameter	Base model (OFV=1412.4)	Final model[b] (OFV=1343.5)		
	Estimate (%RSE)	Estimate (%RSE)	%Shr	Median (95% CI) of bootstrap estimate
Fixed-effect parameters				
CL (liters/h)	4.83 (12.6)	4.27 (8.6)		4.22 (3.51 –5.01)
θ_1		0.018 (12.0)		0.018 (0.013 – 0.022)
V_C (liters)	11.1 (12.7)	9.85 (16.2)		9.98 (6.76 – 12.90)
V_P (liters)	13.9 (13.2)	12.5 (11.5)		12.4 (9.13 – 15.86)
θ_2		2.0 (46.2)		2.12 (0.45 – 11.32)
θ_3		-0.395 (14.6)		-0.378 (-0.637, -0.125)
Q (liters/h)	12.4 (42.5)	15.4 (39.9)		14.5 (6.92 – 28.69)
Interindividual variability (%CV)				
IIV on CL	88.3 (9.3)	63.5 (10.7)	0.9	63.5 (49.4 -76.3)
IIV on V_C	31.6 (31.9)	36.2 (28.7)	23.0	36.6 (14.8 -57.6)
IIV on V_P	77.2 (20.5)	47.7 (30.9)	32.1	47.0 (10.3 – 78.5)
IIV on Q	NE	NE		NE
Cov CL-V_C	-	0.149 (47.7) (r=0.65)		0.141 (0.025 -0.326)
Residual variability (%)				
Proportional	24.6 (9.2)	24.6 (10.1)	17.9	23.4 (18.8 – 28.0)

[a] %RSE, percentage of relative standard error; %Shr, percentage of shrinkage; %CV, percentage of coefficient of variation; OFV, minimum objective function value; NE, not estimated; Cov, covariance; *r*, correlation coefficient; CI, confidence interval; CL, total clearance; V_C, central volume of distribution; V_P, peripheral volume of distribution; Q, intercompartment clearance; GFR_{EPI}, glomerular filtration rate calculates by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation; DA, dopamine use; ALB, serum albumin (g/dL).

[b] The final PK model parameter: $CL\ (L/h) = 4.27 \times exp(\theta_1 \times (GFR_{EPI} - 50))$

$Vp\ (L) = 12.5 \times (1 + \theta_2 \times DA) \times (1 + \theta_3 \times (ALB - 2.5))$

4.1.1 Model evaluation

The goodness-of-fit of the model was investigated by visual inspection in all steps during model development. The diagnostic goodness-of-fit (GOF) plots obtained from the final model are presented in Figure 6. The scatter plots of the population predicted concentration (PRED) and individual predicted concentration (IPRED) versus observed concentration (DV) showed no systemic deviation with a heavier distribution of points on one or other side of the identity line and was improved as compared to the structural model (Figure 3). In the plots of conditional weighted residuals versus PRED and time after dose, most of the data points were randomly distributed around zero and lay within -2 to +2. Figure 7 showed the prediction-corrected Visual Predictive Check plot of the final model. The 5^{th}, 50^{th}, and 95^{th} percentiles of the observed data were laid within the 95% confidence interval (95% CI) of the corresponding percentiles of the model prediction, demonstrating consistency between the observed and simulated concentrations. Also, the PK parameters estimated from the final model were in close agreement with the bootstrap parameter and contained within 95% CI obtained from the converged bootstrap runs (Table 8), indicating the stability of the final model.

Based on overall evaluations, the fit of the final model seemed reasonably good with no obvious biases.

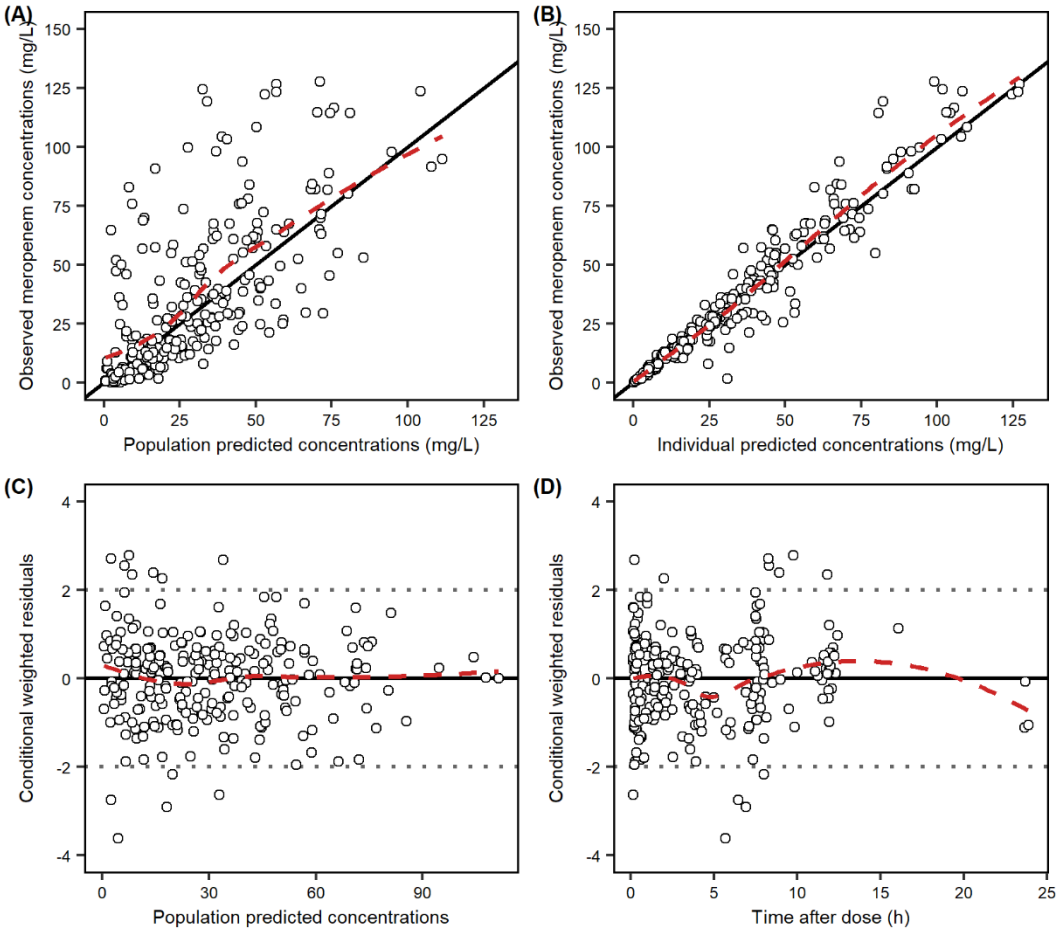


Figure 6 The goodness-of-fit plot of meropenem final pharmacokinetic model. Solid lines represent the line of identity, and the dashed line is the locally weighted smoothing (LOESS) line to indicate trends.

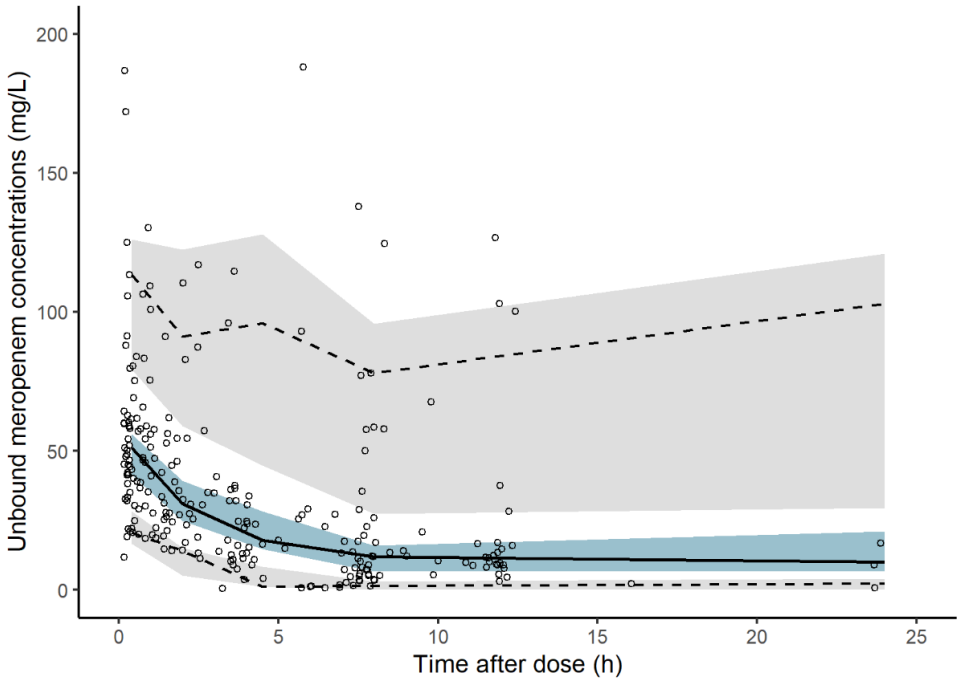


Figure 7 Prediction-corrected visual predictive check (pcVPC) of the meropenem final model. Open circles are observed concentrations. The solid line represents the 50th percentiles of the observation, and dashed lines represent the 5th and 95th percentiles of the observations. The shaded areas are the 95% confidence intervals around the 5th, 50^{th,} and 95th of the simulated data.

4.2 Population pharmacokinetics of imipenem

4.2.1 Demographic and clinical data

Thirty-nine critically ill patients received intravenous imipenem was screened between June 2018 and July 2020. Twenty-one patients who fulfilled eligibility criteria were enrolled in the study. The clinical characteristics of the analyzed patients are described in Table 9. Most of the included patients were male (81%) with a median age of 71 and an APACHE II score of 27. The GFR_{EPI} of included patients were ranged from 6.7 to 114 mL/min, which 30% of the patients had renal impairment (GFR_{EPI} < 30 mL/min).

Imipenem/cilastatin was most commonly prescribed for intra-abdominal (52%) and respiratory tract infection (24%), respectively. The imipenem dosing regimens used in this study were ranged from 0.25 g every 12 hours to 0.5 g every 6 hours, and it was administered as the standard intermittent infusion of 40-60 minutes in all patients.

Table 9 Baseline characteristics of 21 critically ill patients receiving intravenous imipenem therapy[a]

Characteristic	All patients (n=21)
Male, *n* (%)	17 (81)
Age (years), median (IQR)	71 (57 – 73.0)
Body weight (kg), median (IQR)	63 (52 – 71)
Body weight (kg), median (IQR)	62.8 (52 - 71.0)
Ideal body weight (kg), median (IQR)	59.6 (55.1 - 65.9)
Body mass index (kg/m^2), median (IQR)	23.0 (19.3 - 25.4)
Underlying disease, *n* (%)	
Hypertension	10 (47.6)
Diabetes	7 (33.3)
Dyslipidemia	5 (23.8)
Hematologic malignancy	3 (14.5)
Solid malignancy	7 (33.3)
Pulmonary disease	2 (9.5)
Liver disease	2 (9.5)
Ischemic heart disease	1 (4.8)
Intensive care unit (ICU), n (%)	
Medical-ICU	15 (71)
Surgical-ICU	6 (29)
Disease severity score, median (IQR)	
APACHE II score	18 (14 - 25)
SOFA score	7 (3 - 11)
$CL_{CR\text{-}CG}$ (mL/min), median (IQR)	65.8 (22.6 - 85.0)
GFR_{EPI} (mL/min), median (IQR)	57.3 (24.7 – 91.1)
Acute kidney injury, *n* (%)	4 (19 %)
Total bilirubin (mg/dL), median (IQR)	1.38 (0.8 - 5.1)
Serum lactate (mmol/L), median (IQR)	2.8 (1.9 – 5.3)
Septic shock, n (%)	5 (23.8)

Table 9 Baseline characteristics of 21 critically ill patients receiving intravenous imipenem therapy (continued)[a]

Characteristic	All patients
Serum albumin (g/dL), median (IQR)	2.5 (2.2 - 2.7)
Hypoalbuminemia, *n* (%)	10 (47.6)
Mechanical ventilator, *n* (%)	19 (90.5)
Cumulative fluid balance (liters), median (IQR)	4.8 (2.7 - 9.2)
ICU length of stay (days), median (IQR)	7 (4 – 12)
Hospital length of stay (days), median (IQR)	21 (13 – 24)
Nosocomial infection, *n* (%)	18 (85.7)
Primary infection site, *n* (%)	
Intra-abdominal	11 (52.4)
Respiratory	5 (23.8)
Skin and soft tissue	2 (9.5)
Genitourinary	1 (4.76)
Bloodstream	1 (4.8)
Unknown	1 (4.8)
Imipenem dosage regimens, *n* (%)	
LD 1 g, 0.5 g q 6 h	7 (33.3)
LD 1 g, 0.5 g q 12 h	7 (33.3)
LD 1 g, 0.5 g q 8 h	2 (9.5)
LD 1 g, 0.25 g q 8 h	3 (14.3)
0.25 g q 6 h	1 (4.8)
0.25 g q 12 h	1 (4.8)

[a]Data reported on the day of blood collection for pharmacokinetic analysis; IQR, interquartile range; GFR_{EPI}, estimated glomerular filtration rate (GFR) using the Chronic Kidney Disease Epidemiology Collaboration equation and was multiplied by each individual body surface area/1.73 m^2; CL_{CR-CG}, CL_{CR} estimated using standard Cockcroft-Gault formula based on total body weight; APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment score; LD, loading dose.

4.2.2 Structural model of imipenem

A total of 104 unbound imipenem concentrations from 21 critically ill patients were available for PPK model building. There was only one concentration reported as below the limit of detection and was excluded from subsequent PPK analysis. Log-transform concentrations and additive error model was used during the structural model development. After testing different structural model, a 2-compartment model with first-order elimination provided the best fit for imipenem concentration-time profiles. Adding the second compartment resulted in a significant improvement compared to the 1-compartment model (ΔOFV= -28.4). For the residual error model and other processes of model development, un-transform concentrations were used. The proportional error model best described the residual variability. The interindividual variability was able to estimate only for CL and V_C. The FOCE-I estimation algorithm provided a similar parameter estimated compared to the SAEM method with shorter runtimes; therefore, it was used throughout the model building process (Table B9, Appendix B). The diagnostic plots for the imipenem structural model showed adequate fit to the data (Figure 8).

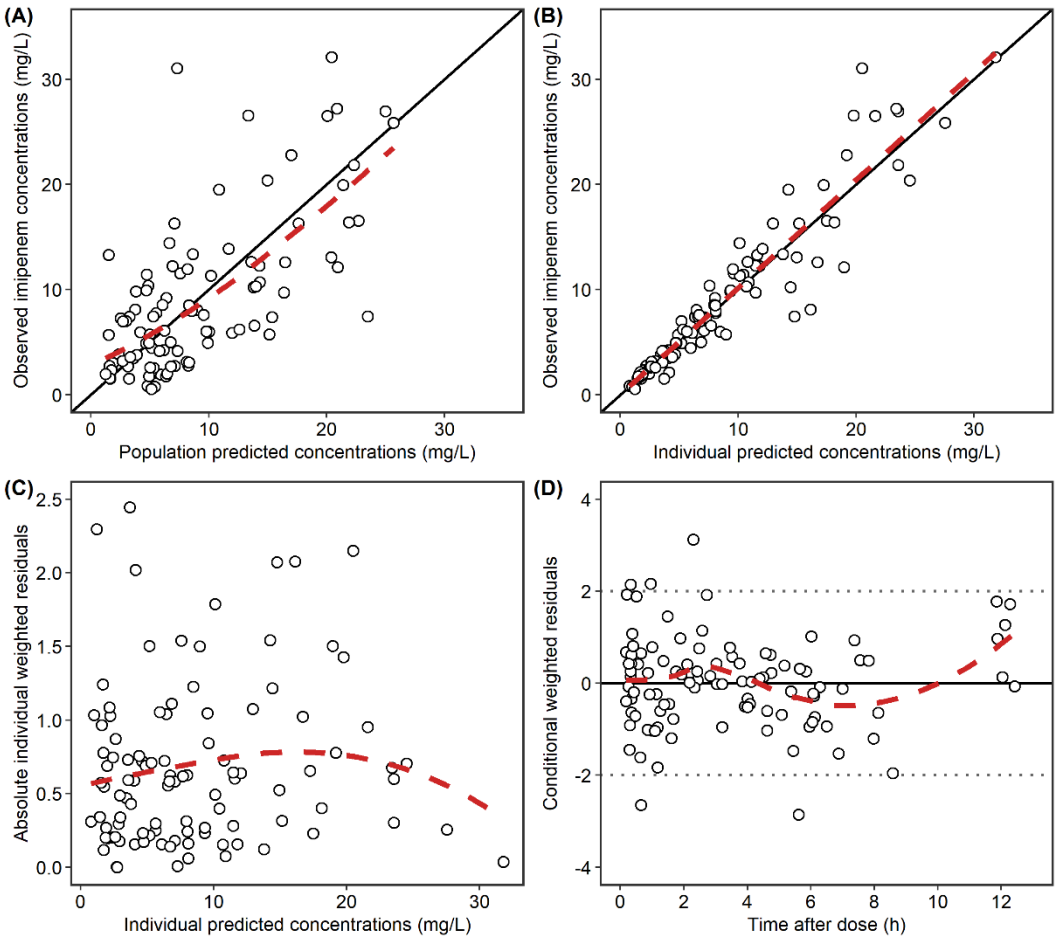


Figure 8 The goodness-of-fit plots of the imipenem structural pharmacokinetic model. Solid lines represent the line of identity, and the dashed line is the locally weighted smoothing (LOESS) line to indicate trends.

4.2.3 Covariate and final model of imipenem

The base two-compartment model was used as a reference for the covariate analysis. The graphical analysis of correlation among covariates and its relationship to PK parameters are presented in Figure B3 (Appendix B) and Figure 9, respectively. The first step of the forward inclusion process revealed that the renal function markers, vasopressor used, and SOFA score significantly affected imipenem clearance, while the cumulative fluid balance was identified as a significant covariate affecting the V_C of imipenem. Among significant covariates, the inclusion of the effect of GFR_{EPI} on imipenem clearance provided the largest reduction in OFV (Table B10, Appendix B). Therefore, it was chosen to retain in the PPK model. After the inclusion of GFR_{EPI}, all other covariates tested were not found to have a significant effect on imipenem parameters; therefore, they were not included in the model (Table B11, Appendix B). A review of the scatter plot matrix between random effect parameters showed a weak correlation between the ETA of CL and V_C (Figure 10). However, including the covariance term between them resulted in a significant decrease of OFV, and it is estimated with acceptable precision; therefore, it was not removed from the final model. For the backward elimination step, removing the GFR_{EPI} from the model resulted in an increase of OFV by 18.6 units. Therefore, it was retained in the final model.

The final population pharmacokinetic model for imipenem clearance was as follows:

$$CL\ (\text{liters/h}) = 8.99 \times (1+0.011\times(GFR_{EPI} - 60)) \times \exp(\eta CL)$$

$$V_C\ (\text{liters}) = 15.2 \times \exp(\eta Vc)$$

$$V_P\ (\text{liters}) = 23.4$$

$$Q\ (\text{liters/h}) = 15.9$$

Where CL is the individual imipenem clearance

GFR_{EPI} is estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation (mL/min)

V_C is the individual central volume of distribution

V_P is the peripheral volume of distribution

Q is the intercompartment clearance

The final parameter estimates, along with its precision and nonparametric bootstrap-derived confidence intervals, are provided in Table 10.

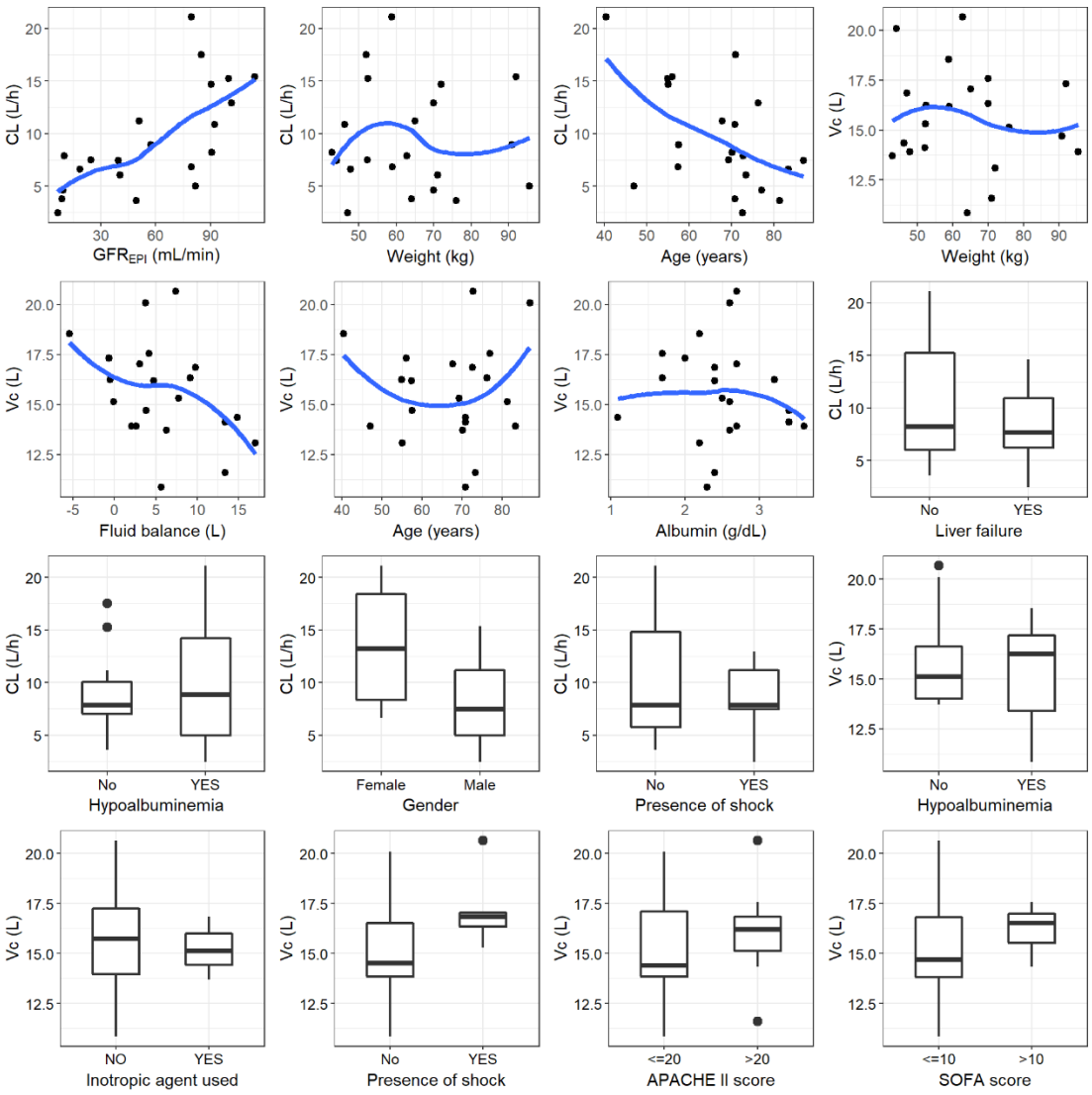


Figure 9 Graphical assessment of relationship between some potential covariates and imipenem pharmacokinetic parameters. CL and Vc are total clearance, and central volume of distribution, respectively.

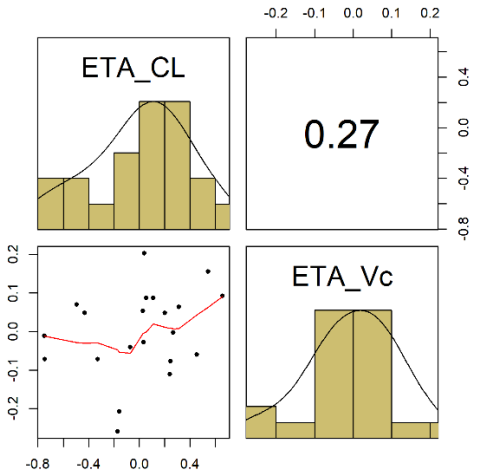


Figure 10 A pair-wise plots and histogram of the empirical Bayes estimated. The correlation coefficient between ETAs was reported in the upper right panel.

Table 10 Population pharmacokinetic parameters of imipenem from the base and final model [a]

Parameter	Base model (OFV=279.13)	Final model[b] (OFV=258.93)		
	Estimate (%RSE)	Estimate (%RSE)	%Shr	Median (95% CI) of bootstrap estimate
Fixed-effect parameters				
CL (liters/h)	8.12 (12.8)	8.99 (10.4)		9.04 (7.32 – 11.16)
θ_1		0.011 (14.7)		0.010 (0.007-0.013)
V_C (liters)	15.4 (15.5)	15.2 (13.5)		15.12 (8.16-19.54)
V_P (liters)	24.3 (14.3)	23.4 (13.5)		24.23 (17.44-32.57)
Q (liters/h)	15.4 (38.1)	15.9 (34.9)		15.69 (7.93-35.68)
Interindividual variability (%CV)				
IIV on CL	56.4 (13.0)	41.6 (15.0)	0.1	39.85 (26.27-52.79)
IIV on V_C	26.7 (57)	39.0 (34.0)	14.0	40.48 (14.31-90.28)
IIV on V_P	NE	NE		NE
IIV on Q	NE	NE		NE
Cov CL-V_C	-	0.125 (63.2) (r=0.77)		0.35 (0.022-0.608)
Residual variability (%)				
Proportional	24.0	23.2	12.8	22.25 (17.11 – 26.81)

[a] %RSE, percentage of relative standard error; %Shr, percentage of shrinkage; %CV, percentage of the coefficient of variation; OFV, minimum objective function value; NE, not estimated; Cov, covariance; *r*, correlation coefficient; CI, confidence interval; CL, total clearance; V_C, central volume of distribution; V_P, the peripheral volume of distribution; Q, intercompartment clearance; GFR_{EPI}, glomerular filtration rate calculates by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

[b] The final PK model parameter: CL (liters/h) = $8.99 \times (1+\theta_1 \times (GFR_{EPI} - 60))$

4.2.4 Model evaluations

Both fixed and random effects parameters in the final model could be estimated with acceptable precision. The goodness-of-fit plots showed that the final model provides an adequate description of the observed imipenem concentrations (Figure 11). There is no clear bias in plots of the observation versus population predicted (PRED) or individual predicted (IPRED) concentrations. The PRED and IPRED data points were evenly distributed around the line of unity. The conditional weighted residuals were normally distributed around zero.

The median parameter estimates from the final model were generally similar to and lie within a 95% confidence interval of bootstrap analysis, demonstrating the robustness of the model (Table 10). The final model was further evaluated using the prediction-corrected visual predictive check (pcVPC). As shown in Figure 12, the pcVPC display a good predictive performance, which evident by the most of the observed concentrations were located within the 95% prediction interval and the 5^{th}, $50^{th,}$ and 95^{th} percentiles of the observed data were lay within the 95% confidence interval of the corresponding percentiles of the model prediction.

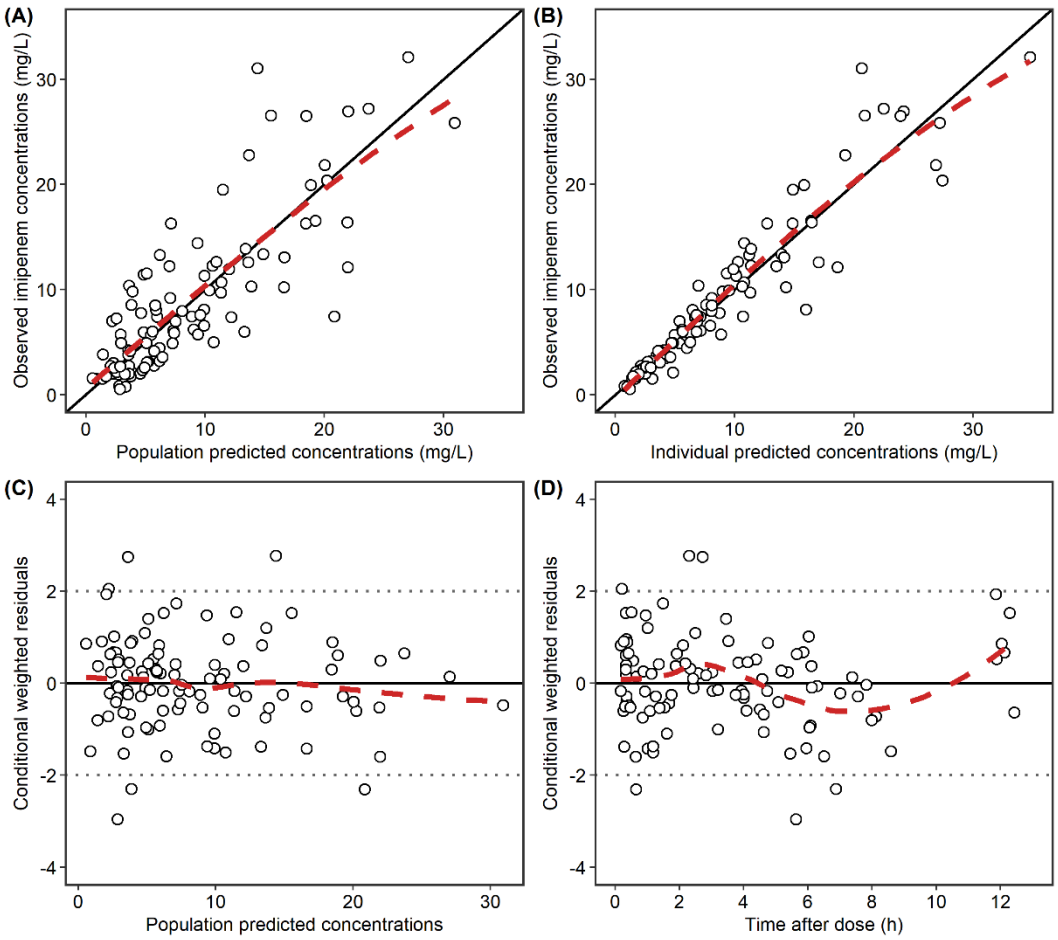


Figure 11 The goodness-of-fit plots of the imipenem final pharmacokinetic model. Solid lines denote the line of identity, and the dashed line is the locally weighted smoothing (LOESS) line to indicate trends.

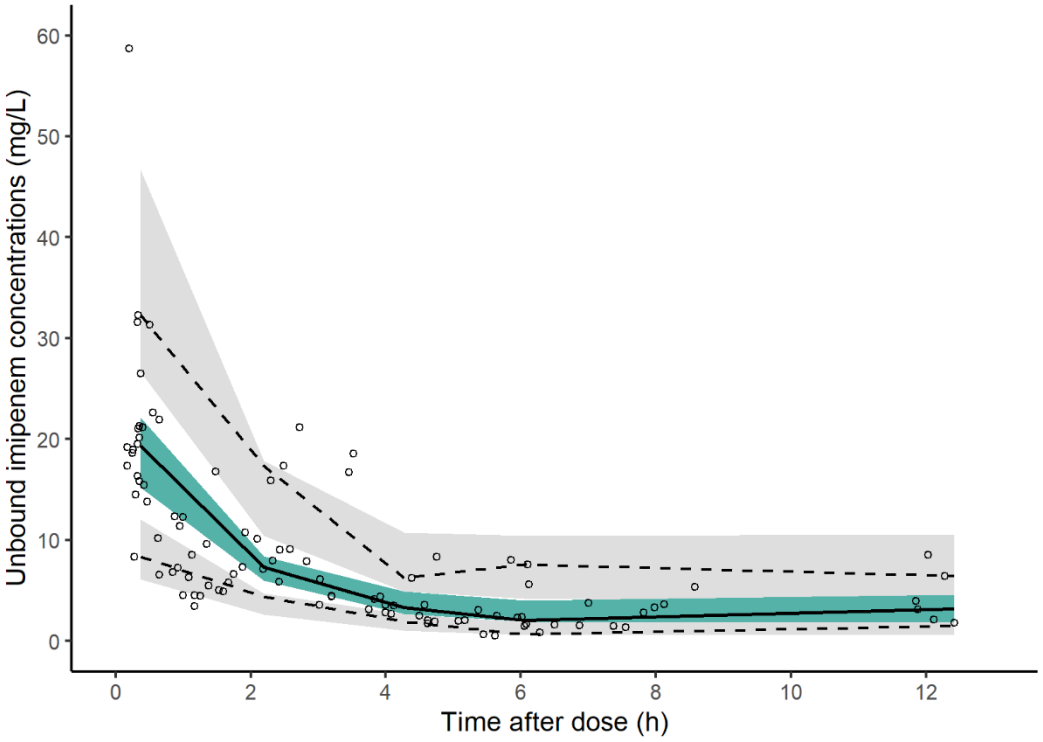


Figure 12 Prediction-corrected visual predictive check (pcVPC) of the imipenem final model. Open circles are observed concentrations. The solid line represents the 50th percentiles of the observation, and dashed lines represent the 5th and 95th percentiles of the observations. The shaded areas are the 95% confidence intervals around the 5th, 50^{th,} and 95th of the simulated data.

4.3 Clinical outcome evaluations

4.3.1 Treatment outcomes of meropenem

According to sepsis-3 criteria, 15% of the included patients had septic shock. These patients had a septic shock on the first day of therapy, and it persistent through the day of blood sample collections. Patient characteristics and dosing regimens of meropenem are shown in Table 7. The primary source of infection was respiratory (63.5%) and intra-abdominal (15.4%), respectively. Meropenem dosage regimens used in this study ranged from 0.5 g every 12 hours to 2 g every 8 hours. The median duration of meropenem therapy was five days (range, 2 to 21 days). Twenty-five percent of included patients received the combination of antimicrobial therapy as part of their treatment, and colistin was administered concomitantly with meropenem in most cases. De-escalations from meropenem to narrow-spectrum antibiotics were 32%. The clinical characteristics of 52 critically ill patients are summarized in Table 7.

A pathogen was identified in 31 patients (60%). The most common isolated microorganisms were *Klebsiella pneumoniae* (33%), *Escherichia coli* (21%), *Pseudomonas aeruginosa* (15%), and *Acinetobacter baumannii* (9%), respectively Table 11.

Table 11 Microbiologic characteristics (n= 85 from 31 patients) and meropenem susceptibility[a]

Pathogen	**No. of isolates**	**Meropenem MIC range (mg/L)**
Klebsiella pneumoniae	12	0.023
Klebsiella pneumoniae (ESBL)	14	0.032 – 0.5
Klebsiella pneumoniae (CRE)	2	≥ 32
Klebsiella pneumoniae (CRE)	1	12
Escherichia coli	15	0.01-0.023
Escherichia coli (ESBL)	3	0.023
Pseudomonas aeruginosa	10	0.064 - 1.0
Pseudomonas aeruginosa (CR-GNB)	3	≥ 32
Acinetobacter baumannii	2	0.38
Acinetobacter baumannii (CR-GNB)	6	≥ 32
Burkholderia pseudomallei	3	0.75
Enterococcus faecium	6	≥ 32
Enterobacter cloacae	1	0.032
Enterobacter aerogenes	1	0.047
Providencia stuartii	3	0.023
Stenotrophomonas maltophilia	2	ND
Moraxella catarrhalis	1	ND
Bacillus spp	1	ND

[a]ESBL, extended-spectrum β-lactamases; CR-GNB, carbapenem-resistant Gram-negative bacteria; CRE, carbapenem-resistant enterobacteriacease; ND, not determined.

Among 31 patients with at least one causative pathogen identified, only 20 patients were included for clinical outcome assessment. Patients were excluded from analysis for the following reasons: specific MIC data of causative pathogens were not available (n=6), infected with *Enterococcus faecium* (n=2), infected with *Stenotrophomonas maltophilia* (n=2), and therapy was continued for only one day (n=1).

Six out of 20 patients had infected with carbapenem-resistant pathogens with MIC value greater than 32 mg/L. Unfortunately, the actual MIC of these pathogens was not available. Sensitivity analyses using MIC values 32, 64, 128 mg/L for calculating individual $fT_{>MIC}$ are demonstrated in Table C1 in Appendix C.

Overall, 90% (18/20) of patients achieved the traditional PK/PD target of 40%$fT_{>MIC}$, and only 55% (11/20) of them achieved the 100%$fT_{>MIC}$ target. The clinical failure and 28-day all-cause mortality rate among these patients was 35% (7/20) and 30% (6/20), respectively. Of note, all seven patients with clinical failure were infected with multidrug-resistant strains with MIC greater than 12 mg/L. The clinical success and survival rate in patients with $fT_{>MIC}$ exceeded 75% was higher than those less than 75%, but the difference was insignificant. (Table 12). For the 100% $fT_{>MIC}$ target evaluation, patients with $fT_{>MIC}$ of 100% had significantly greater clinical success rate than patients with $fT_{>MIC}$ less than 100 (33.3 % vs. 90.9%, *p-value* 0.017). However, there was no statistically significant association between 100% $fT_{>MIC}$ achievement and all-cause mortailiy rate (Table 13).

Table 12 The relationship between 75% $fT_{>MIC}$ target attainment and clinical outcomes of meropenem therapy [a]

Parameter	$fT_{>MIC}$		***p-value*** [#]
	< 75% (n=6)	**≥ 75% (n=14)**	
Meropenem MIC (mg/L)			
0.023 – 0.38	-	10	
0.75 – 1	2	-	
12	-	1	
≥ 32 [b]	4	3	
APACHE II score, median (IQR)	19.5 (18-22)	20 (16 -26)	0.85
SOFA score, median (IQR)	9 (8 -11)	8 (6 – 10)	0.30
Clinical success, *n* (%)	3 (50.0%)	10 (71.4%)	0.61
28 day all-cause mortality, *n* (%)	2 (33.3%)	4 (28.6%)	1.00

[a] MIC, minimum inhibitory concentration (mg/L); $fT_{>MIC}$, the percentage of the dosing interval which the unbound plasma concentration maintain above the MIC value of pathogen; APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment score

[b]MIC value of 32 mg/L was used for calculating $fT_{>MIC}$ in patients infected with a carbapenem-resistant pathogen (MIC ≥ 32 mg/L).

[#]Continuous variables were compared using the Mann–Whitney U-test as data were non-normally distributed, and categorical variables were compared using Fisher's exact test.

Table 13 The relationship between 100% $fT_{>MIC}$ target attainment and clinical outcomes of meropenem therapy[a]

Parameter	$fT_{>MIC}$		
	< 100% (n=9)	**100 % (n=11)**	***p-value*[#]**
Meropenem MIC (mg/L)			
0.023 – 0.38	-	10	
0.75 – 1	2	-	
12	1	-	
≥ 32	6	1	
APACHE II score, median (IQR)	20 (18 -28)	20 (16 -22)	0.324
SOFA score, median (IQR)	9 (8-10)	7 (6 – 11)	0.263
Clinical success, n (%)	3 (33.3%)	10 (90.9%)	0.017
28 day all-cause mortality, n (%)	4 (44.4%)	2 (18.2%)	0.336

[a] MIC, minimum inhibitory concentration (mg/L); $fT_{>MIC}$, the percentage of the dosing interval which the unbound plasma concentration maintain above the MIC value of pathogen; APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment score

[b]MIC value of 32 mg/L was used for calculating $fT_{>MIC}$ in patients infected with a carbapenem-resistant pathogen (MIC ≥ 32 mg/L).

[#]Continuous variables were compared using the Mann–Whitney U-test as data were non-normally distributed, and categorical variables were compared using Fisher's exact test.

4.3.2 Treatment outcomes of imipenem

According to sepsis-3 criteria, five of 21 patients receiving imipenem therapy had septic shock. Of five patients, three of them had a persistent septic shock since the first day of therapy, and 2 of them developed a septic shock after receiving imipenem treatment. Imipenem/cilastatin was most commonly prescribed for intra-abdominal (52%) and respiratory tract infection (24%), respectively. The dosage regimens were ranged from 0.25 g every 12 hours to 0.5 g every 6 hours. The median duration of imipenem/cilastatin treatment was approximately 7 days. (Table 9)

A microbiological culture was documented for 14 out of 21 patients. The most common organisms were *Acinetobacter baumannii* (19%), *Klebsiella pneumoniae* (16%), *Escherichia coli* (12%), and *Enterobacter cloacae* (9%). An overview of the imipenem/cilastatin susceptibility is shown in Table 14. Among 14 patients with a least one causative pathogen identified, only eight patients were included for treatment outcome assessment. Six patients are not assigned for assessment because they had infected with *Enterococcus faecium* (n=1) or *Stenotrophomonas maltophilia* (n=1), had an invasive fungal infection (n=1), and the MIC values were not available (n=3). The treatment outcomes of patients receiving imipenem therapy are described in Table 15. Overall, the median *f*T>MIC of imipenem was 15% (range, 0-100%). The comparison of *f*T>MIC between clinical success and failure was unable to determine because all of the included patients (n=8) were categorized as a clinical failure.

Table 14 Microbiologic characteristics (n= 32 from 14 patients) and imipenem/cilastatin susceptibility[a]

Pathogen	No. of isolates	Imipenem MIC range (mg/L)
Acinetobacter baumannii (CR-GNB)	5	≥ 32
Escherichia coli	3	0.5
Klebsiella pneumoniae (ESBL)	1	8
Klebsiella pneumoniae (CRE)	1	≥ 32
Klebsiella pneumoniae	1	0.38
Pseudomonas aeruginosa	1	2
Enterococcus faecalis	1	3
Enterococcus faecium	3	≥ 32
Enterobacter cloacae	3	0.5 - 8
Haemophilus influenzae	2	0.094
Burkholderia cepacia	1	4
Acinetobacter baumannii	1	ND
Escherichia coli	1	ND
Stenotrophomonas maltophilia	1	ND
Burkholderia cepacia	1	ND
Enterococcus faecalis	1	ND
Klebsiella pneumoniae (ESBL)	1	ND
Klebsiella pneumoniae	1	ND
Pseudomonas aeruginosa	1	ND
Morganella morganii	1	ND
Streptococcus gallolyticus	1	ND

[a]ESBL, extended-spectrum β-lactamases; CR-GNB, carbapenem-resistant Gram-negative bacteria; CRE, carbapenem-resistant enterobacteriacease; ND, not determined.

Table 15 Clinical characteristics and treatment outcome of 8 critically ill patients received imipenem therapy[a]

No	Age	Infection	Pathogen	MIC	$fT_{>MIC}$	APACHE	Clinical response
1	73	IAI	*Escherichia coli*	0.5	100	29	Failure
2	81	HAP	*Haemophilus influenzae*	0.094	100	29	Failure
3	71	IAI, VAP	*Acinetobacter baumannii (CR-GNB)*	≥ 32	0	29	Failure
4	57	BSI	*Enterobacter cloacae*	0.5	100	35	Failure
5	69	IAI	*Klebsiella pneumoniae (ESBL)*	≥ 32	0	24	Failure
6	77	VAP	*Acinetobacter baumannii (CR-GNB)*	≥ 32	0	31	Failure
7	70	IAI, VAP	*Acinetobacter baumannii (CR-GNB)*	≥ 32	0	18	Failure
8	68	IAI	*Enterobacter cloacae*	8	30	29	Failure

[a]IAI, intra-abdominal infection; HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia; BSI, blood stream infection; ESBL, extended-spectrum β-lactamases; CR-GNB, carbapenem-resistant Gram-negative bacteria; APACHE II, acute physiology and chronic health evaluation II; MIC, minimum inhibitory concentration

4.3.3 Treatment outcome of carbapenems

For this analysis, the clinical outcome data of patients treated with meropenem (n=20) and imipenem (n=8) were pooled together. Patients were divided into two groups for clinical outcome assessments according to $fT_{>MIC} \geq 75\%$ or $<75\%$ $fT_{>MIC}$. Most of the patients with $fT_{>MIC}$ less than 75% were infected with carbapenem-resistant pathogens (MIC ≥ 32 mg/L), and these patients had a lower clinical success and survival rate compared to patients with $fT_{>MIC} \geq 75\%$, but statistically insignificant (Table 16).

When categorized patients according to 100% $fT_{>MIC}$ target attainment, similar results were observed. The clinical success rate in patients with $fT_{>MIC}$ of 100% was 71.4%, and it was reduced to 21.4% when this target was not achieved (*p-value* 0.021). For all-cause mortality, patients with $fT_{>MIC}$ of 100% had a lower mortality rate than patients in whom $fT_{>MIC}$ was not achieved 100%. However, the sample size was insufficient to identify a significant relationship between them (Table 17).

Table 16 The relationship between 75% $fT_{>MIC}$ target attainment and clinical outcomes of carbapenem[a]

Parameter	$fT_{>MIC}$		***p-value*[#]**
	< 75% (n=11)	**≥ 75% (n=17)**	
Meropenem and imipenem MIC (mg/L)			
0.023 – 0.38	-	11	
0.5 – 1	2	2	
8-12	1	1	
≥ 32	8	3	
APACHE II score, median (IQR)	20 (18-27)	21 (17-26)	0.98
SOFA score, median (IQR)	11 (8-13)	8 (6-11)	0.19
Clinical success, *n* (%)	3 (27.3)	10 (58.8)	0.17
28 day all-cause mortality, *n* (%)	5 (45.5)	7 (41.2)	1.00

[a] MIC, minimum inhibitory concentration (mg/L); $fT_{>MIC}$, the percentage of the dosing interval which the unbound plasma concentration maintain above the MIC value of pathogen; APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment score

[b] MIC value of 32 mg/L was used for calculating $fT_{>MIC}$ in patients infected with a carbapenem-resistant pathogen (MIC ≥ 32 mg/L).

[#] Continuous variables were compared using the Mann–Whitney U-test as data were non-normally distributed, and categorical variables were compared using Fisher's exact test.

Table 17 The relationship between 100% $fT_{>MIC}$ target attainment and clinical outcomes of carbapenem therapy[a]

Parameter	$fT_{>MIC}$		
	< 100% (n=14)	**100 % (n=14)**	***p*-value[#]**
Meropenem and imipenem MIC (mg/L)			
0.023 – 0.38	-	11	
0.5 – 1	2	2	
8-12	2	-	
≥ 32	10	1	
APACHE II score, median (IQR)	21.5 (18-28)	20.5 (17-25)	0.489
SOFA score, median (IQR)	10 (8-13)	7.5 (6-12)	0.204
Clinical success, n (%)	3 (21.4)	10 (71.4)	0.021
28 day all-cause mortality, n (%)	7 (50.0)	5 (35.7)	0.704

[a] MIC, minimum inhibitory concentration (mg/L); $fT_{>MIC}$, the percentage of the dosing interval which the unbound plasma concentration maintain above the MIC value of pathogen; APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment score

[b] MIC value of 32 mg/L was used for calculating $fT_{>MIC}$ in patients infected with a carbapenem-resistant pathogen (MIC ≥ 32 mg/L).

[#]Continuous variables were compared using the Mann–Whitney U-test as data were non-normally distributed, and categorical variables were compared using Fisher's exact test.

4.4 Pharmacodynamic analysis

4.4.1 Probability of target attainment of meropenem regimens

The final PPK parameter estimates and the significant covariates were used to perform the Monte Carlo simulations. The simulated scenarios were divided into five groups according to the renal function estimated by GFR_{EPI} (<10, 10 – 25, 25.1 – 50, 50.1 – 90, and 90.1 – 130 mL/min). The probability distribution of GFR_{EPI} was generated to follow uniform distribution in each range, while the random effects (IIV and RUV) were considered to follow the log-normal distribution as estimated in the final PPK model. Since the dopamine used and serum albumin showed a significant effect on the V_P of meropenem, they were also included in the simulations. Serum albumin was simulated as a normally distributed variable with a mean and standard deviation of 2.5 ± 0.5 g/dL, and the proportion of dopamine users was set at 12% as in the original dataset. The PTA results of various meropenem regimens for achieving 40%$fT_{>MIC}$, 75%$fT_{>MIC}$, and 100%$fT_{>MIC}$ are presented in Table 18-22.

When considering a conservative of 40%$fT_{>MIC}$ as the target, all studied dose regimens provided the PTA greater than 90% for pathogens with MIC values ranging from 0.0625 to 2 mg/L.

For patients with GFR_{EPI} > 90 mL/min, the standard dose of 1 g every 8 hours administered as an intermittent infusion failed to achieve 75%$fT_{>MIC}$ target for MIC of 2 mg/L. A continuous infusion of meropenem 3 gm with loading dose was required for treating a pathogen with a MIC value of 2 mg/L. In patients with $GFR_{EPI} \leq$ 90 mL/min, the intermittent infusion of standard dosing regimens provided adequate pharmacodynamic exposures against pathogen with MIC values ranging from 0.0625 to 2 mg/L.

For the target 100%$fT_{>MIC}$, almost all of the simulated dosage regimens administered as 0.5-h infusion failed to provide an acceptable PTA for treating pathogens with MIC value of 2 mg/L. In order to provide an optimal PTA for achieving this target, a continuous infusion of a maximum recommended dose of meropenem was required. The graphical display of the PTA results is presented in Figure 13 - 14.

Table 18 Probability of target attainment for various meropenem regimens in patients with eGFR 90.1 - 130 mL/min[a]

Dosage regimen	Infusion (h)	MIC (mg/L)	Probability of attaining following $fT_{>MIC}$ target (%)		
			40%	75%	100%
LD 2 g, 1 g q 8 h* (standard dose)	0.5	0.5	96.9%	80.1%	49.6%
		1	93.1%	69.9%	34.1%
		2	85.3%	55.1%	18.8%
LD 2 g, 1 g q 8 h PI	3	0.5	100.0%	91.6%	60.9%
		1	99.9%	83.7%	45.5%
		2	98.9%	70.4%	26.9%
LD 2 g, 1 g q 6 h	0.5	0.5	99.1%	91.4%	67.2%
		1	97.5%	83.8%	51.4%
		2	93.1%	71.8%	33.1%
		4	83.3%	54.6%	15.8%
LD 2 g, 1 g q 6 h	3	0.5	100.0%	98.3%	80.8%
		1	100.0%	95.1%	66.1%
		2	100.0%	87.8%	46.4%
		4	98.7%	73.1%	23.2%
2 g q 8 h	0.5	0.5	98.6%	86.6%	62.1%
		1	96.8%	78.7%	47.9%
		2	92.5%	67.4%	32.1%
		4	83.5%	51.5%	15.5%
LD 2 g, 2 g q 8 h PI	3	0.5	100.0%	95.8%	75.3%
		1	100.0%	91.8%	61.7%
		2	99.7%	83.9%	44.7%
		4	98.3%	70.8%	26.1%
LD 2 g, 3 g CI	24	0.5	100.0%	100.0%	96.5%
		1	99.9%	99.9%	86.8%
		2	99.4%	98.3%	61.9%
		4	93.4%	86.8%	27.9%
LD 2 g, 6 g CI	24	0.5	100.0%	100.0%	98.7%
		1	100.0%	100.0%	96.4%
		2	100.0%	99.9%	86.4%
		4	99.6%	98.4%	60.7%

* indicate the manufacturer recommends dosage regimen

[a] eGFR, estimated glomerular filtration rate; LD, loading dose; MIC, minimum inhibitory concentration; PI, prolong infusion; CI, continuous infusion.

Table 19 Probability of target attainment for various meropenem regimens in patients with eGFR 50.1 - 90 mL/min[a]

Dosage regimen	Infusion (h)	MIC (mg/L)	Probability of attaining following $fT_{>MIC}$ target (%)		
			40%	75%	100%
LD 2 g, 1 g q 8 h* (standard dose)	0.5	0.5	99.9%	97.1%	85.1%
		1	99.6%	94.5%	74.6%
		2	98.7%	89.4%	58.4%
		4	95.2%	78.7%	35.8%
LD 2 g, 1 g q 8 h PI	3	0.5	100.0%	99.4%	91.1%
		1	100.0%	98.4%	82.1%
		2	100.0%	95.3%	67.1%
		4	99.5%	87.6%	45.3%
LD 2 g, 1 g q 6 h	0.5	0.5	100.0%	99.1%	93.1%
		1	99.9%	98.3%	85.3%
		2	99.6%	95.5%	72.3%
		4	97.9%	88.6%	50.6%
2 g q 8 h	0.5	0.5	99.9%	98.7%	91.1%
		1	99.8%	97.0%	84.4%
		2	99.6%	94.0%	72.7%
		4	98.4%	88.0%	54.0%
LD 2 g, 2 g q 8 h PI	3	0.5	100.0%	99.7%	95.7%
		1	100.0%	99.5%	91.4%
		2	100.0%	98.3%	82.8%
		4	100.0%	95.3%	66.2%
LD 2 g, 3 g CI	24	0.5	100.0%	100.0%	99.0%
		1	100.0%	100.0%	96.6%
		2	99.9%	99.9%	87.3%
		4	99.4%	98.4%	63.2%
		8	94.0%	87.8%	28.5%
LD 2 g, 6 g CI	24	0.5	100.0%	100.0%	99.6%
		1	100.0%	100.0%	98.9%
		2	100.0%	100.0%	96.2%
		4	99.9%	99.9%	87.4%
		8	99.4%	98.5%	61.4%

* indicate the manufacturer recommends dosage regimen

[a] eGFR, estimated glomerular filtration rate; LD, loading dose; MIC, minimum inhibitory concentration; PI, prolong infusion; CI, continuous infusion.

Table 20 Probability of target attainment for various meropenem regimens in patients with eGFR 25.1 - 50 mL/min [a]

Dosage regimen	Infusion (h)	MIC (mg/L)	Probability of attaining following $fT_{>MIC}$ target (%)		
			40%	75%	100%
LD 2 g, 1 g q 12 h*	0.5	0.5	100.0	98.9	90.8
(standard dose)		1	99.9	97.4	82.9
		2	99.5	94.3	68.9
		4	98.5	87.2	47.2
LD 2 g, 1 g q 12 h PI	3	0.5	100.0	99.7	93.7
		1	100.0	99.0	87.1
		2	100.0	97.2	75.0
		4	99.8	91.9	54.0
LD 2 g, 1 g q 8 h	0.5	1	100.0	99.4	93.5
		2	99.9	98.6	84.7
		4	99.4	95.6	67.6
		8	97.7	87.5	41.4
LD 2 g, 1 g q 8 h PI	3	1	100.0	99.9	96.3
		2	100.0	99.7	90.6
		4	100.0	98.5	76.1
		8	99.6	93.6	48.2
2 g q 12 h	1	0.5	100.0	99.3	95.1
		2	100.0	98.7	90.8
		4	99.8	97.1	81.1
		8	97.9	84.4	37.4
LD 2 g, 2 g CI	24	1	100.0	100.0	97.8
		2	100.0	100.0	92.2
		4	99.8	99.4	74.1
		8	97.1	93.6	40.1
LD 2 g, 3 g CI	24	1	100.0	100.0	99.1
		2	100.0	100.0	96.8
		4	100.0	99.9	86.7
		8	99.4	98.5	59.4

* indicate the manufacturer recommends dosage regimen

[a] eGFR, estimated glomerular filtration rate; LD, loading dose; MIC, minimum inhibitory concentration; PI, prolong infusion; CI, continuous infusion.

Table 21 Probability of target attainment for various meropenem regimens in patients with eGFR 10 - 25 mL/min [a]

Dosage regimen	Infusion (h)	MIC (mg/L)	Probability of attaining following $fT_{>MIC}$ target (%)		
			40%	75%	100%
LD 1 g, 0.5 g q 12 h*	0.5	0.5	100.0	99.3	93.6
(standard dose)		1	100.0	98.5	86.3
		2	99.6	96.1	69.0
		4	98.0	89.2	41.2
LD 1 g, 0.5 g q 12 h PI	3	0.5	100.0	99.8	95.6
		1	100.0	99.4	89.2
		2	100.0	98.0	74.1
		4	99.5	93.0	46.7
LD 1 g, 0.5 g q 8 h	0.5	1	100.0	99.6	94.5
		2	99.9	99.1	84.2
		4	99.5	96.6	60.7
		8	96.8	87.2	24.8
LD 1 g, 0.5 g q 8 h PI	3	1	100.0	100.0	96.2
		2	100.0	99.8	88.3
		4	99.9	98.6	67.4
		8	98.6	91.0	30.1
LD 2 g, 1 g q 12 h	0.5	1	100.0	99.5	93.4
		2	99.9	98.8	85.2
		4	99.8	96.5	67.6
		8	98.5	88.9	40.1
LD 2 g, 1 g q 12 h PI	3	1	100.0	99.7	95.0
		2	100.0	99.2	88.4
		4	100.0	97.6	72.5
		8	99.4	92.2	44.6
LD 1 g, 1 g CI	24	0.5	100.0	100.0	96.4
		2	100.0	99.9	85.5
		4	99.2	98.1	58.1
		8	92.8	85.0	21.7
LD 1 g, 2 g CI	24	1	100.0	100.0	98.8
		2	100.0	100.0	95.8
		4	100.0	99.9	83.2
		8	99.4	98.2	49.2

* indicate the manufacturer recommends dosage regimen

[a] eGFR, estimated glomerular filtration rate; LD, loading dose; MIC, minimum inhibitory concentration; PI, prolong infusion; CI, continuous infusion.

Table 22 Probability of target attainment for various meropenem regimens in patients with eGFR less than 10 mL/min[a]

Dosage regimen	Infusion (h)	MIC (mg/L)	Probability of attaining following $fT_{>MIC}$ target (%)		
			40%	75%	100%
LD 1 g, 0.5 g q 24 h* (standard dose)	0.5	0.5	99.8	96.2	80.8
		1	99.2	93.2	67.1
		2	98.0	86.9	45.7
		4	93.9	72.7	21.0
LD 1 g, 0.5 g q 24 h PI	3	0.5	100.0	97.7	82.0
		1	99.9	95.0	67.6
		2	99.6	88.8	47.1
		4	97.2	75.9	22.6
LD 1 g, 0.5 g q 12 h	0.5	0.5	100.0	99.9	96.6
		1	100.0	99.6	91.5
		2	100.0	98.4	78.8
		4	99.5	94.4	51.8
		8	94.9	80.7	18.5
LD 1 g, 0.5 g q 12 h PI	3	0.5	100.0	99.9	97.5
		1	100.0	99.8	93.0
		2	100.0	99.2	82.1
		4	99.8	96.4	56.6
		8	97.1	86.0	21.7
LD 1 g, 0.5 g CI	24	0.5	100.0	100.0	97.9
		1	100.0	100.0	92.9
		2	99.9	99.4	74.9
		4	97.6	94.0	42.3
		8	86.0	72.1	11.2
LD 1 g, 1 g CI	24	0.5	100.0	100.0	99.1
		1	100.0	100.0	97.5
		2	100.0	100.0	90.8
		4	99.8	99.4	68.8
		8	96.9	92.5	30.0

* indicate the manufacturer recommends dosage regimen

[a] eGFR, estimated glomerular filtration rate; LD, loading dose; MIC, minimum inhibitory concentration; PI, prolong infusion; CI, continuous infusion.

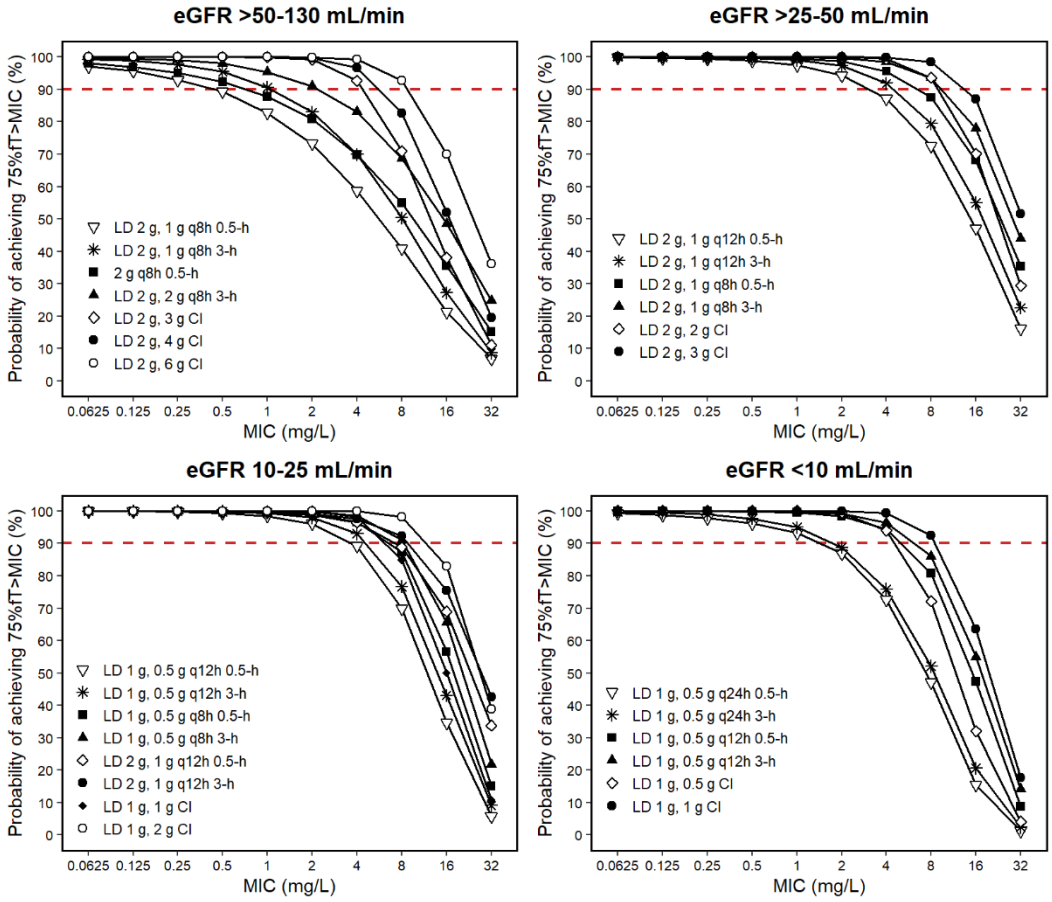


Figure 13 Probability of target attainment for meropenem regimens achieving 75%$fT_{>MIC}$ during the first 48 hours after dosing. Four groups were categorized according to renal function. The horizontal dash line denotes a target attainment of 90%.

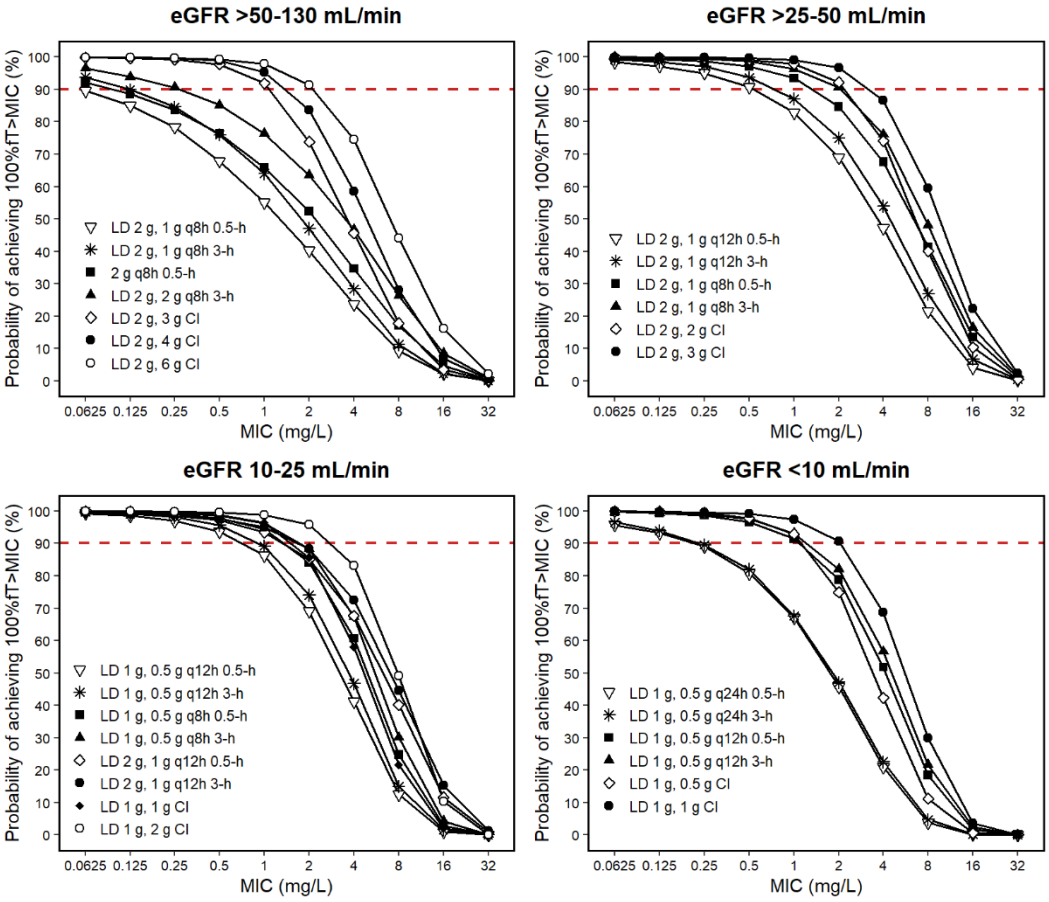


Figure 14 Probability of target attainment for meropenem regimens achieving 100%$fT_{>MIC}$ during the first 48 hours after dosing. Four groups were categorized according to renal function. The horizontal dash line denotes a target attainment of 90%.

4.4.2 Probability of target attainment of imipenem regimens

The final imipenem PK parameters in the final model and the significant covariates were used to perform the Monte Carlo simulations. The GFR_{EPI} was the only significant covariate on imipenem clearance. Therefore it was incorporated in the simulations. Four different renal function levels were categorized based on GFR_{EPI} values (GFR_{EPI} 15 – 29.9, 30 -59.9, 60 – 89.9, 90 – 130 mL/min). For each group, GFR_{EPI} was simulated to follow the uniform distribution. The abilities of various imipenem dosing regimens to achieve a 40%$fT_{>MIC}$, 75%$fT_{>MIC}$, and 100%$fT_{>MIC}$ target are summarized in Table 23 -26.

When considering 40%$fT_{>MIC}$ as the target, all of the simulated dosing regimens were sufficient to provide a PTA greater than 90% against pathogen with MIC values ranging from 0.0625 – 2 mg/L.

For the 75% $fT_{>MIC}$ target, the currently recommended doses administered by standard intermittent infusion were shown to ensure the PTA higher than 90% across normal and renal-impaired groups. Furthermore, the 3-hours infusion regimens provided a higher PTA than those with 1-hours infusion regimens across all ranges of renal function.

When considering 100%$fT_{>MIC}$ as the target, none of the candidate regimens, including 24-hours continuous infusion of maximum daily dose regimens, provide satisfactory target attainment against pathogens with MIC values of 2 mg/L.

Table 23 Probability of target attainment for various imipenem regimens in patients with eGFR 90-130 mL/min[a]

Dosage regimen	Infusion (h)	MIC (mg/L)	Probability of attaining following $fT_{>MIC}$ target (%)		
			40%	75%	100%
LD 1 g, 0.5 g q 6 h* (standard dose)	1	0.25	100.0	100.0	94.0
		0.5	100.0	99.6	78.6
		1	100.0	95.4	46.1
		2	98.8	77.5	14.0
		4	85.1	36.4	1.3
LD 1 g, 0.5 g q 6 h PI	3	0.25	100.0	100.0	97.4
		0.5	100.0	100.0	87.9
		1	100.0	98.9	60.4
		2	99.9	89.5	21.6
		4	93.2	52.3	2.4
1 g q 8 h* (standard dose)	1	0.25	100.0	99.9	94.1
		0.5	100.0	99.3	78.0
		1	99.9	95.5	49.0
		2	99.0	77.6	17.0
		4	86.8	41.3	2.0
LD 1 g, 1 g q 8 h PI	3	0.25	100.0	100.0	97.7
		0.5	100.0	100.0	88.8
		1	100.0	99.1	64.2
		2	100.0	91.8	28.6
		4	98.7	61.9	4.9
1 g q 6 h* (standard dose)	1	0.25	100.0	100.0	98.4
		0.5	100.0	99.9	93.4
		1	100.0	99.2	74.9
		2	99.8	94.0	40.0
		4	97.0	69.8	7.5
LD 1 g, 1 g q 6 h PI	3	0.25	100.0	100.0	99.4
		0.5	100.0	100.0	97.6
		1	100.0	100.0	88.1
		2	100.0	98.9	59.3
		4	99.8	88.2	19.3

Table 23 Probability of target attainment for various imipenem regimens in patients with eGFR 90-130 mL/min (continued)[a]

Dosage regimen	Infusion (h)	MIC (mg/L)	Probability of attaining following $fT_{>MIC}$ target (%)		
			40%	75%	100%
LD 1 g, 2 g CI	24	0.25	100.0	100.0	99.4
		0.5	100.0	100.0	97.8
		1	100.0	100.0	86.3
		2	99.7	98.7	43.9
		4	88.8	74.3	5.5
LD 1 g, 3 g CI	24	0.25	100.0	100.0	99.7
		0.5	100.0	100.0	98.8
		1	100.0	100.0	95.2
		2	100.0	100.0	73.7
		4	98.4	94.8	22.5
LD 1 g, 4 g CI	24	0.25	100.0	100.0	99.8
		0.5	100.0	100.0	99.5
		1	100.0	100.0	97.4
		2	100.0	100.0	85.2
		4	99.8	98.7	38.6

* indicate the manufacturer recommends dosage regimen

[a] eGFR, estimated glomerular filtration rate; LD, loading dose; MIC, minimum inhibitory concentration; PI, prolong infusion; CI, continuous infusion.

Table 24 Probability of target attainment for various imipenem regimens in patients with eGFR 60.0 – 89.9 mL/min[a]

Dosage regimen	Infusion (h)	MIC (mg/L)	Probability of attaining following $fT_{>MIC}$ target (%)		
			40%	75%	100%
LD 1 g, 0.5 g q 6 h* (standard dose)	1	0.25	100.0	100.0	98.8
		0.5	100.0	100.0	92.1
		1	100.0	99.2	70.5
		2	99.9	92.2	31.0
		4	93.1	60.9	5.3
LD 1 g, 0.5 g q 6 h PI	3	0.25	100.0	100.0	99.4
		0.5	100.0	100.0	96.7
		1	100.0	99.9	81.9
		2	100.0	98.1	44.9
		4	98.4	77.2	9.5
LD 1 g, 0.75 g q 8 h* (standard dose)	1	0.25	100.0	100.0	97.3
		0.5	100.0	99.9	88.2
		1	100.0	98.5	63.7
		2	99.6	88.8	27.0
		4	93.3	55.7	4.4
LD 1 g, 0.75 g q 8 h PI	3	0.25	100.0	100.0	98.9
		0.5	100.0	100.0	94.0
		1	100.0	99.8	75.1
		2	100.0	96.0	39.1
		4	98.8	72.6	8.5
1 g q 8 h	1	0.25	100.0	100.0	98.5
		0.5	100.0	100.0	93.0
		1	100.0	99.4	73.7
		2	99.9	93.3	37.4
		4	96.9	69.1	8.0
LD 1 g, 1 g 8 h PI	3	0.25	100.0	100.0	99.2
		0.5	100.0	100.0	96.4
		1	100.0	99.9	84.3
		2	100.0	98.4	54.4
		4	99.8	84.5	17.3

Table 24 Probability of target attainment for various imipenem regimens in patients with eGFR 60.0 – 89.9 mL/min (continued)[a]

Dosage regimen	Infusion (h)	MIC (mg/L)	Probability of attaining following $fT_{>MIC}$ target (%)		
			40%	75%	100%
0.75 g q 6 h	1	0.25	100.0	100.0	99.4
		0.5	100.0	100.0	96.5
		1	100.0	99.8	83.7
		2	100.0	97.3	48.3
		4	98.5	79.3	9.3
LD 1 g, 0.75 q 6 h PI	3	0.25	100.0	100.0	99.7
		0.5	100.0	100.0	98.7
		1	100.0	100.0	92.4
		2	100.0	99.7	68.6
		4	99.9	93.2	24.0
LD 1 g, 2 g CI	24	0.25	100.0	100.0	99.6
		0.5	100.0	100.0	98.8
		1	100.0	100.0	93.5
		2	99.9	99.8	65.2
		4	97.0	91.1	17.2
LD 1 g, 3 g CI	24	0.25	100.0	100.0	99.7
		0.5	100.0	100.0	99.3
		1	100.0	100.0	97.7
		2	100.0	100.0	85.1
		4	99.8	99.0	40.2

* indicate the manufacturer recommends dosage regimen.

[a] eGFR, estimated glomerular filtration rate; LD, loading dose; MIC, minimum inhibitory concentration; PI, prolong infusion; CI, continuous infusion.

Table 25 Probability of target attainment for various imipenem regimens in patients with eGFR 30.0 – 59.9 mL/min[a]

Dosage regimen	Infusion (h)	MIC (mg/L)	Probability of attaining following $fT_{>MIC}$ target (%)		
			40%	75%	100%
LD 1 g, 0.5 g q 8 h* (standard dose)	1	0.25	100.0	100.0	98.4
		0.5	100.0	99.9	93.2
		1	100.0	99.4	74.5
		2	99.8	93.9	37.5
		4	94.9	68.2	7.3
LD 1 g, 0.5 g q 8 h PI	3	0.25	100.0	100.0	99.2
		0.5	100.0	100.0	95.8
		1	100.0	99.8	82.2
		2	100.0	97.3	46.6
		4	98.3	79.3	11.3
LD 1 g, 0.5 g q 6 h* (standard dose)	1	0.25	100.0	100.0	99.6
		0.5	100.0	100.0	98.1
		1	100.0	99.9	89.8
		2	100.0	99.0	61.7
		4	99.1	87.7	20.4
LD 1 g, 0.5 g q 6 h PI	3	0.25	100.0	100.0	99.7
		0.5	100.0	100.0	99.1
		1	100.0	100.0	93.9
		2	100.0	99.7	69.9
		4	99.7	94.1	25.7
0.75 g q 8 h	1	0.25	100.0	100.0	99.7
		0.5	100.0	100.0	97.2
		1	100.0	99.9	85.0
		2	100.0	97.5	51.0
		4	98.7	81.7	9.9
LD 1 g, 0.75 q 8 h PI	3	0.25	100.0	100.0	99.7
		0.5	100.0	100.0	98.3
		1	100.0	100.0	91.9
		2	100.0	99.6	68.7
		4	99.9	91.7	26.2

* indicate the manufacturer recommends dosage regimen

[a] eGFR, estimated glomerular filtration rate; LD, loading dose; MIC, minimum inhibitory concentration; PI, prolong infusion; CI, continuous infusion

Table 25 Probability of target attainment for various imipenem regimens in patients with eGFR 30.0 – 59.9 mL/min (continued)[a]

Dosage regimen	Infusion (h)	MIC (mg/L)	Probability of attaining following $fT_{>MIC}$ target (%)		
			40%	75%	100%
LD 1 g, 1.5 g CI	24	0.25	100.0	100.0	99.6
		0.5	100.0	100.0	98.9
		1	100.0	100.0	94.7
		2	100.0	99.9	68.8
		4	98.2	93.1	19.7
LD 1 g, 2 g CI	24	0.25	100.0	100.0	99.7
		0.5	100.0	100.0	99.3
		1	100.0	100.0	97.4
		2	100.0	100.0	83.7
		4	99.6	98.1	35.6
LD 1 g, 3 g CI	24	0.25	100.0	100.0	99.8
		0.5	100.0	100.0	99.4
		1	100.0	100.0	98.8
		2	100.0	100.0	93.2
		4	100.0	99.9	58.8

* indicate the manufacturer recommends dosage regimen

[a] eGFR, estimated glomerular filtration rate; LD, loading dose; MIC, minimum inhibitory concentration; PI, prolong infusion; CI, continuous infusion

Table 26 Probability of target attainment for various imipenem regimens in patients with eGFR 15.0 – 29.9 mL/min[a]

Dosage regimen	Infusion (h)	MIC (mg/L)	Probability of attaining following $fT_{>MIC}$ target (%)		
			40%	75%	100%
0.25 g q 6 h* (standard dose)	1	0.25	100.0	100.0	99.2
		0.5	100.0	100.0	95.0
		1	100.0	99.9	65.3
		2	99.8	96.9	10.1
		4	91.8	66.4	0.0
LD 1 g, 0.25 g q 6 h PI	3	0.25	100.0	100.0	99.6
		0.5	100.0	100.0	98.5
		1	100.0	100.0	90.8
		2	100.0	99.7	58.6
		4	98.4	87.8	14.3
LD 1 g, 0.5 g q 12 h* (standard dose)	1	0.25	100.0	100.0	98.4
		0.5	100.0	99.9	91.7
		1	100.0	99.4	69.5
		2	99.8	93.1	32.8
		4	95.2	64.3	6.0
LD 1 g, 0.5 g q 12 h PI	3	0.25	100.0	100.0	98.6
		0.5	100.0	100.0	93.9
		1	100.0	99.7	75.9
		2	100.0	96.3	39.3
		4	98.4	73.6	8.4
LD 1 g, 1 g CI	24	0.25	100.0	100.0	99.8
		0.5	100.0	100.0	99.0
		1	100.0	100.0	94.2
		2	100.0	99.8	66.7
		4	97.7	92.0	16.9
LD 1 g, 2 g CI	24	0.25	100.0	100.0	99.9
		0.5	100.0	100.0	99.7
		1	100.0	100.0	98.8
		2	100.0	100.0	92.5
		4	100.0	99.8	55.2

* indicate the manufacturer recommends dosage regimen

[a] eGFR, estimated glomerular filtration rate; LD, loading dose; MIC, minimum inhibitory concentration; PI, prolong infusion; CI, continuous infusion.

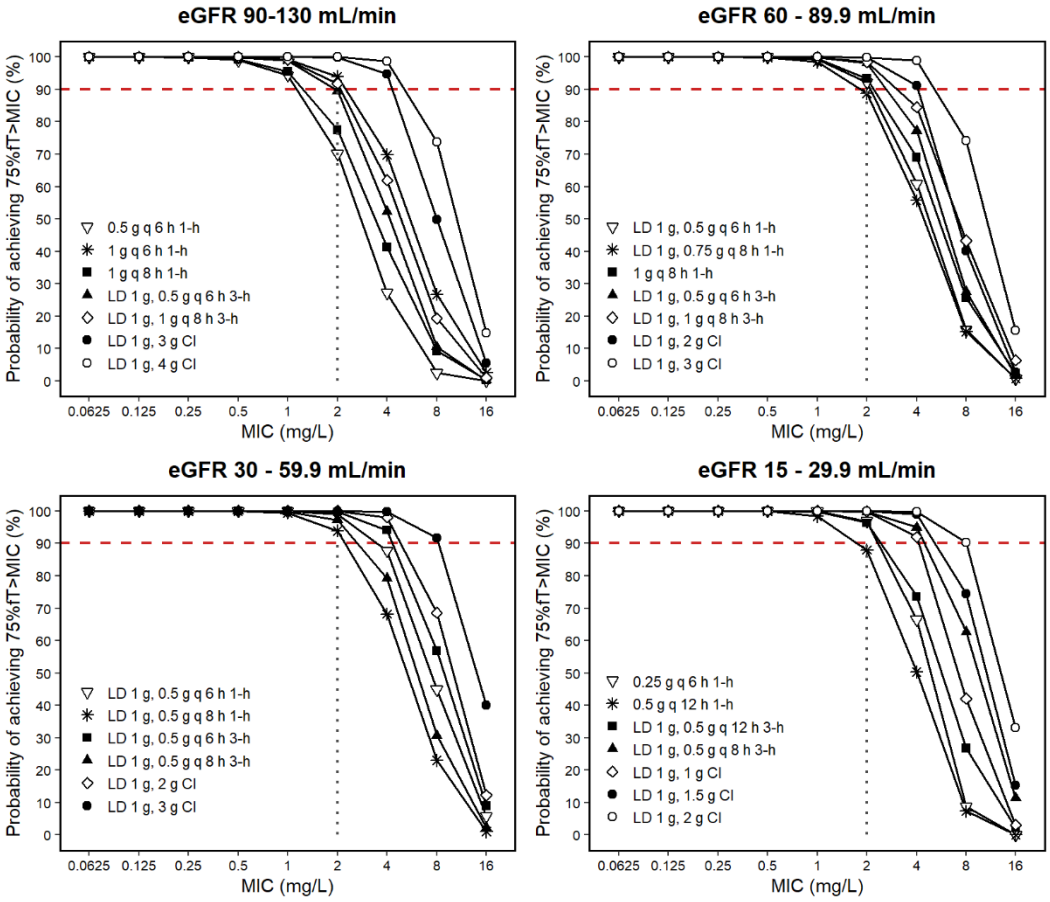


Figure 15 Probability of target attainment for imipenem regimens achieving 75%$fT_{>MIC}$ during first 48 hours after dosing. Four groups were categorized according to renal function. The horizontal dash line denotes a target attainment of 90%.

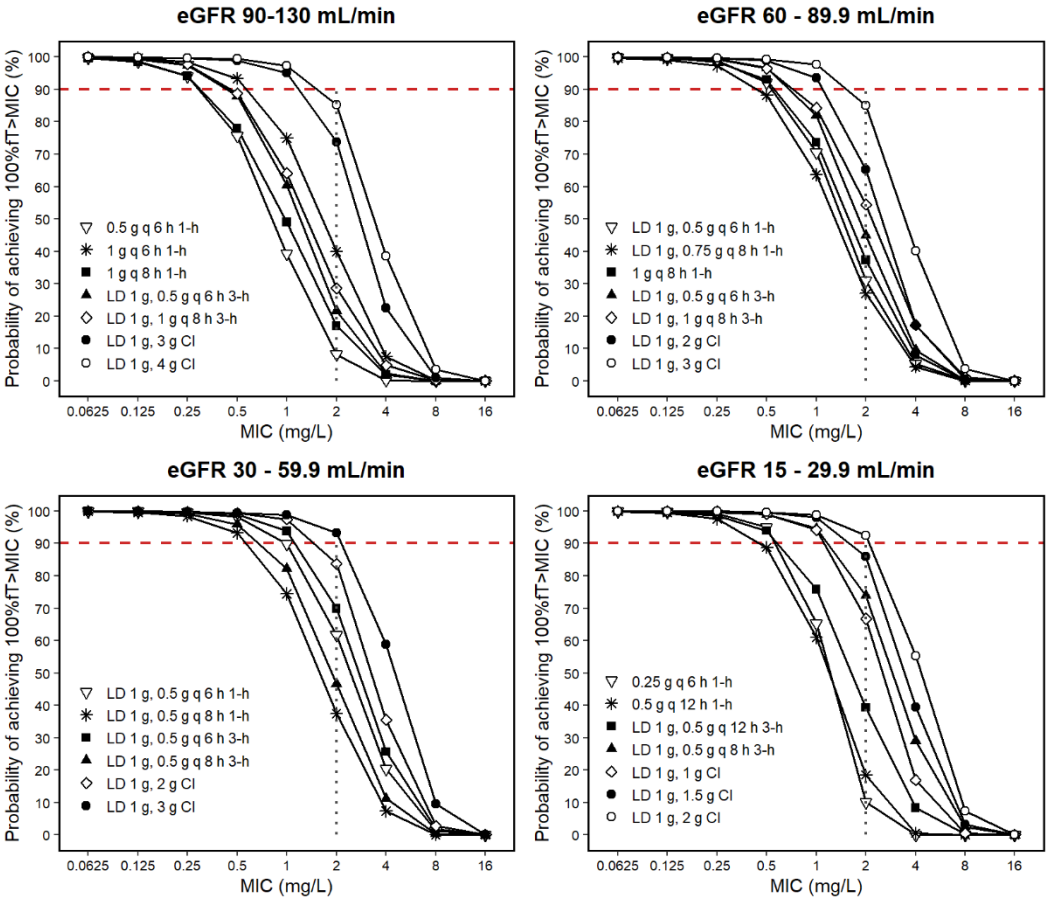


Figure 16 Probability of target attainment for imipenem regimens achieving 100%$fT_{>MIC}$ during first 48 hours after dosing. Four groups were categorized according to renal function. The horizontal dash line denotes a target attainment of 90%.

CHAPTER 5

DISCUSSION

Carbapenem remains the cornerstone for the management of severe infections in critically ill patients. The early achievement of an optimal PK/PD index may have an impact on clinical responses. However, this specific population exhibits several factors that may significantly alter carbapenem pharmacokinetics. Therefore, this study aimed to characterize the pharmacokinetics of carbapenems in critically ill patients, investigate patient factors that account for sources of variability in carbapenem PK parameters and identify the best regimen for achieving appropriate PK/PD targets.

There were several previously reported on meropenem population PK studies in critically ill patients. [20-26] Most of the published studies were conducted in a small cohort of critically ill patients range from 9 to 34 subjects. The disease severity of these patients differed across studies. Most of them had an APACHE II score less than 35 with a median score of 19 to 26. In the present study, we specially selected only patients with APACHE II scores less than 35, and the median severity scores of our patients were 20, which is comparable with other studies. The 2-compartment model with linear elimination was chosen to characterize the PK of meropenem in most studies, which are in accordance with our result. However, a one-compartment model was used to describe the PK data in a study performed by Jaruratanasirikul et al. [24] In their study, intensive blood samplings were obtained from 9 critically ill patients to describe meropenem concentration-time profiles during the early phase of severe sepsis. The results show that a two-compartment model provided a better fit than the one-compartment but did not achieve a significant improvement in terms of OFV. The insignificant results in their study might be partly due to the small number of patients. A recently published PPK study further confirmed the multi-compartment PK characteristic of meropenem. [56] A total of 50 critically ill patients were used to develop the PPK model, and the two-compartment linear model was the best fit model for describing the PK data of meropenem.

The renal function (by CL_{CR}, GFR) had been identified as a significant covariate for meropenem clearance in almost all studies. This was consistent with expectation given that a large proportion of meropenem is renally excreted. The mean meropenem clearance (CL) reported for critically ill patients ranged from 7.34 – 14.1 L/h. [20-22, 24-26, 56] The mean CL in the current study (4.3 L/h) was lower compare with those previously published studies. The high value of clearance reported in most literature might be partly due to the better renal function in the studied population (CL_{CR} 70-106 mL/min). The volume of distribution (V_D) at steady-state in our study (22.4 L) were in agreement with the previously reported in critically ill patients (range, 20.7 -27.5 L) [20-22, 24-26, 56] and also similar with those observed in other patient populations (14.6 -34 L). [57-63] The use of dopamine was found to have a significant effect on the V_D of meropenem. To our knowledge, we are the first study to report the impact of inotropic use as a significant covariate. The inclusion of dopamine used as a covariate on V_D is clinically justified, as dopamine is often prescribed for restoring mean arterial pressure in patients with septic shock who remain hypotensive after receiving aggressive fluid resuscitation and norepinephrine. Dopamine dosage prescribed in this study were ranged from 2.0-7.3 μg/kg/min, and more than half of these patients received a dose greater than 5 μg/kg/min. Using dopamine at a dosage of 5 – 10 μg/kg/min acts on β_1 adrenergic receptors in the heart and increases cardiac output by increasing stroke volume and heart rate, and it could affect the V_D of meropenem. Low serum albumin level was also found to increase the V_D of meropenem significantly. When serum albumin level decreased from 3.5 to 2.5, 2, 1.5 g/dL, the V_D of meropenem increased by 65%, 98%, 130%, respectively. The alterations of carbapenem pharmacokinetics caused by hypoalbuminemia have been documented in several studies. [18, 21, 64] By reducing intravascular oncotic pressure, hypoalbuminemia promotes fluid extravasation and tissue edema formation, which leads to an increase in V_D of antibiotics. The hydrophilic nature of meropenem makes it sensitive to this phenomenon.

Since the prescribing rate of imipenem in our institution was low, and a new subject enrollment was delayed due to the COVID-19 pandemic situation. We were not able to recruit the participants to a target of 50. Therefore, a total of 103 unbound imipenem concentrations from 21 patients were used for population pharmacokinetic analysis. The PPK model of imipenem was successfully developed. With regard to various diagnostic plots and the precision of PK parameter estimates, the final imipenem PPK model derived from these 21 critically ill patients has adequately characterized imipenem pharmacokinetic properties. The concentration-time profiles of imipenem were best described by a two-compartment model, which in line with previously published studies. [18, 19, 65] Mean imipenem clearance and V_D at steady state (V_{ss}) were 8.99 L/h and 38.6 L, respectively. These results were similar to those previously published studies in critically ill patients (CL 12.3 - 13.2 L/h, V_{ss} 22.9 - 32.3 L). [18, 19, 65] The renal function marker was the only variable that had a significant effect on imipenem clearance.

Carbapenems exhibit a time-dependent antibacterial; that is, its antibacterial activity is best correlates with $fT_{>MIC}$. It has been generally suggested that the $fT_{>MIC}$ of carbapenems should be at least 40-50% for an optimal anti-bactericidal effect. However, clinical data from immunocompromised hosts and critically ill patients have not consistently supported this target. Ariano et al. [13] investigated the PD indices of meropenem in 60 febrile neutropenic patients. The results showed that an 80% clinical response rate was evident when $fT_{>MIC}$ exceeded 75%. Zhou et al. [61] evaluated the relationship of various PK/PD indices of meropenem in 45 patients with lower respiratory tract infections. Logistic regression analysis showed that $fT_{>MIC}$ was the only factor for influencing clinical success. The cut-off value of 76%$fT_{>MIC}$ provided good sensitivity (84%) and specificity (85%) for predicting clinical success. In the present study, the patient outcome was evaluated when grouped according to whether $fT_{>MIC}$ of imipenem and meropenem achieved 75%$fT_{>MIC}$ or 100%$fT_{>MIC}$ or not. We were also found that the clinical success and survival rate in 75%$fT_{>MIC}$ and 100%$fT_{>MIC}$ achievement groups were higher than those whose not achieved. However, the 100%$fT_{>MIC}$ achievement was the only factor significantly associated with clinical success. Moreover, when $fT_{>MIC}$ was evaluated as the continuous variable, no statistically significant association was found with

clinical success or all-cause mortality rate. Due to the insufficient sample size in this study, the optimal PD index of carbapenem in critically ill patients was left inconclusive. Future studies with larger populations are required to elucidate the appropriate pharmacodynamic cut-offs of carbapenems in critically ill patients.

Since most of the plasma concentrations in this study were measure on the second day of therapy and early attaining the optimal PD index in the first 24 to 48 hours is the key factor for treatment success in sepsis. [66] Therefore, the PTA of various dosing regimens were calculated for the first 48 hours of therapy. The 75%$fT_{>MIC}$ was chosen as the main PK/PD target in the current study. In patients with GFR ≤ 90 mL/min, the standard dosing of meropenem according to renal functions provide adequate target attainment for susceptible pathogens (MIC ≤ 2 mg/L). In addition, sufficient coverage for intermediate resistant strains (MIC 4 mg/L) was observed when the standard dosing regimens were administered by prolonged infusion (3 hours) or escalate the dose to maximum recommended doses. For resistant microorganisms with a MIC value of 8 mg/L, the continuous infusion of the maximum daily dose of meropenem was necessitated. At the higher GFR levels of 90.1 - 130 mL/min, the standard dose of 1 gm every 8 hours did not provide adequate pharmacodynamic exposure against pathogen with MIC ≤2 mg/L. A dose of 3 g daily administered as a continuous infusion was required to achieve 75%$fT_{>MIC}$ target for susceptible pathogens. A continuous infusion of a maximum recommended dose of meropenem was the only regimen that achieve 100%$fT_{>MIC}$ target.

For imipenem dosing optimization to achieve 75%$fT_{>MIC}$ target, the results showed that the current standard dosing regimens of imipenem could provide sufficient coverage for susceptible pathogens with MIC ≤ 2 mg/L across normal and all renal-impaired groups. The prolonged infusion of the maximum daily dose of imipenem showed a higher PTA than intermittent infusion, but it still failed to provide sufficient coverage for intermediate resistant pathogens (MIC 4 mg/L). In order to achieve an acceptable PTA against these organisms, the dosage regimens should be increased to the maximum daily dose and administered as continuous infusion.

The stability of meropenem and imipenem at room temperatures need to be considered before introducing prolonged or continuous infusion regimens into routine practices. The stability of carbapenems is influenced by several factors, such

as storage temperature and the solution's concentration. Meropenem diluted with normal saline (NS) to a concentration between 1 to 20 mg/L is stable for 4 to 12 hours at temperature 25 ˚C. [67-69] For a tropical country with an average room temperature range from 32-37 ˚C, meropenem solution at 5 mg/L was stable for 6-8 hours.[70, 71] Similarly, it was found that imipenem 5 mg/L in NS is stable for approximately 4 hours at 25 ˚C and 3-6 hours at a temperature of 30 – 40 ˚C.[10, 71] These results indicating that the carbapenems should be reconstituted at least six to eight times a day to allow a continuous infusion, hence increasing the workload of caregivers. Therefore, a 3-hour prolonged infusion administered seems to be more feasible.

The strength of the current study was (i) the population pharmacokinetic model was developed based on large sample size (ii) Both drug exposure and antibiotic MIC were determined; therefore, the relationship between pharmacodynamic parameter and clinical outcome was able to evaluate. The present study also has some limitations. First, the final PK model showed a moderate level of ETA shrinkage associated with the V_D. Therefore the individual model fit should be interpreted with caution. Second, the small study population of 21 patients could be considered a limitation for imipenem PPK analysis. This sample size was reasonable for determining PK in this population, but it may limit the power to detect other potential covariates from being shown to be significantly affecting PK parameters. Third, most of the patient's body weight data during ICU admission was not available; therefore, the nearest outpatient visit data was used instead. Incorporating this weight into the model as a covariate might not represent the actual weight during critical illness. Fourth, all critically ill patients included in this study were patients who had APACHE II less than 35. Therefore, the results of this study should be used with caution in patients with APACHE II greater than 35. Fifth, this study was not powered for the evaluation of clinical outcomes, and therefore we cannot make any conclusions with regard to pharmacodynamic index and treatment outcome.

In conclusion, the population pharmacokinetic model presented here contributes to a better understanding of carbapenem pharmacokinetics in critically ill patients. Renal function was strongly associated with carbapenem clearance, while dopamine use and low serum albumin levels were the factors that increase the volume of distribution of meropenem. The simulations using the final PPK model suggested that the standard dosing regimens of carbapenems provide sufficient coverage for susceptible pathogens in patients with GFR less than 90 mL/min. A continuous infusion should be applied for patients with higher GFR levels.

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APPENDIX

APPENDIX A

Serum creatinine-based equations for estimate renal function

1. Body size descriptors

1.1 Ideal body weight (IBW)

IBW was estimated by Devine equation:

For males, IBW = 50 + 2.3×(height (inch) – 60)

For female, IBW = 45.5 + 2.3×(height (inch) – 60)

1.2 Lean body weight (LBW)

LBW was calculated using the following formula[46]:

$$\mathrm{LBW_{male}(kg)} = \frac{9270 \times \mathrm{BW(kg)}}{6680 + 216 \times \mathrm{BMI}\left(\frac{\mathrm{kg}^2}{\mathrm{m}}\right)}$$

$$\mathrm{LBW_{female}(kg)} = \frac{9270 \times \mathrm{BW(kg)}}{8780 + 244 \times \mathrm{BMI(kg/m^2)}}$$

1.3 Adjusted body weight (ABW)

ABW was employed if total body weight greater than IBW 20%, otherwise BW was used. ABW was calculated using the formula[47] :

$$\mathrm{ABW} = \mathrm{IBW} + (0.4 \times (\mathrm{BW\text{-}IBW}))$$

1.4 Body mass index (BMI)

$$\mathrm{BMI(kg/m^2)} = \frac{\mathrm{BW(kg)}}{\mathrm{Ht(m)^2}}$$

1.5 Body surface area (BSA)

BSA was calculated using following Gehan and George formula[53]:

$$\mathrm{BSA\ (m^2)} = \mathrm{Weight\ [kg]}^{0.5378} \times \mathrm{Height\ [cm]}^{0.3964} \times 0.024265$$

2. Equations for estimating creatinine clearance (CL_{CR}) and glomerular filtration rate (GFR)

2.1 Creatinine clearance estimated by Cockcroft-Gault equation (CL_{CRCG}, mL/min)

$$CL_{CRCG} = \frac{(140 - age) \times BW \times [0.85 \text{ if female}]}{72 \times S_{cr}}$$

The CL_{CRCG} based on ideal body weight (CL_{CRCG_IBW}), adjusted body weight (CL_{CRCG_ABW}), and lean body weight (CL_{CRCG_LBW}) was calculated in a similar manner with CL_{CRCG_BW}, but change BW to IBW, ABW, LBW, respectively.

The CL_{CRCG} based on Scr rounding to 1 mg/dL (CL_{CRCG_round}) was calculated by the same equation but used Scr 1 mg/dL instead of actual Scr, which was less than 1 mg/dL.

2.2 Creatinine clearance estimated by Jelliffe equation (CL_{CRJEL}, mL/min)

Creatinine production (P) = [29.305 – (0.203 × Age)]× weight (kg)

R = P1/P2

P1 = 1344.3 – 43.76 × C_{avg}, and

P2 = 1344.3 – 48.136

P_{adj} = P × R

Only 95% of this production value was used in the next equation, and 90% of the value was taken if the patient was female.

$$CL_{CRJEL} = \frac{P_{adj} - [0.4 \times 10 \times BW(kg) \times (Scr_2 - Scr_1)/T]}{C_{avg} \times 1440} \times 100$$

Where

BW is the actual body weight (kg)

Scr_1 is serum creatinine on day 1 (mg/dL)

Scr_2 is serum creatinine on day 2 (mg/dL)

T is the time in days between the two serum creatinine

C_{avg} is the average of Scr_1 and Scr_2

if Scr is rising the Scr_2 was used instead of C_{avg}

The estimated value of CL_{CRJEL} (mL/min) is adjusted to body surface area and express per 1.73 m^2 (CL_{CRJEL_BSA}). The body surface area was estimated using the Gehan and George equation[53].

2.3 Creatinine clearance estimated by modified Jelliffe equation (CL_{CRmJEL})

The CL_{CRmJEL} was also calculate using the Jelliffe equation. However, a modification was made for each serum creatinine according to cumulative fluid balance using following equation:

Adjusted serum creatinine = serum creatinine × correction factor

$$\text{Correction factor} = \frac{\text{weight (kg)} \times 0.6 + \sum(\text{daily fluid balance})}{\text{weight (kg)} \times 0.6}$$

The adjusted serum creatinine was substituted for actual Scr in the Jelliffe equation to compute the modified Jelliffe CL_{CR}. The CL_{CRmJEL} was also indexed to 1.73 m^2 body surface area (Gehan and George equation).

2.4 The glomerular filtration rate (GFR) estimated by the 4-variable simplified Modification of Diet in Renal Disease (MDRD) study equation (mL/min/1.73 m^2)

$$GFR_{MDRD4} = 186 \times Scr^{-1.154} \times Age^{-0.203} \text{"} \times 0.742\ if\ female \times 1.21\ if\ black\text{"}$$

This GFR_{MDRD4} was multiplied by individual BSA/1.73 m^2 to return each individual's raw GFR (GFR_{MDRD4_noBSA}, mL/min), where individual BSA was estimated by the Du Bois formula.

2.5 The glomerular filtration rate (GFR) estimated by the 6-variable simplified Modification of Diet in Renal Disease (MDRD) study equation (mL/min/1.73 m^2)

$$GFR_{MDRD6} = 170 \times Scr^{-0.999} \times Age^{-0.176} \times BUN^{-0.170} \times Alb^{0.318} \times [0.762 \text{ if famale}] \times [1.180 \text{ if black}]$$

Where

Scr is serum creatinine (mg/dL)

BUN is blood urea nitrogen (mg/dL)

Alb is serum albumin (g/dL)

This GFR_{MDRD6} was multiplied by individual BSA/1.73 m^2 to return each individual's raw GFR (GFR_{MDRD6_noBSA}, mL/min), where individual BSA was estimated by the Du Bois formula.

2.6 The glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration (EPI) equation (mL/min/1.73 m^2) [51]

$$GFR_{EPI} = 141 \times \left(\min\left(\frac{S_{cr}}{\kappa}, 1\right)\right)^{\alpha} \times \left(\max\left(\frac{S_{cr}}{\kappa}, 1\right)\right)^{-1.209} \times 0.993^{age} \times 1.018\,[if\ femal] \times 1.159\,[if\ black]$$

Where

Scr is serum creatinine (mg/dL)

κ is 0.7 for female and 0.9 for males

α is -0.329 for female and -0.411 for males

min indicates the minimum of Scr/κ or 1

max indicates the maximum of Scr/κ or 1

This GFR_{EPI} was multiplied by individual BSA/1.73 m^2 to return each individual's raw GFR (GFR_{EPI_noBSA}, mL/min), where individual BSA was estimated by the Du Bois formula.

APPENDIX B

Supplement information on population pharmacokinetic modeling

Table B1 Comparison of parameter estimates using a different method for handling the data below the lower limit of quantification [a]

Parameter	Discard	LLOQ/2	Beal M3	All data
OFV	1395.936	1415.489	1439.606	1412.365
AIC	1411.936	1431.489	1455.606	1428.365
Fix-effect parameter				
CL (L/h)	4.73	4.86	4.66	4.83
V_c (L)	11.7	12.4	10.2	11.1
V_p (L)	16.0	14.4	13.1	13.9
Q (L/h)	9.47	7.87	15.2	12.4
Interindividual variability				
ω^2_{CL}	0.73	0.77	0.78	0.78
ω^2_{Vc}	0.08	0.07	0.11	0.10
ω^2_{Vp}	0.18	0.32	0.35	0.59
ω^2_{Q}	NE	NE	NE	NE
Residual variability				
σ^2_{prop}	0.06	0.08	0.06	0.06

Data models fit using FOCE-I estimation method and were reported as estimated (% relative standard error)

[a]OFV, objective function value; AIC, Alkaike's Information Criterion; CL, total clearance; V_c, central volume of distribution; $V_{p,}$ peripheral volume of distribution; Q, intercompartment clearance; ω^2_{CL}, interindividual variability of CL; ω^2_{Vc}, interindividual variability of V_c; ω^2_{Vp}, interindividual variability of V_p; ω^2_{Q}, interindividual variability of Q; NE, not estimated; σ^2_{Prop}, proportional residual variability

Table B2 Comparison of meropenem population pharmacokinetic parameters obtained from FOCE-I and SAEM estimation method[#]

Parameter	FOCE-I method	SAEM method
OFV	1412.365	1406.720
Run time (seconds)	4.81	171.7
Fix-effect parameter		
CL (L/h)	4.83	4.57
V_c (L)	11.1	10.8
V_p (L)	13.9	13.6
Q (L/h)	12.4	12.6
Interindividual variability		
ω^2_{CL}	0.779	0.83
ω^2_{Vc}	0.10	0.12
ω^2_{Vp}	0.60	0.63
ω^2_{Q}	NE	NE
Residual variability		
σ^2_{prop}	0.06	0.06

Data were reported as estimated (% relative standard error)

[#]OFV, objective function value; FOCE-I, first-order conditional estimation with eta-epsilon interaction method; SAEM, Stochastic Approximation Expectation Maximization estimation method; CL, total clearance; V_c, central volume of distribution; V_p, peripheral volume of distribution; Q, intercompartment clearance; ω^2_{CL}, interindividual variability of CL; ω^2_{Vc}, interindividual variability of V_c; ω^2_{Vp}, interindividual variability of V_p; ω^2_{Q}, interindividual variability of Q; NE, not estimated; σ^2_{Prop}, proportional residual variability

Table B3 Change in OFV after inclusion of renal functions into the model [a]

No	PK	Added covariates		OFV	ΔOFV	Sig*
		Base model: $CL_i = \theta_{TVCL}$		1412.4		
1	CL	CL_{CRCG_BW} (mL/min)	Exp	1383.0	-29.4	Yes
2	CL	CL_{CRCG_IBW} (mL/min)	Exp	1378.3	-34.1	Yes
3	CL	CL_{CRCG_LBW} (mL/min)	Exp	1378.2	-34.2	Yes
4	CL	CL_{CRCG_ABW} (mL/min)	Exp	1380.1	-32.2	Yes
5	CL	CL_{CRCG_ROUND} (mL/min)	Exp	1383.5	-28.9	Yes
6	CL	$CL_{CR\text{-}JEL}$ (mL/min/1.73 m^2)	Exp	1384.7	-27.7	Yes
7	CL	$CL_{CR\text{-}JELnoBSA}$ (mL/min)	Exp	1385.3	-27.1	Yes
8	CL	$CL_{CR\text{-}mJEL}$ (mL/min/1.73 m^2)	Exp	1388.1	-24.2	Yes
9	CL	$CL_{CR\text{-}mJEL\_noBSA}$ (mL/min)	Exp	1388.1	-24.3	Yes
10	CL	GFR_{MDRD} (mL/min/1.73 m^2)	Exp	1386.4	-26.0	Yes
11	CL	GFR_{MDRD_noBSA}[#] (mL/min)	Exp	1382.6	-29.8	Yes
12	CL	GFR_{EPI} (mL/min/1.73 m^2)	Exp	1382.0	-30.3	Yes
13	CL	GFR_{EPI_noBSA}[#] (mL/min)	Exp	1380.4	-32.0	Yes

*OFV decrease at least 3.84 (p value < 0.05, χ^2, *df*=1)

[a]PK, pharmacokinetic parameter; CL, clearance (L/h); Exp, exponential relation; CL_{CRCG}, estimated using standard Cockcroft-Gault formula; CL_{CRCG_BW}, CL_{CRCG} based on total body weight; CL_{CRCG_IBW}, CL_{CRCG} based on ideal body weight; CL_{CRCG_LBW}, CL_{CRCG} based on lean body weight; CL_{CRCG_ABW}, CL_{CRCG} based on adjusted body weight; $CR_{CL\text{-}JEL}$, CL_{CR} estimated using the Jelliffe equation; $CR_{CL\text{-}mJEL}$, CL_{CR} estimated using the modified Jelliffe equation; GFR_{EPI}, estimated glomerular filtration rate (GFR) using the Chronic Kidney Disease Epidemiology Collaboration equation; GFR_{MDRD}, estimated GFR using the four-variable Modification of Diet in Renal Disease equation; AKI, acute kidney injury

[#]GFR unit express as mL/min, it was calculated by multiplied original GFR by each individual body surface area divided by 1.73

Table B4 A change in OFV of meropenem base model after the first round of covariate forward addition procedure [a]

No	PK	Added covariates	Relation	OFV	ΔOFV	Sig*
		Base model		1412.4		
1	CL	GFR_{EPI_noBSA}	Lin	1384.9	-27.4	Yes
2	CL	GFR_{EPI_noBSA}	Pow	1387.2	-25.1	Yes
3	CL	GFR_{EPI_noBSA}	Expo	1380.4	-32.0	Yes
4	CL	Age	Lin	1396.0	-16.4	Yes
5	CL	Gender	Frac	1409.8	-2.5	
6	CL	Body weight	Pow	1412.2	-0.2	
7	CL	Adjusted body weight	Pow	1412.4	0.0	
8	CL	Ideal body weight	Pow	1408.8	-3.6	
9	CL	Body mass index	Pow	1409.8	-2.5	
10	CL	Serum albumin	Lin	1410.8	-1.6	
11	CL	Hypoalbuminemia	Frac	1412.3	-0.1	
12	CL	Total bilirubin	Lin	1412.3	-0.1	
13	CL	Direct bilirubin	Lin	1412.3	-0.1	
14	CL	Aspartate transaminase	Lin	1412.4	0.0	
15	CL	Alanine transaminase	Lin	1412.4	0.0	
16	CL	Alkaline phosphatase	Lin	1412.3	-0.1	
17	CL	Liver failure	Frac	1412.3	-0.1	
18	CL	Norepinephrine use	Frac	1411.7	-0.7	
19	CL	Dopamine use	Frac	1410.8	-1.6	
20	CL	Epinephrine use	Frac	1412.4	0.0	
21	CL	High dose vasopressor use	Frac	1412.3	-0.1	
22	CL	Mechanical ventilator	Frac	1412.1	-0.3	
23	CL	Septic shock	Frac	1409.8	-2.5	
24	CL	APACHE II score	Lin	1403.0	-9.4	Yes
25	CL	SOFA score	Lin	1404.0	-8.4	Yes

Table B4 A change in OFV of meropenem base model after the first round of covariate forward addition procedure (continued)[a]

No	PK	Added covariates	Relation	OFV	ΔOFV	Sig*
		Base model		1412.4		
26	V_C	Age	Lin	1410.5	-1.9	
27	V_C	Gender	Frac	1411.9	-0.5	
28	V_C	Body weight	Pow	1411.4	-1.0	
29	V_C	Adjusted body weight	Pow	1411.0	-1.4	
30	V_C	Ideal body weight	Pow	1410.0	-2.4	
31	V_C	Body mass index	Pow	1412.3	-0.1	
32	V_C	Serum albumin	Lin	1407.1	-5.3	Yes
33	V_C	Hypoalbuminemia	Frac	1407.1	-5.3	Yes
34	V_C	Norepinephrine use	Frac	1411.1	-1.3	
35	V_C	Dopamine use	Frac	1408.3	-4.1	Yes
36	V_C	Epinephrine use	Frac	1412.4	0.0	
37	V_C	High dose vasopressor use	Frac	1410.5	-1.9	
38	V_C	Mechanical ventilator	Frac	1412.3	-0.1	
39	V_C	Septic shock	Frac	1412.1	-0.3	
40	V_C	APACHE II score	Lin	1411.8	-0.6	
41	V_C	SOFA score	Lin	1406.8	-5.6	Yes
42	V_C	Fluid balance	Lin	1411.8	-0.5	
43	V_P	Age	Lin	1411.6	-0.7	
44	V_P	Gender	Frac	1410.9	-1.5	
45	V_P	Body weight	Pow	1411.3	-1.1	
46	V_P	Adjusted body weight	Pow	1411.8	-0.4	
47	V_P	Ideal body weight	Pow	1412.4	0.0	
48	V_P	Body mass index	Pow	1411.2	-1.2	
49	V_P	Serum albumin	Lin	1406.9	-5.5	Yes
50	V_P	Hypoalbuminemia	Frac	1410.2	-2.2	
51	V_P	Age	Lin	1411.6	-0.7	

Table B4 A change in OFV of meropenem base model after the first round of covariate forward addition procedure (continued)[a]

No	PK	Added covariates	Relation	OFV	ΔOFV	Sig*
		Base model		1412.4		
52	V_P	Norepinephrine use	Frac	1412.2	-0.2	
53	V_P	Dopamine use	Frac	1405.5	-6.9	Yes
54	V_P	Epinephrine use	Frac	1412.4	0.0	
55	V_P	High dose vasopressor use	Frac	1408.2	-4.1	Yes
56	V_P	Mechanical ventilator	Frac	1410.9	-1.5	
57	V_P	Septic shock	Frac	1412.3	-0.1	
58	V_P	APACHE II score	Lin	1412.4	0.0	
59	V_P	SOFA score	Lin	1410.7	-1.7	
60	V_P	Fluid balance	Lin	1409.4	-3.0	
61	V_P	24-h fluid balance	Lin	1410.2	-2.2	

[a]OFV, objective function values; PK, pharmacokinetic parameter; Lin, linear relation; Frac, fraction change relation; Pow, power relation; Expo, exponential relation; CL, clearance; Vc, Central volume of distribution; Vp, peripheral volume of distribution; GFR_{EPI_noBSA}, estimated glomerular filtration rate (GFR) using the Chronic Kidney Disease Epidemiology Collaboration equation (mL/min)

*OFV decrease at least 3.84 (p value < 0.05, χ^2, *df*=1)

Table B5 A change in OFV of meropenem base model after the second round of covariate forward addition procedure [a]

No	PK	Added covariates	Relation	OFV	ΔOFV	Sig*
	Base model with inclusion of GFR_{EPI} on CL:			1380.4		
1	CL	Gender	Frac	1378.2	-2.2	
2	CL	Body weight	Pow	1380.1	-0.3	
3	CL	Adjusted body weight	Pow	1380.3	-0.1	
4	CL	Ideal body weight	Pow	1379.6	-0.8	
5	CL	Body mass index	Pow	1379.4	-1.0	
6	CL	Serum albumin	Lin	1377.7	-2.7	
7	CL	Hypoalbuminemia	Frac	1380.1	-0.3	
8	CL	Total bilirubin	Lin	1380.3	-0.1	
9	CL	Direct bilirubin	Lin	1380.3	-0.1	
10	CL	Aspartate transaminase	Lin	1380.4	0.0	
11	CL	Alanine transaminase	Lin	1380.4	0.0	
12	CL	Alkaline phosphatase	Lin	1379.9	-0.5	
13	CL	Liver failure	Frac	1380.3	-0.1	
14	CL	Norepinephrine use	Frac	1380.4	0.0	
15	CL	Dopamine use	Frac	1376.4	-4.0	Yes
16	CL	Epinephrine use	Frac	1380.4	0.0	
18	CL	Mechanical ventilator	Frac	1380.3	-0.1	
19	CL	Septic shock	Frac	1380.3	-0.1	
20	V_C	Gender	Frac	1379.9	-0.5	
21	V_C	Body weight	Pow	1377.9	-2.5	
22	V_C	Adjusted body weight	Pow	1379.1	-1.3	
23	V_C	Ideal body weight	Pow	1377.9	-2.5	
24	V_C	Body mass index	Pow	1380.4	0.0	
25	V_C	Serum albumin	Lin	1374.4	-6.0	Yes
26	V_C	Hypoalbuminemia	Frac	1380.9	-5.5	Yes
27	V_C	Norepinephrine use	Frac	1378.9	-1.5	

Table B5 A change in OFV of meropenem base model after the second round of covariate forward addition procedure (continued)[a]

No	PK	Added covariates	Relation	OFV	ΔOFV	Sig[*]
	Base model with inclusion of GFR_{EPI} on CL:			1380.4		
28	V_C	Dopamine use	Frac	1376.6	-3.8	
29	V_C	Epinephrine use	Frac	1380.4	0.0	
30	V_C	High dose vasopressor use	Frac	1378.5	-1.9	
31	V_C	Mechanical ventilator	Frac	1380.3	-0.1	
32	V_C	Septic shock	Frac	1380.1	-0.3	
33	V_C	Fluid balance	Lin	1379.8	-0.6	
34	V_P	Gender	Frac	1379.3	-1.1	
35	V_P	Body weight	Pow	1379.3	-0.1	
36	V_P	Adjusted body weight	Pow	1379.8	-0.6	
37	V_P	Ideal body weight	Pow	1380.4	0.0	
38	V_P	Body mass index	Pow	1379.4	-1.0	
39	V_P	Serum albumin	Lin	1374.7	-5.7	Yes
40	V_P	Hypoalbuminemia	Frac	1378.0	-2.4	
41	V_P	Norepinephrine use	Frac	1380.0	-0.4	
42	V_P	Dopamine use	Frac	1373.5	-6.9	Yes
43	V_P	Epinephrine use	Frac	1380.4	0.0	
44	V_P	High dose vasopressor use	Frac	1376.0	-4.4	
45	V_P	Mechanical ventilator	Frac	1379.0	-1.4	
46	V_P	Septic shock	Frac	1380.3	-0.1	
47	V_P	Fluid balance	Lin	1377.3	-3.1	

[a]OFV, objective function values; PK, pharmacokinetic parameter; Lin, linear relation; Frac, fraction change relation; Pow, power relation; Expo, exponential relation; CL, clearance; Vc, Central volume of distribution; Vp, peripheral volume of distribution; GFR_{EPI_noBSA}, estimated glomerular filtration rate (GFR) using the Chronic Kidney Disease Epidemiology Collaboration equation (mL/min)

[*]OFV decrease at least 3.84 (p value < 0.05, χ^2, df=1)

Table B6 A change in OFV of meropenem base model after the third round of covariate forward addition procedure [a]

No	PK	Added covariates	Relation	OFV	ΔOFV	Sig*
	Base model with inclusion of					
	- GFR_{EPI} on CL			1373.5		
	- Dopamine used on Vp					
1	CL	Gender	Frac	1371.1	-2.4	
2	CL	Body weight	Pow	1373.3	-0.2	
3	CL	Adjusted body weight	Pow	1373.5	0.0	
4	CL	Ideal body weight	Pow	1372.7	-0.8	
5	CL	Body mass index	Pow	1372.6	-0.9	
6	CL	Serum albumin	Lin	1370.7	-2.8	
7	CL	Hypoalbuminemia	Frac	1373.2	-0.3	
8	CL	Total bilirubin	Lin	1373.4	-0.1	
9	CL	Direct bilirubin	Lin	1373.5	0.0	
10	CL	Aspartate transaminase	Lin	1373.5	0.0	
11	CL	Alanine transaminase	Lin	1373.5	0.0	
12	CL	Alkaline phosphatase	Lin	1373.1	-0.4	
13	CL	Liver failure	Frac	1373.4	-0.1	
14	CL	Mechanical ventilator	Frac	1373.5	0.0	
15	V_C	Gender	Frac	1373.0	-0.5	
16	V_C	Body weight	Pow	1372.7	-0.8	
18	V_C	Adjusted body weight	Pow	1372.3	-1.2	
19	V_C	Ideal body weight	Pow	1371.0	2.5	
20	V_C	Body mass index	Pow	1373.5	0.0	
21	V_C	Serum albumin	Lin	1368.4	-5.10	Yes
22	V_C	Hypoalbuminemia	Frac	1368.7	-4.8	Yes

Table B6 A change in OFV of meropenem base model after the third round of covariate forward addition procedure (continued)[a]

No	PK	Added covariates	Relation	OFV	ΔOFV	Sig*
	Base model with inclusion of					
	- GFR_{EPI} on CL			1373.5		
	- Dopamine used on V_P					
23	V_C	Mechanical ventilator	Frac	1373.5	0.0	
24	V_C	Septic shock	Frac	1373.2	-0.3	
25	V_C	Fluid balance	Lin	1372.9	-0.6	
26	V_P	Gender	Frac	1371.2	-2.3	
27	V_P	Body weight	Pow	1372.9	-0.6	
28	V_P	Adjusted body weight	Pow	1373.3	-0.2	
29	V_P	Ideal body weight	Pow	1373.5	0.0	
30	V_P	Body mass index	Pow	1372.9	-0.6	
31	V_P	Serum albumin	Lin	1365.8	-7.7	Yes
32	V_P	Hypoalbuminemia	Frac	1371.1	-2.36	
33	V_P	Mechanical ventilator	Frac	1372.7	-0.8	
34	V_P	Septic shock	Frac	1373.2	-0.3	
35	V_P	Fluid balance	Lin	1370.8	-2.7	

[a]OFV, objective function values; PK, pharmacokinetic parameter; Lin, linear relation; Frac, fraction change relation; Pow, power relation; Expo, exponential relation; CL, clearance; Vc, Central volume of distribution; Vp, peripheral volume of distribution; GFR_{EPI_noBSA}, estimated glomerular filtration rate (GFR) using the Chronic Kidney Disease Epidemiology Collaboration equation (mL/min)

*OFV decrease at least 3.84 (p value < 0.05, χ^2, *df*=1)

Table B7 A change in OFV of meropenem base model after the fourth round of covariate forward addition procedure [a]

No	PK	Added covariates	Relation	OFV	ΔOFV	Sig[*]
	Base model with inclusion of - GFR_{EPI} on CL - Dopamine used on V_P - Albumin on V_P			1365.8		
1	CL	Gender	Frac	1363.4	-2.4	
2	CL	Total bilirubin	Lin	1365.7	-0.1	
3	CL	Direct bilirubin	Lin	1365.7	-0.1	
4	CL	Aspartate transaminase	Lin	1365.8	0.0	
5	CL	Alanine transaminase	Lin	1365.8	0.0	
6	CL	Alkaline phosphatase	Lin	1365.5	-0.3	
7	V_C	Gender	Frac	1365.4	-0.4	
8	V_C	Body weight	Pow	1364.7	-1.1	
9	V_C	Adjusted body weight	Pow	1364.4	-1.4	
10	V_C	Ideal body weight	Pow	1363.4	-2.3	
11	V_C	Septic shock	Frac	1365.6	-0.2	
12	V_C	Fluid balance	Lin	1365.3	-0.6	
13	V_P	Gender	Frac	1363.3	-2.5	
14	V_P	Body weight	Pow	1363.5	-2.3	
15	V_P	Adjusted body weight	Pow	1364.9	-0.9	
16	V_P	Ideal body weight	Pow	1365.7	-0.1	
18	V_P	Septic shock	Frac	1365.8	0.0	
19	V_P	Fluid balance	Lin	1365.0	-0.8	

[a]OFV, objective function values; PK, pharmacokinetic parameter; Lin, linear relation; Frac, fraction change relation; Pow, power relation; Expo, exponential relation; CL, clearance; Vc, Central volume of distribution; Vp, peripheral volume of distribution; GFR_{EPI_noBSA}, estimated glomerular filtration rate (GFR) using the Chronic Kidney Disease Epidemiology Collaboration equation (mL/min)

[*]OFV decrease at least 3.84 (p value < 0.05, χ^2, *df*=1)

Table B8 The results of stepwise backward deletion step 1 [a]

No	PK	Removed covariate	Relation	OFV	ΔOFV	Sig[*]
	Full model including covariance term between CL and V_C and 3 covariates inclusion: - GFR_{EPI_noBSA} on CL - Dopamine used on V_P - Albumin on V_P			1359.1		
1	CL	GFR_{EPI_noBSA}	Expo	1396.7	+37.7	Yes
2	V_P	Dopamine used	Frac	1368.1	+9.0	Yes
3	V_P	Serum albumin	Lin	1367.6	+8.5	Yes

[a]OFV, objective function values; PK, pharmacokinetic parameter; Lin, linear relation; Frac, fraction change relation; Expo, exponential relation; CL, clearance; Vp, peripheral volume of distribution; GFR_{EPI_noBSA}, estimated glomerular filtration rate (GFR) using the Chronic Kidney Disease Epidemiology Collaboration equation (mL/min)

[*]OFV increase at least 6.64 (p value < 0.01, χ^2, *df*=1)

Table B9 Population pharmacokinetic parameters of imipenem structural model obtained from FOCE-I and SAEM estimation method [a]

Parameter	FOCE-I method	SAEM method
OFV	279.132	278.164
Run time (seconds)	1.53	260.01
Fix-effect parameter		
CL (L/h)	8.12	7.93
V_c (L)	15.4	15.2
V_p (L)	24.3	24.0
Q (L/h)	15.4	15.0
Interindividual variability		
ω^2_{CL}	0.32	0.344
ω^2_{Vc}	0.071	0.105
ω^2_{Vp}	NE	NE
ω^2_{Q}	NE	NE
Residual variability		
σ^2_{prop}	0.0574	0.0574

[a]OFV, objective function value; FOCE-I, first-order conditional estimation with eta-epsilon interaction method; SAEM, Stochastic Approximation Expectation Maximization estimation method; CL, total clearance; V_c, central volume of distribution; $V_{p,}$ peripheral volume of distribution; Q, intercompartment clearance; ω^2_{CL}, interindividual variability of CL; ω^2_{Vc}, interindividual variability of V_c; ω^2_{Vp}, interindividual variability of V_p; ω^2_{Q}, interindividual variability of Q; NE, not estimated; σ^2_{Prop}, proportional residual variability

Table B10 Change in OFV of imipenem base model after the first round of covariate forward addition procedure [a]

No	PK	Added covariates	Relation	OFV	ΔOFV	Sig*
		Base model		279.1		
1	CL	CL_{CRCG_BW}	Lin	265.1	-14.0	Yes
2	CL	CL_{CRCG_ABW}	Lin	264.0	-15.1	Yes
3	CL	CL_{CRCG_IBW}	Lin	264.6	-14.5	Yes
4	CL	CL_{CRCG_LBW}	Lin	264.9	-14.2	Yes
5	CL	CL_{CRCG_ROUND}	Lin	268.7	-10.4	Yes
6	CL	CL_{CR_JEL}	Lin	263.1	-16.0	Yes
7	CL	GFR_{MDRD_BSA}	Lin	266.1	-13.0	Yes
8	CL	GFR_{MDRD_noBSA}	Lin	266.4	-12.7	Yes
9	CL	GFR_{EPI_BSA}	Lin	262.5	-16.6	Yes
10	CL	GFR_{EPI_noBSA}	Lin	264.4	-14.7	Yes
11	CL	Age	Lin	274.6	-4.5	Yes
12	CL	Gender	Frac	276.4	-2.7	
13	CL	Body weight	Pow	279.1	0.0	
14	CL	Adjusted body weight	Pow	279.1	0.0	
15	CL	Ideal body weight	Pow	278.6	-0.5	
16	CL	Body mass index	Pow	279.1	0.0	
17	CL	Serum albumin	Lin	279.1	0.0	
18	CL	Hypoalbuminemia	Frac	279.1	0.0	
19	CL	Total bilirubin	Lin	278.0	-1.1	
20	CL	Direct bilirubin	Lin	277.9	-1.2	
21	CL	Aspartate transaminase	Lin	276.8	-2.3	
22	CL	Alanine transaminase	Lin	278.6	-0.5	
23	CL	Alkaline phosphatase	Lin	278.0	-1.1	
24	CL	Liver failure	Frac	278.6	-0.5	
25	CL	Norepinephrine use	Frac	270.8	-8.3	Yes
26	CL	Dopamine use	Frac	277.2	-1.9	
27	CL	Epinephrine use	Frac	273.3	-5.8	Yes

Table B10 Change in OFV of imipenem base model after the first round of covariate forward addition procedure (continued)[a]

No	PK	Added covariates	Relation	OFV	ΔOFV	Sig[*]
		Base model		279.1		
28	CL	High dose vasopressor use	Frac	276.7	-2.4	
29	CL	Mechanical ventilator	Frac	278.2	-0.9	
30	CL	Septic shock	Frac	278.9	-0.2	
31	CL	APACHE II score	Lin	276.5	-2.6	
32	CL	SOFA score	Lin	272.2	-6.9	Yes
33	V_C	Age	Lin	279.1	0.0	
34	V_C	Gender	Frac	279.1	0.0	
35	V_C	Body weight	Pow	278.8	-0.3	
36	V_C	Adjusted body weight	Pow	278.7	-0.4	
37	V_C	Ideal body weight	Pow	278.6	-0.5	
38	V_C	Body mass index	Pow	279.1	0.0	
39	V_C	Serum albumin	Lin	279.0	-0.1	
40	V_C	Hypoalbuminemia	Frac	278.6	-0.5	
41	V_C	Norepinephrine use	Frac	277.5	-1.6	
42	V_C	Dopamine use	Frac	278.9	-0.2	
43	V_C	Epinephrine use	Frac	278.6	-0.5	
44	V_C	High dose vasopressor use	Frac	276.4	-2.7	
45	V_C	Septic shock	Frac	275.3	-3.8	
46	V_C	APACHE II score	Lin	278.0	-1.1	
47	V_C	SOFA score	Lin	278.9	-0.2	
48	V_C	Fluid balance	Lin	274.4	-4.7	Yes

[a]OFV, objective function values; PK, pharmacokinetic parameter; Lin, linear relation; Frac, fraction change relation; Pow, power relation; Expo, exponential relation; CL, clearance; Vc, Central volume of distribution; CL_{CRCG}, estimated using standard Cockcroft-Gault formula; CL_{CRCG_BW}, CL_{CRCG} based on total body weight; CL_{CRCG_IBW}, CL_{CRCG} based on ideal body weight; CL_{CRCG_LBW}, CL_{CRCG} based on lean body weight; CL_{CRCG_ABW}, CL_{CRCG} based on adjusted body weight; $CR_{CL\text{-}JEL}$, CL_{CR} estimated using the Jelliffe equation; GFR_{EPI}, estimated glomerular filtration rate (GFR) using the Chronic Kidney Disease Epidemiology Collaboration equation; GFR_{MDRD}, estimated GFR using the four-variable Modification of Diet in Renal Disease equation

[*]OFV decrease at least 3.84 (p value < 0.05, χ^2, df=1)

Table B11 Change in OFV of imipenem base model after the second round of covariate forward addition procedure [a]

No	PK	Added covariates	Relation	OFV	ΔOFV	Sig*
		Base model after inclusion GFR_{EPI}		264.4		
1	CL	Age	Lin	264.0	-0.4	
2	CL	Body weight	Pow	263.6	-0.8	
3	CL	Serum albumin	Lin	264.0	-0.4	
4	CL	Hypoalbuminemia	Frac	264.2	-0.2	
5	CL	Total bilirubin	Lin	264.3	-0.1	
6	CL	Direct bilirubin	Lin	264.3	-0.1	
7	CL	Aspartate transaminase	Lin	264.3	-0.1	
8	CL	Alanine transaminase	Lin	264.0	-0.4	
9	CL	Alkaline phosphatase	Lin	263.7	-0.7	
10	CL	Liver failure	Frac	264.0	-0.4	
11	CL	Septic shock	Frac	263.4	-1.0	
12	CL	APACHE II score	Lin	264.2	-0.2	
13	CL	SOFA score	Lin	263.4	-1.0	
14	V_C	Age	Lin	264.2	-0.2	
15	V_C	Gender	Frac	264.1	-0.3	
16	V_C	Body weight	Pow	263.8	-0.6	
17	V_C	Adjusted body weight	Pow	263.6	-0.8	
18	V_C	Ideal body weight	Pow	264.0	-0.4	
19	V_C	Body mass index	Pow	264.2	-0.2	
20	V_C	Serum albumin	Lin	264.1	-0.3	
21	V_C	Hypoalbuminemia	Frac	263.8	-0.6	
22	V_C	Norepinephrine use	Frac	262.6	-1.8	
23	V_C	Dopamine use	Frac	264.1	-0.3	
24	V_C	Epinephrine use	Frac	263.6	-0.8	

Table B11 Change in OFV of imipenem base model after the second round of covariate forward addition procedure (continued)[a]

No	PK	Added covariates	Relation	OFV	ΔOFV	Sig*
		Base model after inclusion GFR_{EPI}		264.4		
25	V_C	High dose vasopressor use	Frac	261.8	-2.6	
26	V_C	Septic shock	Frac	260.7	-3.7	
27	V_C	APACHE II score	Lin	263.3	-1.1	
28	V_C	SOFA score	Lin	264.1	-0.3	

[a]OFV, objective function values; PK, pharmacokinetic parameter; Lin, linear relation; Frac, fraction change relation; Pow, power relation; Expo, exponential relation; CL, clearance; Vc, Central volume of distribution; GFR_{EPI}, estimated glomerular filtration rate (GFR) using the Chronic Kidney Disease Epidemiology Collaboration equation
*OFV decrease at least 3.84 (p value < 0.05, χ^2, *df*=1)

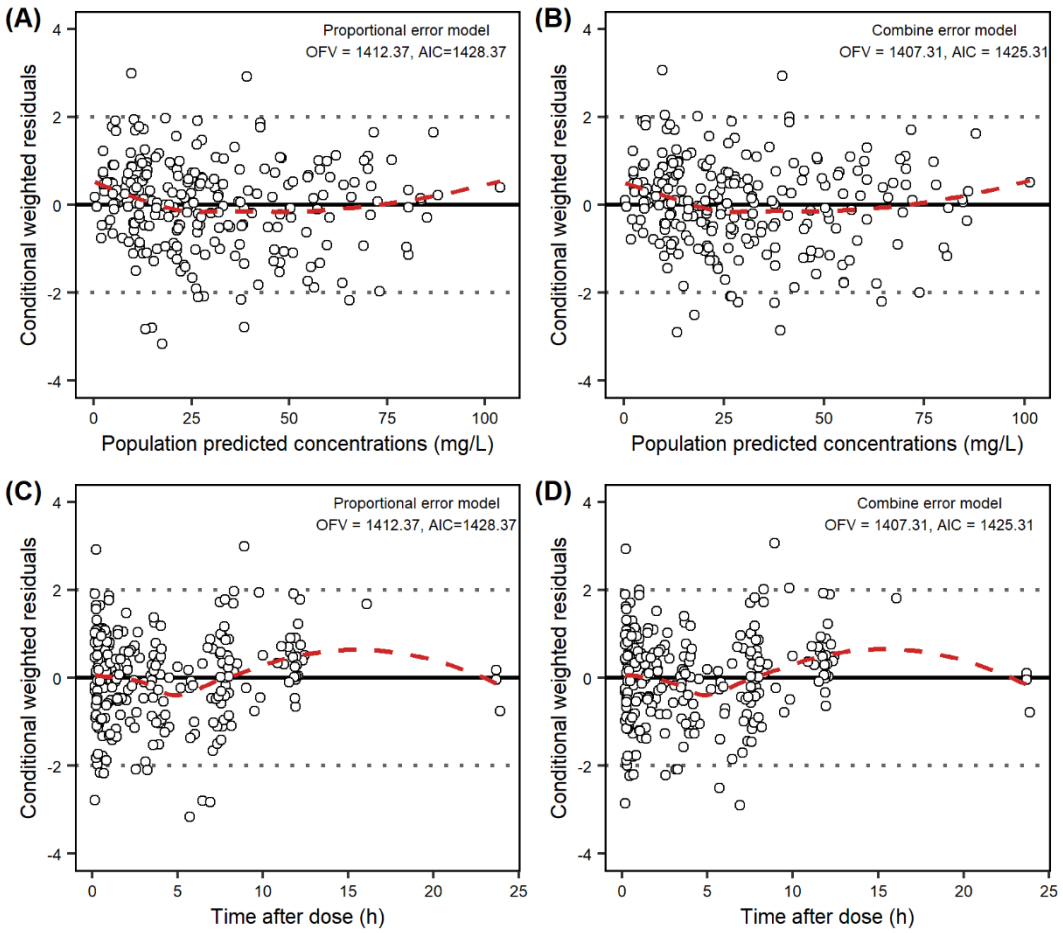

Figure B1 Conditional weighted residuals versus population prediction or time of proportional and combine error model. OFV and AIC are objective function and Alkaike's information criterion values, respectively.

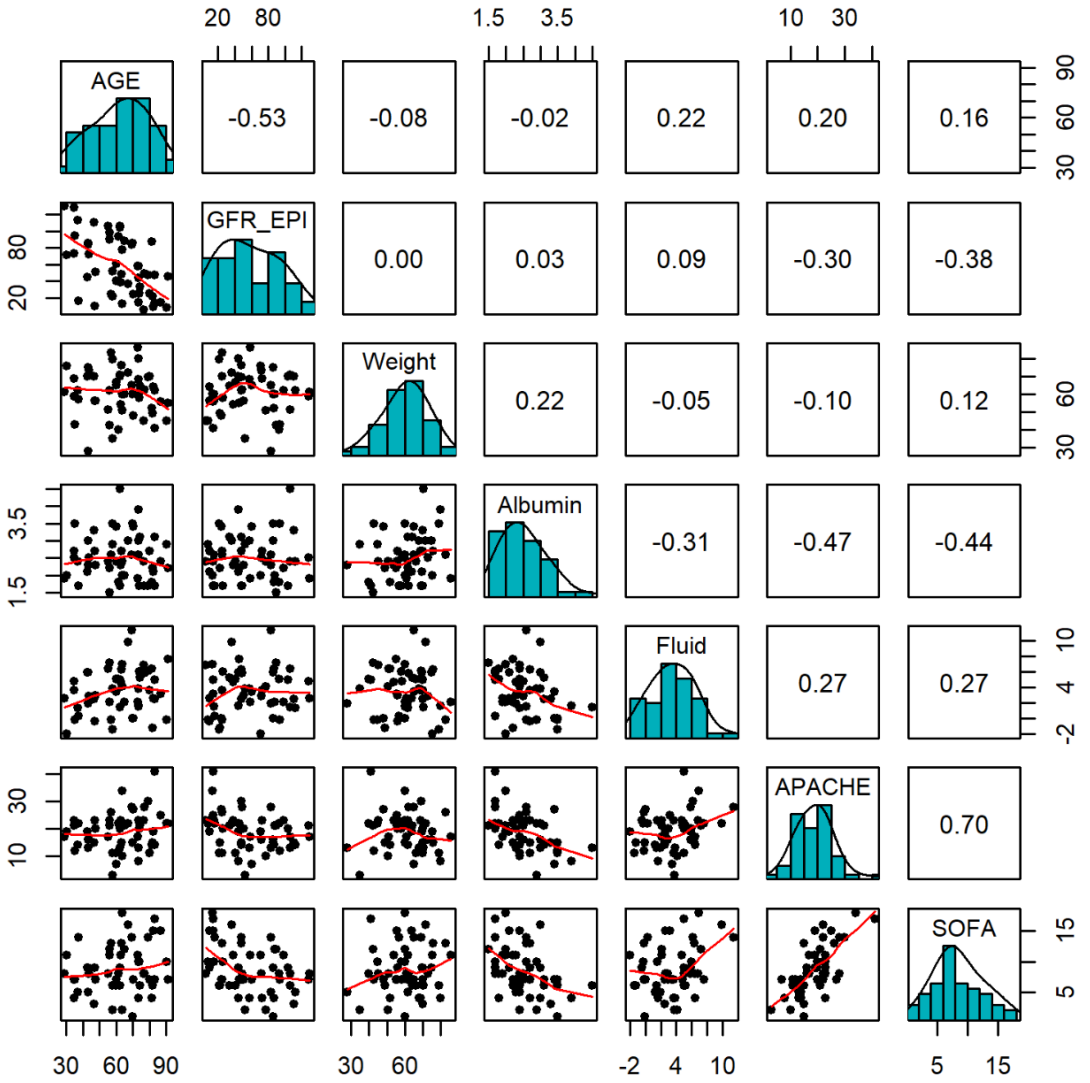

Figure B2 The scatterplot correlation matrix and histogram of covariates in meropenem cohort. The correlation coefficients between paired covariate are displayed on the top of diagonal.

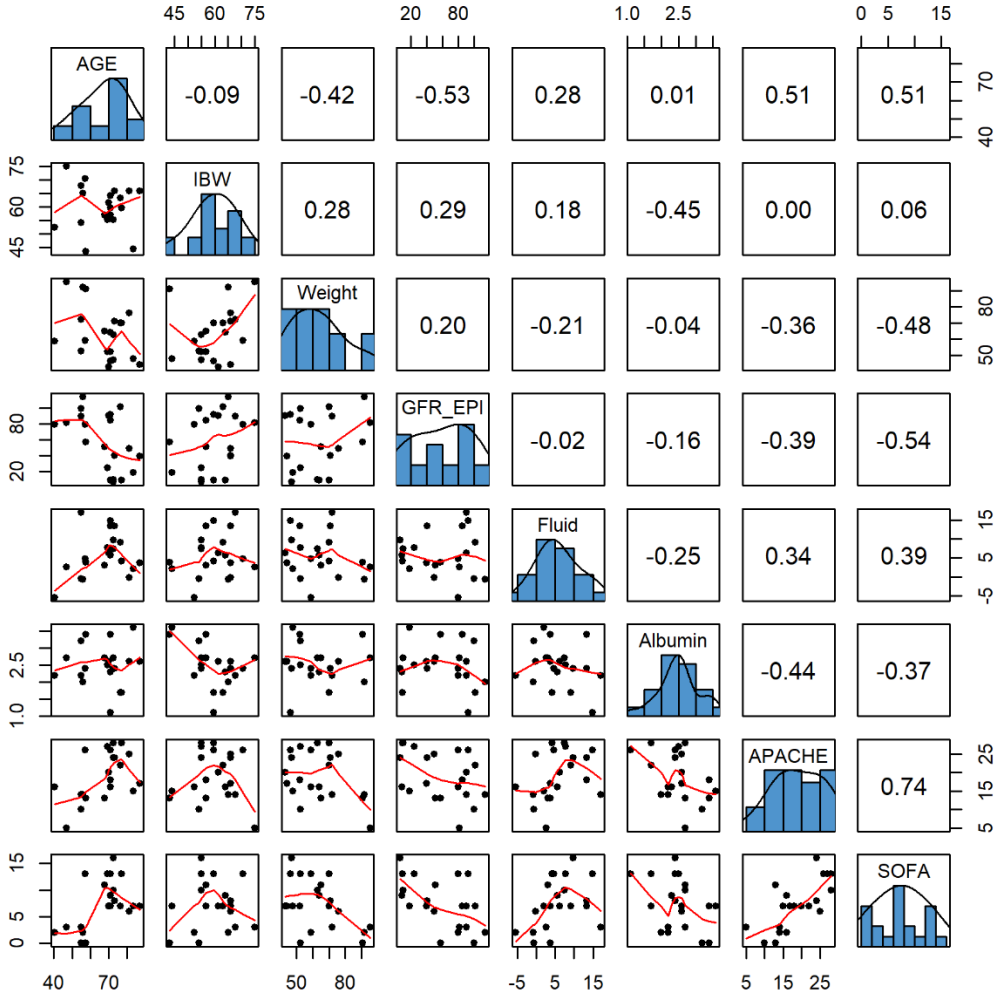

Figure B3 The scatterplot correlation matrix and histogram of covariates in the imipenem cohort. The correlation coefficients between paired covariate are displayed on the top of the diagonal.

APPENDIX C

Carbapenem-resistant bacterial infections

Table C1 The pharmacodynamic index of meropenem in patients infected with carbapenem-resistant pathogens [a]

ID	Dosage	CL_{CR}	Carbapenem-resistant strain	MIC	Individual $\%fT_{>MIC}$ above following MIC:		
					32	64	128
1	1g q8h	83.8	*A. baumannii*	≥32	6.3	0	0
9	2g q12h	45.5	*P. aeruginosa*	≥32	50.0	14.2	0
18	2g q8h	80.4	*A. baumannii*	≥32	86.3	22.5	3.8
25	1g q8h	95.5	*A. baumannii*	≥32	8.8	0	0
28	1g q8h	69.2	*K. pneumoniae*	≥32	100	43.8	2.5
48	1g q8h	36.7	*K. pneumoniae*	≥32	81.3	11.3	0
51	2g q8h, 1g q24h	14.7	*K. pneumoniae*	≥32	55.8	9.2	0

[a] CL_{CR}, creatinine clearance (mL/min); MIC, minimum inhibitory concentration

APPENDIX D

Disease severity scoring system in intensive care unit

Table D1 The sequential organ failure assessment (SOFA) score

SOFA score	0	1	2	3	4
PaO_2/FiO_2, mmHg (kPa)	❍ ≥400 (53.3)	❍ <400 (53.3)	❍ <300 (40)	❍ <200 (26.7) with respiratory support	❍ <100 (13.3) with respiratory support
Platelets, $x10^3$ /μL	❍ ≥ 150	❍ <150	❍<100	❍<50	❍<20
Bilirubin, mg/dL	❍ <1.2	❍ 1.2-1.9	❍ 2.0-5.9	❍ 6.0-11.9	❍ >12.0
Cardiovascular	❍ MAP≥70	❍ MAP <70	❍ DA<5 or DU (any dose)	❍ DA 5.1-15 or EN≤0.1 or NE≤0.1	❍ DA>15 or EN>0.1 or NE>0.1
GCS score	❍ 15	❍ 13-14	❍ 10-12	❍ 6-9	❍ <6
Creatinine (mg/dL) or	❍ <1.2	❍ 1.2-1.9	❍ 2.0-3.4	❍ 3.5-4.9 or	❍ >5.0 or
Urine output (mL/day)				<500	<200

DA, dopamine; DU, dobutamine; EN, epinephrine; GCS, glasgow coma score

Table D2 Acute Physiologic and Chronic Health Evaluation (APACHE) II score

Physiologic variable	**Value**	**+4**	**+3**	**+2**	**+1**	**0**	**+1**	**+2**	**+3**	**+4**
Temperature (°C)		❍ ≥41°	❍ 39-40.9		❍38.5-38.9	❍ 36-38.4	❍ 34-35.9	❍ 32-33.9	❍ 30-31.9	❍≤29.9
MAP		❍≥160	❍ 130-159	❍ 110-129		❍ 70-109		❍ 50-69		❍≤49
Heart rate		❍≥180	❍ 140-179	❍ 110-139		❍ 70-109		❍ 50-69	❍ 40-54	❍≤39
Respiratory rate		❍ ≥50	❍ 35-49		❍ 25-34	❍ 12-24	❍ 10-11	❍ 6-9		❍ ≤5
Oxygenation a. FiO_2≥0.5 ($A\text{-}aDO_2$)		❍ ≥500	❍ 350-499	❍ 200-349		❍<200				
b. FiO_2 <0.5 (PaO_2)						❍ >70	❍61-70		❍55-60	❍<55
Arterial pH		❍≥7.7	❍7.6-7.69		❍7.5-7.59	❍7.33-7.49		❍7.25-7.32	❍7.15-7.24	❍<7.15
Sodium (mEq/L)		❍≥180	❍160-179	❍155-159	❍150-154	❍130-149		❍120-129	❍111-119	❍≤110
potassium (mEq/L)		❍≥7	❍6-6.69		❍5.5-5.9	❍3.5-5.4	❍3.0-3.4	❍2.5-2.9		❍<2.5
Scr (mg/dL) (❍AKIx2)		❍≥3.5	❍2.0-3.4	❍1.5-1.9		❍0.6-1.4		❍<0.6		
Hematocrit (%)		❍≥60		❍50.0-59.9	❍46.0-49.9	❍30.0-45.9		❍20.0-29.9		❍<20
WBC(x10^3/mm3)		❍≥40		❍20.0-39.9	❍15.0-19.9	❍ 3.0-14.9		❍1.0-2.9		❍<1.0
GCS (15-actual GCS)										
HCO_3 (if no ABG)		❍≥52	❍41-51.9		❍32-40.9	❍22-31.9		❍18-21.9	❍15-17.9	❍<15
Part A: APS										

Part B: Age points	
≤44	0
45-54	2
55-64	3
65-74	5
≥75	6

Part C: Chronic health points	
❍ No chronic diagnosis	0
❍ Nonoperative	5
❍ Emergency postoperative	5
❍ Elective operative	2

Definition
❍ **LIVER** : Biopsy proven cirrhosis *and* documented portal HT;UGIB; hepatic encephalopathy/coma

Definition
❍ **CVS** : NYHA IV (symptom HF at rest)
❍ **RESPIRATORY :**COPD with severe exercise restriction, documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary HT(>40mmHg), respiratory dependency
❍ **RENAL**: chronic dialysis
❍ **IMMUNO-COMPROMISED:** chemotherapy, long-term or recent high-dose steroid, disease e.g leukemia, AIDS,lymphoma

Total APACHE II	
Part A	_____
Part B	_____
Part C	_____
Total	

APPENDIX E

Ethical Approval

AL-011_TH

คณะกรรมการจริยธรรมการวิจัยในมนุษย์
คณะแพทยศาสตร์ มหาวิทยาลัยสงขลานครินทร์

หนังสือรับรองฉบับนี้ให้ไว้เพื่อแสดงว่า

รหัสโครงการ :	REC.61-061-14-1	
ชื่อโครงการ :	**การศึกษาเภสัชจลนศาสตร์/เภสัชพลศาสตร์ และผลลัพธ์ทางคลินิกของยากลุ่ม β-lactams ในผู้ป่วยวิกฤต (Pharmacokinetics/Pharmacodynamics and Clinical Outcomes of β-lactams in Critically Ill Patients)**	
ผู้วิจัยหลัก:	สุเทพ จารุรัตนศิริกุล	**สังกัด :** ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยสงขลานครินทร์
ผู้ร่วมวิจัย :	อภิญญา บุญเป็ง	**สังกัด :** สาขาวิชาเภสัชกรรมคลินิก คณะเภสัชศาสตร์ มหาวิทยาลัยสงขลานครินทร์
ผู้ร่วมวิจัย :	รังสรรค์ ภูรยานนทชัย	**สังกัด :** สาขาวิชาเวชบำบัดวิกฤต ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยสงขลานครินทร์
ผู้ร่วมวิจัย :	สุทธิพร ภัทรชยากุล	**สังกัด :** สาขาวิชาเภสัชกรรมคลินิก คณะเภสัชศาสตร์ มหาวิทยาลัยสงขลานครินทร์
ผู้ร่วมวิจัย :	มนชนา นวกิจรังสรรค์	**สังกัด :** เภสัชวิทยาคลินิก ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยสงขลานครินทร์
ผู้ร่วมวิจัย :	มาซีเต๊าะ สาแม็ง	**สังกัด :** เภสัชวิทยาคลินิก ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยสงขลานครินทร์

เอกสารที่รับรอง:

1. โครงการวิจัยฉบับสมบูรณ์ เวอร์ชั่น 2.0 ฉบับวันที่ 10 พฤษภาคม 2561
2. เอกสารชี้แจงอาสาสมัคร เวอร์ชั่น 2.0 ฉบับวันที่ 10 พฤษภาคม 2561
3. เอกสารแสดงเจตนายินยอมของอาสาสมัคร เวอร์ชั่น 2.0 ฉบับวันที่ 10 พฤษภาคม 2561
4. แบบบันทึกข้อมูล
5. เอกสารกำกับยา
6. ประวัติผู้วิจัย

ได้ผ่านการพิจารณาและรับรองจากคณะกรรมการจริยธรรมการวิจัยในมนุษย์คณะแพทยศาสตร์ มหาวิทยาลัยสงขลานครินทร์ โดยยึดหลักจริยธรรมของประกาศเฮลซิงกิ (Declaration of Helsinki) และแนวทางการปฏิบัติการวิจัยทางคลินิกที่ดี (The International Conference on Harmonization in Good Clinical Practice) ข้อมูลการพิจารณา บรรจุในบันทึกการประชุมคณะกรรมการ ครั้งที่ 10/2561 ชุดที่ 3 วาระที่ 4.2 วันที่ 9 เมษายน พ.ศ. 2561

ขอให้นักวิจัยรายงานความก้าวหน้าโครงการวิจัย ทุก 12 เดือน และยื่นต่ออายุก่อนถึงวันหมดอายุอย่างน้อย 30 วัน

(รศ.นพ.บุญสิน ตั้งตระกูลวนิช)
ประธานคณะกรรมการจริยธรรมการวิจัยในมนุษย์
คณะแพทยศาสตร์ มหาวิทยาลัยสงขลานครินทร์

วันที่รับรอง : 22 มิถุนายน พ.ศ. 2561
หมดอายุ : 21 มิถุนายน พ.ศ. 2562

คณะกรรมการจริยธรรมการวิจัยในมนุษย์
คณะแพทยศาสตร์ มหาวิทยาลัยสงขลานครินทร์
15 ถนนกาญจนวณิชย์ อำเภอหาดใหญ่ จังหวัดสงขลา 90110
โทรศัพท์ 074451149, 074451157
โทรสาร 074212900

Ref no. Lle4i-ubVsA-aGS0X-sEopT-JB26X

AF/11-06/01.2

Memorandum

At: Human Research Ethics Committee Faculty of Medicine, Prince of Songkla University

Ref: PSU.351.7.2/ 63-00905 Date 8/1/2020

Subject: The result of REC's consideration

Principal Investigator	Sutep Jaruratanasirikul, M.D.
Affiliation	Faculty of Medicine, Prince of Songkla University
REC	61-061-14-1
Protocol Number	-
Protocol Title	Pharmacokinetics/Pharmacodynamics and Clinical Outcomes of β-lactams in Critically Ill Patients

According to the reference document No. PSU.372/63-00186 date 7/10/2019

As you notified the committee about the amendment (major)

The document(s) including:

Protocol version 6.0 date 20 December 2019

Have/has been reviewed and acknowledged by the committee.

This issue was placed in the minutes agenda 4.6 meeting 33 / 2019 date 25/11/2019

Faithfully Yours,

(Assoc. Prof.Boonsin Tangtrakulwanich)
Chairman of Research Ethics Committee
Faculty of Medicine, Prince of Songkla University

Date of approval 1/1/2020

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VITAE

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Student ID 5810730004

Educational Attainment

Degree	Name of Institution	Year of Graduation
Doctor of Pharmacy	Naresuan university	2008

Scholarship Awards during Enrolment

1. Scholarship to support tuition fee discipline of excellence in pharmacy project
2. Scholarship support for the thesis
3. Doctor Kasem Foundation financial support for buying NONMEM software

List of Publication and Processing

- Chaijamorn W, Charoensareerat T, Srisawat N, Pattharachayakul S, **Boonpeng A.** Cefepime dosing regimens in critically ill patients receiving continuous renal replacement therapy: a Monte Carlo simulation study. J Intensive Care. 2018 Sep 12;6:61.
- Charoensareerat T, Chaijamorn W, **Boonpeng A**, Srisawat N, Pummangura C, Pattharachayakul S. Optimal vancomycin dosing regimens for critically ill patients with acute kidney injury during continuous renal replacement therapy: A Monte Carlo simulation study. J Crit Care. 2019 Dec;54:77-82.
- Chaijamorn W, Puchsaka P, Pattharachayakul S, Charoensareerat T, Srisawat N, **Boonpeng A**, Pummangura C. Doripenem dosing regimens in Asian critically ill patients with continuous renal replacement therapy. J Crit Care. 2019 Aug;52:233-236.
- Charoensareerat T, Bhurayanontachai R, Sitaruno S, Navasakulpong A, **Boonpeng A,** Lerkiatbundit S, Pattharachayakul S. Efficacy and Safety of Enteral Erythromycin Estolate in Combination With Intravenous Metoclopramide vs Intravenous Metoclopramide Monotherapy in Mechanically Ventilated Patients With Enteral Feeding Intolerance: A Randomized, Double-Blind, Controlled Pilot Study. JPEN J Parenter Enteral Nutr. 2020.